THE COMPELLING NEED FOR GAME-CHANGING INFLUENZA VACCINES

AN ANALYSIS OF THE INFLUENZA VACCINE ENTERPRISE AND RECOMMENDATIONS FOR THE FUTURE

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CIDRAP
Center for Infectious Disease Research & Policy
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An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future

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The Center for Infectious Disease Research and Policy (CIDRAP), founded in 2001, is a global leader in addressing public health preparedness and emerging infectious disease response. Part of the Academic Health Center at the University of Minnesota, CIDRAP works to prevent illness and death from targeted infectious disease threats through research and the translation of scientific information into real-world, practical applications, policies, and solutions. For more information, visit: www.cidrap.umn.edu.

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Preface

Dating back to Hippocrates, influenza has been and continues to be one of the "lion kings" of infectious diseases. It occurs in two different patterns: (1) annual seasonal epidemics during winter months in the temperate countries and year-round in the tropics, and (2) global pandemics, which can occur during any season and last more than a year. An estimated 3,000 to 49,000 individuals in the United States die every year from seasonal influenza.

Influenza pandemics occur when novel influenza viruses in animals undergo genetic changes that allow the viruses to infect humans, who in turn transmit the new human-adapted virus to others. Four pandemics have occurred in the last 100 years: 1918, 1957, 1968, and 2009. Influenza pandemics can vary in severity; in 1918 an estimated 50 million to 100 million people died worldwide. In the 1957 and 1968 pandemics, an estimated 1.5 million and 750,000 people died, respectively. An official estimate of worldwide deaths from the 2009 pandemic is not expected until late 2012.

Today more than 500 infectious diseases are known to occur in humans, yet in the United States, public health officials recommend routine childhood or adult vaccinations for only 17 of these diseases. And, for only one of these diseases is there a recommendation for universal annual vaccination: namely, influenza. In 2010 the Advisory Committee on Immunization Practices (ACIP) established the first national universal seasonal influenza vaccination recommendation. Annual vaccination is currently recommended with trivalent inactivated influenza vaccine for all persons 6 months of age and older or with live-attenuated influenza vaccine for healthy nonpregnant persons aged 2 to 49 years. Influenza vaccine availability also is the cornerstone of influenza pandemic preparedness.

THE INITIATIVE

In 2009, the world experienced its first influenza pandemic of the 21st century; it occurred 41 years after the previous one. Since the re-emergence of H5N1 influenza in birds and humans in 2003 in Asia, the international public health community and influenza vaccine manufacturers have worked to expand the global influenza vaccine manufacturing capacity to respond to an emerging pandemic. However, early on in the 2009 pandemic there were many questions about the adequacy of our influenza vaccine response.

In December 2009 the Alfred P. Sloan Foundation provided a grant to the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota to support the CIDRAP Comprehensive Influenza Vaccine Initiative (CCIVI). The primary objectives of CCIVI were to provide a comprehensive review of all aspects of 2009-2010 pandemic A(H1N1)pdm09 influenza vaccine preparedness and response based on the events of the pandemic vaccine effort and to review the scientific and programmatic basis for the current seasonal influenza vaccine efforts. This review included all aspects of influenza vaccine research and development, financing, manufacturing, efficacy, safety, regulatory issues, procurement, distribution, vaccine usage, public education, consumer acceptance, and public policy.

And now, almost 3 years later, we share with you the completed CCIVI report; it represents one of the most exhaustive reviews of any vaccine ever undertaken. When we started, we had no idea where this initiative would take us. It was like peeling back the proverbial onion; the more extensively we examined the "cradle to grave" aspects of our current seasonal and pandemic influenza vaccines, the more questions—and lack of answers—we identified. In short, we found that current influenza vaccine protection is substantially lower than for most routinely recommended vaccines and is suboptimal. It is clear, however, that during some influenza seasons vaccination offers substantially more protection for most of the population than being unvaccinated. For this reason, we believe current influenza vaccines will continue to have a role in reducing influenza morbidity until more effective interventions are available. But we can no longer accept the status quo regarding vaccine research and development.

This final CCIVI report includes 14 chapters and an executive summary; it has 505 unique references. But to target the actions that we believe are necessary to move the international influenza vaccine enterprise toward critically needed novel-antigen, game-changing vaccines, we have identified just 10 key findings and six "high-level" recommendations. While our review and analysis effort was exhaustive, we have made every

effort to produce a report that allows the reader to distinguish the forest from the trees!

The Alfred P. Sloan Foundation generously provided unrestricted funding for the first year of the study and allowed us to complete the final report when we finished our "onion peeling." The remainder of the support for this effort came from the general budget of CIDRAP and the ongoing efforts of a very dedicated CIDRAP team. We have no potential conflicts of interest to report. In total, 13 CIDRAP staff and 2 affiliated researchers provided thousands of hours of painstaking "document detective work," literature review, and subject matter interviews.

I have never been part of any project this exhaustive. For example, we reviewed in detail more than 12,000 articles, documents, transcripts, and notes dating back to 1936. The review included such material as all peer-reviewed literature on influenza vaccines indexed in PubMed from 1936 to April 2012; all documents available for public review from the Commission on Influenza, Armed Forces Epidemiological Board (1941-1973); US Surgeon General's influenza vaccine recommendations (1957-1964); all ACIP statements (1964-2012) and meeting records (1997-2012); ClinicalTrials.gov (1999-June 2012); the Cochrane Collaboration influenza vaccine reviews (10); and many hundreds of documents from the US government, foreign governments, international public health organizations like the World Health Organization, and non-governmental agencies. We also interviewed and in some instances had briefings with 88 experts in influenza vaccine research, development, and use; many were consulted numerous times.

As part of the initiative, we established a 13-member CCIVI Expert Advisory Group (EAG) comprising internationally recognized experts in all aspects of vaccine research and development, manufacturing, safety, delivery, and financing. (See below.) The EAG was chaired by Alfred Sommer, MD, MHS, former dean of the Bloomberg School of Public Health at Johns Hopkins University. EAG members actively participated in our initiative through conference calls, meetings, and extensive review of documents, including drafts of this report. We deeply appreciate their very generous expert support. We listened carefully to their input.

The CCIVI Expert Advisory Group

- **Alfred Sommer, MD, MHS (Chair)**
  Professor and Dean Emeritus, Johns Hopkins Bloomberg School of Public Health
- **Ruth Berkelman, MD**
  Director, Center for Public Health Preparedness and Research, Emory University
- **Gail Cassell, PhD**
  Visiting Professor, Harvard Medical School
  Ret. VP, Scientific Affairs and Distinguished Research Scholar, Eli Lilly and Company
- **Walt Dowdle, PhD**
  Consulting Director, the Task Force for Global Health
- **William M. Egan, PhD**
  VP, PharmaNet, Inc
- **Neal Halsey, MD**
  Director, Institute for Vaccine Safety, and Professor, Johns Hopkins Bloomberg School of Public Health
  Professor, John Hopkins School of Medicine
- **George E. Hardy, Jr, MD, MPH**
  Public Health Practice Consultant
  Former Executive Director, Association of State and Territorial Health Officials
- **Stanley M. Lemon, MD**
  Professor of Medicine, Microbiology, and Immunology, School of Medicine, University of North Carolina
- **Thomas Monath, MD**
  Partner, Kleiner Perkins Caufield & Byers
- **George Poste, DVM, PhD, DSc**
  Chief Scientist, Complex Adaptive Systems Initiative
  Regents Professor and Del E. Webb Chair in Health Innovation, Arizona State University
- **James Robinson, MS**
  VP, Vaccine Product and Technology Operations, Merck & Co
- **Ret. Major General Philip Russell, MD**
  Board of Trustees, Sabin Vaccine Institute
- **Peter Sandman, PhD**
  Risk Communication Consultant

We convened two EAG meetings in Washington, DC. The first, held in July 2010 and focused on research and development, manufacturing, and financing, involved 40 experts in these fields. They included senior

leadership from all five manufacturers of US-licensed influenza vaccines and five promising manufacturers who are using new approaches to influenza vaccines, as well as senior science and policy leaders from the US government. The second EAG meeting was held in September 2010 and focused on vaccine safety, distribution, procurement, risk communication, and public acceptance. There were 32 experts in these fields in attendance at this working group meeting, including the chairs of all four committees that advise the US government on influenza vaccine licensing and use.

It is impossible for me to adequately thank everyone who contributed to this remarkable effort. But first and foremost, I thank my co-investigators. Nicholas Kelley, PhD, helped direct this initiative and was the invaluable glue that held it all together. His ability to find, catalogue, remember, and understand in detail thousands of documents is legendary. The other coauthors included Jill Manske, PhD, MPH; Katie Ballering, PhD; Tabitha Leighton, MPH; and Kristine Moore, MD, MPH; their untiring contributions are deeply admired and appreciated. I also want to acknowledge the important efforts of other CIDRAP staff, including Jim Wappes, Aaron Desmond, Laura Grangaard, Megan Schlossmacher, Kyle Willems, Lissa Tenuta, and Laurel O'Neil.

The invaluable contributions of four other individuals deserve special note. Edward Belongia, MD, from the Marshfield Clinic Research Foundation, played a seminal role in our meta-analysis of current influenza vaccines published in *The Lancet Infectious Diseases*. He also mentored us on the critical aspects of study design for determining influenza vaccine efficacy and effectiveness. Pritish Tosh, MD, of the Mayo Clinic has spent the past 8 months as a research fellow at CIDRAP; he provided a very important perspective through his many hours of engaged discussions regarding our analysis and recommendations. Paula J. Olsiewski, PhD, program director at the Alfred P. Sloan Foundation, believed that our team could tackle the issue of moving the influenza vaccine enterprise forward. Her support of our early efforts was critical in getting this initiative off the ground. And last but not least is my heartfelt appreciation to Alfred Sommer, the chair of the EAG. Al has long been an admired colleague and friend. He was asked to serve as the EAG chair not because of expertise in influenza vaccines, but rather because of his ability to comprehend "big picture" public health policy issues and, in turn, clearly articulate a consequential path forward. His contributions were immeasurable and deeply appreciated.

We thank the 88 subject matter experts whom we consulted for their time and wisdom. Every one of them was very kind in giving their time. Some provided extraordinary support, engaging in many conversations over 2 years and also agreeing to review documents for us. We also thank the individuals who participated in the two meetings in Washington, DC.

In the end, the analysis and findings of this report, including any errors, are the sole responsibility of the CCIVI team and CIDRAP. This report may not reflect the opinions or conclusions of the Alfred P. Sloan Foundation, EAG members, the subject matter experts we consulted, or those who attended our meetings.

Finally, I close with quotes from two individuals whom I greatly admire. Daniel Boorstin was the 12th Librarian of the United States Congress from 1975 until 1987. Richard Feynman was the 1965 Nobel Prize laureate in physics.

"The greatest obstacle to discovering the shape of the earth, the continents, and the oceans was not ignorance but the illusion of knowledge."

–Daniel Boorstin

"For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled."

–Richard Feynman

I believe these quotes capture the essence of this report. We hope that our efforts will serve as a catalyst to rapidly move the international influenza enterprise closer to developing game-changing influenza vaccines. In turn, we know that such vaccines will begin to tame one of the lion kings of infectious diseases: our old nemesis, influenza.

Michael T. Osterholm, PhD, MPH
CIDRAP, University of Minnesota

EXECUTIVE

Summary

Influenza is a respiratory-transmitted viral infection and historically one of the most important infectious diseases in humans. It occurs in two different patterns: annual seasonal epidemics during our winter months and global pandemics, which can occur during any season and last more than a year. An estimated 3,000 to 49,000 individuals in the United States die every year from seasonal influenza. The World Health Organization has estimated for more than a decade that seasonal influenza results in about 3 million to 5 million cases of severe illness worldwide and about 250,000 to 500,000 deaths annually, but this is likely an underestimation of the disease's true global impact.

Influenza pandemics occur when novel influenza viruses in animals undergo genetic changes that allow them to infect humans and in turn humans to transmit the new human-adapted virus to each other. Four pandemics have occurred in the last 100 years: 1918, 1957, 1968, and 2009. Influenza pandemics can vary in severity; in 1918 an estimated 50 million to 100 million people died worldwide. In the 1957 and 1968 pandemics, an estimated 1.5 million and 750,000 people died, respectively. An official global estimate of deaths from the 2009 pandemic is not expected until later this year.

Human influenza vaccine research began shortly after the virus was discovered in 1933. Following the devastating impact on US military personnel who were engaged in World War I during the 1918-19 influenza pandemic, the US government made it a national priority to never again allow soldiers on the battlefield to be so vulnerable to the disease. Once the pathogen had been identified, addressing this concern ushered in the modern era of influenza vaccine research and development. As a result of these efforts, seasonal influenza vaccines are now generated and widely distributed each year. Influenza vaccine availability is also the cornerstone for pandemic preparedness.

The current US-licensed trivalent inactivated influenza vaccine (TIV) is a split-virus or subunit vaccine not much different from the split-virus vaccine originally licensed in 1968. A live-attenuated influenza vaccine (LAIV) was licensed in the United States in 2003. TIV and LAIV are produced in pathogen-free embryonated chicken eggs using techniques from the 1930s. Because of minor mutational changes in the circulating viruses, influenza vaccines are typically reformulated annually on the basis of the strains predicted to circulate during the upcoming influenza season.

Influenza vaccine was first recommended for use in US military personnel in 1945. The Advisory Committee on Immunization Practices (ACIP) thereafter made a number of incremental changes to the annual influenza vaccine recommendations, leading to recommended coverage for an ever-increasing proportion of the US population. In 2010 the ACIP recommended the first national universal seasonal influenza vaccination for all persons 6 months old and older. With the vast majority of Americans now recommended for vaccination, the public health benefits of the current influenza vaccination strategy have largely been maximized.

Current hemagglutinin (HA)-head antigen influenza vaccines, regardless of the platform in which they are manufactured, are inadequate to provide robust clinical protection across multiple strains or long-term protection. Evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those 65 years old or older. The ongoing public health burden caused by seasonal influenza and the potential global effect of a severe pandemic create an urgent need for a new generation of highly effective and cross-protective vaccines that can be manufactured rapidly. A universal vaccine should be the goal, with a novel-antigen game-changing vaccine the minimum requirement.

KEY FINDINGS

1. During some influenza seasons vaccination offers substantially more protection for most of the population than being unvaccinated; however, influenza vaccine protection is markedly lower than for most routinely recommended vaccines and is suboptimal.

We reviewed all studies that evaluated influenza vaccine efficacy and effectiveness published from 1967 to 2012 and summarized those that used rigorous methodology and had specific infection outcome end points. For TIV, results demonstrated: (1) evidence of moderate protection (pooled estimate of 59%) for

healthy adults 18 to 64 years of age, (2) inconsistent evidence of protection in children age 2 to 17 years, and (3) a paucity of evidence for protection in adults 65 years of age and older. For LAIV, results demonstrated: (1) evidence of high protection (pooled estimate of 83%) for young children 6 months to 7 years of age, (2) inconsistent evidence of protection in adults 60 years of age and older, and (3) a lack of evidence for protection in individuals between 8 and 59 years of age.

2. A major barrier to the development of game-changing influenza vaccines is the perception that current vaccines are already highly effective in preventing influenza infection.

The perception that current vaccines are already highly effective in preventing influenza is a major barrier to pursuing game-changing alternatives. Indeed, hundreds of influenza vaccine efficacy and effectiveness studies have been conducted since the 1940s, and vaccine efficacy in healthy adults of 70% to 90% is frequently cited. However, the preponderance of the available influenza vaccine efficacy and effectiveness data is derived from studies with suboptimal methodology, poorly defined end points, or end points not proven to be associated with influenza infection. Studies using optimal methodology have not found the level of protection often attributed to the current vaccines.

3. In an effort to reduce influenza morbidity and mortality, over the last three decades the ACIP has expanded the populations recommended to receive influenza vaccine. These recommendations, however, often were based on professional judgment and not on scientifically sound data.

Since 1964, the ACIP has had the responsibility of recommending which persons should receive annual vaccination. From 1964 to 1986, the categories of persons recommended for influenza vaccination remained largely unchanged and primarily focused on persons at high risk for complications. In 1986, the ACIP expanded on the concept of the "indirect benefit" of vaccination by including people in contact with individuals at high risk of serious illness or death. From 1999 through 2010, the ACIP embarked on a path of incrementally adding more and more subgroups to its recommendations. The movement toward a universal recommendation for vaccination did not occur primarily as a result of a preponderance of newly published evidence; rather, changes were made in part on the basis of expert and organizational opinion. Furthermore, the ACIP statements have not always accurately reflected the evidence used to support the recommendations and routinely have cited studies with suboptimal methodology (eg, that use serology as an end point for infection among TIV recipients) as supportive.

4. Novel-antigen influenza vaccines in investigational research offer the potential of lasting, broad, and potent protection; however, substantial research support is needed to further develop and evaluate these vaccines.

More than 170 influenza vaccines representing a wide range of technologies are now undergoing clinical trials around the world. Most of them, however, use the same mechanism of action as the currently licensed vaccines aimed at eliciting antibodies to the HA head. In contrast, some of the vaccines under investigational research use novel vaccine technologies or target novel antigens and as such have the potential to be game-changing. Investigators are exploring antigens such as the HA stalk, nucleoprotein, and the matrix 2 protein, all of which contain segments that are conserved across influenza strains, which raises the prospect of universal vaccines. Novel methods of presenting these antigens to elicit broad immunologic responses are also in development and include technologies such as recombinant proteins, virus-like particles, non-replicating viruses, viral vectors, and DNA vaccines. Adequate investigational research support is needed to develop and evaluate these vaccines so their potential as game-changing vaccines can be determined.

5. The current US government regulatory process for approving influenza vaccines is primarily designed for incremental changes to existing vaccines and presents a barrier to the development of game-changing vaccines.

Approval and licensure of all vaccines by the US Food and Drug Administration (FDA) understandably requires documentation of potency, sterility, and effectiveness. But despite more than 60 years of licensing influenza vaccines in this country, critical issues remain, including the establishment of appropriate correlates of

protection, improvement of assays for potency, and development of models that can be used for evaluation when human clinical trials are unethical or not feasible. Modernizing and moving vaccine development toward novel game-changing vaccine technologies will require addressing all of these issues and more. A substantial shift in regulatory science by both government and industry is needed, along with revitalization of the FDA, to move from the current incremental approach to a broader vision.

6. Substantial financial risks and inadequate incentives create significant barriers to bringing game-changing vaccines to market.
Vaccine companies incur substantial financial risks to bring new vaccines to market. The entire process, from preclinical research through licensure, can take up to 15 years and cost more than $1 billion. Novel-antigen influenza vaccines that are potential game-changers face the same hurdles for approval as more traditional new vaccines do; however, the already daunting approval process will be even longer and more extensive and the financial risk substantially higher for such novel vaccines. A novel influenza vaccine that provides protection for a number of years will need to cost substantially more per dose than current vaccines in order for investors and manufacturers to recoup their costs, since less frequent vaccine administration will lead to sale of fewer doses over time. If the per-unit cost requirement for profitability exceeds what the market will bear, then the likelihood that this type of vaccine will be developed is minimal, even if such a vaccine would bring a greater benefit to society and thereby save the government and society the costs associated with each influenza outbreak. These and other market challenges represent major barriers to developing game-changing influenza vaccines.

7. Coordinated partnerships involving national governments, the pharmaceutical industry, the investment community, and academia will be critical to move such vaccines through clinical trials and the licensure process.
While manufacturers of influenza vaccines are beginning to acknowledge the limitations of current vaccines, no fundamental changes have been implemented by the industry to facilitate development of novel-antigen game-changing influenza vaccines. Current influenza vaccines provide a relatively stable market for manufacturers, which could be disrupted by game-changing influenza vaccines, reducing manufacturers' desire to support the development of these vaccines. Owing to regulatory challenges facing novel-antigen vaccines, start-up companies are not able to obtain sufficient funding to ensure they can move through the "valley of death" of clinical trials—where substantial research, development, and licensure costs are incurred but no revenue is generated—and develop a licensed product. The US government needs to increase its support of game-changing influenza vaccines, and coordination among government, academia, and industry is needed to ensure that novel-antigen game-changing influenza vaccines become licensed.

8. Current policy goals for influenza vaccines focus on increasing production capacity and have not addressed key public health challenges related to the effectiveness of current vaccines.
Current influenza vaccine public health policy focuses on: (1) expanding current seasonal influenza vaccination campaigns to vaccinate an increasing proportion of the population each year using current HA-head vaccines, (2) ensuring that capacity is available to rapidly produce HA-head vaccines at the onset of an influenza pandemic, and (3) improving vaccine access, particularly in developing countries. While these are all laudable goals, they provide only for incremental improvements. Public health policy has not yet recognized the critical limitations of the current HA-head vaccines or the limited impact of our current strategies. While officials are now recognizing that better vaccines are needed, the current policy focus and the lack of acknowledgment of the current vaccines' shortcomings have created an environment lacking the political will to develop novel-antigen game-changing vaccines. Public health policy leaders must overcome these barriers and make development of game-changing vaccines a national priority.

9. Significant policy, investment, organizational, and leadership barriers must be overcome to achieve novel-antigen game-changing influenza vaccines.
In the current landscape, no US government or international agency or organization has the

responsibility or capability to effectively manage the influenza vaccine enterprise to bring about game-changing vaccines. Our findings indicate that moving influenza vaccinology forward in a way that effects meaningful change requires a new paradigm in the organization and leadership of the influenza vaccine enterprise—both in the United States and globally. First, the paradigm needs be driven by a vision of the future that takes into account available resources and how best to allocate and use them. Second, it needs to be based on an understanding of the limitations of our current influenza vaccines and the importance of developing truly game-changing alternatives. Third, it needs to employ project management principles and processes commensurate with the scope and complexity of the project.

10. Pandemic influenza remains a clear and compelling threat to our national security and requires commensurate prioritization and an unprecedented coordinated effort among government, academia, and the private sector to mitigate this threat.

Influenza vaccines were first developed in response to the national security threat of a severe influenza pandemic, as experienced in 1918. The cornerstone of pandemic preparedness should be the availability of a highly effective pandemic influenza vaccine, ideally before the pandemic virus emerges. We recognize the current environment of fiscal austerity; however, the economic and political consequences of a severe influenza pandemic in the absence of a readily available and effective vaccine cannot be overstated.

RECOMMENDATIONS

Recommendation 1. Novel-antigen game-changing seasonal and pandemic influenza vaccines that have superior efficacy and effectiveness compared with current vaccines are urgently needed. In particular, game-changing vaccines must demonstrate increased efficacy and effectiveness for populations at increased risk for severe influenza morbidity and mortality. They must also have a similar or better safety profile than current influenza vaccines.

Recommendation 2. Scientifically sound estimates of influenza vaccines' efficacy and effectiveness must become the cornerstone of policy recommendations regarding vaccine use and for driving efforts to develop new, more protective vaccines. Therefore, an internationally adopted standard for evaluating influenza vaccine efficacy and effectiveness, which takes into account diagnosis, study design, and analytical methods, needs to be developed.

Recommendation 3. Any pandemic influenza vaccine should demonstrate high efficacy and effectiveness for different pandemic epidemiologic patterns. As with game-changing seasonal influenza vaccines, only pandemic influenza vaccines that can demonstrate this protection based on an internationally accepted standard should be considered as a primary medical countermeasure. The vaccine also needs to be available in sufficient quantities to protect the global population either before or in the earliest days of the pandemic.

Recommendation 4. To overcome the many barriers to bringing game-changing influenza vaccines to market, a newly designed model adapted specifically to the development and licensure of novel-antigen influenza vaccines must be implemented. Several areas must be addressed. First, development of novel-antigen game-changing influenza vaccines must be declared a national priority by the US government. With that declaration must come the commitment to provide the resources and project management processes required to make novel-antigen game-changing vaccines a reality. Second, a financially sound pathway must be implemented to overcome the current financial disincentives that impede the advancement of new influenza vaccines to market. A substantial investment by the US government in research and development and regulatory science, with new private-sector investment incentives, will be imperative in accomplishing this objective. Third, a new organizational and leadership structure for the influenza vaccine enterprise must be established to provide strong science and business leadership and exemplary project management processes so that barriers are identified and overcome to maximize available resources. Achieving these goals and bringing novel influenza vaccines to the global market will require a highly coordinated leadership effort, similar to the mission-critical prioritization and project management approach of the Manhattan Project.

Recommendation 5. The US government should assume a primary leadership role in moving the global influenza vaccine enterprise forward to develop game-changing influenza vaccines and bring them to market. The World Health Organization, other international agencies and governments, and private-sector partners should make support of this US government–led effort a mission-critical priority.

Recommendation 6. An internationally accepted standard for evaluating influenza vaccine efficacy and effectiveness should be used for calculating cost-effectiveness of influenza vaccines. This will allow purchasers to accurately determine the reduction in morbidity and mortality associated with influenza vaccination in their covered populations. Purchasers can then use information on vaccine performance to generate appropriate standards for reimbursement, which will be an important factor in driving the market toward improved influenza vaccines.

CHAPTER 1

UNDERSTANDING INFLUENZA AS A VACCINE-PREVENTABLE DISEASE

INTRODUCTION

To understand the role, impact, and limitations of current and future influenza vaccines in preventing human infection, it is necessary to have a reasonable grasp of the unique virologic characteristics of influenza viruses and the basic epidemiology of influenza infection. This background includes the burden of disease and associated mortality in different human populations. In this chapter we provide a high-level overview of influenza viruses and influenza disease.

THE INFLUENZA VIRUS

Influenza virus is the causative agent of influenza infection. Three types of influenza viruses (A, B, and C) cause infections in humans, although infections with type C are rare. Influenza A and B routinely circulate around the world, causing seasonal epidemics. Influenza A is typically characterized by two distinct proteins located on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Seventeen different HA and 10 different NA influenza A subtypes are found in nature and, when combined, yield 170 subtypes.[1] However, only a few combinations (such as H1N1, H2N2, and H3N2) have been documented to cause pandemic or seasonal influenza A in humans.[2] Influenza B has two distinct lineages that cause human infections; neither causes human pandemics.

The heads of the HA and NA proteins are the primary antigens that elicit the immune response following infection in humans and are also the primary components of influenza vaccines; however, HA is considered the more important of the two. Since 1977, two influenza A subtypes (one H1N1 and one H3N2) and, more recently, two influenza B strains, circulate annually around the globe, causing seasonal influenza epidemics each year. Small mutations (referred to as antigenic drift) result in slight changes to the HA and NA antigens of each subtype between influenza seasons. Because of antigenic drift, the influenza vaccine is reformulated annually on the basis of the most likely strains that are predicted to circulate during the upcoming influenza season. This is the only human infection for which we must routinely reformulate the vaccine to accommodate the mutational process and maximize the potential protective immune response.

The primary reservoir for influenza A viruses is wild aquatic birds; however, these viruses can infect a wide variety of animal species, including horses, dogs, cats, pigs, turkeys, and chickens. These zoonotic infections can become an animal welfare or food production issue, but the primary concern is the potential for emergence of a new human pandemic strain. Occasionally, major antigenic changes occur in influenza viruses (antigenic shift), either through recombination of human and animal influenza strains or mutational changes in an animal strain, resulting in a new strain. If the new strain can be efficiently

transmitted to and between humans and the human population has limited immunity to the strain, a pandemic will ensue. Antigenic shifts led to the four global human pandemics that have occurred since 1900 (these began in 1918, 1957, 1968, and 2009). In 1977, H1N1 re-emerged following a 20-year absence in human circulation. The reappearance of H1N1 did not occur as the result of antigenic shift in a human or animal population; rather, it was likely due to an accidental release related to research studies using this virus. Unlike seasonal influenza, which has a defined seasonality, a pandemic can emerge at any time of year.

INFLUENZA EPIDEMIOLOGY

Influenza is a respiratory-transmitted, usually self-limited viral infection in humans; primary clinical features include fever, cough, malaise, and myalgia. Influenza occurs in two different epidemiologic patterns: annual seasonal epidemics and global pandemics. Illnesses associated with seasonal influenza typically occur during the winter months in the Northern and Southern Hemispheres and year-round in the tropics. While the greatest concern regarding influenza is often directed at the threat of a pandemic, only four influenza pandemics, each lasting approximately 1 to 3 years (7 years total), have occurred since the beginning of the 20th century.

Seasonal Influenza

In between pandemics, influenza continuously poses an ongoing public health challenge. An estimated 3,000 to 49,000 individuals in the United States die every year from seasonal influenza; the number of deaths increases in years when influenza A(H3N2) predominates.[3] More than 90% of influenza-related deaths occur in persons 65 years of age and older.[3] On a global level, the annual burden caused by seasonal influenza is less clear. While the World Health Organization (WHO) Global Influenza Surveillance Network (GISN) provides valuable information on circulating influenza viruses for influenza vaccine formulation, it has limited ability to track the disease burden of influenza in developing countries.[4] However, the limited data that are available support that influenza is common in countries of the developing world and contributes substantially to the use of healthcare resources.[5-11] The WHO has estimated for more than a decade that, worldwide, annual seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths; however, this is likely an underestimation of the true global impact of influenza.[12] These figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years.

Based on data from clinical trials, an estimated 1% to 10% of adults from 18 to 64 years of age and 6% to 18% of children younger than 7 years will experience illness caused by seasonal influenza in a given year.[13-16] The highest risk of complications occurs among adults age 65 years and older, children younger than 2 years of age, pregnant women, and people of any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood, or metabolic diseases like diabetes; compromised immune systems; or morbid obesity. Since the population of persons older than 65 years of age is increasing around the globe, including in developing countries, public health officials can anticipate that the number of deaths due to seasonal influenza in this age-group will rise substantially in the next 20 years if not prevented through the use of effective vaccines.

Despite the increasing levels of vaccination among persons 65 years of age and older in the United States, there has not been a corresponding reduction in influenza-related mortality in this age-group.[17]

Pandemic Influenza

As noted above, four pandemics have occurred since the beginning of the 20th century (with onsets in 1918, 1957, 1968, and 2009). The 1918 pandemic was caused by an influenza A H1N1 strain. The pandemic began with a relatively mild "herald" wave in the spring of 1918; this was followed by more severe waves in the fall and winter of 1918-19. Additional waves that were not as severe occurred in 1919 and 1920. About one third of the world's population was infected and had clinically apparent illness (about 500 million people), and an estimated 50 million to 100 million died.[18,19] Adjusting for today's population, a similar pandemic would yield a modern death toll of 175 million to 350 million.

The 1957-58 pandemic was caused by an H2N2 strain and originated in China.[20] The pandemic strain acquired three genes from the avian influenza gene pool in wild ducks by genetic reassortment and obtained five other genes from the then-circulating human strain. About 69,800 people in the United States died, and mortality was spread over three seasons. Globally, approximately 1.5 million people died during this pandemic.[11]

The 1968-69 pandemic was caused by an H3N2 strain. The strain acquired two genes from the duck reservoir by reassortment and kept six genes from the virus circulating at the time in humans. During the pandemic, about 33,800 people died in the United States and 750,000 globally.[11]

The 2009 pandemic was caused by a triple-reassortant H1N1 strain that had acquired seven of the eight genes from avian and swine populations, with one gene coming from seasonal H3N2.[21] Approximately 12,500 people died in the United States from infection with the A(H1N1)pdm09 pandemic influenza virus.[22] An official estimate on the number of deaths globally is not expected until late 2012.[23]

In addition to the total number of cases and deaths, the mean age at death is an important epidemiologic feature of influenza pandemics. **Table 1-1** details the mean age of death for influenza cases in the United States in the 1918, 1957, 1968, and 2009 pandemics, as well as for seasonal influenza epidemics with influenza A/H3N2 for 1979 to 2001. For the 1957 and 1968 pandemics, when adjusting for average life expectancy at birth, the mean ages of death were similar to those documented for seasonal A/H3N2 influenza from 1979 to 2001. Although the number of deaths and the incidence of serious illness were substantially higher during these pandemics than seen with seasonal influenza epidemics, the overall epidemiology was similar. For the 1918 and 2009 pandemics (caused by H1N1 viruses), the mean age of death, adjusted for average life expectancy at the time of the pandemic, was significantly lower than for either of the two other influenza pandemics or for seasonal influenza. During the 2009 pandemic, pregnant women, young children, persons with asthma, and obese persons were disproportionately more likely to die as a result of their infection. During the 1918 pandemic, pregnant women, children, and young adults had disproportionally high mortality rates. It's unclear if in the 1918 pandemic persons with asthma and obese persons were at increased risk of death similar to that documented in 2009, as such information was not routinely recognized or recorded at the time.

TABLE 1-1. The Mean Age of Death for Influenza Cases in the 1918, 1957, 1968, and 2009 Influenza Pandemics and for Seasonal Influenza A/H3N2 (1979-2001) and Average Life Expectancy at Birth in the United States

Pandemic/Seasonal (Year and Subtype)	Mean Age of Death (yr)[24,25]	Average Life Expectancy at Birth (yr)[26]
1918 (H1N1)	27	56
1957 (H2N2)	65	69
1968 (H3N2)	62	71
2009 (H1N1)	40	79
1979-2001 (A/H3N2)	76	–

WHY HAVE A HUMAN INFLUENZA VACCINE?

Why We Have Vaccines for Some Diseases but Not Others

Today more than 500 infectious diseases are known to occur in humans, yet in the United States public health officials recommend routine childhood or adult vaccinations of civilians for only 17 of these.[27] Additional vaccines are recommended for those in the military and for international travelers. How and why a vaccine is developed, licensed, and recommended for use in a population involves a complex interaction of immunology, clinical medicine, epidemiology, public policy, economics, risk analysis, and advocacy. For example, each year AIDS and malaria kill an estimated 2.8 million people worldwide, yet we don't have an

effective vaccine for either disease.[28] Additionally, while most of the global population will experience a rhinovirus infection (ie, common cold) each year, no vaccine is on the horizon for that inconvenient, yet not life-threatening, condition.

Three aspects of an infectious disease make it a primary candidate for the development of a vaccine. First, the disease must have a significant public health impact. This is evidenced by the total number of infections and (in order of priority) the number of persons who die, become severely ill and require hospitalization, experience long-term disabilities, or miss work or other critical activities. For many infectious diseases, the public health impact is related primarily to the endemic or expected annual occurrence of the disease. For some diseases, the potential impact of seasonal or periodic epidemics makes them a higher priority for vaccine development. Finally, for those diseases that have pandemic potential, such as influenza, the public health impact can be catastrophic. This impact, if the pandemic were to be severe, has the potential to exhaust critical supply chains, giving rise to shortages of critical products (eg, medicine, food, and fuel), which may result in an even greater public health impact than the pandemic itself.[29,30]

Second, researchers must be able to develop a highly effective vaccine that is safe and affordable. This can be incredibly challenging. AIDS and malaria, for example, are major global public health problems, yet despite extensive efforts over decades, effective and safe vaccines for the diseases have not been forthcoming because of the complexity of the pathogens and the human immune response. Finally, vaccination of the population should greatly reduce transmission of the infectious agent among the nonvaccinated population, thus limiting disease occurrence even among those who are not vaccinated or those who are unable to mount an immune response following vaccination. This phenomenon is known as herd immunity and is reviewed in greater detail in Chapter 3.

Influenza and Vaccines

Human influenza vaccine research began shortly after the virus was discovered in 1933. A brief history of the early influenza vaccine research is reviewed in Chapter 2. Following the devastating impact on US military personnel who were engaged in World War I during the 1918-19 influenza pandemic, the US government made it a national priority to never again allow soldiers on the battlefield to be so vulnerable to influenza. This experience vividly demonstrated the national security implications of a severe influenza pandemic. Once the pathogen had been identified, addressing this concern ushered in the modern era of influenza vaccine research and development. As a result of these efforts, seasonal influenza vaccines are now generated and widely distributed each year.

Influenza vaccine availability also is the cornerstone of preparedness against an influenza pandemic. If an influenza pandemic should emerge in the near future, it's possible, depending on the subtype of the new pandemic virus, that available efficacy and effectiveness data for currently licensed influenza vaccines will be a good predictor of how well the pandemic vaccines will protect those at highest risk of death. For example, as outlined in **Table 1-1**, if a pandemic causes increased morbidity and mortality primarily in adults over 65 years of age, then how well influenza vaccines work in that population will be an important consideration for a successful pandemic response.

SUMMARY

Influenza meets the first criterion outlined above for vaccine consideration, given that both seasonal and pandemic influenza can pose serious public health threats. With regard to the second criterion, safe and somewhat effective vaccines can be developed for population-wide use. In this report, we discuss the efficacy and effectiveness of influenza vaccines in detail in Chapter 3. From that analysis, we conclude that new influenza vaccines are urgently needed to improve the overall effectiveness of a population-based vaccination strategy. Influenza researchers are still not clear on how influenza vaccination affects the third criterion, which is herd immunity. This issue is also addressed in greater detail in Chapter 3. Despite the limitations of current vaccines, we believe that influenza vaccination is an important public health activity that warrants new paradigms in vaccine research, development, licensing, regulation, and use. In this report, we discuss the current state of the art with regard to all of these issues and we present our rationale for advocating these paradigm shifts.

REFERENCES

1. Tong S, Li Y, Rivailler P, et al. A distinct lineage of influenza A virus from bats. *Proc Natl Acad Sci* 2012;109(11):4269-74
2. Treanor JJ. Influenza virus, including avian influenza and swine influenza. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, ed 7. Philadelphia: Elsevier, 2010
3. Thompson M, Shay D, Zhou H, et al. Estimates of deaths associated with seasonal influenza—United States, 1976-2007. *MMWR* 2010;59(33):1057-62
4. Ortiz JR, Sotomayor V, Uez OC, et al. Strategy to enhance influenza surveillance worldwide. *Emerg Infect Dis* 2009;15(8):1271-8
5. Nguyen HLK, Saito R, Ngiem HK, et al. Epidemiology of influenza in Hanoi, Vietnam, from 2001 to 2003. *J Infect* 2007;55(1):58-63
6. Brooks W, Terebuh P, Bridges C. Influenza A and B infection in children in urban slum, Bangladesh. *Emerg Infect Dis* 2007;13(10):1507-8
7. Chow A, Ma S, Ling AE, et al. Influenza-associated deaths in tropical Singapore. *Emerg Infect Dis* 2006;12(1):114-21
8. Feng L, Shay DK, Jiang Y, et al. Influenza-associated mortality in temperate and subtropical Chinese cities, 2003-2008. *Bull World Health Organ* 2012;90(4):279B-88
9. Homaira N, Luby SP, Alamgir AS, et al. Influenza-associated mortality in 2009 in four sentinel sites in Bangladesh. *Bull World Health Organ* 2012;90(4):272-8
10. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011;378(9807):1917-30
11. Simonsen L, Viboud C, Taylor RJ, et al. The epidemiology of influenza and its control. In: Rappuoli R, Del Giudice G, eds. *Influenza Vaccines for the Future,* ed 2. Basel: Springer Basel; 2011:27-55
12. WHO. Influenza (seasonal): Fact Sheet. 2009. Available at: http://www.who.int/mediacentre/factsheets/fs211/en/
13. Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009;361(13):1260-7
14. Beran J, Wertzova V, Honegr K, et al. Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. *BMC Infect Dis* 2009;9:2
15. Lum LCS, Borja-tabora CF, Breiman RF, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. *Respir Med* 2010;28:1566-74
16. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. *N Engl J Med* 1998;338(20):1405-12
17. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005;165(3):265–72
18. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. *Bull Hist Med* 2002;76(1):105-15
19. Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. *Emerg Infect Dis* 2006;12(1):15-22
20. Glezen WP. Emerging infections: pandemic influenza. *Epidemiol Rev* 1996;18(1):64-76
21. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood S, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;360(25):2605-15
22. CDC. Updated CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009-April 10, 2010. Available at: http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm
23. WHO. Summary of WHO technical consultation: H1N1pdm mortality estimates. 2011. Available at: http://www.who.int/influenza/surveillance_monitoring/updates/MortalityEstimates/en/index.html
24. Viboud C, Miller M, Olson D, et al. Preliminary estimates of mortality and years of life lost associated with the 2009 A/H1N1 pandemic in the US and comparison with past influenza seasons. *PLoS Curr* 2010;Mar 20:RRN1153
25. CDC. Average and median ages of 2009 H1N1-

related deaths in the United States, spring and fall 2009. Available at: http://www.cdc.gov/H1N1flu/ages_deaths.htm
26. Shrestha LB. Life expectancy in the United States. Congressional Research Service. 2006. Available at: http://aging.senate.gov/crs/aging1.pdf
27. Heymann DL, ed. *Control of Communicable Disease Manual*, ed 19. APHA Press; 2008
28. Rappuoli R, Aderem A. A 2020 vision for vaccines against HIV, tuberculosis and malaria. *Nature* 2011;473(7348):463-9
29. Osterholm MT. Preparing for the next pandemic. *Foreign Aff* 2005 Jul/Aug;84(4)
30. Osterholm MT. Unprepared for a pandemic. *Foreign Aff* 2007 Mar/Apr;86(2)

CHAPTER 2

CURRENTLY LICENSED INFLUENZA VACCINES: HISTORICAL PERSPECTIVE

INTRODUCTION

Among the vaccines currently recommended routinely in the United States for 17 different infectious diseases, influenza vaccine stands alone. It is the only vaccine that is frequently reformulated, often annually; is based on an antigen technology developed in the 1930s and 1940s, most currently refined in the 1960s; and is universally recommended for annual administration. This chapter provides a brief history of influenza vaccines and a foundation for the remainder of this report.

For any vaccine to have a maximum public health benefit, it must be efficacious and effective, safe, readily available, and acceptable to the general population. In this report, we review current influenza vaccines from each of these perspectives.

INFLUENZA VACCINE DEVELOPMENT

Following identification of influenza viruses in humans in 1933, work began on the development of a vaccine to prevent infection.[1,2] Early influenza vaccines were crude preparations of whole virus made in mouse lungs or embryonated chicken eggs and concentrated by high-speed centrifugation.[3,4] In the 1960s, the introduction of continuous-flow zonal ultracentrifugation allowed for enrichment of the virus-containing fraction of allantoic fluid of chicken egg embryos, leading to the development of more highly purified products and the introduction of "split" virus vaccines that contained the major antigenic determinants, HA and NA. These developments paved the way for the licensure in 1968 of the split-virus inactivated influenza vaccine.[5] The subunit vaccine uses centrifugation, similar to the split vaccine, to highly purify HA and NA surface antigens.

The trivalent inactivated influenza vaccines (TIVs) currently licensed in the United States are split-virus or subunit vaccine similar to the split-virus vaccine originally licensed in 1968. They are produced in pathogen-free embryonated chicken eggs using techniques identified in the 1930s and refined over the following decades to concentrate the HA and NA antigens. Available TIV formulations contain purified HA and NA antigens for the three influenza strains (two influenza A and one influenza B) predicted to circulate during the upcoming influenza season.

Influenza vaccine is the only vaccine for which an annual decision on antigen composition is necessary. This requires global influenza surveillance throughout the year to predict the likely strains that will circulate the following winter. Once the recommended strains are identified and the appropriate antigens are selected, the process of producing, packaging, and distributing influenza vaccines takes 6 to 8 months.[6] The live-attenuated influenza vaccine (LAIV) was licensed for use in the United States in 2003.[7] LAIV also is produced in pathogen-free embryonated chicken eggs, using an attenuated influenza virus that is cold-adapted to 25°C, so it can replicate in human nasal passages but not in the lungs.[8] The viral strains in LAIV are engineered each year, in a similar manner to

TIV, to ensure that recommended HA and NA antigens are expressed.

Currently, seasonal and pandemic influenza vaccines are produced using the same manufacturing processes. In the United States, the only difference between a seasonal influenza vaccine and a pandemic vaccine is the number of virus strains included. The 2009 pandemic vaccine had a single strain, A(H1N1)pdm09, while seasonal vaccines typically have three: two influenza A and one influenza B. (A quadrivalent LAIV was licensed by the US Food and Drug Administration [FDA] in 2012 and will be available in 2013.)

TABLE 2-1. Key Events in Influenza Vaccine History in the United States [5,7,9-14]

Year	Event
1945	First military vaccine approved for use
1946	Civilian vaccine approved for use
1960	First recommendation for annual vaccination
1968	Split inactivated vaccine approved for use (akin to current inactivated vaccine)
1976	Swine flu vaccination effort
1977	Recognition of the value and role of US government in purchasing, delivering, and administrating influenza vaccines
1978	Trivalent vaccine usage became routine
1981	Antigen concentration of vaccine increased from 7 mcg per HA antigen to 15 mcg
2003	LAIV vaccine approved for use
2009	Monovalent H1N1 pandemic vaccine approved for use
2009	Fluzone High-Dose vaccine licensed (60 mcg per HA antigen)
2012	Quadrivalent LAIV licensed

HA: hemagglutinin, mcg: micrograms, LAIV: live-attenuated influenza vaccine

Owing to concerns about the potential for a severe pandemic, particularly since the re-emergence of highly pathogenic avian influenza (HPAI) H5N1 in 2003, the global capacity to manufacture seasonal influenza vaccines has increased in recent years because officials recognize the potential secondary use of such facilities. This capacity was tested during the 2009 pandemic, and, unfortunately, the pandemic vaccine was only available in industrialized countries and only in limited quantities until after the peak of the pandemic (when vaccine became more plentiful). The vaccine was not available at all during the pandemic in most of the developing world. This lack of timely availability of pandemic vaccine has raised significant questions about the utility of the current antiquated manufacturing platform (ie, chicken eggs).

Key events relating to the development and use of currently licensed influenza vaccines in the United States are summarized in **Table 2-1**.

Recommendations for Influenza Vaccine Use

Inactivated influenza vaccine was first recommended for use in US military personnel in 1945.[5] In 1960, following the 1957-58 influenza pandemic, the US surgeon general recommended annual influenza vaccination for certain segments of the American population at increased risk for severe morbidity or mortality: pregnant women, persons 65 years of age and older, and persons with chronic debilitating diseases.[9] In 1964, the newly established Advisory Committee on Immunization Practices (ACIP) reaffirmed the recommendations, even though data supporting vaccine efficacy in these high-risk populations were lacking. These recommendations were based on the inference that protection provided to these high-risk individuals would be similar to the protection documented for healthy young adults.[15] Since these recommendations have been in place, placebo-controlled influenza vaccine efficacy studies in the United States in these populations have been considered unethical.[13]

In 1984, the ACIP recommended influenza vaccination for healthcare workers, and in 1987, household

TABLE 2-2. Populations Recommended to Receive an Annual Vaccination Against Seasonal Influenza, by Year [9,13,16-22]

Year	Additions to Recommendation
1960 (US Surgeon General)	• Persons aged 65 and older • Person with chronic medical conditions that make them more likely to have complications from influenza • Pregnant women in 2nd or 3rd trimester[a]
1984	• Healthcare workers • "Influenza-control options should also be made available to individuals who wish to reduce their chances of acquiring influenza infection or to reduce the severity of disease"
1986	• Household contacts and out-of-home caregivers of individuals in identified high-risk groups
2000	• Adults 50 and older
2004	• Children aged 6-23 months • Household contacts and out-of-home caregivers of children aged 0-23 months
2006	• Children aged 24-59 months • Household contacts and out-of-home caregivers of children aged 0-59 months
2008	• All children aged 6 months–18 years, ***if feasible***
2009	• All children aged 6 months–18 years
2010	• All healthy nonpregnant adults aged 18-49 years

[a] In 2004, all women who will be pregnant during the influenza season were recommended for vaccination regardless of trimester

contacts of persons in high-risk groups were added. From 2000 to 2010, the ACIP made a number of incremental changes to the annual influenza vaccine recommendations, which led to recommended coverage for an ever-increasing proportion of the US population (**Table 2-2**). Finally, in 2010 the ACIP established the first national universal seasonal influenza vaccination recommendation.[13] Annual vaccination is currently recommended with TIV for all persons 6 months of age and older or with LAIV for healthy nonpregnant persons aged 2 to 49 years.[13] Most of the recommendation changes over recent years were made without new or additional efficacy or effectiveness data demonstrating the benefit of influenza vaccination; rather, they were based on an effort to increase overall vaccination rates (see Chapter 5 and 7). The current universal recommendation makes it unethical to conduct any placebo-controlled clinical trials using influenza vaccines in the United States, except in infants younger than 6 months old.[13]

SUMMARY

Over the past 50 years, the public health recommendations for influenza vaccination have continued to expand; however, we have now reached a critical crossroads in the prevention and control of influenza. We have nearly maximized the benefit that can be achieved with current vaccine recommendations and technology. To move forward, the scientific and public policy communities need to commit to the allocation of resources and public policy development necessary to advance new game-changing influenza vaccines. Such vaccines must provide improved efficacy, effectiveness, and cost-effectiveness for seasonal influenza and also provide the ability to more effectively combat emergent pandemic strains. Without this renewed commitment, the public health impact of the last 50 years will have reached a plateau, with limited prospects for further reducing overall influenza morbidity and mortality.

REFERENCES

1. Smith W, Andrews C, Laidlaw P. A virus obtained from influenza patients. *Lancet* 1933;2:66-8
2. Davenport FM. The search for the ideal influenza vaccine. *Postgrad Med J* 1979;55(640):78-86
3. Hampson A. Vaccines for pandemic influenza: the

history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. *Ann Acad Med Singapore* 2008;37(6): 510-7

4. Stanley W. The preparation and properties of influenza virus vaccines concentrated and purified by differential centrifugation. *J Exp Med* 1945;81(2):193-218

5. Wood J, Williams M. History of inactivated influenza vaccines. In: Nicholson KG, ed. *Textbook of Influenza*. Oxford, UK: Blackwell Science; 1998

6. Treanor J. Weathering the influenza vaccine crisis. *N Engl J Med* 2004;351(20):2037-40

7. FDA. Approval letter—influenza virus vaccine live, intranasal. 2003. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm123753.htm

8. Ambrose CS, Luke C, Coelingh K. Current status of live attenuated influenza vaccine in the United States for seasonal and pandemic influenza. *Influenza Other Respi Viruses* 2008;2(6):193-202

9. Burney LE. Influenza immunization: statement. *Public Health Rep* 1960;75(10):944

10. Anonymous. Influenza vaccine used by Army is on sale to civilians. *JAMA* 1945;129(8):1274

11. CDC. Recommendations of the Public Health Service Immunization Practices Advisory Committee: influenza vaccine 1981-1982. *MMWR* 1981;30(23):279-82

12. FDA. Approval letter—Fluzone High-Dose. 2009. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm195481.htm

13. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62

14. FDA. Approval letter—FluMist Quadrivalent. 2012. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm294293.htm

15. Long PH. Recommendations for influenza immunization and control 1964-1965. *Med Times* 1964;92(11):1203-5

16. CDC. Recommendation of the Immunization Practices Advisory Committee (ACIP) prevention and control of influenza. *MMWR* 1984;33(19):253-60

17. CDC. Recommendations of the Immunization Practices Advisory Committee prevention and control of influenza. *MMWR* 1986;35(20): 317-26, 31

18. Bridges CB, Winquist AG, Fukuda K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-3):1-38

19. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2004;53(RR-10):1-40

20. Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-10):1-42

21. Fiore AE, Shay DK, Broder K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2008;57(RR-7):1-60

22. Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2009;58(RR-8):1-52

CHAPTER 3

EFFICACY, EFFECTIVENESS, AND COST-EFFECTIVENESS OF THE CURRENTLY LICENSED INFLUENZA VACCINES

INTRODUCTION

We summarize here the available efficacy, effectiveness, and cost-effectiveness data of the currently licensed influenza vaccines; this summary is largely based on our meta-analysis, which was recently published in *The Lancet Infectious Diseases*.[1] The European Centre for Disease Prevention and Control (ECDC) noted that this publication was "an authoritative independent evidence-based review and meta-analysis of the efficacy and effectiveness of influenza vaccines" that differed from previous reviews in our effort to focus on the highest quality of evidence currently available.[2]

The public health and medical communities generally accept the premise that currently licensed influenza vaccines are largely effective in preventing influenza infection in most populations.[3] We conclude, however, that the currently licensed influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Furthermore, even though TIV provides some protection for healthy adults 18 to 64 years of age, evidence for protection in adults 65 years of age and older with TIV is lacking. Evidence is also limited regarding the efficacy and effectiveness of TIV in children age 2 to 17 years. LAIVs have consistently shown highest efficacy in young children (from 6 months to 7 years old), while evidence of protection is not available for individuals from 8 to 59 years of age.

In this report we also examine efficacy and effectiveness data for influenza vaccines licensed outside of the United States and vaccines that are likely to be licensed in the United States in the near future. In addition, we discuss other issues with potential to affect influenza vaccine efficacy and effectiveness, including antigenic match between the vaccine strains and circulating influenza strains, herd immunity, and epidemiologic features of influenza infection. Finally, we comment on the impact that lower vaccine-effectiveness estimates may have on the overall perspective of the cost-effectiveness of influenza vaccines. We also conclude that the perception that currently licensed influenza vaccines are largely effective in preventing influenza infection in most populations is a primary barrier to developing game-changing influenza vaccines.

ASSESSING INFLUENZA VACCINE EFFICACY, EFFECTIVENESS, AND COST-EFFECTIVENESS

In the 1970s, Archie Cochrane popularized three concepts that changed the way an intervention (eg, vaccine, pharmaceutical, surgery) is assessed by the medical, veterinary, and public health communities: "Can it work?," "Does it work?," and "Is it worth it?"[4]

"Can it work?" refers to the efficacy of an intervention, usually determined by a randomized, placebo-controlled trial (RCT), which is the gold standard of intervention measurement. Such efficacy studies tend to be highly controlled experiments that aim to avoid potential factors such as bias and confounding, which might affect the results.

"Does it work?" refers to the effectiveness of an intervention, usually determined through observational studies in which persons receiving medical practice or public health interventions are followed to evaluate the occurrence of a predetermined outcome. Such studies are far more likely than efficacy studies to be influenced by unintended factors such as bias and confounding. Observational studies measuring effectiveness demonstrate how well an intervention actually works in everyday practice, which can offer a realistic perspective on the real-world impact of an intervention.

Finally, "Is it worth it?" refers to the cost-effectiveness of the intervention, which includes a variety of societal and financial costs. When assessing cost-effectiveness, the main consideration is whether or not the cost of the intervention justifies its routine or targeted use.

EFFICACY AND EFFECTIVENESS FOR INFLUENZA VACCINES CURRENTLY LICENSED IN THE UNITED STATES

Impact of Clinical End Points

Hundreds of influenza vaccine efficacy and effectiveness studies have been conducted since the 1940s. The design of these studies has varied widely, with most not meeting minimal requirements for unbiased recruitment and outcome ascertainment, as outlined in **Table 3-1**. The results of these studies, therefore, offer little value in understanding actual vaccine effectiveness and efficacy. In fact, such studies have clouded the real impact of influenza vaccination on morbidity and mortality and, as a result, have hindered informed public health and public policy decisions about the need for improved influenza vaccines.

The frequently cited estimate of 70% to 90% for influenza vaccine efficacy in healthy adults was originally documented in studies conducted mostly in military personnel between 1943 and 1969.[5] These studies included vaccines that are not comparable to currently licensed vaccines (eg, they used different production methods such as whole-virus vaccines and the vaccine antigen concentration was not measured in micrograms of HA as vaccines are today). In addition, the investigators used HA inhibition (HAI) serology as the primary end point to confirm influenza infection in clinically ill individuals (with only limited use of viral culture for confirmation).[6,7] The HAI assay provides an approximation of the antibody titer present in a sample by determining the lowest concentration of a person's serum that can inhibit the influenza virus's ability to agglutinate red blood cells.[8] In 1955, McDonald and Andrews demonstrated in influenza vaccine trials that study participants who were vaccinated with inactivated influenza vaccine were less likely to have a significant HAI serologic response when subsequently infected with culture-confirmed influenza.[9] They concluded:

> *"…until it is shown that serological methods are able to detect cases of influenza equally well in persons who have received an influenza vaccine and in those who have not, serological diagnosis should not be the only method of diagnosis in a vaccine field trial."* [9]

Given the limitations of HAI to document subsequent influenza infection in influenza vaccine recipients, the early estimates of vaccine efficacy must be reconsidered. This suboptimal methodology nonetheless continued to be used extensively for diagnosis of influenza infection in the decades that have passed since these early studies.[7] This persistent reliance on HAI may be, in part, due to the potential to not detect cases of influenza infection by using viral culture because of asymptomatic infection (study subjects present for viral culture only if symptomatic),

short duration of viral shedding after influenza infection (especially in adults), or influenza strain characteristics that result in suboptimal growth in viral culture.

In 2011, 56 years after McDonald and Andrews made their initial observation, Petrie and colleagues reported that only 23% of study participants who underwent vaccination with TIV and later had an H3N2 influenza infection also had a fourfold rise in HAI antibody titer between samples obtained before vaccination and at the end of the influenza season (ie, a positive serologic test).[10] (The H3N2 was confirmed by real-time reverse-transcriptase polymerase chain reaction [RT-PCR].) Conversely, 90% of participants in the unvaccinated placebo group who developed confirmed H3N2 influenza infection had a positive serologic test. These results illustrate that the antibody response to infection after vaccination is muted and if the only end point being measured is a serologic response, then a substantial number of postvaccination infections will not be detected. Thus, a significant built-in case-detection bias is present in TIV studies that use serology (rather than RT-PCR or culture) as the primary end point for infection. Because fewer vaccinated persons will have a positive HAI serologic test following infection with influenza than will unvaccinated persons, the efficacy or effectiveness of the vaccine will be overestimated in such studies.

TABLE 3-1. Inclusion Criteria for Studies of Inactivated Influenza Vaccine and LAIV Published from 1967-2011

Efficacy Studies
• A published, masked, randomized controlled trial indexed by Medline • Study reported overall vaccine efficacy against all circulating influenza strains irrespective of match or number of strains identified in surveillance • Outcome defined as RT-PCR or viral culture confirmation of influenza infection of wild strains • Comparison group received placebo or vaccine other than influenza • Study assessed inactivated influenza vaccines that were licensed at the time of study or eventually licensed in the USA and antigen concentrations reported as mcg of haemagglutinin, or live attenuated influenza vaccines licensed at the time of study or eventually licensed in the USA and active virus reported as tissue-culture infective doses of $10^{6.5}$-$10^{7.5}$
Effectiveness Studies
• A published case test-negative control, case cohort, or prospective cohort study design indexed by Medline • Vaccine effectiveness reported for individual seasons and adjusted (as necessary on the basis of study design) for age and calendar time (week or month of enrolment); interim or partial season estimates were excluded as were studies assessing the effectiveness of seasonal influenza vaccines for the prevention of pandemic H1N1 • Eligible patients were tested on the basis of systematic sampling with defined clinical criteria irrespective of vaccination status; studies allowing enrolment of patients based on clinical judgment were excluded to reduce selection bias • Vaccination status established by self-report, medical record review, or immunization registry • Cases had influenza confirmed by RT-PCR or viral culture • Controls had a negative RT-PCR or viral culture for influenza (test-negative control design) or had no influenza-like illness (cohort design)

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Recent meta-analyses of TIV and LAIV efficacy and effectiveness have included studies that used diagnostic end points with low sensitivity or specificity to confirm influenza infection, such as HAI.[11–14] To further complicate matters, reviews by the Cochrane Collaboration, an organization recognized for expertise in evaluating clinical intervention outcomes, used inadequate standards for assessing influenza vaccine efficacy and effectiveness.[11–13] Many studies included in the Cochrane meta-analyses had an HAI-based end point, which, as noted in the discussion above, resulted in an overestimation of efficacy or effectiveness of TIV. For

example, an often-cited RCT of adults older than 65 did not use RT-PCR or viral culture to confirm influenza infection, but rather relied on HAI as the clinical end point. This study, which was included in a Cochrane analysis, reported a vaccine efficacy of 58% for clinically defined influenza confirmed only by HAI.[15] On the basis of the data from McDonald and Andrews and Petrie and colleagues, these results may be explained entirely by the lack of HAI response among patients infected with influenza who had been vaccinated.

Types of Outcome End Points to Evaluate Influenza Efficacy and Effectiveness

Two primary types of outcome end points are used to evaluate the efficacy and effectiveness of influenza vaccines: specific and nonspecific. A specific outcome end point includes the use of a diagnostic test that can identify influenza infections with high sensitivity (ie, doesn't miss infections) and specificity (ie, doesn't determine someone is infected when they are not). Using such end points allows for the most accurate estimate of the efficacy or effectiveness of an influenza vaccine. Several laboratory tests have been or can be used to confirm influenza infection; however, each test method has varying specificity and sensitivity. Today, the gold standard for confirming influenza infection is RT-PCR, with the use of viral culture being equally specific but less sensitive.

A nonspecific outcome end point typically measures clinical observations such as all-cause mortality, absenteeism, or influenza-like illness (ILI). These outcomes are associated with the population-related impact of influenza infection, such as days ill or time off of work needed to care for an ill child with ILI. Nonspecific outcome end points have a relatively low sensitivity (since not all influenza cases meet the clinical parameter being assessed) and have a relatively low specificity (since other respiratory infectious agents can lead to the same outcome). Without appropriate diagnostic testing, researchers cannot accurately determine what portion of the clinical illness or outcome being assessed can be attributed to the influenza virus.

Results of a Recent Meta-analysis

We recently completed an extensive review of influenza vaccine efficacy and effectiveness studies that was published in *The Lancet Infectious Diseases* and is available in Appendix B.[1] For this review, we searched Medline (PubMed database) for articles on influenza vaccine efficacy and effectiveness published in English from January 1, 1967, February 15, 2011. The full search strategy is outlined in the *Lancet Infectious Diseases* Web appendix (Appendix B). Studies were included if efficacy or effectiveness was reported against all circulating influenza viruses during individual influenza seasons and RT-PCR, viral culture, or both were used as the end point(s) for confirming influenza infection (**Table 3-1**).

We identified 5,707 studies on influenza vaccines in humans through our PubMed search. Of these, 992 were identified as cohort studies, case-control studies, clinical trials, or RCTs; we also included studies that did not have Medical Subject Headings (MeSH) terms. A review of the abstracts of these studies identified 176 (18%) potentially eligible studies; 73 of those (41%) were RCTs estimating vaccine efficacy, and 103 (59%) were observational studies estimating vaccine effectiveness.

From the 176 potentially eligible studies, we identified 31 (18%) studies (17 RCTs and 14 observational studies) that met the criteria for adequate study design and conduct. All excluded studies and reasons for their exclusion are detailed in Appendix B.

Efficacy of TIV was shown in 8 (67%) of the 12 seasons analyzed in 10 RCTs (pooled efficacy 59% [95% confidence interval (CI), 51% to 67%] in adults 18 to 65 years of age). No such trials met inclusion criteria for children 2 to 17 years of age or adults 65 years of age or older. Efficacy of LAIV was shown in 9 (75%) of the 12 seasons analyzed in 10 RCTs (pooled efficacy 83% [95% CI, 69% to 91%]) in children 6 months to 7 years of age. No such trials met inclusion criteria for children 8 to 17 years of age.

In our review, vaccine effectiveness was variable for seasonal influenza; 6 (35%) of 17 analyses in nine studies showed significant protection against medically attended influenza in outpatient and inpatient settings.

On the basis of our review, we conclude that the currently licensed influenza vaccines can provide

moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Furthermore, even though TIV provided some protection for healthy adults 18 to 65 years of age, there is a paucity of evidence for protection in adults 65 years of age and older. Evidence is also limited to determine the efficacy and effectiveness of TIV in children age 2 to 17 years. LAIVs have consistently shown highest efficacy in young children (from 6 months to 7 years old), while evidence of protection is not available for individuals from 8 to 59 years of age.

We believe that the results and implications of this study are best summarized in the last paragraph of our *Lancet Infectious Diseases* paper:

> *"Seasonal influenza is an important public health and medical challenge. Pandemic influenza would cause a substantial burden of disease and seriously threaten the global economy. Based on a track record of substantial safety and moderate efficacy in many seasons, we believe the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available. However, evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older. The ongoing public health burden caused by seasonal influenza and the potential global effect of a severe pandemic suggests an urgent need for a new generation of more highly effective and cross-protective vaccines that can be manufactured rapidly.[16,17] New vaccines based on novel antigens that differ from the presently licensed vaccines are in development. Active partnerships between industry and government are needed to accelerate research, reduce regulatory barriers to licensure, and support financial models that favor the purchase of vaccines that provide improved protection. Active pursuit of this goal now will save lives every year and when the next influenza pandemic occurs. In the meantime, we should maintain public support for present vaccines that are the best intervention available for seasonal influenza."*[1]

Additional Efficacy and Effectiveness Studies Published Following Our Meta-analysis

Our *Lancet Infectious Diseases* review included papers published through February 15, 2011. We extended our review from February 16, 2011, to April 8, 2012, using the same search methodology and inclusion criteria for evaluating TIV and LAIV efficacy and effectiveness. We identified eight additional studies from this review.[18-25] All of these studies support the conclusions stated in our *Lancet Infectious Diseases* paper. While high-dose TIV and quadrivalent LAIV are both licensed in the United States, at this time no efficacy or effectiveness data are available for either vaccine; therefore, they are not included in these analyses.

Vaccine Efficacy and Effectiveness in Groups Identified at Increased Risk for Severe Morbidity and Morality

As noted in Chapter 1, the highest-risk groups for severe morbidity and mortality for both pandemic and seasonal influenza includes persons 65 years of age and older, children younger than 2 years of age, pregnant women, and people of any age who have certain medical conditions, such as chronic heart, lung, kidney, liver, blood, or metabolic diseases like diabetes, compromised immune systems, or morbid obesity.[3,26] Therefore, the most significant population-based health impact of influenza vaccines will be for these groups, in particular for persons 65 years of age and older, as approximately 90% of deaths from influenza occur in this group.

Impact of Influenza Vaccination on Influenza-Related Morbidity and Mortality among Persons 65 Years of Age and Older

Vaccine Efficacy and Effectiveness Studies

Three studies were identified in our *Lancet Infectious Diseases* review that evaluate the efficacy and effectiveness of influenza vaccines in persons 65 years of age and older. Thirteen additional vaccine effectiveness studies that were in our review included persons 65 years of age or older but did not include an adequate number of individuals in this age-group to determine age-specific vaccine effectiveness. As of April 8, 2012, no additional studies have been identified. For the three studies included in our review, LAIV was evaluated in one and TIV in two.

The LAIV study, which included participants aged 60 years and older, reported a significant overall efficacy of 42% (95% CI, 21% to 57%), but efficacy seemed to be lower in individuals aged 60 to 69 years (31%) and higher in those aged 70 years and older (57%).[1,27] Similar results have not been reported elsewhere, given the limited use of LAIV in this population because LAIV is not licensed or recommended for persons over 49 years of age. Also, these results should be interpreted cautiously, since in our review none of three LAIV studies involving younger adults demonstrated significant protection in healthy persons 18 to 49 years of age.

The other two studies included in our *Lancet Infectious Diseases* review for persons 65 years of age and older reported vaccine effectiveness results. In one of the studies that included 103 individuals, vaccine effectiveness against medically attended influenza was 79% (95% CI, -26% to 96%),[28] and in the other study with 292 individuals it was 59% (95% CI, 15% to 80%).[29] In the study with 103 individuals, many reported at least one chronic condition. There was not sufficient information to characterize the health of the individuals in the larger study.

Population-Based Studies of Influenza-Related Severe Morbidity and Mortality

Studies in the 1990s and early 2000s found that the reduction in all-cause mortality in persons over 65 years of age after influenza vaccination ranged from 25% to 75%.[30-32] Subsequent reviews of these studies indicated that these reductions in mortality overestimated the true benefit because of the "healthy vaccine recipient effect." This results in vaccine-associated protections that are not biologically possible, such as reductions in influenza-associated mortality during the summer when influenza is not circulating. This confounding effect occurs because reasonably healthy older adults, who are less likely to die during a short observational period, are more likely to receive influenza vaccine than are frail, chronically ill older adults, who are more likely to die during the period of observation.[33-42] As a result, fewer deaths will occur in the vaccinated group than in the unvaccinated group, regardless of the impact of vaccination. Studies that addressed this confounding effect found that influenza vaccination decreased all-cause mortality in this age-group by only 4.6% (95% CI, 0.7% to 8.3%) and hospital admissions for pneumonia and influenza by only 8.5% (95% CI, 3.3% to 13.5%).[35,42] Another study using a different method to control for this confounding effect and in a different population of people 65 years or older found that influenza vaccination decreased a combined outcome of all-cause mortality or hospitalization for pneumonia and influenza by 14% (95% CI, 8% to 21%); a decrease in all-cause mortality alone was nonsignificant at 6%.[43] While these recent studies suggest a limited benefit of influenza vaccination in reducing hospitalization rates and possibly in reducing all-cause mortality, the actual impact is significantly lower than originally reported.

Averting Influenza-Related Mortality and the Use of Influenza Vaccines

Various sources have stated that influenza vaccination programs have saved millions of lives and if all persons 65 years and older were vaccinated, influenza-related mortality could be reduced by 50% in that age-group.[44-46] The US Centers for Disease Control and Prevention (CDC) estimates that 731,831 individuals died from seasonal influenza in the United States from 1976 to 2007, 89% (654,046) of whom were people 65 years of age and older.[26]

From this information, we calculated a crude estimate for the number of influenza-related deaths averted among persons 65 years of age or older as a result of influenza vaccination over a 31-year period in the United States. If we assume an overly optimistic estimate of 100% vaccine coverage in this age-group (during those 31 years, coverage actually ranged from <20% to >70%), a 5% mortality reduction, and that herd immunity had a negligible impact on mortality, 32,702 deaths attributable to seasonal influenza would have been averted. As noted above, the most comprehensive studies to date that have estimated the mortality reduction for influenza vaccine use in persons 65 years of age and older indicate that mortality is reduced by a maximum of only 5%.[42,43] The CDC estimated that the A(H1N1)pdm09 vaccine prevented from 200 to 520 deaths owing to the late arrival of the vaccine.[47]

Our estimate of fewer than 33,000 deaths with maximum vaccine coverage over 31 years is not the

"millions of lives" that some sources have suggested. While this reduction is an important public health accomplishment, it falls far short of the mortality reduction necessary to conclude that influenza vaccination is having a significant impact on influenza mortality in either the United States or globally.

Impact of Influenza Vaccination on Influenza-Related Morbidity and Mortality Among Other Risk Groups

Vaccine Efficacy and Effectiveness Studies in Children 2 Years of Age and Younger

We identified five studies that specifically reported vaccine efficacy or effectiveness data for TIV among children 2 years of the age or younger. One of the TIV studies is an RCT that reported vaccine efficacy over a 2-year period with a good match between the vaccine and circulating strain each year. During the first year, vaccine efficacy was 66%, and in the following year it was -7%.[48] Similar results were reported in the four effectiveness studies that provided data for this age-group. These studies included 7 years of data; for 4 years, vaccine effectiveness was not significant and ranged from -42% to 66%.[49-52] Given these inconsistent findings, the efficacy and effectiveness of influenza vaccines in children younger than 2 years of age cannot be adequately characterized.

While five of the six LAIV efficacy and effectiveness studies in children included children under 2 years of age, estimates of efficacy and effectiveness were not available for subsets by age. In our review, we found that LAIV provided a higher level of protection against laboratory-confirmed influenza in children aged 6 months to 7 years than TIV did. We are not aware of any data to suggest that the vaccine would not protect children 2 years of age or younger, but LAIV is not licensed for children of that age.

Pregnant Women

We are not aware of any efficacy or effectiveness studies that met the criteria in the *Lancet Infectious Diseases* review and specifically reported data on pregnant women.

Chronic Health Conditions

A single study reported vaccine efficacy for individuals with a chronic health condition. This study was conducted in HIV-positive adults with a median overall CD4+ count over 300 per µl, without additional underling risk factors.[53] Vaccine efficacy in this study was 76% (95% CI, 9% to 96%), similar to what has been reported for healthy adults in other studies.[53] While many of the studies we identified included individuals with chronic health conditions, the investigators did not focus their analyses on these populations, so we are unable to provide further insight into the efficacy or effectiveness of influenza vaccines in protecting persons with chronic health conditions.

Population-Based Studies of Influenza-Related Severe Morbidity and Mortality

We are not aware of any studies that report significant reductions in severe morbidity or mortality related to influenza vaccination in children 2 years of age and younger, pregnant women, or individuals with chronic health conditions.

Averting Influenza-Related Mortality and the Use of Influenza Vaccines

There are no reliable data to estimate the number of deaths that might have been averted with influenza vaccination in children 2 years of age and younger, pregnant women, and individuals with chronic health conditions.

EFFICACY AND EFFECTIVENESS OF INFLUENZA VACCINES NOT LICENSED IN THE UNITED STATES

Alternative-Manufacturing-Platform Vaccines

Companies continue to move forward with development of influenza vaccines that involve new manufacturing platforms (eg, mammalian cell culture) and technologies (eg, antigens produced using recombination techniques) using the current HA-head antigen (see Chapter 8 for additional discussion on HA antigens). Efforts are ongoing to submit applications for licensure of such vaccines to the FDA. Despite a high level of interest in new vaccine technologies, data addressing the efficacy of vaccines using alternative manufacturing platforms are somewhat limited. Three published trials have reported the efficacy of influenza vaccines produced using novel manufacturing platforms against RT-PCR or culture-confirmed influenza in healthy adults under 65 years of age. A vaccine with viral strains grown in Madin-Darby canine kidney (MDCK) cells had an efficacy of 70% (1-sided

97.5% CI, lower limit 55%),[54] a vaccine with viral strains grown in Vero cells had an efficacy of 72% (95% CI, 55% to 82%),[55] and a vaccine in which the HA was produced via a baculovirus-expression system inside of insect cells had an efficacy of 45% (95% CI, 19% to 63%).[56] These results are similar to efficacies reported for vaccines currently licensed in the United States and suggest that vaccines developed using these alternative manufacturing platforms will not offer an additional benefit over currently licensed vaccines.

While not directly related to efficacy or effectiveness, another important practical consideration is the amount of time it takes to produce influenza vaccines. New HA and NA antigen vaccine-manufacturing platforms using cell culture are postulated to reduce production time and enhance the volume that can be produced in a limited time (which is an important consideration when developing a new vaccine against an emerging pandemic strain). In December 2011, a mammalian-cell-culture–based influenza vaccine manufacturing facility opened in North Carolina.[57] Although this influenza vaccine is not currently licensed in the United States, it is licensed in at least 13 countries, including Canada and countries in Europe. While the potential exists for this manufacturing platform to reduce the time necessary to manufacture influenza vaccines, recent use of this vaccine-manufacturing platform in Europe did not demonstrate a time benefit during the 2009 H1N1 pandemic.[58]

ADJUVANTED VACCINES

Some of the earliest influenza vaccines, which were produced in the 1940s, contained adjuvants to increase the immunogenicity of the vaccine antigens.[59,60] Adjuvants, primarily mineral-oil emulsions, were used until the 1960s, when issues related to abscesses at injection sites resulted in their falling out of favor.[61] Oil-in-water emulsions, a significant advance over the mineral-oil emulsions, are the most common type of adjuvant currently used in influenza vaccines[62]; however, other licensed adjuvants are available, and several new adjuvants are in development (see Chapter 8 for further discussion of adjuvants).[63,64] No adjuvanted influenza vaccines are currently licensed for use in the United States. In 1997, the first contemporary oil-in-water adjuvant (MF59) was licensed for use in Europe. To date, approximately 125 million doses of influenza vaccine using this adjuvant have been administered around the world; most of these doses were of the 2009 influenza pandemic vaccine.[62,65] Another oil-in-water adjuvant (ASO3) also was used extensively in vaccine production during the 2009 pandemic.

The 2009 pandemic provided the first opportunity for a rigorous evaluation of adjuvanted vaccines. As of April 8, 2012, six effectiveness studies that included adjuvanted pandemic influenza vaccines fulfilling the study selection criteria in the CIDRAP Comprehensive Influenza Vaccine Initiative (CCIVI) meta-analysis had been published, with a median vaccine effectiveness of 72% (range, 60%-93%) primarily in healthy young adults.[1] Three of these studies evaluated the ASO3 adjuvant and showed vaccine effectiveness estimates ranging from 60% to 93%.[66–68] The other three studies included several vaccines using both MF59 and ASO3 adjuvanted and unadjuvanted vaccines; vaccine effectiveness estimates ranged from 66% to 89%.[25,58,69]

In October 2011, the first randomized clinical trial was published that demonstrated efficacy of an adjuvanted seasonal influenza vaccine against a placebo with RT-PCR confirmation as the clinical end point.[70] This study was conducted over two seasons in children from 6 months to 72 months of age. Owing to an insufficient number of infections during the first year, the efficacy of the vaccine was aggregated across both years. This resulted in a vaccine efficacy of 86% (95% CI, 74% to 93%) against all strains detected, most of which were H3N2.

Numerous studies have demonstrated the immunogenicity of adjuvanted vaccines, supporting the role of adjuvants as immune stimulators. Despite years of use and millions of people vaccinated, however, no rigorous evaluations had been conducted on the efficacy and effectiveness of these vaccines before the 2009 pandemic, and their role in enhancing vaccine effectiveness remains unclear.[63] Furthermore, most of the available data are based on the use of adjuvanted vaccines in individuals younger than 65 years old, even though adjuvants were originally licensed to improve the effectiveness of influenza vaccines in persons 65 years of age or older.[63] Additional vaccine effectiveness

studies over several seasons, particularly in persons 65 years of age and older, are needed to clarify the role of adjuvants in significantly improving the effectiveness of current influenza vaccines.

ANTIGENIC MATCH AND VACCINE EFFICACY AND EFFECTIVENESS

The head of the HA protein is the dominant antigen on the influenza virus that triggers neutralizing antibody production following natural infection or vaccination. Influenza viruses undergo continuous antigenic evolution through the process of antigenic drift, which occurs when amino acid substitutions take place at epitopes (regions on the antigen that are recognized by the immune system) on the HA head. Therefore, antigenic variability occurs in circulating influenza strains each year, which necessitates the development of new vaccines annually. Despite efforts to predict which strains will circulate in a given year and thus account for strain variability, a mismatch can occur between wild-type and vaccine strains.

Antigenic variability between wild-type and vaccine strains typically is measured by HAI. A virus isolate generally is considered antigenically matched to the vaccine if there is a fourfold or less difference in the titer of the isolate and the corresponding vaccine strain used to obtain a reference ferret antiserum. No standard methodology exists for determining the significance of a fourfold-or-greater difference in titer. Scientists widely believe that antigenic distance is strongly associated with clinical vaccine efficacy or effectiveness.[71]

Published reviews have addressed antigenic distance and its impact on vaccine efficacy and effectiveness. However, all such studies suffer from the same problem: They used the results of previously published vaccine efficacy and effectiveness studies that had methodological flaws as noted above, making interpretation of the antigenic match results questionable. For example, an often-cited comprehensive review of this topic included only one vaccine efficacy and effectiveness study identified in our recent meta-analysis, but the review included four other studies that were excluded from our meta-analysis owing to methodological issues.[72] Such reviews have limited information to offer on this topic because of the limitations in the underlying data.

We attempted in our meta-analysis to relate vaccine efficacy and effectiveness to reported antigenic match; however, we were unable to identify a clear protective impact associated with a good antigenic match across influenza seasons. In addition, in a study supported by the CDC, the effectiveness of the monovalent A(H1N1)pdm09 vaccine was only 56% despite the close match between the vaccine strain and the circulating pandemic virus.[22]

It is becoming increasingly clear that the impact of vaccine antigenic match (based on HAI) on the immune response to an influenza vaccine is not well understood, particularly when considering prior vaccinations or exposures to antigenically related viruses. Efforts to link quantitative antigenic match data to clinical efficacy or effectiveness are beginning; however, no studies have compared antigenic distance and clinical effectiveness using culture or RT-PCR–confirmed influenza illness over multiple seasons.[73] Until more data on antigenic match and vaccine effectiveness are available to clarify this relationship, we believe that public health officials should not overstate the importance of this aspect of vaccine effectiveness to the medical community or general public.

HERD IMMUNITY AND VACCINE EFFICACY AND EFFECTIVENESS

Herd immunity is a well-defined concept in public health that occurs when most of a population is immune to an infectious agent (either through previous infection or through vaccination). This widespread immunity prevents circulation of the agent within the entire population, thereby protecting the small number of nonimmune persons in the population. This is a key component of immunization strategies for diseases of childhood, where vaccine coverage rates typically exceed 85% and individual vaccines have efficacies of over 90%. Public health officials have assumed that herd immunity plays a role in population protection following widespread influenza vaccination; however, given the varied coverage rates following vaccination campaigns and the wide ranges of efficacy and effectiveness of influenza vaccines in any given season, it remains unclear whether or not herd immunity plays

a significant role in influenza prevention and control. While several studies suggest that influenza vaccination campaigns provide some level of herd immunity, specifically in reducing influenza morbidity and mortality in those 65 years of age or older, data from these studies are based on nonspecific outcomes such as ILI.[74–77] One study that used RT-PCR–confirmed influenza as an outcome demonstrated that vaccinating children can provide some level of communitywide protection.[78] However, participants were members of Hutterite communities (relatively closed populations similar to the Amish or Mennonites); therefore, these findings cannot be extrapolated to the general population.

Recently, a reanalysis of country-level data in Japan provided evidence for a significant reduction in influenza-related mortality in those 65 years of age and older because of childhood influenza immunization efforts.[79] These findings suggest that vaccinating children for influenza may provide some protection to those 65 years of age and older. However, the existing data are not compelling and the impact that influenza vaccination in children has on influenza outcomes at the population level remains uncertain.

IMPACT OF INFLUENZA EPIDEMIOLOGY ON DETERMINING VACCINE EFFICACY AND EFFECTIVENESS

A significant challenge in determining vaccine effectiveness is the variability in incidence of influenza infections in a given season. The proportion of the population that develops influenza during a given season depends on a number of variables, including which strain is primarily circulating in the population. This poses a challenge for designing studies to evaluate influenza vaccines. If insufficient cases of influenza occur in the population being studied, then the power of the study will not be sufficient to accurately estimate vaccine efficacy or effectiveness.

This is a particular problem in estimating vaccine effectiveness in at-risk populations. For example, several studies have attempted to estimate vaccine effectiveness in persons 65 years of age and older but have been unsuccessful because of the limited number of cases in this age-group.[22,58] However, even if the point estimate that is determined is not statistically significant (ie, $P > 0.05$), such studies may still provide useful estimates of vaccine efficacy or effectiveness.[80,81]

Another significant issue in determining vaccine efficacy or effectiveness is the nonspecific nature of influenza infections. The symptoms of influenza are similar to several other infectious diseases that also occur during the same season. Influenza infection also can be asymptomatic. It is not logistically or financially feasible for researchers to routinely test everyone in a population to determine exactly how many patients in a given week are infected with the influenza virus. Testing is typically done after a person presents with an ILI to a medical care provider. The proportion of individuals with an ILI that tests positive for influenza varies by year, age, and risk factors for influenza complications. These seasonal variations add to the complexity of influenza research and highlight additional gaps in knowledge about the true burden of influenza.

IMPACT OF NONSPECIFIC OUTCOME MEASUREMENTS ON COST-EFFECTIVENESS ESTIMATES

In the last several decades, investigators have made extensive efforts to document the cost-effectiveness of influenza vaccines. However, all of these cost-effectiveness analyses were performed without using highly specific outcome criteria for determining vaccine effectiveness.[1] Such criteria are necessary to ensure that actual influenza infections are being prevented by use of influenza vaccine. For example, a reduction in ILI or absenteeism associated with influenza vaccination should not be considered a reasonable proxy for demonstrating the cost-effectiveness of influenza vaccination in preventing true influenza. In addition, most of these studies were performed without taking into account the significant overestimation of the benefit of vaccinations in persons 65 years of age and older.[1] As with all models, these studies are only as good as the data that are used and the assumptions that are made. A major challenge for researchers is the ability to accurately identify the burden and impact of respiratory disease in various populations, particularly in persons older than 50 years; this issue can make cost-effectiveness studies inconclusive.[82]

These limitations have been addressed by conducting sensitivity analyses that provide a range of impact based on a range of variables. In most cases, we now know that even the lower limit for vaccine efficacy was overestimated in these studies.[83–85] The most common outcome end point used to determine the cost-effectiveness of influenza vaccination is a reduction in ILI. The proportion of ILI caused by influenza during a given influenza season varies. In a recent study in adults older than 50 years, the number of medically attended ILI patients who tested positive for influenza was between 6% and 21%.[86] During the 2009 pandemic, a study from New Zealand found that only 33% of ILI cases in adults and children were serologically confirmed as A(H1N1)pdm09 infections.[87] (This study was an example of the proper use of serology, by assessing the immune response in an unvaccinated population.) In a setting in which ILI correctly predicted influenza infection roughly 33% of the time, an observed 50% reduction in ILI would actually be only a 16% reduction in influenza infections. However, most studies involving ILI as an outcome do not indicate what proportion of ILI cases were actually caused by laboratory-confirmed influenza; therefore, such adjustments are not possible and an accurate interpretation of the data generated cannot be made.

Investigators recently conducted a cost-effectiveness analysis to determine if the recent universal influenza vaccination recommendation from ACIP was cost-effective.[88] This analysis estimated the vaccine impact in reducing ILI in various populations in the United States (among other variables). Currently, the CDC projects that from 3,000 to 49,000 individuals in the United States die from influenza every year.[26] Yet this study concluded that universal influenza vaccination prevents approximately 140,000 deaths from ILI every year.[88] Given how poorly correlated ILI is with laboratory-confirmed influenza and the range of deaths from influenza that the CDC projects for each year, this study clearly overestimates the cost-effectiveness of influenza vaccines. As new evidence emerges about the public health impact of influenza vaccination, the cost-effectiveness of influenza vaccines needs to be reassessed, and better evidence is needed to refine the degree of benefit derived from currently licensed vaccines.[89]

SUMMARY

Most studies since the 1940s that have assessed influenza vaccine efficacy or effectiveness have relied on suboptimal methodology, such as potentially biased participant recruitment and using HAI and nonspecific clinical end points, thus making the results difficult to interpret. The few remaining studies, which provide the highest quality of evidence to assess the true impact of influenza vaccines, have found a level of protection lower than that often attributed to the vaccine.

We believe that our recent *Lancet Infectious Diseases* review provides a critical and comprehensive state-of-the art assessment of the efficacy and effectiveness of currently licensed and available influenza vaccines. On the basis of our review, we conclude that the currently licensed influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. It also supports the conclusion that, "Based on a track record of substantial safety and moderate efficacy in many seasons, we believe the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available. However, evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older."[1]

Studies assessing the role of influenza vaccines in reducing mortality in those 65 years of age and older have been mired by serious study design issues. The reductions in mortality demonstrated in many of these studies result from an overestimation of the true benefit because of the "healthy vaccine recipient effect."

Future studies employing rigorous methodology are needed to fill the knowledge gaps regarding the true efficacy, effectiveness, and cost-effectiveness of influenza vaccines. This same methodologically sound approach is needed to provide a more comprehensive understanding of the impacts of antigenic match, herd immunity, and the use of adjuvants and novel antigen vaccine technologies on seasonal and pandemic influenza morbidity and mortality across all populations.

REFERENCES

1. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12(1):36-44
2. ECDC. Systematic review and meta-analysis concerning the efficacy and effectiveness of seasonal influenza vaccines—(part 1). 2011. Available at: http://www.ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC_Reviews/ECDC_DispForm.aspx?List=512ff74f-77d4-4ad8-b6d6-bf0f23083f30&ID=1212&RootFolder=/en/activities/sciadvice/Lists/ECDC_Reviews
3. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62
4. Haynes B. Can it work? Does it work? Is it worth it? *BMJ* 1999;319(Sep):652-3
5. Department of Health, Education and Welfare. *Summary Report of Conference on Influenza Vaccine Activity for 1977-78*. 1977
6. Francis TJ. The development of the 1943 vaccination study of the commission on influenza. *Am J Hyg* 1945;42(1):1-11
7. Meiklejohn G. Viral respiratory disease at Lowry Air Force Base in Denver, 1952-1982. *J Infect Dis* 1983;148(5):775-84
8. Salk J. A simplified procedure for titrating hemagglutinating capacity of influenza virus and the corresponding antibody. *J Immunol* 1944;49(2):87-98
9. McDonald JC, Andrews BE. Diagnostic methods in an influenza vaccine trial. *Br Med J* 1955;2(4950):1232-5
10. Petrie JG, Ohmit SE, Johnson E, et al. Efficacy studies of influenza vaccines: effect of end points used and characteristics of vaccine failures. *J Infect Dis* 2011;203(9):1309-15
11. Jefferson T, Di Pietrantonj C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010
12. Jefferson T, Di Pietrantonj C, Rivetti A, et al. Vaccines for preventing influenza in healthy adults. In: Collaboration TC, Jefferson T, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010
13. Jefferson T, Rivetti A, Harnden A, et al. Vaccines for preventing influenza in healthy children. In: Collaboration TC, Jefferson T, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2008
14. Vu T, Farish S, Jenkins M, et al. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. *Vaccine* 2002;20(13-14):1831-6
15. Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. *JAMA* 1994;272(21):1661-5
16. Lambert LC, Fauci AS. Influenza vaccines for the future. *N Engl J Med* 2010;363(21):2036-44
17. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. *Nat Med* 2010;16(12):1389-91
18. Belongia EA, Kieke BA, Donahue JG, et al. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. *Vaccine* 2011;29(38):6558-63
19. Castilla J, Martinez-Artola V, Salcedo E, et al. Vaccine effectiveness in preventing influenza hospitalizations in Navarre, Spain, 2010-2011: cohort and case-control study. *Vaccine* 2012;30(2):195-200
20. Fielding JE, Grant KA, Garcia K, et al. Effectiveness of seasonal influenza vaccine against pandemic (H1N1) 2009 virus, Australia, 2010. *Emerg Infect Dis* 2011;17(7):1181-7
21. Fielding JE, Grant KA, Papadakis G, et al. Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007-2008. *BMC Infect Dis* 2011;11(1):170
22. Griffin MR, Monto AS, Belongia EA, et al. Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. *PLoS One* 2011;6(8):e23085
23. Jimenez-Jorge S, Savulescu C, Pozo F, et al. Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study. *Vaccine* 2012;30(24):3595-602

24. Staat MA, Griffin MR, Donauer S, et al. Vaccine effectiveness for laboratory-confirmed influenza in children 6-59 months of age, 2005-2007. *Vaccine* 2011;29(48):9005-11
25. Castilla J, Moran J, Martinez-Artola V, et al. Effectiveness of the monovalent influenza A(H1N1)2009 vaccine in Navarre, Spain, 2009-2010: cohort and case-control study. *Vaccine* 2011;29(35):5919-24
26. Thompson M, Shay D, Zhou H, et al. Estimates of deaths associated with seasonal influenza—United States, 1976-2007. *MMWR* 2010;59(33):1057-62
27. De Villiers P, Steele D, Hiemstra L, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. *Vaccine* 2009;28(1):228-34
28. Savulescu C, Valenciano M, de Mateo S, et al. Estimating the influenza vaccine effectiveness in elderly on a yearly basis using the Spanish influenza surveillance network—pilot case-control studies using different control groups, 2008-2009 season, Spain. *Vaccine* 2010;28(16):2903-7
29. Kissling E, Valenciano M, Falcao JM, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. *Euro Surveill* 2009;14(44):pii=19388
30. Nichol K. Efficacy/clinical effectiveness of inactivated influenza virus vaccines in adults. In: Nicholson KG, ed. *Textbook of Influenza*. Oxford, UK: Blackwell Science; 1998
31. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis* 2001;184(6):665-70
32. Hak E, Wei F, Grobbee DE, et al. A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis. *J Clin Epidemiol* 2004;57(9):875-80
33. Campitelli MA, Rosella LC, Stukel T, et al. Influenza vaccination and all-cause mortality in community-dwelling elderly in Ontario, Canada, a cohort study. *Vaccine* 2010;29(2):240-6
34. Jackson ML. Confounding by season in ecologic studies of seasonal exposures and outcomes: examples from estimates of mortality due to influenza. *Ann Epidemiol* 2009;19(10):681-91
35. Baxter R, Ray GT, Fireman BH. Effect of influenza vaccination on hospitalizations in persons aged 50 years and older. *Vaccine* 2010;28(45):7267-72
36. Baxter R, Lee J, Fireman B. Evidence of bias in studies of influenza vaccine effectiveness in elderly patients. *J Infect Dis* 2010;201(2):186-9
37. Ortqvist A, Granath F, Askling J, et al. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area. *Eur Respir J* 2007;30(3):414-22
38. Simonsen L, Viboud C, Taylor RJ, et al. Influenza vaccination and mortality benefits: new insights, new opportunities. *Vaccine* 2009;27(45):6300-4
39. Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol* 2006;35(2):345
40. Jackson LA, Jackson ML, Nelson JC, et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol* 2006;35(2):337
41. Simonsen L, Taylor RJ, Viboud C, et al. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis* 2007;7(10):658-66
42. Fireman B, Lee J, Lewis N, et al. Influenza vaccination and mortality: differentiating vaccine effects from bias. *Am J Epidemiol* 2009;170(5): 650-6
43. Wong K, Campitelli M , Stukel T, et al. Estimating influenza vaccine effectiveness in community-dwelling elderly patients using the instrumental variable analysis method. *Arch Intern Med* 2012;172(6):484-91
44. Poland G. If you could halve the mortality rate, would you do it? *Clin Infect Dis* 2002;35(4):378-80
45. Poland G, Morse D. Improving the public health: the U.S. recommendation for universal influenza immunization. *Vaccine* 2010;28(16):2799-800
46. Palese P, Wang TT. H5N1 influenza viruses: facts, not fear. *Proc Natl Acad Sci* 2012;109(7):2211-3
47. CDC. Notice to readers: revised estimates of the public health impact of 2009 pandemic influenza A (H1N1) vaccination. *MMWR* 2011;60(38):1321
48. Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children.

JAMA 2003;290(12):1608-16
49. Szilagyi PG, Fairbrother G, Griffin MR, et al. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Arch Pediatr Adolesc Med* 2008;162(10):943-51
50. Eisenberg KW, Szilagyi PG, Fairbrother G, et al. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003-2004 and 2004-2005 influenza seasons. *Pediatrics* 2008;122:911-9
51. Heinonen S, Silvennoinen H, Lehtinen P, et al. Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study. *Lancet Infect Dis* 2011;11(1):23-9
52. Staat MA, Griffin MR, Donauer S, et al. Vaccine effectiveness for laboratory-confirmed influenza in children 6-59 months of age, 2005-2007. *Vaccine* 2011;29(48):9005-11
53. Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus : double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis* 2011;52(1):128-37
54. Frey S, Vesikari T, Szymczakiewicz-Multanowska A, et al. Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults. *Clin Infect Dis* 2010;51(9): 997-1004
55. Barrett PN, Berezuk G, Fritsch S, et al. Efficacy, safety, and immunogenicity of a vero-cell-culture-derived trivalent influenza vaccine: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2011;9767(377):751-9
56. Treanor JJ, El Sahly H, King J, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok) against influenza in healthy adults: a randomized, placebo-controlled trial. *Vaccine* 2011;29(44):7733-9
57. HHS. First U.S. cell-based flu vaccine plant set for dedication. 2011. Available at: http://www.hhs.gov/news/press/2011pres/12/20111212a.html
58. Valenciano M, Kissling E, Cohen JM, et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* 2011;8(1):e1000388
59. Friedewald WF. Adjuvants in immunization with influenza virus vaccines. *J Exp Med* 1944;80(6): 477-91
60. Hagan DTO, Tsai T, Reed S. Emulsion-based adjuvants for improved influenza vaccines. In: Rappuoli R, Del Giudice G, eds. *Influenza Vaccines for the Future*. Basel: Springer Basel; 2011:327-57
61. Stuart-Harris C. Adjuvant influenza vaccines. *Bull World Health Organ* 1969;41(3):617-21
62. Holdren JP, Lander E, Varmus H, et al. Report to the president on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. 2010
63. Parodi V, de Florentiis D, Martini M, et al. Inactivated influenza vaccines: recent progress and implications for the elderly. *Drugs Aging* 2011;28(2):93-106
64. Durando P, Iudici R, Alicino C, et al. Adjuvants and alternative routes of administration towards the development of the ideal influenza vaccine. *Hum Vaccin* 2011;7(Feb):29-40
65. Tsai TF. MF59 adjuvanted seasonal and pandemic influenza vaccines. *Yakugaku Zasshi* 2011;131(12):1733-41
66. Hardelid P, Fleming DM, McMenamin J, et al. Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010. *Euro Surveill* 2011;16(2):pii=19763
67. Andrews N, Waight P, Yung CF, et al. Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. *J Infect Dis* 2011;203(1):32-9
68. Skowronski DM, Janjua NZ, Serres GD, et al. Effectiveness of ASO3 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. *BMJ* 2011;342:c7297
69. Castilla J, Moran J, Martinez-Artola V, et al. Effectiveness of the monovalent influenza A(H1N1)2009 vaccine in Navarre, Spain, 2009-2010: cohort and case-control study. *Vaccine* 2011;29(35):5919-24
70. Vesikari T, Knuf M, Wutzler P, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *N Engl J Med* 2011;365(15):1406-16

71. CDC. *Epidemiology and Prevention of Vaccine-Preventable Disease,* ed 19. (Atkinson W, Wolfe C [Skip], Hamborsky J, eds). Washington DC: Public Health Foundation; 2011
72. Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. *Vaccine* 2007;25(39-40):6852-62
73. Gupta V, Earl DJ, Deem MW. Quantifying influenza vaccine efficacy and antigenic distance. *Vaccine* 2006;24(18):3881-8
74. Jordan R, Connock M, Albon E, et al. Universal vaccination of children against influenza: are there indirect benefits to the community? A systematic review of the evidence. *Vaccine* 2006;24:1047-62
75. Glezen WP, Gaglani MJ, Kozinetz C, et al. Direct and indirect effectiveness of influenza vaccination delivered to children at school preceding an epidemic caused by 3 new influenza virus variants. *J Infect Dis* 2010;202(11):1626-33
76. Grijalva CG, Zhu Y, Griffin MR. Evidence of effectiveness from a large county-wide school-based influenza immunization campaign. *Vaccine* 2009;27(20):2633-6
77. King JC, Beckett D, Snyder J, et al. Direct and indirect impact of influenza vaccination of young children on school absenteeism. *Vaccine* 2011;30(2):289-93
78. Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA* 2010;303(10):943-50
79. Charu V, Viboud C, Simonsen L, et al. Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. *PLoS One* 2011;6(11):e26282
80. Beran J, Wertzova V, Honegr K, et al. Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. *BMC Infect Dis* 2009;9:2
81. Ohmit SE, Victor JC, Teich ER, et al. Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines. *J Infect Dis* 2008;198:312-7
82. Mogasale V, Barendregt J. Cost-effectiveness of influenza vaccination of people aged 50-64 years in Australia: results are inconclusive. *Aust NZ J Public Health* 2011;35(2):180-6
83. Prosser LA, Brien MAO, Molinari N, et al. Non-traditional settings for influenza vaccination of adults costs and cost effectiveness. *Pharmacoeconomics* 2008;26(2):163-78
84. United States Congress Office of Technology Assessment. *Cost Effectiveness of Influenza Vaccination*. 1981
85. Maciosek MV, Solberg LI, Coffield AB, et al. Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. *Am J Prev Med* 2006;31(1):72-9
86. Talbot HK, Griffin MR, Chen Q, et al. Effectiveness of seasonal vaccine in preventing confirmed influenza-associated hospitalizations in community dwelling older adults. *J Infect Dis* 2011;203(4): 500-8
87. Jutel A, Baker MG, Stanley J, et al. Self-diagnosis of influenza during a pandemic: a cross-sectional survey. *BMJ* 2011;1(2):e000234
88. Clements KM, Chancellor J, Nichol K, et al. Cost-effectiveness of a recommendation of universal mass vaccination for seasonal influenza in the United States. *Value Health* 2011;14(6):800-11
89. Kelly H, Valenciano M. Estimating the effect of influenza vaccines. *Lancet Infect Dis* 2012;12(1):5-6

CHAPTER 4

HOW SAFE ARE CURRENT INFLUENZA VACCINES?

INTRODUCTION

Influenza vaccines are among the most frequently administered vaccines in the United States; more than 1 billion doses have been administered since 1990 (data compiled from Vellozzi[1] and Table 6-2, Chapter 6). Owing to this widespread use, extensive safety information is available that demonstrates that the licensed vaccines are safe, with only rare serious vaccine-associated adverse events documented. This chapter summarizes that safety information.

INFLUENZA VACCINE SAFETY

Most of the safety information for influenza vaccines comes from postlicensure surveillance data (ie, reports of adverse events postvaccination). This postlicensure surveillance is vital, as prelicensure clinical trials are generally not large enough to detect rare adverse events. Passive postlicensure surveillance in the United States primarily is conducted through the Vaccine Adverse Event Reporting System (VAERS). Similar systems for monitoring adverse events following vaccination are in place in other countries.[2] In the United States additional safety monitoring occurs within the vaccine safety datalink program (VSD).[3] The VSD has the ability to conduct near real-time surveillance for adverse events in the managed care organizations that participate in this system.[4] These reporting systems can detect events such as seizures, spontaneous abortions, and sudden death that may occur following vaccination. Since such events occur at certain well-defined background rates in the general population regardless of vaccination history, detection of an event following a vaccination does not necessarily imply a causal relationship between the vaccination and the event.[5] Once a signal of a possible new adverse event is identified, further investigation is needed to determine whether or not the rate of the event in vaccinated persons is statistically higher than the rate in the general population. If a statistical association can be shown, then a causal relationship may exist between the vaccine and the adverse event.

Recent reviews of postlicensure surveillance data for TIV and LAIV administration in adults have not identified any new substantial safety issues associated with either vaccine.[1,6] Available data indicate that TIV and LAIV are safe and well-tolerated vaccines for those recommended to receive them.[7] Injection-site reactions, such as pain and inflammation, are the most common adverse events for TIV, and a runny nose is the most common adverse event for LAIV.[7] While not licensed for use in the United States, adjuvanted influenza vaccines are used around the world. The safety profile for adjuvanted vaccines is similar to nonadjuvanted TIVs; the adjuvanted vaccines induced higher rates of local reactions and, in studies with limited numbers of participants, did not reveal new serious adverse events.[8] A recent review of safety data for pregnant women found no detectable adverse events or fetal harm from TIV formulations administered during any trimester of pregnancy; however, only limited data address this issue.[9]

The Institute of Medicine (IOM) of the National Academy of Sciences recently completed an extensive review of US vaccine safety that included licensed influenza vaccines. The IOM reaffirmed the safety of influenza vaccines, noting that anaphylaxis (potentially life-threatening allergic reaction with rapid onset) was the only severe adverse event for which sufficient evidence was available to support a causal association with influenza vaccination.[10] Severe allergic and anaphylactic reactions can occur in response to a number of influenza vaccine components, but such reactions are rare. Because influenza vaccines are produced in embryonated chicken eggs, hypersensitivity to egg protein (ovalbumin) has traditionally been considered a potential risk factor for anaphylaxis and therefore has been a contraindication to influenza vaccination. In 2011, however, the ACIP revised the guidance for administration of influenza vaccines to those with egg allergies, noting that in most cases influenza vaccination is well tolerated in individuals with mild allergic reactions to eggs (such as hives alone). Egg allergy, however, remains a concern for those with a history of severe allergic reactions to eggs. Such persons should be referred to a physician who has expertise in the management of allergic conditions for further risk assessment before they receive influenza vaccine.[11]

Concern has been raised regarding the risk of Guillain-Barré syndrome (GBS) following influenza vaccination as a result of the increased rates of GBS seen in 1976 during the swine flu vaccine campaign (see below). GBS is a relatively rare neurologic disorder that can occur as a complication of certain conditions, including some infections. The IOM report noted that, "While the weight of epidemiologic evidence does not support a causal link between influenza vaccinations [and GBS] evaluated over the last 30 years, an association cannot be confidently ruled out, particularly for future vaccine strains."[10] During the 2009 pandemic there was concern that the vaccine may be associated with GBS like the 1976 vaccine (see below). Studies have now shown, however, that with the A(H1N1)pdm09 influenza vaccine there was "approximately 1 extra case of GBS per million persons vaccinated."[12-16] Additional work is needed to determine if the A(H1N1)pdm09 influenza vaccine is causally linked to an increased risk of GBS or if this increase was associated with other factors, such as concurrent infection. In addition, recent work has demonstrated that receiving an influenza vaccine after a prior episode of GBS did not result in an increased risk of GBS recurrence.[7,17]

UNIQUE ADVERSE EVENTS ASSOCIATED WITH INFLUENZA VACCINES

Despite an excellent overall safety record, the inactivated influenza vaccine has been associated with several unique adverse events. Although rare, these events are worth noting, given the current recommendation for annual universal vaccination of all persons in the United States beginning at 6 months of age, which means that large numbers of people are being vaccinated each year.

1976 H1N1 Vaccine and GBS

In 1976, an outbreak of a novel strain of H1N1 influenza occurred among military recruits at Fort Dix, New Jersey; more than 200 cases, including 13 severe respiratory infections and 1 death, were reported.[18] At the time, public health officials were concerned that the novel strain could result in a pandemic, so a strain-specific vaccine was produced and a national influenza vaccination campaign was undertaken. During the campaign, public health officials noted a rate of GBS among vaccine recipients about nine times higher than the expected background rate of less than one case per million vaccinated.[19,20] This increased risk resulted in suspension of the campaign. Researchers still do not know why this particular vaccine caused an increased risk of GBS.

Febrile Seizures Associated with Seasonal Influenza Vaccine: 2010 and 2011

In the spring of 2010, an increased rate of febrile seizures was detected in Australia and New Zealand in children younger than 5 years of age who had received the seasonal influenza vaccine produced by CSL Limited.[21,22] This vaccine was used primarily in Australia and New Zealand, although it also was available in limited quantities in the United States and was used infrequently. The rate of febrile seizures in Australia was 3.3 per 1,000 children vaccinated, which is significantly higher than the rate of 0.014 per 1,000 children vaccinated noted previously in the

United States.[23,24] As a result of this finding, the ACIP recommended that this vaccine not be used in children younger than 8 years of age unless another appropriate vaccine was unavailable and the child was at high risk for complications. The overall rate of febrile seizures was not elevated during the 2011 influenza season in Australia.[25]

In June 2012, CSL released the preliminary results of its 2-year investigation into the cause of these febrile seizures.[26] The initial findings were that the A(H1N1)pdm09 and influenza B strains, when split during the manufacturing process, resulted in more gene fragments and lipids from these strains than other similar influenza vaccines.[27] The 2010 CSL vaccine elicited a more robust immune response, largely cytokine associated, than vaccines produced in previous years. No manufacturing process changes, raw material issues, or manufacturing deviations were identified that could explain the increased rate of febrile seizures. These results suggest that the cause of the increased rate of febrile seizures is "complex and multi-factorial."[27]

On the basis of these events, increased surveillance for febrile seizures in young children was conducted in the United States during the 2010-11 influenza season.[28] This surveillance effort identified 43 children 5 years of age and younger who had a febrile seizure within 1 day of receiving the influenza vaccine.[28] This rate of detection exceeded the predetermined threshold for febrile seizures set in VAERS. In addition, 14 of the 43 children had received a 13-valent pneumococcal conjugate vaccine at the same time that they received their influenza vaccine.

To further elucidate the risk of febrile seizure following influenza vaccination in children, additional analysis was performed. This analysis confirmed an increased risk of febrile seizures in children under 5 years of age and younger and also demonstrated that the risk increased when 13-valent pneumococcal conjugate vaccine was co-administered.[29] This increased risk was not associated with the vaccine produced by CSL Limited, and researchers believed that this finding was not related to the situation seen in Australia and New Zealand during 2010. At the time of this report, it remains unclear if this increased risk of febrile seizures was associated with the strains used in the 2010-11 influenza vaccine or was confounded by concurrent administration of the 13-valent pneumococcal conjugate vaccine.

Narcolepsy Associated with A(H1N1)pdm09 Vaccine: 2010

In the fall of 2010, an increased rate of narcolepsy was observed in several EU countries among persons receiving the A(H1N1)pdm09 influenza vaccine.[30] The vaccine, Pandemrix, an adjuvanted vaccine, was manufactured by GlaxoSmithKline and used only in Europe, although a similar vaccine was used in Canada.[31] On September 1, 2011, the National Institute for Health and Welfare in Finland released its final report on the association between narcolepsy and administration of Pandemrix.[32] It found an increased risk of narcolepsy in children and young adults 4 to 19 years of age when compared with those who did not receive the vaccine. Narcolepsy is rare in this age-group; in children under the age of 17, the average annual incidence in Finland is 0.31 cases per 100,000 children. In 2010 the narcolepsy rate in this age-group was 5.46 cases per 100,000 children, a 17-fold increase that was associated with the administration of Pandemrix.[33] Children and young adults 4 to 19 years of age experienced a 12.7-fold increased risk for narcolepsy within 8 months of receiving the Pandemrix vaccine.[34] In all cases of narcolepsy that were examined, the individuals had a genetic predisposition for developing narcolepsy; they possessed the HLA (human leukocyte antigen) DQB1*0602 allele, which is found in 95% of Caucasian/Asian narcolepsy cases.[35] The mechanism by which the vaccine induced narcolepsy in these at-risk individuals remains unclear and is under investigation. Increased rates of narcolepsy have not been demonstrated with any other influenza vaccine.

SUMMARY

The currently licensed influenza vaccines in the United States are among the safest of all available vaccines. While unique adverse events can occur with use of these vaccines, such events are extremely rare. Given the level of safety of the current influenza vaccines, it will be challenging for new influenza vaccines to match or exceed the current safety profile. Despite this excellent safety record, the legacy of the three unusual adverse events outlined above (particularly

the absence of a cause for the increased incidence of GBS associated with administration of H1N1 vaccine in 1976) demonstrates the importance of ongoing population-based adverse event monitoring for new influenza vaccines as they become available.

REFERENCES

1. Vellozzi C, Burwen DR, Dobardzic A, et al. Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine* 2009;27(15):2114-20
2. WHO. Global status of immunization safety: report based on the WHO/ UNICEF Joint Reporting Form, 2004 update. *Wkly Epidemiol Rec* 2005;80(42):361-7
3. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics* 2011;127(May suppl):S45–53
4. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol* 2010;171(2):177–88
5. Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet* 2010;374(9707):2115-22
6. Izurieta HS, Haber P, Wise RP, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. *JAMA* 2005;294(21):2720
7. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62
8. Principi N, Esposito S. Adjuvanted influenza vaccines. *Hum Vaccin Immunother* 2012;8(1):1-8
9. Manske J. *Influenza Vaccination During Pregnancy: What Do We Know?* [master's thesis] University of Minnesota; 2011
10. IOM Committee to Review Adverse Effects of Vaccines Board on Population Health and Public Health Practice. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: National Academy Press; 2011
11. Grohskopf L, Uyeki T, Bresee J, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011;60(33):1128-32
12. Nelson KE. Invited commentary: Influenza vaccine and Guillain-Barre syndrome--is there a risk? *Am J Epidemiol* 2012;175(11):1129–32
13. Burwen DR, Sandhu SK, Macurdy TE, et al. Surveillance for Guillain-Barré Syndrome After Influenza Vaccination Among the Medicare Population, 2009-2010. *Am J Public Health* 2012;102(10):1921–1927
14. Wise ME, Viray M, Sejvar JJ, et al. Guillain-Barre syndrome during the 2009-2010 H1N1 influenza vaccination campaign: population-based surveillance among 45 million Americans. *Am J Epidemiol* 2012;175(11):1110–9
15. Greene SK, Rett M, Weintraub ES, et al. Risk of confirmed Guillain-Barre syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009-2010. *Am J Epidemiol* 2012;175(11):1100–9
16. Yih WK, Lee GM, Lieu T a, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system, 2009-2010. *Am J Epidemiol* 2012;175(11):1120–8
17. Baxter R, Lewis N, Bakshi N, et al. Recurrent guillain-barre syndrome following vaccination. *Clin Infect Dis* 2012;54(6):800-4
18. Gaydos JC, Top FH, Hodder RA, et al. Swine influenza A outbreak , Fort Dix, New Jersey, 1976. *Emerg Infect Dis* 2006;12(1):23-8
19. Stratton K. Immunization safety review: influenza vaccines and neurological complications. Washington, DC: National Academy Press; 2004
20. Safranek T, Lawrence D, Kurland L, et al. Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two-state study: Expert Neurology Group. *Am J Epidemiol* 1991;133(9):940-51
21. Therapeutic Goods Administration. *Investigation into Febrile Reaction in Young Children Following 2010 Seasonal Trivalent Influenza Vaccination*. 2010. Available at: http://www.tga.gov.au/pdf/alerts-medicine-seasonal-flu-100702.pdf
22. Petousis-Harris H, Poole T, Booy R, et al. Fever following administration of two inactivated

influenza vaccines: a survey of parents of New Zealand infants and children 5 years of age and under. *Vaccine* 2011;29(16):2933-7
23. Armstrong PK, Dowse GK, Effler PV, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ* 2011;1(1):e000016
24. Hambidge SJ, Glanz JM, France EK, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA* 2006;296(16):1990
25. Wood N, Sheppeard V, Cashman P, et al. Influenza vaccine safety in children less than 5 years old: the 2010 and 2011 experience in Australia. *Pediatr Infect Dis J* 2012;31(2):199-202
26. CLS Biotherapies. CLS Biotherapies provides update on Fluvax investigation. June 2012. Available at: http://www.csl.com.au/s1/cs/auhq/1255929043091/news/1255929042869/prdetail.htm
27. CSL Biotherapies. Summary of investigations into the paediatric adverse events associated with Fluvax vaccine in 2010. June 2012. Available at: http://www.cslbiotherapies.com.au/s1/cs/aucb/1255929051660/content/1255929051619/content.htm
28. Leroy Z, Broder K, Menschik D, et al. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. *Vaccine* 2012;30(11):2020-3
29. Tse A, Tseng HF, Greene SK, et al. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine* 2012;30(11):2024-2031
30. EMA. European Medicines Agency starts review of Pandemrix. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/08/WC500096005.pdf
31. EMA. European Medicines Agency reviews further data on narcolepsy and possible association with Pandemrix. 2011. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/02/news_detail_001211.jsp
32. National Institute for Health and Welfare. Association between Pandemrix and narcolepsy confirmed among Finnish children and adolescents. 2011. Available at: http://www.thl.fi/doc/en/26352
33. Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS One* 2012;7(3):e33723
34. Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS One* 2012;7(3):e33536
35. National Narcolepsy Task Force. *National Narcolepsy Task Force Interim Report*. Helsinki, Finland; 2011:1-25. Available at: http://www.thl.fi/thl-client/pdfs/dce182fb-651e-48a1-b018-3f774d6d1875

CHAPTER 5

PUBLIC ACCEPTANCE OF INFLUENZA VACCINES

INTRODUCTION

For several decades, the US government has set 10-year goals for the health of the nation and specifically for influenza vaccination coverage. By 2020, the target for seasonal influenza vaccination coverage in the United States is 80% for children and adults and 90% for high-risk individuals.[1] Several tools are used to track progress toward this goal, including the Behavioral Risk Factor Surveillance System (BRFSS), the National Health Interview Survey (NHIS), the National Immunization Survey (NIS), and the Sentinel Immunization Information System (IIS).[2,3] These tools or their predecessors have been used to track influenza vaccination coverage in selected US populations since the 1960s.[4] This chapter primarily focuses on US influenza vaccine acceptance, with a discussion of pandemic vaccine acceptance in selected countries.

INFLUENZA VACCINE ACCEPTANCE

Since 1960, the US government has recommended that the following groups of persons at high risk for severe morbidity or morality be vaccinated annually against influenza: those 65 years of age and older, those with chronic medical conditions that place them at increased risk for complications from influenza, and pregnant women. From 1960 to 1985 approximately 20% of these high-risk individuals received the influenza vaccine annually.[5] The acceptance rate increased during the 1976 "swine flu" vaccine campaign, in part because of an extensive promotional effort that was coordinated by the federal government in response to the potential emergence of a pandemic H1N1 strain in that year.[6] On the basis of this trend, and a growing body of literature suggesting that the influenza vaccine was extremely effective at preventing mortality in persons 65 years of age and older, the Department of Health and Human Services (HHS) established a goal of vaccinating 60% of those at high risk annually by 1990.[7]

However, as noted in Chapter 3, the results of studies reporting significant reductions in mortality in vaccinated persons 65 years of age and older had significant bias and therefore overestimated this potential benefit. Thus, the data supporting the 1990 goal actually were less robust than believed at the time.

In 1987, Congress authorized the Influenza Vaccine Demonstration Project. This project was the culmination of several years of work to secure Medicare reimbursement for influenza vaccines in order to bolster vaccination rates.[5] If the project showed that the influenza vaccine was cost-effective and led to increased vaccination rates among Medicare beneficiaries, then the cost of the influenza vaccine and its administration would be covered by Medicare.[5,8] The

Influenza Vaccine Demonstration Project was deemed a success, and Medicare coverage for vaccination was adopted; by 1997 over 60% of those 65 years of age and older were being vaccinated annually for influenza. This rate has remained relatively constant since that time during years without vaccine shortages, according to annual vaccination data from NHIS (**Figure 5-1**).

In 2000, the ACIP embarked on a series of recommendations that gradually increased the percentage of the general population recommended to receive influenza vaccine. These changes culminated in 2010 with a universal recommendation for everyone 6 months of age and older to be vaccinated. While the universal recommendation is relatively recent, extensive national and local public health promotional campaigns to increase influenza vaccination levels have been in place for more than 10 years. Despite this, most Americans in recent years (particularly those under 65 years of age) did not report receiving an influenza vaccine in the preceding year (**Table 5-1**). This finding is in marked contrast to vaccination rates for routine childhood immunizations, which often exceed 90%.[10]

In 2010, the Rand Corporation conducted a nationally representative survey of adults to evaluate seasonal

FIGURE 5-1. Percentage of Individuals Who Reported Receiving Influenza Vaccines in Preceding 12 Months Based on NHIS Data[9]

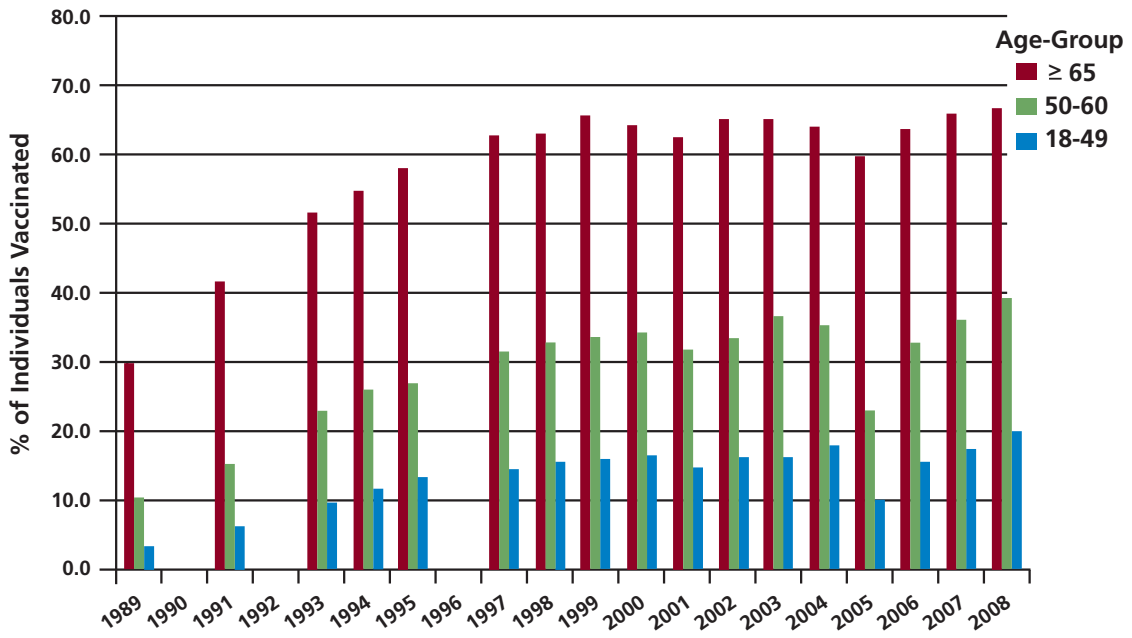


TABLE 5-1. Influenza Vaccine Coverage Estimates, US 2008-2011

Age-Group	2008-2009[3]	2009-2010[11]	Pandemic H1N1[11]	2010-2011[12]
>6 Months	32.2%	41.2%	27.0%	37.7%
6 Months to 17 Years	24.0%	43.7%	40.5%	37.2%
>18 Years	Not reported	40.4%	22.7%	Not reported
18-49 Years	22.2%	28.4%	Not reported	25.3%
18-49 Years, High Risk	32.1%	38.2%	Not reported	32.2%
50-64 Years	42.3%	45.0%	Not reported	43%
>65 Years	67.2%	69.6%	28.9%	68.2%

influenza vaccine acceptance. Among adults who did not receive the influenza vaccine (60.9% of respondents), the primary reason given for forgoing vaccination was the belief that they did not need the vaccine (27.6%). Other top reasons for not being vaccinated included not believing in the effectiveness of influenza vaccines (15.6%), concern about getting sick from the vaccine or experiencing side effects (14.2%), and "not getting around to it" (13.8%).[13] These responses are similar to data obtained from a survey conducted more than 50 years ago.[14] The earlier survey found that reasons respondents did not seek vaccination were they believed they were not at risk of contracting influenza, they believed any illness would be mild, and they were concerned about the efficacy and safety of the vaccine.[14]

Concern about the safety of the influenza vaccine was heightened in response to the 1976 "swine flu" vaccine campaign, during which an excessive occurrence of GBS cases were noted among vaccinees and the campaign was suspended after a flurry of media attention.[15] As new influenza vaccines are developed, the public's acceptance of these vaccines will continue to be an issue. For example, a recent review of the public's acceptance of the 2009 A(H1N1)pdm09 vaccine (which many considered to be a "new" vaccine even though the manufacturing process was the same as for routine seasonal vaccines) showed that acceptance of the vaccine varied considerably.[16] In the 10 studies that addressed this issue (8 of which were conducted before vaccine campaigns commenced), the proportion of respondents willing to be vaccinated ranged from 8% to 67%.[16] Driving forces behind acceptance of the pandemic vaccine included perceived risk of infection, extent of the pandemic, severity of illness from the pandemic strain, risk of harm from the vaccine, and previous acceptance of influenza vaccines. These data demonstrate that issues around public acceptance of influenza vaccines are complex and that the public will likely continue to have concerns about new vaccines.

While adjuvanted vaccines were not used in the United States during the recent pandemic, they were used in several other countries as part of their pandemic vaccine response. Although adjuvants have been used in seasonal influenza vaccines outside of the United States since 1997, the A(H1N1)pdm09 vaccine campaign was the first significant test of the public's willingness to accept a modification to currently licensed vaccines: the addition of adjuvants. In Germany an adjuvanted vaccine was the primary vaccine used during the 2009 campaign. Despite a widespread recommendation for vaccination, only about 13% of Germans were vaccinated with the A(H1N1)pdm09 vaccine.[17] The primary reason healthcare workers rejected vaccination was inclusion of the adjuvant.[18] The primary reason the general public refused vaccination was fear of adverse events, with only 28% of survey respondents believing adjuvants were partially or fully safe.[19] Harris and colleagues provide this reminder about public acceptance drawn from the experience of the A(H1N1)pdm09 vaccine campaign: "No matter how quickly a safe and effective vaccine is produced, it will do little good if large numbers of people refuse to be vaccinated."[20] Progress has been made in recent years toward delivering consistent messages on influenza vaccines and on reaching target populations. Although these improvements may enhance public acceptance, their ongoing impact remains unclear.[21]

SUMMARY

Influenza continues to be a significant public health problem in the United States and globally; therefore, efforts to reduce influenza morbidity and mortality are essential. Currently, pursuing programs and public education activities that support universal vaccination are the primary strategies available to reduce the health burden caused by influenza. While efforts to enhance public acceptance of the currently licensed influenza vaccines should continue to be a priority, public health leaders should also provide with clarity the scientific evidence supporting the effectiveness of these vaccines by type of vaccine (ie, TIV and LAIV) and recipient age and underlying health conditions. If the general public or professional groups such as healthcare workers perceive that public health officials have "oversold" the effectiveness of the current influenza vaccines, substantial backlash and mistrust could occur. Efforts now to increase vaccination rates must be consistent with building a strong and lasting foundation for vaccine acceptance over time, which will be even more valuable as new and better vaccines become available.

REFERENCES

1. HHS. Healthy People 2020 objectives. 2010. Available at: http://www.healthypeople.gov/2020/topicsobjectives2020/pdfs/HP2020objectives.pdf
2. CDC. Influenza vaccination coverage. 2011. Available at: http://www.cdc.gov/flu/fluvaxview/index.htm
3. CDC. Influenza vaccination coverage among children and adults—United States, 2008-09 influenza season. *MMWR* 2009;58(39):1091-5
4. Simpson DM, Ezzati-Rice TM, Zell ER. Forty years and four surveys: how does our measuring measure up? *Am J Prev Med* 2001;20(4 suppl):6-14
5. Fedson DS. Influenza project: vaccination demonstration goal an expanded policy. *Infect Control Hosp Epidemiol* 1990;11(7):357-61
6. Department of Health Education and Welfare. *Summary Report of Conference on Influenza Vaccine Activity for 1977-78*. 1977
7. Anonymous. Preventive health services: immunization. *Public Health Rep* 1983;Sep-Oct(suppl):40-9
8. CDC. Perspectives in disease prevention and health promotion influenza vaccination coverage levels in selected sites--United States, 1989. *MMWR* 1990;39(10):159-60, 165-7
9. CDC. Influenza vaccination coverage trends 1989-2008 (NHIS). 2009. Available at: http://www.cdc.gov/flu/pdf/professionals/nhis89_08fluvaxtrendtab.pdf
10. Hinman AR, Orenstein WA, Schuchat A. Vaccine-preventable diseases, immunizations, and MMWR—1961-2011. *MMWR* 2011;60(suppl):49-57
11. CDC. Final estimates for 2009-10 seasonal influenza and influenza A (H1N1) monovalent vaccination coverage—United States, August 2009 through May, 2010. 2010. Available at: http://www.cdc.gov/flu/professionals/vaccination/coverage_0910estimates.htm
12. CDC. Influenza vaccination coverage 2010-2011 influenza season. 2011. Available at: http://www.cdc.gov/flu/fluvaxview/1011season.htm
13. Harris K, Maurer J, Uscher-Pines L. Seasonal influenza vaccine use by adults in the U.S.: detailed survey data tables, 2009-2010. Santa Monica; 2010:OP-311/1-GSK. Available at: http://www.rand.org/pubs/occasional_papers/OP311z1.html
14. Rosenstock IM. Public acceptance of influenza vaccination programs. *Am Rev Resp Dis* 1961;83(2):171-4
15. Neustadt R, Fineberg HV. *The Swine Flu Affair: Decision-Making on a Slippery Disease*. Honolulu: University Press of the Pacific; 2005
16. Nguyen T, Henningsen KH, Brehaut JC, et al. Acceptance of a pandemic influenza vaccine: a systematic review of surveys of the general public. *Infect Drug Resist* 2011;4:197-207
17. Walter D, Bohmer MM, Heiden M, et al. Monitoring pandemic influenza A(H1N1) vaccination coverage in Germany 2009/10—results from thirteen consecutive cross-sectional surveys. *Vaccine* 2011;29(23):4008-12
18. Brandt C, Rabenau HF, Bornmann S, et al. The impact of the 2009 influenza A(H1N1) pandemic on attitudes of healthcare workers toward seasonal influenza vaccination 2010/11. *Euro Surveill* 2011;16(17):pii=19854
19. Walter D, Bohmer M, Reiter S, et al. Risk perception and information-seeking behaviour during the 2009/10 influenza A(H1N1)pdm09 pandemic in Germany. *Euro Surveill* 2012;17(13):pii=20131
20. Harris KM, Maurer J, Kellermann AL. Influenza vaccine—safe, effective, and mistrusted. *N Engl J Med* 2010;363(23):2183-5
21. GAO (US Government Accountability Office). Influenza vaccine: issues related to production, distribution, and public health messages. GAO-08-27. Released Nov 16, 2007. Available at: http://www.gao.gov/assets/270/268915.pdf

CHAPTER 6

SEASONAL AND PANDEMIC INFLUENZA VACCINE AVAILABILITY

INTRODUCTION

Every year, 6 to 8 months before seasonal influenza vaccine administration begins, vaccine manufacturers provide projections on the number of doses they intend to produce. These projections are based on the antigen characteristics of the vaccine, which remain relatively constant from year to year, and the demand for vaccine, which also is relatively constant and comes primarily from a limited number of developed countries. Even with these relatively constant variables, accurately predicting vaccine availability can be challenging.

Estimating production projections for a pandemic vaccine, however, poses even more significant challenges, as production will be based on the characteristics of the pandemic virus strain and the characteristics of the vaccine (such as antigen concentration needed to elicit an appropriate response). These factors cannot be determined quickly and require time to sort out. Despite such challenges, a timely, effective, and widely available pandemic vaccine is a critical public health priority for governments around the world, as it is the primary defense against an influenza pandemic.

Currently, seasonal and pandemic influenza vaccines are manufactured in exactly the same manner. This situation theoretically provides surge capacity for production of a global pandemic influenza vaccine, as facilities can switch from producing seasonal vaccine to producing a pandemic vaccine rapidly. This type of manufacturing will likely not allow for sufficient quantities of a pandemic vaccine to be available in time to have an impact during a first pandemic wave.

GLOBAL AVAILABILITY OF PANDEMIC INFLUENZA VACCINES

Global production capacity for influenza vaccines has increased over the past 20 years. This increase is in part a response to the reemergence of HPAI A/H5N1 in 2003 (following its initial occurrence in Hong Kong in 1997), which created a new sense of urgency regarding the potential threat of a severe influenza pandemic.

Since seasonal influenza vaccines and anticipated pandemic influenza vaccines are manufactured using the same processes, public officials have assumed that an increase in production capacity for seasonal influenza vaccines also will increase the production capacity for pandemic influenza vaccines.[1] In 2006, the WHO developed the Global Pandemic Influenza Action Plan to Increase Vaccine Supply. In the short term, this

plan would enable rapid production of approximately 2 billion pandemic influenza vaccine doses to be used during the first year of an influenza pandemic and, in the long term, would provide greater production capacity so that the entire global population (6.9 billion) could be vaccinated over a relatively short period.[1]

Global pandemic vaccine production capability was tested during the recent 2009 H1N1 pandemic. In May 2009, as vaccine manufacturers scaled up to produce the pandemic vaccine, the WHO estimated worldwide production capacity for a monovalent vaccine at 4.9 billion doses per year.[2] However, these capacity estimates were revised on September 14, 2009, to approximately 3 billion doses per year.[3] The final number of doses of A(H1N1)pdm09 vaccine that could have been produced through June 1, 2010, is unknown, as pandemic vaccine demand had dropped significantly by that time, which resulted in a scaling back of vaccine manufacturing efforts. However, it appears that even if a substantially higher vaccine demand occurred, the total global production would have been far below the estimated 3 billion doses in the 12 months following declaration of the pandemic. In 2009, when commenting on A(H1N1) pdm09 pandemic vaccine production capacity, the WHO acknowledged that supplies would be inadequate to cover a world population of 6.9 billion people, indicating, "Global manufacturing capacity for influenza vaccines is limited, inadequate, and not readily augmented."[3] This recent experience provides valuable insight into global pandemic vaccine production capacity and serves as a warning to public health officials planning for a pandemic involving a highly virulent strain of influenza.

In 2010, seasonal influenza vaccines were produced in 41 facilities, primarily in the United States, Canada, the European Union (EU), Russia, China, Japan, and Australia.[2] During the 2009-10 pandemic, the WHO estimated that over 85% of the pandemic H1N1 vaccine was produced by only seven manufacturers in facilities located in Western Europe, Canada, Japan, China, Russia, Australia, and the United States.[4] Given the need to distribute pandemic vaccines globally and the fact that not all countries have the financial assets to purchase sufficient quantities of vaccine for their populations during a pandemic, the WHO coordinates a program for donation and distribution of pandemic influenza vaccines. As of November 10, 2010, the last WHO update, only 78 million doses of donated A(H1N1)pdm09 vaccine had been distributed to 77 countries.[5] All of these doses were distributed well after the second wave of the pandemic, months after developed countries had started their vaccine campaigns. Again, this experience highlights the current inadequacies in global distribution of influenza vaccines during a pandemic.

Recognizing the limitations of the A(H1N1)pdm09 vaccine response, the WHO Review Committee on the Functioning of the International Health Regulations (2005) in Relation to Pandemic (H1N1) 2009 provided three recommendations specifically targeted to influenza vaccines[6]: (1) develop in advance agreements on vaccine distribution and delivery, (2) develop in advance agreements on sharing viral isolates and access to the products derived from those isolates (ie, vaccines), and (3) embark on a research and evaluation program on influenza with a goal of creating "…broader spectrum, highly effective, safe, and longer-lasting vaccines; hasten vaccine production; and increase throughput." This review is also discussed in Chapter 13.

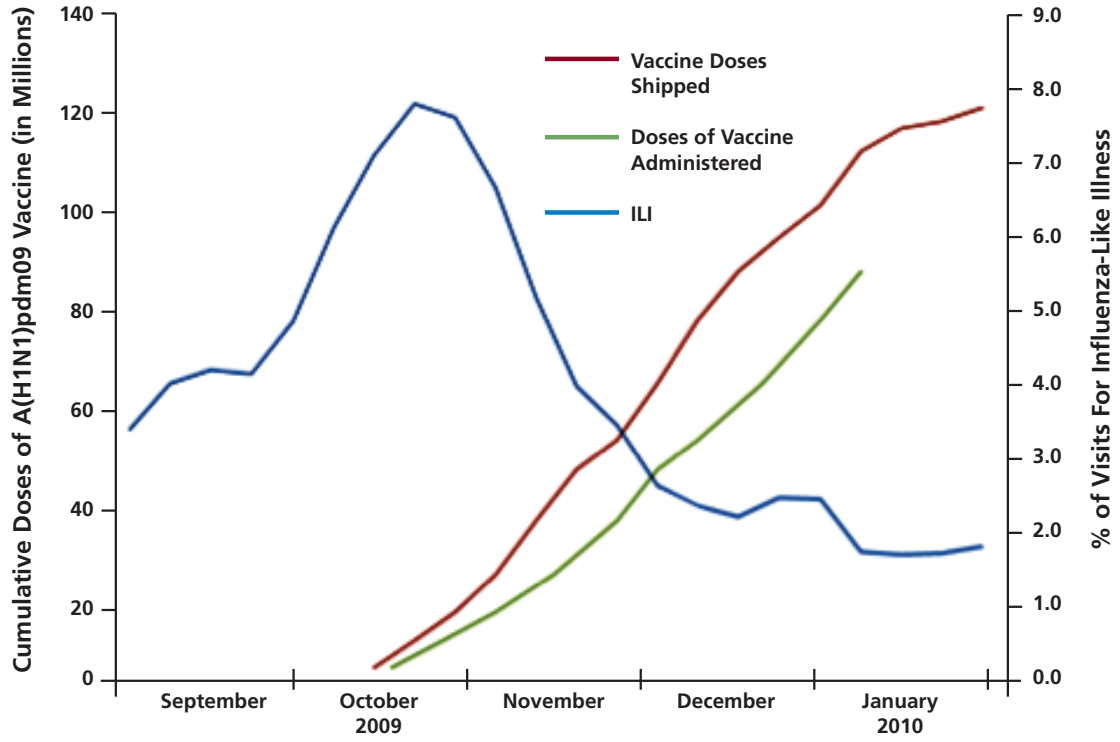
AVAILABILITY OF PANDEMIC INFLUENZA VACCINES IN THE UNITED STATES

Experience with the 2009-10 Pandemic

In late spring of 2009, officials estimated the number of doses of the 2009 A(H1N1)pdm09 monovalent vaccine that would be available in the United States before the anticipated second wave of illness in early fall 2009. At a US National Biodefense Science Board (NBSB) meeting in July 2009, the director of the Biomedical Advanced Research and Development Authority (BARDA), the agency within HHS tasked with the development and procurement of pandemic vaccines, estimated that 120 million doses of the pandemic H1N1 vaccine would be available for use in the United States in October 2009.[7] In August 2009, at another NBSB meeting on pandemic H1N1 activities, this number was revised to 45 million doses.[7] However, by October 28, 2009, the federal government had shipped only 16.8 million doses of A(H1N1)pdm09

vaccine to states.[8] Ample supply of the vaccine was not available until after the second wave had subsided; by that time, demand for the vaccine had dropped dramatically (**Figure 6-1**).

FIGURE 6-1. A(H1N1)pdm09 Vaccine By Date Shipped and Estimated Date of Administration, and Incidence of Influenza-Like Illness (ILI) in the United States[8,9 a,b]



[a] The number of administered doses likely overestimates the population vaccinated, since pediatric patients received two doses. The data set acknowledges only the first dose, even if two doses were administered.

[b] Vaccine administration data were estimated based on guidance provided by Jay Butler, MD, former director of the CDC's H1N1 Vaccine Task Force, November 11, 2010.

The first allotment of pandemic vaccine was shipped on October 1, 2009, about 2 weeks before the peak of the second pandemic wave.[10] This shipment was LAIV, which is only approved for healthy nonpregnant persons between 2 and 49 years of age; thus, the potential for vaccine use among those in the highest priority groups was limited.[11] As vaccine became available, it was shipped from national vaccine depots to state distribution points, such as state health departments. State officials then established state-specific priorities for persons to be vaccinated and provided vaccine to public clinic locations and private healthcare providers. Once vaccine was shipped to public clinics and providers, it was then administered to the priority population groups. Since it takes 10 to 14 days for potential immunity to develop in vaccine recipients, the public health benefit of initial vaccination efforts was not realized for approximately 2 additional weeks.

The CDC maintains a network of sentinel healthcare providers around the United States that provides weekly data on the number of patients seen and the number with ILI, to approximate the burden of influenza in the United States. During the 2009 pandemic, the ILI data closely mirrored virologically confirmed cases and served as a proxy for the number of A(H1N1)pdm09 infections. As **Figure 6-1** demonstrates, the ILI peak, which approximates the second wave of pandemic influenza illness, occurred shortly after the pandemic vaccine was first shipped. Because of the time necessary to produce, distribute, and administer the vaccine, the time necessary for recipients to develop immunity, and the relatively low number of persons vaccinated, the pandemic vaccine campaign had limited public health impact on reducing the incidence of pandemic A(H1N1)pdm09 infections. In addition, a significant disconnect occurred between vaccine availability and demand for the vaccine. Public demand for the

vaccine was substantial at the height of the second wave in October 2009, during which time vaccine was in short supply; however, this demand quickly waned as cases naturally diminished and vaccine became plentiful.[12] The CDC estimates that 27% of Americans received the pandemic vaccine, which was less than the proportion of the population that received the 2009-10 seasonal influenza vaccine.[13]

Review of Public Health Impact of Pandemic Vaccination Programs

Recognizing that the "less-than-optimal experience…raised new awareness of the limitations of the system by which influenza vaccines are produced today," the Executive Office of the President asked the President's Council of Advisors on Science and Technology (PCAST) to review the influenza vaccines enterprise. (This report is discussed in more detail in Chapter 12.) The ultimate goal of this review was to ensure that "the nation can more rapidly and reliably produce effective vaccines, at a sufficient scale to protect all of the nation's residents, in response to the emergence of pandemic influenza."[14] This same approach was espoused in the National Strategy for Pandemic Influenza, which was released in 2006.[15] The CDC estimated that the 2009-10 pandemic resulted in 43 million to 89 million influenza cases in the United States from April 2009 to April 2010, with 195,000 to 403,000 hospitalizations and 8,900 to 18,300 deaths.[16] The CDC also estimated the 2009 A(H1N1) pdm09 pandemic vaccine prevented 713,000 to 1,500,000 cases, 3,900 to 10,400 hospitalizations, and 200 to 520 deaths.[16] However, the fact that the vaccine was not available until after the peak of the second wave significantly reduced the potential public health impact of the vaccine.

In the previous two pandemics of 1957 and 1968, pandemic influenza vaccine also arrived in quantities too small and too late to have a significant public health impact in the United States (**Table 6-1**).

TABLE 6-1. Key Events in Past Three Pandemic Vaccine Responses in the United States

Year	Identification of New Strain	Strain Released to Manufacturers	Vaccine Orders Placed	First Lot Released	Doses of Vaccine Before Peak Incidence of Major Wave[a]
1957-58	4/57[17]	5/12/57[18]	7/2/57[18]	8/12/57[18]	48.8 million doses[b,c] — 11/9/57[18]
1968-69[19]	8/68	9/9/68	9/24/69	11/15/68	15.3 million doses[c] — 1/3/69
2009-10	4/21/09[20]	5/27/09[21]	5/22/09[22]	10/1/09[10]	11.2 million doses— 10/22/09[8]

[a] The amount of vaccine released for public use before the peak of the major wave of infections.

[b] These vaccines contained approximately one half of the amount of antigen as the 1968-69 vaccine.

[c] The antigen concentrations for the 1957-58 and 1968-69 vaccines were measured by CCA (chick cell–agglutinating) units rather than mcg of HA antigen, which has been used since 1978. CCA and mcg are not comparable measures of the amount of antigen in a vaccine dose; therefore, the numbers of vaccines doses produced are not directly comparable.

1957 provided the first opportunity to respond to a pandemic with a vaccine. During that pandemic, 181 days transpired between the release of the seed strain to manufacturers and the point at which the peak of the first pandemic wave occurred.[18] By the peak of the first wave, which was the largest wave, manufacturers were able to produce 48.8 million doses of pandemic vaccine. However, owing to production issues, vaccine produced before November 1957 contained half the typical amount of antigen and had poor efficacy.[17] Because of the shortage of vaccine, physicians were advised to stretch their vaccine supply by providing 0.1 mL rather than 1.0 mL of vaccine.[23] Using 0.1 mL of vaccine was subsequently found to be ineffective in preventing infection with influenza.[24] During that situation, the public health vaccine response was clearly inadequate.

As during the 1957 and 2009 pandemics, the public health vaccine response in the United States was also inadequate during the 1968 pandemic. In 1968, 67 days transpired from the release of the seed strain to manufacturers until the peak of the first pandemic wave, which was the wave that had the greatest impact in the United States.[19] By the peak of the first pandemic wave, only 15.3 million doses of influenza vaccine were available. In 2009, vaccine was not available until the second wave of the pandemic, which was the largest pandemic wave; 127 days transpired from release of the seed strain to manufacturers until the peak of the second wave,[21] and only 11.2 million doses of TIV and LAIV combined were available at that point.[8]

Mammalian-Cell-Culture–Based Vaccines for Pandemic Influenza

The US government recently spent more than $700 million to support construction of a mammalian-cell-culture–based influenza vaccine manufacturing plant in Holly Springs, North Carolina.[25] The goal of constructing this plant is to boost domestic production capacity once the vaccine is licensed for use in the United States. The US government has stated that the manufacturing capacity of this plant will significantly increase our readiness for a future influenza pandemic. However, on the basis of the experience with mammalian-cell-culture–based influenza vaccine manufacturing in Europe during the 2009 A(H1N1) pdm09 pandemic, it is unclear if the availability of this facility would have changed the vaccine response during the 2009 pandemic, or if it will significantly improve vaccine response for a future pandemic.

Mammalian-cell-culture–based pandemic vaccines were licensed for use in the European Union in 2009 and were used there during the pandemic response. However, both the egg-produced and the cell-culture–produced influenza vaccines arrived too late and in too little quantity to have a significant impact on the pandemic in the European Union. According to the date of marketing authorization in Europe, a mammalian-cell-culture–based vaccine was available only after three adjuvanted egg-based influenza vaccines were already in distribution. The European experience with cell-culture–based vaccine did not demonstrate a measureable improvement in vaccine production speed, nor was it sufficient to alter the overall public health impact of the pandemic.

SEASONAL INFLUENZA VACCINES

The annual manufacturing process for seasonal influenza vaccines involves numerous steps and takes from 6 to 8 months.[26] The overall manufacturing process depends on steps that may not be under direct control of the manufacturers, such as viral growth and potency testing; therefore, the availability of seasonal influenza vaccines both in terms of timing and number of doses can be somewhat difficult to predict. Influenza

TABLE 6-2. Seasonal Influenza Vaccine Production and Issues 1999-2009

	99-00[27]	00-01[27]	01-02[27]	02-03[28]	03-04[28]	04-05[29]	05-06[28]	06-07[28]	07-08[28]	08-09[28]
Doses Produced, in Millions	77.2	77.9	87.7	95	86.9	61	88.5	120.9	140.6	135.9
Doses Distributed (Percent of All Doses Produced)	76.7 (99)	70.4 (90)	77.7 (89)	83.5 (88)	83.1 (96)	57 (93)	81.5 (92)	102.5 (85)	112.8 (80)	113 (83)
Production Issues[a]	No	Yes	Yes	No	No	Yes	Yes[30]	Yes[31]	No	No
Shortages Reported	No	Yes[b]	Yes[b]	No	Yes[32]	Yes	Yes	Yes[b]	No	No
Rationing of Vaccine	No	No	No	No	No	Yes	Yes[33]	No	No	No

[a] Issues in the manufacturing the vaccine (eg, slow viral growth, low potency, Good Manufacturing Practice violations).

[b] Vaccine became readily available later than anticipated, resulting in supply not meeting demand, which was reported as a shortage.

vaccines are the only currently used vaccines that have this challenge with predicting availability annually. During 5 of the 10 years from 1999 through 2009, seasonal vaccine production was delayed or original estimates for vaccine production were reduced because of manufacturing issues (**Table 6-2**).

SUMMARY

In this chapter, we demonstrate that current influenza vaccine production capacity is inadequate to consistently meet the annual needs for seasonal influenza vaccines or to meet the surge capacity needs for pandemic influenza vaccine production. Furthermore, global influenza vaccine production methods have not changed significantly during the past half century. Three influenza pandemics have now occurred in that time, during which a pandemic influenza vaccine was eventually available but did not significantly affect the outcome of the pandemic. Even now, current influenza vaccine production capacity is not sufficient for the anticipated public health needs of a future pandemic, particularly if it were to involve a highly virulent strain, as was seen in the 1918 pandemic. Given the current vaccine efficacy and effectiveness issues already discussed in this report and the limitations around potential availability of pandemic influenza vaccines, it is difficult to quantify the global public health benefit of these vaccines. Regardless, the information presented here clearly demonstrates that influenza vaccines and their respective manufacturing platforms need to fundamentally change to meet future demands.

REFERENCES

1. WHO. *Global Pandemic Influenza Action Plan to Increase Vaccine Supply*. 2006. Available at: http://www.who.int/csr/resources/publications/influenza/CDS_EPR_GIP_2006_1.pdf
2. Partridge J, Kieny MP, World Health Organization H1N1 Influenza Vaccine Task Force. Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009-2010 and comparison with previous estimates and global action plan targets. *Vaccine* 2010;28(30):4709-12
3. WHO. Pandemic influenza vaccines: current status. 2009. Available at: http://www.who.int/csr/disease/swineflu/notes/pandemic_influenza_vaccines_20090924/en/index.html
4. Collin N, de Radigues X. Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza. *Vaccine* 2009;27(38):5184-6
5. WHO. *Pandemic (H1N1) 2009 Vaccine Deployment Update*. 2010. Available at: http://www.who.int/csr/disease/swineflu/action/h1n1_vaccine_deployment_final_update_2010_11_10.pdf
6. WHO. *Implementation of the International Health Regulations (2005): Report of the Review Committee on the Functioning of the International Health Regulations (2005) in Relation to Pandemic (H1N1) 2009*. 2011. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf
7. NBSB. Summary report of the National Biodefense Science Board Public Teleconference. 2009. Available at: http://www.phe.gov/Preparedness/legal/boards/nbsb/Documents/nbsb-mtgsum-090814.pdf
8. CDC. 2009 H1N1 influenza vaccine doses allocated, ordered, and shipped by project area. 2009. Available at: http://www.cdc.gov/h1n1flu/vaccination/vaccinesupply.htm
9. CDC. Percentage of visits for influenza-like-illness reported by sentinel providers 2009-2010. 2010. Available at: http://www.cdc.gov/flu/weekly/weeklyarchives2009-2010/data/senAllregt52.htm
10. CDC. Weekly 2009 H1N1 flu media briefing, transcript. 2009. Available at: http://www.cdc.gov/media/transcripts/2009/t091001.htm
11. Roos R. First H1N1 vaccine doses headed to states, cities. CIDRAP News. 2009. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/oct0109cdc-jw.html
12. Rambhia KJ, Watson M, Sell TK, et al. Mass vaccination for the 2009 H1N1 pandemic: approaches, challenges, and recommendations. *Biosecur Bioterror* 2010;8(4):321-30
13. CDC. Final estimates for 2009-10 seasonal influenza and influenza A (H1N1) monovalent vaccination coverage—United States, August 2009 through May, 2010. 2010. Available at: http://www.cdc.gov/flu/professionals/vaccination/coverage_0910estimates.htm
14. Holdren JP, Lander E, Varmus H, et al. Report to the president on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. 2010
15. White House Homeland Security Council. *National*

Strategy for Pandemic Influenza. 2006. Available at: http://www.flu.gov/planning-preparedness/federal/pandemic-influenza.pdf

16. CDC. Notice to readers: revised estimates of the public health impact of 2009 pandemic influenza A (H1N1) vaccination. *MMWR* 2011;60(38):1321

17. Jensen K, Dunn F, Robinson R. Influenza, 1957: a variant and the pandemic. *Prog Med Virol* 1958;1:165-209

18. Murray R. Some problems in the standardization and control of influenza vaccine in 1957. *Am Rev Respir Dis* 1961;83:160-7

19. Murray R. Production and testing in the USA of influenza virus vaccine made from the Hong Kong variant in 1968-69. *Bull World Health Organ* 1969;41(3-4-5):493-6

20. CDC. Swine influenza A (H1N1) infection in two children--southern California, March-April 2009. *MMWR* 2009;58(dispatch):1-3

21. Roos R. CDC releases viruses for novel H1N1 vaccine development. CIDRAP News. 2009. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/may2709strain.html

22. HHS. HHS takes additional steps toward development of vaccine for the novel influenza A (H1N1). 2009. Available at: http://www.hhs.gov/news/press/2009pres/05/20090522b.html

23. Anonymous. Asian influenza; a special report to physicians. *JAMA* 1957;165(4):356-9

24. Boger W, Liu O. Subcutaneous and intradermal vaccination with Asian influenza vaccine. *JAMA* 1957;165(13):1687-9

25. HHS. Report to Congress: Pandemic influenza preparedness spending. Jan 2009. Available at: https://www.medicalcountermeasures.gov/BARDA/documents/hhspanflu-spending-0901.pdf

26. Hampson A. Vaccines for pandemic influenza: the history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. *Ann Acad Med Singapore* 2008;37(6):510-7

27. Fukuda K, O'Mara D, Singleton JA. How the delayed distribution of influenza vaccine created shortages in 2000 and 2001. *Pharm Ther* 2002;27(5):235-42

28. HIDA. 2008-2009 influenza vaccine production and distribution: Market brief. 2009. Available at: http://www.hida.org/Content/NavigationMenu/MarketResearch/EmergingTrends1/Influenza/09_FluBrief.pdf

29. CDC. Interim influenza vaccination recommendations, 2004-05 influenza season. *MMWR* 2004;53(39):923-4

30. Gerberding J. Telebriefing transcript—November 10, 2005. *CDC*. 2005. Available at: http://www.cdc.gov/media/transcripts/t051110.htm

31. Staff. Flu vaccine delay affects toddlers. CIDRAP News. 2006. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/general/news/oct1706influenza.html

32. Harper SA, Fukuda K, Uyeki TM et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2004;53(RR-10):1-40

33. CDC. Update: influenza vaccine supply and recommendations for prioritization during the 2005-06 influenza season. *MMWR* 2005;54(34):850

CHAPTER 7

RECOMMENDATIONS FOR INFLUENZA VACCINE USE AND PUBLIC HEALTH PROMOTION

INTRODUCTION

The previous chapters of this report discuss the efficacy and effectiveness, safety, public acceptance, and availability of influenza vaccines—the four components that should drive and direct public policy and public health promotion activities regarding influenza vaccination. This chapter explores the evolution of public health policies related to US influenza vaccination recommendations by providing an analysis of the current universal vaccination recommendation and a review of recent public messaging on this issue.

In recent years, the science of influenza vaccine efficacy and effectiveness studies has improved substantially. Studies that use RT-PCR and/or culture-confirmed outcomes and rigorous study designs are now available and provide the best evidence of vaccine efficacy and effectiveness (see Chapter 3). To reflect the best available evidence, recommendations for influenza vaccine use and public health promotion must be based on the results of these studies.

PUBLIC HEALTH RECOMMENDATIONS AND DEVELOPMENT OF SUCCESSFUL IMMUNIZATION PROGRAMS

The practice of using vaccines to prevent diseases in humans began more than 200 years ago when Edward Jenner demonstrated in 1796 that inoculation with cowpox could protect against smallpox. The next human vaccine, against rabies, was introduced nearly 100 years later. It was not until the latter half of the 20th century, however, that a true vaccine revolution was born. Currently in the United States routine vaccination, beginning in infancy and continuing into old age, is recommended to prevent 17 different infectious diseases. In addition, other vaccines, such as those for rabies, anthrax, yellow fever, typhoid, and Japanese encephalitis, are recommended for use in certain pre-exposure or postexposure scenarios, such as international travel to endemic areas.

The ready availability of these modern vaccines and the public health programs to support their use have dramatically reduced the associated vaccine-preventable diseases in the United States. In a recent review in the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*), 15 vaccines were highlighted for their significant role in reducing morbidity in the last 60 years.[1] Of note, the influenza vaccine was not one of these, despite accounting for 26% of the citations in the review.[1]

While modern vaccine technology, based on cutting-edge research and development and quality manufacturing, is necessary to generate effective and safe vaccines, additional infrastructure is needed to realize a major public health benefit. Such a benefit primarily occurs when vaccines are proactively supported by official public health recommendations and when public health programs are available to assist with vaccine purchase, distribution, administration, and promotion.

Public health agencies, and their officially designated advisory bodies such as the ACIP, have a mandate to advocate for health promotion behaviors, including routine immunizations. Similarly, medical, nursing, and pharmacy organizations, patient-advocacy groups, and health insurance payers can play a key role in this process. As health promotion recommendations are developed, however, they should be formulated on the basis of the best scientific data available. Ideally, this should include sound evidence-based outcome measures that demonstrate the individual and societal benefits of the recommendations compared with the cost of implementation. It is also important for the clinical care community and the general public to be given accurate information from policy makers about the costs, risks, and benefits of any health promotion or protection activity.

PRE-1964 RECOMMENDATIONS FOR INFLUENZA VACCINE USE IN THE MILITARY AND CIVILIANS

Military Personnel

Given the significant morbidity and mortality among US military forces as a result of the 1918 influenza pandemic, the US government was determined to prevent influenza transmission among troops during the World War II era. Throughout the 1940s and 1950s, a federal commission studied a number of different influenza vaccine formulations and processes, primarily using military recruits and occasionally state mental hospital patients as vaccine recipients. In 1943 and 1944, a group of simultaneous trials in the Army Student Training Program and among other military personnel showed that inactivated vaccines produced in chicken eggs had a 69% efficacy against symptomatic influenza.[2,3] The commission concluded that the studies demonstrated that the "vaccine used was highly, although not completely, effective in preventing influenza A."[2] Along with influenza surveillance data, these results prompted the approval in August 1945 of the first general recommendation for influenza vaccination among US Army personnel, and a vaccination campaign was carried out in October and November of that year. Subsequent information demonstrated a lower incidence of influenza infection in vaccinated Army units compared with unvaccinated Navy units.[2,4]

Civilian Populations

Although US civilians had been allowed access to influenza vaccine since 1946, the vaccine was not formally recommended for their annual use until 1960, when Surgeon General Leroy E. Burney took that step in the wake of the increased number of deaths associated with the 1957-58 influenza pandemic.[5,6] Burney identified three groups for which influenza vaccination was recommended: persons with chronic conditions that placed them at increased risk for complications from influenza, pregnant women, and those 65 years of age and older. Vaccination was recommended for these groups because they were identified as having the highest mortality associated with influenza.[6] The surgeon general recognized that the available influenza vaccine was not a perfect tool, but he believed it was worth the costs and risks in the groups for which the risk of death from influenza was high.[7] At the time of this first recommendation, however, no influenza vaccine efficacy data were available to support routine vaccination for these populations. These early years were important in setting the course for future US influenza vaccination policies and illustrate the tendency for public officials to make policy decisions that are believed to be in the best interest of the population, even in the absense of strong scientific data to support them.

THE ACIP AS A FEDERAL ADVISORY COMMITTEE ON INFLUENZA VACCINATION POLICIES

Since 1964, the ACIP has been chartered as a federal advisory committee to provide expert external advice and guidance to the director of the CDC and the secretary of HHS.[8,9] The ACIP was established to "provide advice for the control of diseases for which a vaccine is licensed in the United States."[10] The ACIP

makes policy recommendations for vaccines and related agents that are licensed by the FDA and may provide guidance for use of unlicensed vaccines, as circumstances warrant. As part of this process, the ACIP may "alter or withdraw their recommendation(s) regarding a particular vaccine as new information becomes available or the risk of disease changes."[10] According to the ACIP, recommendations are made on the basis of careful review of available scientific data, including disease morbidity and mortality in the general US population and in specific risk groups, vaccine safety and efficacy, cost-effectiveness, and related factors.[11]

The role of the ACIP is to provide advice that will lead to a reduction in the incidence of vaccine-preventable diseases and an increase in the safe use of vaccines and related biological products. The committee develops written recommendations for the routine administration of vaccines to children and adults in civilian populations, including age for vaccine administration, number of doses and dosing interval, precautions for vaccine use, and contraindications.

The ACIP includes three membership groups: 15 voting members, who are the primary decision makers; 8 ex officio members, who represent federal government agencies; and 30 liaison representatives, who represent the interests of various organizations.[12] The voting members are appointed to the committee by the secretary of HHS (formerly the Department of Health, Education, and Welfare), are paid nominally, and are intended to represent a variety of medical specialties and viewpoints, such as pediatric, family medicine, internal medicine, immunology, and consumer interests.[12] Voting members of the ACIP are held to strict conflict-of-interest policies.[12]

ACIP recommendations are changed and added through voting, with a simple majority required to enact changes or additions. Voting can take place only at full ACIP public meetings, and for a specific vote to take place, a quorum of eight voting or ex officio members must be present. If an addition or change pertaining to influenza vaccination attains a majority of votes, it is then refined by members of the Influenza Working Group of the ACIP and sent to the CDC for clearance. Recommendations must be "cleared for technical accuracy, clarity, and acceptance of policy through all administrative layers of the CDC."[12] Once approved, the recommendations are published in *MMWR* and become official.[12]

In addition to approving the recommendations, CDC professionals staff the committee and provide all meeting preparations and support. For example, the CDC compiles background documents, provides summaries of important issues, and facilitates activities of the various ACIP working groups.[12] ACIP members must consider and vote on recommendations for all vaccines under the ACIP purview, which is a sizeable task; therefore, members must rely on objective information from CDC professionals. CDC public health experts on influenza and the delivery of vaccine programs serve as important subject matter experts to the ACIP. This is potentially an issue, however, because the CDC has a vested interest in the outcomes of ACIP deliberations and plays a significant role in promoting influenza vaccination. Furthermore, CDC programs are held to standards and goals, such as those promoted in Healthy People 2010 and 2020. For example, the Healthy People 2020 10-year goals for advancing the health of all Americans have an important focus on reducing influenza mortality, particularly in persons 65 and older.[13]

One group that frequently presents on influenza prevention and control to the ACIP is the ACIP Influenza Working Group, composed of voting members, liaisons, and governmental program representatives. As might be expected, this group is tasked with exploring issues in more in-depth detail than is possible for ACIP members as a whole. The Influenza Working Group must have two voting members and has limitations on the extent to which vaccine manufacturers can participate. As of February 2012, the Influenza Working Group had 50 members, including 4 current ACIP members, 2 former ACIP members, 18 liaison members, 20 CDC staff members, 4 FDA staff members, and 2 staff members from HHS.[14]

As a result of its status as a federal advisory committee and the wide-ranging input that occurs from so many organizations, the ACIP serves as the preeminent US voice on the use of vaccines. In addition, the annual ACIP statement for prevention and control of influenza is viewed worldwide as a primary guidance document.

Hundreds of international, national, and local public health and medical information sources print the ACIP statements verbatim, and they are often considered the standard of practice for influenza vaccine use not only in the United States but around the globe. Today the 2010 ACIP statement, which is 62 pages, serves as the current comprehensive overview on the topic.[9] The 2011 ACIP influenza statement provided only updated information on the 2011-12 vaccine antigen composition, made a few minor clarifications, and referred to the 2010 statement as the standing current recommendations.

EVOLUTION OF ACIP INFLUENZA VACCINE RECOMMENDATIONS

Since the ACIP assumed responsibility for the promulgation of influenza vaccine recommendations in 1964, it has engaged in two broad categories of activities. The primary activity of the ACIP is to determine persons who are recommended to receive annual vaccination by dose and type of vaccine. In addition, in the early years of the ACIP, the committee also recommended changes in vaccine antigen composition, antigen concentration, or type of vaccine.

Determining Who Is Recommended to Receive Annual Vaccination

From 1964 to 1984, categories of persons recommended for influenza vaccination remained largely unchanged and focused primarily on persons at high risk for complications from influenza (see Table 2-2, Chapter 2).

In the early 1980s, however, a conceptual shift in the approach toward influenza vaccination occurred following recognition of inconsistent vaccine effectiveness and an acknowledgment of indirect benefits from vaccination. Prior to 1981, field studies demonstrated "mixed results" for what was described as vaccine efficacy (consistent with current effectiveness studies). In 1981, the ACIP in its annual influenza vaccine statement noted the following:

> *"Field studies of influenza vaccines conducted on many occasions since the 1940s have shown marked variation in vaccine efficacy, ranging from undemonstrable to 70%-80%. The general explanation for these findings has been the relative 'match' between vaccine-antigens, necessarily selected almost a year in advance, and the viruses ultimately causing disease—an example of antigen drift. In recent years, titers of antibody induced by vaccines were sometimes low with respect to strains which become prevalent—one explanation for the lower-than-expected vaccine effectiveness sometimes observed. One way to improve vaccine effectiveness against viruses that have undergone some antigen drift is to increase the concentration of related antigens in the vaccine. This increases antibody levels not only against vaccine strains but also against related strains."*[15]

For this reason, the ACIP recommended that the antigen potency of influenza vaccines for the 1981-82 influenza season be doubled from 7 mcg to 15 mcg. Of note, the ACIP did not base this decision on actual effectiveness data comparing the two vaccine dosages, because such data were not available. Rather, it was based on limited laboratory data demonstrating increased HAI responses with the use of the higher-dosage vaccines.

At that time, the potential indirect benefit of influenza vaccination was acknowledged. This concept implies that the person being vaccinated is not doing so only to protect himself or herself but also to minimize the risk of transmitting influenza to others. In 1981, vaccination of healthcare workers was initially proposed, and in 1984, this group was added to the list of persons for whom influenza vaccination was recommended. This change was made primarily to benefit patients, not necessarily healthcare workers.[16] In 1986, the ACIP further expanded on the concept of the indirect benefit of vaccination by including contacts of individuals at high risk of serious illness or death from influenza. This recommendation stated that, given the substantial disease burden among high-risk groups, the indirect benefits of vaccination were justified, even though studies had not been conducted to demonstrate this benefit.[17]

Beginning in 1999, another shift occurred in the influenza vaccination paradigm. This decade and through 2010 saw the population recommended for annual vaccination grow from 185 million to a universal recommendation targeting the entire US population 6 months of age and older (see Table 2-2, Chapter 2). These changes were primarily made to increase

population coverage rates, bolster indirect benefits, and improve outcomes indirectly related to morbidity, such as antibiotic use for secondary infections or work absenteeism linked to ILI.

During this time, ACIP members and others in public health held a general consensus that if influenza vaccine was administered to more people, regardless of risk status, influenza morbidity and mortality would significantly decrease in the United States. This assumption was based, in part, on a belief that high immunization rates would provide enough herd immunity to protect those at greatest risk of complications, even if such persons remained unvaccinated or unprotected by the vaccine (as discussed in Chapter 3). The paragraphs below explore the ACIP's process for moving toward a universal vaccination policy.

A REVIEW OF ACIP PROMULGATION OF INFLUENZA VACCINE RECOMMENDATIONS

As part of the CCIVI project, we completed a comprehensive review of the role of the ACIP in expanding influenza vaccine recommendations. We reviewed in detail each ACIP statement on influenza vaccination from 1964 to 2011 and the minutes of each ACIP meeting from 1997 to 2011, when there were extensive changes to the recommendations. We also conducted interviews regarding the ACIP recommendation process with members, ex officio members, and liaison representatives who served in their respective roles from the early 1970s to 2011.

Incremental Expansions of Recommendations: The Role of Advocacy and the Power of Consensus

A systematic review of the ACIP minutes and statements revealed that two factors were apparently instrumental in shaping public health policies on influenza vaccination over the years. First, there was a strong desire on the part of the ACIP membership to prevent influenza-associated morbidity and mortality. Second, there was a growing sense of disappointment over the inability to vaccinate more Americans who were most at risk of influenza-related complications and over the lack of impact that vaccination was having on the overall influenza disease burden in the United States. The incremental expansion of annual influenza vaccination recommendations was a logical effort to address these issues. However, as with earlier public policy decision making, scientific data to support such changes were often not available. Rather, changes were made at least in part on the basis of expert and organizational professional opinions, with the strong belief that such changes would decrease the overall burden of influenza in the United States.

For example, the ACIP states, "published, peer-reviewed studies are the primary source of data used by ACIP in making recommendations."[9] While this may be an accurate statement overall, our review supports that the movement toward a universal recommendation for vaccination did not occur primarily as a result of a preponderance of newly published evidence or a reanalysis of older evidence using more modern science approaches. On average, for each of the years between 1999 and 2010 during which an expansion of the vaccine recommendations occurred, approximately 20% of references were newly added to each report (range, 8% to 35%).[9,18-28] We found that a number of the new references cited to support the revised recommendations were actually unrelated to specific aspects of the new recommendations and did not present findings from new studies. For example, the 2000 ACIP statement had 77 new references, 22 of which were potentially related to vaccination. Of those 22, only unpublished data from the CDC and a 5-year-old recommendation from the National Vaccine Advisory Committee (NVAC) were used to justify the new position of recommending vaccination for everyone over the age of 50.[19,29]

In addition to reviewing scientific data, the ACIP meeting agendas often included conclusions or statements of expert groups. When the ACIP discussed the issue of expanding the recommendations for annual influenza vaccination, these discussions typically occurred in the context of a presentation from a government agency or professional group to the voting members of the ACIP. These often were provided by organizations such as the CDC, the National Vaccine Program Office, the American Medical Association, the Council of State and Territorial Epidemiologists, and the National Foundation for Infectious Diseases (NFID).[12,30-51] The group to present to the ACIP most often was the ACIP Influenza Working Group.

From October 2005 to October 2008, the Influenza Working Group identified several issues around gaps in knowledge for expanding influenza vaccination recommendations. In October 2005, the gaps identified included: (1) vaccine effectiveness in persons 65 and older, (2) indirect benefits of vaccination of persons not at increased risk of complications, (3) cost-effectiveness of vaccination strategies, and (4) safety of repeated vaccination.[36] A statement from the Influenza Working Group in the June 2006 minutes says, "Several critical factors must be assessed before changing current recommendations and advancing toward a universal policy."[47] It is clear that for a significant part of the decade, there was uncertainty among committee members as to the scientific basis for moving toward a universal recommendation for influenza vaccination.

Our review of the ACIP documents found that no data were presented at ACIP meetings or in other records from 1999 to 2011 that addressed the gaps in knowledge noted above before recommendations expanded to include universal vaccination. However, even though data to address these concerns were generally not available, the ACIP gradually developed a consensus that a universal vaccination policy would be beneficial to the public's health. In October 2007, the summary of the ACIP Influenza Working Group stated, "No one in the group felt there were critical data gaps" against moving toward the universal vaccination recommendation.[42] The minutes of the ACIP meetings suggest that the ACIP moved toward a recommendation for universal vaccination on the basis of professional opinions from supporters of the approach, rather than on compelling data, and on the gradual development of a consensus among members that this was the appropriate proactive strategy for decreasing influenza morbidity and mortality. Again, this approach is consistent with earlier patterns for developing influenza vaccination policy.

Critical Review of the 2010 ACIP Statement on Influenza Regarding Vaccine Efficacy and Effectiveness

As a result of our efforts to define the efficacy and effectiveness of the currently licensed influenza vaccines in the United States (see Chapter 3), we realized that influenza vaccine performance has been significantly overstated in the scientific literature. To understand how this issue affected the ACIP recommendation process and its subsequent recommendations for influenza vaccine use, we conducted a critical, comprehensive, and systematic review of the sections of the 2010 ACIP statement pertaining to efficacy and effectiveness of the influenza vaccines. All references cited in these sections were reviewed in detail by CCIVI researchers, and the ACIP statement was then compared with the literature cited.

Our review identified 30 instances in which the authors of the current ACIP influenza vaccine statement did not apply current standards of scientific rigor to their analysis or did not cite relevant work. As a result, the ACIP statement overestimates influenza vaccine efficacy and effectiveness. For example, we found the inclusion of references supporting the use of current vaccines that were based on studies of influenza vaccines not comparable to current vaccines (eg, HA concentration not reported in micrograms or at levels other than 15 mcg), and these citations were not identified as such. In addition, some studies cited by the ACIP combined multiple influenza seasons into a single estimate for vaccine efficacy and effectiveness, despite the use of different vaccines each year.

We also noted that methods and standards for laboratory confirmation of influenza varied greatly among the studies cited, from confirmation via rapid tests to confirmation via RT-PCR. No distinctions were made to examine the data by sensitivity and specificity of the tests used to confirm infection. For example, including HAI serology as an outcome end point for infection overestimates TIV vaccine efficacy and effectiveness, as we discussed in detail in Chapter 3.

Finally, the ACIP statement includes studies in which the results were not reported accurately. For example, the 2010 ACIP guidance document states, "When the vaccine and circulating viruses are antigenically similar, TIV prevents laboratory-confirmed influenza illness among approximately 70% to 90% of healthy adults aged <65 years in randomized controlled trials."[9] Five references were provided in the ACIP document to support this statement. Two referenced studies did not include laboratory confirmation for illness,[52,53] one is a review (which included the other studies that were cited),[54] one reported 2 years of outcomes, but one

year's results did not support the ACIP statement,[55] and one was included in our recent *Lancet Infectious Diseases* review of influenza vaccine efficacy and effectiveness, reporting efficacy of 68% for RT-PCR and culture-confirmed illness; these results come very close to meeting the ACIP mark of at least 70% efficacy.[56] In this study, though, all the participants were under the age of 49, with a mean age of 23.2.[56] Only one study reported laboratory-confirmed data that actually support the ACIP criteria[55]; however, this study did not fit the criteria for inclusion in our *Lancet Infectious Diseases* review, as laboratory confirmation was a fourfold rise in HAI antibody titer between acute and convalescent serum samples. Two studies included in our recent *Lancet Infectious Diseases* review of influenza vaccine efficacy and effectiveness fit the criteria for this ACIP statement and were publicly available at the time the draft recommendations were being written but were not included in the final ACIP statement.[57,58] Both of these studies reported influenza vaccine efficacies below 70%.

ACIP and an Evidence-Based Framework Using GRADE Criteria

The ACIP is transitioning its recommendations to a new evidence-based framework based on the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluation).[59] The ACIP handbook for developing evidence-based recommendations highlights the five criteria for assessing limitations to studies and adjusting their evidence level according to the GRADE criteria.[60] The assessment of study limitations is based on criteria established by the Cochrane Collaboration that focus on several key issues that can affect the quality of a study. Currently the ACIP Influenza Working Group is implementing the GRADE criteria for recommendations pertaining to prevention of influenza in young children through vaccination.[61] This process may be a significant improvement over the current recommendation process, as the strength of the evidence for the recommendations will be clear. However, a recent review of the evidence using the GRADE criteria continued to include studies using serology as a laboratory-confirmed outcome in persons vaccinated with TIV.[62] As we have pointed out, this methodology does not lead to an accurate assessment of vaccine efficacy and effectiveness. Without broad consensus regarding methodologic and diagnostic issues in evaluating influenza vaccine efficacy and effectiveness studies, consistency in applying the GRADE criteria to influenza vaccines will be lacking.

The 2006 statement on influenza vaccination of healthcare personnel (HCP) from the Healthcare Infection Control Practices Advisory Committee (HICPAC) and ACIP illustrates potential concerns with using a grading scale.[63] This recommendation used the HICPAC grading scale, which is similar to the GRADE criteria in that it provides a structure for ranking the evidence. All recommendations were approved by the HICPAC and the ACIP. This document has been used widely as evidence to support HCP vaccination policies, including mandating vaccination. It offers six recommendations, and one was deemed to have the highest possible evidence, category IA. Category IA recommendations are "strongly supported by well-designed experimental, clinical, or epidemiological studies."[63] The recommendation in the HICPAC document that received a category IA rating states:

> *"Offer influenza vaccine annually to all eligible HCP to protect staff, patients, and family members and to decrease HCP absenteeism. Use of either available vaccine (inactivated and live, attenuated influenza vaccine [LAIV]) is recommended for eligible persons. During periods when inactivated vaccine is in short supply, use of LAIV is especially encouraged when feasible for eligible HCP."*[63]

This recommendation is supported in part by this key summary statement in the HICPAC document: "Vaccination of HCP reduces transmission of influenza in healthcare settings, staff illness and absenteeism, and influenza-related morbidity and mortality among persons at increased risk for severe influenza illness.[64-67]" In the first study cited, the authors did not find a statistically significant reduction in patient mortality associated with HCP vaccination, after adjusting for covariates.[64] In the second study, the authors concluded that "we do not have any direct evidence that the reductions in rates of patient mortality and influenza-like illness that were associated with HCW vaccination were due to prevention of influenza."[65] In the third study, vaccination did not reduce the episodes of self-reported respiratory infection or the number of days ill with a respiratory infection, but it did reduce the time employees were

unable to work because of a respiratory infection.[66] In the fourth study, the authors reported reductions in absenteeism and illness among HCP that were not statistically significant.[67] The authors did, however, report serologically confirmed vaccine effectiveness of 88% for H3N2 and 89% for influenza B across three influenza seasons.[67]

Since only two of the four studies cited provide some support for the HICPAC statement and the others no support, it is unclear how the quality of evidence in these studies received a category IA evidence grade. Another review conducted in the same time frame by the Cochrane Collaboration noted that the two RCTs cited in this recommendation were at "moderate risk of bias."[68] They concluded that "both elderly people in institutions and the healthcare workers who care for them could be vaccinated for their own protection, but an incremental benefit of vaccinating healthcare workers for elderly people has yet to be proven in well-controlled clinical trials."[68]

In summary, the above example illustrates that the use of evidence-based recommendations by the ACIP will not necessarily support the strength of the actual evidence unless the criteria used are clarified and agreed upon by study design experts. Furthermore, standards are needed for evaluating the evidence beyond the GRADE criteria for influenza vaccine studies. Such standards should take into account variables such as diagnostic tests used to confirm influenza infection, study design, and potential for bias.

HEALTH PROMOTION ACTIVITIES RELATED TO INFLUENZA VACCINE USE

As we reviewed in Chapter 3, seasonal influenza is an important public health and medical challenge. In addition, pandemic influenza could cause a substantial burden of disease and seriously threaten the global economy. Given a track record of substantial safety and moderate efficacy in many seasons, the current influenza vaccines will continue to have an important role in reducing influenza morbidity until more effective interventions are available. Therefore, it is highly appropriate and necessary for public health agencies; medical, nursing, and pharmacy organizations; patient-advocacy groups; and health insurance payers to promote the use of current influenza vaccines to reduce influenza-related morbidity and mortality.

Health promotion is defined as the process of enabling people to increase control over, and to improve, their health.[69] Health promotion moves beyond a focus on individual behavior toward a wide range of social and environmental interventions. Over the past decade, the promotion of influenza vaccination represents one of the most comprehensive and proactive health promotion activities in the United States. It is strongly supported by federal, state, and local public health agencies; medical, nursing, and pharmacy organizations; patient-advocacy groups; and health insurance payers.

US Federal Government Promotion Activities

The US federal government's investment in influenza vaccine promotion is substantial. For example, the only Web site maintained by HHS for a vaccine-preventable disease (www.flu.gov) is for influenza. The following departments and HHS agencies serve as partners in maintaining the www.flu.gov Web site: the Department of Education, the Department of Homeland Security, the Federal Trade Commission, the CDC, the National Institutes of Health (NIH), and the FDA. While the Web site serves as a central source for influenza content from the above departments and agencies, it has a primary focus of promoting influenza vaccination. In addition, the CDC maintains a Web site for influenza (http://www.cdc.gov/flu/index.htm). This site contains extensive information on the basics of influenza infection, prevention and vaccine, treatment and antivirals, information for health professionals, vaccine promotional materials that can be downloaded, and a "pledge page" on which individuals can sign a pledge to get vaccinated.

HHS also supports an annual National Influenza Vaccination Week (NIVW), an observance that was established to highlight the importance of annual influenza vaccination (http://www.cdc.gov/flu/nivw/index.htm). It is usually held in late fall each year to promote seasonal influenza vaccination. The most recent NIVW was December 4 through 10, 2011. More than 140 state and local public health agencies, professional organizations, businesses, and other influenza-vaccine advocacy groups held

vaccine-promotion events or provided their members, employees, customers, or contacts with promotional materials supporting influenza vaccination. As part of NIVW, the CDC widely disseminated a 23-page CDC Influenza Awareness Campaign Media Relations Toolkit to all of the above-noted partners; this is also posted on the CDC Web site. The primary purpose of the toolkit is to enlist all of the vaccination-promotion partners in a local and state media-driven campaign to "get people vaccinated."[70]

As part of the CCIVI project, we completed an extensive review of federal promotion materials for messaging regarding vaccine efficacy and effectiveness. We found that materials through mid-2011 consistently reflected the overstatement of vaccine efficacy and effectiveness found in the ACIP statements reviewed above. For example, we identified numerous statements on Web-based and printed materials indicating that influenza vaccine prevents laboratory-confirmed influenza illness among approximately 70% to 90% of healthy adults younger than 65 years of age in randomized controlled trials.

Beginning in mid-2011, the CDC began to revise its vaccine efficacy and effectiveness statements to be more accurate. CDC materials, however, remain inconsistent with regard to measuring and reporting influenza vaccine efficacy and effectiveness. For example, a question-and-answer document from October 2011 notes the problems with determining vaccine efficacy and effectiveness when using serology to determine infection status in persons vaccinated with TIV, but in the very next paragraph it reports the vaccine efficacy for a study that used serology to determine infection status.[71]

In another example, the CDC National Center for Chronic Disease Prevention and Health Promotion sent an e-mail on November 18, 2011, to thousands of US healthcare providers titled, "Diabetes and the Flu: What Can I Do?" It urged healthcare providers to get all diabetic patients vaccinated, as they are three times more likely to be hospitalized or to die from influenza than persons without diabetes. The e-mail states, "Get a flu shot every year! It's the single best way to protect yourself against the flu, reducing the risk of getting flu by about 80%."

Since mid-2011, we have found that CDC documents on influenza vaccination more frequently do not provide estimates of vaccine effectiveness and efficacy. Instead, blanket statements about vaccine protection have become more common. For example, in the 2011 CDC media toolkit, the only reference to vaccine performance is the statement, "The 2011-2012 flu vaccine will protect against an influenza A(H1N1) virus, an influenza A(H3N2), and an influenza B virus."[70] We believe that the general public will generally interpret this type of statement to imply the vaccine will protect "most of the time."

Recently, the CDC was criticized by risk communication experts and a state public health official (ACIP member) for the manner in which the agency has overstated influenza vaccine efficacy to the public.[72] One national expert in risk communication has raised concerns that the public will lose confidence in the influenza vaccination establishment, and public health in general, if they perceive that influenza vaccine effectiveness studies have not been accurately represented.[72]

Other Promotion Activities

State and local public health agencies; medical, nursing, and pharmacy organizations; patient-advocacy groups; and health insurance payers also provide extensive influenza vaccination promotional materials to health professionals and the general public. In addition, many vaccine-promotion activities are supported by these agencies, organizations, and businesses. We identified more than 45 US nongovernmental organizations that take an active role in promoting influenza vaccination.

For example, the NFID, a nonprofit organization dedicated to educating the public and healthcare professionals about the causes, treatment, and prevention of infectious diseases, started a campaign in 2011 called "Leading by Example: An NFID Commitment to Influenza Prevention."[73] This new initiative calls on community leaders in healthcare, business, education, and policy to "lead by example" through making a commitment to influenza prevention. It challenges healthcare professionals, employers, school administrators, insurers, and legislators to support annual influenza vaccination practice and policy, making it a national health

priority. Other supporters of this initiative include the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Pharmacists Association, the Johns Hopkins Hospital, the National Association of Pediatric Nurse Practitioners, the National Association of School Nurses, the National Influenza Vaccine Summit, the National Medical Association, and the Vaccine Education Center at the Children's Hospital of Philadelphia. This initiative is just one example of a number of similar efforts in the United States to promote influenza vaccination.

The messaging by these organizations regarding influenza vaccine efficacy and effectiveness mirrors the issues detailed above for federal agencies. Of note, when our *Lancet Infectious Diseases* findings were released in October 2011, many members of these same organizations were interviewed by the media regarding the results. While some spokespersons indicated the study supported the need to reconsider and possibly revise conclusions regarding the efficacy and effectiveness of influenza vaccines for health professionals and the general public, others publicly minimized the results for a variety of non-science–based reasons.

SUMMARY

A major finding from our review is that, since influenza vaccination programs were first implemented in the United States in the 1940s, influenza vaccination policies often have been developed with a strong intention to protect the population against influenza, but without compelling and scientifically sound data to support them. This was acknowledged in 1960, when influenza vaccine was recommended for certain high-risk populations. This was also acknowledged in the 1980s, when the concept of indirect benefit was introduced and implemented, even though limited information was available to support the strategy. Finally, various decisions from 1999 to 2010 to expand the groups for whom vaccine is recommended were at times made by the ACIP on the basis of group consensus and professional opinions from participating organizations, most notably the CDC, rather than on the body of scientific evidence. While we believe the US government, and later the ACIP, had the best interest of the public's health as a priority in promulgating recommendations regarding influenza vaccination, we also believe it's important for those making the recommendations to clearly communicate their approach and acknowledge gaps or discrepancies in available data.

A second major finding from our review is that public policy makers have not always used state-of-the-art scientific data to make recommendations. Over the years, the scientific methodology for assessing influenza efficacy and effectiveness has evolved and standards have changed (such as the use of RT-PCR to document influenza infection in clinical studies); this has not been taken into account consistently by policy makers. Applying rigorous scientific methodology to this issue clearly shows that current influenza vaccines do not offer the level of protection necessary to significantly lessen influenza morbidity and mortality. In fact, despite significant increases in influenza vaccine coverage for those over 65 years of age since the late 1990s, a minimal impact on influenza morbidity and mortality has been noted in this country (see Chapter 3). Furthermore, influenza vaccination research has shown that this is a very complicated topic and that it is difficult to make general statements on the basis of the existing scientific data.

A third major finding is that federal policy documents and statements have overestimated the effectiveness of current influenza vaccines. We believe this is problematic for two reasons. First, overestimating vaccine effectiveness may cause the public to lose faith in vaccination recommendations. Second, if the current vaccines are considered to offer an acceptable level of protection, then little incentive exists for research and development companies and manufacturers to generate new and improved vaccines that could have a significant impact on the influenza disease burden. Overestimating current efficacy and effectiveness, therefore, can be an important barrier toward generation of improved vaccines. Recognizing the limitations of current vaccines and acknowledging that we can do better need to be important aspects of the public policy debate on influenza vaccines.

Even though influenza vaccine efficacy and effectiveness have been overestimated, available data support that in some populations influenza vaccination offers a moderate level of protection.

Therefore, we believe that influenza vaccination is an important health promotion activity that should be widely encouraged and supported. We can and should maintain this infrastructure and use the best technology currently available (ie, existing influenza vaccines) to protect the public's health to the degree possible. However, we cannot allow this approach to stifle public policy makers from moving the influenza vaccine enterprise forward toward game-changing vaccines.

REFERENCES

1. Hinman AR, Orenstein WA, Schuchat A. Vaccine-preventable diseases, immunizations, and MMWR—1961-2011. *MMWR* 2011;60(suppl):49-57
2. Meiklejon G. Commission on influenza. In: Woodward T, ed. *The Histories of the Commissions*. Falls Church, VA: The Borden Institute, Office of the Surgeon General, Department of the Army, 1994
3. Hale WM, Mckee AP. The value of influenza vaccination when done at the beginning of an epidemic. *Am J Hyg* 1945;42(1):21-7
4. Francis TJ. Influenza. In. Coates, JB, ed. *Preventive Medicine in WWII*, Volume IV, Communicable Diseases, transmitted chiefly through respiratory and alimentary tracts. Washington, DC: Office of the Surgeon General, Department of the Army, 1958
5. Williams MS, Wood JM. A brief history of inactivated influenza vaccines. In: *Options for the Control of Influenza II*. Elsevier Science Publishers; 1993:169-70
6. Burney LE. Influenza immunization: statement. *Public Health Rep* 1960;75(10):944
7. Langmuir AD, Henderson DA, Serfling RE. The epidemiological basis for the control of influenza. *Am J Public Health* 1964;54(4):563-71
8. Anonymous. Federal Advisory Committee Act. 1972. Available at: http://www.gsa.gov/graphics/ogp/FACALegislationHistory1972.pdf
9. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62
10. HHS. *Charter: Advisory Committee on Immunization Practices*. 2012. Available at: http://www.cdc.gov/vaccines/acip/committee/charter.html
11. HHS, CDC, AAP, AAFP. *The Advisory Committee on Immunization Practices*. 2011. Available at: http://www.cdc.gov/vaccines/spec-grps/hcp/downloads/vacsafe-acip-color-office.pdf
12. Smith JC. The structure, role, and procedures of the U.S. Advisory Committee on Immunization Practices (ACIP). *Vaccine* 2010;28(suppl 1):A68-75
13. HHS. Immunization and infectious disease. 2012. Available at: http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=23
14. Keitel W. Influenza workgroup: introduction. 2012. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-feb-2012/01-influenza-keitel.pdf
15. CDC. Recommendations of the Public Health Service Immunization Practices Advisory Committee: influenza vaccine 1981-1982. *MMWR* 1981;30(23):279-82
16. CDC. Recommendation of the Immunization Practices Advisory Committee (ACIP) prevention and control of influenza. *MMWR* 1984;33(19):253-60,65-6
17. CDC. Recommendations of the Immunization Practices Advisory Committee prevention and control of influenza. *MMWR* 1986;35(20): 317-26, 31
18. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 1999;48(RR04): 1-28
19. Bridges CB, Winquist AG, Fukuda K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; 49(RR-3):1-38
20. Bridges CB, Fukuda K, Cox NJ, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2001;50(RR-4):1-44
21. Bridges CB, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2002;51(RR-3):1-31
22. Bridges CB, Harper SA, Fukuda K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2003;52(RR-8):1-36

23. Harper SA, Fukuda K, Uyeki TM et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2004;53(RR-10):1-40

24. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2005;54(RR-8):1-40

25. Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-10):1-42

26. Fiore AE, Shay DK, Haber P, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices, 2007. *MMWR* 2007;56(RR06):1-54

27. Fiore AE, Shay DK, Broder K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2008;57(RR-7):1-60

28. Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2009;58(RR-8):1-52

29. CDC. Notice to readers assessing adult vaccination status at age 50 years. *MMWR* 1995;44(29):561-3

30. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: June 29-30, 2005. 2005. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun05.pdf

31. ACIP. Summary report: February 27-28, 2008. 2008. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb08.pdf

32. ACIP. Summary report: June 23-24, 2010. 2010. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun10.pdf

33. ACIP. Summary report: July 29, 2009. 2009. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jul09.pdf

34. ACIP. Summary report: June 24-26, 2009. 2009. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun09.pdf

35. ACIP. Summary report: February 25-26, 2009. 2009. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb09.pdf

36. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: October 26-27, 2005. 2005. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct05.pdf

37. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: February 10-11, 2005. 2005. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb05.pdf

38. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: February 21-22, 2006. 2006. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb06.pdf

39. ACIP. Record of the proceedings: June 27-28, 2007. 2007. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun07.pdf

40. ACIP. Summary report: February 24-25, 2010. 2010. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb10.pdf

41. ACIP. Summary report: October 21-22, 2009. 2009. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct09.txt

42. ACIP. Record of the proceedings: October 24-25, 2007. 2007. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct07.pdf

43. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: October 27-28, 2004. 2004. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct04.pdf

44. ACIP. Summary report: August 5, 2010. 2010. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-aug10.pdf

45. ACIP. Summary report: October 22-23, 2008. 2008. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-oct08.pdf

46. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: February 24-25, 2004. 2004. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb04.pdf

47. ACIP. Record of the proceedings: June 29-30, 2006. 2006. Available at: http://www.cdc.gov/vaccines/

acip/meetings/downloads/min-archive/min-jun06.pdf
48. ACIP. Record of the proceedings: October 25-26, 2006. 2006. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun06.pdf
49. ACIP. Summary report: June 25-26, 2008. 2008. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun07.pdf
50. ACIP. Record of the proceedings: February 21-22, 2007. 2007. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb07.pdf
51. ACIP. Record of the meeting of the Advisory Committee on Immunization Practices: June 23-24, 2004. 2004. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun04.pdf
52. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy, working-age population. *J Occup Environ Med* 1997;39(5):408-14
53. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med* 1995;333(14):889-93
54. Demicheli V, Pietrantonj C, Jefferson T, et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2009;(3):1-112
55. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA* 2000;284(13):1655-63
56. Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009;361:1260-7
57. Jackson LA, Gaglani MJ, Keyserling HL, et al. Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. *BMC Infect Dis* 2010;10:71
58. Beran J, Vesikari T, Wertzova V, et al. Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. *Vaccine* 2009;200(12):1861-9
59. Ahmed F, Temte JL, Campos-Outcalt D, et al. Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine* 2011;29(49):9171-6
60. Ahmed F. US Advisory Committee on Immunization Practices (ACIP) handbook for developing evidence-based recommendations. March 1, 2012. Available at: http://www.cdc.gov/vaccines/acip/recs/GRADE/downloads/handbook.pdf
61. Keitel W. Influenza workgroup: introduction. 2011. Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-oct-2011/01-influenza-keitel.pdf
62. Michiels B, Govaerts F, Remmen R, et al. A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. *Vaccine* 2011;29(49):9159-70
63. Pearson M, Bridges C, Harper S, et al. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-2):1-16
64. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;355(9198):93-7
65. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 1997;175(1):1-6
66. Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatr Infect Dis* 1999;18(9):779-83
67. Wilde JA, McMillan JA, Serwint J, et al. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA* 1999;281(10):908-13
68. Thomas RE, Jefferson TO, Demicheli V, et al. Influenza vaccination for health-care workers who work with elderly people in institutions: a systematic review. *Lancet Infect Dis* 2006;6:273-9
69. WHO. Health promotion. 2012. Available at: http://www.who.int/topics/health_promotion/en/

70. CDC. CDC influenza awareness campaign: media relations toolkit. 2011. Available at: http://www.cdc.gov/flu/pdf/nivw/nivw_media_toolkit_112011.pdf
71. CDC. Flu vaccine effectiveness: questions and answer for health professionals Oct 12, 2011. Available at: http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm
72. Roos R. Flu vaccine efficacy: time to revise public messages? CIDRAP News. Nov 4, 2011.Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/general/news/nov0411messages.html
73. National Foundation for Infectious Disease. Leading by example: an NFID commitment to influenza. 2011. Available at: http://www.nfid.org/influenza/leadingbyexample

CHAPTER 8

INFLUENZA IMMUNOLOGY: INFECTION, CURRENT VACCINES, AND NEW DEVELOPMENTS

INTRODUCTION

Investigators have researched the immune response to influenza virus infection for more than 70 years[1] but until recently have had a limited understanding of the immunology involved. For many years, the prevailing theory has been that, upon infection, individuals mount innate and adaptive immune responses, culminating in the activation of cytotoxic T cells (CTLs) (which eliminate virally infected cells and clear the infection) and B cells (which secrete antibodies that play a role in resistance to re-infection by the same viral strain). Historically, researchers have measured the ability to induce circulating antibodies specific to the influenza HA antigen head as the primary correlate for vaccine protection. Today, our understanding of the influenza infection–related immune response continues to evolve in light of new insights into the immune system, new tools to explore complex and detailed molecular processes, and the ongoing discovery of cellular subsets, receptors, and the interconnected pathways of this immune response. As this information is used to develop innovative strategies for vaccine development, new correlates for vaccine protection also will be needed.

THE IMMUNE RESPONSE TO NATURAL INFECTION WITH INFLUENZA

When an influenza virus infects a host cell, it subverts the host cell's normal function and resets the cell to make more viral particles, essentially turning the cell into a virus-generating factory.[2] This infection initiates a cascade of events within the host that activate the immune system. The human immune system has two main components, the innate and adaptive responses.

Innate Immunity

Initially, infection with influenza virus mobilizes a series of responses from the nonspecific, innate immune system; these provide the first line of defense through a rapid, immediate response to the pathogen. Invading viruses are detected by cells via toll-like receptors (TLRs) that recognize viral RNA.[3,4] This initial response is activated by signals detected from the virus and by "distress signals" sent out from the infected cells. The innate response attempts to limit viral replication and spread until an adaptive response can be activated to eliminate the viruses.[5]

The primary cells of innate immunity against influenza infection are natural killer (NK) cells, neutrophils, and macrophages. NK cells can be detected in the lung as early as 48 hours after infection, providing protection via direct cytotoxicity of virally infected cells and

the production of antiviral cytokines.[6,7] Neutrophils work to limit viral replication through secretion of an array of proinflammatory mediators, while alveolar macrophages recognize and engulf virally infected cells, thereby limiting viral spread.[8,9] Macrophages serve additional roles of communicating to other cells, particularly antigen-specific T cells, and regulating the immune response.[10]

The innate immune system can detect and destroy pathogens but lacks the ability to recognize and remember specific pathogens. However, through initial responses to infection, innate immune cells activate the adaptive response, which is responsible for pathogen-specific responses. Adaptive immunity refers to antigen-specific mechanisms that take several days to become active but retain the ability to remember and respond to future challenges from the same initial pathogen.

Adaptive Immunity

Adaptive immunity has two major branches, humoral immunity and cell-mediated immunity. Humoral immunity is mediated by B cells and involves the production of antibodies in response to a specific antigen. Cell-mediated immunity is mediated by T cells and involves the production of CTLs, activated macrophages, activated NK cells, and cytokines in response to an antigen. When stimulated appropriately during a primary exposure to a pathogen, both B cells and T cells are able to generate memory toward that specific pathogen, allowing for a faster, more effective immune response upon rechallenge with the same pathogen.

Overall, the adaptive immune response involves a complex series of interactions between functionally different varieties of cells, including antigen-specific $CD4^+$ helper T cells (Th cells), $CD8^+$ CTLs, and antibody-secreting B cells. Upon infection with influenza, Th cells are activated after recognizing viral antigens present on the surface of antigen-presenting cells (APCs). While Th cells do not normally eliminate viruses, they orchestrate the immune response by providing the signals necessary for optimal activation of CTLs and B cells, and are critical for the establishment of CTL memory cells.[3] Furthermore, it has been suggested that Th cells also can directly attack virally infected cells.[11]

Virus-specific $CD8^+$ CTLs, which are a second subset of T cells, are activated in lymphoid tissue and recruited to the site of infection, where they recognize and eliminate virally infected cells. After the infection is cleared, CTLs are found in lymphoid tissue and in the bloodstream. These memory CTLs can respond to subsequent influenza infection; the reactivity of memory CTLs depends on co-stimulation that they received from the APCs during initial activation and differentiation.[3,12]

In concert with cellular immune responses, infection with influenza virus induces humoral immunity through an influenza-specific antibody response. Antibody production is directed toward proteins present on the surface of the influenza virus, most frequently the outermost portion of the HA protein called the head, which mutates frequently.[13,14] Antibodies also are produced that recognize NA and other proteins but are produced in much smaller quantities.[15,16] Recent studies have documented antibodies that are produced against a highly conserved region of the HA-stalk domain of the virus that can bind across multiple subtypes of influenza.[17–19]

Antibodies produced against the HA head inhibit viral attachment to host cells, thereby blocking viral binding and entry, while antibodies produced against NA limit the release and spread of newly formed virus particles from infected cells. Antibodies that bind to the HA stalk block fusion of the virus to the host cell membrane, limiting the ability of the virus to invade host cells. Antibodies to nucleoprotein (NP), an important target for T cell immunity, also may contribute to protection, although the exact mechanism remains unclear.[20] Additionally, antibodies facilitate phagocytosis of viral particles, as well as other processes that lead to clearance of virally infected cells.

Unlike the immune response to many other viral infections, an immune response to influenza virus does not induce lifelong, broadly protective immunity against future infection. However, induction of antibodies can afford strain-specific protection, and this strain-specific immunity can be very long lasting.[21] This was demonstrated by the observation that a substantial proportion of the population over 65 had immunologic protection against the 2009 A(H1N1)pdm09 influenza

virus, most likely as a result of remote exposure to a similar virus before 1957.[22–24]

IMMUNE RESPONSE TO INFLUENZA VACCINATION

Trivalent Inactivated Vaccine

TIVs are delivered primarily via intramuscular injection, where they stimulate an initial, limited, innate immune response. Unlike natural infection, which stimulates multiple components of the immune system, resulting in both humoral and cell-mediated responses, currently licensed TIVs primarily stimulate humoral responses. This provides limited protective immunity in the upper respiratory tract, where the infectious process begins.[12,14,25] Currently licensed TIVs and other influenza vaccines, whether produced in eggs or using other platforms, including recombinant technology, all primarily induce antibodies to the globular head of HA and, depending on formulation, NA. These antibodies are strain-specific and are not effective in combating the yearly variants of the virus or emergent novel subtypes.[26]

Because antigens in TIV formulations do not infect cells, only partial activation of cellular immunity occurs. While HA- and NA-specific Th cell responses are induced following both natural infection and vaccination with TIV and are required for effective antibody responses, very few virus-specific $CD8^+$ T cells are directed against HA and NA, even in natural infection.[27,28] Therefore, vaccines composed solely of purified HA and NA antigens fail to induce strong anti-influenza CTL responses.[27,28] And while evidence exists for some limited cross-subtype immunity following natural infection,[29] no evidence demonstrates that current inactivated vaccines confer such protection.[30]

Live-Attenuated Influenza Vaccine

Owing to limitations associated with TIV, LAIV was developed with the goal of producing a vaccine that more closely mimics natural infection, with broader and more durable immunity. Since LAIV involves live replicating viruses, this vaccine has the potential to more completely engage innate and cellular immune mechanisms, leading to a more effective immune response.

LAIV is administered intranasally, and the attenuated viruses replicate in the nasopharynx, efficiently stimulating both systemic and local (mucosal) antibody responses.[31] Like TIV, LAIV induces influenza-specific serum antibody production but, in addition, induces nasal secretory antibodies that may be important for enhanced protection at the site of viral entry.[32] Additional protection may be mediated by T cells, as several studies have demonstrated that LAIV induces superior T cell responses compared with TIV.[33–36] LAIV also has been reported to induce better cross-strain, heterosubtypic immunity (defined as cross-reactive protection between different influenza viral strains) than TIV in both children and elderly individuals.[33,37,38] Recent studies also indicate that LAIV can elicit T cell responses toward rapidly drifting variant regions of HA that are prone to escape from antibody responses.[39]

Comparative analysis of TIV and LAIV suggests different efficacies depending on the population. Several studies demonstrate an advantage of LAIV over TIV in people with limited prior immunity to influenza,[4] and a consensus is emerging that LAIV is more efficacious among infants and younger children in whom pre-existing immunity to influenza is limited or lacking.[39-41] Older persons have a more limited response to LAIV, which may be because of prior exposure to influenza viruses over the course of their lifetimes. In response to natural influenza infection, protective antibody is produced at mucosal sites, where the primary wave of viral replication occurs, and this mucosal immunity is long lasting. Live-virus vaccines require replication of virus in the nasal passages of the host to induce an immune response, so if this process is blocked by pre-existing mucosal immunity from a remote exposure, the vaccine could be less effective. Current evidence suggests that pre-existing immunity likely blunts the immunogenicity of LAIV among vaccine recipients.[39,42] This concept is supported further by evidence presented in this report, which indicates that LAIV shows consistent efficacy in young children (from 6 months to 7 years of age), while no studies clearly demonstrate LAIV effectiveness in older children and adults.[41]

TRANSLATING THE IMMUNOLOGY OF INFECTION INTO VACCINE PROTECTION

Vaccine development, manufacturing, and correlates of protection for all currently licensed vaccines, whether TIV or LAIV, are based on the paradigm that an immune response resulting in the production of antibodies to the globular head of HA will provide protection from influenza infection and illness. However, little evidence exists that this paradigm can provide consistent, high-level protection from infection across populations, over time, or across influenza subtypes. As long as the vaccine industry and government regulatory agencies remain focused on developing vaccines aimed at the globular head of HA, and to a limited extent NA, improvement in influenza vaccines will be minimal and incremental.

Pulendran recently expressed, "What's happened in the past is that most vaccines have been made empirically without a real immunological rationale."[43] This approach to vaccine design has not produced highly effective influenza vaccines and is unlikely to produce game-changing vaccines in the future, even with the inclusion of adjuvants, higher levels of antigen, or new manufacturing platforms. Development of a forward-thinking, rational approach to vaccine design will require increased focus on and understanding of how different vaccines and vaccine strategies affect the various interrelated components of the immune system.

To move forward, basic immunology must inform vaccinology; scientists must use insights into influenza-specific immune responses to both natural infection and vaccination to identify new viral targets and vaccine strategies. Scientists need to explore basic, overarching questions, including:

- Which influenza virus antigens have the greatest potential to stimulate broadly protective immunity against more than one influenza strain and provide long-term protection?
- What role can stimulation of cellular immunity play in the development of new influenza vaccines?
- What are the impacts of mucosal immunity, innate immunity, and pre-existing immunity on long-term protection against influenza?
- What role can adjuvants play in enhancing vaccine effectiveness?
- What is the role of individual host genetic and age differences in responses to specific vaccines?

These questions are explored further below.

Vaccine Targets for Induction of Protective Immunity: Future Antigen Prospects

Globular Head of Hemagglutinin

As noted above, currently licensed vaccines focus on development of antibodies to the globular head of HA. Generally, these antibodies do not cross-react with other viral subtypes. However, a recent study showed that a novel monoclonal antibody specific to an epitope (ie, portion of an antigen to which an antibody binds) on the HA globular head adjacent to the receptor binding domain demonstrated cross-reactive neutralization against a range of influenza A viruses.[44] Furthermore, passive immunization of mice with this monoclonal antibody provided heterosubtypic protection. These results suggest that there may be conserved epitopes on the globular head of HA that could serve as immunogens capable of producing a heterosubtypic antibody response.

Neuraminidase

Currently available inactivated vaccines induce NA-specific antibody responses. Antibodies to NA are non-neutralizing and therefore do not prevent infection. However, they can limit the extent of viral replication by restricting the intercellular spread of virus, which may contribute to the clinical effectiveness of influenza vaccines.[45] Human challenge studies with seasonal H1N1 and H3N2 strains, and clinical outcomes in children immunized with a vaccine that matched the NA but not the HA antigen of the circulating strain, suggest that NA antibodies may contribute to immunologic protection.[4,14,46] Investigators have postulated that supplementation of human seasonal influenza vaccines with exogenous NA may produce an immune response that results in increased protection against disease.[47,48] However, since no immune correlate exists for NA, investigators have done little to evaluate NA as a benefit in vaccines. In addition, the quantity of NA in licensed vaccines is not standardized and may vary greatly from different manufacturers, which is an additional factor that has limited the evaluation of NA in vaccine effectiveness.[49,50]

Alternative Antigens

The induction of immunity to conserved viral antigens is an attractive approach for the development of more universal, broadly protective vaccines that could be used as stand-alone vaccines or to enhance the protective potential of existing vaccines.[21] Following natural infection with influenza in humans, antibodies are induced against highly conserved structural proteins, including matrix protein 2 (M2), NP, and regions of the HA stalk of the virus. These conserved proteins have been proposed as alternative antigens to the HA head and NA.

M2 is a membrane protein that is expressed on the surface of infected cells. Compared with the HA head and NA, M2 is scarcely present on the virus but is abundantly expressed on virally infected cells. M2 is highly conserved across viral subtypes, even between subtypes of influenza A originating from various animal species,[19] making it a candidate antigen for a vaccine with potential to induce a broadly protective immune response. While immunogenicity to M2 in response to natural infection is limited, it can be increased in vaccines by coupling the protein to carriers.[1,3,51] Since 1999, a number of studies have demonstrated protection against influenza A virus challenge in animal models using chemical or genetic M2 external domain (M2e) fusion constructs. More recently, phase 1 clinical studies have been conducted with M2e vaccine candidates, demonstrating their safety and immunogenicity in humans.[51]

One of the most abundant viral proteins made by virally infected cells is NP, an important target for T cell immunity that also may contribute to humoral immune protection. Antibodies to NP can be induced by vaccination, and non-neutralizing anti-NP antibodies may contribute to cross-protective immunity. Although NP-specific antibodies cannot neutralize influenza virus, studies in animals suggest that they may indirectly contribute to protective immunity by promoting virus-specific CD8+ T cell responses and the production of viral-neutralizing antibodies.[52]

The stalk region of the HA protein connects the HA head to the viral membrane and contains epitopes that are highly conserved across many viral subtypes.[18,19,53] During natural infection, antibodies against areas in the stalk region of HA are generated in addition to antibodies directed to the head region; however, the stalk antibodies make up a small proportion of the elicited response. This finding suggests that the stalk is poorly immunogenic, possibly because it is hidden by the bulky HA head.[4] Investigators have demonstrated that monoclonal antibodies directed against conserved regions of the HA stalk can neutralize a variety of viral subtypes.[19,45,54-58] Some studies also have shown that such monoclonal antibodies can afford heterosubtypic protection through passive immunization in mouse models.[58-60] In another study, researchers were able to construct a novel immunogen comprising the conserved HA stalk domain and lacking the HA globular head.[61] Vaccination of mice with this headless HA construct elicited a broad-based immune response and provided complete protection against death and partial protection against disease following lethal viral challenge. Other researchers designed a bacterially produced HA stalk immunogen construct that also was highly immunogenic in mice.[62] These findings and other similar work raise the possibility of a new approach to influenza vaccination that targets cross-protective shared HA-stalk epitopes and induces immune responses of sufficient magnitude to provide broad protection.[53,63]

Role of Cellular Immunity

Because regulatory agencies require manufacturers to demonstrate that inactivated influenza vaccines can elicit HAI titers greater than 1:40, the vast majority of clinical studies related to influenza vaccines have focused on antibody responses. (See Chapter 10 for further discussion of regulatory requirements for influenza vaccines.) Vaccine development strategies rarely address cellular immunity, so its role in contributing to protection from culture-confirmed influenza remains poorly defined.

Regardless of progress with conventional surface-antigen vaccines, the ultimate quest is a vaccine that will provide broad, heterosubtypic protection. This will require a vaccine that is more effective than natural immunity, since limited protective heterosubtypic immunity appears to be induced by natural infection.[29] Investigators have proposed that such vaccines could exploit cellular immune responses, and that induction of cross-reactive T cell responses may

be a promising approach for development of more broadly protective vaccines.[12]

The role of Th cells in the immune response to influenza is widely accepted. For example, Th cells interact with B cells for optimal antibody production, promote activation and differentiation of $CD8^+$ cells, and affect macrophages and other antigen-presenting cells. However, further studies are required to analyze both the role of these cells and how to most effectively activate them in response to vaccination. A vaccine that induces potent Th cell responses could provide a strong stimulus to both humoral and cell-mediated immunity. Since responses of Th cells are less sensitive to mutations in the virus than are B cells, recognition of conserved viral proteins can provide activation of Th cells across viral strains.[4] This suggests that vaccines that promote Th cell responses may provide broadened cross-protective immunity and supports the concept that effective stimulation of these cells to shared influenza proteins could contribute to strategies for developing broadly protective vaccines.

Most human CTLs induced by influenza infection are directed against viral NP and M1 proteins.[64–67] Since certain epitopes on these proteins are highly conserved, they are potential candidates for inclusion in vaccines aimed at inducing broadly protective cell-mediated immunity. Additional approaches that may stimulate cell-mediated immunity include use of adjuvants that stimulate CD8+ T cell immunity or use of novel generations of vaccines such as viral-vector vaccines.[21,68–70]

An important consideration in developing T cell–based vaccines is that T cell immunity does not, by itself, generate sterilizing immunity similar to that provided by neutralizing antibody.[71,72] T cells recognize only antigens generated after viral entry and infection of cells. Thus, T cell immunity will be delayed until infection is established, a mechanism different from that of the current antibody-based vaccines, and will require a different correlate of protection. Researchers are exploring options for development of T cell–based responses to NP or M2; combining these approaches with HA-directed antibody vaccines may generate broadly protective vaccines.[53,63]

The Impact of Mucosal Immunity on Vaccine Effectiveness

Influenza virus infects cells of the respiratory tract. Mucosal immunity acts as the first line of host defense by blocking influenza virus from infecting the upper respiratory tract and spreading to the lower respiratory tract and deeper tissues.[73,74] Therefore, to prevent infection, any immune mechanism must account for immunity at the mucosal surface. Both mucosal and systemic immunity contribute to protection against influenza infection and disease. Mucosal and secretory immunoglobulin A (IgA) responses are produced locally, providing protection to the epithelial cells of the respiratory tract, and are major factors in resistance to natural infection. In addition, serum immunoglobulin G (IgG) passes into the respiratory tract, providing long-term protection.[31] The currently licensed TIVs primarily elicit circulating serum antibody responses but are not effective in inducing mucosal IgA antibodies and cell-mediated immunity. In contrast, LAIVs induce broad mucosal and systemic responses.[75] While the most effective approach to preventing influenza will likely include both mucosal and systemic immunity, this strategy is complicated by the possible role of pre-existing mucosal immunity in interfering with LAIV effectiveness.

The Impact of Innate Immunity on Vaccine Effectiveness

While questions remain regarding the role of innate immunity in vaccine response, observations to date suggest that immune responses and subsequent memory are largely influenced by initial innate responses. These responses can differ, depending on whether the first response is to natural infection, to a live-virus vaccine, or to an inactivated vaccine delivered with or without adjuvant.[24] Vaccination with TIV results in only limited stimulation of an innate response. This incomplete activation and engagement of innate immunity is likely part of the reason that vaccination with TIV does not lead to activation of virus-specific CD8+ (CTLs) or, perhaps more important, memory CTLs that can respond to subsequent influenza infections. TIV does not activate memory CTLs, because reactivity of memory CTLs during secondary infection depends on the co-stimulation that they receive during initial activation and differentiation.

The Role of Pre-existing Immunity on Vaccine Effectiveness

The effect of pre-existing immunity on TIV and LAIV effectiveness has been questioned. The HA and NA molecules in the vaccines share certain antigenic determinants across viral subtypes but also possess unique, strain-specific determinants. Thus, the secondary immune response after infection or vaccination actually comprises two responses: a secondary response to the shared determinants and a primary response to the novel antigens.[76,77] Therefore, prior exposure may influence the immune response to subsequent exposures. Some studies have reported that high prevaccination HA antibody levels may compromise vaccine effectiveness.[78] Studies in animals suggest that TIV can induce protective antibodies against the strains in the vaccine but may decrease the CTL response induced by infection with other strains, leading to increased susceptibility to the other strains.[21] These observations emphasize that, to establish vaccination policies that not only address seasonal influenza viruses but also take into account the possibility of new influenza virus introductions, scientists will need to determine the role of pre-existing heterosubtypic immunity on vaccine effectiveness.

Understanding Adjuvants

A strategy to boost the innate immune response to TIV is the addition of adjuvants. Adjuvants are compounds that amplify the immune response, primarily through enhancement of innate responses such as increased recruitment of immune cells to the injection site, enhanced uptake of antigen by macrophages, and increased differentiation of monocytes into dendritic cells, which are required for priming of naïve T cells.[79] Adjuvanted vaccines can produce stronger, more durable antibody responses than unadjuvanted vaccines.

The most common adjuvants for human vaccination are aluminum salts, which were approved for human use in the 1920s. Over the past several decades, scientists have shown renewed interest in the development of additional adjuvants. The oil-in-water adjuvant MF59 was approved in Europe in 1997 for influenza vaccines. MF59, which induces local inflammatory responses and promotes potent Th cell help, can enhance antibody responses in both adults and children.[4,80] Next-generation adjuvants currently under investigation include purified bacterial outer-membrane proteins, TLRs, and a variety of TLR agonists.[81] Each distinct adjuvant has the potential to trigger different innate responses and thus instruct diverse adaptive responses.[25]

While studies of adjuvants in immunologically naïve animals show significant immune-boosting effects, the impact of using adjuvants for seasonal influenza vaccines in immunologically primed human populations has been marginal,[82,83] suggesting that adjuvants may be most beneficial in pandemic situations, where the population to be vaccinated has little pre-existing immunity.[29] This concept is supported by observations that adjuvants may increase the magnitude and breadth of immunity in immunologically naïve individuals and in older adults whose immune responses have declined with age.[79,84-86] Furthermore, the addition of certain types of adjuvants to vaccines has been reported to induce broadly protective cross-reactive immunity to viral strains not included in the vaccine.[22]

While considerable attention is being focused on the potential of adjuvants to improve vaccine effectiveness, consistent epidemiologic evidence for increased efficacy of adjuvanted influenza vaccines is limited, even for pandemic vaccines. As noted in Chapter 3, very little evidence is available to assess the efficacy and effectiveness of adjuvanted influenza vaccines, and additional data are needed, particularly for persons over 65 years of age.

SUMMARY

Mimicking natural infection may appear to be the gold standard to aim for when developing game-changing influenza vaccines. However, to provide enhanced protection against influenza, new vaccines will have to stimulate immunity that is better than what occurs with natural infection.[53] Ideally, such vaccines would elicit humoral and cellular responses as seen in natural infection and, in addition, provide robust long-lasting, broad protection across multiple viral strains, something not acquired through natural infection. The goal for new vaccines, therefore, is to stimulate an "unnatural" immune response to influenza. Development of vaccines with the potential to induce

broadly protective "unnatural" immunity will require a better understanding of the molecular nature of new antigens, how to appropriately stimulate immune responses to them, and how to incorporate a potent T-cell or innate response into the overall immunogenic process.[53] For example, as discussed above, a viable strategy may be to target vaccines to conserved antigens on the HA stalk. This approach could be coupled with development of T cell–based responses to NP or M2.[53,63] The resulting combination could achieve the type of vaccine protection that has remained elusive for so many years.

Although progress has been made over the past 70-plus years, major gaps remain in our understanding of the various components of the human immune system and its response to viral antigens. Moving beyond the current vaccines requires exploiting and expanding our understanding of the mechanisms of immunity against influenza. Ultimately, expanded knowledge of the immune response to influenza infection and vaccination must provide the foundation for strategies to develop game-changing 21st century vaccines.

REFERENCES

1. Andrewes CH. Immunity in influenza: the bearing of recent research work. *Proc R Soc Med* 1938;32(3):145-52
2. Wright P, Neumann G, Kawaoka Y. Othomyxoviruses. In: Knipe D, Howley P, eds. *Fields Virology,* ed 5. Philadelphia: Lippincott Williams & Wilkins; 2007
3. Mintern C, Turner S, Doherty PJG. The immune response to influenza A viruses. *Influenza Vaccines for the Future,* ed 2
4. Dormitzer PR, Galli G, Castellino F, et al. Influenza vaccine immunology. *Immunol Rev* 2011;239(1):167-77
5. McElhaney JE. The unmet need in the elderly: designing new influenza vaccines for older adults. *Vaccine* 2005;23(suppl 1):S10-25
6. Leung KN, Ada GL. Induction of natural killer cells during murine influenza virus infection. *Immunobiology* 1981;160(3-4):352-66
7. Biron CA, Nguyen KB, Pien GC, et al. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Ann Rev Immunol* 1999;17:189-220
8. Kim HM, Lee YW, Lee KJ, et al. Alveolar macrophages are indispensable for controlling influenza viruses in lungs of pigs. *J Virol* 2008;82(9):4265-74
9. Tumpey TM, Garcia-Sastre A, Taubenberger JK, et al. Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. *J Virol* 2005;79(23):14933-44
10. Wijburg OL, DiNatale S, Vadolas J, et al. Alveolar macrophages regulate the induction of primary cytotoxic T-lymphocyte responses during influenza virus infection. *J Virol* 1997;71(12):9450-7
11. Brown DM, Roman E, Swain SL. CD4 T cell responses to influenza infection. *Sem Immunol* 2004;16(3):171-7
12. Kreijtz JH, Fouchier RA, Rimmelzwaan GF. Immune responses to influenza virus infection. *Virus Res* 2011;162(1-2):19-30
13. Staudt LM, Gerhard W. Generation of antibody diversity in the immune response of BALB/c mice to influenza virus hemagglutinin, I: significant variation in repertoire expression between individual mice. *J Exp Med* 1983;157(2):687-704
14. Clements ML, Betts RF, Tierney EL, et al. Serum and nasal wash antibodies associated with resistance to experimental challenge with influenza A wild-type virus. *J Clin Microbiol* 1986;24(1):157-60
15. Kilbourne ED, Laver WG, Schulman JL, et al. Antiviral activity of antiserum specific for an influenza virus neuraminidase. *J Virol* 1968;2(4):281-8
16. Black RA, Rota PA, Gorodkova N, et al. Antibody response to the M2 protein of influenza A virus expressed in insect cells. *J Gen Virol* 1993;74(Pt 1):143-6
17. Corti D, Voss J, Gamblin SJ, et al. A neutralizing antibody selected from plasma cells that binds to group 1 and group 2 influenza A hemagglutinins. *Science* 2011;333(6044):850-6
18. Ekiert DC, Bhabha G, Elsliger MA, et al. Antibody recognition of a highly conserved influenza virus epitope. *Science* 2009;324(5924):246-51
19. Sui J, Hwang W, Perez S, et al. Structural and functional bases for broad-spectrum neutralization of avian and human influenza A viruses. *Nature Struct Mol Biol* 2009;16(3):265-73

20. Sambhara S, Kurichh A, Miranda R, et al. Heterosubtypic immunity against human influenza A viruses, including recently emerged avian H5 and H9 viruses, induced by FLU-ISCOM vaccine in mice requires both cytotoxic T-lymphocyte and macrophage function. *Cell Immunol* 2001;211(2):143-53
21. Bodewes R, Osterhaus AD, Rimmelzwaan GF. Targets for the induction of protective immunity against influenza A viruses. *Viruses* 2010;2(1):166-88
22. Galli G, Hancock K, Hoschler K, et al. Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. *Proc Natl Acad Sci* 2009;106(19):7962-7
23. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009;361(20):1945-52
24. Xu R, Ekiert DC, Krause JC, et al. Structural basis of preexisting immunity to the 2009 H1N1 pandemic influenza virus. *Science* 2010;328(5976):357-60
25. Castellino F, Galli G, Del Giudice G, et al. Generating memory with vaccination. *Eur J Immunol* 2009;39(8):2100-5
26. Jelley-Gibbs DM, Strutt TM, McKinstry K, et al. Influencing the fates of CD4 T cells on the path to memory: lessons from influenza. *Immunol Cell Biol* 2008;86(4):343-52
27. Askonas BA, Mullbacher A, Ashman RB. Cytotoxic T-memory cells in virus infection and the specificity of helper T cells. *Immunology* 1982;45(1):79
28. Blazevic V, Trubey CM, Shearer GM. Analysis of the costimulatory requirements for generating human virus-specific in vitro T helper and effector responses. *J Clin Immunol* 2001;21(4):293-302
29. Epstein SL. Prior H1N1 influenza infection and susceptibility of Cleveland Family Study participants during the H2N2 pandemic of 1957: an experiment of nature. *J Infect Dis* 2006;193(1):49-53
30. Hampson A. Vaccines for pandemic influenza: the history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. *Ann Acad Med Singapore* 2008;37(6):510-7
31. Murphy BR, Nelson DL, Wright PF, et al. Secretory and systemic immunological response in children infected with live attenuated influenza A virus vaccines. *Infect Immun* 1982;36(3):1102-8
32. Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. *Pediatr Infect Dis J* 2004;23(3):189-97
33. Hoft DF, Babusis E, Worku S, et al. Live and inactivated influenza vaccines induce similar humoral responses, but only live vaccines induce diverse T-cell responses in young children. *J Infect Dis* 2011;204(6):845-53
34. He XS, Holmes TH, Zhang C, et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. *J Virol* 2006;80(23):11756-66
35. Zeman AM, Holmes TH, Stamatis S, et al. Humoral and cellular immune responses in children given annual immunization with trivalent inactivated influenza vaccine. *Pediatr Infect Dis J* 2007;26(2):107-15
36. Subbramanian RA, Basha S, Shata MT, et al. Pandemic and seasonal H1N1 influenza hemagglutinin-specific T cell responses elicited by seasonal influenza vaccination. *Vaccine* 2010;28(52):8258-67
37. Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med* 2007;356(7):685-96
38. Gorse GJ, Belshe RB. Enhancement of anti-influenza A virus cytotoxicity following influenza A virus vaccination in older, chronically ill adults. *J Clin Microbiol* 1990;28(11):2539-50
39. Basha S, Hazenfeld S, Brady RC, et al. Comparison of antibody and T-cell responses elicited by licensed inactivated- and live-attenuated influenza vaccines against H3N2 hemagglutinin. *Hum Immunol* 2011;72(6):463-9
40. Rhorer J, Ambrose CS, Dickinson S, et al. Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. *Vaccine* 2009;27(7):1101-10
41. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12(1):36-44
42. Sasaki S, Jaimes MC, Holmes TH, et al. Comparison of the influenza virus-specific effector and memory B-cell responses to immunization of children and

adults with live attenuated or inactivated influenza virus vaccines. *J Virol* 2007;81(1):215-28
43. von Budnoff A. An immunological rationale for vaccines. *IAVI Rep* 2010;14(6):4-7
44. Yoshida R, Igarashi M, Ozaki H, et al. Cross-protective potential of a novel monoclonal antibody directed against antigenic site B of the hemagglutinin of influenza A viruses. *PLoS Pathog* 2009;5(3):e1000350
45. Kilbourne ED. Comparative efficacy of neuraminidase-specific and conventional influenza virus vaccines in induction of antibody to neuraminidase in humans. *J Infect Dis* 1976;134(4):384-94
46. Beutner KR, Chow T, Rubi E, et al. Evaluation of a neuraminidase-specific influenza A virus vaccine in children: antibody responses and effects on two successive outbreaks of natural infection. *J Infect Dis* 1979;140(6):844-50
47. Tanimoto T, Nakatsu R, Fuke I, et al. Estimation of the neuraminidase content of influenza viruses and split-product vaccines by immunochromatography. *Vaccine* 2005;23(37):4598-609
48. Aymard M. Quantification of neuraminidase (NA) protein content. *Vaccine* 2002;20(suppl 2):S59-60
49. Sylte MJ, Suarez DL. Influenza neuraminidase as a vaccine antigen. *Curr Top Microbiol Immunol* 2009;333:227-41
50. Bright RA, Neuzil KM, Pervikov Y, et al. WHO meeting on the role of neuraminidase in inducing protective immunity against influenza infection, Vilamoura, Portugal, September 14, 2008. *Vaccine* 2009;27(45):6366-9
51. Schotsaert M, De Filette M, Fiers W, et al. Universal M2 ectodomain-based influenza A vaccines: preclinical and clinical developments. *Expert Rev Vaccines* 2009;8(4):499-508
52. Rangel-Moreno J, Carragher DM, Misra RS, et al. B cells promote resistance to heterosubtypic strains of influenza via multiple mechanisms. *J Immunol* 2008;180(1):454-63
53. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. *Nat Med* 2010;16(12):1389-91
54. Wang TT, Palese P. Universal epitopes of influenza virus hemagglutinins? *Nature Struct Mol Biol* 2009;16(3):233-4
55. Sanchez-Fauquier A, Villanueva N, Melero JA. Isolation of cross-reactive, subtype-specific monoclonal antibodies against influenza virus HA1 and HA2 hemagglutinin subunits. *Arch Virol* 1987;97(3-4):251-65
56. Okuno Y, Isegawa Y, Sasao F, et al. A common neutralizing epitope conserved between the hemagglutinins of influenza A virus H1 and H2 strains. *J Virol* 1993;67(5):2552-8
57. Smirnov YA, Lipatov AS, Gitelman AK, et al. An epitope shared by the hemagglutinins of H1, H2, H5, and H6 subtypes of influenza A virus. *Acta Virol* 1999;43(4):237-44
58. Tan GS, Krammer F, Eggink D, et al. A pan-H1 anti-hemagglutinin monoclonal antibody with potent broad-spectrum efficacy in vivo. *J Virol* 2012;86(11):6179-88
59. Wang TT, Tan GS, Hai R, et al. Broadly protective monoclonal antibodies against H3 influenza viruses following sequential immunization with different hemagglutinins. *PLoS Pathog* 2010;6(2):e1000796
60. Kashyap AK, Steel J, Rubrum A, et al. Protection from the 2009 H1N1 pandemic influenza by an antibody from combinatorial survivor-based libraries. *PLoS Pathog* 2010;6(7):e1000990
61. Steel J, Lowen AC, Wang TT, et al. Influenza virus vaccine based on the conserved hemagglutinin stalk domain. *mBio* 2010;1(1):e00018
62. Bommakanti G, Citron MP, Hepler RW, et al. Design of an HA2-based *Escherichia coli* expressed influenza immunogen that protects mice from pathogenic challenge. *Proc Natl Acad Sci* 2010;107(31):13701-6
63. Wei CJ, Boyington JC, McTamney PM, et al. Induction of broadly neutralizing H1N1 influenza antibodies by vaccination. *Science* 2010;329(5995):1060-4
64. Boon AC, de Mutsert G, Graus YM, et al. The magnitude and specificity of influenza A virus-specific cytotoxic T-lymphocyte responses in humans is related to HLA-A and -B phenotype. *J Virol* 2002;76(2):582-90
65. Gotch F, McMichael A, Smith G, et al. Identification of viral molecules recognized by influenza-specific human cytotoxic T lymphocytes. *J Exp Med* 1987;165(2):408-16
66. Jameson J, Cruz J, Ennis FA. Human cytotoxic T-lymphocyte repertoire to influenza A viruses.

J Virol 1998;72(11):8682-9

67. Wang M, Lamberth K, Harndahl M, et al. CTL epitopes for influenza A including the H5N1 bird flu; genome-, pathogen-, and HLA-wide screening. *Vaccine* 2007;25(15):2823-31

68. Rimmelzwaan GF, McElhaney JE. Correlates of protection: novel generations of influenza vaccines. *Vaccine* 2008;26(suppl 4):D41-4

69. Laddy DJ, Yan J, Kutzler M, et al. Heterosubtypic protection against pathogenic human and avian influenza viruses via in vivo electroporation of synthetic consensus DNA antigens. *PLoS One* 2008;3(6):e2517

70. Prasad SA, Norbury CC, Chen W, et al. Cutting edge: recombinant adenoviruses induce CD8 T cell responses to an inserted protein whose expression is limited to nonimmune cells. *J Immunol* 2001;166(8):4809-12

71. Swain SL, Agrewala JN, Brown DM, et al. CD4+ T-cell memory: generation and multi-faceted roles for CD4+ T cells in protective immunity to influenza. *Immunol Rev* 2006;211:8-22

72. Ulmer JB, Donnelly JJ, Parker SE, et al. Heterologous protection against influenza by injection of DNA encoding a viral protein. *Science* 1993;259(5102):1745-9

73. Corrigan EM, Clancy RL. Is there a role for a mucosal influenza vaccine in the elderly? *Drugs Aging* 1999;15(3):169-81

74. Chen D, Periwal SB, Larrivee K, et al. Serum and mucosal immune responses to an inactivated influenza virus vaccine induced by epidermal powder immunization. *J Virol* 2001;75(17):7956-65

75. Cox RJ, Brokstad KA, Ogra P. Influenza virus: immunity and vaccination strategies: comparison of the immune response to inactivated and live, attenuated influenza vaccines. *Scand J Immunol* 2004;59(1):1-15

76. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103(1-2):133-8

77. Ahmed AH, Nicholson KG. The efficacy of influenza vaccine. *Rev Med Microbiol* 1996;7:23-30

78. Demicheli V, Jefferson T, Rivetti D, et al. Prevention and early treatment of influenza in healthy adults. *Vaccine* 2000;18(11-12):957-1030

79. O'Hagen DT, Tsai T, Reed S. Emulsion-based adjuvants for improved influenza vaccines. In *Influenza Vaccines for the Future,* ed 2. 2011 (pt 2):327-36

80. Vesikari T, Groth N, Karvonen A, et al. MF59-adjuvanted influenza vaccine (FLUAD) in children: safety and immunogenicity following a second year seasonal vaccination. *Vaccine* 2009;27(45):6291-5

81. Lambert LC, Fauci AS. Influenza vaccines for the future. *N Engl J Med* 2010;363(21):2036-44

82. Potter CW, Jennings R. Effect of priming on subsequent response to inactivated influenza vaccine. *Vaccine* 2003;21(9-10):940-5

83. Couch RB, Keitel WA, Cate TR. Improvement of inactivated influenza virus vaccines. *J Infect Dis* 1997;176(suppl):S38-44

84. Ansaldi F, Zancolli M, Durando P, et al. Antibody response against heterogeneous circulating influenza virus strains elicited by MF59- and non-adjuvanted vaccines during seasons with good or partial matching between vaccine strain and clinical isolates. *Vaccine* 2010;28(25):4123-9

85. Galli G, Medini D, Borgogni E, et al. Adjuvanted H5N1 vaccine induces early CD4+ T cell response that predicts long-term persistence of protective antibody levels. *Proc Natl Acad Sci* 2009;106(10):3877-82

86. Ferguson M, Risi G, Davis M, et al. Safety and long-term humoral immune response in adults after vaccination with an H1N1 2009 pandemic influenza vaccine with or without AS03 adjuvant. *J Infect Dis* 2012;205(5):733-44

CHAPTER 9

POTENTIAL GAME-CHANGING INFLUENZA VACCINES IN THE RESEARCH PIPELINE: FRAMING THE DISCUSSION

INTRODUCTION

Currently, more than 170 influenza vaccines are undergoing clinical trials around the world. The vaccines under evaluation represent a wide range of different technologies. Most of these vaccines use the same immunologic approach as the currently licensed vaccines, which is aimed at eliciting antibodies to the HA head. Based on our analysis of clinicaltrials.gov data through June 18, 2012, only 13 (7%) of 177 influenza vaccines undergoing clinical trials are designed to elicit a response to antigens different from the HA head. This chapter describes the characteristics of future potentially game-changing influenza vaccines. Also, we provide a brief overview of the most promising innovative approaches under consideration. We believe there is an urgent need to frame the discussion of how game-changing influenza vaccine are identified, prioritized for comprehensive phase 3 trials, and eventually licensed.

GAME-CHANGING INFLUENZA VACCINES

Influenza viruses undergo continuous antigenic evolution through the process of antigenic drift (ie, small changes in the antigenic composition of the virus caused by mutation). Because of this constant antigenic evolution, new viral subtypes emerge each year. These new viral subtypes are genetically different enough from previous subtypes to avoid recognition by the human immune system upon re-exposure to influenza virus. Because of the need to predict vaccine strains for the upcoming influenza season each year, global influenza surveillance data are used to predict year-round circulation patterns. This approach has significant drawbacks, including: (1) the uncertainty of being able to accurately predict which subtypes will circulate from year to year, (2) the need to develop and manufacture a new vaccine each year, and (3) the need to vaccinate the population each year. Furthermore, if a novel pandemic influenza strain emerges either through a process of gradual adaptation or through antigenic shift (ie, more sudden and extensive changes or reassortments in the viral genome), currently existing vaccines will provide little to no protection. In such situations, researchers would need to "start from scratch" with the new strain and develop a strain-specific vaccine, which would take valuable time away from effectively combating the new pandemic.

To address these unique challenges, influenza vaccines of the future must generate immune responses to more conserved regions of the influenza virus that

are not subject to antigenic drift or shift and thus be more broadly protective and possibly longer lasting. Such vaccines often are conceptually referred to as "universal influenza vaccines." Ideally, a universal influenza vaccine should provide protection against all HA subtypes. At a minimum, such a vaccine will need to protect against the HA subtypes that have previously been associated with human seasonal and pandemic influenza (H1, H2, and H3) and those subtypes that have resulted in occasional human infections and which the WHO considers to be the most likely subtypes to become pandemic viruses (H5 and H9).[1] We believe, however, that the concept of a universal influenza vaccine should not become a roadblock to how novel-antigen vaccines are conceptualized. For example, an influenza vaccine that greatly expands protection across large segments of the population for multiple years of duration and for those HA subtypes most likely to cause seasonal and pandemic illness, but does not protect against all subtypes of influenza (ie, not a true universal influenza vaccine), would still represent a major step forward in the prevention of human influenza.

TABLE 9-1. Critical, Important, and Desired Characteristics of Game-Changing Influenza Vaccines

Critical
• Provide protection against all HA subtypes and at a minimum protection against H1, H2, H3, H5, and H9 subtypes.
• Provide immunologic protection for those populations most at risk for severe disease and increased mortality.
• Rarely cause adverse events, and any adverse events are mild and temporary.
Important
• Provide a decade or more of protection.
• Use inexpensive manufacturing technology that permits rapid and highly scalable production, particularly to address emergence of a pandemic virus.
Desired
• Use manufacturing technology that can be readily transferred to developing-world countries.
• Offer heat stability, thereby eliminating the need to maintain a cold chain.
• Do not require injection for administration.

While development of universal influenza vaccines would represent a quantum leap forward in the prevention of both seasonal and pandemic influenza, these vaccines alone will not be sufficient to address all of the requirements of a game-changing influenza vaccine. Additional characteristics of a game-changing influenza vaccine are summarized in **Table 9-1**.

Another characteristic of a game-changing vaccine is that it be inexpensive to manufacture, distribute, and administer. This issue is addressed in greater detail in Chapter 11.

ALTERNATIVE VACCINE PLATFORMS, ANTIGENS, AND DELIVERY METHODS

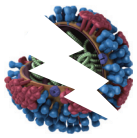
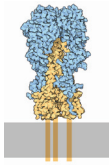
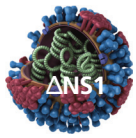
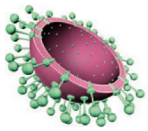
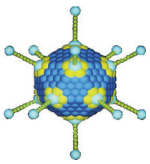
Potential game-changing influenza vaccines will likely require major changes in vaccine platforms, antigens, and antigen-delivery methods (**Figure 9-1** details current and potential technologies). Described below are examples of current vaccine research efforts into potential game-changing influenza vaccines. The platforms, antigens, and methods of delivery described are not meant to be an all-inclusive list of the technologies that may be used in development of future influenza vaccines; rather, they provide a general framework for reviewing this topic. Using new modes of delivery also may play a role in game-changing vaccines.

HA-HEAD VACCINES

Alternative Platforms Using HA-Head Antigens

Vaccines produced using alternatives to egg-based production platforms, such as mammalian-cell culture, insect-cell culture, and bacterial-cell culture are in clinical development.[2-5] Such methods offer an improvement over current egg-based technology in that they are likely to decrease the time required for

FIGURE 9-1. Current and Potential Influenza Vaccine Technologies

	Old Technologies					
						
Influenza Vaccine Technology Type	**Inactivated or Live Attenuated (LAIV)**	**Recombinant Protein/Peptide**	**Non-Replicating (ΔNS1) Influenza Virus**	**Virus-like Particle (VLP)**	**Viral Vector**	**DNA**
Description	Inactivated influenza virus that has been enriched for HA (split) or an influenza virus that has been attenuated so that it can replicate only in specific areas of the human body (LAIV).	Exogenously produced immunogenic influenza proteins or peptides, expressed and purified from a non-influenza source.	Influenza viruses that have been genetically modified by deletion of the genomic segment that encodes for the NS1 protein. This results in a replication deficiency in humans.	A non-infectious particle of highly similar three-dimensional structure to that of the influenza strain from which the genetic material was removed.	Attenuated non-influenza viruses that can carry and express proteins from influenza can be used to express antigenic influenza proteins.	Plasmid DNA that encodes for a mechanism that allows for the expression of antigenic influenza proteins in human cells.
Manufacturing Platform	Egg/Mammalian-cell culture	Bacterial-cell culture Yeast-cell culture Plant-cell culture Insect-cell culture	Mammalian-cell culture	Bacterial-cell culture Yeast-cell culture Plant-cell culture Mammalian-cell culture Insect-cell culture	Mammalian-cell culture	Bacteria-cell culture
Clinical Trial Status	In use currently	Phase 3	Phase 2	Phase 2	Phase 1	Phase 1

VLP image is copyrighted by John Wiley & Sons, Inc www.interscience.wiley.com and used with permission (License # 2585870385879).
Recombinant protein/peptide image is from the April 2006 feature on hemagglutinin by David S. Goodsell and the PCSB PDB (http://dx.doi.org/10.2210/rcsb_pdb/mom_2006_4). It is copyrighted and used with permission.

vaccine production, are less prone to contamination, and will therefore increase overall vaccine-production capacity. However, as long as such vaccines continue to be directed toward the HA-head antigen, they will have little potential to improve vaccine effectiveness or to provide broad, durable protection against disease.

Adjuvanted HA-Head Vaccines

As noted in Chapter 8, an adjuvant is any vaccine ingredient that is not an antigen but is included in the vaccine to stimulate the immune system to mount a more robust and protective response, which may in turn increase vaccine efficacy and effectiveness. Most data to date regarding adjuvants result from the use of two specific adjuvants, AS03 and MF59.

Throughout the CCIVI review process we have heard from influenza vaccine experts, large pharmaceutical company representatives, and government scientists and policy makers that adjuvants represent game-changers for influenza vaccines. Although new adjuvants are in development, the available data on existing adjuvanted HA-head influenza vaccines is far from convincing, especially for use in those at greatest risk.

For example, the median vaccine effectiveness of adjuvanted influenza vaccines used during the 2009 pandemic (using the inclusion criteria of our *Lancet Infectious Diseases* meta-analysis and summarized in Chapter 3) was only 72% (range, 60% to 93%). The performance of these vaccines represents a best-case scenario whereby the effectiveness data were derived largely from healthy adults younger than 65 and there was a near-perfect match between vaccine antigen and circulating virus. Furthermore, high-quality studies of adjuvanted vaccines demonstrating significant effectiveness in those over 65 years for pandemic or seasonal influenza are lacking. As we discussed in Chapter 1, future pandemics that resemble those of 1957 and 1968 will disproportionately affect older individuals.

For seasonal influenza, improved effectiveness of adjuvanted HA-head vaccines has been demonstrated only in children younger than 6 years old and only in a single study. Because of substantial immunologic differences, these data cannot be extrapolated to other

populations, including adults age 65 years and older. As noted in Chapter 8, the impact of using adjuvants for seasonal influenza vaccines in immunologically primed human populations has been marginal, which suggests that adjuvants may be most beneficial in children and during pandemics, where the population to be vaccinated has little pre-existing immunity.

Adjuvanted vaccines are associated with increased rates of local pain, induration, myalgia, and erythema compared with their unadjuvanted counterparts.[6,7] These local reactions could prompt patients to choose unadjuvanted vaccines over adjuvanted ones. Also, while adjuvanted influenza vaccines have had a good safety record based on their limited use to date, the health effects of repeated exposure to vaccines containing adjuvant are not well understood. New adjuvants will require rigorous testing to determine safety, efficacy, and effectiveness.

For these reasons, additional data are needed to determine how, or if, adjuvants will contribute to game-changing influenza vaccines.

Augmenting HA-Head Antigen Vaccines

Another approach to improve current HA-head antigen vaccines is the addition of immunogenic components, such as M2 or other proteins.[8] These vaccines have been tested in phase 2 clinical trials but have not been evaluated for efficacy.

Novel Antigens

Research is ongoing to design influenza vaccines that elicit broad responses to antigens other than the HA head and NA. Influenza A and B viruses consist of 11 proteins encoded by eight gene segments. Three of these proteins (HA, NP, and M2) contain segments that are conserved across influenza A strains, while highly conserved regions of HA are found in influenza B subtypes.[9–11] Portions of these conserved proteins could be used for the production of broadly protective B and T-cell immune responses. Many recombinant vaccine technologies currently in testing can be used to express and present these conserved antigens to the immune system, making a broadly protective response a realistic possibility in the future.[9,11–14]

Candidate vaccines based on various genetic conjugates incorporating M2 antigen have been produced by several groups and have been shown to be immunogenic.[15–22] Another approach is to develop vaccines to the conserved regions of the HA stalk. The HA protein comprises the head, which mutates frequently and is the primary antigen source for current influenza vaccines, and the HA stalk. Unlike the head, the stalk contains epitopes that are conserved, which makes this region a potential target for new vaccines. Broadly neutralizing antibodies that bind to the stalk and prevent infection recently have been identified and are described in detail in Chapter 8.[23–25] During natural infection or vaccination with currently licensed vaccines, the bulky and highly immunogenic HA head appears to mask these conserved domains.[23] However, several groups have developed methods to express and present epitopes from the HA stalk to the immune system in ways that stimulate the production of cross-neutralizing antibodies, which have been shown to afford protection in animal models.[22,25]

ANTIGEN CONSTRUCTS

Recombinant Proteins

An alternative manufacturing process to purifying the target vaccine antigen from the desired pathogen (eg, HA and NA from influenza virus grown in eggs) is to clone the gene(s) encoding the target vaccine antigen(s) into a vector that expresses the recombinant protein in infected cells (eg, HA gene expressed by a baculovirus vector grown in insect cell-culture).[9] The protein can then be harvested from the infected cells, purified, and used as the primary antigen (or in combination with other antigens) in a new vaccine. Recombinant technology for influenza vaccine antigens has potential advantages over traditional methods, such as being able to produce vaccine antigens at lower cost, in greater quantity, and with better purity, but does not substantively alter the vaccine antigen itself.

Virus-Like Particles (VLPs)

Virus-like particles (VLPs) are biological constructs that self-assemble using proteins of the viral coat to allow for self-assembly but are noninfectious since they do not contain any viral genetic material. VLPs can be thought of as an "empty shell," because they

retain most, if not all, of the structure of the virus they mimic but have no DNA or RNA. VLPs can be produced in a variety of platforms, including, plant-, insect-, or mammalian-cell culture, and have been used to develop vaccines containing HA-head, NA, and M2 proteins. Unlike TIVs, these vaccines maintain the general appearance of the influenza virus, and, unlike the LAIV, they are generally injected intramuscularly and therefore have had more success stimulating both cellular and humoral immunity, unlike currently licensed influenza vaccines.[26,27]

Non-replicating Virus

An alternative approach to cold-adaptation for attenuation of live viruses is the use of reverse genetics to design genetically modified viruses that encode altered non-structural protein 1 (NS1). The resulting vaccines are replication-deficient and noninfective.[28] NS1-deficient vaccines have been shown to promote both humoral and cellular responses and to offer cross-protection against antigenically divergent strains in both animals and humans.[28–32]

Viral Vectors

A variety of viral vectors are being evaluated as means to deliver influenza antigens to the immune system. With viral vectors, the influenza antigen protein is expressed on the surface of a "carrier" virus; the carrier virus is nonpathogenic and incapable of causing disease. HA has been expressed in various different viral vectors, including alphavirus, vaccinia, and adenovirus.[22,33–37] Clinical trials evaluating the immunogenicity and safety of adenovirus-based HA-head vaccines are ongoing.[9,37–39]

DNA Vaccines

DNA vaccination involves the intramuscular injection of plasmid DNA encoding for HA or NA, either alone or in combination, with gene segments for internal viral protein.[9] Following inoculation, the viral proteins are synthesized by the host cells, leading to generation of immune responses. Nucleic acid vaccines are proposed to induce broader immune responses than conventional vaccines, and this approach has elicited cross-strain protection in animal models.[40-42] Phase 1 clinical trials have demonstrated safety and immunogenicity of DNA vaccines in humans.[43–45]

MODES OF VACCINE ADMINISTRATION

Prime-Boost Vaccination

To stimulate a broader, more effective immune response, researchers are investigating an alternative two-step method of delivering vaccine antigens called heterologous prime-boost. During the first, "priming," step, a vaccine such as a DNA-based HA vaccine is administered, followed by a second, "boosting" step with an inactivated, attenuated, or viral-vector vaccine. The priming antigen in the first vaccine initiates memory cells, and the boosting vaccine expands the memory response.[46] These heterologous prime-boost immunizations may elicit immune responses of greater magnitude and breadth than can be achieved by priming and boosting with the same vaccine. This principle has been applied to influenza vaccines employing HA, M2, and conserved domains from the NP protein, resulting in the production of cross-reactive antibodies and protection in animal models.[9,47,48]

Researchers also are exploring different modes of administration for delivering vaccine antigens to recipients. These include electroporation, jet injection, patches, and oral delivery.[49] All of these methods are in the earliest phases of study and will require more investigation to determine if they are safe and effective.

SUMMARY

Novel, potential game-changing influenza vaccines are in research and development. However, all involved must be aware of the major differences in the purposes of innovation in two key areas of influenza vaccine research and development. Innovation in the manufacturing platform (cell culture, VLPs, DNA, etc) will allow for added speed and increased volume, whereas the antigen (HA head vs HA stalk, M2, NA, etc) is the mediator of protection from disease. While data to demonstrate superior efficacy and effectiveness over currently licensed vaccines are not currently available, the initial immunologic results are encouraging. The pathway toward licensure for these vaccines is complicated. First, large randomized, controlled efficacy trials will be required that employ defined end points of laboratory-confirmed influenza. In addition, because such vaccines cannot rely on generating antibodies to the HA head, new correlates

of protection will need to be developed and assessed. Finally, to have a meaningful impact and to be financially worthwhile for the manufacturers, such vaccines will need to demonstrate superior efficacy to currently licensed vaccines.

REFERENCES

1. WHO. Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness. Available at: http://www.who.int/influenza/vaccines/virus/201202_h5_h9_vaccinevirusupdate.pdf
2. Pushko P, Kort T, Nathan M, et al. Recombinant H1N1 virus-like particle vaccine elicits protective immunity in ferrets against the 2009 pandemic H1N1 influenza virus. *Vaccine* 2010;28(30):4771-6
3. King JC Jr, Cox MM, Reisinger K, et al. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy children aged 6-59 months. *Vaccine* 2009;27(47):6589-94
4. Song L, Nakaar V, Kavita U, et al. Efficacious recombinant influenza vaccines produced by high yield bacterial expression: a solution to global pandemic and seasonal needs. *PLoS One*. 2008;3(5):e2257
5. Dormitzer PR, Galli G, Castellino F, et al. Influenza vaccine immunology. *Immunol Rev* 2011;239(1):167-77
6. Hagan DTO, Tsai T, Reed S. Emulsion-based adjuvants for improved influenza vaccines. In: Rappuoli R, Del Giudice G, eds. *Influenza Vaccines for the Future*. Basel: Springer Basel; 2011:327-57
7. Parodi V, de Florentiis D, Martini M, et al. Inactivated influenza vaccines: recent progress and implications for the elderly. *Drugs Aging* 2011;28(2):93-106
8. Wu F, Yuan XY, Huang WS, et al. Heterosubtypic protection conferred by combined vaccination with M2e peptide and split influenza vaccine. *Vaccine* 2009;27(43):6095-101
9. Lambert LC, Fauci AS. Influenza vaccines for the future. *N Engl J Med* 2010;363(21):2036-44
10. Russell CJ. Stalking influenza diversity with a universal antibody. *N Engl J Med* 2011;365(16):1541-2
11. Du L, Zhou Y, Jiang S. Research and development of universal influenza vaccines. *Microbes Infect* 2010;12(4):280-6
12. Atsmon J, Kate-Ilovitz E, Shaikevich D, et al. Safety and immunogenicity of multimeric-001-a novel universal influenza vaccine. *J Clin Immunol* 2012;32(3):595-603
13. Doherty PC, Kelso A. Toward a broadly protective influenza vaccine. *J Clin Invest* 2008;118(10):3273-5
14. Zhou D, Wu T, Lasaro MO, et al. A universal influenza A vaccine based on adenovirus expressing matrix-2 ectodomain and nucleoprotein protects mice from lethal challenge. *Mol Ther* 2010;18(12):2182-9
15. Fiers W, De Filette M, El Bakkouri K, et al. M2e-based universal influenza A vaccine. *Vaccine* 2009;27(45):6280-3
16. El Bakkouri K, Descamps F, De Filette M, et al. Universal vaccine based on ectodomain of matrix protein 2 of influenza A: Fc receptors and alveolar macrophages mediate protection. *J Immunol* 2011;186(2):1022-31
17. Jegerlehner A, Schmitz N, Storni T, et al. Influenza A vaccine based on the extracellular domain of M2: weak protection mediated via antibody-dependent NK cell activity. *J Immunol* 2004;172(9):5598-605
18. Fan J, Liang X, Horton MS, et al. Preclinical study of influenza virus A M2 peptide conjugate vaccines in mice, ferrets, and rhesus monkeys. *Vaccine* 2004;22(23-24):2993-3003
19. Huleatt JW, Nakaar V, Desai P, et al. Potent immunogenicity and efficacy of a universal influenza vaccine candidate comprising a recombinant fusion protein linking influenza M2e to the TLR5 ligand flagellin. *Vaccine* 2008;26(2):201-14
20. Turley CB, Rupp RE, Johnson C, et al. Safety and immunogenicity of a recombinant M2e-flagellin influenza vaccine (STF2.4xM2e) in healthy adults. *Vaccine* 2011;29(32):5145-52
21. Talbot HK, Rock MT, Johnson C, et al. Immunopotentiation of trivalent influenza vaccine when given with VAX102, a recombinant influenza M2e vaccine fused to the TLR5 ligand flagellin. *PLoS One* 2010;5(12):e14442
22. Shaw AR. New technologies for new influenza vaccines. *Vaccine* 2012;30(33):4927-33

23. Steel J, Lowen AC, Wang TT, et al. Influenza virus vaccine based on the conserved hemagglutinin stalk domain. *mBio* 2010;1(1):e00018
24. Corti D, Voss J, Gamblin SJ, et al. A neutralizing antibody selected from plasma cells that binds to group 1 and group 2 influenza A hemagglutinins. *Science* 2011;333(6044):850-6
25. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. *Nat Med* 2010;16(12):1389-91
26. Haynes J. Influenza virus-like particle vaccines. *Expert Rev Vaccines* 2009;8(4):435-45
27. Kang SM, Pushko P, Bright RA, et al. Influenza virus-like particles as pandemic vaccines. *Curr Top Microbiol Immunol* 2009;333:269-89
28. Ferko B, Stasakova J, Romanova J, et al. Immunogenicity and protection efficacy of replication-deficient influenza A viruses with altered NS1 genes. *J Virol* 2004;78(23):13037-45
29. Hale BG, Randall RE, Ortin J, et al. The multifunctional NS1 protein of influenza A viruses. *J Gen Virol* 2008;89(pt 10):2359-76
30. Kappes MA, Sandbulte MR, Platt R, et al. Vaccination with NS1-truncated H3N2 swine influenza virus primes T cells and confers cross-protection against an H1N1 heterosubtypic challenge in pigs. *Vaccine* 2012;30(2):280-8
31. Talon J, Salvatore M, O'Neill RE, et al. Influenza A and B viruses expressing altered NS1 proteins: a vaccine approach. *Proc Natl Acad Sci* 2000;97(8):4309-14
32. Wacheck V, Egorov A, Groiss F, et al. A novel type of influenza vaccine: safety and immunogenicity of replication-deficient influenza virus created by deletion of the interferon antagonist NS1. *J Infect Dis* 2010;201(3):354-62
33. Schultz-Cherry S, Dybing JK, Davis NL, et al. Influenza virus (A/HK/156/97) hemagglutinin expressed by an alphavirus replicon system protects chickens against lethal infection with Hong Kong-origin H5N1 viruses. *Virology* 2000;278(1):55-9
34. Hubby B, Talarico T, Maughan M, et al. Development and preclinical evaluation of an alphavirus replicon vaccine for influenza. *Vaccine* 2007;25(48):8180-9
35. Breathnach CC, Clark HJ, Clark RC, et al. Immunization with recombinant modified vaccinia Ankara (rMVA) constructs encoding the HA or NP gene protects ponies from equine influenza virus challenge. *Vaccine* 2006;24(8):1180-90
36. Ben-Yehuda A, Ehleiter D, Hu AR, et al. Recombinant vaccinia virus expressing the PR/8 influenza hemagglutinin gene overcomes the impaired immune response and increased susceptibility of old mice to influenza infection. *J Infect Dis* 1993;168(2):352-7
37. Van Kampen KR, Shi Z, Gao P, et al. Safety and immunogenicity of adenovirus-vectored nasal and epicutaneous influenza vaccines in humans. *Vaccine* 2005;23(8):1029-36
38. ClinicalTrials.gov. Safety and immunogenicity study of adenovirus-vectored intranasal pandemic influenza vaccine. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00755703
39. ClinicalTrials.gov. Safety and immunogenicity of replication-competent adenovirus 4-vectored vaccine for avian influenza H5N1. Available at: www.clinicaltrials.gov/ct2/show/NCT01006798
40. Kim JH, Jacob J. DNA vaccines against influenza viruses. *Curr Top Microbiol Immunol* 2009;333: 197-210
41. Laddy DJ, Yan J, Corbitt N, et al. Immunogenicity of novel consensus-based DNA vaccines against avian influenza. *Vaccine* 2007;25(16):2984-9
42. Park KS, Seo YB, Lee JY, et al. Complete protection against a H5N2 avian influenza virus by a DNA vaccine expressing a fusion protein of H1N1 HA and M2e. *Vaccine* 2011;29(33):5481-7
43. Drape R, Macklin M, Barr L, et al. Epidermal DNA vaccine for influenza is immunogenic in humans. *Vaccine* 2006;24(21):4475-81
44. Jones S, Evans K, McElwaine-Johnn H, et al. DNA vaccination protects against an influenza challenge in a double-blind randomised placebo-controlled phase 1b clinical trial. *Vaccine* 2009;27(18): 2506-12
45. Smith LR, Wloch MK, Ye M, et al. Phase 1 clinical trials of the safety and immunogenicity of adjuvanted plasmid DNA vaccines encoding influenza A virus H5 hemagglutinin. *Vaccine* 2010;28(13):2565-72
46. Robinson HL. Prime boost vaccines power up in people. *Nat Med* 2003;9(6):642-3
47. Wei CJ, Boyington JC, McTamney PM, et al. Induction of broadly neutralizing H1N1

influenza antibodies by vaccination. *Science* 2010;329(5995):1060-4

48. Price GE, Soboleski MR, Lo CY, et al. Vaccination focusing immunity on conserved antigens protects mice and ferrets against virulent H1N1 and H5N1 influenza A viruses. *Vaccine* 2009;27(47):6512-21

49. Giudice EL, Campbell JD. Needle-free vaccine delivery. *Adv Drug Deliv Rev* 2006;58(1):68-89

CHAPTER 10

REGULATION OF THE INFLUENZA VACCINE ENTERPRISE

INTRODUCTION

Current regulations regarding all aspects of the licensure of and manufacturing of influenza vaccines are intended to ensure vaccine safety, efficacy, and potency. While this regulatory process was built on decades of experience with the current influenza vaccines, the present-day regulatory scheme provides only a limited framework when it comes to the creation and development of novel-antigen game-changing influenza vaccines. This chapter reviews regulatory issues for currently licensed influenza vaccines in the United States and explores the role of regulatory science in facilitating or encumbering progress toward game-changing influenza vaccines.

OVERVIEW OF LICENSURE OF CURRENTLY AVAILABLE INFLUENZA VACCINES

All vaccines in the United States are licensed and regulated by the FDA. The FDA is required by the Public Health Service Act to ensure that vaccines are "safe, pure, and potent."[1] Potency is recognized to include the efficacy of the vaccine.[2] The FDA's Center for Biologics Evaluation and Research (CBER) administers the vaccine regulatory program.[3] To obtain a license for marketing a new vaccine, the applicant must submit a biologics license application (BLA) to CBER, which is then delegated to the Office of Vaccines Research and Review.

The current regulatory framework used for influenza vaccines is guided by two 2007 documents that describe the clinical data necessary to support licensure of seasonal and pandemic influenza vaccines.[4,5] The traditional licensure pathway for influenza vaccines is based on evaluation of data demonstrating the manufacturer's ability to produce the vaccine in a consistent manner and on evaluation of results from clinical trials demonstrating safety and effectiveness.[6] The licensure process using this pathway typically takes several years to acquire the necessary data to submit a BLA. Once a BLA is submitted, the application is reviewed in 6 to 10 months.

At times accelerated approval of a seasonal influenza vaccine is needed because of actual or expected vaccine shortages. The primary purpose of accelerated approvals is to increase the amount of vaccines available to prevent serious or life-threatening disease. As with the traditional licensure pathway, clinical studies must demonstrate safety and effectiveness of the vaccine. In certain situations, immunogenicity studies based on HAI antibody response may be adequate to demonstrate effectiveness.[4] Correlates other than HAI antibody response can be used if CBER determines that the study design is acceptable and the proposed surrogate end point(s) is reasonably likely to

predict clinical benefit. If a seasonal influenza vaccine is licensed on the basis of immunogenicity data, a follow-up efficacy study is required postlicensure. The recently has licensed three seasonal TIVs through this regulatory mechanism.[6]

Currently, there are six TIV formulations and two LAIV formulations distributed for seasonal influenza in the United States, each containing antigens or attenuated viruses from three or four different influenza strains. The newly licensed quadrivalent LAIV is expected to be available during the 2013-14 influenza season. Each year, any of the previous three or four vaccine strains may be replaced with a new strain on the basis of surveillance data that demonstrate a change in circulating wild-type strains and recommendations of the WHO and the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the FDA. The process of selecting the strains and manufacturing and distributing the vaccine involves numerous steps that can take 6 to 8 months.[6] Changing the vaccine strains in previously licensed vaccines requires submission of a prior approval manufacturing supplement to the existing BLA. Clinical data are not required by the FDA for annual strain change supplements for US-licensed manufacturers of influenza vaccines.[6]

Regulatory Challenges for Currently Licensed Vaccines

Approval and licensure of all vaccines requires documentation of potency, sterility, and effectiveness. Despite more than 60 years of licensing influenza vaccines in this country, critical issues remain, including establishing appropriate correlates of protection, improving assays for potency, and finding models that can be used for evaluating when human clinical trials are unethical or not feasible.[6] Modernizing and moving vaccine development toward novel-antigen game-changing vaccine technologies will involve all of these issues and more. Critically needed changes and improvements to the assays or study methods used to evaluate each of the above criteria will be required for novel vaccines. Unfortunately, given the track record for addressing the above-noted regulatory issues with the currently licensed vaccines, it's clear that significant regulatory challenges lie ahead for novel-antigen influenza vaccines.

Although moving toward game-changing vaccines will require more than improvements to assays for potency testing and correlates of protection, knowledge of the current issues is instructive to understanding the scope of the challenge for licensing novel-antigen influenza vaccines.

Potency Testing

An important step in vaccine quality control is the testing of each individual batch of vaccine for purity and potency prior to use. The potency test is designed to measure the ability of a vaccine to protect against subsequent challenge from the active component responsible for pathogenicity. The single radial immunodiffusion (SRID) assay has been used to determine potency of all inactivated influenza vaccines licensed by the FDA since 1978. This assay adds considerable time to the vaccine development cycle; it requires production of large quantities of specific reagents for each viral strain in the vaccine, which is a process that can take up to 2 months. Because the composition of seasonal vaccines may vary annually, potency-testing reagents must be generated each year to accurately evaluate these vaccines. This timeframe generally is acceptable for seasonal vaccine changes, but it can pose a critical challenge when urgently responding to a new pandemic strain. FDA scientists currently are evaluating improved influenza vaccine potency assays, as well as alternate methods for more timely production of potency reagents.[7] Nonetheless, after 34 years, SRID, even with its well-known limitations, remains the only potency assay in use for licensing influenza vaccines in the United States.

Correlates of Protection

Demonstration of immunogenicity is a key requirement for licensure of influenza vaccines in the United States and around the world. For most influenza vaccines, the primary historic immunogenicity target is the production of serum antibody to the HA surface protein as measured by HAI.

A correlate of protection is a measurable marker that results from vaccination and serves as a predictor that an immunized individual is protected from a particular infection or disease. For inactivated influenza vaccines, the correlate of vaccine protection is based on the ability of the vaccine to stimulate a serum antibody

response. Achievement of specific serum HA antibody titers of 1:40 or greater postvaccination has been considered for decades to be an adequate surrogate for protection against influenza infection.[8,9] However, the FDA notes that: "To date, prospectively designed studies to evaluate the effectiveness of influenza vaccines have not identified a specific HI antibody titer associated with protection against culture-confirmed influenza illness."[5]

Since 1961 researchers have questioned whether HA antibody levels actually predict protection from disease.[10] More recently, studies have shown that HA antibody levels are not the most informative measure of vaccine efficacy across sub-populations.[11–13] For example, in healthy adults, an examination of HAI titers following vaccination with either TIV or LAIV found that postvaccination HAI titers alone were not sufficient correlates for vaccine efficacy and that seroconversion did not consistently predict protection.[14] Similarly, investigators have demonstrated that older adults can become infected with influenza virus in spite of having "protective" levels of antibody, which indicates that antibody titer is not well correlated with protection in such individuals. In addition, evidence is mounting that cellular immunity, not antibody, is more appropriately correlated with protection.[15-17] Finally, studies in children have reported that the 1:40 HAI titer was not appropriate for evaluating the efficacy of influenza vaccine in that age-group.[18]

Unlike TIV, no general immune correlates of protection have been established for LAIV. Furthermore, researchers have noted that LAIV protects despite its limited ability to elicit serum HAI titers,[19,20] with no documented correlation between serum antibody responses and protection from culture-confirmed influenza.[21]

These observations—as well as the low-to-moderate levels of influenza vaccine efficacy documented with current vaccines as noted in Chapter 3 of this report—support that HAI is at best a crude correlate of protection. A major challenge to game-changing vaccine development is identifying a reliable correlate of protection that can serve as the sole predictor of vaccine efficacy. Such a correlate may involve either antibody production or some marker of cellular immunity. Alternatively, a combination of correlates may be necessary to accurately predict vaccine efficacy. A critical consideration for all non-HA vaccine candidates is the challenge of demonstrating protectiveness, since the correlates of protection are not yet known for non-HA antigens. Development of vaccines based on novel antigens or cellular immunity calls for identifying new correlates of protection that can assess antibody (mucosal and serum) and cellular responses to such vaccines and that, most important, can accurately predict clinical protection.

Ongoing Issues with Current Vaccines: Impact on Game-Changing Vaccines

The European Medicines Agency (EMA) recently developed a concept paper urging revisions to the guidelines for regulating and approving influenza vaccines.[22] In this document, the EMA expressed concern that issues involving current vaccines, such as efficacy and correlates of protection across age-groups, generate unanswered questions that "not only raise problems during the assessment of new TIVs but also hamper to some extent the assessment of other types of seasonal vaccines (eg, including those that incorporate an adjuvant or live attenuated viruses) and will have important implications for the evaluation of anticipated novel vaccines."[22]

To address these issues, the EMA advocates updating the guidelines and preparing a single consolidated guidance document on the manufacturing and nonclinical and clinical development of current and future influenza vaccines.[22] The new guidelines should include:

- Guidance regarding expectations for the serological evaluation of vaccine immunogenicity
- Consideration of the selection of antibody assays and evaluation of their performance
- Consideration of how to improve on the current understanding of the predictive value of the immunogenicity data for vaccine efficacy
- Specific guidance regarding the evaluation of immune responses in population sub-groups
- Expectations for estimating vaccine efficacy in specific circumstances and populations.

These recommendations represent an important step toward updating and clarifying regulatory guidelines and are critical in pandemic preparedness. However,

while laudable and important, even these efforts fall short by focusing on current seasonal, prepandemic, and pandemic influenza vaccines. Moving past current influenza vaccines to actual game-changing vaccines will require even more sweeping reforms to the regulatory environment.

Improvements in potency assays will enhance speed and capacity of currently licensed vaccines. In addition, improved correlates of protection are needed to foster the development of novel vaccines. Although these issues are important interim considerations for pandemic preparedness before improved vaccines become available, overhaul of current influenza vaccine correlates, assays, and reagents will not result in the substantive changes required to move development of novel-antigen vaccines forward. In fact, a focus that is limited to issues applicable to currently licensed vaccines has the potential to stifle progress toward truly game-changing vaccines. We cannot be lulled into thinking that improvements in these areas will provide great improvements in influenza vaccines; they will not. These are interim concerns and must be prioritized as such.

Regulatory Challenges for Game-Changing Vaccines

As described above, even with intense focus on the regulatory challenges of current vaccines, significant problems remain after decades of licensing these vaccines. This conclusion begs the question, "How can we move forward with game-changing vaccines when we lack the ability to adequately address the basic regulatory issues of our current vaccines?" Answering that question requires a conceptual shift as well as sweeping changes to the regulatory science guiding development and licensure of influenza vaccines.

The FDA defines regulatory science as "the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products."[23] As such, regulatory science represents the bridge between basic science discoveries, the early work of industry, and the approval of novel products.[24] Moving toward evermore effective vaccines will require enhancement of current regulatory science in order to provide clear pathways for developing and licensing novel influenza vaccines. However, regulatory science itself appears to be a large factor impeding progress toward better influenza vaccines.

As part of the CCIVI project, we interviewed or received formal presentations from 88 experts in influenza vaccine research, development, or use over the 2-year period of our study. A number of these experts were interviewed multiple times. These experts included:

- International senior science, business, and policy leaders from companies that are delivering current influenza vaccines and companies that are researching and developing novel-antigen vaccines
- Experts from nongovernmental research, funding, and program organizations
- Current and past HHS employees from the Office of the Secretary, the FDA, BARDA, the NIH, and the CDC
- Current and former members of vaccine advisory boards and committees advising the US government on vaccine licensure and recommendations for use
- Academic-based vaccine development researchers
- Private-sector consultants to the vaccine industry
- Officials of nongovernmental agencies involved in vaccine development and distribution.

These interviews revealed a general consensus that any meaningful movement toward game-changing vaccines will require changes in the current regulatory pathway, which is cumbersome and lacks fruitful public-private integration. Furthermore, we also noted a general consensus that the problems facing the development of game-changing influenza vaccines are not limited solely to regulatory science obstacles.

Findings from our interviews identified significant problems within the current culture of regulatory science that are impeding the development and licensure of game-changing vaccines, including:

- The pervasive and seemingly intractable dogma that current HA-head vaccines, particularly with changes in manufacturing platforms or use of adjuvants, are adequate to provide high levels of efficacy and timely availability for the entire population for both seasonal and pandemic influenza
- A culture that lacks adequate public or private-sector leadership or vision to identify and

implement radically different approaches to novel-antigen influenza vaccine development and the pathways by which they are licensed
- Regressive, cumbersome, and unproductive interactions between the FDA and industry partners regarding pathways and requirements for novel vaccines

These challenges are explored below.

Belief That the Current HA-Head Vaccines Are Adequate

The major impediment to developing a forward-looking vision is the pervasive belief that current HA-based vaccines are adequate. As long as this view endures, efforts will remain narrowly focused on small, incremental changes to the current vaccines, and we cannot expect any real movement toward superior novel-antigen vaccines.

An example of this is the ongoing discussion regarding the use of adjuvants in influenza vaccines. As noted in Chapter 3, adjuvanted influenza vaccines are used in several countries outside the United States. These countries have approved the use of adjuvanted influenza vaccines in part because they generate a more robust humoral immune response and therefore are believed to be more effective than unadjuvanted vaccines. Because the influenza vaccine industry now realizes that unadjuvanted TIV formulations are less effective than previously stated, there is increased interest in licensing adjuvanted seasonal influenza vaccines in the United States. Currently, two manufacturers of adjuvanted seasonal and pandemic influenza vaccines are seeking licensure from the FDA. However, the course that the FDA will take with regard to licensure of these vaccines remains unclear, given recent discussions that occurred at the February 2012 VRBPAC meeting.[25]

In that regard, during our interviews, individuals from the vaccine industry as well as the FDA noted that the lack of guidance from the FDA complicates the regulatory pathway for adjuvanted vaccines. For example, in December 2008, the FDA in partnership with the NIH convened a workshop pertaining to adjuvants and adjuvanted vaccines.[26] Despite the fact that a number of adjuvants are under development, the FDA has not released an overarching written guidance specifically addressing novel-adjuvant vaccines since this workshop occurred almost 4 years ago.

Leadership and Vision to Support Development of Game-Changing Vaccines in the United States

Through our interviews, a picture emerged of a regulatory culture lacking the vision and leadership required to advocate for superior, game-changing vaccines. We found a similar lack of visionary leadership in industry, academia, governmental agencies, and federal advisory bodies. In particular, in their current form, government advisory bodies cannot or will not articulate the vision needed to effect real change in this area, which includes addressing the larger issues around developing game-changing influenza vaccines.

Our survey of the 88 experts provided a general consensus that these federal agencies were largely so "entrenched in the 'current licensed influenza vaccine environment' that they lacked the vision to set forward a game-changing vaccine agenda." Conversely, we also found that substantial expertise regarding potential game-changing vaccine technology exists at both the FDA and the NIH. Moving beyond current vaccines requires better use of existing expertise and creation of a new paradigm away from the entrenched culture. A strong, clear government voice must declare the need and path forward for game-changing influenza vaccines as a national preparedness and public health priority. The US government, in partnership with the private sector, must provide the leadership necessary to launch an initiative to develop this vision. Furthermore, federal and industry leadership should work in cooperation and close consultation with, but independent from, the FDA, the CDC, BARDA, and NIH on pathways for moving novel vaccines forward. Without such leadership and vision, we are likely to remain mired in the well-worn path of "incremental only" changes to current vaccines.

Interactions between FDA and Industry

During our interviews, interactions between industry and the FDA were portrayed to us as not forward thinking and often counterproductive. We found that industry representatives often blamed the FDA for a lack of leadership. FDA representatives were frustrated by these complaints, noting that industry has not brought forward innovative findings or

product development initiatives (eg, new correlates of protection) for the FDA to evaluate and form a response.

Developing novel game-changing vaccines will require greatly improved communication and productive interactions between government and industry partners. Currently, no mechanism exists to allow industry leaders to have substantial formal or informal discussions on critical issues related to all aspects of licensure and securing superior recommendation for vaccines with government agencies (eg, the FDA, the CDC) or federal advisory groups (eg, the ACIP, VRBPAC, the NVAC, the NBSB), nor is there an articulated plan issued by these agencies to assist companies in bringing novel vaccines through the licensure pathway. Companies are consistently looking for such guidance, particularly with regard to creating a process that is not cost prohibitive. Without means to enter into frank discussions with agencies, companies are left without clear guidance on how to navigate the licensure process.

Our interviews showed that industry partners were universally frustrated by FDA operations and were particularly concerned with staff competency and number. While our discussions with industry experts clearly indicated that there are some very highly regarded regulatory and basic science researchers at the FDA and other federal agencies, respondents found current resources to be inadequate for the task at hand. Creating game-changing vaccines requires a team of the best and the brightest scientific minds, and adequate resources are critical to attract and retain this talent pool. Unfortunately, FDA staff faces intense workloads and large administrative burdens, leaving little time for creative thinking. Lack of time and resources to proactively develop pathways for novel products (either in advance of submission or soon after the preclinical stage) has resulted in a situation in which FDA regulators generally wait until an industry partner submits its data, and only then do they begin a back-and-forth determination of whether the data are sufficient. To move beyond this approach and generate a blueprint for developing truly novel vaccines, FDA scientists need time to think, meet, discuss, and proactively focus on new ideas before all of the data have been generated.

Resources in support of such enhancements have been limited. The 2007 report from the FDA Science Board, *FDA Science and Mission at Risk*, concluded that the FDA had major deficiencies in science.[27] It also found that the agency was not positioned to meet current or emerging regulatory responsibilities. The board concluded that the deficiencies were the result of: (1) demands on FDA resources and staff that had escalated owing to increased scope and complexity of products submitted for FDA review and (2) resources not keeping up with demand.[27]

A 2010 report issued by the NBSB concluded that the "FDA has not been able to fulfill its implicit national security mission, in large part because of a lack of resources… It is imperative for America's health and progress for the FDA to be provided adequate resources to bring its regulatory science in to the 21st century."[28] The chief medical officer and deputy director of BARDA recently stated that BARDA is looking for the FDA to have the expertise to keep up with advances in science, be able to engage creatively with product developers, and adapt to new technologies.[24]

Apart from the FDA's unwillingness or inability to take a leadership role with this issue, the influenza vaccine industry also shares responsibility for the lack of any meaningful movement toward creating game-changing influenza vaccines. Our interviews revealed the frequent perception that major vaccine manufacturers lack any real incentive to develop novel-antigen influenza vaccines and therefore are uninterested in taking the lead in their development, instead preferring to maintain the status quo with current vaccines. Against this backdrop, the only current efforts that appear to be moving forward toward truly game-changing vaccines are coming from small, often start-up companies. While laudable, this is not enough.

In June 2011, the US Government Accountability Office (GAO) issued a report titled, *Influenza Vaccine: Federal Investments in Alternative Technologies and Challenges to Development and Licensure*.[29] To understand challenges to the development and license of influenza vaccines using alternative technologies, GAO interviewed approximately 40 experts. Of note, while the GAO stated that its review

was focused on influenza vaccines using alternative technologies, it primarily involved technologies or platforms for producing HA-head vaccines. The GAO concluded from their interviews and review of other federal reports that three challenges are impeding the development and licensure of influenza vaccines using alternative technologies: low demand, high research and development costs, and regulatory challenges. Specifically, two regulatory challenges were identified: (1) weaknesses in FDA's "regulatory science capacity" (2) and the lack of clear written guidance and consultation with manufacturers on some of the requirements for licensure of new influenza vaccines.[29]

Our findings, which were based on interviews with an even broader and more diverse group of vaccine industry experts and other non-industry experts, together with our extensive review of available public documents and the published literature, fully support the findings of the GAO report.

International Regulatory Leadership

Additionally, there is a lack of international leadership or vision necessary to develop and license game-changing influenza vaccines. Entities such as the WHO have provided no guidance on game-changing vaccine development and instead remain focused on increasing the world's production of and access to current vaccines. Although regulatory processes in countries outside of the United States have led to approval of adjuvanted HA-head vaccines in Europe, a near uniform silence persists on providing the critical guidance that the vaccine industry needs, coupled with incentives, to bring forth game-changing vaccines at the global level.

SUMMARY

In summary, novel influenza vaccine technologies face complicated, unclear, and uncertain regulatory pathways. To have a real global impact on seasonal and pandemic influenza preparedness, we need game-changing vaccines. The regulatory structure as it currently exists will not get us there. A substantial shift in the regulatory paradigm by both government and industry is required, along with revitalization of the FDA, to move from the current, incremental, "nibbling around the edges" approach to a broader vision on influenza vaccines. This significant, consequential change in culture will require strong leadership. Without such, we are likely to remain mired in the well-worn path of "incremental only" changes to current vaccines and little real impetus to move toward truly game-changing vaccines that will improve the public's health.

REFERENCES

1. Public Health Service Act, section 351. (42 U.S.C.§ 262). Available at: http://www.fda.gov/RegulatoryInformation/Legislation/ucm149278.htm
2. FDA. Code of Federal Regulations Title 21. (21 CFR 600.3(s)). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3
3. FDA. Vaccine product approval process. 2009. Available at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/ucm133096.htm
4. FDA. Guidance for industry: clinical data needed to support licensure of seasonal inactivated influenza vaccines. 2007. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm
5. FDA. Guidance for industry: clincal data needed to support licensure of pandemic influenza vaccines. 2007. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm
6. Baylor NW, Houn F. Considerations for licensure of influenza vaccines with pandemic and prepandemic indications in vaccines for pandemic influenza. *Curr Top Microbiol Immunol* 2009;333(5):453-70
7. Khurana S, Larkin C, Verma S, et al. Recombinant HA1 produced in *E. coli* forms functional oligomers and generates strain-specific SRID potency antibodies for pandemic influenza vaccines. *Vaccine* 2011;29(34):5657-65
8. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg* 1972;70(4): 767-77
9. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* 2010;17(7):1055-65

10. Langmuir AD, Henderson DA, Serfling RE. The epidemiologicial basis for the control of influenza. *Am J Public Health* 1964;54(4):563-71
11. Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. *J Infect Dis* 2000;181(3):1133-7
12. McMichael AJ, Gotch FM, Noble GR. Cytotoxic T cell immunity to influenza. *N Engl J Med* 1983;309(1):13-7
13. Treanor J, Wright PF. Immune correlates of protection against influenza in the human challenge model. *Dev Biol (Basel)* 2003;115:97-104
14. Ohmit SE, Petrie JG, Cross RT, et al. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. *J Infect Dis* 2011;204(12):1879-85
15. McElhaney JE. Influenza vaccine responses in older adults. *Ageing Res Rev* 2011;10(3):379-88
16. Gorse GJ, O'Connor TZ, Newman FK, et al. Immunity to influenza in older adults with chronic obstructive pulmonary disease. *J Infect Dis* 2004;190(1):11-9
17. McElhaney JE, Ewen C, Zhou X, et al. Granzyme B: correlates with protection and enhanced CTL response to influenza vaccination in older adults. *Vaccine* 2009;27(18):2418-25
18. Black S, Nicolay U, Vesikari T, et al. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. *Pediatr Infect Dis J* 2011;30(12):1081-5
19. Beyer WE, Palache AM, de Jong JC, et al. Cold-adapted live influenza vaccine versus inactivated vaccine: systemic vaccine reactions, local and systemic antibody response, and vaccine efficacy: a meta-analysis. *Vaccine* 2002;20(9-10):1340-53
20. Dormitzer PR, Galli G, Castellino F, et al. Influenza vaccine immunology. *Immunol Rev* 2011;239(1):167-77
21. Ambrose CS, Luke C, Coelingh K. Current status of live attenuated influenza vaccine in the United States for seasonal and pandemic influenza. *Influenza Other Respi Viruses* 2008;2(6):193-202
22. EMA. Concept paper on the revision of guidelines for influenza vaccines. 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/10/WC500115612.pdf
23. FDA. The promise of regulatory science. 2010. Available at: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228206.htm
24. National Research Council. *Advancing Regulatory Science for Medical Countermeasure Development: Workshop Summary*. Washington, DC: The National Academies Press; 2011
25. FDA. Summary minutes Vaccines and Related Biological Products Advisory Committee. 2012 Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/esandRelatedBiologicalProductsAdvisoryCommittee/UCM296193.pdf
26. FDA. Adjuvants and adjuvanted preventative and therapeutic vaccines for infectious disease indications. 2008. Available at: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm095698.htm
27. FDA Science Board. FDA science and mission at risk: report of the Subcommittee on Science and Technology. 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf
28. National Biodefense Science Board. Where are the countermeasures? Protecting America's health from CBRN threats. 2010. Available at: http://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/nbsb-mcmreport.pdf
29. GAO (US Government Accountability Office). Influenza vaccine: federal investments in alternative technologies and challenges to development and licensure. GAO-11-435. 2011

CHAPTER 11

MARKET CONSIDERATIONS, CHALLENGES, AND BARRIERS TO ACHIEVING GAME-CHANGING INFLUENZA VACCINES

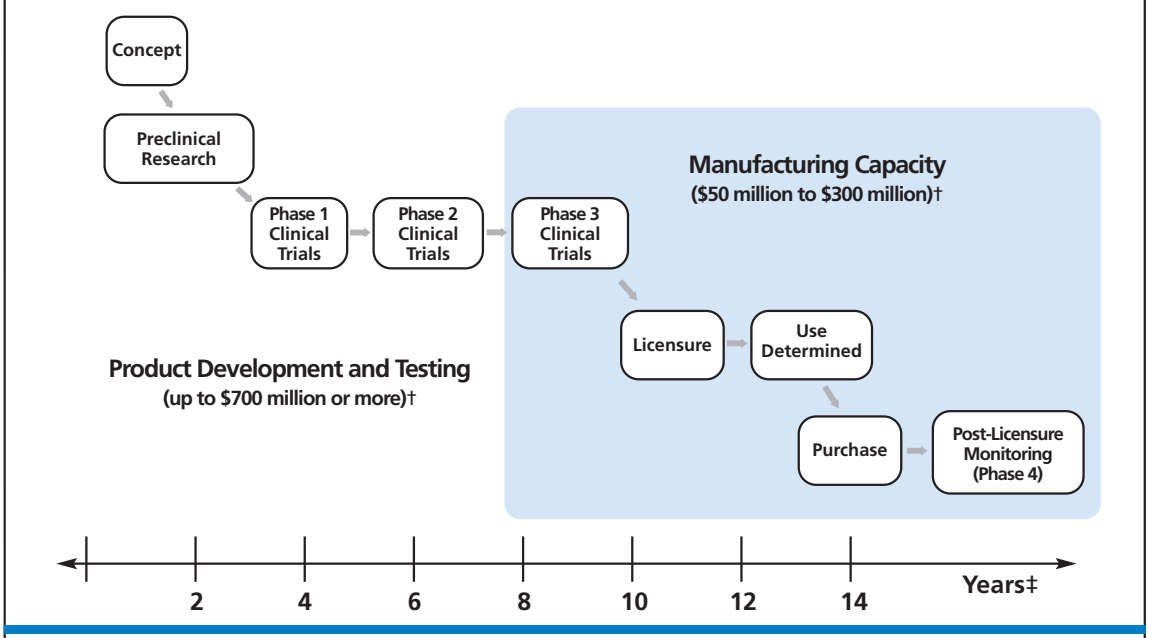
INTRODUCTION

Influenza vaccine manufacturing exists in a largely for-profit business world, and, as with other for-profit businesses, manufacturers have a responsibility to their shareholders, owners, and investors to maximize profits.[1] However, the public perceives that vaccines exist for the common good and are part of the public health infrastructure. As a result of these potentially conflicting perspectives, influenza vaccine manufacturers must navigate these divergent financial and social pressures. Despite this challenge, the influenza vaccine market is substantial, and the US government is the single largest purchaser of influenza vaccines in the world. During the 2009-10 influenza pandemic alone, the United States bought more than $2 billion in influenza vaccine and components.[2] In a typical seasonal influenza year, the global influenza vaccine market is estimated to be $2.8 billion; this figure will be several times larger during a pandemic.[3] For comparison, the annual global market for all vaccines combined is estimated to be $20 billion.[4] Even though the market for influenza vaccines is potentially lucrative, a number of challenges face companies that bring new vaccines to market. This chapter focuses on the market challenges facing game-changing influenza vaccines.

INITIAL COSTS AND REGULATORY APPROVAL

As described in Chapter 10, all vaccines follow a common pathway for FDA approval before they can be made available for purchase in the United States. Key steps in the process to take a vaccine from concept to licensed product include preclinical research, followed by phase 1, phase 2, and phase 3 clinical trials (**Figure 11-1**). Phase 1 clinical trials assess safety, phase 2 clinical trials assess safety, dosing and preliminary effectiveness, and phase 3 clinical trials are definitive safety and efficacy studies. After each step in the process, the company analyzes the scientific data generated as well as the potential for return on investment and then decides whether or not to continue investment or abandon the product.[5] If the company completes phase 3 clinical trials, the next step is to submit an application to the FDA for licensure to market and sell the vaccine in the United States. As part of this process, the FDA will determine if the vaccine's approval is limited to certain age-groups or risk populations. This entire process, from preclinical research through licensure, can take up to 15 years and more than $1 billion to complete.[6]

FIGURE 11-1. The Vaccine Technology Pathway[5-7]



†The cost estimates are typical ranges.
‡This is a timeline of the entire process, if it proceeds without delay. The timeline varies significantly from product to product.

Despite a significant investment in time and money, most new-concept vaccines fail to make it from concept to phase 3 clinical trials, which are pivotal for bringing a new vaccine to the market. This phase demonstrates whether a new vaccine performs as well as (noninferiority) or better than (superiority) vaccines already on the market. To date, all influenza vaccines licensed in the United States have been licensed on the basis of demonstrating noninferiority. Demonstrating superiority in a phase 3 clinical trial requires showing significantly higher vaccine efficacy compared with licensed vaccines. This superiority must be demonstrated across multiple risk populations (eg, persons 65 years of age or older, immunocompromised persons) against the backdrop of potential variability in influenza incidence and in circulating influenza strains during any given influenza season. These variables present significant challenges to accurately assessing the efficacy of new influenza vaccines and demonstrating superiority. For example, a single strain of influenza may dominate in a given year, or the influenza incidence in a key study population may be too low (ie, <10% attack rate among study participants) for researchers to detect statistically significant protection from a new vaccine without unrealistically large study populations. Such unforeseen and uncontrollable variables can require clinical trials to be conducted over several influenza seasons, significantly increasing costs. These trials also need to have significantly more participants than noninferiority trials, increasing cost and time substantially.

Licensure of an influenza vaccine in other countries requires further extensive expenditures of time and resources. Most countries have domestic regulatory authorities that must approve a product before it can be used. The licensing procedures in various countries may require different processes, inspections, and clinical trials. The expansion or duplication of costly activities adds to the initial licensure investment costs.

CHALLENGES OF BRINGING A GAME-CHANGING INFLUENZA VACCINE TO MARKET

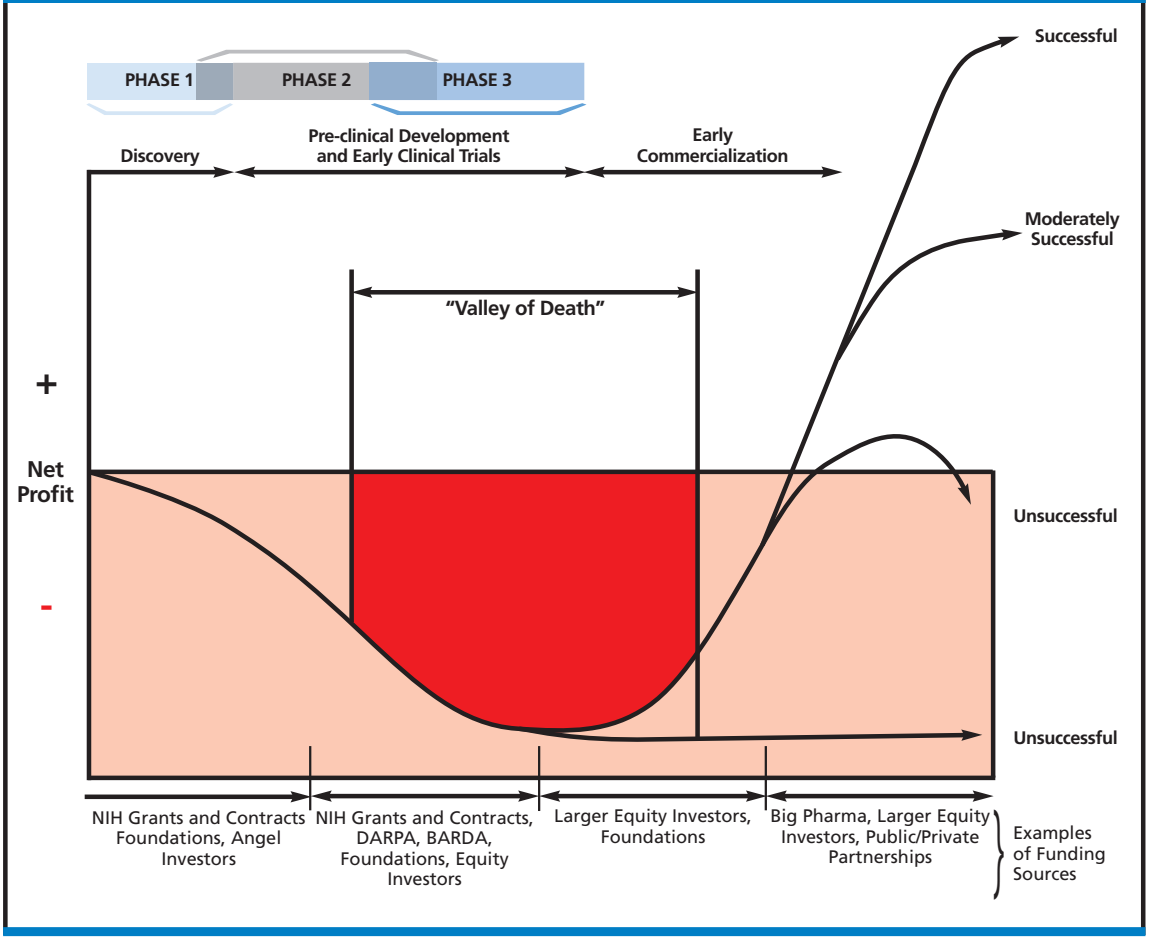
The process of bringing any influenza vaccine to market involves some uncertainty as well as potential risks and costs. Novel-antigen influenza vaccines that are potential game-changers and that are significantly different from currently licensed vaccines in terms of antigen, production technologies, or route of administration face the same hurdles for approval as more traditional new vaccines. The already daunting approval process, however, will be even longer and more extensive and the financial risk substantially greater for these vaccines.

For example, the makers of novel-antigen vaccines likely will strive to demonstrate superiority in order to justify a higher cost per dose of vaccine purchased. Therefore, the sample sizes for phase 3 clinical trials will need to be much larger than those for noninferiority studies. As discussed in Chapter 10, an additional challenge is evaluation of vaccine effectiveness if the vaccine cannot be assessed using current regulatory correlates of protection for existing vaccines (such as HA antibody).

The implications of these research, regulatory, and market hurdles clearly discourage investment in revolutionary influenza vaccines. For example, MedImmune, the maker of the LAIV vaccine, FluMist, which is currently only licensed in the United States and Canada, expended almost 30 years from concept to licensure and more than $1 billion to move from late preclinical trials through the licensure process in the United States.[5,8] In 2009, FluMist sales amounted to $145 million, which demonstrates that MedImmune has yet to gain a critical market share for this vaccine since its licensure.[3] Approval of the technology used in developing FluMist required additional studies and, even with such efforts, the vaccine is licensed only for persons 2 to 49 years of age. Moreover, the vaccine cannot be administered to persons with asthma or children under 5 years of age who have a history of recurrent wheezing. Likewise, safety has not been established in immunocompromised persons or persons with underlying medical conditions that put them at risk for complications following influenza infection.[9] These constraints limit the potential market for this type of vaccine.

A major challenge with the licensure process of any new vaccines is that they must make it through the often referred to "valley of death" product development experience (see **Figure 11-2**). The valley of death is where the majority of vaccines that make it to phase 2 and 3 testing fail, owing to significant costs and limited financial support. For all the reasons noted

FIGURE 11-2. Market Dynamics for Developing Novel-Antigen Game-Changing Influenza Vaccines



This image was adapted from Figure 3 in Steinmetz KL, Spack EG. The basics of preclinical drug development for neurodegenerative disease indications. *BMC Neurology* 2009;9 Suppl 1:S2 and used under terms of the Creative Commons Attribution License.

above, novel-antigen influenza vaccines run an even a greater challenge for surviving the valley of death. In addition, as we have detailed throughout this report, two common beliefs held by the public health, medical, and policy communities are that the current influenza vaccines are largely effective and that the greatest challenge to preventing both seasonal and pandemic influenza is to find ways to make more of the current vaccines faster. These perceptions present an almost insurmountable barrier to securing the necessary public- and private-sector investments to take even one candidate novel-antigen influenza vaccine, yet alone multiple vaccines, through to licensure. Even if a novel-antigen influenza vaccine makes it across the valley of death, no guarantee exists that it will receive a superior recommendation for use over existing vaccines.

Because of the constraints and financial disincentives against developing novel-antigen vaccines, adjuvanted influenza vaccine research, using HA-head antigens, is being pursued by many of the current manufacturers. Such a course allows them to increase both production capacity and may increase vaccine effectiveness for some populations. This approach also allows manufacturers of the adjuvanted vaccines to utilize the same regulatory approval process as is currently used (ie, HAI as the primary correlate of protection). Also, some manufacturers are pursuing research into other manufacturing platforms, including cell culture and recombinant technologies; however, vaccines derived from these new platforms are still based on the HA-head antigen.

INFRASTRUCTURE COSTS

A major cost in new vaccine development is the construction and licensing of manufacturing facilities for vaccine production, both for phase 2 and phase 3 studies as well as for postlicensure production. Most vaccines require dedicated facilities specifically designed for a particular product and staffed by a skilled workforce. In anticipation of meeting postlicensure production demands, a company must begin designing and building new facilities 4 to 6 years before it expects a new vaccine to be licensed.[5] Developing vaccine manufacturing facilities can cost between $30 million and $500 million, depending on their size and type, with an additional $6 million to $100 million to meet current Good Manufacturing Practices (cGMP) validation activities and requirements.[5] Throughout the building process, the manufacturer must work with the FDA to ensure that the facility and the manufacturing processes meet cGMP requirements. For example, the Novartis manufacturing plant in Holly Springs, North Carolina, which was designed to produce a cell-culture–based influenza vaccine and was completed in 2009, cost approximately $1 billion to build, equip, and meet cGMP requirements for FDA approval.[10]

THE COST OF DOING BUSINESS

Once a facility is fully operational, the ongoing costs of manufacturing a vaccine also are significant. Included among the essential requirements for manufacturing vaccines are cGMP-approved equipment and manufacturing processes, strict quality control, and a highly skilled workforce. Analysts have estimated that 60% of vaccine costs are unavoidable fixed costs, which do not vary by quantity of vaccine produced, and are separate from research and development costs.[11] Another 25% of costs are tied to the batch of vaccine produced. As with the fixed costs, these batch-specific costs do not vary with the number of doses produced. In fact, only 15% of the costs are variable.[11] Understandably, the high level of fixed costs forces manufacturers to produce and sell only vaccines that can be marketed at near-capacity levels because the fixed costs must be spread across the greatest number of doses, thereby lowering the per-unit costs. Because of this need to offset high manufacturing costs and high costs associated with research and development, revenues must be high enough to justify investment in a new influenza vaccine. New vaccine technologies may be more scalable than current vaccine technologies, which could help address the cost burden, but this remains to be seen.[5]

POSTLICENSURE COSTS RELATED TO SURVEILLANCE

Even after their vaccine is sold, companies remain responsible for conducting a certain level of postlicensure surveillance to identify adverse events or quality issues. If postlicensure surveillance demonstrates issues with a vaccine, the manufacturer may recall the vaccine, either voluntarily or under a requirement from the FDA. For example, during the 2009 H1N1 pandemic, MedImmune recalled almost 5 million doses of pandemic vaccine and Sanofi-Aventis recalled

800,000 doses because of potency inconsistencies, not safety concerns.[4] As noted in Chapter 6, manufacturing issues are relatively common for influenza vaccines. The costs and lost revenue associated with such recalls are substantial and can significantly reduce profits.

In addition to the costs discussed above, vaccine manufacturing companies may face lawsuits from individuals possibly adversely affected by influenza vaccines. Influenza manufacturers work on limited profit margins, so legal liability can quickly turn this small profit into a loss. To address this issue, the US government has attempted to shield companies from liabilities other than negligence, such as manufacture error, by providing an alternative to the traditional tort system.[12] In 2004, President Bush added influenza vaccines to the Vaccine Injury Compensation Program (VICP).[13] This program was created in 1986 to halt the exodus of manufacturers from the vaccine market.[1] However, the liability protection provided under the program faces continual legal challenges in part because some claims in civil court are not prevented by the VICP, so vaccine manufacturers can never be certain that existing protections will shield them from potentially costly lawsuits. Of note, the US Supreme Court recently issued a favorable opinion in the monumental vaccine-liability case, Bruesewitz versus Wyeth, whereby the Court confronted and upheld the liability protections provided by the VICP.[13] If Wyeth had lost that case, some experts believe many vaccine manufacturers would have left the market because the legal risks would be too high to justify the investment.[14–16]

SIZE AND LIKELIHOOD OF RETURN ON INVESTMENT FOR VACCINES

The first considerations a manufacturer will make when trying to decide whether or not to invest in a new influenza vaccine technology are the size of the investment, the time involved to bring the product to market, and the possible risks incurred if a new vaccine is produced for use. Next, the investor will evaluate how these costs and risks affect a standard return-on-investment analysis. To assess potential revenues from vaccine sales, investors will consider the following three questions:

- How many doses of the vaccine can be sold and over what period?
- At what price can the vaccine be sold to both the public and private sectors?
- Can these revenues be expected to be maintained, and if so, how?

GOVERNMENT-SUPPORTED RECOMMENDATION FOR USE AND FOR COMMANDING A SUPERIOR PRICE

Once a new influenza vaccine is licensed by the FDA, it can be sold within the United States. However, it will not be purchased at high volumes unless the ACIP specifically recommends its use over other influenza vaccines. For example, although FluMist was added to the list of recommended influenza vaccines in 2003, the ACIP did not recommend it as superior to TIV, particularly in children, and as a result, it has failed to obtain a substantial market share.[9,13] Approval and recommendations from the ACIP allow the US government to purchase new vaccines. Since the US government is the largest purchaser, the optimum outcome for the manufacturer is for the ACIP to approve a vaccine for a wide segment of the population. Many insurance providers also base coverage policies on ACIP recommendations, which means the recommendations are essentially required before a manufacturer can attain significant market share and associated revenues.[4] Recommendations from the ACIP change incrementally, and new influenza vaccines may require additional time or studies to gain ACIP support. Uncertainty around whether or not a new vaccine will gain support from the ACIP can decrease vaccine revenues and contributes to the list of challenges faced by manufacturers.

MATURITY OF THE MARKET

While the recommendations of the ACIP are important to pricing and revenue, the maturity of the market also makes a significant difference. There are two general pricing models for new vaccines.[1] The first is for vaccines that target a new problem, resulting in an entirely new market. Manufacturers of these vaccines can command a much higher price because there are no alternatives. Two examples are vaccines produced by Merck & Co., Inc.: Gardasil (for human papillomavirus [HPV]), which sells for $130 per dose, and Zostavax (for herpes zoster), which sells for $161 per dose on the private market.[17]

The second model involves new vaccines that target a disease for which vaccines already exist (referred to as a "mature market"). Many childhood vaccines fall into this category, and such vaccines are typically produced by more than one manufacturer; examples include *Haemophilus influenzae* type B (Hib) vaccine and pediatric diphtheria-tetanus-pertussis (DTaP) vaccine. On the private market, these vaccines sell for approximately $21 and $23 per dose, respectively.[17] These vaccines are seen as commodities.[1] New influenza vaccines fit into this second category, in that manufacturers seeking to manufacture such vaccines will face a mature market where potential prices will be lower than in a new market.

When an improved version of an existing vaccine enters a mature market, it typically sells for several times the price of the vaccine it replaces, but still not as much as if it were produced for a new market. For example, in 1988 the licensed Hib plain polysaccharide vaccine sold for $6.68 per dose. It was replaced by a new, more effective, conjugate vaccine that sold for $13.75 per dose, double the price of the original.[18] Thus, even though prices for new vaccines in mature markets are higher than the vaccines they are replacing, the prices do not reach the level that can be charged for a vaccine in a new market.

TIME FRAME FOR RECOUPING COSTS

Even if a new influenza vaccine gains a substantial market share after licensure, the time that it can hold a prominent position in the market is uncertain. Given this uncertainty, investors may hesitate to devote capital to new influenza vaccine technologies or facilities if they have concerns that the product may become obsolete before the investment can be recovered and real profits can be generated. In this instance, "best" could be the enemy of "better," in that a new vaccine could offer an improvement over current vaccines and benefit society (ie, be a "better" vaccine), but not be developed or marketed because of concerns that an improved technology, and thus an even more improved or "best" product, may come along and take over the market share. Also, companies that already have an investment in a licensed influenza vaccine and its production facilities have a huge disincentive to promote or accelerate new technologies and better vaccines. It is not in the companies' best interests to have new vaccines enter the market before they can recoup a return on their existing investments.

MAGNITUDE AND LIKELIHOOD OF RETURN ON INVESTMENT FOR INFLUENZA VACCINES

Even during the best economic times, novel influenza vaccine technologies face uncertain profits because the high development costs are matched with uncertain revenues. Profit depends on selling a substantial quantity at a price and in a time frame that can offset the costs incurred.

Industry's memory is influenced by MedImmune's experience with FluMist. It was considered a novel product in that it was a nasal spray instead of intramuscular injection. Its safety profile was demonstrated to be acceptable, and its efficacy was higher in children than with TIV. Initially, the price for FluMist was twice that of existing TIV.[17,19] Following entry of FluMist into the market, MedImmune was able to sell only a fifth of the doses it produced for the 2003-04 season, even though TIV was in short supply. While the initial release of FluMist was complicated by refrigeration requirements, the product has yet to be as widely accepted as TIV. After decades of investment costs, the anticipated windfall of revenue has not occurred. This scenario does not bode well for the willingness of the influenza vaccine market to accept and pay for innovation.[13]

Consumer acceptance of new influenza vaccines also plays an important role in the economics of the influenza vaccine market. Simply because they are new and unfamiliar, new products often are seen as less safe than traditional products, even if their safety profiles are identical or superior.[20] Consumers can be suspicious of new technologies for any number of reasons. For example, LAIV is a live-virus product, which is an important issue for some consumers. Similarly, the use of adjuvants may raise concerns for consumers. Adjuvants, however, may be a necessary component of a new vaccine to achieve a superior immune response. Given the experience in other countries, consumer perceptions of unknown components such as adjuvants can decrease acceptance and could create issues with liability if the added component is perceived by the public as unsafe.

DEMAND AND DIFFERENTIATION OF INFLUENZA VACCINES

New influenza vaccines will face similar issues that affect currently licensed vaccines, including the potential for variable demand in any given influenza season as well as the inability to store vaccine from one season to another (since vaccine composition varies from year to year). In the current influenza vaccine market, demand and the amount of any particular vaccine purchased are affected by other manufacturers. For example, one manufacturer might sell more vaccine in a given year than a competitor that experienced problems with production or quality. This adds to the uncertainty surrounding annual vaccines, which can be difficult to predict in terms of disease incidence and population-based demand.

One way for a manufacturer to avoid some of the uncertainties inherent in the vaccine market is to have a "differentiated" vaccine, which is a vaccine that consumers can distinguish from other vaccines on the market. If a differentiated vaccine can be shown to offer a unique advantage over other vaccines on the market, it may gain a significant market share and be able to monopolize the market until a rival product emerges. Monopolies are coveted market positions, because they give a manufacturer power to command a higher price for its product and an ability to sell more product than if the market is uniformly competitive. This is seen in current childhood vaccine markets, which are dominated by only one or two manufacturers.[1]

There are several ways in which a new influenza vaccine could be positively differentiated, all of which require the product to be as safe as or safer than currently licensed vaccines:

- Superior efficacy across populations at increased risk for influenza-related complications or death
- Broad protection against more than one strain of influenza
- Shorter production time
- Longer duration of protection
- More accepted mode of administration
- Increased stability

By definition, a future game-changing influenza vaccine will be differentiated from currently licensed influenza vaccines. However, this does not ensure a windfall or even a profit, since it's possible for the public to perceive a new vaccine as being negatively differentiated. For example, as noted above, new products may be perceived as less safe, ineffective, or too expensive, and consumers may prefer a familiar vaccine over a vaccine produced with a new technology. Furthermore, if a company—to decrease the costs of development or increase public acceptance—tries to produce an influenza vaccine that is only minimally different from others, the new vaccine might not be differentiated enough to stand above the competition. If a new vaccine fails to be positively differentiated and capture a significant market share, the price paid may fall because of increased competition between manufacturers. Also, since the manufacturer of the new vaccine might not be able to sell as many doses, the per-unit costs will rise. In combination, these factors will result in an undifferentiated or minimally differentiated new vaccine being considerably less profitable than a highly differentiated product.

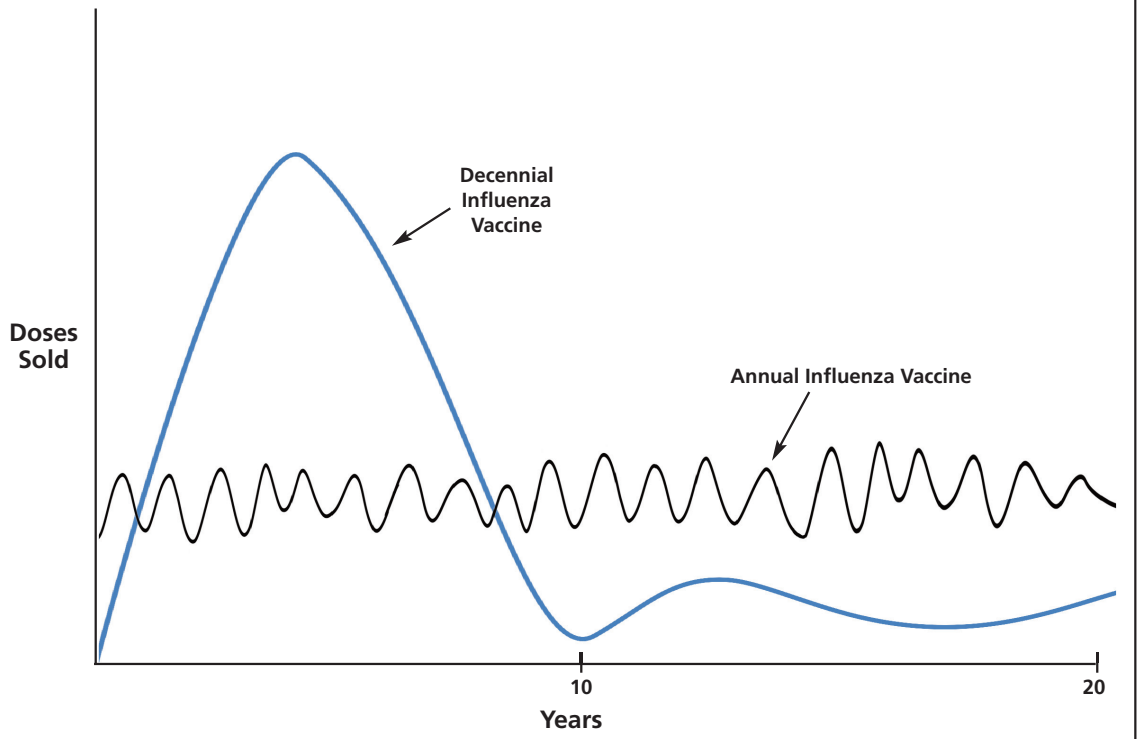
Finally, it is not easy to determine at the beginning of product investment whether a new influenza vaccine will be positively differentiated enough. This uncertainty, which is driven by the characteristics of the influenza vaccine market, creates yet another barrier to development of potentially game-changing influenza vaccines.

CATCH-22 OF THE INFLUENZA VACCINE MARKET

One of the highest priorities in advancing population-based protection against influenza is to have an influenza vaccine that can be administered infrequently (such as every 10 years), provides high levels of protection against a number of influenza subtypes and antigenic variants, and is highly effective in populations at risk for increased morbidity or mortality or who experience reduced efficacy with current vaccines. Obviously, the safety profile of such a new vaccine must be at least as good as the current vaccines. Should a vaccine be able to meet these specifications and enter the market, it will dominate and the other influenza vaccines will leave the market. Initially, the demand for this new vaccine will be extensive, but once a large proportion of the population is vaccinated, the demand will be limited largely to each new birth cohort

or groups needing booster doses, since most individuals will no longer need an annual vaccination (**Figure 11-3**). This is a dramatically different business model than the current model, where annual vaccination is recommended for the entire population. For this new vaccine model to be attractive to manufacturing companies, the demand must be stable and there must be indications that the significant profits in the initial years will more than compensate for the lower demand in subsequent years. Unfortunately, the profit-driven model for manufacturing vaccines will make it potentially unlikely for this type of vaccine to ever be developed absent perhaps governmentally supplied incentives, even though it would be of the greatest benefit to the public's health.

FIGURE 11-3. Hypothetical Comparison in Doses Sold Over Time for an Annual Vaccine and a Vaccine Administered Every 10 Years



A novel influenza vaccine that provides protection for a number of years will need to cost substantially more per dose than current vaccines for investors and manufacturers to recoup costs, since less-frequent vaccine administration will lead to sale of fewer doses over time. It is unclear whether policymakers will be willing to provide financial incentives to reduce these costs and if purchasers (particularly government purchasers) will be willing or able to pay these increased initial costs. Furthermore, those 65 years of age and older traditionally have had the highest rates of annual influenza vaccination, which means Medicare reimbursement policies will have significant implications for revenue generation with use of new influenza vaccines. Loss of this critical source of annual revenue could lessen the potential profitability of a new vaccine. Further analysis of these issues may reveal that this type of new vaccine cannot be profitable unless the per-unit cost can somehow be lowered, again, perhaps through governmental incentives. If the per-unit cost requirement for profitability exceeds what the market will or can bear, then the chance that this type of vaccine will be developed is minimal, even if, as noted above, such a vaccine would bring a greater benefit to society and thereby save the societal costs associated with seasonal and pandemic occurrences of influenza.

MAGNITUDE AND LIKELIHOOD OF RETURN ON INVESTMENT AS A BARRIER FACING NEW PRODUCTS

Revenues for novel influenza vaccines will likely not be as large as for vaccines in new markets because of the maturity of the influenza-vaccine market, issues with vaccine differentiation, the potential of changing the paradigm away from annual seasonal vaccination, and society's willingness to pay for innovation. While

significant investments have been made in influenza vaccine technology and manufacturing in the last decade, a small proportion of these resources have been devoted to truly novel-antigen vaccines that are potentially game-changing.

US GOVERNMENT'S ROLE IN ENSURING INVESTMENT IN INFLUENZA VACCINE

The US government has provided major support for influenza vaccine manufacturing over the past several decades, particularly since 2005, as part of significant pandemic preparedness efforts (**Table 11-1**). In addition to this support, the government purchases seasonal influenza vaccines each year and potential pandemic vaccines for stockpiling.
To illustrate this point, BARDA has invested approximately $2 billion since 2005 on domestic and international manufacturing capacity using current HA-head, egg-based, or cell-culture–based vaccines. These technologies are not game-changing and may be considered "low-hanging fruit" with less uncertainty and lower costs than truly novel technologies. During the same period, BARDA contracted with three companies for approximately $250 million (with a potential option for more resources) to assist in the development of three differentiated influenza vaccine technologies.[21] None of these three vaccine technologies meet the criteria for a game-changing vaccine (**Table 9-1**, Chapter 9). While other federal funding sources exist, such as the NIH and the Defense Advanced Research Projects Agency (DARPA), which provide some incentive to move these technologies forward, BARDA is the congressionally mandated federal authority responsible for development and procurement of medical countermeasures for public health emergencies, such as pandemic influenza. As noted in Chapter 9, 13 influenza vaccines with novel antigens are currently in clinical trials. None of them are funded by the US government; rather, they are being funded by industry, foundations, or university partnerships.

TABLE 11-1. United States Government Funding* for Influenza Vaccine Manufacturing, 2005-2011[21]

Domestic cell culture–based	$1,707,400,000
Domestic egg-based	$178,000,000
International	$54,000,000

* Funding from Assistant Secretary for Preparedness and Response/Biomedical Advanced Research and Development Authority to build/develop capacity for influenza vaccine manufacturing. It does not include any purchases of influenza vaccines or R&D.

The United States is the only country that has a universal recommendation for influenza vaccination. In addition, influenza vaccine is the only vaccine recommended for annual administration to all US citizens over 6 months of age and older. Because of this universal recommendation, the quantity of influenza vaccine that the US government buys each year is substantial, effectively guaranteeing a routine order for influenza vaccines.

NOVEL-ANTIGEN VACCINE INVESTMENT AND THE VALLEY OF DEATH

As we noted above, the major challenge with the research, development, and licensure of novel-antigen, game-changing influenza vaccines is successfully bringing one or more of them through the "valley of death" product development experience. We interviewed subject matter experts in the venture capital and equity investment communities who have experience in early-stage investment in new vaccines, executives of leading start-up companies researching novel-antigen influenza vaccines technologies, and executives from the manufacturers of the current influenza vaccines. We could find no evidence that any private-sector investment source, including venture capital or other equity investors or current vaccine manufacturers, will be sufficient to carry one, yet alone multiple, potential novel-antigen influenza vaccines across the valley of death. The primary reasons given for this finding include the current lack of consensus that such vaccines are needed, the unclear regulatory path to licensure, and the unclear return on investment. Finally, while the US government's support for novel-antigen influenza vaccine research and development—primarily through NIH and BARDA funding—exceeds that of other countries, it is clearly insufficient to move even one such vaccine through the valley of death.

SUMMARY

Although the major pharmaceutical manufacturers of the current influenza vaccines are beginning to acknowledge the growing body of data supporting limited effectiveness of these vaccines, the existing vaccines represent a reasonably stable source of annual income for them. This steady income stream exists despite uncertainty regarding the antigen composition of the seasonal influenza vaccines each year and the annual variability in vaccine virus production and vaccine manufacturing. Given this reality, these companies have little incentive to change the status quo. Furthermore, start-up companies with promising novel-antigen technologies are unable to secure sufficient public- or private-sector investment to move their vaccines through the valley of death. Since so many negative marketing issues and financial uncertainties work against the development and realization of new influenza vaccine technologies, we conclude that game-changing influenza vaccines are very unlikely to become a reality without a new financially sound pathway supported by the US government, other national governments, and/or private-sector investment.

REFERENCES

1. Klein J, Myers M. Vaccine shortages: why they occur and what needs to be done to strengthen vaccine supply. *Pediatrics* 2006;117(6):2269-75
2. HHS. Fact sheet: HHS 2009 vaccine development activities. Available at: https://www.medicalcountermeasures.gov/barda/pandemic-influenza/hhs-2009-h1n1-vaccine-factsheet.aspx
3. Datamonitor. Abbott's flu vaccine business may represent a good deal for acquisitive drug makers. *Datamonitor* 2010. Available at: http://www.datamonitor.com/store/News/abbotts_flu_vaccine_business_may_represent_a_good_deal_for_acquisitive_drug_makers?productid=9ACE8CAA-1CBE-46E5-9D91-54673F5E4C7A
4. Weschler J. Manufacturers look to vaccines for growth and innovation. *Pharm Tech* 2010;34(2): 30-7
5. Plotkin S, Orenstein W, Offit P, et al. Vaccine industry. In: *Vaccines*. Elsevier Health Sciences; 2008:37-44
6. Orenstein WA, Douglas RG, Rodewald LE, et al. Immunizations in the United States: success, structure, and stress. *Health Affairs* 2005;24(3):599-610
7. GAO (US Government Accountability Office). Efforts under way to address constraints on using antivirals and vaccines to forestall a pandemic. GAO-08-92. 2008
8. Gruber WC. Vaccine shortages R&D challenges and possible solutions. 2005 Available at: http://www.secebt.org/uploads/documents/Gruber1.ppt
9. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62
10. Roos R. Novartis says cell-based flu vaccine facility ready to produce. CIDRAP News 2011. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/dec1311novartis.html
11. CBO. *U.S. Policy Regarding Pandemic-Influenza Vaccines*. 2008. Available at: http://www.cbo.gov/publication/41721
12. McAbee GN, McDonnell WM, Donn SM. Bruesewitz v Wyeth: ensuring the availability of children's vaccines. *Pediatrics* 2011;127(6):1180-1
13. Pasternak A, Sabow A, Chadwick-Jones A. Vaccines: market on the rebound. *Pharm Exec* 2006;26(5):110-20
14. Meier B. Supreme Court to consider vaccine case. *New York Times*. 2010
15. Bloomberg News. U.S. Supreme Court justices signal split on vaccine-injury lawsuits against pharmaceutical industry. *NJ.com*. 2010 Available at: http://www.nj.com/business/index.ssf/2010/10/us_supreme_court_justices_sign.html
16. Courtney B, Morhard R. Anticipating the impact of Bruesewitz v. Wyeth on vaccine and medical countermeasure injury compensation and availability. *BiosecurBioterror* 2010;8(4):315-20
17. CDC. CDC vaccine price list. 2012
18. CDC. CDC vaccine price list. 1988
19. CDC. CDC vaccine price list. 2004
20. Slovic P. Perception of risk. *Science* 1987;236(4799):280-5
21. CIDRAP. Based on compilation of several sources for which URLs are not currently valid; available on request. 2012

CHAPTER 12

PUBLIC HEALTH POLICY BARRIERS TO ACHIEVING GAME-CHANGING INFLUENZA VACCINES

INTRODUCTION

In this chapter, we describe the public health policy barriers to achieving novel-antigen, game-changing influenza vaccines. These barriers were identified through a comprehensive review of leading reports and documents on influenza vaccines generated by international and national government agencies or advisory groups and nongovernmental organizations and through our interviews with 88 subject matter experts as described in Chapter 10.

US GOVERNMENT POLICIES AND ACTIVITIES

We review US influenza vaccine policy efforts during two periods: (1) following HPAI A/H5N1 reemergence and prior to the 2009 A(H1N1)pdm09 pandemic (2003 to April 2009) and (2) subsequent to the recognition of the pandemic in April 2009 (May 2009 to June 2012).

Influenza Vaccine Policy: 2003-2009 (Pre-pandemic)

In 2003, the reemergence of widespread HPAI A/H5N1 influenza outbreaks in poultry, including domestic waterfowl, in Asia brought new importance to the need for global pandemic influenza vaccine preparedness. In response to this need, the Homeland Security Council of the Executive Office of the President issued a national comprehensive strategy for pandemic influenza.[1] The national strategy focused on three pillars: preparedness and communication, surveillance and detection, and response and containment. Under the area of preparedness, policies around influenza vaccines were driven by two different but complimentary goals: (1) to be able to vaccinate the entire US population within 6 months after the beginning of an influenza pandemic using a domestically produced influenza vaccine and (2) to expand public health recommendations for seasonal influenza vaccine to include all residents of the United States 6 months of age or older.[1-3] With regard to development of new influenza vaccines, the strategy included the following two statements:

> *"Accelerate the development of cell culture technology for influenza vaccine production and establish a domestic production base to support vaccination demands."*[1]

> *"Use novel investment strategies to advance the development of next-generation influenza diagnostics and countermeasures, including new antivirals, vaccines, adjuvant technologies, and countermeasures that provide protection across multiple strains and seasons of the influenza virus."*[1]

As part of this strategy, HHS was charged with carrying out the mission to "facilitate the development, production, distribution, and utilization of pre-pandemic and pandemic vaccines."[4] To address this mission, HHS developed the HHS Pandemic Response Plan and identified a series of deliverables. First, HHS announced that, to accomplish the mission, it would "expand seasonal influenza domestic vaccine production [to cover the US population for whom vaccine is recommended] through normal commercial markets."[2] This approach intrinsically linked seasonal vaccine production with pandemic vaccine preparedness. HHS clearly articulated goals for developing novel manufacturing platforms, such as mammalian-cell–culture vaccines; however, this approach primarily focused on ways to make more HA-head vaccines quickly. While the strategy included a goal to develop universal influenza vaccines, this goal was not based on a recognition of the limitations of the efficacy and effectiveness of the currently licensed seasonal or pandemic influenza vaccines, but rather on an effort to improve vaccine manufacturing capacity.

In 2006, the national strategy was further codified with the passage of the Pandemic and All-Hazards Preparedness Act (PAHPA), which established the Office of the Assistant Secretary for Preparedness and Response (ASPR), provided the authority and funding for BARDA, and required the development of a national health security strategy.[5] ASPR is responsible for ensuring that medical countermeasure are available, such as a pandemic influenza vaccine, during a national public health emergency. Its initial plan for public health emergency medical countermeasure enterprise (PHEMCE), released in 2007, did not include pandemic influenza vaccines, as they were covered under the HHS pandemic influenza plan.[6]

In accordance with existing plans, ASPR and BARDA pursued the national policy directives to ensure domestic manufacturing capacity for influenza vaccines so that 300 million individuals could be vaccinated within 6 months following the beginning of a pandemic. The primary focus of these efforts was summarized as follows: "Cell-based development represents the core of the HHS intermediate and long-term pandemic influenza preparedness strategy for larger, more flexible, and less vulnerable domestic manufacturing surge capacity for production of seasonal and pandemic influenza vaccines."[7] However, as of July 2012, cell-based HA-head vaccines had yet to be licensed in the United States. Furthermore, this strategy did not have a significant impact on the 2009 pandemic response. Finally, we could not identify any policy efforts by the US government initiated between 2003 and 2009 that addressed any potential concerns about the efficacy and effectiveness of currently licensed influenza vaccines for either pandemic influenza preparedness or for control of seasonal influenza.

Influenza Vaccine Policy: Response During and Since the 2009 H1N1 Pandemic

The 2009 H1N1 pandemic response highlighted multiple challenges in providing sufficient influenza vaccine to the US population before the second wave of pandemic illness. In addition, vaccine effectiveness studies conducted in the United States, Europe, and Canada demonstrated the limited effectiveness of the pandemic vaccine despite the fact that the strain of 2009 A(H1N1)pdm09 included in the vaccines represented one of the closest matches between a vaccine virus strain and the circulating influenza virus in several decades (see Chapter 3).

We have identified five critical and publically available US government documents completed since 2009 that summarize the state of influenza vaccine policy priorities. Four of the documents address influenza vaccine and pandemic preparedness, and one addresses seasonal influenza vaccine. The documents, listed in chronological order, are:

- Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(RR-8):1-62[8]
- PCAST. "Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza" (August 2010)[9]
- ASPR. "The Public Health Emergency Medical Countermeasures Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs" (August 2010)[10]

- HHS. "2009 H1N1 Influenza Improvement Plan" (May 2012)[11]
- HHS. "An HHS Retrospective on the 2009 H1N1 Influenza Pandemic to Advance All Hazards Preparedness" (June 2012)[12]

Key points from these documents were incorporated into three additional US government documents that largely reiterated the points made in the first five. These documents, listed chronologically, are:

- HHS. "National Health Security Strategy of the United States of America" (December 2009)[13]
- ASPR. "BARDA Strategic Plan 2011-2016" (October 2011)[14]
- ASPR. "2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy" (June 2012)[15]

The 2010 ACIP Statement

We believe that the 2010 ACIP statement, which includes the current vaccine recommendations (and its previous iterations), has played a seminal role in overall policy development for influenza vaccines in the United States and worldwide. It set the stage for future policy efforts and therefore can be best described as a "foundation policy document." The 2010 ACIP statement puts forth the basic premise that the current HA-head vaccines generally are adequate to prevent and control influenza, provided that a good match exists between the circulating and vaccine strains and that a substantial portion of the population is vaccinated against influenza each year.[8] The statement also asserts that the key element needed for control of an influenza pandemic is rapid mobilization to develop and manufacture a strain-specific pandemic vaccine using current vaccine technology. As we noted in Chapter 7, the ACIP statements, including the 2010 statement, have consistently overestimated the effectiveness of influenza vaccination and thus affected influenza vaccine policy development accordingly. Given the international prominence of the ACIP, it is understandable how policy makers could conclude that "we just need to get everyone vaccinated and make more of the current vaccines faster."

PCAST and the HHS Emergency Medical Countermeasures (MCM) Enterprise Reviews

The US government conducted two major reviews of the US response to the A(H1N1)pdm09 pandemic. One was conducted by PCAST and the other was led by HHS.[9,10] The PCAST report focused specifically on influenza vaccines, while the HHS document reviewed the US all-hazards MCM enterprise, which included issues related to pandemic influenza vaccines.

PCAST, appointed by the president, is an advisory group of the nation's leading scientists and engineers that is intended to augment the science and technology advice available to the president from inside the White House and from other federal agencies. The PCAST Influenza Vaccinology Working Group includes members as well as outside consultants. PCAST was charged to "determine how the federal government can help to reduce the time required for the nation to supply effective vaccine to its population when the next influenza pandemic occurs." The subsequent summary report, "Report to the President on Re-engineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza" was issued in August 2010.[9] The report detailed problems with the vaccine response to the 2009 pandemic and identified both short- and long-term solutions for the influenza vaccine production enterprise.

Short-term issues and solutions included areas such as improving vaccine potency and sterility testing of currently licensed vaccines. Most of the long-term recommendations focused on time and capacity of vaccine production. The report included recommendations for the use of adjuvants for dose-sparing vaccines, mammalian cell-based and recombinant technology manufacturing of the current influenza vaccines, and the increased use of LAIV. The report recommendations focused almost exclusively on current vaccine production speed and capacity. In addition, the report did not address HA-head vaccine effectiveness, regardless of manufacturing platform used, or the lack of data supporting the efficacy of LAIV in older children or adults. Furthermore, while its primary purpose was to address pandemic preparedness, no evidence was presented in the report to suggest the group was even aware of the very different epidemiologic patterns of influenza pandemics (ie, 1918 and 2009 versus 1957 and 1968). Older populations were more affected by the 1957 and 1968 pandemics, whereas younger populations were more affected during the 1918 and 2009 pandemics.

The observation that age-groups were affected differently in past pandemics supports the need for influenza vaccines that are highly effective in persons 65 years of age and older.

The HHS Public Health Emergency MCM Enterprise Review was conducted by the staff of HHS under the direction of HHS Secretary Kathleen Sebelius. A number of other federal agencies, including ASPR, the NIH, the FDA, the CDC, and the Departments of Defense (DoD), Homeland Security (DHS), and Veterans Affairs (VA) were involved with the review. The goal of the review was to address the requirements for a modernized medical-countermeasure production process that includes more promising discoveries, more advanced development, more robust manufacturing, better stockpiling, and more advanced distribution practices. The review identified immediate needs for pandemic influenza vaccine development, including better methods for potency assays and sterility testing and rapid development of optimized virus seed strains for vaccine production. It also recommended that, to increase the capacity and speed of vaccine production, HHS support the development of at least three influenza vaccine candidates whose manufacturing does not depend on virus grown in eggs or cells. While these are laudable recommendations, many of these issues have been raised over the past 50 years and have not yet been successfully addressed. For example, determining potency and vaccine sterility was a serious challenge in the pandemic response in 1957.[16] Testing for vaccine potency also was a problem in the 1968 pandemic response.[17]

Like the PCAST report, the MCM review did not reference or discuss the critical issues with current HA-head vaccine efficacy and effectiveness or the relative absence of data supporting the potential benefit of adjuvanted HA-head vaccines. At the time that the review was being written, a CDC-supported effectiveness study of A(H1N1)pdm09 vaccine was available, but it is not mentioned in the review. That study demonstrated an overall vaccine effectiveness of only 56%.[18] Among persons 50 years of age and older, the vaccine effectiveness was -6% (95% CI, -231% to 66%).

HHS Reviews of the 2009 H1N1 Pandemic Response

HHS has conducted two reviews, in addition to the MCM review, examining the US public health response to the 2009 A(H1N1)pdm09 pandemic: the "2009 H1N1 Influenza Improvement Plan," issued on May 29, 2012, and "An HHS Retrospective on the 2009 H1N1 Influenza Pandemic to Advance All Hazards Preparedness," issued on June 15, 2012.[11,12] Both of these reviews examined multiple aspects of the HHS response to the 2009 pandemic and included specific issues related to the pandemic vaccine response.

The retrospective covered a variety of successes and issues related to advancing all-hazards preparedness. The influenza vaccine-related problems identified and solutions suggested were generally similar to those in PCAST and the MCM reviews and largely focused on increasing production of current HA-head vaccines. The assumptions and conclusions in the improvement plan were based on findings from the retrospective (even though the retrospective was released 2 weeks after the improvement plan). Secretary Sebelius noted in the improvement plan that, "we articulate HHS's key priorities for modifying and updating prior pandemic plans on many fronts, including . . . vaccines and other medical countermeasures."[11]

We identified two major shortcomings with the retrospective.[12] First, it included no discussion of the effectiveness of the pandemic vaccine, even though a CDC multicenter analysis (mentioned above) was available and showed an overall vaccine effectiveness of only 56%.[18] Second, the document contained several inconsistencies with regard to availability of the pandemic vaccine. In the section on vaccination, the first topic reviewed is "Vaccine Development and Production." The initial finding in the "Successes" section of that topic states, "HHS's large investments in pandemic preparedness, including existing contracts and ongoing relationships with vaccine manufacturers, enabled manufacturers to develop and establish the safety and immunogenicity of the 2009 H1N1 vaccine in fewer than 6 months and in quantities sufficient for the US population—the stated goal of pandemic planning." In the next section, "Opportunities for Improvement," the authors of the report note that "even though the 6-month goals for initial vaccine delivery were met, most of the vaccine arrived too late

to vaccinate much of the public before the pandemic peaked." The national goal was to have sufficient domestic capacity for vaccine production to be able to vaccinate the US population within 6 months after the onset of an influenza pandemic. That clearly did not happen. A mechanism or process for ensuring accountability with future national goals was not articulated in the retrospective or the improvement plan.

The improvement plan provides the strategy for improving the response to the next pandemic and builds on the retrospective. As in the retrospective, the improvement plan did not discuss the effectiveness of the pandemic vaccine. However, the authors of the plan noted, "Continued improvement will increase effectiveness of the next pandemic vaccination campaign in many different areas, including: Quicker access to more effective vaccines." More effective vaccines were not defined, but emphasis was placed on adjuvanted influenza vaccines and their benefits. As discussed in Chapters 3 and 9, many unanswered questions remain regarding the effectiveness of adjuvanted influenza vaccines. The improvement plan also urged scientists to "refine mechanisms for vaccine safety monitoring and effectiveness studies"; however, the plan did not provide a discussion of the protocols and procedures for conducting effectiveness studies or ways to improve them and did not provide any targeted completion dates for these activities.

Other US Government Activities

BARDA

BARDA is moving forward with implementing its plan to accomplish the stated national goals for pandemic preparedness.[14] In March 2011, Nicole Lurie, MD, MSPH, Assistant Secretary for Preparedness and Response, in a briefing to PCAST, noted that BARDA had awarded contracts to Novartis, GSK, Sanofi Pasteur, Intercell, and Protein Sciences to develop adjuvants for use with influenza vaccines.[19] In June 2012, BARDA awarded three contracts, renewable for up to 20 years, for the Centers for Innovation in Advanced Development and Manufacturing.[20] Funding these centers was recommended in the MCM report as a strategy to overcome some of the regulatory and manufacturing challenges for medical countermeasures. Two of the centers highlight their value in producing pandemic influenza vaccines; however, the vaccines that both centers will produce are not yet licensed and are based on the HA-head antigen.[21,22] As detailed in Chapter 9, recombinant and mammalian-cell–based influenza vaccines using the HA-head antigen have been in review for licensure for some time in the United States. HHS Secretary Sebelius indicated in her Senate testimony in September 2010 that it was possible that licensed mammalian-cell influenza vaccines would be available for the 2011-12 influenza season.[23] As of July 2012, these vaccines had not been licensed for use in the United States.

In June 2012, BARDA also issued a request for proposals for the "advanced development of novel hemagglutinin-based molecular and recombinant influenza vaccine candidates."[24] While this leaves open the potential for game-changing HA-stalk–based influenza vaccines, the requirement for the "demonstration of significant immune responses in humans against different influenza subtypes as ascertained from hemagglutination inhibition and microneutralization assays" makes it clear that BARDA is focusing on HA-head vaccines.

The FDA and the CDC

The roles and responsibilities that both the FDA and the CDC play in the US government policy development for influenza vaccines have been detailed in Chapters 7 and 10 as well as previously in this chapter.

The NIH

The NIH supports influenza vaccine research and development through both extramural and intramural funding and applied program and research support. The National Institute of Allergy and Infectious Diseases (NIAID) is the primary NIH institute involved with all aspects of influenza vaccine work. The NIH is not usually considered a leader in vaccine policy development, as it does not make recommendations for vaccine use (as does the ACIP), regulate the vaccine enterprise (as does the FDA), or make large purchases of seasonal influenza vaccine (as do the Centers for Medicare and Medicaid Services [CMS], DoD, VA, Vaccines for Children program [VFC], Federal Occupational Health [FOH], and Immunization Grant Program).

However, the NIH is a key player in US government activities regarding influenza vaccine in two regards. First, the NIH collaborates with other HHS agencies to improve current vaccine technology and address potential "next-generation" influenza vaccines.[19] For example, the NIH is involved with developing high-production-yield vaccine-virus seed strains and improving potency reagent production for current vaccines. The NIH also supports discovery and early development of adjuvants for influenza vaccines, research on prime-boost approaches to enhancing the immunogenicity of LAIV, and assessment of high-dose HA-head influenza vaccines in elderly and immunocompromised populations. Second, the NIAID Vaccine Research Center (VRC) of the NIH has a specific research focus on potential universal influenza vaccines. The VRC work, together with NIAID extramural research funding for early novel antigen vaccine evaluation, represents the single most forward-leaning effort for game-changing influenza vaccines that we could identify in the US government. Nonetheless, we could not identify any process or system within HHS to link these efforts to a US government goal or comprehensive plan to bring universal vaccines to licensure and ultimately to market.

This point is further illustrated in three recent NIAID publications addressing influenza vaccines. Approximately every 5 years, the NIAID publishes the highly respected Jordan Report, a review of progress in vaccine development. The 2012 edition has a very informative chapter on influenza vaccine work at the NIAID. [25] In that chapter, new vaccine strategies are summarized in the following two statements:

> *"The ideal vaccine, one providing protection against any strain of influenza and not needing to be updated or administered every year to protect against newly emerging strains, is a goal not yet realized."*

> *"Innovative vaccine technologies provide new options to develop vaccines rapidly in response to a newly emergent strain. If successful, such advances could further increase vaccine production capacity and enhance preparedness against seasonal and potential pandemic influenza strains."*

Similarly, two recent review articles from NIAID leaders summarize influenza vaccines of the future.[26,27] While the Jordan Report chapter on influenza vaccines and the recent review articles provide excellent overviews of potential influenza vaccines of the future, they do not discuss the urgency for future vaccines as a result of the poor to moderate levels of protection that current vaccines provide against seasonal and pandemic influenza infection. These articles address the development of novel antigen, game-changing vaccines as important, but not a critically needed effort. In addition, no road map is provided for how these future vaccine evaluations will be financially supported through phase 4 studies, licensed, and then marketed. While these latter issues may not be considered part of the NIH mission, for HHS not to address them leaves the basic influenza vaccine science with no connection to a future real countermeasure.

In June 2012, NIAID and FDA hosted a 2-day meeting on universal influenza vaccines.[28] Interviews with subject matter experts who attended this meeting revealed that no scientific, regulatory, or organizational road map for advancing novel-antigen vaccines emerged from this meeting.

The DoD

The DoD maintains an extensive program to vaccinate the US military and support staff. Information regarding the safety and effectiveness of the vaccine program is shared routinely with the FDA and other agencies. In addition, the DoD is actively involved in influenza vaccine research and development activities, which are typically coordinated with BARDA, the NIH, and the FDA. The DoD's primary objective is to produce sufficient quantities of a vaccine rapidly to ensure protection of the armed forces. As a result, DARPA has funded projects that would allow accelerated development of HA-head vaccines to ensure that such vaccines can be manufactured in weeks.[29] This work has primarily involved the production of HA-head antigen in tobacco plants. We have not identified DoD documents, reports, or testimony that calls for the improved efficacy of current influenza vaccines.

Government Accountability Office

The GAO has published extensively on pandemic preparedness, including generating reports addressing

the production and use of influenza vaccines.[30-38] The primary focus of these reports has related to how much and how fast our current influenza vaccines could be produced in response to an emerging pandemic. These reports also highlight several management and leadership issues regarding the production and use of pandemic influenza vaccines. It is worth noting that some of the challenges discussed in this chapter and the previous 11 chapters are also raised in a recent GAO report.[38] However, as with all of the other federal government documents reviewed, this GAO report, and earlier GAO reports, do not recognize the limitations of our current vaccines.

Federal Purchase of Influenza Vaccines

Over the course of the CCIVI project, we undertook extensive efforts to determine the annual US government expenditures for seasonal influenza vaccines. Given that the CMS, the DoD, the VA, the VFC, the FOH, and the Immunization Grant Program (Section 317) all provide seasonal influenza vaccines, the government expenditure is very sizeable. Despite our efforts, which included detailed document and budget reviews, as well as interviews with current and former senior members of the US government agencies purchasing these vaccines, we could not identify the annual expenditures. It is widely known in the vaccine industry, however, that the US government is the largest buyer of seasonal influenza vaccine (and pandemic influenza vaccine in 2009) in the world. Despite this large expenditure, we could find no evidence that the US government has used its purchasing power to demand measurement of outcomes for the influenza vaccines it purchases (ie, vaccine effectiveness or reduction in deaths or hospitalizations).

On May 4, 2011, the CMS proposed a new rule regarding influenza vaccination, which expands upon several previous rules to increase influenza vaccine coverage rates.[39] As required by Executive Order 12866, the CMS evaluated the policy impact, including cost and benefit, associated with this new rule.[40] While acknowledging the uncertainty regarding the cost effectiveness and disease-prevention effectiveness of the influenza vaccine in persons over age 65, the CMS concluded that this rule would result in a net benefit of $380 million to the payer if enacted, largely due to reduced medical costs.[39] This assessment, however, is based on the generally accepted estimates of vaccine effectiveness, which (as we described in Chapter 3) are not accurate. Although the CMS has a tangible opportunity to require certain performance characteristics for influenza vaccines (such as improved vaccine effectiveness), to date it has not done so. The only requirements we could identify for US government purchase of either seasonal or pandemic vaccine is that the purchase follows ACIP guidance and adheres to Executive Order 12866.

IMPLEMENTATION OF US INFLUENZA VACCINE POLICY

Up to this point, the focus of this chapter has been on federal policies regarding the use of influenza vaccine. Such policies are, however, primarily implemented by state or local health departments. Health departments depend on federal policies to direct their activities and assume they are based on the best science-based evidence available. State and local health departments do not act as a secondary reviewer of these policies and in any event lack the resources to do so. Health departments nonetheless are responsible for pandemic influenza preparedness as well as carrying out seasonal influenza vaccine promotion and distribution, all with dwindling budgets and limited staff.

INTERNATIONAL POLICIES AND ACTIVITIES

While the focus of the CCIVI review was on the Unites States, international partners also have a major stake in the prevention and control of seasonal and pandemic influenza. We provide here a brief review of influenza vaccine policy priorities of the WHO and countries other than the United States.

The WHO

Similar to the US situation, the 2009 H1N1 pandemic response highlighted multiple challenges for providing sufficient influenza vaccine on an international level to even a small segment of the world's population prior to the second wave of pandemic illness. While the WHO had prioritized the need for a more robust global pandemic influenza vaccine agenda following the re-emergence of H5N1 in 2003, the global "too little, too late" vaccine response to the 2009 pandemic brought a new sense of urgency

to influenza vaccines. Therefore, we have focused our review of the WHO policy-related activities and consultations for influenza vaccines for the period during and following the 2009 pandemic. The WHO report "Implementation of the International Health Regulations (2005): Report of the Review Committee on the Functioning of the International Health Regulations (2005) in Relation to Pandemic (H1N1) 2009" is discussed in Chapter 13.

The WHO relies primarily on country- or expert-based consultations for developing its policy and science summary documents, including for influenza vaccines. We have identified four documents developed since 2009 that provide the basis for our review. They are:

- Report of the First Global Consultation: WHO Public Health Research Agenda for Influenza (2009)[41]
- Pandemic Influenza Preparedness Framework for Sharing of Influenza Viruses and Access to Vaccines and Other Benefits[42]
- Report of the Second Consultation on the Global Action Plan for Influenza Vaccines (GAP) (2011)[43]
- Meeting of the Strategic Advisory Group of Experts on Immunization, April 2012—Conclusions and Recommendations (2012)[44]

As we found with the review of the US government documents and activities related to influenza vaccine policy, the WHO documents focus primarily on how to deliver more of the current HA-head vaccines to the global population more quickly during an emerging influenza pandemic and on gradually increasing the number of people who are annually vaccinated for seasonal influenza. Little attention has been paid to the effectiveness of the current vaccines or barriers to developing game-changing vaccines.

A review of vaccine effectiveness was undertaken for one of the reports, the summary of the April 2012 meeting of the Strategic Advisory Group of Experts (SAGE) on immunization.[45] Similar to the ACIP and Cochran reviews, the SAGE review contained studies that had methodological flaws and therefore overestimated vaccine efficacy and effectiveness.

Report of the First Global Consultation WHO Public Health Research Agenda for Influenza

The WHO recognized that the 2009 A(H1N1)pdm09 pandemic highlighted many areas for which scientific information is lacking. In November 2009, 7 months after the start of the pandemic, the WHO held a global consultation on "lessons learned" to date and gaps in our knowledge about the prevention and control of influenza. This consultation brought together more than 90 public health decision makers, academic and clinical investigators, donors/funding organizations, and other key stakeholders from 35 countries.[41] The agenda for the consultation had four objectives. None specifically addressed influenza vaccines; however, all of them either directly or indirectly related to vaccines. The meeting was organized around five research streams, one of which was "minimizing the impact of pandemic, zoonotic, and seasonal epidemic influenza."

The report resulting from the meeting primarily emphasized a number of recommendations around improving existing vaccines (ie, production, dose-sparing formulations, and reductions in bottlenecks to improve rapid response and surge capacity). The consultants concluded that, "the development of vaccines that elicit broader and longer protection against influenza virus strains would facilitate use by under-resourced countries that cannot afford to revaccinate the population every year…" While this conclusion is correct, it misses the point that even annual vaccination with current vaccines does not provide high levels of protection each year, particularly for persons at increased risk for severe morbidity and mortality.

The report also noted that two long-term goals include development of a universal influenza vaccine and a vaccine for children that could induce long-term immunity. The consultants did not, however, describe a possible research road map for realizing these goals. The report identified 12 "topics of interest" around improving immunogenicity, availability, and delivery of influenza vaccines. One of the topics was "development of new vaccines and vaccine platforms especially suitable for under-resourced country settings."

In 2011, the WHO commissioned literature reviews covering the high-priority research recommendations

identified in the Report of the First Consultation.[46] An expert group was convened in November 2011 to present findings from the reviews and prepare a progress report. The group identified major gaps in our capacity to effectively deliver on the development of universal, recombinant, or advanced cell-based vaccines and the use of adjuvants for dose-sparing and enhanced protection.

Report of the Second WHO Consultation on the Global Plan of Influenza Vaccines (GAP)

In 2006, the WHO convened a consultation on the "Global Action Plan for Influenza Vaccines," as there was an emerging international consensus that influenza is truly a concern that crosses international boundaries.[43] The primary outcome of that plan was its role as a catalyst to increase annual global influenza vaccine production from 350 million doses in 2006 to 900 million in 2009. The 5-year review of the plan resulted in a second consultation in July 2011 and generation of the subsequent document, "Report of the Second WHO Consultation on the Global Action Plan for Influenza Vaccines (GAP)."[43]

The second WHO GAP consultation brought together more than 100 representatives from national governments, United Nations agencies, funders, regulatory authorities, WHO technology-transfer projects, manufacturers, nongovernmental organizations (NGOs), and the research community. The purpose of the consultation was to review progress made so far, to learn from the experience of the 2009 influenza pandemic, and to assist the WHO with developing a strategic plan for the next 5 years. The participants were organized into working groups related to the three pillars of GAP activities: the use of seasonal influenza vaccines, increasing vaccine production capacity, and promoting the research and development of new influenza vaccines and related technologies.

For our policy review here, we will focus on findings related to the third pillar: promoting the research and development of new influenza vaccines. The findings were largely similar to the conclusions of the US government agencies and the WHO first consultation noted above. Notably absent from the consultation was any discussion or consideration of the performance characteristics of the current vaccines. Specifically, the report did not address vaccine effectiveness for the current HA-head vaccines. Rather, the findings emphasized the need to broaden cross-protection offered by current influenza vaccines through the use of adjuvants or high-dose formulations and reducing the annual frequency that vaccines must be administered. The report acknowledged that the development of universal vaccines is a high priority; however, the report executive summary stated:

> *"Although the 'holy grail' of a universal vaccine ideally suited for manufacture in developing world countries is receiving increasing attention, this forward-looking approach remains unproven. Universal vaccine candidates are in phase 1 trials and safety studies have been conducted or are in progress. There are, however, major technical and financial obstacles to the development of universal vaccines, including a lack of assays based on suitable correlates of protection and regulatory issues."*[43]

The report identified 10 proposed actions related to promoting influenza vaccine research and development. Three of the proposed actions directly relate to potential game-changing vaccines; they are:

- The long-term goal of developing "universal" vaccines should remain a priority.
- Clear short-term, medium-term, and long-term research and development goals should be identified and the underlying assumptions driving these goals should be made explicit and periodically revisited.
- The influenza vaccine research and development landscape is active and rapidly evolving but faces significant funding challenges that will require continued stakeholder support and strategic prioritizing.

While these action steps are laudable, an organized program of accountability to ensure their success does not exist, and dedicated resources to accomplish them are not available.

SAGE Conclusions and Recommendations

In 2010, the WHO SAGE on immunization requested that an Expert Working Group on Influenza Vaccines and Immunization (WGIVI) be established to prepare for a SAGE evidence-based review and an update of the recommendations on the use of seasonal influenza

vaccine.[45] The WGIVI assessed 23 reviews of influenza vaccine to develop a series of recommendations regarding influenza vaccine use.[45] The WGIVI did not establish objective inclusion and exclusion criteria for vaccine efficacy and effectiveness studies or meta-analyses of vaccine efficacy and effectiveness before it embarked on its review. As a result, the group included a number of studies that had methodological flaws (see Chapter 3).

For example, the WGIVI concluded that "inactivated vaccines are effective in reducing maternal morbidity due to respiratory disease." The data to support this conclusion came from immunogenicity studies that are well known to have serious limitations in correlating protection and antibody levels (see Chapter 10). Similarly, the working group concluded that vaccination of healthcare workers "should reduce morbidity and /or mortality in patients." We described in Chapters 3 and 7 the problems with interpreting the findings of studies addressing this issue. Finally, the WGIVI concluded that in children aged 6 to 23 months, vaccine effectiveness is "particularly dependent on the matching of vaccine strains to circulating viruses." Our meta-analysis did not identify any studies that support this conclusion. Given these shortcomings, the conclusions reached in this review contribute to the perception that our current HA-head vaccines protect much better than they actually do.

Pandemic Influenza Preparedness (PIP) Framework

We include the PIP framework here as an important WHO policy document related to influenza vaccines because of what it doesn't say, rather than what it says.[42] The document provides the framework for sharing of influenza viruses and access to vaccines and other benefits during an influenza pandemic. Vaccine efficacy and effectiveness are not addressed in the document; rather, it is assumed that the primary factor in vaccine-related protection is vaccine access. As we have noted previously, if most people in the world had immediate access to current HA-head vaccines during a pandemic in which the median age of death is greater than 65 years of age, the incidence of serious morbidity and mortality would still be substantial, owing to the lack of protective efficacy of current vaccines in this age-group.

Other National Governments and the European Union

Access to vaccines is the primary issue related to both seasonal and pandemic influenza vaccine use outside of the United States, Canada, the EU, Australia, and Japan. For most national governments and their respective health agencies, we were unable to identify policy-related activities that address the need for novel-antigen, game-changing influenza vaccines.

The EU is the one major exception to this finding; its health officials are increasingly addressing the need for new influenza vaccines. The ECDC supports a consortium of researchers that conduct annual multisite case-control studies evaluating influenza vaccine effectiveness using a standard protocol (I-MOVE).[47,48] These studies have been critical in establishing a scientifically rigorous methodological design for evaluating influenza vaccine effectiveness annually. As a result of these efforts, the ECDC has concluded that "the effectiveness of seasonal influenza vaccines is unacceptably low."[49] The ECDC also has noted that "many of the seasonal vaccines that are used may be little improved in their effectiveness from what was used three decades ago. The case for more investment in better seasonal vaccines using public and industry resources is unanswerable."[49] While other countries, such as Australia, Canada, and the United States support similar influenza vaccine effectiveness studies, the EU is the acknowledged leader in defining and addressing the issue of effectiveness with the current HA-head vaccines.

Non-governmental Organizations (NGOs)

There are several NGOs working on various aspects of influenza vaccine policy and management. Most of these organizations have as their primary mission to increase global access to influenza vaccines in pursuit of the goals established by the WHO and national governments. While some NGOs are working on modifications to current HA-head vaccines, we did not identify a clear recognition by any of them for the need to develop novel-antigen influenza vaccines.

SUMMARY

Our extensive review of US and international public health policies for influenza vaccines found that influenza vaccine policy efforts since 2003 have been

focused on: (1) expanding current seasonal influenza vaccination campaigns to vaccinate an increasing proportion of the population each year using current HA-head vaccines, (2) ensuring that capacity is available to rapidly produce HA-head vaccines at the onset of an influenza pandemic, and (3) improving vaccine access, particularly in developing countries.

While all of these goals are important interim measures given the current landscape of influenza vaccine science, we believe that critical shortcomings in public health policies are limiting our ability to propel influenza vaccine technology deep into the 21st century. These shortcomings can be summarized as follows. First, public health policy experts have not focused attention on the critical limitations of the current HA-head vaccines with regard to vaccine efficacy and effectiveness. Second, the current policy approach to improving influenza vaccines is to make incremental changes to existing HA-head vaccines, such as focusing on adding adjuvants or using mammalian-cell–based platforms. While these efforts can improve prevention and control of influenza somewhat, the overall impact will likely be small. Third, while many policy documents have recognized the need to develop game-changing influenza vaccines using completely different approaches and technologies, the political will to provide the resources and strategies necessary to make this a reality has been lacking.

REFERENCES

1. Homeland Security Council (HSC). National strategy for pandemic influenza. Nov 2005. Available at: http://www.flu.gov/planning-preparedness/federal/pandemic-influenza.pdf
2. HHS. HHS pandemic influenza plan. Nov 2005. Available at: http://www.flu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf
3. Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-10):1-42
4. HHS. HHS pandemic influenza implementation plan. Nov 2006. Available at: http://www.hhs.gov/pandemicflu/implementationplan/
5. Public Law 109-417: Pandemic and All-Hazards Preparedness Act. (120 Stat. 2831; Dec 19, 2006) Available at: http://www.gpo.gov/fdsys/pkg/PLAW-109publ417/pdf/PLAW-109publ417.pdf
6. HHS. Public health emergency medical countermeasures enterprise strategy. Mar 2007. Available at: http://www.gpo.gov/fdsys/pkg/FR-2007-03-20/pdf/E7-5066.pdf
7. HHS. Report to Congress: Pandemic influenza preparedness spending. Jan 2009. Available at: https://www.medicalcountermeasures.gov/BARDA/documents/hhspanflu-spending-0901.pdf
8. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59(RR-8):1-62
9. Holdren JP, Lander E, Varmus H, et al. Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. 2010
10. ASPR (Assistant Secretary for Preparedness and Response, HHS). The public health emergency medical countermeasures enterprise review: transforming the enterprise to meet long-range national needs. Aug 2010. Available at: https://www.medicalcountermeasures.gov/media/1138/mcmreviewfinalcover-508.pdf
11. HHS. 2009 H1N1 influenza improvement plan. May 2012. Available at: http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Documents/2009-h1n1-improvementplan.pdf
12. HHS. An HHS retrospective on the 2009 H1N1 influenza pandemic to advance all hazards preparedness. Jun 2012. Available at: http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Documents/h1n1-retrospective.pdf
13. HHS. National health security strategy of the United States of America. Dec 2009. Available at: http://www.phe.gov/Preparedness/planning/authority/nhss/strategy/Documents/nhss-final.pdf
14. ASPR. BARDA strategic plan 2011-2016. Oct 2011. Available at: http://www.phe.gov/about/barda/Documents/barda-strategic-plan.pdf
15. ASPR. 2012 public health emergency medical countermeasures enterprise (PHEMCE) strategy. Jun 2012. Available at: http://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf
16. Murray R. Some problems in the standardization

and control of influenza vaccine in 1957. Am Rev Respir Dis 1961;83:160-7
17. Murray R. Production and testing in the USA of influenza virus vaccine made from the Hong Kong variant in 1968-69. Bull World Health Organ 1969;41(3-4-5):493-6
18. Griffin MR, Monto AS, Belongia EA, et al. Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. PLoS One 2011;6(8):e23085.
19. Lurie, N. HHS efforts to improve the influenza vaccine production enterprise. Briefing to PCAST. Mar 2011. Available at: http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-lurie-march.pdf
20. HHS. HHS creates new centers to develop, manufacture medical countermeasures. Jun 2012. Available at: http://www.hhs.gov/news/press/2012pres/06/20120618a.html
21. Texas A&M Center for Innovation. $285.6 million public-private partnership to enhance the nation's biosecurity preparedness and create jobs in Texas. Jun 2012. Available at: http://ciadm.tamus.edu/news/tamus-awarded-national-center-for-innovation/
22. Roos R. HHS launches partnerships to make biodefense products. Jun 2012. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/jun1812hhs.html
23. Roos R. Sebelius envisions cell-based flu vaccine in 2011. Sep 2010. Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/general/news/sep2910hearing.html
24. BARDA. Advance development of medical countermeasures for pandemic influenza. Solicitation number: BARDA-12-100-SOL-00018. Jun 2012. Available at: https://www.fbo.gov/spg/HHS/OOS/OASPHEP/BARDA-12-100-SOL-00018/listing.html
25. Lambert LC, Cassels FJ. Influenza. In Jordan Report: Accelerated Development of Vaccines 2012. Jan 2012. Available at: http://www.niaid.nih.gov/topics/vaccines/Documents/JordanReport2012.pdf
26. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. Nat Med 2010;16(12):1389-91
27. Lambert LC, Fauci AS. Influenza vaccines for the future. *N Engl J Med* 2010;363(21):2036-44
28. FDA. FDA's medical countermeasure initiative (MCMi). Available at: http://www.fda.gov/EmergencyPreparedness/MedicalCountermeasures/ucm263084.htm
29. Defense Sciences Office, DARPA. H1N1 acceleration (blue angel). Available at: http://www.darpa.mil/Our_Work/DSO/Programs/H1N1_Acceleration_%28BLUE_ANGEL%29.aspx
30. GAO. Influenza pandemic: continued focus on the nation's planning and preparedness efforts remains essential. Jun 3, 2009. Available at: http://www.gao.gov/new.items/d09760t.pdf
31. GAO. Influenza pandemic: efforts to forestall onset are under way; identifying countries at greatest risk entails challenges. Jun 20, 2007. Available at: http://www.gao.gov/new.items/d07604.pdf
32. GAO. Influenza pandemic: efforts under way to address constraints on using antivirals and vaccines to forestall a pandemic. Dec 21, 2007. Available at: http://www.gao.gov/new.items/d0892.pdf
33. GAO. Influenza pandemic: further efforts are needed to ensure clearer federal leadership roles and an effective national strategy. Aug 14, 2007. Available at: http://www.gao.gov/new.items/d07781.pdf
34. GAO. Influenza pandemic: gaps in pandemic planning and preparedness need to be addressed. Jul 29, 2009. Available at: http://www.gao.gov/new.items/d09909t.pdf
35. GAO. Influenza pandemic: HHS needs to continue its actions and finalize guidance for pharmaceutical interventions. Sep 30, 2008. Available at: http://www.gao.gov/new.items/d08671.pdf
36. GAO. Influenza pandemic: sustaining focus on the nation's planning and preparedness efforts. Feb 26, 2009. Available at: http://www.gao.gov/assets/290/286548.pdf
37. GAO. Influenza pandemic: lessons from the H1N1 pandemic should be incorporated into future planning. Jun 27, 2009. Available at: http://www.gao.gov/assets/330/320176.pdf
38. GAO. Influenza vaccine: federal investments in alternative technologies and challenges to development and licensure. Jun 27, 2009. Available at: http://www.gao.gov/assets/330/320154.pdf
39. Medicare & Medicaid programs; influenza

vaccination standard for certain participating providers and suppliers (proposed rule). May 4, 2011. Fed Reg 76;86:25460-77. Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-05-04/pdf/2011-10646.pdf

40. White House. Executive order 12866 regulatory planning and review. Sep 30, 1993. Available at: http://www.plainlanguage.gov/populartopics/regulations/eo12866.pdf

41. WHO. Report of the first global consultation: WHO public health research agenda for influenza. Nov 2009. Available at: http://www.who.int/influenza/resources/research/2010_11_report_of_the_first_global_consultation_november_2009.pdf

42. WHO. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. May 2009. Available at: http://apps.who.int/gb/ebwha/pdf_files/A62/A62_5Add1-en.pdf

43. WHO. Report of the second WHO consultation on the Global Action Plan for Influenza Vaccines (GAP). Jul 2011. Available at: http://whqlibdoc.who.int/publications/2012/9789241564410_eng.pdf

44. WHO. Meeting of the strategic advisory group of experts on immunization, April 2012—conclusions and recommendations. Wkly Epidemiol Rec 2012;21(87):201-16

45. WHO. Background paper on influenza vaccines and immunizations, SAGE Working Group. Mar 2012. Available at: http://www.who.int/immunization/sage/meetings/2012/april/1_Background_Paper_Mar26_v13_cleaned.pdf

46. Perdue ML, Nguyen L. The WHO research agenda for influenza: two years later. Bull World Health Organ 2012;90(4):246

47. Valenciano M, Ciancio B, Moren A, et al. First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States. Euro Surveill 2008;13(43):pii=19015

48. Kissling E, Valenciano M, Falcao J, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Euro Surveill 2009;14(44):pii=19388

49. ECDC. Lower than usual: early influenza vaccine effectiveness in parts of Europe in season 2011/12. Apr 2012. Available at: http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f-77d4-4ad8-b6d6-bf0f23083f30&ID=1266&RootFolder=%2Fen%2Factivities%2Fsciadvice%2FLists%2FECDC%20Reviews

CHAPTER 13

ORGANIZATION AND LEADERSHIP BARRIERS TO ACHIEVING NOVEL-ANTIGEN, GAME-CHANGING VACCINES

INTRODUCTION

In Chapters 11 and 12, we outlined the major investment and public health policy barriers to achieving novel-antigen, game-changing influenza vaccines. Addressing those barriers alone, however, will not solve all the issues necessary to move the influenza vaccine enterprise forward. In this chapter, we outline additional barriers in the area of organization and leadership barriers that need to be addressed in order to realize the vision of achieving game-changing influenza vaccines.

Before reviewing organization and leadership issues specifically related to the influenza vaccine enterprises, we acknowledge that pandemic preparedness is part of an overall strategy for public health emergency preparedness and that pandemic influenza vaccines are an important component of an overall MCM enterprise. However, because the influenza vaccine enterprise includes protective measures against both seasonal and pandemic influenza, it doesn't completely fit within the paradigm for public health emergency preparedness and thus is somewhat distinct from the US strategy for emergency MCM. To illustrate this point, as was discussed in Chapter 12, the 2007 PHEMC plan did not include pandemic influenza vaccines, as they were covered under the HHS pandemic influenza plan; however, pandemic influenza vaccines were included in the 2012 PHEMC strategy review.[1,2] Of note, seasonal influenza vaccines, while clearly linked to the technology and manufacturing of pandemic influenza vaccines, were not considered as part of the 2012 PHEMC strategy. Because an inescapable link exists between the need for effective annual seasonal influenza vaccines and the need for improved pandemic influenza vaccines, the national strategy for influenza countermeasures must be different from the strategy for other emergency MCM. Furthermore, influenza vaccines don't fit into a traditional bioterrorism response–related vaccine stockpile and distribution model. Our interviews with subject matter experts in government, the private sector, and academia support this conclusion.

Given these distinctions, we will not address the HHS-led efforts with other countermeasures included in the MCM enterprise. We note, however, that

despite some accomplishments as the result of HHS-led efforts, such as smallpox preparedness, the US government's MCM efforts have been criticized by a variety of experts, committees, commissions, and organizations. Russell and Gronvall, as well as Hoyt, provide comprehensive and critical reviews of the MCM activities and describe areas of urgently needed improvement.[3,4] Many of these concerns are relevant to the influenza vaccine preparedness issue but will be addressed from that perspective. We will concentrate on the mission-critical and project-management aspects needed for novel-antigen, game-changing influenza vaccine development.

MISSION-CRITICAL PRIORITY AND PROJECT MANAGEMENT

Mission-Critical Priority

As discussed in Chapter 9, the ultimate public health goal for the prevention and control of influenza in humans is the availability of an effective universal vaccine. While such a vaccine may ultimately elude us owing to the considerable scientific and investment challenges associated with influenza vaccinology, we won't know until we make a "mission-critical" effort to accomplish the development of such vaccines. "Mission critical" refers to any factor of a system or activity (personnel, equipment, process, procedure, etc) whose failure will result in the downfall of the entire operation. For a system or activity to achieve mission-critical status, it must rank as an exceptionally high priority for an organization or responsible party.

We believe that the highest priority for the influenza vaccine enterprise today is to develop a highly efficacious, safe, and cost-effective influenza vaccine that can be produced in sufficient quantity in advance of its domestic and international need and ideally can provide protection against the most common strains of influenza virus, as well as emerging pandemic strains. As discussed in Chapter 1, the global health, economic, and social impacts of a severe influenza pandemic will be substantial without such vaccines. The national security implication of this scenario demands the establishment and execution of a national priority to secure game-changing influenza vaccines. Yet, we have been unable to identify any mission statement or program priority of any agency or office in the US government or among any other governments or health agencies that explicitly addresses the issue of vaccine efficacy across the entire population, including people at increased risk for severe morbidity or mortality. Instead, mission statements or program priorities focus largely on vaccine availability and public acceptance and use. Therefore, a critical shortcoming in our current efforts to develop a highly efficacious influenza vaccine is a general lack of awareness of the importance of such a need. Without the ACIP or other leading science policy bodies clearly articulating this priority with strong support by policy makers, any subsequent management efforts to improve vaccines for seasonal or pandemic influenza will fall short of what is necessary to deliver game-changing influenza vaccines.

Project Management

Project management is the application of knowledge, skills, tools, and techniques to project activities to achieve project requirements. It is accomplished through application and integration of a range of processes, including initiating, planning, executing, monitoring and controlling, and closing.[5] We propose that project management for bringing one or more universal influenza vaccines to the global market must be considered one of the most important factors in determining success or failure. Managing a project often is seen as being led by a subject matter expert. That is why scientists often manage science-based activities. Their project oversight may appropriately include discovery or development, but it also often includes many other program areas such as finance, procurement, employee relations, legal issues, and logistics. Science experts frequently do not have the project management skills necessary to address all of the complex aspects involved in complicated enterprises like advancing new influenza vaccines.

We analyzed the current organizational mission, administrative structure, personnel, legal authority, and resources of HHS, specifically those of ASPR and BARDA, to carry out the realization of a game-changing influenza vaccine. We also discussed our findings with relevant subject matter experts, including members of PCAST, science leaders, influenza vaccine company executives and those at start-up companies with promising vaccine technologies, and current and former HHS staff. Based on this review, we conclude that substantial changes are needed in the management of the influenza vaccine enterprise if we are to realize success in achieving game-changing influenza vaccines. This enterprise, which includes both public- and private-sector vaccine-related partners that need to coordinate activities to judiciously use resources, share knowledge, and strategize efforts, must be led by an individual with the authority, resources, and project management expertise to bring about these new vaccines. We could not identify any US government or international agency or organization that currently possesses all of the capabilities necessary to lead such an effort. In the paragraphs below, we outline statements by PCAST and the WHO's Review Committee on the Functioning of the International Health Regulations (2005) in Relation to Pandemic (H1N1) 2009 that address the management efforts necessary to bring about new influenza vaccine technologies. These are the most comprehensive statements on this topic from a national or international influenza vaccine review conducted in recent years.

PCAST Report

The PCAST report concluded that a "new way of doing business" is necessary for the US government in order to re-engineer the influenza vaccine enterprise.[6] It recommended to the President that the federal government "implement a new management structure for overseeing the mission-driven enterprise to re-engineer the Nation's influenza vaccine development and production enterprise." The PCAST report specifically recommended:

> *"HHS should vest ASPR with the authority to coordinate and task its component agencies with activities necessary to support the goals of the influenza enterprise. In addition, HHS should establish a small advisory committee, comprised of representatives from the biotechnology, pharmaceutical, and investment communities to guide the engagement with industry. The committee's input should be considered seriously in all decisions and actions by the Department, given importance of the relationship between the federal government and industry partners."*[6]

While we agree with the general conclusions regarding the federal government's role for leading the vaccine enterprise toward new influenza vaccines, we believe one essential aspect was not adequately addressed by the PCAST report, which is the need for an understanding about and vision for game-changing influenza vaccines. In addition, we do not believe the PCAST recommendation sufficiently details the need to declare at the highest levels of government (ie, the Executive Office of the President) that developing game-changing vaccines is a national priority. Without this declaration, this effort will lack the authority necessary to bring about the complicated public-private partnerships required for such a task or the necessary project management expertise.

IHR Review of 2009 H1N1 Pandemic

Following the 2009 influenza pandemic, WHO Director-General Margaret Chan proposed that a committee provided for in Chapter III of Part IX of the International Health Regulations 2005 (IHR) be convened "to review the experience gained in the global response to the influenza A (H1N1) 2009 pandemic in order to inform the functioning of the Regulations; to help assess and, where appropriate, to modify the ongoing response and to strengthen preparedness for future pandemics."[7] The IHR review was led by Chairman Harvey V. Fineberg, MD, PhD, president of the IOM, and included 25 members from 24 countries. The final report was delivered to the WHO on May 5, 2011.

(Of note, the final report did not include findings from any of the pandemic vaccine effectiveness studies that had been published though early 2011 or special communication citations of yet-unpublished data from member country–based public health agencies that had conducted these studies. Referencing and discussing these findings [as noted in Chapter 3] would have provided an important perspective on the public health impact of the 2009 pandemic vaccine.)

The IHR report provided a comprehensive list of

recommendations to the WHO that were based on the 2009 pandemic experience. One of the summary recommendations was: "Member states, individually and in cooperation with one another, and WHO were urged to pursue a comprehensive influenza research and evaluation programme."[7] A specific research recommendation in this category was to "create broader spectrum, highly effective, safe, and longer-lasting vaccines." The timeline for realizing such an effort was defined as long term (2 years or longer). We interpret this recommendation to mean that the WHO should oversee, or even lead, a global collaborative effort to realize potential game-changing influenza vaccines. As noted in Chapter 12, however, the WHO has not provided meaningful leadership in addressing the issue of the effectiveness of our current HA-head influenza vaccines. Nor could we identify similar critical leadership in any foreign government public health agency. Rather, the WHO and other public health agencies continue to emphasize global efforts to expand production and availability of HA-head vaccines. Therefore, even though the IHR review provided a timely and important mandate for global leadership for managing the influenza vaccine enterprise, no apparent movement toward this vision has yet been realized.

A MODEL OF SUCCESS

One well-known way to solve complicated scientific challenges is to implement a "Manhattan Project" approach. The Manhattan Project was the US government's urgent secret program to research, develop, and test an atomic weapon. This term has become synonymous with an endeavor of great effort, expertise, and resources to achieve a specific objective. Most germane to this report, the Manhattan Project has been recognized as one of the most successful project management efforts of modern times.[8,9] The scope of the project was enormous; in 1944 it employed 129,000 workers and included highly skilled scientists, construction workers, plant operators, and military personnel. It involved major construction at 10 different sites in three countries and required tight security. The cost at the time was over $2 billion (roughly equivalent to $26 billion today). While scientists such as Robert Oppenheimer and Enrico Fermi provided critical scientific leadership and are the names most remembered for this effort, the real hero of the project was US Army Corps of Engineers Lieutenant General Leslie R. Groves. General Groves had no prior experience or expertise in the sciences or in international relations. Rather, he brought expert project management skills to the many complicated aspects of the overall effort. His ability to make timely command decisions across the project enterprise still serves as a case study for management students.

After coming to understand the many scientific, logistic, legal, procurement, public- and private-partnership relations, resource priorities, and management requirements involved in the influenza vaccine enterprise, we believe that applicable lessons can be learned from studying the Manhattan Project. First, the project was determined to be mission critical by the highest levels of the US government. Second, it was resourced accordingly. Finally, the best principles of project management were employed to complete the mission.

We recognize the current environment of fiscal austerity; however, the economic and political consequences of a severe influenza pandemic in the absence of a readily available and effective vaccine cannot be overstated. In addition, a highly effective influenza vaccine for those at highest risk for increased severe morbidity and mortality for seasonal influenza must be considered a timely investment in reducing future healthcare costs.

SUMMARY

In the current landscape, no US government or international agency or organization has the responsibility or capability to effectively manage the influenza vaccine enterprise to bring about game-changing vaccines. Our findings indicate that moving influenza vaccinology forward in a way that effects meaningful change requires a new paradigm in the management of the influenza vaccine enterprise—both in the United States and globally. We believe that this paradigm requires a three-tiered approach. First, it needs be driven by a vision of the future that takes into account available resources and how best to allocate and use those resources. Second, it needs to be based on an understanding and acknowledgment of the limitations of our current influenza vaccines and the importance of developing truly game-

changing vaccines. Third, it needs to employ project management principles that are applicable to the scope and complexity of the project.

REFERENCES

1. ASPR. 2012 public health emergency medical countermeasures enterprise (PHEMCE) strategy. Jun 2012. Available at: http://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf
2. HHS. Public health emergency medical countermeasures enterprise strategy. Mar 2007. Available at: http://www.gpo.gov/fdsys/pkg/FR-2007-03-20/pdf/E7-5066.pdf
3. Russell PK, Gronvall GK. U.S. medical countermeasure development since 2001: a long way yet to go. Biosecur Bioterror 2012;10(1):66–76
4. Hoyt K. Long shot: vaccines for national defense. Harvard University Press; 2012
5. Project Management Institute. A guide to the project management body of knowledge (PMBOK Guide). Project Management Institute; 2008
6. Holdren JP, Lander E, Varmus H, et al. Report to the President on reengineering the influenza vaccine production enterprise to meet the challenges of pandemic influenza. 2010
7. WHO. Review committee on the functioning of the International Health Regulations (2005) in relation to pandemic (H1N1) 2009. May 2011. Available at: http://www.who.int/ihr/review_committee/en/index.html
8. Rhodes R. The Making of the Atomic Bomb. New York: Simon and Schuster; 1986
9. Groves LR. Now It Can Be Told: The Story Of The Manhattan Project. New York: Da Capo Press; 1983

CHAPTER 14

KEY FINDINGS AND RECOMMENDATIONS

We compiled numerous key findings and recommendations during this exhaustive CCIVI review, many of them related to very specific programmatic or policy issues. However, we have identified 10 key findings and 6 high-level recommendations that we believe are essential to move the international influenza vaccine enterprise toward critically needed novel-antigen, game-changing vaccines. The success or failure of the influenza vaccine enterprise to make the world a safer place against seasonal and pandemic influenza hinges on its ability and commitment to address these six recommendations.

KEY FINDINGS

1. During some influenza seasons vaccination offers substantially more protection for most of the population than being unvaccinated; however, influenza vaccine protection is markedly lower than for most routinely recommended vaccines and is suboptimal.

We reviewed all studies that evaluated influenza vaccine efficacy and effectiveness published from 1967 to 2012 and summarized those that used rigorous methodology and had specific infection outcome end points. For TIV, results demonstrated: (1) evidence of moderate protection (pooled estimate of 59%) for healthy adults 18 to 64 years of age, (2) inconsistent evidence of protection in children age 2 to 17 years, and (3) a paucity of evidence for protection in adults 65 years of age and older. For LAIV, results demonstrated: (1) evidence of high protection (pooled estimate of 83%) for young children 6 months to 7 years of age, (2) inconsistent evidence of protection in adults 60 years of age and older, and (3) a lack of evidence for protection in individuals between 8 and 59 years of age.

2. A major barrier to the development of game-changing influenza vaccines is the perception that current vaccines are already highly effective in preventing influenza infection.

The perception that current vaccines are already highly effective in preventing influenza is a major barrier to pursuing game-changing alternatives. Indeed, hundreds of influenza vaccine efficacy and effectiveness studies have been conducted since the 1940s, and vaccine efficacy in healthy adults of 70% to 90% is frequently cited. However, the preponderance of the available influenza vaccine efficacy and effectiveness data is derived from studies with suboptimal methodology, poorly defined end points, or end points not proven to be associated with influenza infection. Studies using optimal methodology have not found the level of protection often attributed to the current vaccines.

3. In an effort to reduce influenza morbidity and mortality, over the last three decades the ACIP has expanded the populations recommended to receive influenza vaccine. These recommendations, however, often were based on professional judgment and not on scientifically sound data.

Since 1964, the ACIP has had the responsibility of recommending which persons should receive annual vaccination. From 1964 to 1986, the categories of

persons recommended for influenza vaccination remained largely unchanged and primarily focused on persons at high risk for complications. In 1986, the ACIP expanded on the concept of the "indirect benefit" of vaccination by including people in contact with individuals at high risk of serious illness or death. From 1999 through 2010, the ACIP embarked on a path of incrementally adding more and more subgroups to its recommendations. The movement toward a universal recommendation for vaccination did not occur primarily as a result of a preponderance of newly published evidence; rather, changes were made in part on the basis of expert and organizational opinion. Furthermore, the ACIP statements have not always accurately reflected the evidence used to support the recommendations and routinely have cited studies with suboptimal methodology (eg, that use serology as an end point for infection among TIV recipients) as supportive.

4. Novel-antigen influenza vaccines in investigational research offer the potential of lasting, broad, and potent protection; however, substantial research support is needed to further develop and evaluate these vaccines.
More than 170 influenza vaccines representing a wide range of technologies are now undergoing clinical trials around the world. Most of them, however, use the same mechanism of action as the currently licensed vaccines aimed at eliciting antibodies to the HA head. In contrast, some of the vaccines under investigational research use novel vaccine technologies or target novel antigens and as such have the potential to be game-changing. Investigators are exploring antigens such as the HA stalk, nucleoprotein, and the matrix 2 protein, all of which contain segments that are conserved across influenza strains, which raises the prospect of universal vaccines. Novel methods of presenting these antigens to elicit broad immunologic responses are also in development and include technologies such as recombinant proteins, virus-like particles, non-replicating viruses, viral vectors, and DNA vaccines. Adequate investigational research support is needed to develop and evaluate these vaccines so their potential as game-changing vaccines can be determined.

5. The current US government regulatory process for approving influenza vaccines is primarily designed for incremental changes to existing vaccines and presents a barrier to the development of game-changing vaccines.
Approval and licensure of all vaccines by the US Food and Drug Administration (FDA) understandably requires documentation of potency, sterility, and effectiveness. But despite more than 60 years of licensing influenza vaccines in this country, critical issues remain, including the establishment of appropriate correlates of protection, improvement of assays for potency, and development of models that can be used for evaluation when human clinical trials are unethical or not feasible. Modernizing and moving vaccine development toward novel game-changing vaccine technologies will require addressing all of these issues and more. A substantial shift in regulatory science by both government and industry is needed, along with revitalization of the FDA, to move from the current incremental approach to a broader vision.

6. Substantial financial risks and inadequate incentives create significant barriers to bringing game-changing vaccines to market.
Vaccine companies incur substantial financial risks to bring new vaccines to market. The entire process, from preclinical research through licensure, can take up to 15 years and cost more than $1 billion. Novel-antigen influenza vaccines that are potential game-changers face the same hurdles for approval as more traditional new vaccines do; however, the already daunting approval process will be even longer and more extensive and the financial risk substantially higher for such novel vaccines. A novel influenza vaccine that provides protection for a number of years will need to cost substantially more per dose than current vaccines in order for investors and manufacturers to recoup their costs, since less frequent vaccine administration will lead to sale of fewer doses over time. If the per-unit cost requirement for profitability exceeds what the market will bear, then the likelihood that this type of vaccine will be developed is minimal, even if such a vaccine would bring a greater benefit to society and thereby save the government and society the costs associated with each influenza outbreak. These and other market challenges represent major barriers to developing game-changing influenza vaccines.

7. Coordinated partnerships involving national governments, the pharmaceutical industry, the investment community, and academia will be critical to move such vaccines through clinical trials and the licensure process.
While manufacturers of influenza vaccines are beginning to acknowledge the limitations of current vaccines, no fundamental changes have been implemented by the industry to facilitate development of novel-antigen game-changing influenza vaccines. Current influenza vaccines provide a relatively stable market for manufacturers, which could be disrupted by game-changing influenza vaccines, reducing manufacturers' desire to support the development of these vaccines. Owing to regulatory challenges facing novel-antigen vaccines, start-up companies are not able to obtain sufficient funding to ensure they can move through the "valley of death" of clinical trials—where substantial research, development, and licensure costs are incurred but no revenue is generated—and develop a licensed product. The US government needs to increase its support of game-changing influenza vaccines, and coordination among government, academia, and industry is needed to ensure that novel-antigen game-changing influenza vaccines become licensed.

8. Current policy goals for influenza vaccines focus on increasing production capacity and have not addressed key public health challenges related to the effectiveness of current vaccines.
Current influenza vaccine public health policy focuses on: (1) expanding current seasonal influenza vaccination campaigns to vaccinate an increasing proportion of the population each year using current HA-head vaccines, (2) ensuring that capacity is available to rapidly produce HA-head vaccines at the onset of an influenza pandemic, and (3) improving vaccine access, particularly in developing countries. While these are all laudable goals, they provide only for incremental improvements. Public health policy has not yet recognized the critical limitations of the current HA-head vaccines or the limited impact of our current strategies. While officials are now recognizing that better vaccines are needed, the current policy focus and the lack of acknowledgment of the current vaccines' shortcomings have created an environment lacking the political will to develop novel-antigen game-changing vaccines. Public health policy leaders must overcome these barriers and make development of game-changing vaccines a national priority.

9. Significant policy, investment, organizational, and leadership barriers must be overcome to achieve novel-antigen game-changing influenza vaccines.
In the current landscape, no US government or international agency or organization has the responsibility or capability to effectively manage the influenza vaccine enterprise to bring about game-changing vaccines. Our findings indicate that moving influenza vaccinology forward in a way that effects meaningful change requires a new paradigm in the organization and leadership of the influenza vaccine enterprise—both in the United States and globally. First, the paradigm needs be driven by a vision of the future that takes into account available resources and how best to allocate and use them. Second, it needs to be based on an understanding of the limitations of our current influenza vaccines and the importance of developing truly game-changing alternatives. Third, it needs to employ project management principles and processes commensurate with the scope and complexity of the project.

10. Pandemic influenza remains a clear and compelling threat to our national security and requires commensurate prioritization and an unprecedented coordinated effort among government, academia, and the private sector to mitigate this threat.
Influenza vaccines were first developed in response to the national security threat of a severe influenza pandemic, as experienced in 1918. The cornerstone of pandemic preparedness should be the availability of a highly effective pandemic influenza vaccine, ideally before the pandemic virus emerges. We recognize the current environment of fiscal austerity; however, the economic and political consequences of a severe influenza pandemic in the absence of a readily available and effective vaccine cannot be overstated.

RECOMMENDATIONS

Recommendation 1. Novel-antigen game-changing seasonal and pandemic influenza vaccines that have superior efficacy and effectiveness compared with

current vaccines are urgently needed. In particular, game-changing vaccines must demonstrate increased efficacy and effectiveness for populations at increased risk for severe influenza morbidity and mortality. They must also have a similar or better safety profile in comparison with current influenza vaccines.

Recommendation 2. Scientifically sound estimates of influenza vaccines' efficacy and effectiveness must become the cornerstone of policy recommendations regarding vaccine use and for driving efforts to develop new, more protective vaccines. Therefore, an internationally adopted standard for evaluating influenza vaccine efficacy and effectiveness, which takes into account diagnosis, study design, and analytical methods, needs to be developed.

Recommendation 3. Any pandemic influenza vaccine should demonstrate high efficacy and effectiveness for both pandemic epidemiologic patterns. As with game-changing seasonal influenza vaccines, only pandemic influenza vaccines that can demonstrate this protection based on an internationally accepted standard should be considered as a primary medical countermeasure. The vaccine also needs to be available in sufficient quantities to protect the global population either before or in the earliest days of the pandemic.

Recommendation 4. To overcome the many barriers to bringing game-changing influenza vaccines to market, a newly designed model adapted specifically to the development and licensure of novel-antigen influenza vaccines must be implemented. Several areas must be addressed. First, development of novel-antigen game-changing influenza vaccines must be declared a national priority by the US government. With that declaration must come the commitment to provide the resources and project management processes required to make novel-antigen game-changing vaccines a reality. Second, a financially sound pathway must be implemented to overcome the current financial disincentives that impede the advancement of new influenza vaccines to market. A substantial investment by the US government in research and development and regulatory science, with new private-sector investment incentives, will be imperative in accomplishing this objective. Third, a new organizational and leadership structure for the influenza vaccine enterprise must be established to provide strong science and business leadership and exemplary project management processes so that barriers are identified and overcome to maximize available resources. Achieving these goals and bringing novel influenza vaccines to the global market will require a highly coordinated leadership effort, similar to the mission-critical prioritization and project management approach of the Manhattan Project.

Recommendation 5. The US government should assume a primary leadership role in moving the global influenza vaccine enterprise forward to develop game-changing influenza vaccines and bring them to market. The World Health Organization, other international agencies and governments, and private-sector partners should make support of this US government–led effort a mission-critical priority.

Recommendation 6. An internationally accepted standard for evaluating influenza vaccine efficacy and effectiveness should be used for calculating cost-effectiveness of influenza vaccines. This will allow purchasers to accurately determine the reduction in morbidity and mortality associated with influenza vaccination in their covered populations. Purchasers can then use information on vaccine performance to generate appropriate standards for reimbursement, which will be an important factor in driving the market toward improved influenza vaccines.

Appendix A: List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
APC	antigen-presenting cell
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BLA	biologics license application
BRFSS	Behavioral Risk Factor Surveillance System
CBER	Center for Biologics Evaluation and Research
CCA	chick cell–agglutinating
CCIVI	CIDRAP Comprehensive Influenza Vaccine Initiative
CDC	Centers for Disease Control and Prevention
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIDRAP	Center for Infectious Disease Research and Policy
CMS	Centers for Medicare and Medicaid Services
CTL	cytotoxic T lymphocyte
DARPA	Defense Advanced Research Project Agency
DHS	Department of Homeland Security
DoD	Department of Defense
DTaP	pediatric diptheria-tetanus-pertussis vaccine
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FOH	Federal Occupational Health
GAO	Government Accountability Office
GAP	Global Action Plan
GBS	Guillain-Barré syndrome
GISN	Global Influenza Surveillance Network
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	hemagglutinin
HAI	hemagglutination inhibition
HCP	healthcare personnel
HCW	healthcare worker
HHS	Health and Human Services
Hib	*Haemophilus influenzae* type B
HICPAC	Healthcare Infection Control Practices Advisory Committee
HLA	human leukocyte antigen
HPAI	highly pathogenic avian influenza
IgA	immunoglobulin A
IgG	immunoglobulin G
IHR	International Health Regulations
IIS	Immunization Information System
ILI	influenza-like illness
IOM	Institute of Medicine
LAIV	live-attenuated influenza vaccine
M2	matrix protein 2
M2e	matrix protein 2 external domain
mcg	micrograms

MDCK	Madin-Darby canine kidney cells
MMWR	*Morbidity and Mortality Weekly Report*
NA	neuraminidase
NBSB	National Biodefense Science Board
NFID	National Foundation for Infectious Diseases
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NIVW	National Influenza Vaccination Week
NK	natural killer cell
NP	nucleoprotein
NS1	non-structural protein 1
NVAC	National Vaccine Advisory Committee
MCM	medical countermeasures
PAHPA	Pandemic and All-Hazards Preparedness Act
PCAST	President's Council of Advisors on Science and Technology
PHEMCE	Public Health Emergency Medical Countermeasure Enterprise
PIP	Pandemic Influenza Preparedness
RCT	randomized controlled trial
RT-PCR	reverse-transcriptase polymerase chain reaction
SAGE	Strategic Advisory Group of Experts
SRID	single radial immunodiffusion
Th	helper T cell
TIV	trivalent inactivated influenza vaccine
TLR	toll-like receptor
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VLP	virus-like particle
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WHO	World Health Organization

Appendix B: Reprint of Osterholm et al 2012 *Lancet Infectious Diseases* paper and Web appendix

Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

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Summary

Background No published meta-analyses have assessed efficacy and effectiveness of licensed influenza vaccines in the USA with sensitive and highly specific diagnostic tests to confirm influenza.

Methods We searched Medline for randomised controlled trials assessing a relative reduction in influenza risk of all circulating influenza viruses during individual seasons after vaccination (efficacy) and observational studies meeting inclusion criteria (effectiveness). Eligible articles were published between Jan 1, 1967, and Feb 15, 2011, and used RT-PCR or culture for confirmation of influenza. We excluded some studies on the basis of study design and vaccine characteristics. We estimated random-effects pooled efficacy for trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV) when data were available for statistical analysis (eg, at least three studies that assessed comparable age groups).

Findings We screened 5707 articles and identified 31 eligible studies (17 randomised controlled trials and 14 observational studies). Efficacy of TIV was shown in eight (67%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 59% [95% CI 51–67] in adults aged 18–65 years). No such trials met inclusion criteria for children aged 2–17 years or adults aged 65 years or older. Efficacy of LAIV was shown in nine (75%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 83% [69–91]) in children aged 6 months to 7 years. No such trials met inclusion criteria for children aged 8–17 years. Vaccine effectiveness was variable for seasonal influenza: six (35%) of 17 analyses in nine studies showed significant protection against medically attended influenza in the outpatient or inpatient setting. Median monovalent pandemic H1N1 vaccine effectiveness in five observational studies was 69% (range 60–93).

Interpretation Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. LAIVs consistently show highest efficacy in young children (aged 6 months to 7 years). New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.

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Introduction

The main strategy for prevention and control of seasonal and pandemic influenza for the past 60 years has been vaccination.[1,2] The first population-scale use of an inactivated influenza vaccine was in US military personnel in 1945.[3] In 1960, the US Surgeon General, in response to substantial morbidity and mortality during the 1957–58 pandemic, recommended annual influenza vaccination for individuals with chronic debilitating disease, people aged 65 years or older, and pregnant women.[4] This recommendation was made without data for vaccine efficacy or effectiveness for these high-risk populations. Instead, it was made on the basis of studies showing efficacy in young, healthy military recruits with clinical illness or seroconversion as primary measures of infection. In 1964, the Advisory Committee on Immunization Practices (ACIP) reaffirmed this recommendation but noted the absence of efficacy data.[5] Because of the longstanding public health recommendation of annual vaccination in the elderly and other high-risk groups, such patients have been excluded from placebo-controlled randomised clinical trials in the USA for the past 50 years. The ACIP supports the widely held view that inclusion of individuals at high-risk of influenza in placebo-controlled trials would be unethical.[2]

In 2010, the ACIP established the first recommendation of national universal seasonal influenza vaccination.[2] Vaccination every year is now recommended with trivalent inactivated vaccine (TIV) for all individuals aged 6 months or older, or live attenuated influenza vaccine (LAIV) for healthy non-pregnant people aged 2–49 years.[2] In the USA, TIV has been used since 1978 and accounts for approximately 90% of influenza vaccine given at present.[6] The LAIV was first approved for use in the USA in 2003 and accounts for approximately 9% of the vaccine given.[7,8] The universal influenza vaccination recommendation came after a decade of incremental changes during which the ACIP expanded recommendations to include an ever-increasing proportion of the US population.

Previous meta-analyses of TIV or LAIV efficacy and effectiveness have included studies that used diagnostic

endpoints with little sensitivity or specificity to confirm influenza infection in recipients of vaccine and placebo.[9–12] For example, the use of serology to confirm influenza infection in participants who were vaccinated with an inactivated vaccine had been recognised as problematic since the 1940s and 1950s.[13–16] Investigators noted that the increased antibody titres after vaccination in individuals given an inactivated vaccine made it difficult to document a four-fold rise in hemagglutinin antibodies necessary to confirm an influenza infection. Studies into the efficacy and effectiveness of TIV continue to use serology as a primary endpoint for confirmation of influenza infection in study participants, without addressing concerns raised by the studies done in the 1940s and 1950s. Petrie and colleagues[17] showed that, in participants who had received TIV, only 23% who had RT-PCR-confirmed H3N2 influenza had serological evidence of infection. By contrast, 90% of cases confirmed by RT-PCR in the placebo group had serologically confirmed infection. This biased case detection contributes to overestimation of the effect of vaccines in studies of TIV that rely on serological confirmation of influenza infection.

To assess the highest quality evidence about the efficacy and effectiveness of licensed influenza vaccines in the USA, we did a meta-analysis of randomised controlled trials and observational studies that used RT-PCR or viral culture to confirm influenza infections.

Panel: Inclusion criteria for studies of inactivated influenza vaccine and live attenuated influenza vaccine published from 1967 to 2011

Efficacy studies

- A published, masked, randomised controlled trial indexed by Medline
- Study reported overall vaccine efficacy against all circulating influenza strains irrespective of match or number of strains identified in surveillance
- Outcome defined as RT-PCR or viral culture confirmation of influenza infection of wild strains
- Comparison group received placebo or vaccine other than influenza
- Study assessed inactivated influenza vaccines that were licensed at the time of study or eventually licensed in the USA and antigen concentrations reported as μg of haemagglutinin, or live attenuated influenza vaccines licensed at the time of study or eventually licensed in the USA and active virus reported as tissue-culture infective doses of $10^{6.5}$–$10^{7.5}$

Effectiveness studies

- A published case test-negative control, case cohort, or prospective cohort study design indexed by Medline
- Vaccine effectiveness reported for individual seasons and adjusted (as necessary on the basis of study design) for age and calendar time (week or month of enrolment); interim or partial season estimates were excluded as were studies assessing the effectiveness of seasonal influenza vaccines for the prevention of pandemic H1N1
- Eligible patients were tested on the basis of systematic sampling with defined clinical criteria irrespective of vaccination status; studies allowing enrolment of patients based on clinical judgment were excluded to reduce selection bias
- Vaccination status established by self-report, medical record review, or immunisation registry
- Cases had influenza confirmed by RT-PCR or viral culture
- Controls had a negative RT-PCR or viral culture for influenza (test-negative control design) or had no influenza-like illness (cohort design)

Methods

Definitions and outcomes

We defined influenza vaccine efficacy as the relative reduction in influenza risk after vaccination as established by a randomised placebo-controlled clinical trial. We defined influenza vaccine effectiveness as relative reduction in influenza risk in vaccinated individuals in observational studies that used medically attended, laboratory-confirmed influenza as the primary outcome of interest.[18] Observational study designs included case-control (with test-negative controls), case-cohort, and prospective cohort. We defined laboratory-confirmed influenza as RT-PCR-confirmed or culture-confirmed influenza. RT-PCR is the preferred diagnostic test for influenza because of its high sensitivity and low likelihood of false positives.[19] TIV efficacy and effectiveness studies that used serology endpoints to diagnose influenza were excluded because of biased case detection in vaccinated individuals as already described.[13,17] We assessed published randomised controlled trials and observational studies with the criteria defined in the panel. For all studies, efficacy and effectiveness were regarded as statistically significant if the 95% CI for efficacy or effectiveness did not cross 0.

Search strategy and selection criteria

We searched Medline (PubMed database) for articles on influenza vaccine efficacy and effectiveness published in English between Jan 1, 1967, and Feb 15, 2011 (for the full search strategy see webappendix p 2). Studies were included if efficacy or effectiveness was reported against all circulating influenza viruses during individual seasons and influenza was confirmed by RT-PCR or viral culture, or both. The panel lists additional inclusion criteria. NSK assessed studies for potential eligibility and studies needing adjudication of methods or results were reviewed by EAB and MTO.

Influenza vaccine challenge studies were excluded from review because they might not be directly comparable with natural infection. Nearly all challenge studies have used homologous strains[20] and challenge virus tissue deposition might not be analogous to natural infection. We also excluded studies that employed only non-specific outcomes, such as mortality, influenza-like illness, or reduction in sick days. Efficacy studies that used non-specific clinical outcomes are not directly comparable with those that used virological endpoints, and use of non-specific outcomes complicates interpretation of observational studies because of unmeasured confounding.

We excluded studies if efficacy or effectiveness estimates were not reported (or calculable) for individual seasons, or if estimates were only reported for specific influenza types or subtypes rather than all influenza infections occurring in study participants. We included this

See Online for webappendix

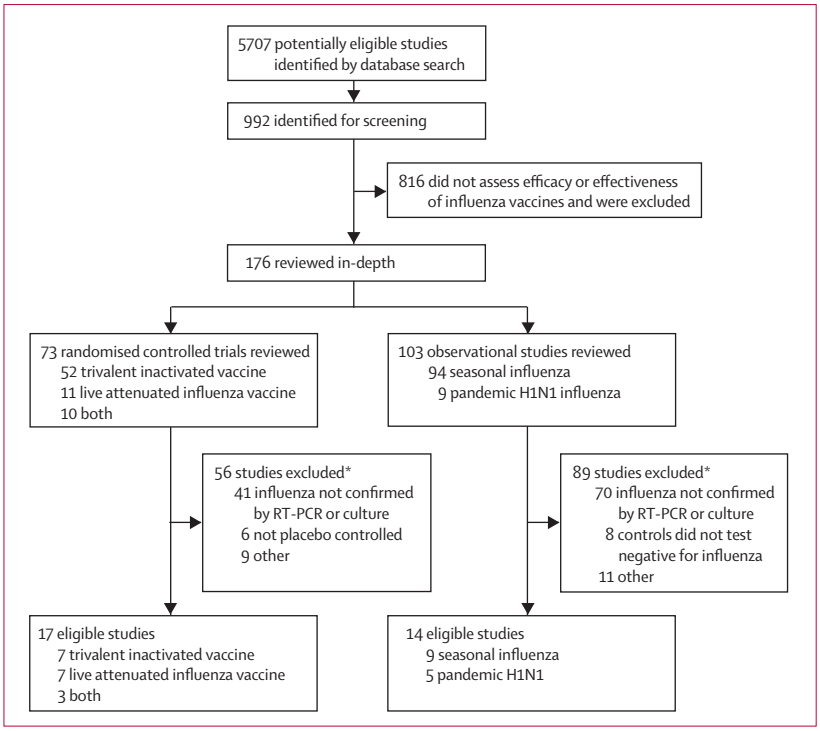

Figure 1: **Study selection**
*See webappendix pp 3–17 for more details.

	Number of trials
Trivalent inactivated vaccine	
6–23 months	1
2–17 years	0
18–64 years	6
≥65 years	0
Overall	8*
Live attenuated influenza vaccine	
6 months–7 years	8
8–17 years	0
18–49 years	0
50–59 years	0
≥60 years	1
Overall	9

*One study[23] included all age groups and showed combined significant efficacy.

Table 1: **Number of randomised controlled trials showing significant vaccine efficacy (lower 95% CI >0%) by age, 1967–2011**

restriction because efficacy or effectiveness against all circulating influenza viruses is the most relevant endpoint from a clinical and public health perspective. Effectiveness studies had to have employed systematic sampling of participants on the basis of well-defined symptom criteria; we excluded studies that allowed enrolment and testing based on clinical judgment. Finally, we excluded studies that reported effectiveness of seasonal influenza vaccines (before the 2009 pandemic) for prevention of illness caused by pandemic H1N1 (pH1N1). We calculated vaccine efficacy by season for one study using the raw data provided in the report.[21]

Statistical analysis

We calculated Mantel-Haenszel fixed effect and random effect pooled odds ratios and corresponding 95% CI for influenza vaccine recipients versus placebo when there were three or more randomised controlled studies with equivalent age ranges and vaccine characteristics.[22] We assessed homogeneity of the odds ratios by calculating the Breslow-Day statistic. We report the vaccine efficacy with the random-effects odds ratio; the point estimates were the same for the fixed and random effect calculations. The pooled odds ratios were used to establish pooled vaccine efficacy with the following formula: (1−odds ratio)×100.

We interpreted vaccine efficacy point estimates and CIs that included a negative estimate as zero efficacy. With presently accepted statistical methods for calculating vaccine efficacy, negative estimates are possible. A negative point estimate or CI does not necessarily imply that the vaccine is associated with an increased risk of influenza.

All analyses were done with SAS version 9.2.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 5707 studies on influenza vaccines in human beings with our PubMed search (figure 1). Of these, 992 were identified as cohort studies, case-control studies, clinical trials, randomised controlled trials, or did not have MeSH terms. A review of the abstracts of these studies suggested 176 (18%) potentially eligible studies; 73 (41%) were randomised controlled trials estimating vaccine efficacy and 103 (59%) were observational studies estimating vaccine effectiveness. 31 of these studies were eligible; webappendix pp 3–17 lists excluded studies and reasons for their exclusion.

17 (23%) of 73 randomised controlled trials met inclusion criteria. These trials had data for 24 influenza seasons and 53 983 participants from 23 countries. Three studies assessed TIV and LAIV. 17 (71%) of the 24 influenza seasons covered by the 17 trials suggested significant overall efficacy, but data were incomplete for specific age groups (table 1).

Ten randomised controlled trials assessed TIV efficacy during 12 influenza seasons; eight (67%) analyses for these seasons showed significant efficacy and four (33%) did not (table 2). None of these trials exclusively assessed adults aged 65 years or older or children aged 2–17 years;

	Population (dates)	Patients randomly allocated to receive TIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (18–64 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	728	75% (42 to 90)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1205	16% (–171 to 70)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Beran et al (2009)[26]	Healthy adults aged 18–64 years (2005–06)	6203	22% (–49 to 59)	Type A: similar H3N2 and H1N1; type B: lineage mismatch
Beran et al (2009)[27]	Healthy adults aged 18–64 years (2006–07)	7652	62% (46 to 73)	Type A: similar H3N2; type B: lineage mismatch
Monto et al (2009)[28]	Healthy adults aged 18–49 years (2007–08)	1139	68% (46 to 81)	Type A: drifted H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2005–06)	3514	50%† (14 to 71)	Type A: similar H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2006–07)	4144	50%† (–3 to 75)	Type A: similar H3N2; type B: mixed lineage
Frey et al (2010)[29]	Healthy adults aged 18–49 years (2007–08)	7576	63% (one-sided 97·5% lower limit of 47%)	Type A: mixed strains; type B: lineage mismatch
Madhi et al (2011)[30]	Adults aged 18–55 years with HIV infection (2008–09)	506	76% (9 to 96)	Type A: drifted H1N1; type B: not reported
Children (6–24 months)				
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (1999–2000)	411	66% (34 to 82)	Type A: similar H3N2 and H1N1; type B: not reported
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (2000–01)	375	–7% (–247 to 67)	Type A: similar H3N2 and H1N1; type B: lineage match

No studies were available for adults aged 65 years or older or children aged 2–17 years. *One other study by Loeb and colleagues[23] met inclusion criteria and contained data for all age groups. †Our calculation.

Table 2: **Randomised controlled trials of trivalent inactivated vaccine (TIV) meeting inclusion criteria***

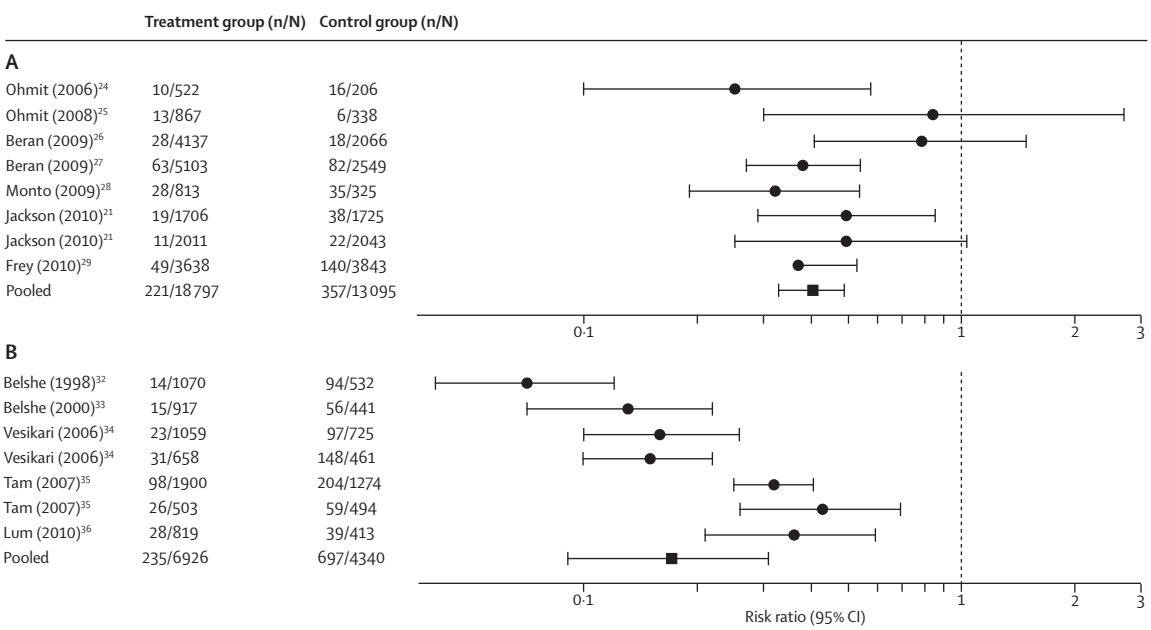

Figure 2: **Vaccine efficacy compared with placebo (Mantel-Haenszel random-effects model)**
(A) Trivalent inactivated influenza vaccine in adults aged 18–64 years. (B) Live attenuated influenza vaccine in children aged 6 months to 7 years. Studies were prospective (risk ratio) which are equivalent to case-control (odds ratio). n=cases of influenza. N=group size.

and nine of ten studies were done in healthy individuals. Eight studies were done in adults aged 18–64 years, covering nine influenza seasons. The random-effects pooled vaccine efficacy was 59% (95% CI 51–67; figure 2) and the median vaccine efficacy was 62% (range 16–76).[21,24–30] One study[31] assessing efficacy in children aged 6–24 months was done over two seasons with good matches between vaccine and circulating strains in both years. In the first year vaccine efficacy was 66% and in the second year it was –7%.[31] A cluster-randomised trial in children aged 6 months to 15 years reported combined direct and indirect vaccine efficacy in members of Hutterite communities (aged 6 months to >65 years), which is not directly comparable with the other randomised trials.[23] In this study, the combined vaccine efficacy was 59% (95% CI 4–82).

	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (≥60 years)				
De Villiers et al (2010)[37]	Community-dwelling ambulatory adults aged ≥60 years (2001–02)	3242	Overall 42% (21 to 57); 31% (–3 to 53) for patients aged 60–69 years; 57% (29 to 75) for patients aged ≥70 years	Type A: similar H3N2; type B: lineage match
Adults (18–49 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	725	48% (–7 to 74)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1191	8% (–194 to 67)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Monto et al (2009)[28]*	Healthy adults aged 18–49 years (2007–08)	1138	36% (0 to 59)	Type A: drifted H3N2; type B: lineage mismatch
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: similar H3N2; type B: lineage match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	Type A: drifted H3N2; type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	Type A: similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119	85% (78 to 90)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)	1886	72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2000–01)	3174	68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2001–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy children aged 11–<24 months (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage

No studies were available for adults aged 50–59 years or children aged 8–17 years. *Authors reported culture, RT-PCR, and RT-PCR/culture; we report RT-PCR/culture results.

Table 3: **Randomised controlled trials of live attenuated influenza vaccine (LAIV) meeting inclusion criteria**

Ten randomised controlled trials assessed LAIV efficacy during 12 influenza seasons; nine (75%) analyses for these seasons showed significant efficacy (table 3). All these trials were undertaken in healthy individuals. The one study[37] done in adults aged 60 years or older reported significant overall efficacy (42%, 95% CI 21–57), but efficacy seemed to be lower in individuals aged 60–69 years (31%) and higher in those aged 70 years or older (57%). There were three randomised controlled trials of LAIV in adults aged 18–49 years; none showed significant protection.[24,25,28] In children aged 6 months to 7 years, there were six studies covering eight influenza seasons. In all eight seasons, the vaccine provided significant protection against infection; the random-effects pooled vaccine efficacy was 83% (95% CI 69–91; figure 2) and median vaccine efficacy was 78% (range 57–93).[32–36,38] The pooled vaccine efficacy estimate excluded one study[38] because of a lack of sufficient data.

14 (14%) of 103 observational studies about effectiveness of influenza vaccines met the inclusion criteria. Nine studies reported effectiveness for seasonal influenza vaccine, and five did for monovalent pH1N1 vaccine.

The nine published reports of seasonal influenza vaccine effectiveness included 17 embedded seasonal or cohort analyses (table 4). The percentage of participants receiving TIV or LAIV in these studies was not explicitly stated, but based on the age of individuals in the study and the licensed use of the specific influenza vaccines, vaccine effectiveness estimates were mainly for TIV. Six (35%) of 17 analyses showed significant effectiveness (lower 95% CI >0%) against medically attended, laboratory-confirmed influenza in the outpatient or inpatient setting. In children aged 6–59 months, significant vaccine effectiveness was reported in three (38%) of eight seasons.[39,40,43,46] Vaccine effectiveness against medically attended influenza was noted in one (33%) of three seasons in individuals in a community cohort who were recommended to receive influenza vaccine based on ACIP criteria for age group or high-risk medical status during each season.[41] Vaccine effectiveness was shown in one of two studies in adults aged 65 years or older.[44,45] In one study of adults aged 50 years or older, vaccine effectiveness for prevention of hospital admission due to influenza was 56–73% in each of three seasons, but the CI crossed 0 for each season.[47]

Five studies assessed the effectiveness of the monovalent pH1N1 vaccine for prevention of medically attended, RT-PCR confirmed pH1N1 infection (webappendix p 18). These studies were done in Europe or Canada, and four of the studies[48–51] enrolled and obtained samples from participants with influenza-like illness. Median vaccine effectiveness for prevention of medically attended influenza was 69% (range 60–93%), but comparatively few cases of influenza occurred in individuals aged 65 years or older.[48–51] The fifth study[52] reported vaccine effectiveness of 90% (95% CI 48–100%) for prevention of hospital admission with RT-PCR confirmed pH1N1 infection. The mean age of 145 patients admitted to hospital with influenza was 37·9 years (SD 22·0; range 9 to 91 years).[52] Monovalent vaccines containing adjuvant were used in all five studies,

	Population (dates)	Participants	Vaccine effectiveness against medically attended influenza (95% CI)
Eisenberg et al (2008)[39]	All patients aged 6–59 months admitted to hospital, seen in emergency department or by primary-care doctors for acute respiratory illness (2003–05)	2003–04 (927 patients); 2004–05 (1502 patients)	44% (–42 to 78); 57% (28 to 74)
Szilagyi et al (2008)[40]	All patients aged 6–59 months admitted to hospital, seen in emergency department (inpatient) or by primary-care doctors (outpatient) for acute respiratory illness (2003–05)	2003–04 (4760 inpatients); 2003–04 (696 outpatients); 2004–05 (4708 inpatients); 2004–05 (742outpatients)	12% (–120 to 60); 52% (–100 to 90); 37% (–50 to 70); 7% (–80 to 50)
Belongia et al (2009)[41]	Residents recommended for vaccination by ACIP with acute respiratory illness: <24 months, ≥65 years, or high-risk (2004–05); <24 months, ≥50 years, or high-risk (2005–06); <59 months, ≥50 years, or high risk (2006–07)	 2004–05 (818 patients); 2005–06 (356 patients); 2006–07 (932 patients)	 10% (–36 to 40); 21% (–52 to 59); 52% (22 to 70)
Skowronski et al (2009)[42]	All patients aged ≥9 years presenting with ILI to sentinel primary-care practitioners	841	47% (18 to 65)
Heinonen et al (2011)[43]	Cohort of patients aged 6–35 months presenting with ILI enrolled in a randomised controlled trial for antivirals (2007–08)	340	72% (35 to 88)
Savulescu et al (2010)[44]	All patients ≥65 years old presenting with ILI (2008–09)	103	79% (–26 to 96)
Kissling et al (2009)[45]	All patients ≥65 years old presenting with ILI (2008–09)	292	59% (15 to 80)
Kelly et al (2011)[46]	All patients aged 6–59 months presenting with ILI (2008)	289	68%* (26 to 86)
Talbot et al (2011)[47]	Adults aged >50 years admitted to hospital with respiratory symptoms or non-localising fever (2006–09)	2006–07 (168 patients); 2007–08 (68 patients); 2008–09 (181 patients)	57% (–44 to 87)†; 56% (–63 to 88)†; 73% (–15 to 94)†

*Controls tested negative for influenza but positive for other respiratory viruses. †Vaccine effectiveness against hospitalisation. ACIP=Advisory Committee on Immunization Practices. ILI=influenza-like illness.

Table 4: **Vaccine effectiveness of seasonal influenza vaccine in studies meeting inclusion criteria**

and most vaccinated participants received a vaccine containing an adjuvant.

Discussion

Our analysis differs from previous reviews of influenza vaccine efficacy and effectiveness because of our use of restrictive study inclusion criteria to minimise bias and confounding. Our approach uses only very specific outcome endpoint data for virologically confirmed influenza. When these more stringent criteria were applied, we noted substantial gaps in the evidence base for some age groups with regard to efficacy data for TIV and LAIV.

There are no randomised controlled trials showing efficacy of TIV in people aged 2–17 years or adults aged 65 years or older. For LAIV, there are no randomised controlled trials showing efficacy for people aged 8–59 years. The evidence from trials and observational studies suggests that presently available influenza vaccines can provide moderate overall protection against infection and illness, with LAIV providing a consistently higher level of protection in children aged 7 years or younger. The studies included in our review—excluding LAIV in young children—also show substantial variability by season and age group that cannot be attributed to differences in study design or outcome measures. In some influenza seasons, and especially in some age groups, the level of protection was low or not evident. Interpretation of age-stratified estimates is difficult when there were few cases and wide CIs. Seasonal influenza vaccines have been reported to be 70–90% effective in prevention of laboratory-confirmed influenza in healthy adults when the vaccines are well matched to the circulating strains.[2,53] We noted this magnitude of effectiveness only for LAIV use in children aged 7 years or younger. The ACIP has not preferentially recommended LAIV over TIV in children aged 2–7 years. However, we found consistent evidence for moderate to high efficacy of LAIV in this age group.

Studies with few participants or few cases of influenza had low statistical power to detect a difference between groups. The incidence of influenza in a specific season is very variable and unpredictable, and thus the precision of vaccine effectiveness measures was reduced during mild seasons with fewer than expected cases. As a result, interpretation of estimates of efficacy or effectiveness that are based on few cases with a wide CI is difficult.

Although many studies failed to meet our inclusion criteria, we believe that the results of this meta-analysis provide the most accurate estimates of the efficacy and effectiveness of influenza vaccines that are licensed at present in the USA. This information is particularly useful for efforts to estimate the potential public health benefits of influenza vaccination.

Our meta-analysis differs from previously published meta-analyses in two key ways. First, eligible studies of both vaccines were restricted to those that used direct virus detection methods as primary endpoints. Although less specific endpoints can provide useful information when assessed in a randomised and adequately masked clinical trial, the efficacy estimates are not directly comparable with efficacy on the basis of virus-confirmed infections. Second, we excluded randomised controlled trials in which the comparison group did not receive either placebo or a vaccine other than for influenza.

Reviews by the Cochrane Collaboration use a different standard for assessment of influenza vaccine efficacy and effectiveness.[9–11] Many studies included in the Cochrane meta-analysis reviews had a serology-based endpoint, which resulted in overestimation of efficacy or effectiveness of TIV. An often-cited randomised controlled trial[54] included in the Cochrane analysis of adults aged 65 years or older, but not in our meta-analysis (because they did not use RT-PCR or viral culture only), reported an efficacy of 58% for clinically defined influenza that was confirmed by serology. Our meta-analysis also identified studies that were not referenced in the Cochrane analyses despite the use of similar search strategies (see webappendix p 19).

Our review did not include studies of mortality after influenza vaccination, but this topic has received much attention in recent years, especially for individuals aged 65 years or older.[55,56] A series of observational studies undertaken between 1980 and 2001 attempted to estimate the effect of seasonal influenza vaccine on rates of hospital admission and mortality in such adults.[57–59] Reduction in all-cause mortality after vaccination in these studies ranged from 27% to 75%. In 2005, these results were questioned after reports[60] that increasing vaccination in people aged 65 years or older did not result in a significant decline in mortality. Five different research groups in three countries have shown that these early observational studies had substantially overestimated the mortality benefits in this age group because of unrecognised confounding.[55,61–68] This error has been attributed to a healthy vaccine recipient effect: reasonably healthy older adults are more likely to be vaccinated, and a small group of frail, undervaccinated elderly people contribute disproportionately to deaths, including during periods when influenza activity is low or absent. Recent studies in a northern Californian population addressed this confounding and noted that influenza vaccination decreased all-cause mortality in people aged 65 years or older by 4·6% (95% CI 0·7–8·3) and hospital admissions for pneumonia and influenza by 8·5% (3·3–13·5).[62,68] These findings suggest that presently licensed vaccines might prevent some serious complications of influenza in the elderly, but not as many as would be predicted based on results of earlier cohort studies that failed to control for confounding.

Every year, large-scale campaigns in many developed countries are undertaken to vaccinate all people aged 65 years or older to prevent serious illness and mortality. With an estimated 90% of all seasonal influenza-related mortality occurring in this group, an effective intervention is an important public health priority.[69] However, this is the age group for which we have the least data supporting the efficacy or effectiveness of influenza vaccines to reduce morbidity or mortality. Only LAIV has been noted to have a significant efficacy in this age group, and only in one study;[38] this vaccine is not approved for use in adults aged 50 years or older in the USA.

The effectiveness of the pH1N1 pandemic vaccines might be regarded as our best estimate of vaccine effectiveness because the vaccine strain was a very close match to the circulating strain. The vaccine strain was highly effective for prevention of hospitalisation in one study.[52] However, these vaccines, which were mostly adjuvanted, were only 60–93% effective (median 69%) for prevention of medically attended influenza in individuals younger than 65 years. This amount of protection is not adequate for a pandemic setting where the antigenic match is ideal and antigenic drift has not occurred. The difference between 69% effectiveness and 90% effectiveness (or greater) will have a major public health effect in any pandemic that causes serious morbidity or increased mortality.

Routine field studies of the effectiveness of presently licensed influenza vaccines that use virus-confirmed endpoints are needed for all age groups. Because placebo-controlled efficacy studies are not feasible for licensed vaccines, innovative approaches to measurement of vaccine effectiveness will be important. Moreover, studies of new technology vaccines, if undertaken in countries with universal vaccination recommendations, will probably need comparison groups that receive licensed vaccines and are powered to show superiority rather than non-inferiority.

Seasonal influenza is an important public health and medical challenge. Pandemic influenza would cause a substantial burden of disease and seriously threaten the global economy. Based on a track record of substantial safety and moderate efficacy in many seasons, we believe the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available. However, evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older. The ongoing public health burden caused by seasonal influenza and the potential global effect of a severe pandemic suggests an urgent need for a new generation of more highly effective and cross-protective vaccines that can be manufactured rapidly.[70,71] New vaccines based on novel antigens that differ from the presently licensed vaccines are in development. Active partnerships between industry and government are needed to accelerate research, reduce regulatory barriers to licensure, and support financial models that favour the purchase of vaccines that provide improved protection. Active pursuit of this goal now will save lives every year and when the next influenza pandemic occurs. In the meantime, we should maintain public support for present vaccines that are the best intervention available for seasonal influenza.

Contributors

MTO, NSK, and AS designed the study. NSK, EAB, and MTO reviewed potentially eligible studies. All authors wrote and reviewed the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Davenport FM. Current knowledge of influenza vaccine. *JAMA* 1962; **182:** 11–13.

2 Fiore AE, Uyeki TM, Broder K, et al, and the Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010; **59:** 1–62.

3 Meiklejon G. Commission on influenza. The histories of the commissions. Falls Church, VA: The Borden Institute, Office of the Surgeon General, Department of the Army, 1994.

4 Burney LE. Influenza immunization: statement. *Public Health Rep* 1960; **75:** 944.

5 Long PH. Recommendations for influenza immunization and control 1964–1965. *Med Times* 1964; **92:** 1203–05.

6 Influenza vaccine: recommendation of the Public Health Service Advisory Committee on Immunization Practices. *Ann Intern Med* 1978; **89:** 657–59.

7 Feldman S. MedImmune influenza update: 2011 national influenza vaccine summit. http://www.preventinfluenza.org/NIVS_2011/ad-feldman.pdf (accessed Sept 21, 2011).

8 US Centers for Disease Control and Prevention. Seasonal influenza (flu) vaccine—total doses distributed. http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm (accessed Sept 22, 2011).

9 Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010; **2:** CD004876.

10 Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2010; **7:** CD001269.

11 Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2008; **2:** CD004879.

12 Vu T, Farish S, Jenkins M, Kelly H. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. *Vaccine* 2002; **20:** 1831–36.

13 McDonald JC, Andrews BE. Diagnostic methods in an influenza vaccine trial. *BMJ* 1955; **2:** 1232–35.

14 Eaton MD, Martin WP. An analysis of serological reactions after vaccination and infection with the virus of influenza A. *Am J Epidemiol* 1942; **36:** 255–63.

15 Rapmund G, Johnson RT, Bankhead AS, Herman YF, Dandridge OW. The diagnosis of Asian influenza virus infection after recent immunization. *US Armed Forces Med J* 1959; **10:** 637–49.

16 Rickard ER, Thingpen M, Crowley JH. Vaccination against influenza at the University of Minnesota. *Am J Epidemiol* 1945; **42:** 12–20.

17 Petrie JG, Ohmit SE, Johnson E, Cross RT, Monto AS. Efficacy studies of influenza vaccines: effect of end points used and characteristics of vaccine failures. *J Infect Dis* 2011; **203:** 1309–15.

18 Weinberg GA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis* 2010; **201:** 1607–10.

19 Weinberg GA, Erdman DD, Edwards KM, et al, and the New Vaccine Surveillance Network Study Group. Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. *J Infect Dis* 2004; **189:** 706–10.

20 Basta NE, Halloran ME, Matrajt L, Longini IM Jr. Estimating influenza vaccine efficacy from challenge and community-based study data. *Am J Epidemiol* 2008; **168:** 1343–52.

21 Jackson LA, Gaglani MJ, Keyserling HL, et al. Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. *BMC Infect Dis* 2010; **10:** 71.

22 Agresti A. An introduction to categorical data analysis. Wiley: New York, 1996.

23 Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA* 2010; **303:** 943–50.

24 Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med* 2006; **355:** 2513–22.

25 Ohmit SE, Victor JC, Teich ER, et al. Prevention of symptomatic seasonal influenza in 2005–2006 by inactivated and live attenuated vaccines. *J Infect Dis* 2008; **198:** 312–17.

26 Beran J, Wertzova V, Honegr K, et al. Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. *BMC Infect Dis* 2009; **9:** 2.

27 Beran J, Vesikari T, Wertzova V, et al. Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. *J Infect Dis* 2009; **200:** 1861–69.

28 Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009; **361:** 1260–67.

29 Frey S, Vesikari T, Szymczakiewicz-Multanowska A, et al. Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults. *Clin Infect Dis* 2010; **51:** 997–1004.

30 Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis* 2011; **52:** 128–37.

31 Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA* 2003; **290:** 1608–16.

32 Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. *N Engl J Med* 1998; **338:** 1405–12.

33 Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr* 2000; **136:** 168–75.

34 Vesikari T, Fleming DM, Aristegui JF, et al, and the CAIV-T Pediatric Day Care Clinical Trial Network. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. *Pediatrics* 2006; **118:** 2298–312.

35 Tam JS, Capeding MR, Lum LC, et al, and the Pan-Asian CAIV-T Pediatric Efficacy Trial Network. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. *Pediatr Infect Dis J* 2007; **26:** 619–28.

36 Lum LCS, Borja-Tabora CF, Breiman RF, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. *Vaccine* 2010; **28:** 1566–74.

37 De Villiers PJT, Steele AD, Hiemstra LA, et al, and the LAIV Elderly Study Trial Network. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. *Vaccine* 2009; **28:** 228–34.

38 Bracco Neto H, Farhat CK, Tregnaghi MW, et al, and the D153-P504 LAIV Study Group. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. *Pediatr Infect Dis J* 2009; **28:** 365–71.

39 Eisenberg KW, Szilagyi PG, Fairbrother G, et al, and the New Vaccine Surveillance Network. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003–2004 and 2004–2005 influenza seasons. *Pediatrics* 2008; **122:** 911–19.

40 Szilagyi PG, Fairbrother G, Griffin MR, et al, and the New Vaccine Surveillance Network. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Arch Pediatr Adolesc Med* 2008; **162:** 943–51.

41 Belongia EA, Kieke BA, Donahue JG, et al, and the Marshfield Influenza Study Group. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004–2005 season to the 2006–2007 season. *J Infect Dis* 2009; **199:** 159–67.

42 Skowronski DM, De Serres G, Dickinson J, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006–2007. *J Infect Dis* 2009; **199:** 168–79.

43 Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Ziegler T, Heikkinen T. Effectiveness of inactivated influenza vaccine in children aged 9 months to 3 years: an observational cohort study. *Lancet Infect Dis* 2011; **11:** 23–29.

44 Savulescu C, Valenciano M, de Mateo S, Larrauri A, and the cycEVA Study Team. Estimating the influenza vaccine effectiveness in elderly on a yearly basis using the Spanish influenza surveillance network—pilot case-control studies using different control groups, 2008–2009 season, Spain. *Vaccine* 2010; **28:** 2903–07.

45 Kissling E, Valenciano M, Falcao J, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008–9. *Euro Surveill* 2009; **14:** 19388.

46 Kelly H, Jacoby P, Dixon GA, et al, and the WAIVE Study Team. Vaccine effectiveness against laboratory-confirmed influenza in healthy young children: a case-control Study. *Pediatr Infect Dis J* 2011; **30:** 107–11.

47 Talbot HK, Griffin MR, Chen Q, Zhu Y, Williams JV, Edwards KM. Effectiveness of seasonal vaccine in preventing confirmed influenza-associated hospitalizations in community dwelling older adults. *J Infect Dis* 2011; **203:** 500–08.

48 Andrews N, Waight P, Yung C-F, Miller E. Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. *J Infect Dis* 2011; **203:** 32–39.

49 Valenciano M, Kissling E, Cohen JM, et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009–2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* 2011; **8:** e1000388.

50 Hardelid P, Fleming DM, McMenamin J, et al. Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009–2010. *Euro Surveill* 2011; **16:** 19763.

51 Skowronski DM, Janjua NZ, De Serres G, et al. Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. *BMJ* 2011; **342:** c7297.

52 Puig-Barberà J, Arnedo-Pena A, Pardo-Serrano F, et al, and the Surveillance and Vaccine Evaluation Group during the autumn 2009 H1N1 pandemic wave in Castellón, Spain. Effectiveness of seasonal 2008–2009, 2009–2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellón, Spain. A test-negative, hospital-based, case-control study. *Vaccine* 2010; **28:** 7460–67.

53 Influenza vaccines. *Wkly Epidemiol Rec* 2005; **80:** 279–87.

54 Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994; **272:** 1661–65.

55 Campitelli MA, Rosella LC, Stukel TA, Kwong JC. Influenza vaccination and all-cause mortality in community-dwelling elderly in Ontario, Canada, a cohort study. *Vaccine* 2010; **29:** 240–46.

56 Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis* 2007; **7:** 658–66.

57 Nichol K. Efficacy/clinical effectiveness of inactivated influenza virus vaccines in adults. Textbook of influenza. Oxford, UK: Blackwell Science, (1998).

58 Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis* 2001; **184:** 665–70.

59 Hak E, Wei F, Grobbee DE, Nichol KL. A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis. *J Clin Epidemiol* 2004; **57:** 875–80.

60 Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med* 2005; **165:** 265–72.

61 Jackson ML. Confounding by season in ecologic studies of seasonal exposures and outcomes: examples from estimates of mortality due to influenza. *Ann Epidemiol* 2009; **19:** 681–91.

62 Baxter R, Ray GT, Fireman BH. Effect of influenza vaccination on hospitalizations in persons aged 50 years and older. *Vaccine* 2010; **28:** 7267–72.

63 Simonsen L, Viboud C, Taylor RJ, Miller MA, Jackson L. Influenza vaccination and mortality benefits: new insights, new opportunities. *Vaccine* 2009; **27:** 6300–04.

64 Ortqvist A, Granath F, Askling J, Hedlund J. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area. *Eur Respir J* 2007; **30:** 414–22.

65 Baxter R, Lee J, Fireman B. Evidence of bias in studies of influenza vaccine effectiveness in elderly patients. *J Infect Dis* 2010; **201:** 186–89.

66 Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol* 2006; **35:** 337–44.

67 Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol* 2006; **35:** 345–52.

68 Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. *Am J Epidemiol* 2009; **170:** 650–56.

69 Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza—United States, 1976–2007. *MMWR Morb Mortal Wkly Rep* 2010; **59:** 1057–62.

70 Lambert LC, Fauci AS. Influenza vaccines for the future. *N Engl J Med* 2010; **363:** 2036–44.

71 Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. *Nat Med* 2010; **16:** 1389–91.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix

A: Medline Search Methods

Table A1: Potentially Eligible Studies That Were Excluded
Table A2: Vaccine Effectiveness of pH1N1 Influenza Vaccine Meeting Inclusion Criteria
Table A3: Studies not included in Cochrane review

A: Medline Search Methods

We searched MEDLINE using the following medical subject headings (MeSH terms): influenza, human and vaccine in combination with any of the following: case-control study, cohort study, attenuated vaccine, clinical trial, vaccination, randomized controlled trial, phase IV clinical trial. Publication types included clinical trial, randomized controlled trial, and phase IV clinical trial. We also searched for specific text phrases within the construct of clinical trial [Publication Type] and influenza vaccine [MeSH Term]. These included 'culture-confirmed', 'placebo', 'PCR', and 'polymerase chain reaction'. To identify recent studies and studies that did not have MeSH terms, MEDLINE was searched from October 1, 2010, and February 15, 2011, for the text phrase "influenza vaccine" in any field.

MEDLINE was the only data base used for our literature review given that all supporting studies for vaccine licensure in the United States are included on MEDLINE.

We chose January 1, 1967, as the earliest date for assessing currently licensed cold-adapted vaccines because the first characterization of the influenza A strain used for these vaccines was published that year[1]. Inactivated vaccines were not described with hemagglutinin concentrations in micrograms (mcg) until the late 1970s and we chose January 1, 1976, as the earliest date for assessing inactivated vaccines.

Table A1: Potentially Eligible Studies That Were Excluded

The primary reason for exclusion is provided in a bullet point under each study.

1. Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. *Lancet*. 1995 Sep 2;346(8975):591-5.
   - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

2. Ahmed AH, Nicholson KG, Nguyen-van Tam JS, Pearson JC. Effectiveness of influenza vaccine in reducing hospital admissions during the 1989-90 epidemic. *Epidemiol Infect*. 1997 Feb;118(1):27-33.
   - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

3. Armstrong BG, Mangtani P, Fletcher A, Kovats S, McMichael A, Pattenden S, Wilkinson P. Effect of influenza vaccination on excess deaths occurring during periods of high circulation of influenza: cohort study in elderly people. *BMJ*. 2004 Sep 18;329(7467):660.
   - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

4. Ashkenazi S, Vertruyen A, Arístegui J, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Pediatr Infect Dis J*. 2006 Oct;25(10):870-9.
   - Comparison group did not receive placebo

5. Banzhoff A, Kaniok W, Muszer A. Effectiveness of an influenza vaccine used in Poland in the 1998-1999 influenza season. *Immunol Invest*. 2001 May;30(2):103-13.
   - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

6. Barrett PN, Berezuk G, Fritsch S, et al. Efficacy, safety, and immunogenicity of a Vero-cell-culture-derived trivalent influenza vaccine: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet*. 2011 Feb 26;377(9767):751-9.
   - Influenza vaccine evaluated is not licensed in the U.S.

7. Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*. 2007 Feb 15;356(7):685-96.
   - Comparison group did not receive placebo

8. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis*. 2010 Dec 15;51(12):1355-61.
   - Unable to determine effectiveness by influenza season

9. Beran J, Moravík J. Effectiveness of vaccination against influenza in SkodaAuto Company employees during the influenza season 2000-2001. *Cent Eur J Public Health*. 2003 Dec;11(4):209-12.
   - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

10. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. *JAMA*. 2000 Oct 4;284(13):1655-63.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

11. Brotherton JM, Delpech VC, Gilbert GL, Hatzi S, Paraskevopoulos PD, McAnulty JM; Cruise Ship Outbreak Investigation Team. A large outbreak of influenza A and B on a cruise ship causing widespread morbidity. *Epidemiol Infect*. 2003 Apr;130(2):263-71.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

12. Bueving HJ, van der Wouden JC, Raat H, et al. Influenza vaccination in asthmatic children: effects on quality of life and symptoms. *Eur Respir J*. 2004 Dec;24(6):925-31.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

13. Campitelli MA, Rosella LC, Stukel TA, Kwong JC. Influenza vaccination and all-cause mortality in community-dwelling elderly in Ontario, Canada, a cohort study. *Vaccine*. 2010 Dec 16;29(2):240-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

14. Carrat F, Flahault A, Boussard E, Farran N, Dangoumau L, Valleron AJ. Surveillance of influenza-like illness in France. The example of the 1995/1996 epidemic. *J Epidemiol Community Health*. 1998 Apr;52 Suppl 1:32S-38S.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

15. Carrat F, Tachet A, Rouzioux C, Housset B, Valleron AJ. Field investigation of influenza vaccine effectiveness on morbidity. *Vaccine*. 1998 May-Jun;16(9-10):893-8.
    - Controls did not test negative for influenza

16. Centers for Disease Control and Prevention (CDC). Interim within-season estimate of the effectiveness of trivalent inactivated influenza vaccine--Marshfield, Wisconsin, 2007-08 influenza season. *MMWR Morb Mortal Wkly Rep*. 2008 Apr 18;57(15):393-8.
    - Partial season results

17. Centers for Disease Control and Prevention (CDC). Preliminary assessment of the effectiveness of the 2003-04 inactivated influenza vaccine--Colorado, December 2003. *MMWR Morb Mortal Wkly Rep*. 2004 Jan 16;53(1):8-11.
    - Partial season results

18. Centers for Disease Control and Prevention (CDC). Assessment of the effectiveness of the 2003-04 influenza vaccine among children and adults--Colorado, 2003. *MMWR Morb Mortal Wkly Rep*. 2004 Aug 13;53(31):707-10.
    - Controls did not test negative for influenza

19. Chodick G, Heymann AD, Green MS, Kokia E, Shalev V. Late influenza vaccination is associated with reduced effectiveness. *Prev Med*. 2006 Jul;43(1):71-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

20. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. *Eur Respir J*. 2004 Mar;23(3):363-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

21. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. *Lancet*. 2001 Mar 31;357(9261):1008-11.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

22. Christenson B, Lundbergh P. Comparison between cohorts vaccinated and unvaccinated against influenza and pneumococcal infection. *Epidemiol Infect*. 2002 Dec;129(3):515-24.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

23. Christenson B, Pauksen K, Sylvan SP. Effect of influenza and pneumococcal vaccines in elderly persons in years of low influenza activity. *Virol J*. 2008 Apr 28;5:52.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

24. Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. *J Infect Dis*. 1991 Feb;163(2):300-4.
    - Influenza vaccine not used as licensed in the US, drops in nose

25. Colombo C, Argiolas L, La Vecchia C, Negri E, Meloni G, Meloni T. Influenza vaccine in healthy preschool children. *Rev Epidemiol Sante Publique*. 2001 Apr;49(2):157-62.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

26. Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect*. 1997 Dec;119(3):335-41.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

27. Connolly AM, Salmon RL, Lervy B, Williams DH. What are the complications of influenza and can they be prevented? Experience from the 1989 epidemic of H3N2 influenza A in general practice. *BMJ*. 1993 May 29;306(6890):1452-4.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

28. Cowling BJ, Ng S, Ma ES, et al. Protective efficacy of seasonal influenza vaccination against seasonal and pandemic influenza virus infection during 2009 in Hong Kong. *Clin Infect Dis*. 2010 Dec 15;51(12):1370-9.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

29. Crocetti E, Arniani S, Bordoni F, Maciocco G, Zappa M, Buiatti E. Effectiveness of influenza vaccination in the elderly in a community in Italy. *Eur J Epidemiol*. 2001;17(2):163-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

30. Cruijff M, Thijs C, Govaert T, Aretz K, Dinant GJ, Knottnerus A. The effect of smoking on influenza, influenza vaccination efficacy and on the antibody response to influenza vaccination. *Vaccine*. 1999 Feb 5;17(5):426-32.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

31. Dean AS, Moffatt CR, Rosewell A, et al. Incompletely matched influenza vaccine still provides protection in frail elderly. *Vaccine*. 2010 Jan 8;28(3):864-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

32. Deguchi Y, Nishimura K. Efficacy of Influenza Vaccine in Elderly Persons in Welfare Nursing Homes: Reduction in Risks of Mortality and Morbidity During an Influenza A (H3N2) Epidemic. *J Gerontol A Biol Sci Med Sci*. 2001 Jun;56(6):M391-4.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

33. Deguchi Y, Takasugi Y, Nishimura K. Vaccine effectiveness for influenza in the elderly in welfare nursing homes during an influenza A (H3N2) epidemic. *Epidemiol Infect*. 2000 Oct;125(2):393-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

34. Deguchi Y, Takasugi Y, Tatara K. Efficacy of influenza vaccine in the elderly in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. *J Med Microbiol*. 2000 Jun;49(6):553-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

35. Deguchi Y, Takasugi Y. Efficacy of influenza vaccine in the elderly: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic for the elderly in nursing homes. *Int J Clin Lab Res*. 2000;30(1):1-4.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

36. Dille JH. A worksite influenza immunization program. Impact on lost work days, health care utilization, and health care spending. *AAOHN J*. 1999 Jul;47(7):301-9.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

37. Dixon GA, Moore HC, Kelly H, et al. Lessons from the first year of the WAIVE study investigating the protective effect of influenza vaccine against laboratory-confirmed influenza in hospitalised children aged 6-59 months. *Influenza Other Respi Viruses*. 2010 Jul;4(4):231-4.
    - Controls did not test negative for influenza

38. Drinka PJ, Gravenstein S, Krause P, Schilling M, Miller BA, Shult P. Outbreaks of influenza A and B in a highly immunized nursing home population. *J Fam Pract*. 1997 Dec;45(6):509-14.
    - Controls did not test negative for influenza

39. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis*. 1994 Jan;169(1):68-76.
    - Placebo was an influenza vaccine

40. Esposito S, Cecinati V, Scicchitano B, et al. Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy. *Vaccine*. 2010 Feb 10;28(6):1558-65.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

41. Esposito S, Marchisio P, Cavagna R, et al. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. *Vaccine*. 2003 Jul 4;21(23):3162-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

42. Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. *JAMA*. 1993 Oct 27;270(16):1956-61.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

43. Fleming DM, Watson JM, Nicholas S, Smith GE, Swan AV. Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989-90 using a general practice database. *Epidemiol Infect*. 1995 Dec;115(3):581-9.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

44. Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J*. 2006 Oct;25(10):860-9.
    - Comparison group did not receive placebo

45. Foster DA, Talsma A, Furumoto-Dawson A, et al. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. *Am J Epidemiol*. 1992 Aug 1;136(3):296-307.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

46. Gaughran F, Walwyn R, Lambkin-Williams R, et al. Flu: effect of vaccine in elderly care home residents: a randomized trial. *J Am Geriatr Soc*. 2007 Dec;55(12):1912-20.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

47. Gorse GJ, O'connor TZ, Young SL, et al. Impact of a winter respiratory virus season on patients with COPD and association with influenza vaccination. *Chest*. 2006 Oct;130(4):1109-16.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

48. Gorse GJ, O'Connor TZ, Young SL, et al. Efficacy trial of live, cold-adapted and inactivated influenza virus vaccines in older adults with chronic obstructive pulmonary disease: a VA cooperative study. *Vaccine*. 2003 May 16;21(17-18):2133-44.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

49. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA*. 1994 Dec 7;272(21):1661-5.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

50. Gravenstein S, Drinka P, Duthie EH, et al. Efficacy of an influenza hemagglutinin-diphtheria toxoid conjugate vaccine in elderly nursing home subjects during an influenza outbreak. *J Am Geriatr Soc*. 1994 Mar;42(3):245-51.
    - Comparison group did not receive placebo

51. Grotto I, Mandel Y, Green MS, et al. Influenza vaccine efficacy in young, healthy adults. *Clin Infect Dis*. 1998 Apr;26(4):913-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

52. Gruber WC, Belshe RB, King JC, et al. Evaluation of live attenuated influenza vaccines in children 6-18 months of age: safety, immunogenicity, and efficacy. National Institute of Allergy and Infectious Diseases, Vaccine and Treatment Evaluation Program and the Wyeth-Ayerst ca Influenza Vaccine Investigators Group. *J Infect Dis*. 1996 Jun;173(6):1313-9.
    - Vaccine efficacy not reported for all circulating influenza strains

53. Gutierrez EB, Li HY, Santos AC, Lopes MH. Effectiveness of influenza vaccination in elderly outpatients in São Paulo city, Brazil. *Rev Inst Med Trop Sao Paulo*. 2001 Nov-Dec;43(6):317-20.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

54. Hak E, Buskens E, Nichol KL, Verheij TJ. Do recommended high-risk adults benefit from a first influenza vaccination? *Vaccine*. 2006 Apr 5;24(15):2799-802.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

55. Hak E, Wei F, Grobbee DE, Nichol KL. A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis. *J Clin Epidemiol*. 2004 Sep;57(9):875-80.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

56. Hak E, Nordin J, Wei F, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clin Infect Dis*. 2002 Aug 15;35(4):370-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

57. Hara M, Tanaka K, Kase T, Maeda A, Hirota Y. Evaluation of seasonal influenza vaccination effectiveness based on antibody efficacy among the institutionalized elderly in Japan. *Vaccine*. 2010 Aug 9;28(35):5664-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

58. Hara M, Sakamoto T, Tanaka K. Influenza vaccine effectiveness among elderly persons living in the community during the 2003--2004 season. *Vaccine*. 2008 Nov 25;26(50):6477-80.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

59. Hara M, Sakamoto T, Tanaka K. Effectiveness of influenza vaccination in preventing influenza-like illness among community-dwelling elderly: population-based cohort study in Japan. *Vaccine*. 2006 Jul 7;24(27-28):5546-51.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

60. Hashim AB, McKeever T, Kelly SJ, Nguyen-Van-Tam JS. Evaluation of inter-pandemic influenza vaccine effectiveness during eight consecutive winter seasons in England and Wales in patients with cardiovascular risk factors. *J Infect Public Health*. 2010 Dec;3(4):159-65.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

61. Hayward AC, Harling R, Wetten S, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ*. 2006 Dec 16;333(7581):1241.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

62. Hedlund J, Christenson B, Lundbergh P, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. *Vaccine*. 2003 Sep 8;21(25-26):3906-11.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

63. Herrera GA, Iwane MK, Cortese M, et al. Influenza vaccine effectiveness among 50-64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003-2004. *Vaccine*. 2007 Jan 2;25(1):154-60.
    - Controls did not test negative for influenza

64. Honkanen P, Läärä E, Pyhälä R, Kivelä SL, Helena Mäkelä P. Comparison of two vaccination programmes in preventing influenza-related hospitalization among the elderly during two consecutive seasons. *Scand J Infect Dis*. 2006;38(6-7):506-11.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

65. Hoskins TW, Davies JR, Smith AJ, Allchin A, Miller CL, Pollock TM. Influenza at Christ's Hospital: March, 1974. *Lancet*. 1976 Jan 17;1(7951):105-8.
    - Influenza vaccine antigen concentration not reported in MCG

66. Hoskins TW, Davies JR, Smith AJ, Miller CL, Allchin A. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. *Lancet*. 1979 Jan 6;1(8106):33-5.
    - Influenza vaccine antigen concentration not reported in MCG

67. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA*. 2000 Oct 4;284(13):1677-82.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

68. Hurwitz ES, Haber M, Chang A, et al. Studies of the 1996-1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infection, and clinical effectiveness. *J Infect Dis*. 2000 Oct;182(4):1218-21.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

69. Isahak I, Mahayiddin AA, Ismail R. Effectiveness of influenza vaccination in prevention of influenza-like illness among inhabitants of old folk homes. *Southeast Asian J Trop Med Public Health*. 2007 Sep;38(5):841-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

70. Jick H, Hagberg KW. Effectiveness of influenza vaccination in the United kingdom, 1996-2007. *Pharmacotherapy*. 2010 Dec;30(12):1199-206.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

71. Jordan RE, Hawker JI, Ayres JG, et al. A case-control study of elderly patients with acute respiratory illness: effect of influenza vaccination on admission to hospital in winter 2003-2004. *Vaccine*. 2007 Nov 14;25(46):7909-13.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

72. Joshi AY, Iyer VN, St Sauver JL, Jacobson RM, Boyce TG. Effectiveness of inactivated influenza vaccine in children less than 5 years of age over multiple influenza seasons: a case-control study. *Vaccine*. 2009 Jul 16;27(33):4457-61.
    - Unable to determine effectiveness by influenza season

73. Kamada M, Nagai T, Kumagai T, et al. Efficacy of inactivated trivalent influenza vaccine in alleviating the febrile illness of culture-confirmed influenza in children in the 2000-2001 influenza season. *Vaccine*. 2006 Apr 24;24(17):3618-23.
    - Controls did not test negative for influenza

74. Kawai N, Ikematsu H, Iwaki N, et al. A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001-2002 influenza season. *Vaccine*. 2003 Nov 7;21(31):4507-13.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

75. Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. *Vaccine*. 1997 Jul;15(10):1114-22.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

76. Keitel WA, Cate TR, Couch RB. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *Am J Epidemiol*. 1988 Feb;127(2):353-64.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

77. Kelly H, Carville K, Grant K, Jacoby P, Tran T, Barr I. Estimation of influenza vaccine effectiveness from routine surveillance data. *PLoS One*. 2009;4(3):e5079.
    - Not adjusted for calendar time

78. Kheok SW, Chong CY, McCarthy G, et al. The efficacy of influenza vaccination in healthcare workers in a tropical setting: a prospective investigator blinded observational study. *Ann Acad Med Singapore*. 2008 Jun;37(6):465-9.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

79. Kiderman A, Furst A, Stewart B, Greenbaum E, Morag A, Zakay-Rones Z. A double-blind trial of a new inactivated, trivalent, intra-nasal anti-influenza vaccine in general practice: relationship between immunogenicity and respiratory morbidity over the winter of 1997-98. *J Clin Virol*. 2001 Feb;20(3):155-61.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

80. Landi F, Onder G, Cesari M, et al. In a prospective observational study, influenza vaccination prevented hospitalization among older home care patients. *J Clin Epidemiol*. 2006 Oct;59(10):1072-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

81. Legrand J, Vergu E, Flahault A. Real-time monitoring of the influenza vaccine field effectiveness. *Vaccine*. 2006 Nov 10;24(44-46):6605-11.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

82. Lemaitre M, Meret T, Rothan-Tondeur M, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. *J Am Geriatr Soc*. 2009 Sep;57(9):1580-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

83. Libow LS, Neufeld RR, Olson E, Breuer B, Starer P. Sequential outbreak of influenza A and B in a nursing home: efficacy of vaccine and amantadine. *J Am Geriatr Soc*. 1996 Oct;44(10):1153-7.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

84. Looijmans-Van den Akker I, Verheij TJ, Buskens E, Nichol KL, Rutten GE, Hak E. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care*. 2006 Aug;29(8):1771-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

85. Maeda T, Shintani Y, Miyamoto H, Kawagoe H, Nakano K, Nishiyama A, Yamada Y. Prophylactic effect of inactivated influenza vaccine on young children. *Pediatr Int*. 2002 Feb;44(1):43-6.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

86. Maeda T, Shintani Y, Nakano K, Terashima K, Yamada Y. Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. *Pediatr Int*. 2004 Apr;46(2):122-5.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

87. Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. *J Infect Dis*. 2004 Jul 1;190(1):1-10.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

88. Manzoli L, Villari P, Granchelli C, et al. Influenza vaccine effectiveness for the elderly: a cohort study involving general practitioners from Abruzzo, Italy. *J Prev Med Hyg*. 2009 Jun;50(2):109-12.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

89. Marchisio P, Cavagna R, Maspes B, et al. Efficacy of intranasal virosomal influenza vaccine in the prevention of recurrent acute otitis media in children. *Clin Infect Dis*. 2002 Jul 15;35(2):168-74.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

90. Marchisio P, Esposito S, Bianchini S, et al. Efficacy of injectable trivalent virosomal-adjuvanted inactivated influenza vaccine in preventing acute otitis media in children with recurrent complicated or noncomplicated acute otitis media. *Pediatr Infect Dis J*. 2009 Oct;28(10):855-9.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

91. Mazick A, Christiansen AH, Samuelsson S, Mølbak K. Using sentinel surveillance to monitor effectiveness of influenza vaccine is feasible: a pilot study in Denmark. *Euro Surveill*. 2006;11(10):254-6.
    - Controls did not test negative for influenza

92. Menon B, Gurnani M, Aggarwal B. Comparison of outpatient visits and hospitalisations, in patients with chronic obstructive pulmonary disease, before and after influenza vaccination. *Int J Clin Pract*. 2008 Apr;62(4):593-8.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

93. Millot JL, Aymard M, Bardol A. Reduced efficiency of influenza vaccine in prevention of influenza-like illness in working adults: a 7 month prospective survey in EDF Gaz de France employees, in Rhône-Alpes, 1996-1997. *Occup Med (Lond)*. 2002 Aug;52(5):281-92.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

94. Mixéu MA, Vespa GN, Forleo-Neto E, Toniolo-Neto J, Alves PM. Impact of influenza vaccination on civilian aircrew illness and absenteeism. *Aviat Space Environ Med*. 2002 Sep;73(9):876-80.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

95. Miyazaki C, Nakayama M, Tanaka Y, et al. Immunization of institutionalized asthmatic children and patients with psychomotor retardation using live attenuated cold-adapted reassortment influenza A H1N1, H3N2 and B vaccines. *Vaccine*. 1993;11(8):853-8.
    - Comparison group did not receive placebo

96. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *Am J Epidemiol*. 2001 Jul 15;154(2):155-60.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

97. Morio S, Okamoto N, Kawamoto A, Suyama A, Okamoto M, Nakayama H. Three year follow up study of national influenza vaccination practices in Japan. *J Epidemiol Community Health*. 1994 Feb;48(1):46-51.
    - Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

98. Mullooly JP, Bennett MD, Hornbrook MC, et al. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. *Ann Intern Med*. 1994 Dec 15;121(12):947-52.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

99. Murayama N, Suzuki H, Arakawa M, Nerome K, Mizuta K, Kameyama K. Two outbreaks of influenza A (H3N2) in a Japanese nursing home in the winter of 1996-1997, with differing vaccine efficacy. *Tohoku J Exp Med*. 1999 Aug;188(4):289-98.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

100. Mustafa AN, Gessner BD, Ismail R, et al. A case-control study of influenza vaccine effectiveness among Malaysian pilgrims attending the Haj in Saudi Arabia. *Int J Infect Dis*. 2003 Sep;7(3):210-4.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

101. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. *Pediatr Infect Dis J*. 2001 Aug;20(8):733-40.
- Placebo was an influenza vaccine

102. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol*. 1998 Dec 1;148(11):1094-102.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

103. Nichol KL, Margolis KL, Wouremna J, von Sternberg T. Effectiveness of influenza vaccine in the elderly. *Gerontology*. 1996;42(5):274-9.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

104. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med*. 1994 Sep 22;331(12):778-84.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

105. Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. *JAMA*. 1999 Jul 14;282(2):137-44.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

106. Nichol KL, D'Heilly S, Ehlinger EP. Influenza vaccination among college and university students: impact on influenzalike illness, health care use, and impaired school performance. *Arch Pediatr Adolesc Med*. 2008 Dec;162(12):1113-8.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

107. Nichol KL, D'Heilly SJ, Greenberg ME, Ehlinger E. Burden of influenza-like illness and effectiveness of influenza vaccination among working adults aged 50-64 years. *Clin Infect Dis*. 2009 Feb 1;48(3):292-8.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

108. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007 Oct 4;357(14):1373-81.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

109. Nicholson KG, Kent J, Hammersley V. Influenza A among community-dwelling elderly persons in Leicestershire during winter 1993-4; cigarette smoking as a risk factor and the efficacy of influenza vaccination. *Epidemiol Infect*. 1999 Aug;123(1):103-8.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

110. Ohmit SE, Monto AS. Influenza vaccine effectiveness in preventing hospitalization among the elderly during influenza type A and type B seasons. *Int J Epidemiol*. 1995 Dec;24(6):1240-8.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

111. Ortqvist A, Granath F, Askling J, Hedlund J. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area. *Eur Respir J*. 2007 Sep;30(3):414-22.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

112. Patriarca PA, Weber JA, Parker RA, Hall WN, Kendal AP, Bregman DJ, Schonberger LB. Efficacy of influenza vaccine in nursing homes. Reduction in illness and complications during an influenza A (H3N2) epidemic. *JAMA*. 1985 Feb 22;253(8):1136-9.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

113. Pebody R, Hardelid P, Fleming D, McMenamin J, et al. Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11. *Euro Surveill*. 2011 Feb 10;16(6). pii: 19791.
- Partial season results

114. Plasai V, Lertmaharit S, Viputsiri OA, et al. Influenza vaccination among the elderly in Bangkok. *Southeast Asian J Trop Med Public Health*. 2006;37 Suppl 3:140-4.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

115. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis*. 1997 Jan;175(1):1-6.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

116. Praditsuwan R, Assantachai P, Wasi C, Puthavatana P, Kositanont U. The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community. *J Med Assoc Thai*. 2005 Feb;88(2):256-64.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

117. Principi N, Esposito S, Marchisio P, Gasparini R, Crovari P. Socioeconomic impact of influenza on healthy children and their families. Pediatr Infect Dis J. 2003 Oct;22(10 Suppl):S207-10.
- Comparison group did not receive placebo

118. Puig-Barberà J, Diez-Domingo J, Pérez Hoyos S, Belenguer Varea A, González Vidal D. Effectiveness of the MF59-adjuvanted influenza vaccine in preventing emergency admissions for pneumonia in the elderly over 64 years of age. *Vaccine*. 2004 Dec 2;23(3):283-9.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

119. Pyrhönen S, Suni J, Romo M. Clinical trial of a subunit influenza vaccine. *Scand J Infect Dis*. 1981;13(2):95-9.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

120. Saito R, Suzuki H, Oshitani H, Sakai T, Seki N, Tanabe N. The effectiveness of influenza vaccine against influenza a (H3N2) virus infections in nursing homes in Niigata, Japan, during the 1998-1999 and 1999-2000 seasons. *Infect Control Hosp Epidemiol*. 2002 Feb;23(2):82-6.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

121. Salleras L, Domínguez A, Pumarola T, et al. Effectiveness of virosomal subunit influenza vaccine in preventing influenza-related illnesses and its social and economic consequences in children aged 3-14 years: a prospective cohort study. *Vaccine*. 2006 Nov 10;24(44-46):6638-42.
- Influenza vaccine evaluated is not licensed in the U.S.

122. Saxén H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatr Infect Dis J*. 1999 Sep;18(9):779-83.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

123. Schembri S, Morant S, Winter JH, MacDonald TM. Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD. *Thorax*. 2009 Jul;64(7):567-72.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

124. Shuler CM, Iwamoto M, Bridges CB, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. *Pediatrics*. 2007 Mar;119(3):e587-95.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

125. Skowronski DM, Masaro C, Kwindt TL, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005-2006 season of dual A and B vaccine mismatch in Canada. *Vaccine*. 2007 Apr 12;25(15):2842-51.
- Methods note clinical judgment in testing

126. Skowronski DM, Gilbert M, Tweed SA, et al. Effectiveness of vaccine against medical consultation due to laboratory-confirmed influenza: results from a sentinel physician pilot project in British Columbia, 2004-2005. *Can Commun Dis Rep*. 2005 Sep 15;31(18):181-91.
- Methods note clinical judgment in testing

127. Song JY, Cheong HJ, Heo JY, et al. Effectiveness of the pandemic influenza A/H1N1 2009 monovalent vaccine in Korea. *Vaccine*. 2011 Feb 4;29(7):1395-8.
- Not adjusted for calendar time

128. Song JY, Cheong HJ, Ha SH, et al. Clinical impact of influenza immunization in patients with liver cirrhosis. *J Clin Virol*. 2007 Jul;39(3):159-63.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

129. Spaude KA, Abrutyn E, Kirchner C, Kim A, Daley J, Fisman DN. Influenza vaccination and risk of mortality among adults hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2007 Jan 8;167(1):53-9.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

130. Tanaka Y, Ueda K, Miyazaki C, et al. Trivalent cold recombinant influenza live vaccine in institutionalized children with bronchial asthma and patients with psychomotor retardation. *Pediatr Infect Dis J*. 1993 Jul;12(7):600-5.
- Vaccine efficacy were not systematically evaluated by RT-PCR and/or viral culture only

131. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. *Vaccine*. 1998 May-Jun;16(9-10):1039-42.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

132. Tasker SA, Treanor JJ, Paxton WB, Wallace MR. Efficacy of influenza vaccination in HIV-infected persons. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999 Sep 21;131(6):430-3.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

133. Treanor JJ, Mattison HR, Dumyati G, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. *Ann Intern Med*. 1992 Oct 15;117(8):625-33.
- Influenza vaccine not used as licensed in the US, TIV and LAIV both administered

134. Van Buynder PG, Dhaliwal JK, Van Buynder JL, et al. Protective effect of single-dose adjuvanted pandemic influenza vaccine in children. *Influenza Other Respi Viruses*. 2010 Jul;4(4):171-8.
- Not adjusted for calendar time

135. Van Damme P, Arnou R, Kafeja F, et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomized comparative study. *BMC Infect Dis*. 2010 May 26;10:134.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

136. Voordouw AC, Sturkenboom MC, Dieleman JP, et al. Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. *JAMA*. 2004 Nov 3;292(17):2089-95.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

137. Wang CS, Wang ST, Lai CT, Lin LJ, Lee CT, Chou P. Reducing major cause-specific hospitalization rates and shortening hospital stays after influenza vaccination. *Clin Infect Dis*. 2004 Dec 1;39(11):1604-10.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

138. Weingarten S, Staniloff H, Ault M, Miles P, Bamberger M, Meyer RD. Do hospital employees benefit from the influenza vaccine? A placebo-controlled clinical trial. *J Gen Intern Med*. 1988 Jan-Feb;3(1):32-7.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

139. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA*. 1999 Mar 10;281(10):908-13.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

140. Wongsurakiat P, Lertakyamanee J, Maranetra KN, Jongriratanakul S, Sangkaew S. Economic evaluation of influenza vaccination in Thai chronic obstructive pulmonary disease patients. *J Med Assoc Thai*. 2003 Jun;86(6):497-508.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

141. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest*. 2004 Jun;125(6):2011-20.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

142. Wood SC, Alexseiv A, Nguyen VH. Effectiveness and economical impact of vaccination against influenza among a working population in Moscow. *Vaccine*. 1999 Oct 29;17 Suppl 3:S81-7.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

143. Wu J, Xu F, Lu L, et al. Safety and effectiveness of a 2009 H1N1 vaccine in Beijing. *N Engl J Med*. 2010 Dec 16;363(25):2416-23.
- Controls did not test negative for influenza

144. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008 Oct 9;359(15):1555-64.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

145. Zhu T, Carcaillon L, Martinez I, et al. Association of influenza vaccination with reduced risk of venous thromboembolism. *Thromb Haemost*. 2009 Dec;102(6):1259-64.
- Influenza cases were not systematically evaluated by RT-PCR and/or viral culture only

Table A2: Vaccine Effectiveness of Pandemic H1N1 Vaccine Meeting Inclusion Criteria[a]

Study	Population	No. Subjects	Vaccine Effectiveness Against Medically Attended Influenza (95% CI)
Andrews et al (2011)[2]	All patients hospitalized with ILI or patients presenting to GP with ILI in the critical risk group	2,153	All **60%** (27% to 78%) 6 mo – 24 yrs **80%** (32% to 94%) 25+ yrs **1%** (-156% to 62%)
Valenciano et al (2011)[3]	Patients presenting with ILI to sentinel primary care practitioners.	2,902	All **66%** (24% to 84%) <15 yrs **100%** (N/A) 15-64 yrs **66%** (12% to 87%)
Hardelid et al (2011)[4]	Patients presenting with ILI to sentinel primary care practitioners.	5,985	All **72%** (21% to 90%)
Skowronski et al (2011)[5]	Patients presenting with ILI to sentinel primary care practitioners.	552	All **93%** (69% to 98%) <50 yrs **91%** (62% to 98%)
Study	**Population**	**No. Subjects**	**Vaccine Effectiveness Against Hospitalization (95% CI)**
Puig-Barberà et al (2010)[6]	Hospitalized patients with suspected pandemic H1N1	349	All **90%** (48% to 100%)

[a] The vaccine effectiveness estimates are primarily for adjuvanted inactivated vaccines.

Table A3: Studies Eligible for Inclusion in Cochrane Reviews but Excluded

Vaccines for preventing influenza in healthy adults[7] Literature review by Cochrane current through June 2, 2010
• Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *New England Journal of Medicine*. 2006;355(24):2513. • Ohmit S, Victor J, Teich E, et al. Prevention of Symptomatic Seasonal Influenza in 2005–2006 by Inactivated and Live Attenuated Vaccines. *J Infec Dis*. 2008;198(3):312-317. • Skowronski DM, De Serres G, Dickinson J, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006-2007. *J Infect Dis.* 2009 Jan 15;199(2):168-79. • Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *New England Journal of Medicine*. 2009;361(13):1260. • Belongia E, Kieke B, Donahue J, et al. Effectiveness of Inactivated Influenza Vaccines Varied Substantially with Antigenic Match from the 2004–2005 Season to the 2006–2007 Season. *J Infec Dis*. 2009;199(2):159-167. • Jackson LA, Gaglani MJ, Keyserling HL, et al. Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. *BMC Infectious Diseases*. 2010;10(1):71.
Vaccines for preventing influenza in healthy children[8] Literature review by Cochrane current through September 29, 2007
• None identified
Vaccines for preventing influenza in the elderly[9] Literature review by Cochrane current through October 6, 2009
• De Villiers PJ, Steele AD, Hiemstra LA, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. *Vaccine*. 2009;28(1):228–234.

References

1. Maassab, H.F. Adaptation and growth characteristics of influenza virus at 25 degrees c. *Nature* **213**, 612-614 (1967).
2. Andrews, N., Waight, P., Yung, C.-F. & Miller, E. Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. *J. Infect. Dis* **203**, 32-39 (2011).
3. Valenciano, M. et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med* **8**, e1000388 (2011).
4. Hardelid, P. et al. Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010. *Euro Surveill* **16**, (2011).
5. Skowronski, D.M. et al. Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. *BMJ* **342**, c7297 (2011).
6. Puig-Barberà, J. et al. Effectiveness of seasonal 2008-2009, 2009-2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellón, Spain. A test-negative, hospital-based, case-control study. *Vaccine* **28**, 7460-7467 (2010).
7. Jefferson, T. et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* (2010).
8. Jefferson, T., Rivetti, A., Harnden, A., Di Pietrantonj, C. & Demicheli, V. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* (2008).
9. Jefferson, T. et al. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* (2010).

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