The Compelling Need for Game-Changing Influenza Vaccines
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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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 vaccine 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
• 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.

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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.

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.