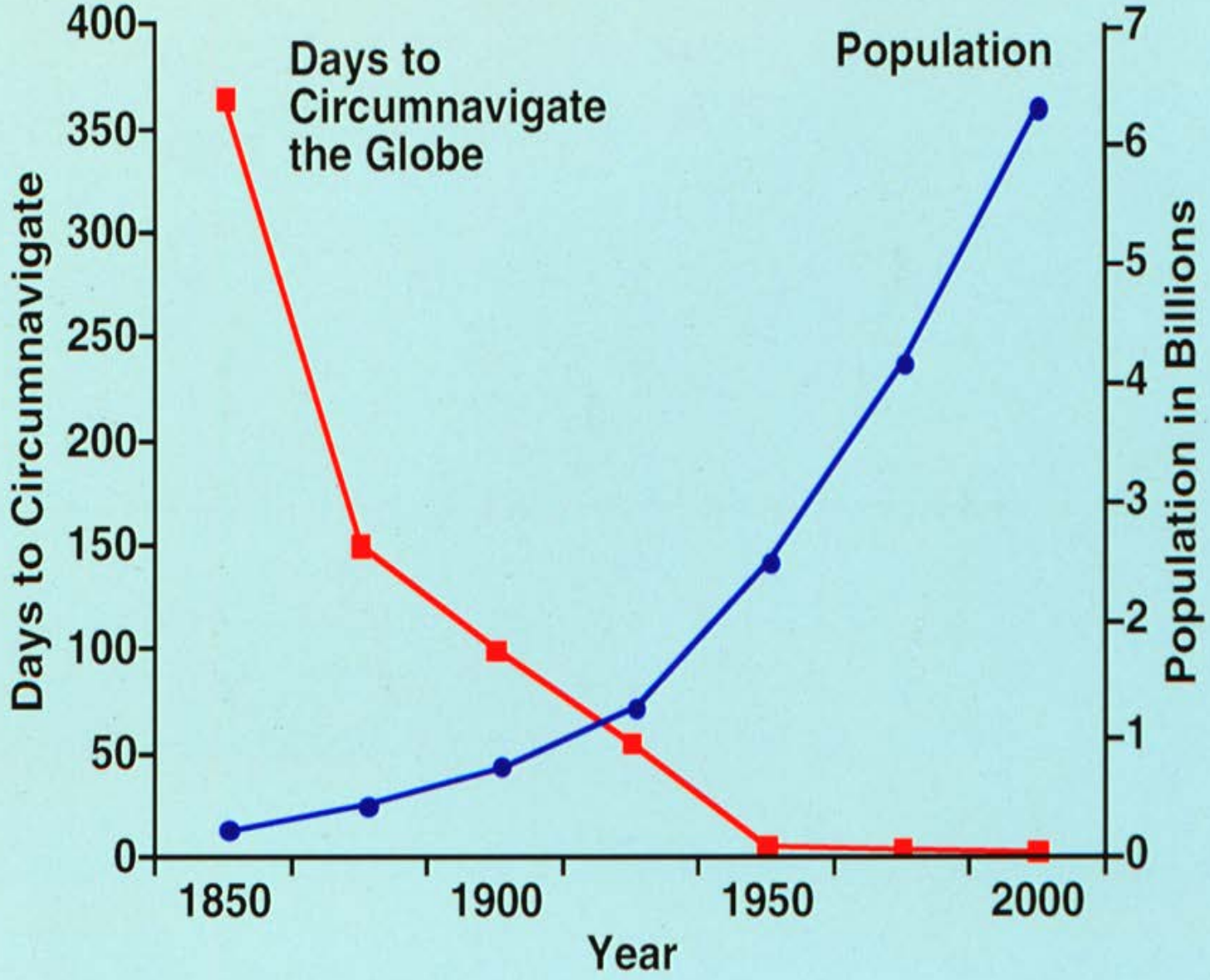
Center for Infectious Disease Research and Policy
University of Minnesota

CIDRAP Leadership Forum
Infectious Disease BRIEFING

October 5th, 2016


Days to Circumnavigate the Globe
Population
Days to Circumnavigate
Population in Billions
Year
400
350
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250
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4
3
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1
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1900
1950
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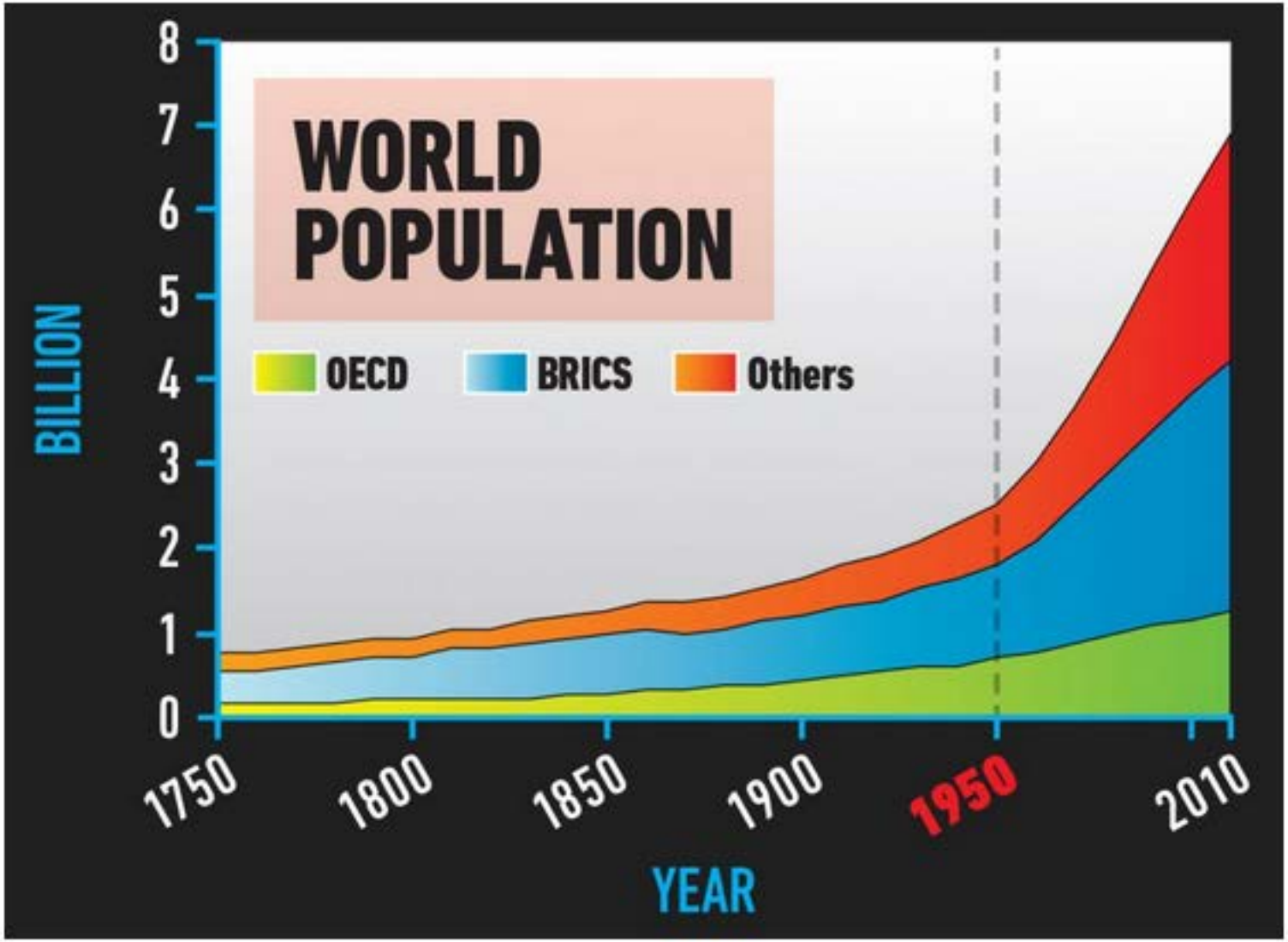


(Steffen et al 2014) Global population data according to the HYDE (History Database of the Global Environment) database. Data before 1950 are modelled. Data are plotted as decadal points.

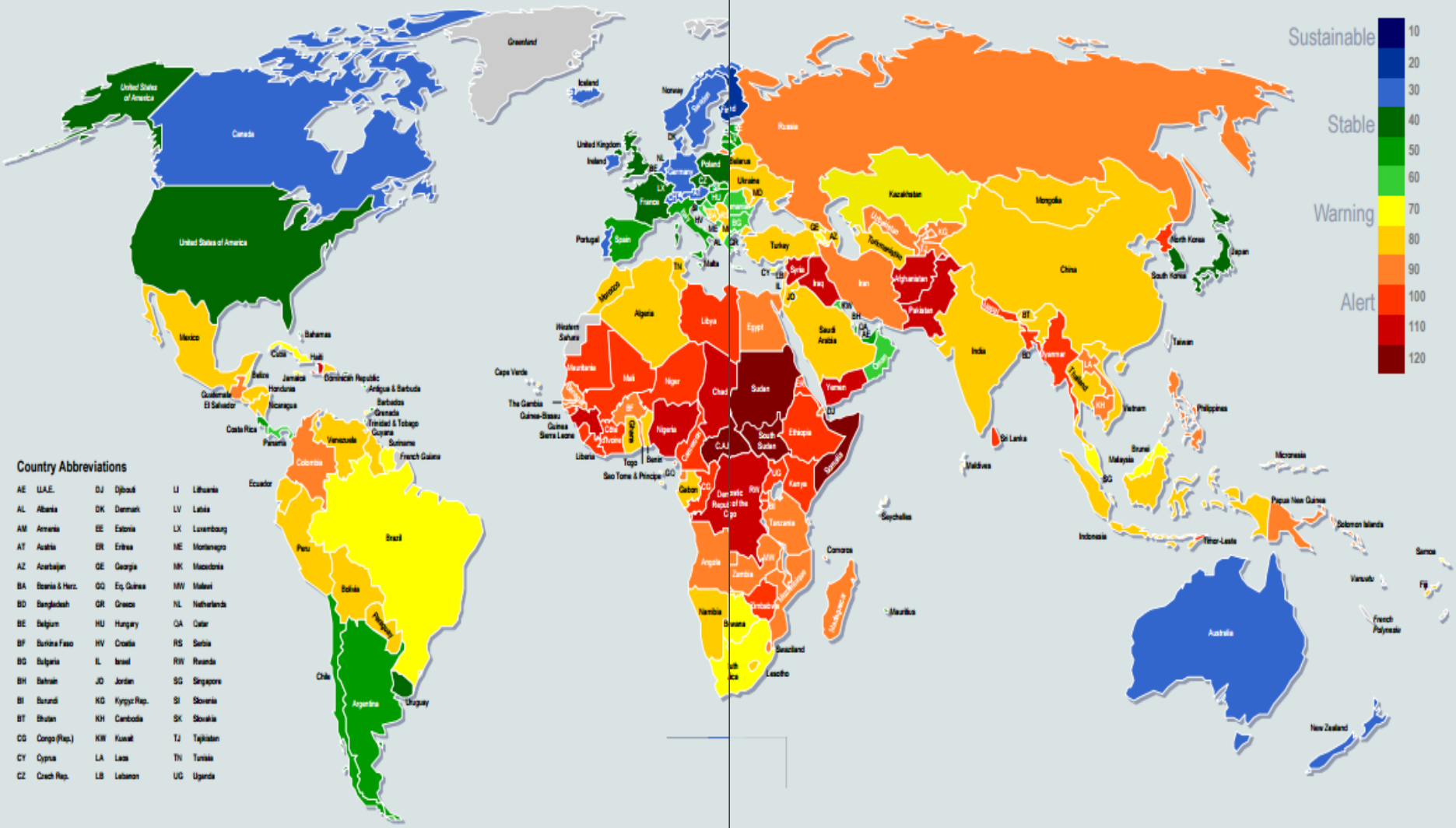
SOURCES: HYDE database 2013; Klein Goldewijk et al. 2010.

FRAGILE STATES INDEX 2015

FFP

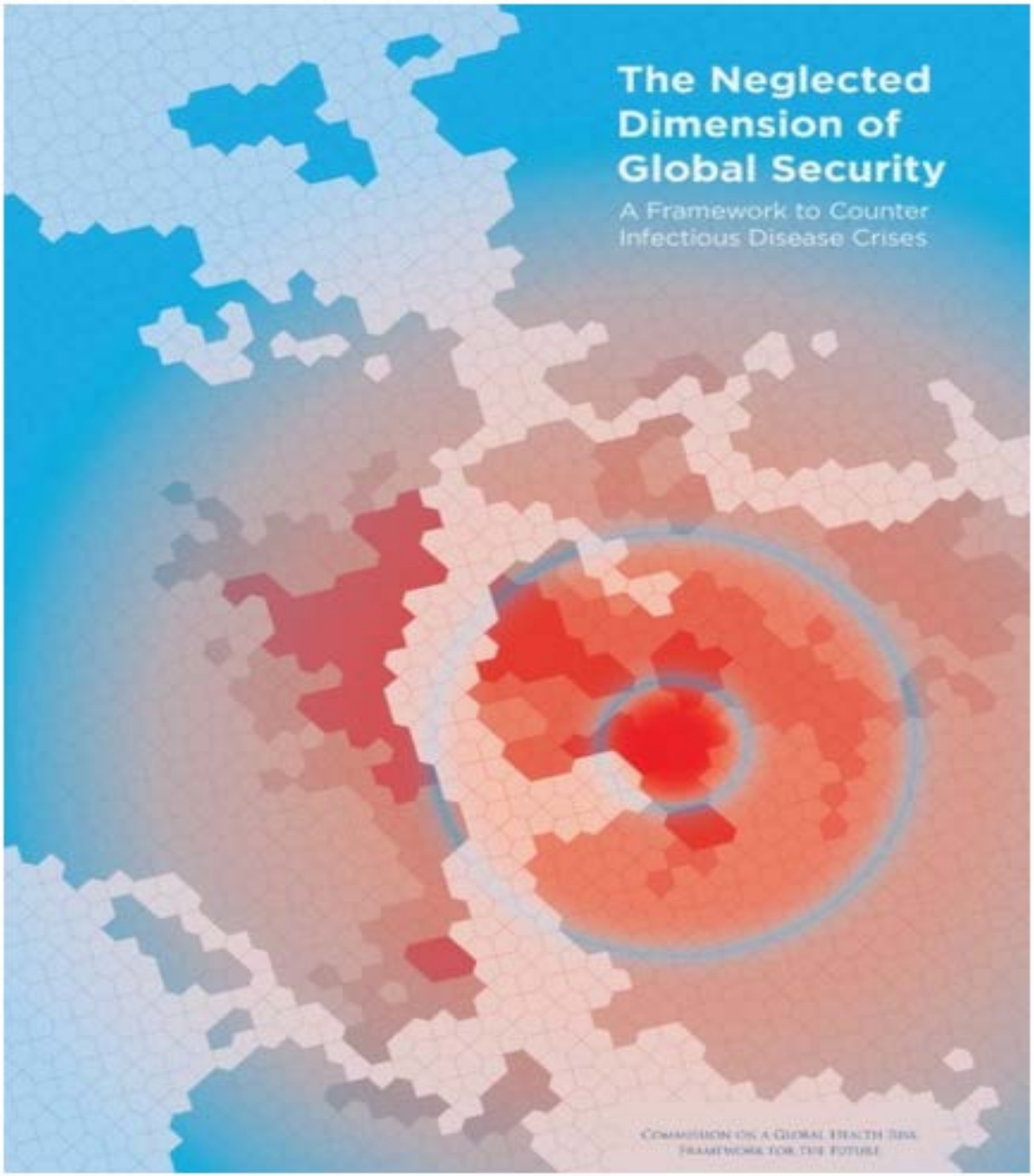
THE FUND FOR PEACE

Fragile States Index:
Fragility in the World 2015



Report of the

Ebola Interim Assessment Panel


The Neglected Dimension of Global Security
A Framework to Counter Infectious Disease Crises

Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola

Suerie Moon, Devi Sridhar, Muhammad A Pate, Ashish K Jha, Chelsea Clinton, Sophie Delaunay, Valnora Edwin, Mosoka Fallah, David P Fidler, Laurie Garrett, Eric Goosby, Lawrence O Gostin, David L Heymann, Kelley Lee, Gabriel M Leung, J Stephen Morrison, Jorge Saavedra, Marcel Tanner, Jennifer A Leigh, Benjamin Hawkins, Liana R Waskie, Peter Piot

Lancet 2015; 386: 2204–21
Published Online November 22, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00946-0
See Editorial page 2118

Harvard Global Health Institute (Prof A Jha MD, S Moon PhD, L R Waskie MSc, J A Leigh MPH), Harvard T.H. Chan School of Public Health (Prof A K Jha, S Moon, L R Waskie, J A Leigh), and Harvard Kennedy School (S Moon), Harvard University, Boston, MA, USA; University of Edinburgh Medical School, Edinburgh (Prof D Sridhar DPhil); Duke Global Health Institute, Durham, NC, USA (M A Pate MD); Bill, Hillary & Chelsea Clinton Foundation, New York, NY, USA (C Clinton DPhil); Médecins Sans Frontières, New York , NY, USA (S Delaunay MA); Campaign for Good Governance, Freetown, Sierra Leone (V Edwin MA); Action Contre La Faim International , Monrovia, Liberia (M Fallah PhD); Indiana University Maurer School of Law, Bloomington, IN, USA (Prof D P Fidler JD); Council on Foreign Relations, New York, NY, USA (L Garrett PhD); University of California, San Francisco, CA, USA (Prof E Goosby MD); Georgetown University, Washington, DC, USA (Prof L Gostin JD); Chatham House, London, UK (Prof D L Heymann MD); Simon Fraser University, Burnaby, BC, Canada (Prof K Lee DPhil); Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China (Prof G M Leung MD); Center for Strategic and International Studies, Washington DC, USA (J S Morrison PhD); AIDS

Executive summary

The west African Ebola epidemic that began in 2013 exposed deep inadequacies in the national and international institutions responsible for protecting the public from the far-reaching human, social, economic, and political consequences of infectious disease outbreaks. The Ebola epidemic raised a crucial question: what reforms are needed to mend the fragile global system for outbreak prevention and response, rebuild confidence, and prevent future disasters? To address this question, the Harvard Global Health Institute and the London School of Hygiene & Tropical Medicine jointly launched the Independent Panel on the Global Response to Ebola. Panel members from academia, think tanks, and civil society have collectively reviewed the worldwide response to the Ebola outbreak. After difficult and lengthy deliberation, we concluded that major reforms are both warranted and feasible. The Panel's conclusions offer a roadmap of ten interrelated recommendations across four thematic areas:

1 Preventing major disease outbreaks

All countries need a minimum level of core capacity to detect, report, and respond rapidly to outbreaks. The shortage of such capacities in Guinea, Liberia, and Sierra Leone enabled Ebola to develop into a national, and worldwide, crisis.

- Recommendation 1: The global community must agree on a clear strategy to ensure that governments invest domestically in building such capacities and mobilise adequate external support to supplement efforts in poorer countries. This plan must be supported by a transparent central system for tracking and monitoring the results of these resource flows. Additionally, all governments must agree to regular, independent, external assessment of their core capacities.
- Recommendation 2: WHO should promote early reporting of outbreaks by commending countries that rapidly and publicly share information, while publishing lists of countries that delay reporting. Funders should create economic incentives for early reporting by committing to disburse emergency funds rapidly to assist countries when outbreaks strike and compensating for economic losses that might result. Additionally, WHO must confront governments that implement trade and travel restrictions without scientific justification, while developing industry-wide cooperation frameworks to ensure private firms such as airlines and shipping companies continue to provide crucial services during emergencies.

2 Responding to major disease outbreaks

When preventive measures do not succeed, outbreaks can cross borders and surpass national capacities. Ebola exposed WHO as unable to meet its responsibility for responding to such situations and alerting the global community.

- Recommendation 3: A dedicated centre for outbreak response with strong technical capacity, a protected budget, and clear lines of accountability should be created at WHO, governed by a separate Board.
- Recommendation 4: A transparent and politically protected WHO Standing Emergency Committee should be delegated with the responsibility for declaring public health emergencies.
- Recommendation 5: An independent UN Accountability Commission should be created to do system-wide assessments of worldwide responses to major disease outbreaks.

3 Research: production and sharing of data, knowledge, and technology

Rapid knowledge production and dissemination are essential for outbreak prevention and response, but reliable systems for sharing epidemiological, genomic, and clinical data were not established during the Ebola outbreak.

- Recommendation 6: Governments, the scientific research community, industry, and non-governmental organisations must begin to develop a framework of norms and rules operating both during and between outbreaks to enable and accelerate research, govern the conduct of research, and ensure access to the benefits of research.
- Recommendation 7: Additionally, research funders should establish a worldwide research and development financing facility for outbreak-relevant drugs, vaccines, diagnostics, and non-pharmaceutical supplies (such as personal protective equipment) when commercial incentives are not appropriate.

WORLD ECONOMIC FORUM

COMMITTED TO IMPROVING THE STATE OF THE WORLD

Insight Report

Global Risks 2015
10th Edition

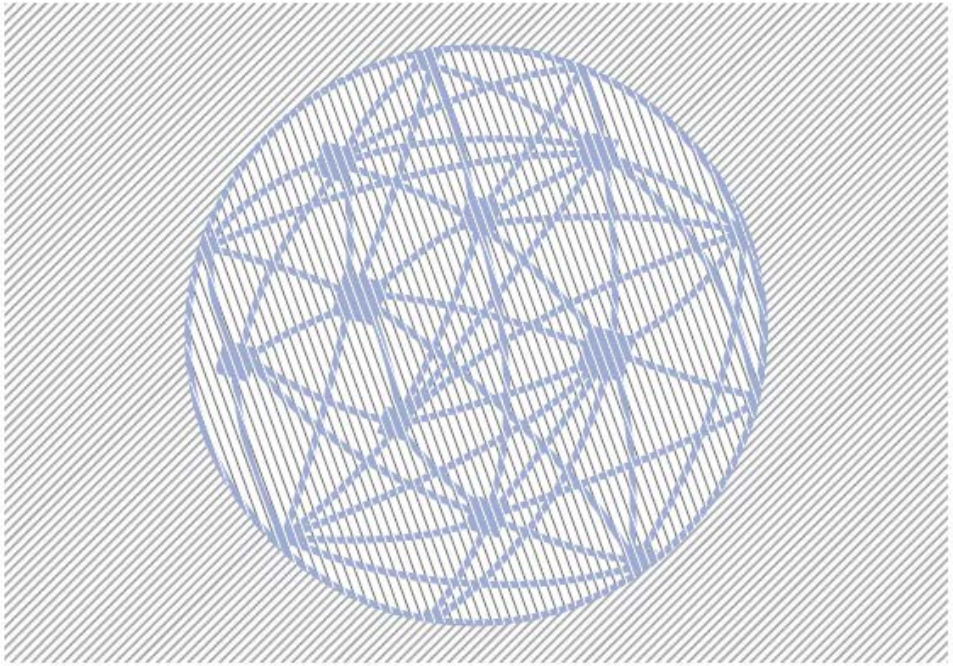
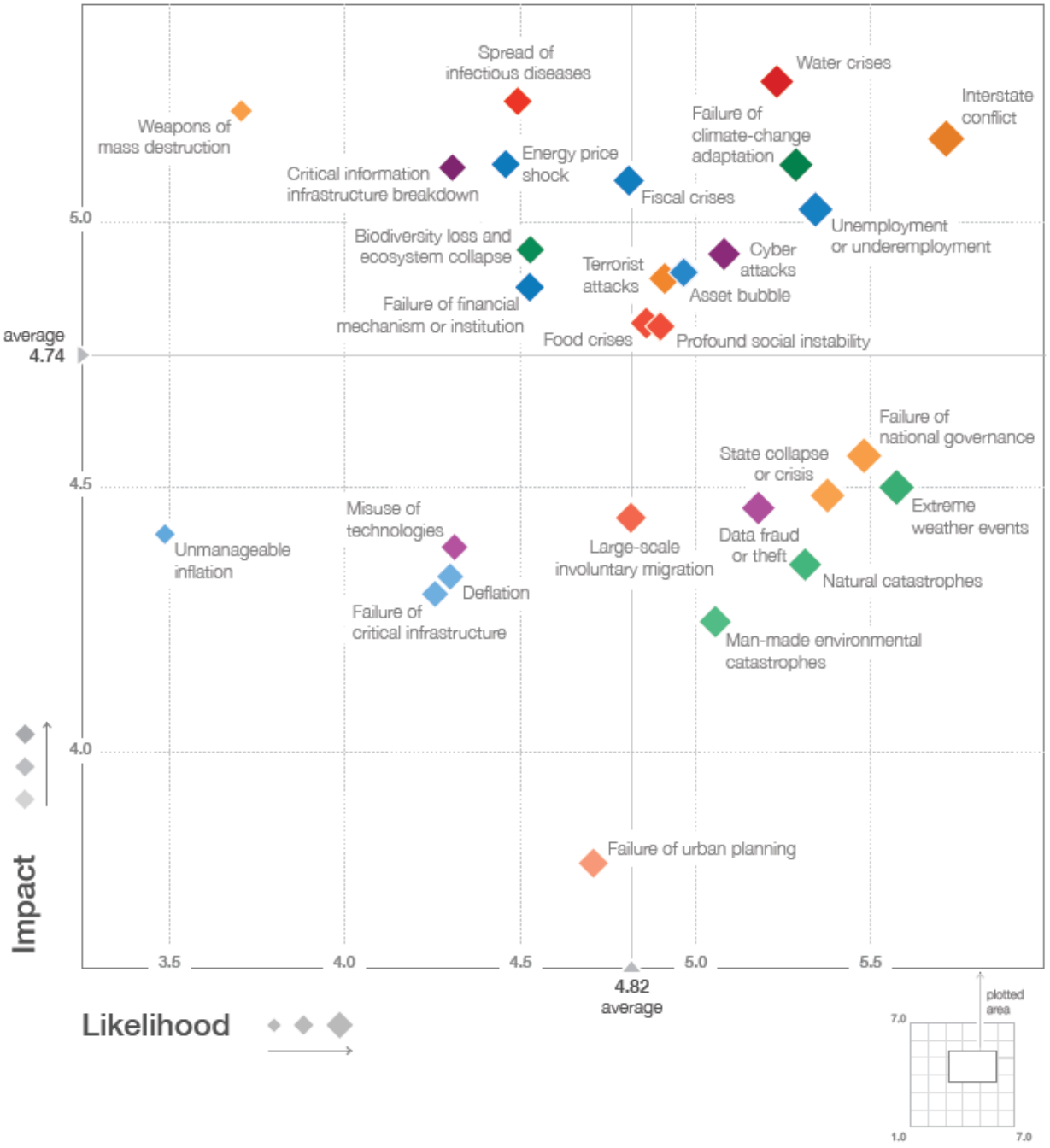


Figure 1: The Global Risks Landscape 2015



Statement for the Record

Worldwide Threat Assessment of the US Intelligence Community

Senate Armed Services Committee

James R. Clapper

Director of National Intelligence

February 9, 2016

Health

Infectious diseases and vulnerabilities in the global supply chain for medical countermeasures will continue to pose a danger to US national security in 2016. Land-use changes will increase animal-to-human interactions and globalization will raise the potential for rapid cross-regional spread of disease, while the international community remains ill prepared to collectively coordinate and respond to disease threats. Influenza viruses, coronaviruses such as the one causing Middle Eastern Respiratory Syndrome (MERS), and hemorrhagic fever viruses such as Ebola are examples of infectious disease agents that are passed from animals to humans and can quickly pose regional or global threats. Zika virus, an emerging infectious disease threat first detected in the Western Hemisphere in 2014, is projected to cause up to 4 million cases in 2016; it will probably spread to virtually every country in the hemisphere. Although the virus is predominantly a mild illness, and no vaccine or treatment is available, the Zika virus might be linked to devastating birth defects in children whose mothers were infected during pregnancy. Many developed and developing nations remain unable to implement coordinated plans of action to prevent infectious disease outbreaks, strengthen global disease surveillance and response, rapidly share information, develop diagnostic tools and countermeasures, or maintain the safe transit of personnel and materials.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

Panel report recommends blueprint for fixing biodefense gaps

Filed Under: Avian Influenza (Bird Flu); Biosecurity Issues; Bioterrorism; Ebola; VHF

Lisa Schnirring | News Editor | CIDRAP News | Oct 29, 2015

Biological threats lack the same attention as other security concerns and need the political muscle of the vice president's office to form a national policy and streamline funding, according to a high-level panel that aired its findings in a Senate hearing yesterday.

sborisov / iStock

The Blue Ribbon Study Panel on Biodefense—headed by seasoned politicians Joseph Lieberman and Tom Ridge—published its complete findings in an 82-page report that contains 33 urgent recommendations and 100 action items.

Lieberman represented Connecticut in the Senate for 24 years, which included 6 years as chair of the Senate Homeland Security Committee. Ridge is a former Secretary of Homeland Security, who also served in the US House of Representatives and as governor of Pennsylvania.

PRESS RELEASE

World Bank Group President: World is 'Dangerously Unprepared' for Future Pandemics

January 27, 2015

Kim outlines vision for private, public sectors to work together to lessen risk

WASHINGTON, January 27, 2015— Saying the world was "dangerously unprepared" for future pandemics, **World Bank Group President Jim Yong Kim** today laid out a vision in which insurance companies, governments, multi-lateral organizations, corporations and international donors worked together to build a system that would help all countries prepare for potentially catastrophic health disasters.

"The Ebola outbreak has been devastating in terms of lives lost and the loss of economic growth in Guinea, Liberia and Sierra Leone," **Kim** told an audience at Georgetown University. *"We need to make sure that we get to zero cases in this Ebola outbreak. At the same time, we need to prepare for future pandemics that could become far more deadly and infectious than what we have seen so far with Ebola. We must learn the lessons from the Ebola outbreak because there is no doubt we will be faced with other pandemics in the years to come."*

Kim said that the World Bank Group has been working for several months with the World Health Organization, other United Nations agencies, academics, re-insurance company officials and others to work on a concept of developing a pandemic facility; discussions also were held in informal sessions at the World Economic Forum in Davos, Switzerland, last week.

He said he expects that a proposal will be presented in the coming months to leaders of developed and developing countries. While a proposal would likely involve a combination of bonds and insurance instruments, he said that in some ways, a future pandemic response facility was similar to a homeowner's insurance policy.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Next Epidemic — Lessons from Ebola

Bill Gates

Perhaps the only good news from the tragic Ebola epidemic in Guinea, Sierra Leone, and Liberia is that it may serve as a wake-up call: we must prepare for future epidemics of diseases that may spread more effectively than Ebola. There is a significant chance that an epidemic of a substantially more infectious disease will occur sometime in the next 20 years; after all, we saw major epidemics during the 20th century, including the Spanish influenza epidemic of 1918–1919 and the ongoing pandemic of human immunodeficiency virus. In fact, of all the things that could kill more than 10 million people around the world, the most likely is an epidemic stemming from either natural causes or bioterrorism.

Ebola is far from the most infectious known disease. Other disease agents (measles and influenza, for example) are far more infectious because they can be spread through the air, rather than requiring direct contact. People may not even be aware that they are infected or infectious. Since a person carrying one of these pathogens can infect many strangers in a marketplace or on an airplane, the number of cases can escalate very quickly.

As the Ebola epidemic fades from the world's attention, we risk missing the opportunity to learn from it. Even if the system we have today had worked perfectly for Ebola, it would fail to contain a more infectious disease.

It's instructive to compare our preparations for epidemics with our preparations for another sort of global threat — war. The North Atlantic Treaty Organization (NATO) has a mobile unit that is ready to deploy quickly. Although the system is not perfect, NATO countries participate in joint exercises in which they work out logistics such as how fuel and food will be provided, what language they will speak, and what radio frequencies will be used. Few, if any, such measures are in place for response to an epidemic. The world does not fund any organization to manage the broad set of coordinated activities required in an epidemic. The last serious simulation of an epidemic in the United States, the Dark Winter exercise, took place in 2001. And few countries have met their commitments under the International Health Regulations, which were adopted by the United Nations after the 2002–2003 outbreak of the severe acute respiratory syndrome (SARS) and were intended to improve the world's ability to prevent and contain outbreaks.[1]

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

Gloomy assessment underpins UN panel's health crisis advice

Filed Under: Ebola; H1N1 2009 Pandemic Influenza; MERS-CoV; Pandemic Influenza; SARS; VHF

Lisa Schnirring | News Editor | CIDRAP News | Feb 09, 2016

The world underestimates the risk of a health threat worse than Ebola, and its capacity to prepare and respond is "woefully insufficient," according to a high-level panel appointed by United Nations (UN) Secretary-General Ban Ki-moon to look at improvements based on lessons learned during the recent outbreak.

Andrew d'Entremont/ Flickr cc

The scope of West Africa's Ebola outbreak in September 2014 led to the UN's first-ever special mission to address a public health crisis. Appointed in April 2015, the six-member group was led by Tanzanian President Jakaya Mrisho Kikwete.

Before making its findings and recommendations, the full panel met six times last year and held six roundtable meetings. The group's unedited, 95-page advance report, dated Jan 25, is posted on the United Nations' Web site.

ADVANCE UNEDITED COPY

Protecting Humanity from Future Health Crises

Report of the

High-level Panel on the Global Response to Health Crises

25 January 2016

Following its extensive consultations, the Panel notes that the high risk of major health crises is widely underestimated, and that the world's preparedness and capacity to respond is woefully insufficient. Future epidemics could far exceed the scale and devastation of the West Africa Ebola outbreak. The Panel was very concerned to learn that the emergence of a highly pathogenic influenza virus, which could rapidly result in millions of deaths and cause major social, economic and political disruption, is not an unlikely scenario.

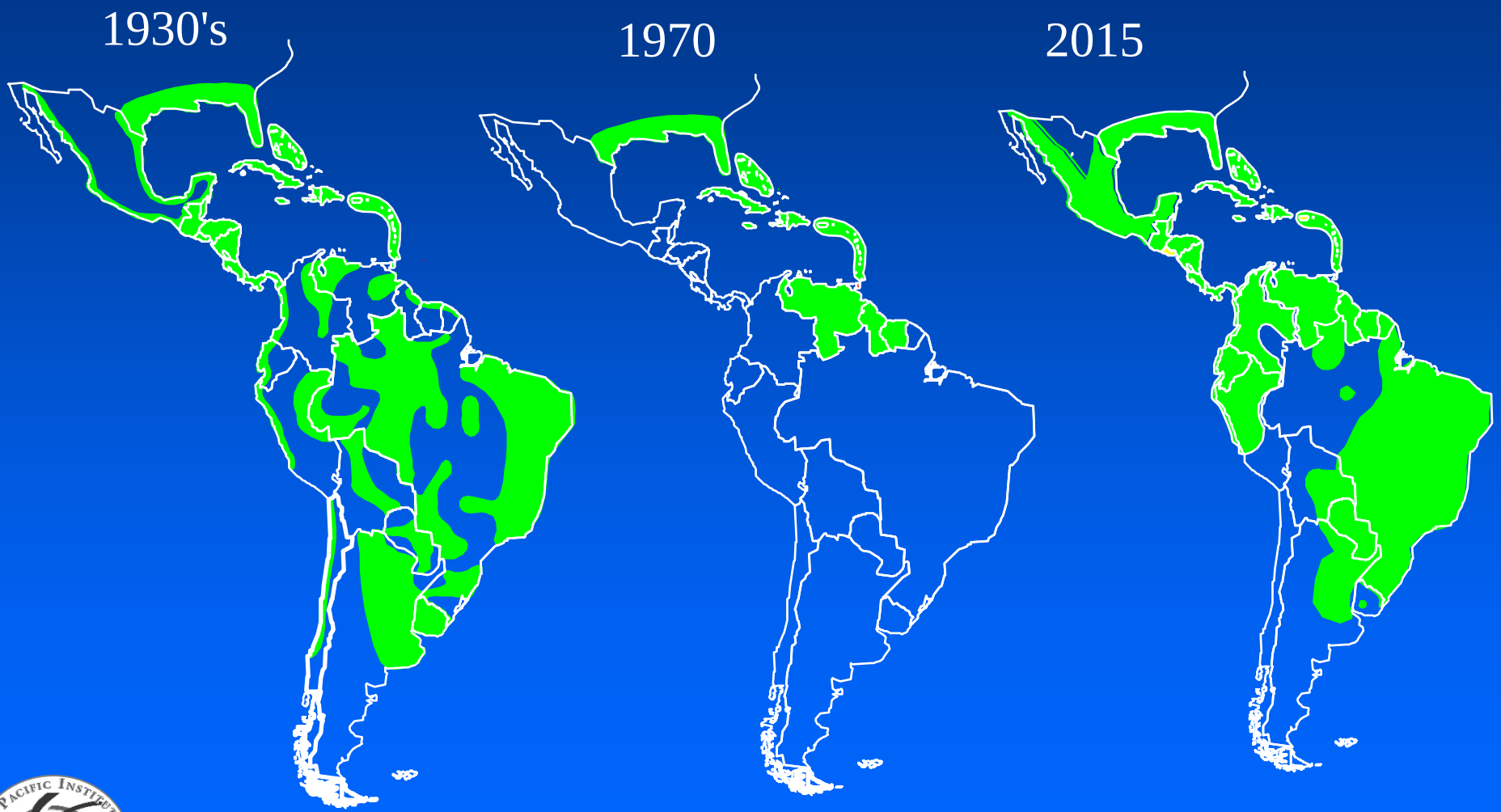
Jakaya Mrisho Kikwete
United Republic of Tanzania
Panel Chair

Peri-urban Slum: Mumbai, India

Urbanization of African Countries of Potential Concern

- Kinshasa, DRC/Brazzaville, RC
  - 13.8 million (four other cities > 1 million)
- Lagos, Nigeria
  - 13.2 million (five other cities > 1 million)
- Nairobi, Kenya
  - 4.1 million
- Acura, Ghana
  - 2.8 million
- Monrovia/Freetown/Conakry
  - 4.2 million

Aedes aegypti Distribution in the Americas



Adapted from Gubler, 1998

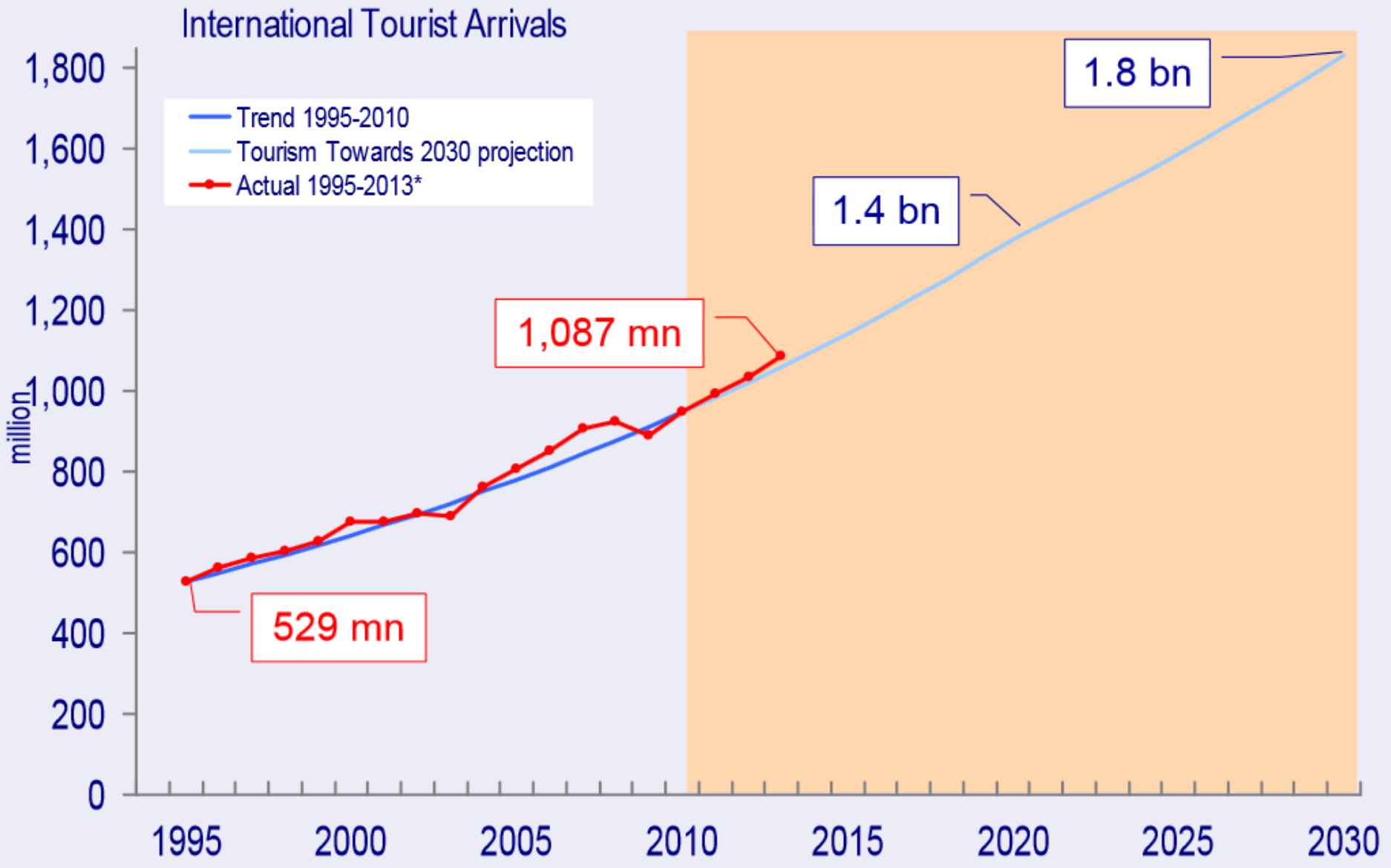
The New York Times

Hard Times in Venezuela Breed Malaria as Desperate Flock to Mines

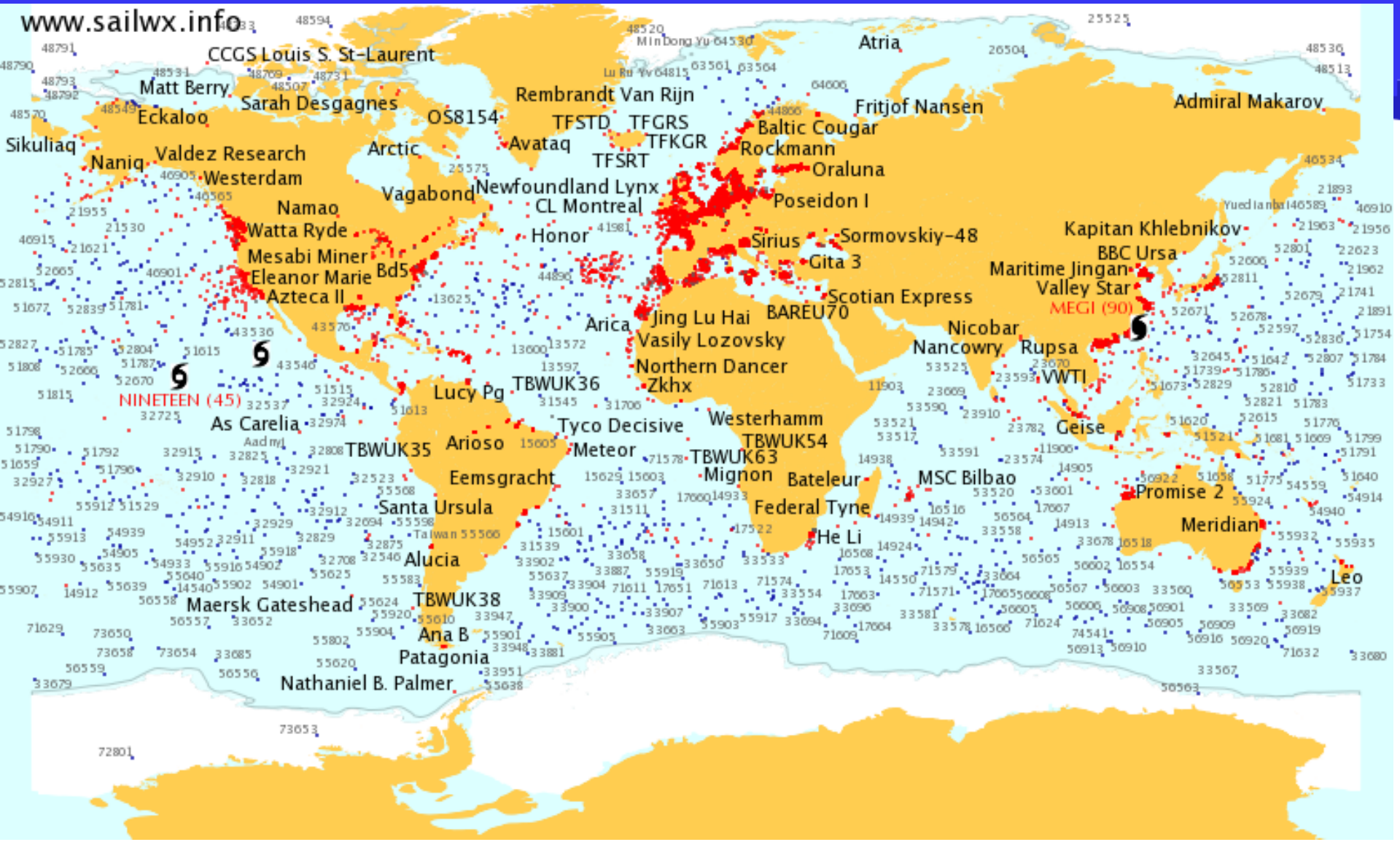
Many turn to panning for black-market gold in the watery pits of mines, where mosquitoes infect them. Once they return home to recover, the disease spreads.

Written by NICHOLAS CASEY; Photographs by MERIDITH KOHUT

Actual Trend vs. Tourism Towards 2030 projection World



Source: World Tourism Organization (UNWTO)



World container ship traffic has doubled since 1997

Ship Traffic Worldwide: Tuesday, Sept 27, 2016, 8:01 PM UTC

Center for Infectious Disease Research & Policy
University of Minnesota

Michael T. Osterholm, PhD, MPH,
and Mark Olshaker

COMMON ENEMY

Dispatches from the War with Deadly Pathogens—
the Fight We Cannot Afford to Lose

Agents of Concern

- Diseases with pandemic potential
  - Influenza
  - Antimicrobial resistance
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Dengue, Chikungunya and Zika
  - Yellow fever

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Agents of Concern
Continued

- Bioterrorism
  - Anthrax
  - Smallpox
- Gain-of-function agents
- Lest We Forget
  - Malaria
  - AIDS
  - TB
  - Hepatitis C
  - Bacterial pneumonia
  - Diarrheal disease
  - Rabies

Agents of Concern

- **Diseases with pandemic potential**
  - **Influenza**
  - Antimicrobial resistance
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Dengue, Chikungunya and Zika
  - Yellow fever


PANDEMIC

World Health Organization

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2015

Country	2003-2009*		2010		2011		2012		2013		2014		2015		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	0	0	0	0	7	1
Cambodia	9	7	1	1	8	8	3	3	26	14	9	4	0	0	56	37
Canada	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1
China	38	25	2	1	1	1	2	1	2	2	2	0	5	1	52	31
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	37	14	136	39	346	116
Indonesia	162	134	9	7	12	10	9	9	3	3	2	2	2	2	199	167
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	2	2	0	0	127	64
Total	**468**	**282**	**48**	**24**	**62**	**34**	**32**	**20**	**39**	**25**	**52**	**22**	**143**	**42**	**844**	**449**

* 2003-2009 total figures. Breakdowns by year available on next table

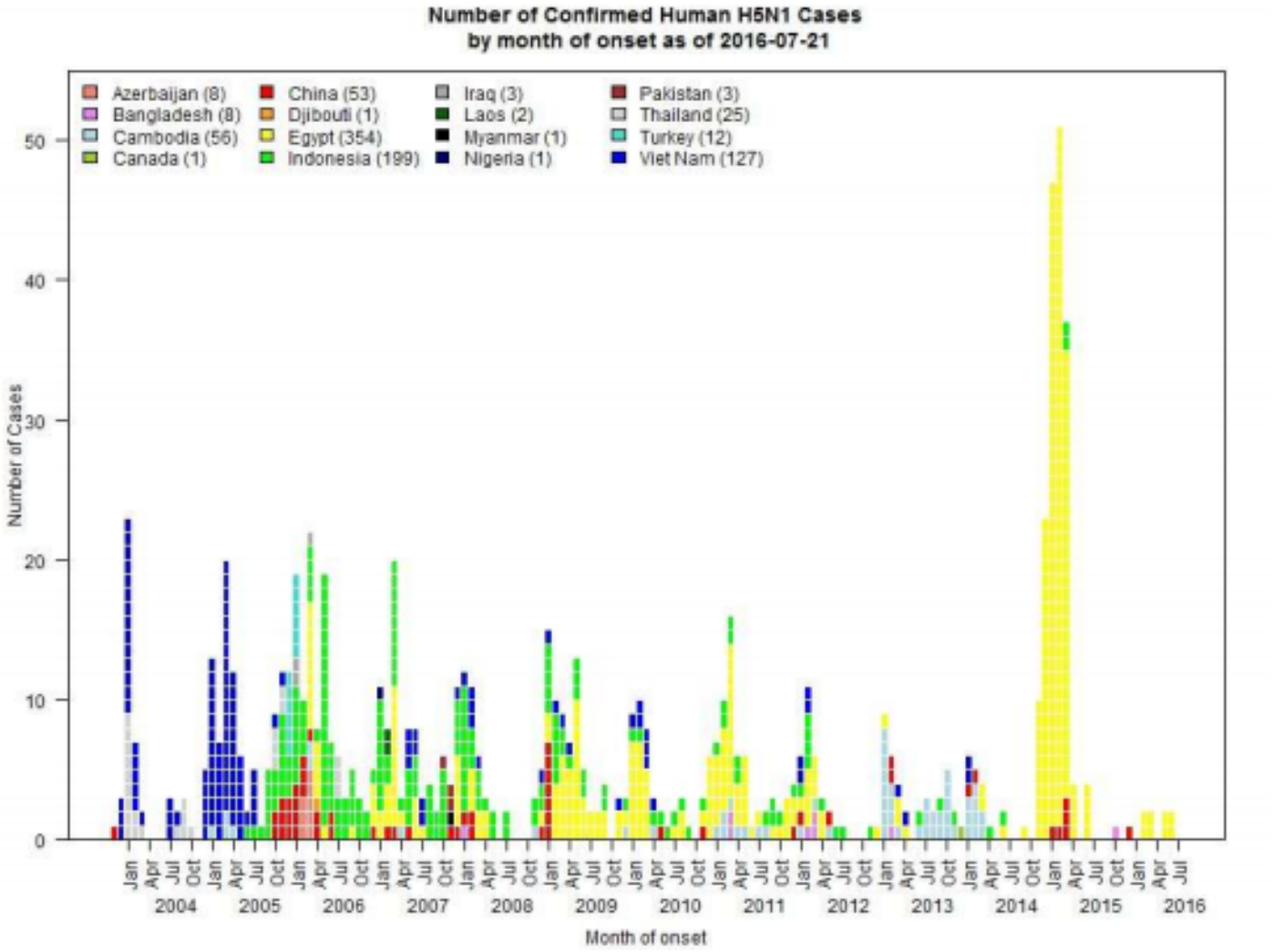
Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

Source: WHO/GIP, data in HQ as of 13 Nov 2015

World Health Organization

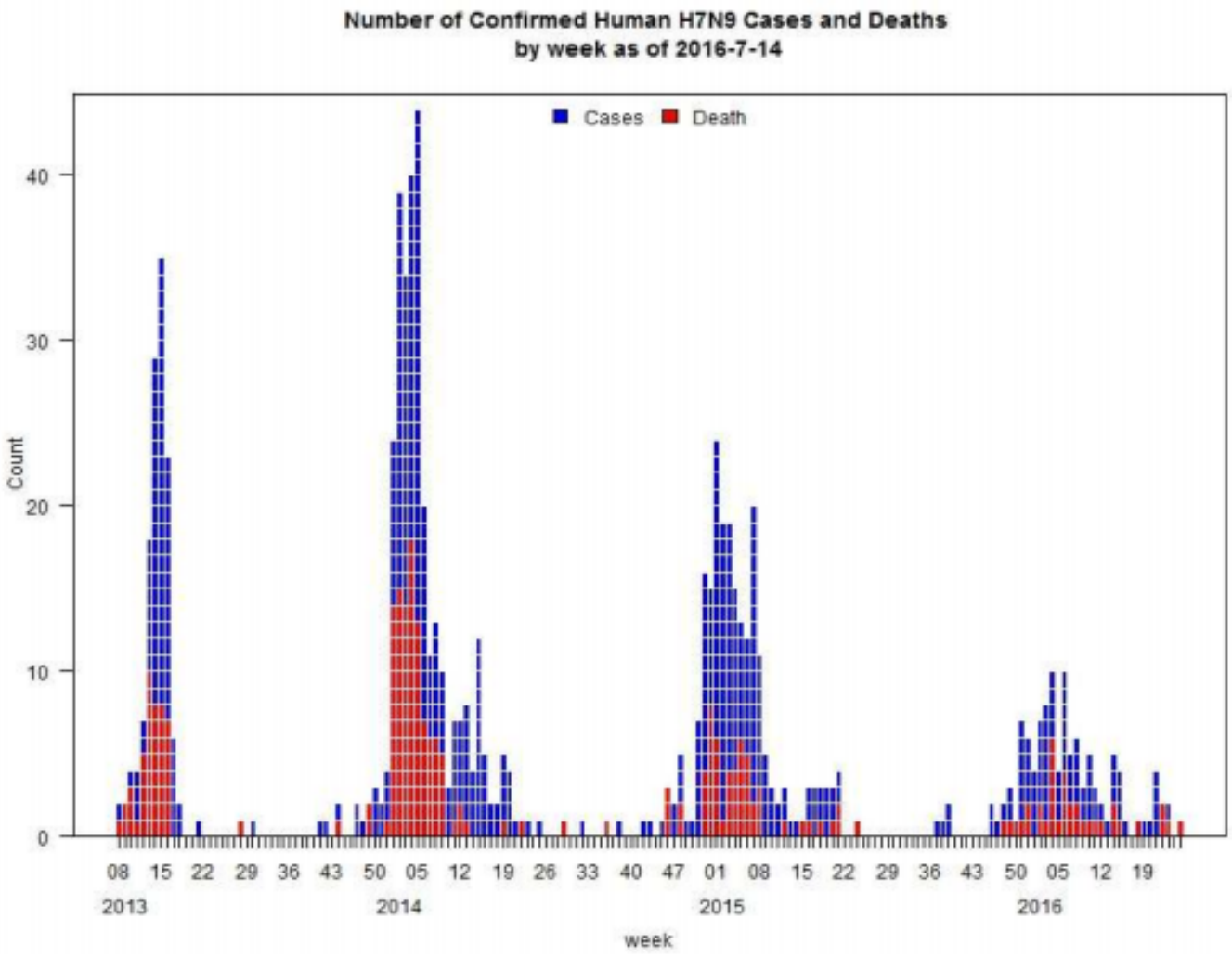
World Health Organization

Figure 1: Epidemiological curve of avian influenza A(H5N1) cases in humans by week of onset, 2003-2016



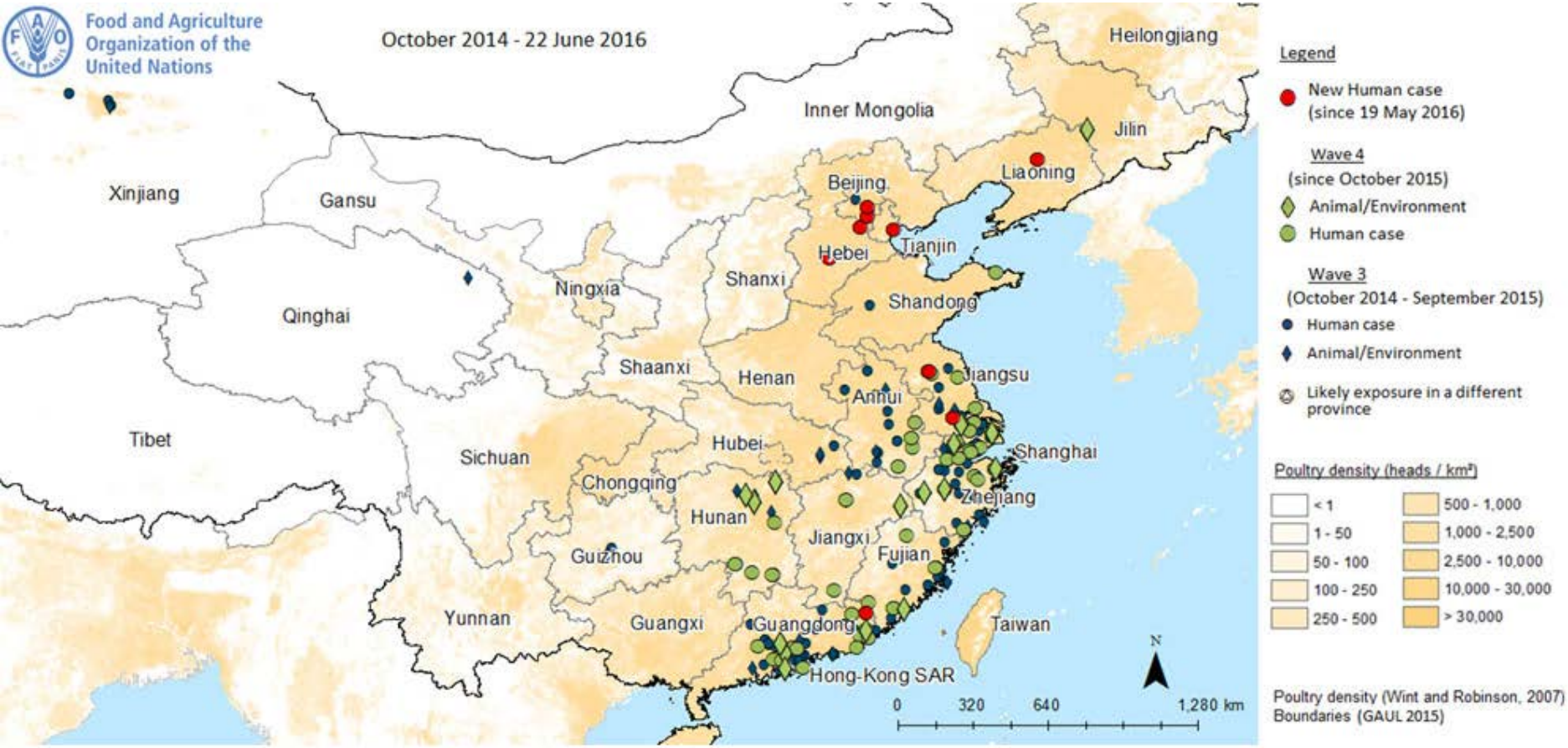
World Health Organization

Figure 2: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2016



Animal Production and Health

Map. *Human cases and positive findings in birds or the environment*



H7N9 situation update

ARCHIVE

22 June 2016, 17:00 hours; Rome

The next update will be issued on **20 July 2016**

Disclaimer

Information provided herein is current as of the date of issue. Information added or changed since the last H7N9 situation update appears in **red**. Human cases are depicted in the geographic location of their report. For some cases, exposure may have occurred in one geographic location but reported in another. For cases with unknown onset date, reporting date was used instead. FAO compiles information drawn from multiple national (Ministries of Agriculture or Livestock, Ministries of Health, Provincial Government websites; Centers for Disease Prevention and Control [CDC]) and international sources (World Health Organization [WHO], World Organisation for Animal Health [OIE]) as well as peer-reviewed scientific articles. FAO makes every effort to ensure, but does not guarantee, accuracy, completeness or authenticity of the information. The designation employed and the presentation of material on the map do not imply the expression of any opinion whatsoever on the part of FAO concerning the legal or constitutional status of any country, territory or sea area, or concerning the delimitation of frontiers.

Overview

Situation: Influenza A(H7N9) virus with pandemic potential.
Country: China; three human cases originated in China and were reported in Malaysia (1) and Canada (2).
Number of human cases: **795 confirmed; 308 deaths** (since February 2013)
Provinces/municipalities: Beijing, Shanghai and **Tianjin** municipalities; Anhui; Fujian; Guangdong; Hubei and **Liaoning** provinces; Henan; Hunan; Jiangsu; Jiangxi; Shandong; Zhejiang; Guangxi; Guizhou; Jilin; Qinghai; Hubei; Taiwan Province of China; Hong Kong SAR; Macao SAR, Ningxia Hui and Xinjiang Uyghur Autonomous Regions; Sabah (Malaysia); British Columbia (Canada).
Animal/environmental findings: over 2,000 virological samples from the environment, chickens, pigeons, ducks and a tree sparrow tested positive; positives mainly from live bird markets, vendors and some commercial or breeding farms.
FAO actions: liaise with China and partners, monitor situation, monitor virus evolution, conduct market chain analysis, risk assessment, surveillance guidance and communication.

World Health Organization

Warning signals from the volatile world of influenza viruses

February 2015

The current global influenza situation is characterized by a number of trends that must be closely monitored. These include: an increase in the variety of animal influenza viruses co-circulating and exchanging genetic material, giving rise to novel strains; continuing cases of human H7N9 infections in China; and a recent spurt of human H5N1 cases in Egypt. Changes in the H3N2 seasonal influenza viruses, which have affected the protection conferred by the current vaccine, are also of particular concern.

Viruses in wild and domestic birds

The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented since the advent of modern tools for virus detection and characterization. The world needs to be concerned.

Viruses of the H5 and H7 subtypes are of greatest concern, as they can rapidly mutate from a form that causes mild symptoms in birds to one that causes severe illness and death in poultry populations, resulting in devastating outbreaks and enormous losses to the poultry industry and to the livelihoods of farmers.

World Health Organization

Warning signals from the volatile world of influenza viruses

February 2015

The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented since the advent of modern tools for virus detection and characterization. The world needs to be concerned.

World Health Organization

Warning signals from the volatile world of influenza viruses

February 2015

Since the start of 2014, the Organisation for Animal Health, or OIE, has been notified of 41 H5 and H7 outbreaks in birds involving 7 different viruses in 20 countries in Africa, the Americas, Asia, Australia, Europe, and the Middle East. Several are novel viruses that have emerged and spread in wild birds or poultry only in the past few years.

ALL Findings

Update on Avian Influenza Findings
Poultry Findings Confirmed by USDA's National Veterinary Services Laboratories

Animal Health

- Contact Us
- Program Overview
- Animal Disease Information
- Emergency Management
- Export from the U.S.
- Import into the U.S.
- Laboratory Information Services

223 Detections Reported	**48,091,293** Birds Affected
12/19/14 First Detection Reported	**6/17/15** Last Detection Reported

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

Airborne flu detection at bird markets hints at human exposure risk

Filed Under: Avian Influenza (Bird Flu)

Lisa Schnirring | News Editor | CIDRAP News | Sep 01, 2016

Viable avian flu virus is easily detectable in the air of live-poultry markets, which may explain why those who visit markets but don't have direct contact with the birds become infected, according to air sampling from sites in China and Hong Kong.

A research team based at Hong Kong University isolated three subtypes during their sampling activities: H5N6, H7N9, and H9N2. They reported their findings today in the latest edition of *Eurosurveillance*.

Their results come just weeks after a report from Chinese researchers who isolated H5N6 during bioaerosol surveillance at live-poultry markets in the Guangdong province city of Zhongshan.

fotokon / iStock

Chicken defeathering at a live-bird market in China.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

FAO warns of H5N1 threat to Middle East

Filed Under: Avian Influenza (Bird Flu)

Lisa Schnirring | News Editor | CIDRAP News | Sep 26, 2016

Recent highly pathogenic H5N1 avian influenza outbreaks in Iraq and Lebanon pose a risk to other countries because of political instability and a host of other factors, such as wild bird migration and wintering habits, the United Nations Food and Agriculture Organization (FAO) warned in a recent report.

United Church / Flickr cc

Countries at highest risk are Iran, Israel, Jordan, Syria, and Turkey, according to the group's recent 8-page report.

Recent outbreaks in Iraq, Lebanon

Iraq officially reported several H5N1 outbreaks from December 2015 through July 2016, affecting backyard bird and commercial farms in five governorates, some not far from the country's borders with Turkey and Iran.

Meanwhile, Lebanon confirmed H5N1 in April, affecting several farms in the eastern part of the country close to the Syrian border where refugees are settled. The investigation suggested illegal poultry movement as the source of the outbreak.

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

Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, Edward A Belongia

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.[3]

In 2010, the ACIP established the first recommendation of national universal seasonal influenza vaccination.[3] 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.[3] 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

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Early-season estimate finds flu vaccine only 23% effective

Filed Under: Influenza Vaccines

Robert Roos | News Editor | CIDRAP News | Jan 15, 2015

A preliminary analysis indicates that this year's flu vaccine, which is not well matched to the predominant circulating flu strain, is only 23% effective in protecting people, the Centers for Disease Control and Prevention (CDC) announced today.

The agency said the finding, which is well below the typical overall flu vaccine effectiveness (VE) of around

Flu Scan for Mar 03, 2015

New estimate puts current flu vaccine's effectiveness a bit lower

The latest estimate of the overall effectiveness of this year's seasonal influenza vaccine puts it at just 19% (95% confidence interval [CI], 7%-29%), slightly lower than the 23% reported in mid-January, the Centers for Disease Control and Prevention (CDC) reported yesterday.

The CDC said the updated estimate of vaccine effectiveness (VE) against H3N2 viruses, the heavily dominant subtype this winter, is 18% (95% CI, 6%-29%). This is similar to the earlier estimate (22%) and confirms reduced protection against H3N2 viruses this season, the agency added.

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CDC's early estimate finds this year's flu vaccine 59% effective

Filed Under: Influenza Vaccines

Robert Roos | News Writer | CIDRAP News | Feb 25, 2016

CDC / Judy Schmidt

A preliminary estimate puts the overall effectiveness of this year's influenza vaccine at 59%, federal officials announced today, which is about triple the number last year, when the vaccine matched up poorly with the dominant circulating flu strain.

The Centers for Disease Control and Prevention (CDC) announced the estimate in a press release as it was presented at a meeting of the agency's Advisory Committee for Immunization Practices (ACIP).

"This means that getting a flu vaccine this season reduced the risk of having to go to the doctor because of flu by nearly 60 percent," Joseph Bresee, MD, chief of the CDC's Epidemiology and Prevention Branch, said in the release. "It's good news and underscores the importance and the benefit of both annual and ongoing vaccination efforts this season."

The agency noted that 59% is similar to past seasons when the vaccine was well-matched to circulating strains. In contrast, overall vaccine effectiveness (VE) in the 2014-15 season was estimated at only 19%, mainly because the vaccine's H3N2 component worked poorly against most circulating H3N2 viruses, offering only 18% protection against that strain. H3N2 was the heavily predominant strain last year.

Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study

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Article published on 11 February 2016

On 11 February 2016, the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) published the 2015–16 interim vaccine effectiveness (VE) estimates against influenza from a multi-centre case control study in 10 study sites: Germany, France, Hungary, Ireland, Italy, Poland, Portugal, Spain, Sweden and the Netherlands, on their website [1].

Adjusted VE interim results against any influenza among all ages were at 46.3% (95% confidence interval (CI): 4.9–69.7%) and 45.2% (95% CI: -12.5–73.3%) among the 18–64 year olds. Among those aged 65 years and older, there were only 14 influenza cases in the study. The adjusted VE against influenza A(H1N1) pdm09 was at 44.2% (95% CI: -3.1–69.8%) among all ages and thus lower compared with end of season estimates published in previous years (55.5% in 2010–11, 50.4% in 2012–13; 47.5% in 2013–14, 54.2% in 2014–15).

Early season influenza VE was measured against medically-attended laboratory-confirmed influenza from week 41/2015 to week 3/2016 using a test-negative design as described in the I-MOVE generic protocol [2] and in the I-MOVE multicentre case–control publications [3]. Some 1,933 influenza-like illness patients among whom 348 were positive to influenza were included: four cases of influenza A not subtyped, 246 A(H1N1)pdm09, 21 A(H3N2), and 77 influenza B cases. Among the 37 influenza B cases where lineage was available, 36 (97.3%) were of the Victoria lineage, a lineage not included in the trivalent vaccine.

The interim estimates should be interpreted with caution. The 2015–16 season started late in the participating countries and the sample size for these interim estimates is low, resulting in low precision. The final estimates will be available at the end of the influenza season.

Read more here.

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Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies

Edward A Belongia, Melissa D Simpson, Jennifer P King, Maria E Sundaram, Nicholas S Kelley, Michael T Osterholm, Huong Q McLean

Summary

Background Influenza vaccine effectiveness (VE) can vary by type and subtype. Over the past decade, the test-negative design has emerged as a valid method for estimation of VE. In this design, VE is calculated as 100% × (1 − odds ratio) for vaccine receipt in influenza cases versus test-negative controls. We did a systematic review and meta-analysis to estimate VE by type and subtype.

Methods In this systematic review and meta-analysis, we searched PubMed and Embase from Jan 1, 2004, to March 31, 2015. Test-negative design studies of influenza VE were eligible if they enrolled outpatients on the basis of predefined illness criteria, reported subtype-level VE by season, used PCR to confirm influenza, and adjusted for age. We excluded studies restricted to hospitalised patients or special populations, duplicate reports, interim reports superseded by a final report, studies of live-attenuated vaccine, and studies of prepandemic seasonal vaccine against H1N1pdm09. Two reviewers independently assessed titles and abstracts to identify articles for full review. Discrepancies in inclusion and exclusion criteria and VE estimates were adjudicated by consensus. Outcomes were VE against H3N2, H1N1pdm09, H1N1 (pre-2009), and type B. We calculated pooled VE using a random-effects model.

Findings We identified 3368 unduplicated publications, selected 142 for full review, and included 56 in the meta-analysis. Pooled VE was 33% (95% CI 26–39; I^2=44·4) for H3N2, 54% (46–61; I^2=61·3) for type B, 61% (57–65; I^2=0·0) for H1N1pdm09, and 67% (29–85; I^2=57·6) for H1N1; VE was 73% (61–81; I^2=31·4) for monovalent vaccine against H1N1pdm09. VE against H3N2 for antigenically matched viruses was 33% (22–43; I^2=56·1) and for variant viruses was 23% (2–40; I^2=55·6). Among older adults (aged >60 years), pooled VE was 24% (–6 to 45; I^2=17·6) for H3N2, 63% (33–79; I^2=0·0) for type B, and 62% (36–78; I^2=0·0) for H1N1pdm09.

Interpretation Influenza vaccines provided substantial protection against H1N1pdm09, H1N1 (pre-2009), and type B, and reduced protection against H3N2. Vaccine improvements are needed to generate greater protection against H3N2 than with current vaccines.

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Introduction

Influenza vaccines are licensed on the basis of findings from immunogenicity studies or randomised clinical trials (RCTs) showing efficacy and safety. In a previous meta-analysis[1] of RCTs in healthy adults, we found that pooled vaccine efficacy was 59% against all strains. Although the RCT is the optimal design to minimise bias and confounding, it has important limitations. RCTs are often limited to one or two seasons, enrol healthy individuals, have low power to measure efficacy by subtype, and are not feasible to do annually. Placebo-controlled trials are not ethical in populations for whom vaccination is routinely recommended, and results from a single season might not predict efficacy in subsequent seasons.

Over the past decade, the test-negative design (TND) has emerged as a valid approach for estimation of influenza vaccine effectiveness (VE). In this design, VE is calculated as 100% × (1 − odds ratio [OR]) for vaccine receipt in influenza cases versus test-negative controls. The first TND study[2] was published in 2005 by Canadian investigators who reported VE in British Columbia during the 2004–05 season. Since then, multiple TND studies have been done to estimate VE in both the northern and southern hemisphere. The TND is similar to a case-control study, but cases and controls are not identified at the time of enrolment. Instead, patients seeking medical care for an acute respiratory illness are enrolled and respiratory tract samples tested for influenza with RT-PCR. Findings from TND simulation studies[3,4] suggest that this method yields a valid estimate of VE in the source population under most scenarios.

Investigators of an increasing number of TND studies are reporting VE estimates separately by type and subtype. We did a systematic review and meta-analysis of published TND studies to estimate seasonal VE against illness caused by H3N2, H1N1pdm09, H1N1 (pre-2009), and type B.

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Study: Flu vaccine efficacy can wane over single season

Filed Under: **Influenza Vaccines**

Natalie Vestin, MPH | News Reporter | CIDRAP | Apr 20, 2016

Inactivated influenza vaccine (IIV) efficacy waned in younger adults yet remained fairly high over a flu season, while live attenuated influenza vaccine (LAIV) efficacy did not wane, according to a study yesterday in *The Journal of Infectious Diseases*.

Researchers from the University of Michigan and the US Centers for Disease Control and Prevention studied flu vaccine efficacy over the 2007-08 flu season in 1,952 healthy adults age 49 and younger, with an average age of 23.

Participants received IIV (814 people), LAIV (813), or a placebo (325) in October or November 2007, and antibody titers were measured before vaccine was given, 30 days after vaccination, and at the end of the flu season.

The efficacy of IIV was 70% (95% confidence interval [CI], 50%-82%) overall and 73% against H3N2, the season's predominant strain. Efficacy was much lower for LAIV, at 38% (95% CI, 5%-52%) overall and at 30% against H3N2, the authors said.

Daniel Paquet / Flickr cc

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Influenza Vaccination

John J. Treanor, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 75-year-old man who has well-controlled hypertension and mild chronic obstructive pulmonary disease, but who is otherwise healthy, visits his physician in the early fall. He has questions about vaccination against influenza. He asks specifically whether he should receive a standard-dose four-component vaccine or the recently licensed high-dose vaccine, which has only three components. What would you advise, and how strong is the evidence that a vaccine will reduce his risk of influenza?

From the University of Rochester Medical Center, Rochester, NY. Address reprint requests to Dr. Treanor at the Infectious Diseases Division, Department of Medicine, University of Rochester Medical Center, 601 Elmwood Ave., Rochester, NY 14642, or at john_treanor@urmc.rochester.edu.

N Engl J Med 2016;375:1261-8.
DOI: 10.1056/NEJMcp1512870

THE CLINICAL PROBLEM

Influenza is a viral infection that is associated with seasonal outbreaks of respiratory illness during the winter months in regions with temperate climates and during rainy seasons in tropical regions. The reasons for seasonal epidemics of influenza are not definitely known. They probably involve a combination of environmental factors such as low humidity and low temperature and social behaviors that facilitate person-to-person transmission of influenza A and B viruses, such as attendance at school and indoor crowding during inclement weather.

At unpredictable intervals, influenza pandemics occur with very high attack rates and severe disease. These pandemics are associated with the emergence of influenza A viruses that, on their surfaces, have hemagglutinin (HA) and neuraminidase (NA) molecules of subtypes that are not currently circulating in human populations. Because of a lack of prior immunity, humans can be highly susceptible to infection and disease from these subtypes. Influenza A viruses with a wide variety of HA and NA subtypes are enzootic in waterfowl, swine, and other animals, which are the probable source of these new viruses.

Influenza in otherwise healthy persons is characterized predominantly by fever, myalgias, cough and other respiratory symptoms, and malaise. In most persons, recovery from these symptoms occurs in 5 to 7 days, but even in healthy persons symptoms of fatigue and malaise may not completely resolve for several weeks. Influenza may cause more severe pulmonary symptoms through direct invasion of the lung (leading to primary viral pneumonia) or by altering lung defense mechanisms in a variety of ways that lead to bacterial superinfection. This superinfection, which may occur simultaneously with influenza or follow it by days to weeks, may be responsible for much of the disease burden associated with influenza. Other potential complications of influenza include myositis and myocarditis, toxic shock syndrome related to *Staphylococcus aureus* superinfection, and various complications in the central nervous system.

An audio version of this article is available at NEJM.org

THE COMPELLING NEED FOR GAME-CHANGING INFLUENZA VACCINES

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

OCTOBER 2012

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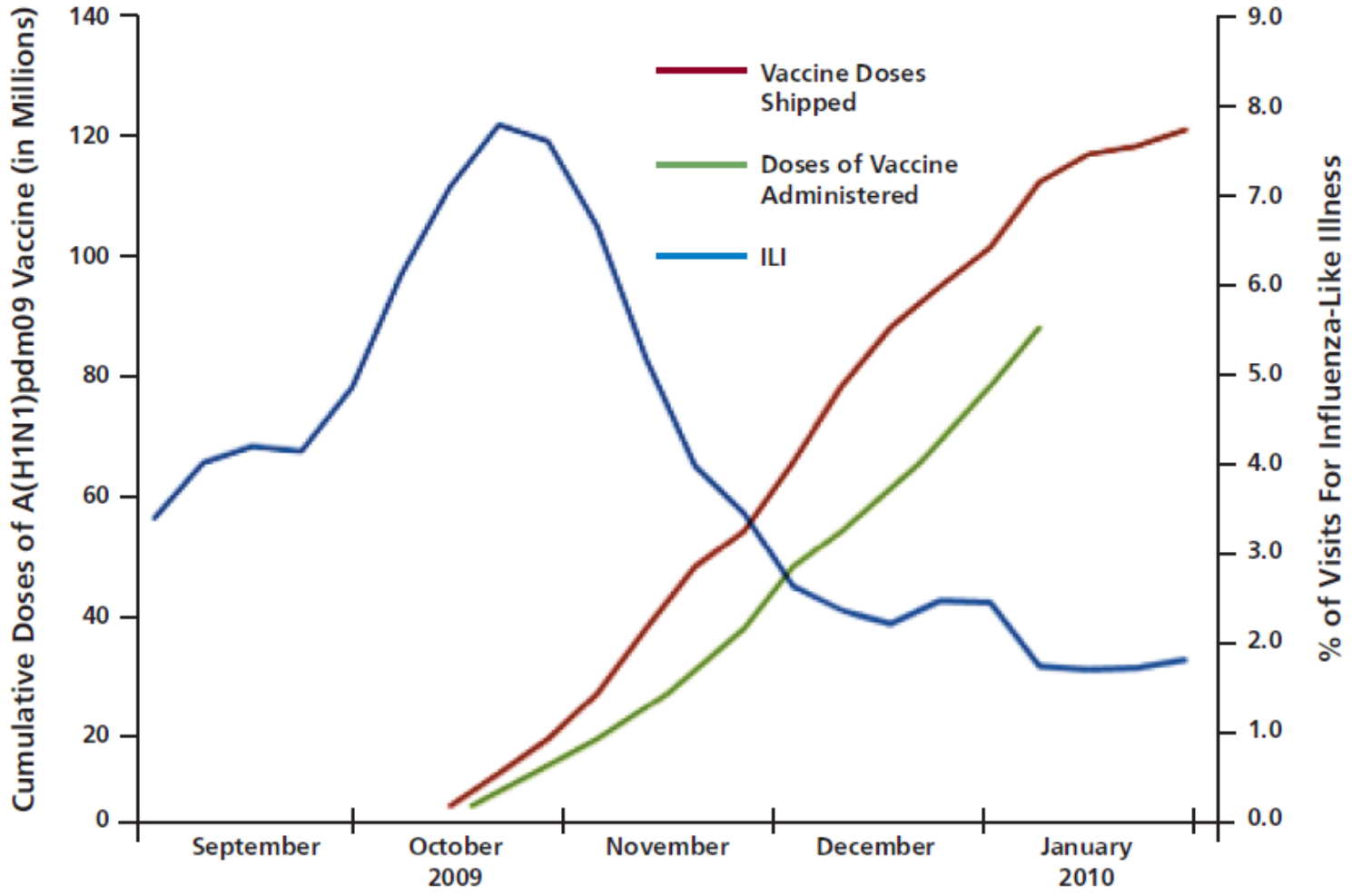
FIGURE 6-1. A(H1N1)pdm09 Vaccine By Date Shipped and Estimated Date of Administration, and Incidence of Influenza-Like Illness (ILI) in the United States[8,9 a,b]



[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.

Agents of Concern

- **Diseases with pandemic potential**
  - Influenza
  - **Antimicrobial resistance**
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Dengue, Chikungunya and Zika
  - Yellow fever

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PLoS one

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

Kirandeep Bhullar[1], Nicholas Waglechner[1], Andrew Pawlowski[1], Kalinka Koteva[1], Eric D. Banks[2], Michael D. Johnston[2], Hazel A. Barton[2], Gerard D. Wright[1]*

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Abstract

Antibiotic resistance is a global challenge that impacts all pharmaceutically used antibiotics. The origin of the genes associated with this resistance is of significant importance to our understanding of the evolution and dissemination of antibiotic resistance in pathogens. A growing body of evidence implicates environmental organisms as reservoirs of these resistance genes; however, the role of anthropogenic use of antibiotics in the emergence of these genes is controversial. We report a screen of a sample of the culturable microbiome of Lechuguilla Cave, New Mexico, in a region of the cave that has been isolated for over 4 million years. We report that, like surface microbes, these bacteria were highly resistant to antibiotics; some strains were resistant to 14 different commercially available antibiotics. Resistance was detected to a wide range of structurally different antibiotics including daptomycin, an antibiotic of last resort in the treatment of drug resistant Gram-positive pathogens. Enzyme-mediated mechanisms of resistance were also discovered for natural and semi-synthetic macrolide antibiotics via glycosylation and through a kinase-mediated phosphorylation mechanism. Sequencing of the genome of one of the resistant bacteria identified a macrolide kinase encoding gene and characterization of its product revealed it to be related to a known family of kinases circulating in modern drug resistant pathogens. The implications of this study are significant to our understanding of the prevalence of resistance, even in microbiomes isolated from human use of antibiotics. This supports a growing understanding that antibiotic resistance is natural, ancient, and hard wired in the microbial pangenome.

Citation: Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, et al. (2012) Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome. PLoS ONE 7(4): e34953. doi:10.1371/journal.pone.0034953

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Competing Interests: The authors have declared that no competing interests exist.

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Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill
December 2014

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Tackling a global health crisis: initial steps

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill

February 2015

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

SECURING NEW DRUGS FOR FUTURE GENERATIONS: THE PIPELINE OF ANTIBIOTICS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2015

SAFE, SECURE AND CONTROLLED: MANAGING THE SUPPLY CHAIN OF ANTIMICROBIALS

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Tackling drug-resistant infections globally

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THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

DECEMBER 2015

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

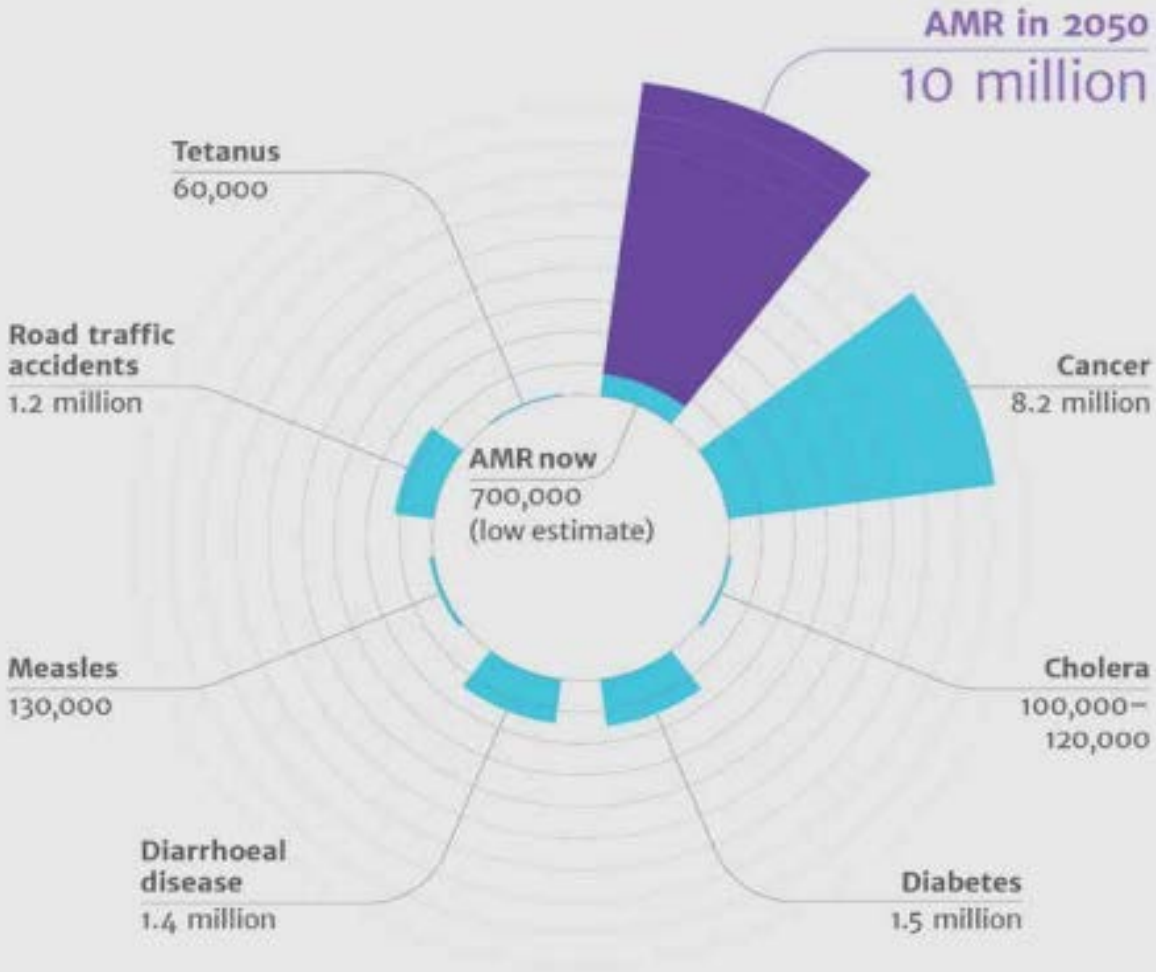
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
AN OVERVIEW OF OUR WORK

THE REVIEW ON ANTIMICROBIAL RESISTANCE

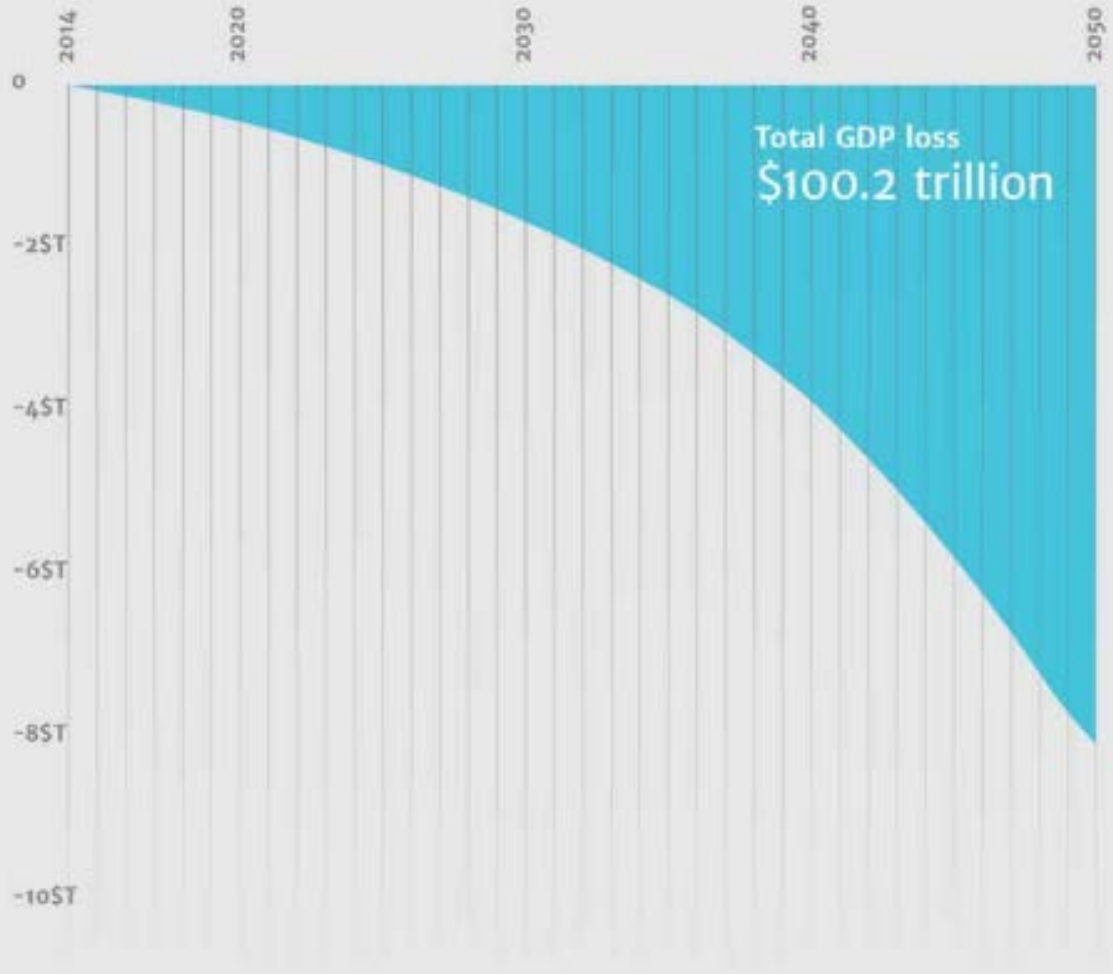
CHAIRED BY JIM O'NEILL

FEBRUARY 2016

Deaths attributable to AMR every year compared to other major causes of death



AMR's impact on World GDP
in trillions of USD



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UN leaders pledge to fight antimicrobial resistance

Filed Under: Antimicrobial Stewardship

Chris Dall | News Reporter | CIDRAP News | Sep 21, 2016

World leaders today made a commitment to work at national, regional, and global levels to address the growing threat of antimicrobial resistance (AMR).

The agreement came at the 71st meeting of the United Nations (UN) General Assembly, where delegates gathered today for a high-level meeting on AMR. It's only the fourth time the UN has held a General Assembly meeting to address a health issue, a fact that underscores how seriously world leaders take the threat of drug-resistant pathogens. Before the meeting, delegates agreed to a draft political declaration in which they committed to developing and implementing national action plans to address rising drug resistance.

Nathan Reading / Flickr cc

Enterobacter cloacae with NDM-1 resistance gene growing in culture.

"Antimicrobial resistance poses a fundamental, long-term threat to human health, sustainable food production and development," UN Secretary-General Ban Ki-moon told the assembled delegates. "We are losing our ability to protect both people and animals from life-threatening infections."

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Experts hope UN meeting on antimicrobial resistance yields action

Filed Under: Antimicrobial Stewardship

Chris Dall | News Reporter | CIDRAP News | Sep 19, 2016

UN, Mark Garten / Flickr cc

For those who've been sounding the alarm about the worrisome rise in drug-resistant bacteria, the upcoming United Nations (UN) General Assembly meeting on antimicrobial resistance (AMR) is a welcome recognition of the gravity of the problem and the need for action. But for many observers, the question that lingers is what that action will look like.

When global leaders meet on Wednesday to discuss AMR, the primary objective will be to "summon and maintain strong national, regional and international political commitment in addressing antimicrobial resistance comprehensively and multi-sectorally," according to a UN press release. What that translates into remains to be seen.

Will the UN set global targets for reduced antibiotic consumption in humans and animals? Commit money to fund the development of novel antibiotics and diagnostic tests? Establish an infrastructure to coordinate these efforts and mobilize governments into action? Or will international leaders simply acknowledge the issue is a serious threat to global health and say that more discussion is needed?

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J Antimicrob Chemother
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Journal of Antimicrobial Chemotherapy

Risk factors for resistance to ciprofloxacin in community-acquired urinary tract infections due to *Escherichia coli* in an elderly population

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Background: Antimicrobial resistance to ciprofloxacin is rising worldwide, especially in bacteria causing urinary tract infections (UTIs). Prudent use of current antibiotic drugs is therefore necessary.

Objectives: We analysed (modifiable) risk factors for ciprofloxacin-resistant *Escherichia coli*.

Methods: Urinary cultures of UTIs caused by *E. coli* were collected from participants in the Rotterdam Study, a prospective cohort study in an elderly population, and analysed for susceptibility to ciprofloxacin. Multivariate logistic regression was performed to investigate several possible risk factors for resistance.

Results: Ciprofloxacin resistance in 1080 *E. coli* isolates was 10.2%. Multivariate analysis showed that higher age (OR 1.03; 95% CI 1.00–1.05) and use of two (OR 5.89; 95% CI 3.45–10.03) and three or more (OR 3.38; 95% CI 1.92–5.97) prescriptions of fluoroquinolones were associated with ciprofloxacin resistance, while no association between fluoroquinolone use more than 1 year before culture and ciprofloxacin resistance could be demonstrated. Furthermore, a high intake of pork (OR 3.68; 95% CI 1.36–9.99) and chicken (OR 2.72; 95% CI 1.08–6.85) and concomitant prescription of calcium supplements (OR 2.51; 95% CI 1.20–5.22) and proton pump inhibitors (OR 2.04; 95% CI 1.18–3.51) were associated with ciprofloxacin resistance.

Conclusions: Ciprofloxacin resistance in community-acquired UTI was associated with a high intake of pork and chicken and with concomitant prescription of calcium supplements and proton pump inhibitors. Modification of antibiotic use in animals as well as temporarily stopping the prescription of concomitant calcium and proton pump inhibitors need further evaluation as strategies to prevent ciprofloxacin resistance.

Introduction

Urinary tract infections (UTIs) are common in women, especially after menopause. Nearly 50% of all women experience at least one UTI during their lifetime.[1] Fluoroquinolones are often prescribed for complicated UTIs, such as pyelonephritis.[2] However, ciprofloxacin, for example, is also widely used in uncomplicated UTIs.[3]

With the increasing use of fluoroquinolones, selection of ciprofloxacin-resistant uropathogens has become widespread worldwide, ranging from 2% to 69% for uncomplicated and up to 98% for complicated UTIs.[4] In Europe, resistance to ciprofloxacin in uncomplicated UTIs varied from 4.8% in France, 20.3% in Germany, 30.8% in Spain, 7.3% in Sweden to 15.3% in the UK in 2014,[5] while in the USA 17.1% resistance to ciprofloxacin was seen in an outpatient population with UTIs.[6] Although antimicrobial resistance (AMR) is low in the Netherlands, resistance of *Escherichia coli* to ciprofloxacin in outpatients was ~10% in 2014,[7] while it was 12% in a study with a mixed population of both inpatients and outpatients with complicated UTIs in 2004–09.[8]

The WHO has proclaimed AMR to be one of the greatest current threats to global health. Furthermore, AMR is directly associated with the use of antibiotics.[9] Unfortunately, there are very few new antibiotic drugs in the pipeline,[10] and prudent use of current antibiotic drugs has been advocated in order to decrease AMR rates.[11] This also involves dose adjustment to obtain proper drug levels, since low levels of ciprofloxacin will influence the

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CIDRAP Center for Infectious Disease Research and Policy

FAO advises nations on curbing ag antimicrobial use

Filed Under: Antimicrobial Stewardship

Lisa Schnirring | News Editor | CIDRAP News | Sep 16, 2016

Cecilia Schubert / Flickr cc

Ahead of a high-level United Nations meeting on antimicrobial resistance (AMR) next week in New York, the group's Food and Agriculture Organization (FAO) this week unveiled an action plan to help countries build strategies to address the problem in their food and agricultural sectors by the middle of 2017.

Grappling with agricultural uses of antimicrobials is considered a key part of curbing the emergence of antimicrobial-resistant pathogens, preserving crucial antibiotics used for human health. The FAO said in a Sep 14 press release that livestock consumption of antimicrobials tops 60,000 metric tons each year, and that their use is likely to grow with the increasing demand for animal-sourced food products.

Agents of Concern

- Diseases with pandemic potential
  - Influenza
  - Antimicrobial resistance
- **Diseases resulting in outbreaks of regional critical importance**
  - **Ebola**
  - MERS
  - Dengue, Chikungunya and Zika
  - Yellow fever

Ebolavirus Ecology

Enzootic Cycle

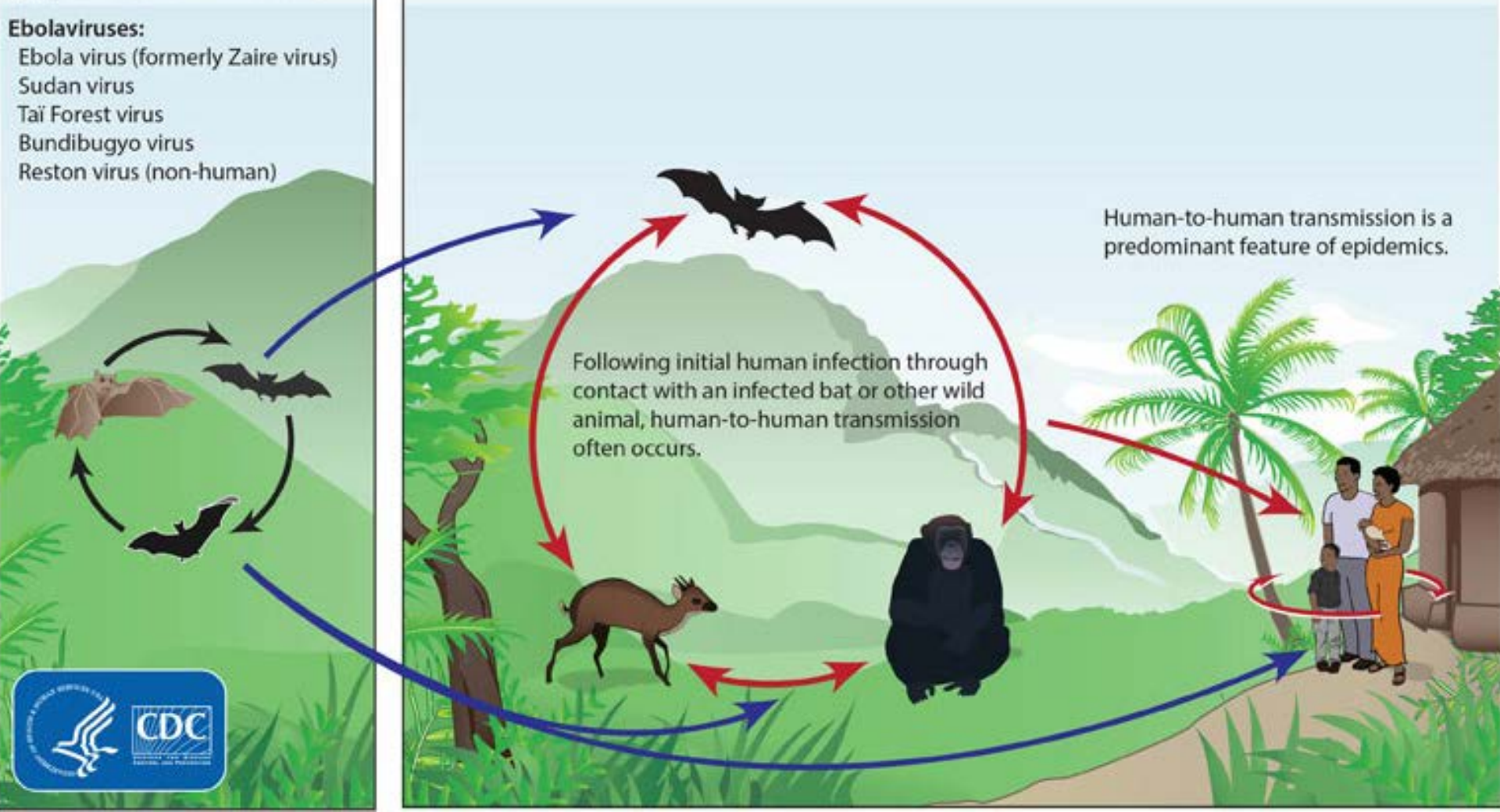
New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintainance and transmission of the virus within bat populations remain unknown.

Ebolaviruses:

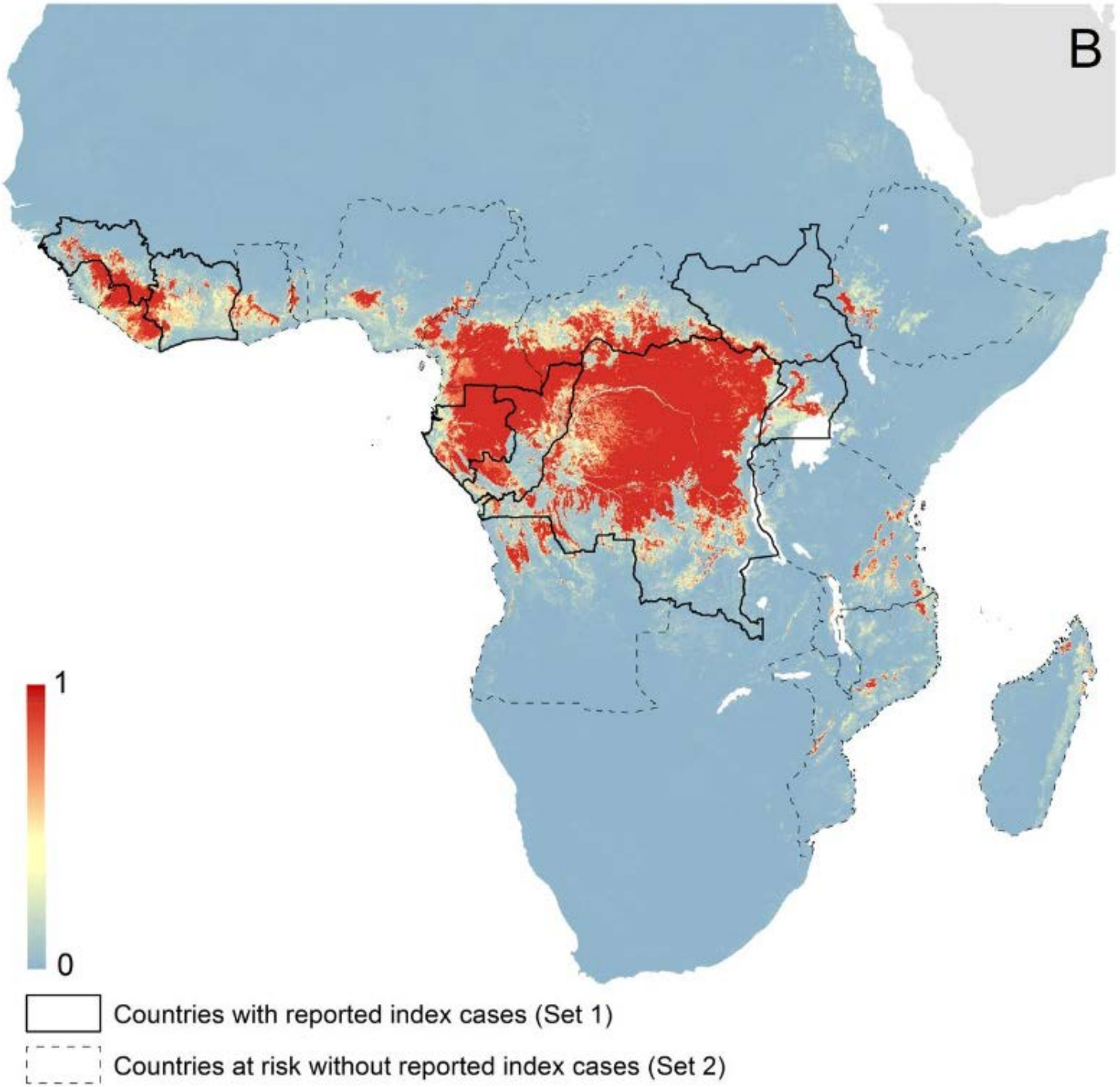
Ebola virus (formerly Zaire virus)
Sudan virus
Taï Forest virus
Bundibugyo virus
Reston virus (non-human)

Epizootic Cycle

Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.



eLife 2014;10.7554/eLife.04395



The Washington Post

Opinions

What we need to fight Ebola

Michael T. Osterholm is the director of the Center for Infectious Disease Research and Policy at the University of Minnesota.

Ebola outbreaks have occurred in Africa on more than two dozen occasions over the past 40 years, and they were brought under control every time. This was possible thanks to reliable techniques, such as preventing direct contact with infected persons and monitoring all people who did come into contact with an infected person. Anyone showing early symptoms was put in isolation. Despite no effective treatment or vaccine, these standard approaches worked.

Unfortunately, today's outbreak is very different. And unless we invest more resources in fighting it — and coordinate the response across countries — the outbreak will spread further. If that happens, economic and political chaos could follow.

What's different about this outbreak? The Ebola virus hasn't changed; Africa has changed. First, residents of the affected countries — Guinea, Liberia and Sierra Leone — travel much farther and have many more contacts than they did in previous decades. Following up on all contacts who live a few miles from a case is much easier than tracking down people who may live far away. With modern transportation, family members may travel hundreds of miles to be with sick loved ones. And more of this outbreak area, in West Africa, is urbanized than where many of the previous outbreaks occurred in Central Africa, so the virus spreads faster.

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WHO declares end to Ebola public health emergency

Filed Under: Ebola; VHF

Lisa Schnirring | News Editor | CIDRAP News | Mar 29, 2016

UK DFID / Flickr cc

The World Health Organization (WHO) today announced the end of the Ebola public health emergency of international concern (PHEIC), noting that West Africa's outbreak nations have stamped out original transmission chains and have shown they can quickly extinguish occasional clusters as virus levels die out in survivors.

The WHO made the announcement after its Ebola emergency committee met today for the ninth time. After hearing updates from all three countries and responders, the panel noted that all three countries have passed observation and extended surveillance periods since the last case in the original transmission chains were reported.

As expected, new clusters continue to be reported, such as a recent one in Guinea, but they are becoming less frequent and the countries have quickly responded and limited the cases to no more than two generations of infection.

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WHO issues Ebola survivor guidance as cases show virus persistence

Filed Under: Ebola; VHF

Jim Wappes | Editorial Director | CIDRAP News | Jan 22, 2016

UNMEER / Martine Perret / Flickr cc

The World Health Organization (WHO) today issued guidance on caring for Ebola survivors, emphasizing integrated care for their diverse needs, while two case reports yesterday demonstrated the persistence of Ebola virus in the breast milk and semen of survivors.

The WHO guidance comes after flare-ups of Ebola virus disease (EVD) in West Africa, some tied to sexual transmission of the virus, and after a high-profile relapse in a nurse survivor in the United Kingdom. Issues with survivors include the ability of the Ebola virus to survive for long periods in some parts of the body like the eyes, breasts, and testicles, as well as emotional trauma and long-lasting physical symptoms.

The WHO said there are more than 10,000 Ebola survivors today, the vast majority of them in West Africa.

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High effectiveness found in Guinea Ebola ring vaccination trial

Filed Under: Ebola; VHF

Lisa Schnirring and Robert Roos | Staff Writers | CIDRAP News | Jul 31, 2015

A ring vaccination trial in Guinea of a Canadian-developed Ebola vaccine showed it was highly effective against the disease, setting the scene for it quickly to become a useful response tool.

UNICEF Guinea / Flickr cc

Researchers found that the vaccine was 100% effective in people who received it soon after possible exposure. The vaccine, called VSV-EBOV, uses an Ebola protein spliced into a vesicular stomatitis virus (VSV). It was developed in Canada and is licensed by NewLink Genetics and Merck.

A World Health Organization (WHO)–sponsored team published the findings today in an early online edition of *The Lancet*.

An independent group that reviewed the findings urged that the trial continue, to look for more conclusive evidence on its ability to provide populations with "herd immunity" against the disease.

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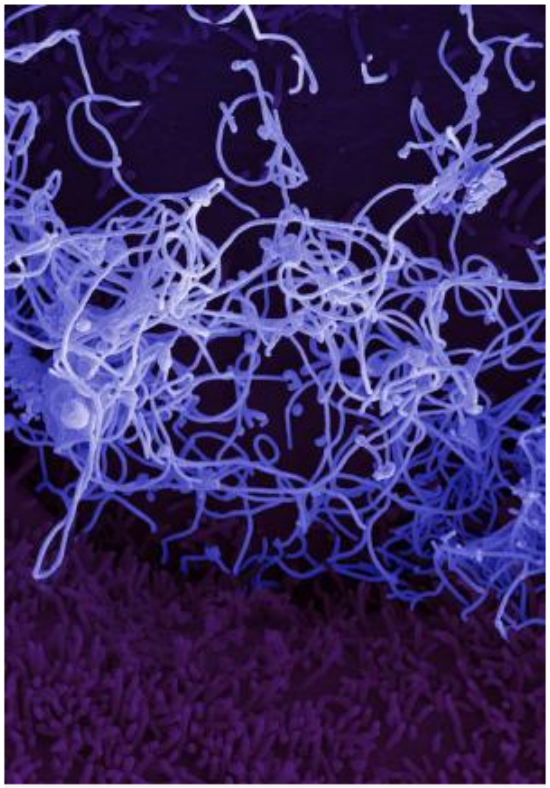
Trial suggests potential for sequential use of 2 Ebola vaccines

Filed Under: Ebola; VHF

Robert Roos | News Writer | CIDRAP News | Apr 20, 2016

In an unusual trial reported yesterday, the use of two different experimental Ebola vaccines in different prime-boost sequences appeared safe and induced detectable immune responses in a small group of volunteers, though one vaccine generated a much stronger initial response than the other.



NIAID / Flickr cc

And in another Ebola development, an experimental Ebola drug called TKM 130803 failed to improve survival in very sick Ebola patients in a Sierra Leone trial, according to a report yesterday in *PLoS Medicine*. The researchers held out hope that the product might still prove helpful in patients with less severe illness.

Two different vectors used

The phase 1 vaccine trial, described in the *Journal of the American Medical Association* (*JAMA*), involved vaccines called Ad26.ZEBOV, developed by Crucell Holland B.V., and MVA-BN-Filo, made by Bavarian Nordic. They are two of several Ebola vaccines currently in development. No Ebola vaccine has yet been licensed, but the vaccine known as VSV-EBOV

Ebola Vaccine Team B

- Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) established the Ebola Vaccine Team B in November, 2014.
- A proactive, science-based approach to critically examine the vaccine development process, challenge assumptions and identify potentially overlooked aspects of all phases of developing and delivering Ebola vaccines.

Ebola Vaccine Team B

- Group co-chaired by Jeremy Farrar (Wellcome Trust) and Michael Osterholm (CIDRAP.)
- Included 26 internationally recognized subject-matter experts with specific expertise in one or more of the areas of vaccine development.

February 2015

Recommendations for Accelerating the Development of Ebola Vaccines

REPORT & ANALYSIS

wellcome trust

CIDRAP

The Ebola Vaccine Team B: a model for promoting the rapid development of medical countermeasures for emerging infectious disease threats

*Michael Osterholm, Kristine Moore, Julie Ostrowsky, Kathleen Kimball-Baker, Jeremy Farrar, for the Wellcome Trust-CIDRAP Ebola Vaccine Team B**

In support of accelerated development of Ebola vaccines from preclinical research to clinical trials, in November, 2014, the Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota established the Wellcome Trust-CIDRAP Ebola Vaccine Team B initiative. This ongoing initiative includes experts with global experience in various phases of bringing new vaccines to market, such as funding, research and development, manufacturing, determination of safety and efficacy, regulatory approval, and vaccination delivery. It also includes experts in community engagement strategies and ethical issues germane to vaccination policies, including eight African scientists with direct experience in developing and implementing vaccination policies in Africa. Ebola Vaccine Team B members have worked on a range of vaccination programmes, such as polio eradication (Africa and globally), development of meningococcal A disease vaccination campaigns in Africa, and malaria and HIV/AIDS vaccine research. We also provide perspective on how this experience can inform future situations where urgent development of vaccines is needed, and we comment on the role that an independent, expert group such as Team B can have in support of national and international public health authorities toward addressing a public health crisis.

Lancet Infect Dis 2015

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Introduction

On Aug 8, 2014, the Director-General of WHO declared that the Ebola virus disease (EVD) outbreak in parts of west Africa represented a Public Health Emergency of International Concern (PHEIC) under the 2005 International Health Regulations.[1] Also in August, 2014, WHO called for fast-track development of Ebola vaccines as part of the Ebola Response Roadmap[2] and in October, 2014, development, to identify potentially overlooked aspects of the vaccine development process, and to synthesise information for distribution in the public domain as quickly as possible. To achieve these objectives, during the period from late November, 2014, to early February, 2015, working subgroups of Ebola Vaccine Team B experts met regularly via international conference calls to discuss and comment on various issues related to the development

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Expert panel urges no letup on Ebola vaccine progress

Filed Under: Ebola; VHF

Jim Wappes | Editorial Director | CIDRAP News | Mar 31, 2016

Although the World Health Organization (WHO) this week ended the global health emergency over Ebola, the world cannot ease up on efforts to maximize development of Ebola vaccines and prepare for the next outbreak, according to an expert panel.

Sally Hodgson, US Embassy-Monrovia / NIAID

A report today by the Ebola Vaccine Team B comes a little over a year after its first report, which detailed desirable qualities to seek in as-yet undeveloped vaccines and included a host of recommendations for quickly responding to the then-accelerating crisis.

Since that time a vaccine produced by Merck has demonstrated impressive efficacy in clinical trials and other vaccines have advanced well along the clinical trial pathway. But no vaccine has yet been approved by the US Food and Drug Administration or other regulatory body, the experts point out in their report, and public health officials must not grow complacent until one or more vaccines are advanced enough to stockpile and respond to the next Ebola epidemic.

March 2016

Ebola Vaccine Team B

Plotting the Course of Ebola Vaccines

CHALLENGES AND UNANSWERED QUESTIONS

wellcome trust

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

Team B Focus: Key Unresolved Issues

- Need for a **business model** to maintain industry involvement in Ebola vaccine R&D, licensure and deployment
- Lack of a comprehensive **regulatory strategy** for Ebola vaccine licensure
- Gaps in **safety/effectiveness data** for rVSV-ZEBOV
- Need for direct input from **African public health leaders** on how Ebola vaccines would be used in Africa to end current epidemic and prevent future epidemics

The Need for a Vaccine Development Paradigm Shift

- The current Ebola epidemic is not a “one-off” event.
- Future Ebola (other emerging diseases) epidemics are inevitable.
- The current vaccine R&D, financing and manufacturing model is not effective for meeting the needs to develop and deploy new vaccines for pathogens that cause outbreaks of regional critical importance.

EDITORIAL

Ebola and Zika: Cautionary tales

The emergence of Zika in the Americas is a stark reminder of how quickly public health challenges of infectious diseases can change. The need for a safe and effective vaccine is immediate. Yet, like the Ebola epidemic 2 years ago, we find ourselves without a vaccine to combat this latest threat. When surveillance points to a possible emergence of a new infectious disease of potential public health importance, we need procedural and funding mechanisms that can quickly identify candidate vaccines and drive research and development toward licensure and production. Even if such a vaccine is not yet licensed, having it ready for immediate large trials when a regional crisis occurs will be a major advantage over our current reactive system.

Two years ago, amidst the Ebola epidemic in West Africa, the international health community was laser-focused on finding an effective and safe vaccine. By heroic public health actions and luck, the crisis was curtailed without one. Today, hardly a word is mentioned about that crisis or the current status of vaccine development. Yet tomorrow, we could experience another explosive Ebola epidemic that begins in the slums of one of equatorial Africa's megacities and spreads in deadly waves, where only the availability of an effective vaccine could halt its ruinous progression.

Now, Zika transmission in Florida dominates news in the United States, along with partisan political theater regarding government funding for the country's response. However, we must not take our eye off the most pressing problem of Zika: the explosive transmission in the Americas outside the continental United States. For example, it is estimated that up to 5% of Puerto Rico's population is getting infected with Zika each month, including thousands of pregnant women, for whom infection could result in fetal microcephaly.

I fear the road to a Zika vaccine may be long and bumpy. Despite optimistic predictions, demonstrating safety will be an immense challenge. It likely will be necessary to conduct studies involving many thousands of participants to determine if Guillain-Barré syndrome (GBS), a serious autoimmune condition caused by natural Zika virus, is also related to vaccine candidates. And recent follow-up of a vaccine efficacy study for dengue, Zika's cousin flavivirus, suggests a diminishing vaccine-induced antibody response over time. This means that antibody-dependent enhancement disease may occur upon infection with a new dengue strain, or possibly even another flavivirus such as Zika or yellow fever.

"How much more incentive is needed to develop candidate vaccines?"

The handwriting is on the wall regarding the current Zika outbreak in the Americas. High human infection rates in the major impact regions, caused by virus-carrying mosquitoes and human sexual transmission, will continue for several more years. Eventually, the number of cases will drop as more of the community develops immunity. Zika vaccine trials in the Americas may be too late to be tested on the current high number of cases.

The Coalition for Epidemic Preparedness Innovations (CEPI) is a new international effort that includes the Wellcome Trust; Bill & Melinda Gates Foundation; World Economic Forum; U.S., Indian, and Norwegian governments; GAVI; academic researchers; international vaccine manufacturers; and the World Health Organization. CEPI (www.cepi.net) is the best hope to fill the vaccine preparedness hole.

These experiences demand better answers than our current vaccine research, development, manufacturing, and distribution system has provided. Based on observation, we could, and should, have anticipated that agents like Zika and Ebola virus would emerge as serious pathogens. The 2013 to 2014 Zika outbreak in French Polynesia produced nearly 9000 suspected cases and a strong association with GBS. How much more incentive is needed to develop candidate vaccines? With the growth of megacities in the developing world and prevalence of *Aedes aegypti* mosquitoes in many areas, this disease should not have come as a surprise—nor should the host of others yet to come that we would be foolish not to expect.

–Michael T. Osterholm

Michael T. Osterholm is a Regents Professor; McKnight Endowed Presidential Chair in Public Health; and director of the Center for Infectious Disease Research and Policy; all at the University of Minnesota, Minneapolis, MN. Email: mto@umn.edu

PHOTOS (INSET): ISTOCKPHOTO.COM; (TOP RIGHT) UNIVERSITY OF MINNESOTA

10.1126/science.aai9078

What We're Afraid to Say About Ebola

By MICHAEL T. OSTERHOLM SEPT. 11, 2014

Jonathon Rosen

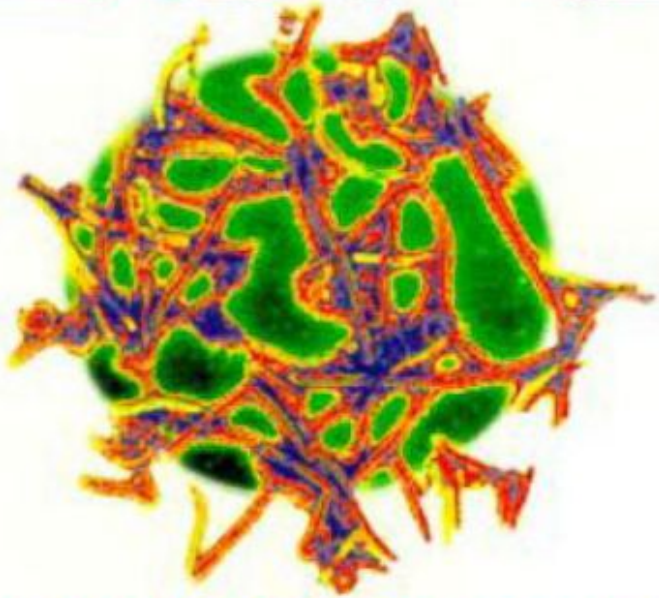
MINNEAPOLIS — THE Ebola epidemic in West Africa has the potential to alter history as much as any plague has ever done.

There have been more than 4,300 cases and 2,300 deaths over the past six months. Last week, the World Health Organization warned that, by early October, there may be thousands of new cases per week in Liberia, Sierra Leone, Guinea and Nigeria. What is not getting said publicly, despite briefings and discussions in the inner circles of the world's public health agencies, is that we are in totally uncharted waters and that Mother Nature is the only force in charge of the crisis at this time.

There are two possible future chapters to this story that should keep us up at night.

The first possibility is that the Ebola virus spreads from West Africa to megacities in other regions of the developing world. This outbreak is very different from the 19 that have occurred in Africa over the past 40 years. It is much easier to control Ebola infections in isolated villages. But there has been a 300 percent increase in Africa's population over the last four decades, much of it in large city slums. What happens when an infected person yet to become ill travels by plane to Lagos, Nairobi, Kinshasa or

THE HOT ZONE



A TERRIFYING TRUE STORY

RICHARD PRESTON

SCIENTIFIC REPORTS

OPEN

Conserved differences in protein sequence determine the human pathogenicity of Ebolaviruses

Received: 08 July 2015
Accepted: 14 March 2016
Published: 24 March 2016

Morena Pappalardo*, Miguel Juliá*, Mark J. Howard, Jeremy S. Rossman, Martin Michaelis & Mark N. Wass

Reston viruses are the only Ebolaviruses that are not pathogenic in humans. We analyzed 196 Ebolavirus genomes and identified specificity determining positions (SDPs) in all nine Ebolavirus proteins that distinguish Reston viruses from the four human pathogenic Ebolaviruses. A subset of these SDPs will explain the differences in human pathogenicity between Reston and the other four ebolavirus species. Structural analysis was performed to identify those SDPs that are likely to have a functional effect. This analysis revealed novel functional insights in particular for Ebolavirus proteins VP40 and VP24. The VP40 SDP P85T interferes with VP40 function by altering octamer formation. The VP40 SDP Q245P affects the structure and hydrophobic core of the protein and consequently protein function. Three VP24 SDPs (T131S, M136L, Q139R) are likely to impair VP24 binding to human karyopherin alpha5 (KPNA5) and therefore inhibition of interferon signaling. Since VP24 is critical for Ebolavirus adaptation to novel hosts, and only a few SDPs distinguish Reston virus VP24 from VP24 of other Ebolaviruses, human pathogenic Reston viruses may emerge. This is of concern since Reston viruses circulate in domestic pigs and can infect humans, possibly via airborne transmission.

Agents of Concern

- Diseases with pandemic potential
  - Influenza
  - Antimicrobial resistance
- **Diseases resulting in outbreaks of regional critical importance**
  - Ebola
  - **MERS**
  - Dengue, Chikungunya and Zika
  - Yellow fever

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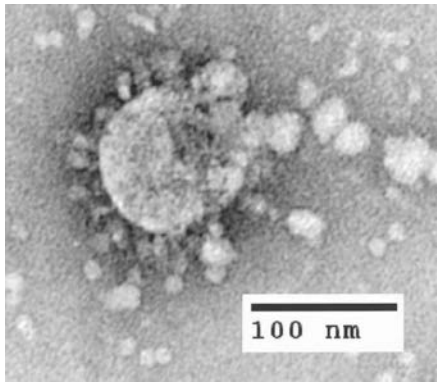

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Articles

Coronavirus as a possible cause of severe acute respiratory syndrome

*J S M Peiris, S T Lai, L L M Poon, Y Guan, L Y C Yam, W Lim, J Nicholls, W K S Yee, W W Yan, M T Cheung, V C C Cheng, K H Chan, D N C Tsang, R W H Yung, T K Ng, K Y Yuen, and members of the SARS study group**

The NEW ENGLAND JOURNAL of MEDICINE

A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome

Thomas G. Ksiazek, D.V.M., Ph.D., Dean Erdman, Dr.P.H., Cynthia S. Goldsmith, M.S., Sherif R. Zaki, M.D., Ph.D., Teresa Peret, Ph.D., Shannon Emery, B.S., Suxiang Tong, Ph.D., Carlo Urbani, M.D.,* James A. Comer, Ph.D., M.P.H., Wilina Lim, M.D., Pierre E. Rollin, M.D., Scott F. Dowell, M.D., M.P.H., Ai-Ee Ling, M.D., Charles D. Humphrey, Ph.D., Wun-Ju Shieh, M.D., Ph.D., Jeannette Guarner, M.D., Christopher D. Paddock, M.D., M.P.H.T.M., Paul Rota, Ph.D., Barry Fields, Ph.D., Joseph DeRisi, Ph.D., Jyh-Yuan Yang, Ph.D., Nancy Cox, Ph.D., James M. Hughes, M.D., James W. LeDuc, Ph.D., William J. Bellini, Ph.D., Larry J. Anderson, M.D., and the SARS Working Group†

Identification of a Novel Coronavirus in Patients with Severe Acute Respiratory Syndrome

Christian Drosten, M.D., Stephan Günther, M.D., Wolfgang Preiser, M.D., Sylvie van der Werf, Ph.D., Hans-Reinhard Brodt, M.D., Stephan Becker, Ph.D., Holger Rabenau, Ph.D., Marcus Panning, M.D., Larissa Kolesnikova, Ph.D., Ron A.M. Fouchier, Ph.D., Annemarie Berger, Ph.D., Ana-Maria Burguière, Ph.D., Jindrich Cinatl, Ph.D., Markus Eickmann, Ph.D., Nicolas Escriou, Ph.D., Klaus Grywna, M.Sc., Stefanie Kramme, M.D., Jean-Claude Manuguerra, Ph.D., Stefanie Müller, M.Sc., Volker Rickerts, M.D., Martin Stürmer, Ph.D., Simon Vieth, Hans-Dieter Klenk, M.D., Albert D.M.E. Osterhaus, Ph.D., Herbert Schmitz, M.D., and Hans Wilhelm Doerr, M.D.

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Coronavirus Scan for Mar 15, 2016

Study: SARS-like virus in Chinese bats could jump to humans

Researchers at the University of North Carolina at Chapel Hill (UNC) say their research shows that viruses much like the SARS (severe acute respiratory syndrome) coronavirus (CoV) are still lurking in horseshoe bats in China and could jump to humans.

The scientists described their research in a Mar 13 article in the *Proceedings of the National Academy of Sciences (PNAS)*.

Previous studies suggest that SARS-CoV originated in horseshoe bats, and recent metagenomics studies of horseshoe bat viruses identified several SARS-like DNA sequences that are at least 90% identical to the SARS virus, the report says. Further, scientists recently isolated a virus called WIV1-CoV that uses human angiotensin-converting enzyme and could replicate at low levels in human cells.

The authors said they took DNA sequences from SARS-like viruses isolated from horseshoe bats and used them to reconstruct the viruses. They then tested the viruses' ability to infect human cells and mice. The results showed that WIV1-CoV could bind to the same receptors as SARS-CoV and readily replicated in cultured human airway cells, according to a UNC press release.

"The capacity of this group of viruses to jump into humans is greater than we originally thought," Vineet Menachery, PhD, the study's first author, said in the release. "While other adaptations may be required to produce an epidemic, several viral strains circulating in bat populations have already overcome the barrier of replication in human cells and suggest reemergence as a distinct possibility."

The report says it appears that the virus would need additional adaptations, possibly involving components other than its spike protein, before it could easily spread in humans. Also, monoclonal antibodies developed to treat SARS were effective against the virus in human and animal cells, the researchers found. Existing SARS vaccines, however, would not prevent infection with it, they said.

Mar 13 *PNAS* report
Mar 14 UNC press release

Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction

V M Corman[1,2], I Eckerle[1], T Bleicker[1], A Zaki[3], O Landt[4], M Eschbach-Bludau[1], S van Boheemen[5], R Gopal[6], M Ballhause[4], T M Bestebroer[5], D Muth[1], M A Müller[1], J F Drexler[1], M Zambon[6], A D Osterhaus[5], R M Fouchier[5], C Drosten (drosten@virology-bonn.de)[1]

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Citation style for this article:
Corman VM, Eckerle I, Bleicker T, Zaki A, Landt O, Eschbach-Bludau M, van Boheemen S, Gopal R, Ballhause M, Bestebroer TM, Muth D, Müller MA, Drexler JF, Zambon M, Osterhaus AD, Fouchier RM, Drosten C. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Euro Surveill. 2012;17(39):pii=20285. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20285

Article submitted on 27 September 2012 / published on 27 September 2012

We present two real-time reverse-transcription polymerase chain reaction assays for a novel human coronavirus (CoV), targeting regions upstream of the E gene (upE) or within open reading frame (ORF)1b, respectively. Sensitivity for upE is 3.4 copies per reaction (95% confidence interval (CI): 2.5–6.9 copies) or 291 copies/mL of sample. No cross-reactivity was observed with coronaviruses OC43, NL63, 229E, SARS-CoV, nor with 92 clinical specimens containing common human respiratory viruses. We recommend using upE for screening and ORF1b for confirmation.

suitable for qualitative and quantitative detection of the new agent. Here we summarise the technical evaluation and analytical performance of these assays.

Materials and methods

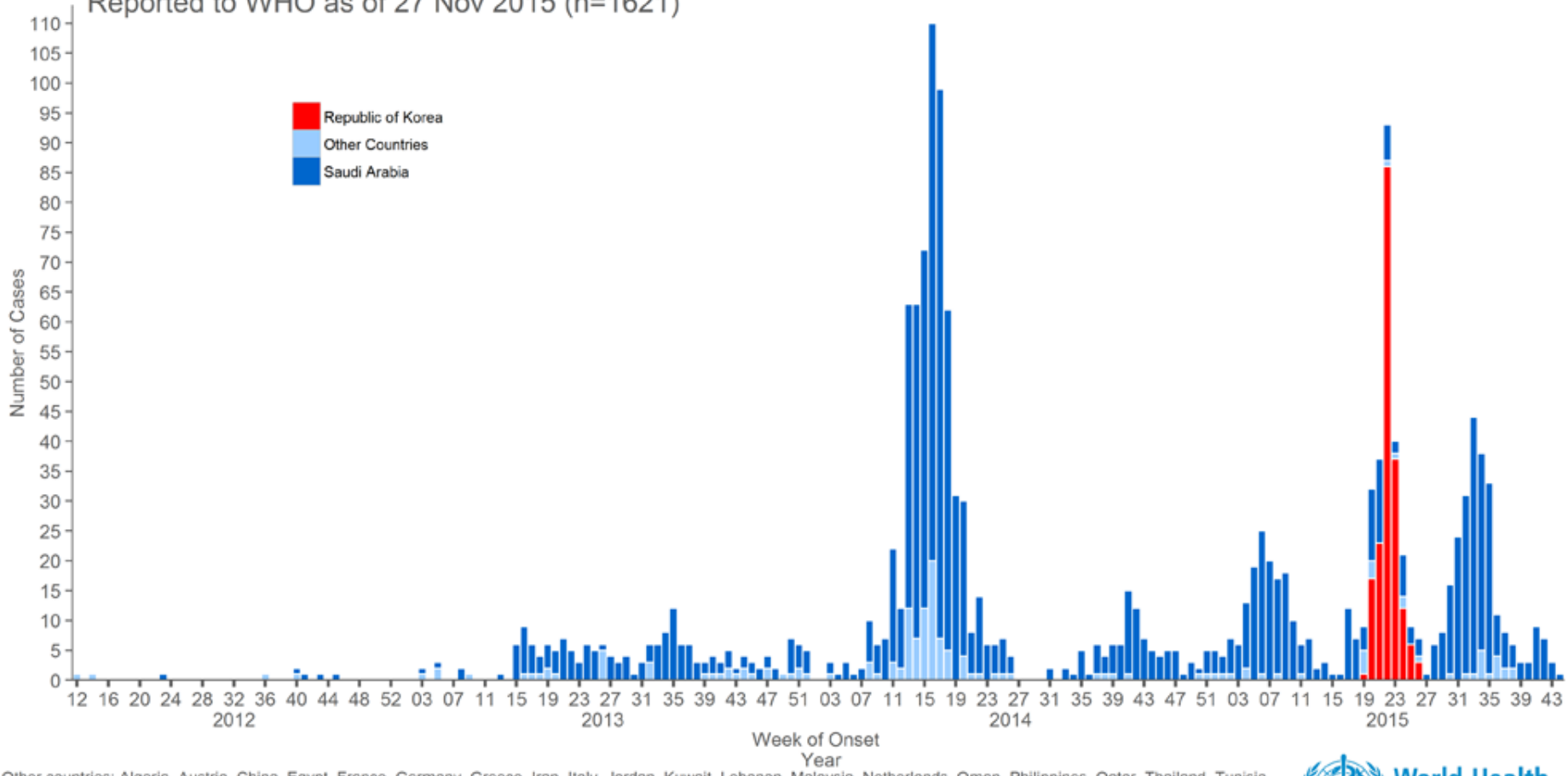
Template for design of assays

A provisional genome sequence as well as an isolate of the new virus were obtained from author RM Fouchier on 24 September 2012, after public notification of the second case case, who was in the United Kingdom

World Health Organization

Confirmed global cases of MERS-CoV

Reported to WHO as of 27 Nov 2015 (n=1621)



Other countries: Algeria, Austria, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, Netherlands, Oman, Philippines, Qatar, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America, Yemen

Please note that the underlying data is subject to change as the investigations around cases are ongoing. Onset date estimated if not available.

World Health Organization

Study: MERS-CoV from Saudi camels matches human isolates

Filed Under: MERS-CoV

Robert Roos | News Editor | CIDRAP News | Apr 29, 2014

US and Saudi scientists reported today that MERS-CoV (Middle East respiratory syndrome coronavirus) isolates from camels in Saudi Arabia match MERS-CoV samples from humans and can be grown in nonhuman primate cells in a lab, further augmenting the evidence that camels are a source of human infections.

Patrycja Zboch / iStockphoto

The team generated complete genetic sequences for MERS-CoV isolates from five camels and determined that they were identical to published sequences of human isolates, according to their report in *mBio*. In addition, they succeeded in culturing viruses from two of the camels in Vero (African green monkey) cells in their lab.

They also found that viral particles from individual camels contained more genetic variation than is true of MERS-CoV isolates from humans, which suggests that, if camels are passing the virus to humans, only certain genotypes can infect humans. That may partially explain why human MERS cases are uncommon, they say.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

News Scan for Sep 19, 2016

New Camel-linked MERS case in Saudi Arabia

On Sep 17 the Saudi Arabia Ministry of Health (MOH) reported one new MERS-CoV case, involving a Saudi man from Riyadh who had contact with camels.

The 50-year-old man is in stable condition after presenting with symptoms of MERS-CoV (Middle East respiratory syndrome coronavirus). The MOH said the patient had direct contact with camels, a known risk factor for contracting the respiratory virus.

Late last week, meanwhile, the World Health Organization (WHO) released details of 8 cases of MERS-CoV reported by Saudi Arabia between Jul 20 and Aug 18. Direct or indirect contact with camels is cited in 3 cases, contact with a sick patient is noted in 1 case, and sources are still unknown for the remaining 4 cases. One of the patients died, on Jul 20.

Two cases were from Jubail city, in a 58-year-old man who had a history of drinking camel's milk and in his 52-year-old female caregiver. The man is on mechanical ventilation, while the woman remains in stable condition in home isolation.

Saudi Arabia's MERS case count since 2012 has now reached 1,453, including 610 deaths. Four patients are still being treated, according to the MOH.

Sep 17 MOH report
Sep 16 WHO report

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News Scan for Sep 22, 2016

WHO: More evidence of camel-MERS link in recent Saudi cases

Yesterday the World Health Organization (WHO) described five recent cases of MERS-CoV in Saudi Arabia, providing more evidence of the risk that camel contact poses in transmitting the disease.

The five cases of MERS-CoV (Middle East respiratory syndrome coronavirus) were documented between Aug 23 and Sep 11. Three of the cases involved direct contact with camels. Both a 55-year-old Saudi man from Arar city, and a 40-year-old expatriate man from Al Hofuf reported drinking raw camel milk in the 14 days before symptom onset. The man from Arar is in stable condition, while the other man is in critical condition and on mechanical ventilation.

A 65-year-old man from Riyadh also was diagnosed as having MERS after he had contact with camels. He remains in stable condition.

Another case was described in a 43-year-old Saudi man from Huraymila, who was a household contact of another MERS patient. He has no co-morbidities and is in stable condition. Finally, a 69-year-old Saudi man from Taif city is in stable condition after contracting the disease. He has no known risk factors.

According to the WHO, since September of 2012 there have been 1,806 laboratory-confirmed cases of MERS-CoV, including at least 643 related deaths.

Sep 21 WHO update

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

News Scan for Sep 23, 2016

MERS sickens 2 more in Saudi Arabia

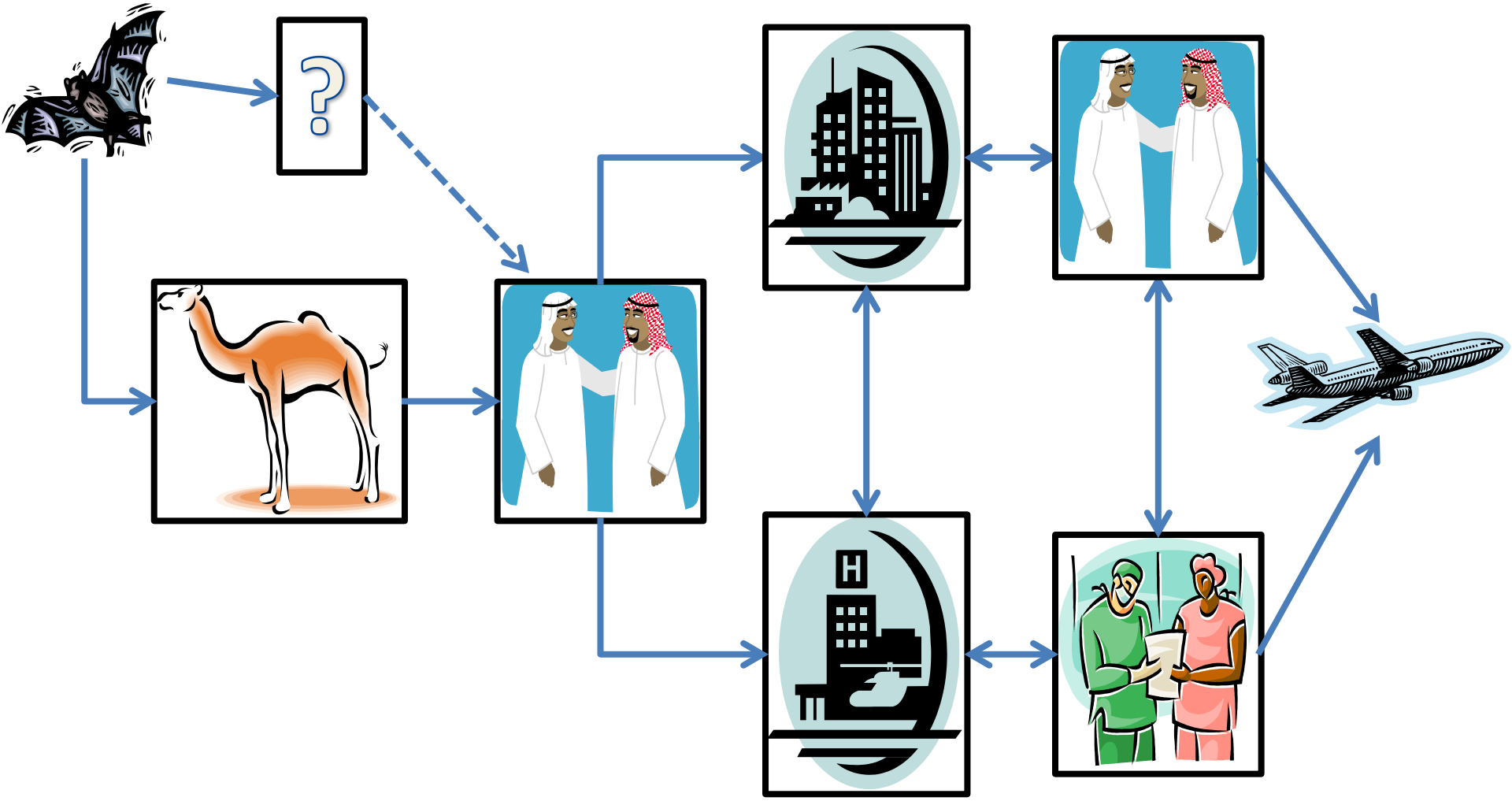
Saudi Arabia's Ministry of Health (MOH) today announced two new MERS-CoV cases, both of them involving men who had primary exposure to the virus, meaning they didn't contract their infections from another person.

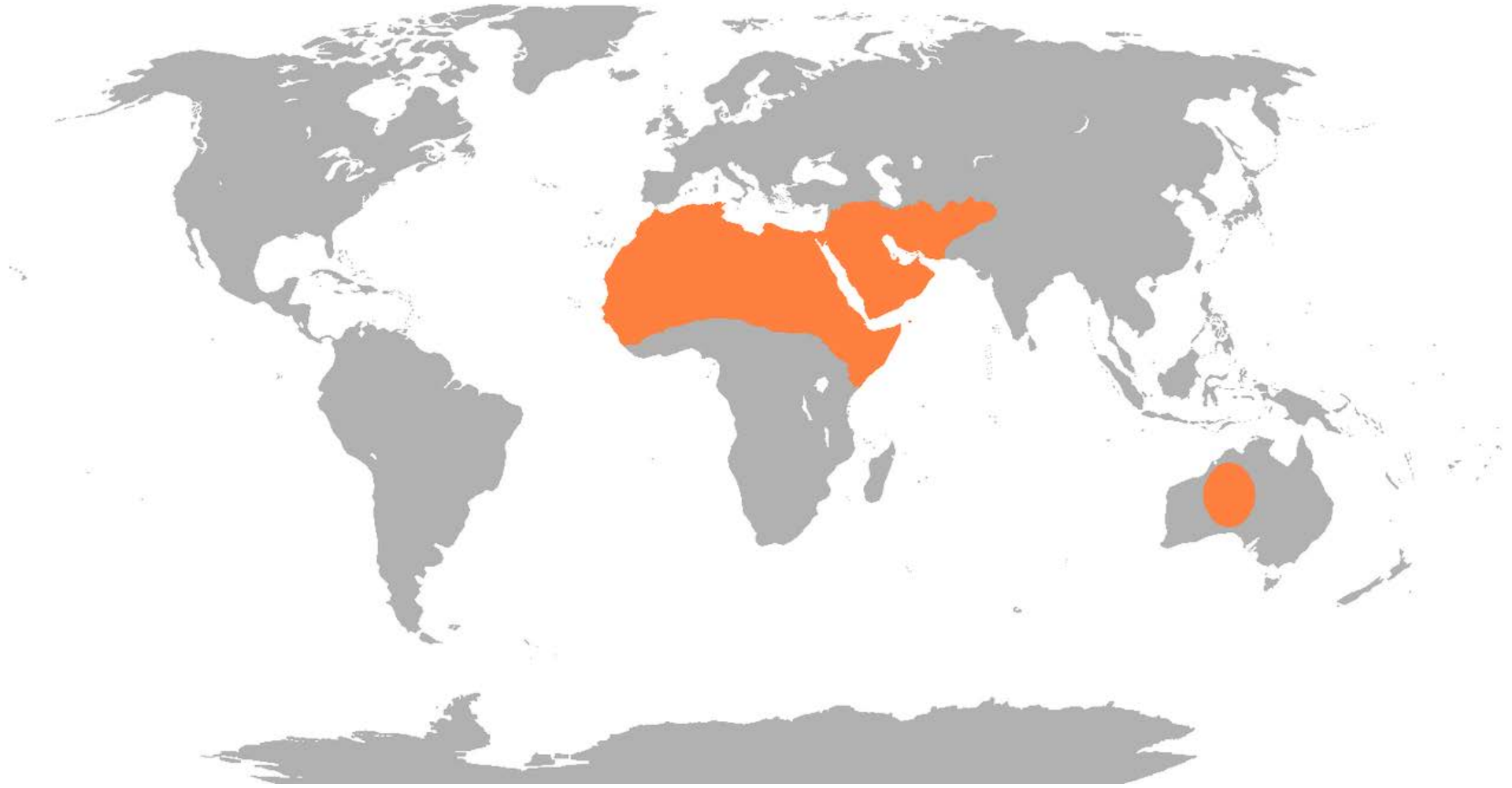
One of the patients is a 43-year-old expatriate from Riyadh who is not a healthcare worker and is listed in stable condition. The other is a 52-year-old Saudi man from Wadi Al Dawisir in the south central part of the country who is also in stable condition.

The pair of cases lifts Saudi Arabia's overall total MERS-CoV (Middle East respiratory syndrome coronavirus) cases to 1,456, of which 610 have proved fatal.

Sep 23 Saudi MOH statement

The MERS Transmission Model





Antibodies against MERS Coronavirus in Dromedary Camels, Kenya, 1992–2013

Victor M. Corman,[1] Joerg Jores,[1] Benjamin Meyer,[1] Mario Younan, Anne Liljander, Mohammed Y. Said, Ilona Gluecks, Erik Lattwein, Berend-Jan Bosch, Jan Felix Drexler, Set Bornstein, Christian Drosten, and Marcel A. Müller

Dromedary camels are a putative source for human infections with Middle East respiratory syndrome coronavirus. We showed that camels sampled in different regions in Kenya during 1992–2013 have antibodies against this virus. High densities of camel populations correlated with increased seropositivity and might be a factor in predicting long-term virus maintenance.

Middle East respiratory syndrome coronavirus (MERS-CoV) was discovered in a patient from Saudi Arabia in 2012 and has since caused ≥250 human infections and 93 deaths (*1*). The evolutionary origins of MERS-CoV and related viral species belonging to the genus *Betacoronavirus* clade C were attributed to insectivorous bats in Europe and Africa (*2–4*). Seroprevalence studies of livestock from diverse species showed that dromedary camels from Oman, Saudi Arabia, the United Arab Emirates, Jordan, Qatar, Spain, and Egypt harbored antibodies against MERS-CoV antigens (*5–8*). Direct evidence for MERS-CoV infection in camels has been found in Qatar, Saudi Arabia, and Egypt. Close similarity of camel-associated and human-associated MERS-CoV sequences suggests that camels are sources of infection for humans and might constitute a zoonotic animal reservoir (*5,9,10*). Where and when the putative introduction of MERS-CoV into camel populations took place and how the virus is maintained in camel populations remains obscure.

Author affiliations: University of Bonn Medical Centre, Bonn, Germany (V.M. Corman, B. Meyer, J.F. Drexler, C. Drosten, M.A. Müller); International Livestock Research Institute, Nairobi, Kenya (J. Jores, A. Liljander, M.Y. Said); Vétérinaires Sans Frontières Germany, Nairobi (M. Younan); Vétérinaires Sans Frontières Suisse, Nairobi (I. Gluecks); EUROIMMUN AG, Lübeck, Germany (E. Lattwein); Utrecht University, Utrecht, the Netherlands (B.-J. Bosch); and National Veterinary Institute, Uppsala, Sweden (S. Bornstein)

Most livestock camels slaughtered in the Arabian Peninsula and in Egypt are imported from the Greater Horn of Africa, in particular Ethiopia, Somalia, Sudan, and Kenya (*11,12*). We investigated MERS-CoV antibody levels and distribution patterns in farmed and nomadic camels from Kenya.

The Study

Samples were obtained from 774 dromedary camels in 3 regions in Kenya (Northeastern, Eastern, and Rift Valley [former administrative provinces]) and 7 counties (Mandera, Wajir, Isiolo, Marsabit, Laikipia, Turkana, and Baringo) during 1992–2013 (Figure). Blood samples were obtained from farmed or nomadic camels by jugular vein puncture. Serum samples originated from the archives of the International Livestock and Research Institute (ILRI) (Nairobi, Kenya). Ethical clearance for collection was part of the agreement between the Government of Kenya and ILRI, which provided ILRI with approval to broadly investigate livestock disease in Kenya.

All serum samples were tested for MERS-CoV antibodies by using a recombinant MERS-CoV spike protein subunit 1–based ELISA (rELISA) as described (*13*). Serum samples were used at a 1:100 dilution, which had been shown to be optimal for screening (*13*). A positive serum sample from recent studies (*6,13*) was used as a reference in all experiments. We used the assay-specific cutoff (optical density ratio 0.3) that had been validated in a previous study of camel serum samples (*13*). A total of 228 (29.5%) of 774 dromedary camels were rated MERS-CoV positive by the rELISA (Table 1). All 228 rELISA-positive serum samples from these 228 camels were subsequently tested at a 1:40 dilution by using an established recombinant immunofluorescence assay and Vero cells expressing MERS-CoV spike protein (*6*). This confirmatory assay showed that 213 (93.4%) of 228 rELISA-positive serum samples had MERS-CoV antibodies (Table 1).

As a final step, antibody specificity was confirmed by using a highly specific MERS-CoV microneutralization assay as described (*6*). All 228 rELISA-positive serum samples were tested at a starting dilution of 1:80 and an ending dilution of 1:800 to identify animals with high neutralization titers. A total of 119 (52.2%) 228 rELISA-positive serum samples had MERS-CoV neutralizing antibody titers (range 1:80–1:800) and 14 (6.1%) of 228 had high (>1:800) titers. The highly reactive camel serum samples originated from 3 counties (Wajir, Mandera, and Marsabit) in 2 regions (Northeastern and Eastern). The highest determined endpoint titer was 1:5,120.

Dromedary camels that had MERS-CoV antibodies were present at all sampling sites and during the 20-year

MERS Coronavirus Neutralizing Antibodies in Camels, Eastern Africa, 1983–1997

Marcel A. Müller,[1] Victor Max Corman,[1] Joerg Jores, Benjamin Meyer, Mario Younan, Anne Liljander, Berend-Jan Bosch, Erik Lattwein, Mosaad Hilali, Bakri E. Musa, Set Bornstein, and Christian Drosten

To analyze the distribution of Middle East respiratory syndrome coronavirus (MERS-CoV)–seropositive dromedary camels in eastern Africa, we tested 189 archived serum samples accumulated during the past 30 years. We identified MERS-CoV neutralizing antibodies in 81.0% of samples from the main camel-exporting countries, Sudan and Somalia, suggesting long-term virus circulation in these animals.

Since 2012, a newly emerged human pathogenic coronavirus (CoV) has caused an ongoing epidemic on the Arabian Peninsula. The designated Middle East respiratory syndrome (MERS)-CoV belongs to the *Betacoronavirus* genus lineage C and causes severe respiratory disease in humans (*1*). As of July 2, 2014, MERS-CoV has caused ≈842 human infections, including 322 deaths (*2*). Dromedary camels are a putative source for MERS-CoV infection in humans. Dromedaries from countries in Africa (Egypt, Tunisia, Nigeria, Sudan, Ethiopia, and Kenya) and Arabia (United Arab Emirates, Saudi Arabia, Oman, Qatar, and Jordan) have shown high rates of MERS-CoV seropositivity in serum samples collected during the past 2 decades (*3*–*9*). In addition, MERS-CoV nucleotide sequences and virus were detected in respiratory swab samples, predominantly from juvenile dromedaries (*5*,*10*). Transmission between humans and camels has been described in Qatar and Saudi Arabia (*11*,*12*). No autochthonous MERS-CoV infections in humans have been reported in Africa. Most dromedary camels traded in the Middle East are bred in the Greater Horn of Africa, primarily in Ethiopia, Sudan, Somalia, and Kenya (*13*). To further analyze the spatial and temporal distribution of MERS-CoV–seropositive camels, we tested archived camel serum samples originating in Egypt, Sudan, and Somalia, accumulated during the past 30 years, for MERS-CoV antibodies.

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The Study

A serum sample from each of 189 dromedary camels was collected by trained personnel as previously described (*14*). Blood samples were taken by jugular vein puncture. The blood was allowed to clot and subsequently centrifuged to obtain serum, or serum was separated from the coagulated blood during slaughter. All serum samples were heat-inactivated at 56°C for 30 min (*14*). Serum from Somalia was collected during 1983 and 1984; samples from Sudan were collected during June and July 1984, and samples from Egypt were collected during June and July 1997. All camels from Sudan were female (>6 years of age) and belonged to the Anafi breed. They were kept locally and used as a means of transport and a source of milk. The camels from Somalia were sampled at slaughterhouses in Afgoi and Mogadishu. Most camels were adults; however, detailed information about sex and age was not available. The camels from Somalia were bred predominantly for milk and meat. No background information was available for the camels from Egypt. Our study fully complied with national regulations and was approved by the ethics committee of the International Livestock Research Institute accredited by the National Council of Science and Technology in Kenya (approval no. ILRI-IREC2013–12).

We tested all serum samples for MERS-CoV antibodies at a 1:100 dilution by a recombinant MERS-CoV spike protein subunit 1–based ELISA (rELISA) as previously described (*3*,*12*). To determine the assay-specific cutoff value, we tested 124 confirmed MERS-CoV antibody–negative and 106 MERS-COV antibody–positive camel serum samples from previous studies (*3*). For inter-assay calibration, we used the same selected positive serum samples in all applications. The optical density (OD) was measured at 450/605 nm. We determined the OD ratio by dividing the OD of each sample by the OD of the positive serum. The cutoff was defined as the 3-fold mean OD ratio of all tested MERS-CoV antibody–negative serum samples (online Technical Appendix Figure 1, http://wwwnc.cdc.gov/EID/article/20/12/14-1026-Techapp1.pdf). To confirm antibody specificity and rule out possible cross-reactivity with other livestock-associated CoVs, we conducted a highly specific MERS-CoV

Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study

Marcel A Müller, Benjamin Meyer, Victor M Corman, Malak Al-Masri, Abdulhafeez Turkestani, Daniel Ritz, Andrea Sieberg, Souhaib Aldabbagh, Berend-J Bosch, Erik Lattwein, Raafat F Alhakeem, Abdullah M Assiri, Ali M Albarrak, Ali M Al-Shangiti, Jaffar A Al-Tawfiq, Paul Wikramaratna, Abdullah A Alrabeeah, Christian Drosten, Ziad A Memish**

Summary

Background Scientific evidence suggests that dromedary camels are the intermediary host for the Middle East respiratory syndrome coronavirus (MERS-CoV). However, the actual number of infections in people who have had contact with camels is unknown and most index patients cannot recall any such contact. We aimed to do a nationwide serosurvey in Saudi Arabia to establish the prevalence of MERS-CoV antibodies, both in the general population and in populations of individuals who have maximum exposure to camels.

Methods In the cross-sectional serosurvey, we tested human serum samples obtained from healthy individuals older than 15 years who attended primary health-care centres or participated in a national burden-of-disease study in all 13 provinces of Saudi Arabia. Additionally, we tested serum samples from shepherds and abattoir workers with occupational exposure to camels. Samples were screened by recombinant ELISA and MERS-CoV seropositivity was confirmed by recombinant immunofluorescence and plaque reduction neutralisation tests. We used two-tailed Mann Whitney *U* exact tests, χ^2, and Fisher's exact tests to analyse the data.

Findings Between Dec 1, 2012, and Dec 1, 2013, we obtained individual serum samples from 10 009 individuals. Anti-MERS-CoV antibodies were confirmed in 15 (0·15%; 95% CI 0·09–0·24) of 10 009 people in six of the 13 provinces. The mean age of seropositive individuals was significantly younger than that of patients with reported, laboratory-confirmed, primary Middle Eastern respiratory syndrome (43·5 years [SD 17·3] *vs* 53·8 years [17·5]; p=0·008). Men had a higher antibody prevalence than did women (11 [0·25%] of 4341 *vs* two [0·05%] of 4378; p=0·028) and antibody prevalence was significantly higher in central versus coastal provinces (14 [0·26%] of 5479 *vs* one [0·02%] of 4529; p=0·003). Compared with the general population, seroprevalence of MERS-CoV antibodies was significantly increased by 15 times in shepherds (two [2·3%] of 87, p=0·0004) and by 23 times in slaughterhouse workers (five [3·6%] of 140; p<0·0001).

Interpretation Seroprevalence of MERS-CoV antibodies was significantly higher in camel-exposed individuals than in the general population. By simple multiplication, a projected 44 951 (95% CI 26 971–71 922) individuals older than 15 years might be seropositive for MERS-CoV in Saudi Arabia. These individuals might be the source of infection for patients with confirmed MERS who had no previous exposure to camels.

Funding European Union, German Centre for Infection Research, Federal Ministry of Education and Research, German Research Council, and Ministry of Health of Saudi Arabia.

Introduction

As of March 8, 2015, Middle East respiratory syndrome coronavirus (MERS-CoV) has caused at least 1082 mostly severe cases of respiratory infection, 439 of these fatal, since its discovery in 2012.[1] Apart from its geographical focus in countries in and around the Arabian Peninsula and laboratory evidence of widespread infection of dromedary camels, little is known about the actual epidemiology of the disease in human beings.[1–5] Few primary infections were acquired through direct camel exposure, but the relevance of this infection pattern is unclear in the absence of systematic determinations of the proportion of infections in individuals who have had contact with camels.[5–7] Moreover, most reported patients with primary MERS-CoV infection have no history of camel exposure, suggesting the existence of other, as-yet-unknown sources of infection. Camel milk as a food-borne source seems unlikely.[8]

For secondary infections acquired through human-to-human contact, mathematical projections predicted that transmission chains in the population cannot be sustained.[9–11] The apparent transmission rate in household settings is low, with fewer than 50% of index patients transmitting the infection to contacts who subsequently had no pronounced clinical symptoms.[12] However, a highly fatal outbreak of MERS-CoV infection centred in Jeddah, Saudi Arabia, in March–April, 2014, was apparently caused by human-to-human transmission in several nosocomial settings, without any evidence that the causative virus differed from other MERS-CoV strains

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See Comment page 495

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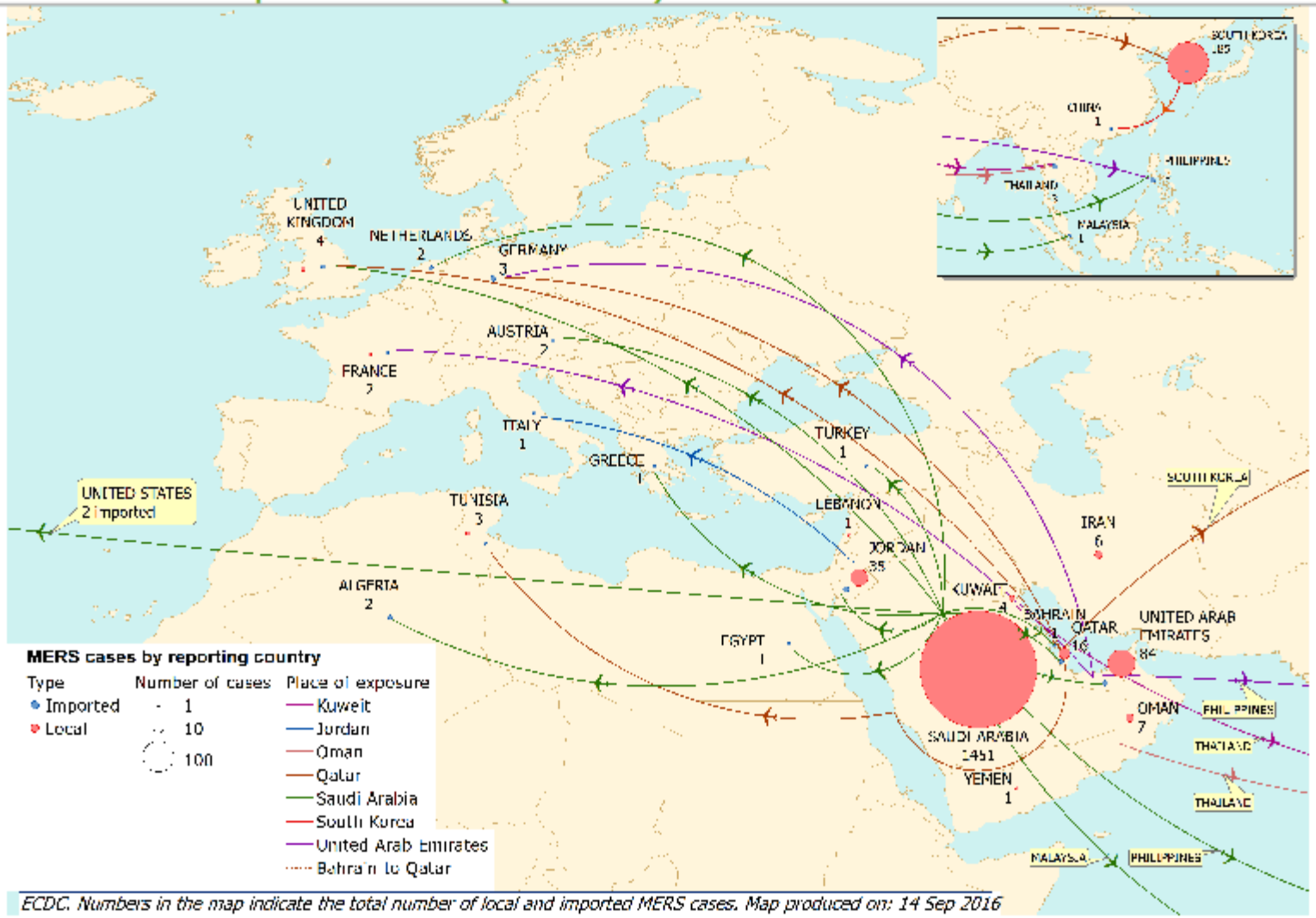
European Centre for Disease Prevention and Control

Distribution of confirmed cases of MERS-CoV by country of reporting and of exposure, March 2012 – 15 September 2016 (n=1 823)



ECDC. Numbers in the map indicate the total number of local and imported MERS cases. Map produced on: 14 Sep 2016

Health | Sun Jun 14, 2015 7:35pm EDT

Related: WORLD, HEALTH, SAUDI ARABIA

MERS cases in South Korea rise to 150 with five more, one death

SEOUL

South Korea's health ministry reported five new cases of Middle East Respiratory Syndrome (MERS) on Monday, taking the total to 150 in an outbreak that is the largest outside Saudi Arabia.

The ministry also said a patient infected with the MERS virus had died, the 16th fatality in an outbreak that began in May.

(Reporting by Ju-min Park; Editing by Paul Tait)

Joint MERS mission finds control lapses in complex outbreak

Filed Under: MERS-CoV

Lisa Schnirring | Staff Writer | CIDRAP News | Jun 13, 2015

A joint mission between the World Health Organization (WHO) and South Korean health officials to probe a MERS-CoV outbreak triggered by an infected traveler said the event is large and complex, but noted that the pattern resembles similar hospital-linked outbreaks in the Middle East.

PAHO/WHO

The WHO's Keiji Fukuda, MD.

The outbreak, which began with a single infected traveler in the middle of May, showed another spike in cases and deaths today, as South Korean health officials reported 12 more infections and 3 more deaths that boost the total to 138 illnesses, 14 of them fatal.

The closely watched event has shown how quickly MERS-CoV (Middle East respiratory syndrome coronavirus) can spread, even in a developed nation's best hospitals.

South Korea's surge of cases has raised worries about possible changes in the virus, but the joint mission said infection control lapses have played a role in the spread and that so far early gene sequencing studies have not found changes that would make the virus more transmissible.

Joint mission findings

An expert team from the WHO arrived in South Korea on Jun 10 for the 4-day joint mission and released its findings today at a media briefing and in joint statements posted on the WHO and South Korean health ministry Web site.

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CIDRAP Center for Infectious Disease Research and Policy

Korea highlights MERS super-spreaders, reports death

Filed Under: MERS-CoV

Jim Wappes | Editorial Director | CIDRAP News | Oct 26, 2015

South Korean health officials said yesterday that five super-spreaders caused 83% of cases in its MERS-CoV outbreak this year, and they confirmed a new death from the disease in a patient who had earlier tested negative.

Marcel Braendi / iStock

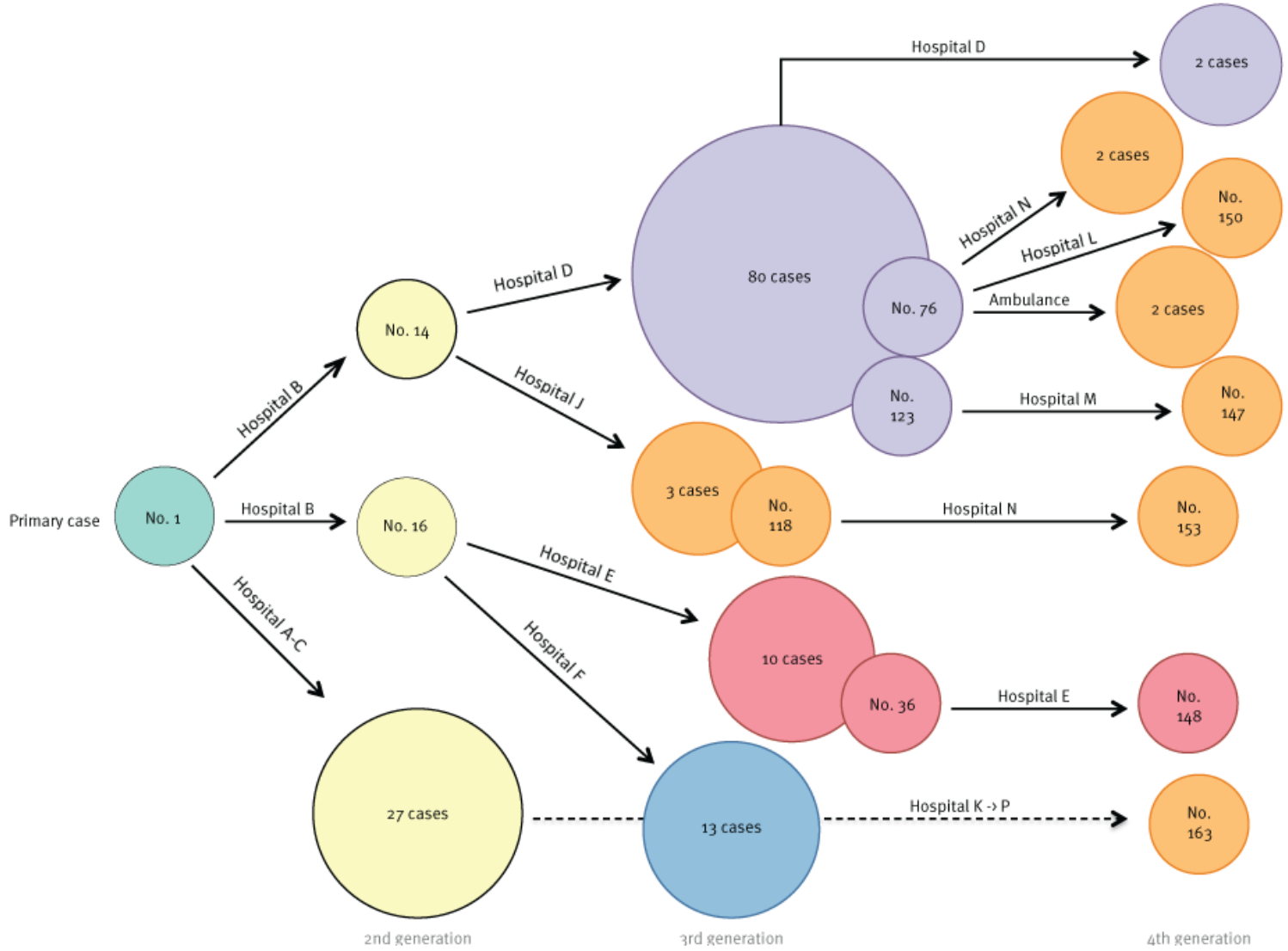
Major role of super-spreaders

The five super-spreaders, all of whom had pneumonia, transmitted the virus to 153 people all told out of the 186 MERS-CoV (Middle East respiratory syndrome coronavirus) cases confirmed this year in South Korea after a traveler brought the virus from the Middle East, *The Korea Herald* reported yesterday.

The findings were highlighted by the country's Centers for Disease Control and Prevention yesterday but were first published Sep 5 in the agency's journal *Osong Public Health and Research Perspectives*.

FIGURE 2

Simplified transmission diagram illustrating the superspreading events associated with Cases 1, 14, 16 and fourth-generation infections of MERS-CoV, South Korea, 11 May–19 June 2015 (n = 166)



MERS-CoV: Middle East respiratory syndrome coronavirus.

Source: *Cowling BJ, Park M, Fang VJ, et al. Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. Euro Surveill 2015 Jun 25;20(25):pii=21163*

AFP August 4, 2015 4:02 AM

South Korea president replaces health minister after MERS outbreak

South Korean President Park Geun-Hye on Tuesday replaced her health minister, who was widely blamed for the government's poor response to the outbreak of Middle East Respiratory Syndrome (MERS) that killed 36 people.

Moon Hyong-Pyo, who had offered to step down after apologising for the public anxiety caused by the biggest MERS outbreak outside Saudi Arabia, was replaced by Chung Chin-Youb, a Seoul National University hospital professor, the president's office said.

The cabinet change came a week after South Korea declared an effective end to the MERS outbreak, with one patient still undergoing treatment in hospital.

No additional MERS infections have been reported since July 4, but World Health Organisation standards call for a four-week waiting period after the last MERS patient fully recovers, before declaring the outbreak definitively over.

Thousands of schools were closed at the peak of the outbreak as anxious parents kept their children home.

The government introduced sweeping quarantine measures and confined nearly 17,000 people to their homes to restrict the spread of the virus to medical facilities.

Voice of America

S. Korea Hospital in Center of MERS Outbreak to Resume Services

Print Comment (1) Share:

FILE - Hospital workers wear masks as a precaution against the Middle East Respiratory Syndrome (MERS) virus as they work in front of an emergency room of Samsung Medical Center in Seoul, South Korea, June 7, 2015.

Reuters
July 17, 2015 1:42 AM

SEOUL, SOUTH KOREA—A South Korean hospital at the center of an outbreak of Middle East Respiratory Syndrome (MERS) will resume normal operations on Monday, the health ministry said, as a health scare that rattled the economy wanes, with no new cases reported since July 4.

South Korea's MERS outbreak was the largest outside Saudi Arabia, with 36 deaths and 186 people infected. It was traced to a South Korean man who returned from a business trip to the Middle East in May.

The Samsung Medical Center, a prominent Seoul hospital run by South Korea's massive Samsung Group, had suspended most services and taken no new patients for more than a month, to focus on stopping MERS, after nearly half of the cases were traced to it.

Assessing the South Korea MERS outbreak: could it happen elsewhere?

Published: Thursday 30 July 2015 at 8am PST

Over the past 2 months, South Korea has been gripped by an outbreak of the Middle East respiratory syndrome coronavirus, but earlier this week the country declared itself to be virtually free of the killer virus.

"It is the judgment of medical experts and the government that people can now feel safe," stated Prime Minister Hwang Kyo-ahn in a government meeting on Tuesday, following the removal of the last person from quarantine the previous day.

The outbreak has caused great alarm across the country, with schools closing, tourists canceling visits and its economy dramatically slowing down as a result of Middle East respiratory syndrome (MERS). To date, there have been 185 confirmed cases in the country, with 36 people dying from the virus.

While South Korea has announced a "de facto end" to the outbreak, the World Health Organization (WHO) will not confirm an end until 28 days have passed without any new infections being reported - the last reported infection in South Korea was on July 4th, 2015.

While South Korea have announced a "de facto end" to the outbreak, WHO will not confirm an end until 28 days have passed without any new infections being reported.

Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

First Confirmed Cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection in the United States, Updated Information on the Epidemiology of MERS-CoV Infection, and Guidance for the Public, Clinicians, and Public Health Authorities — May 2014

On May 14, 2014, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

Weekly
May 16, 2014 / 63(19);431-436

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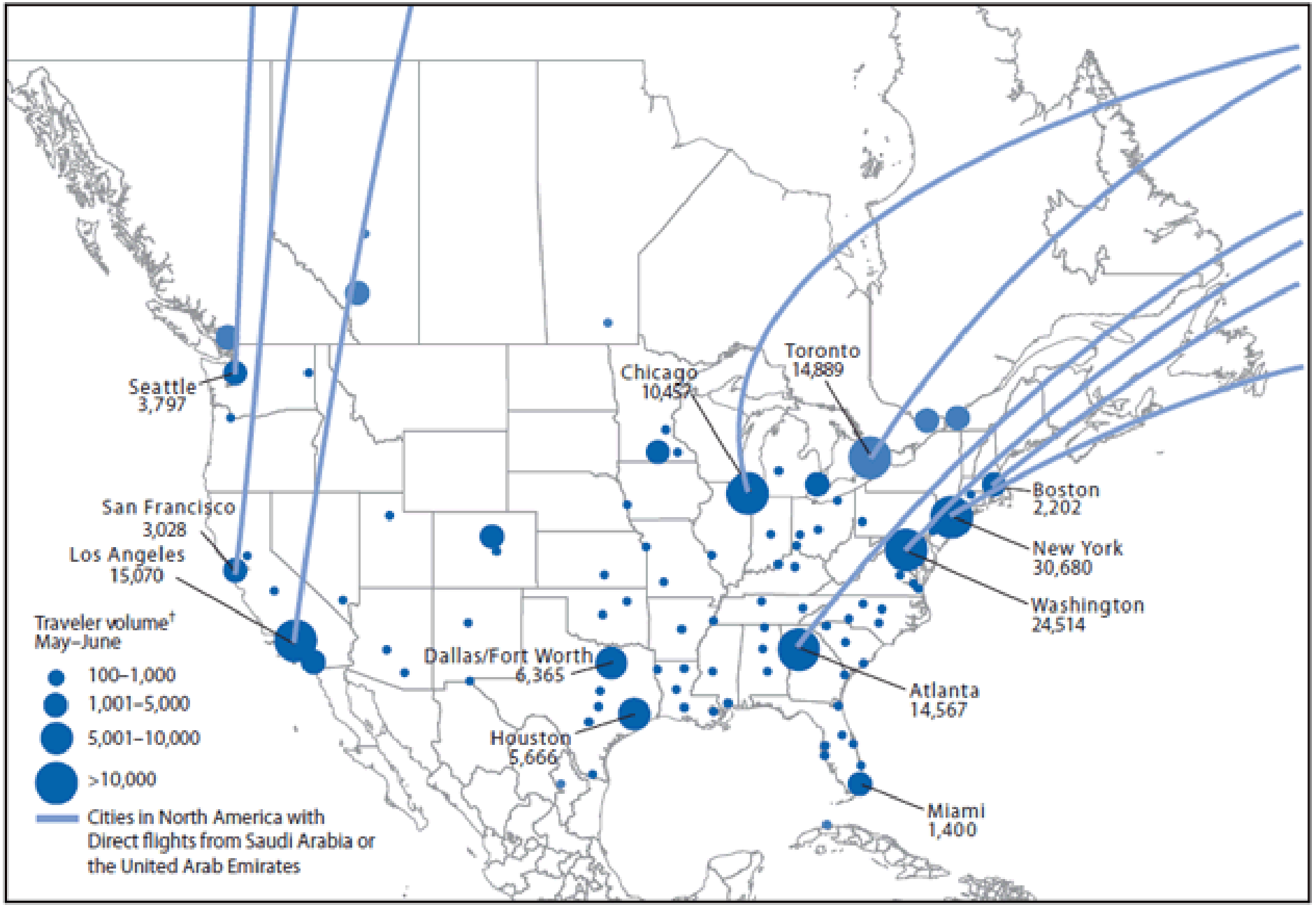
Seattle
3,797
San Francisco
3,028
Los Angeles
15,070
Chicago
10,457
Toronto
14,889
Boston
2,202
New York
30,680
Washington
24,514
Atlanta
14,567
Dallas/Fort Worth
6,365
Houston
5,666
Miami
1,400
Traveler volume†
May–June
100–1,000
1,001–5,000
5,001–10,000
>10,000
Cities in North America with
Direct flights from Saudi Arabia or
the United Arab Emirates

Agents of Concern

- Diseases with pandemic potential
  - Influenza
  - Antimicrobial resistance
- **Diseases resulting in outbreaks of regional critical importance**
  - Ebola
  - MERS
  - **Dengue, Chikungunya and Zika**
  - Yellow fever

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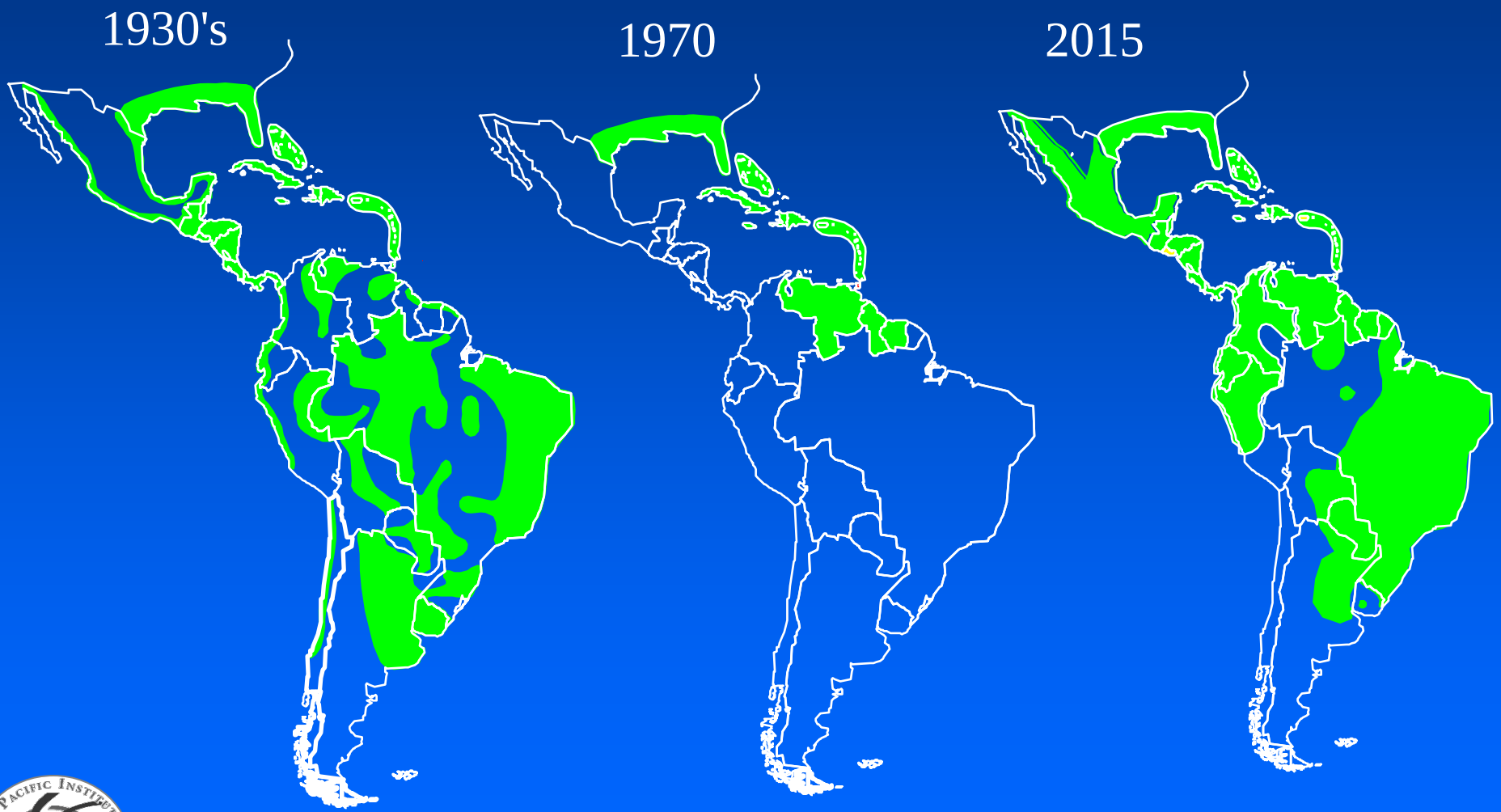
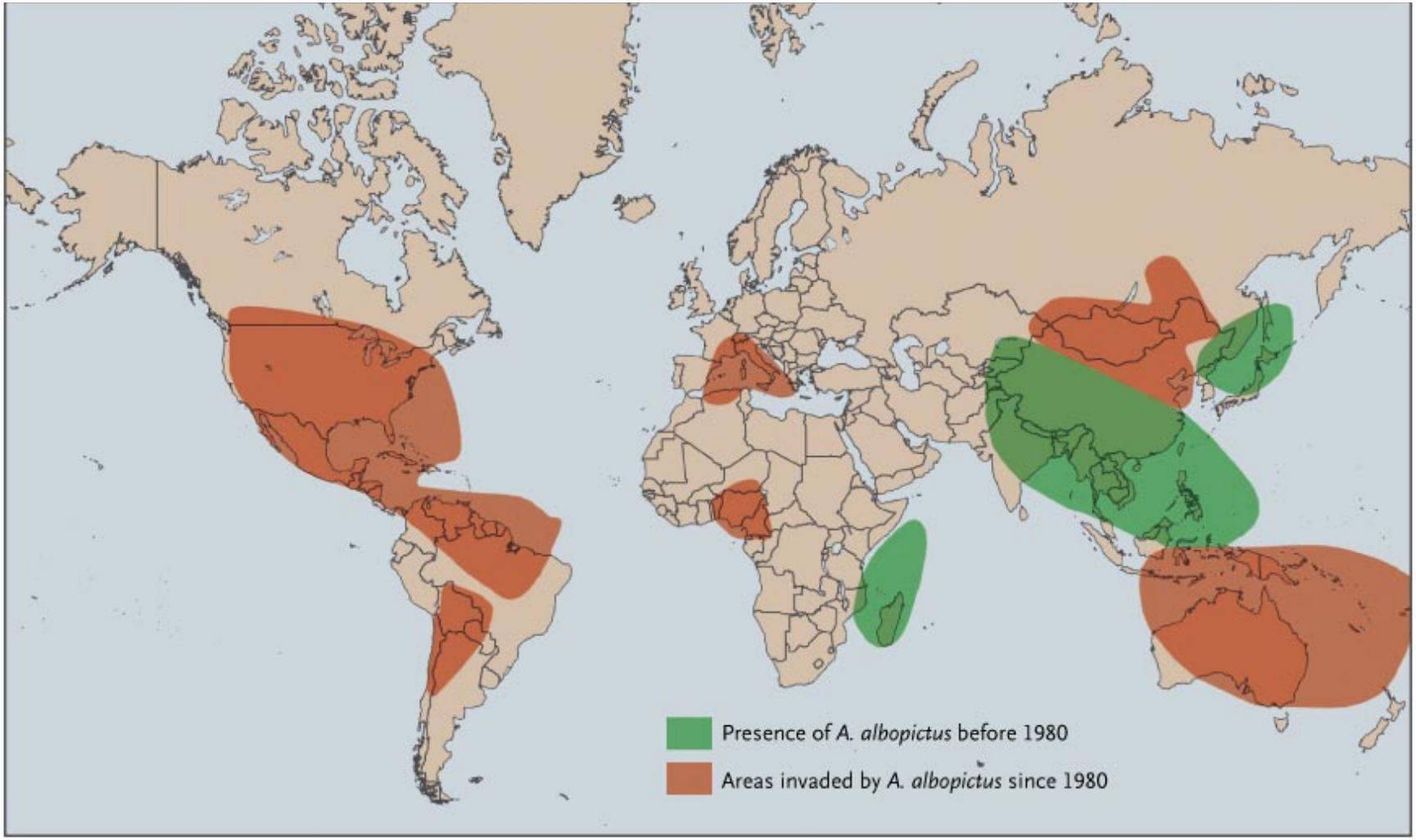
Aedes aegypti

Aedes aegypti Distribution in the Americas



Adapted from Gubler, 1998

World Distribution of the *Aedes albopictus* Mosquito



Charrel R et al. N Engl J Med 2007;356:769-771

The NEW ENGLAND JOURNAL of MEDICINE

About ESTIMATED range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2016 Maps

Aedes aegypti

Aedes albopictus


AQUI


BARRACA DA VÂNIA E JUNIOR

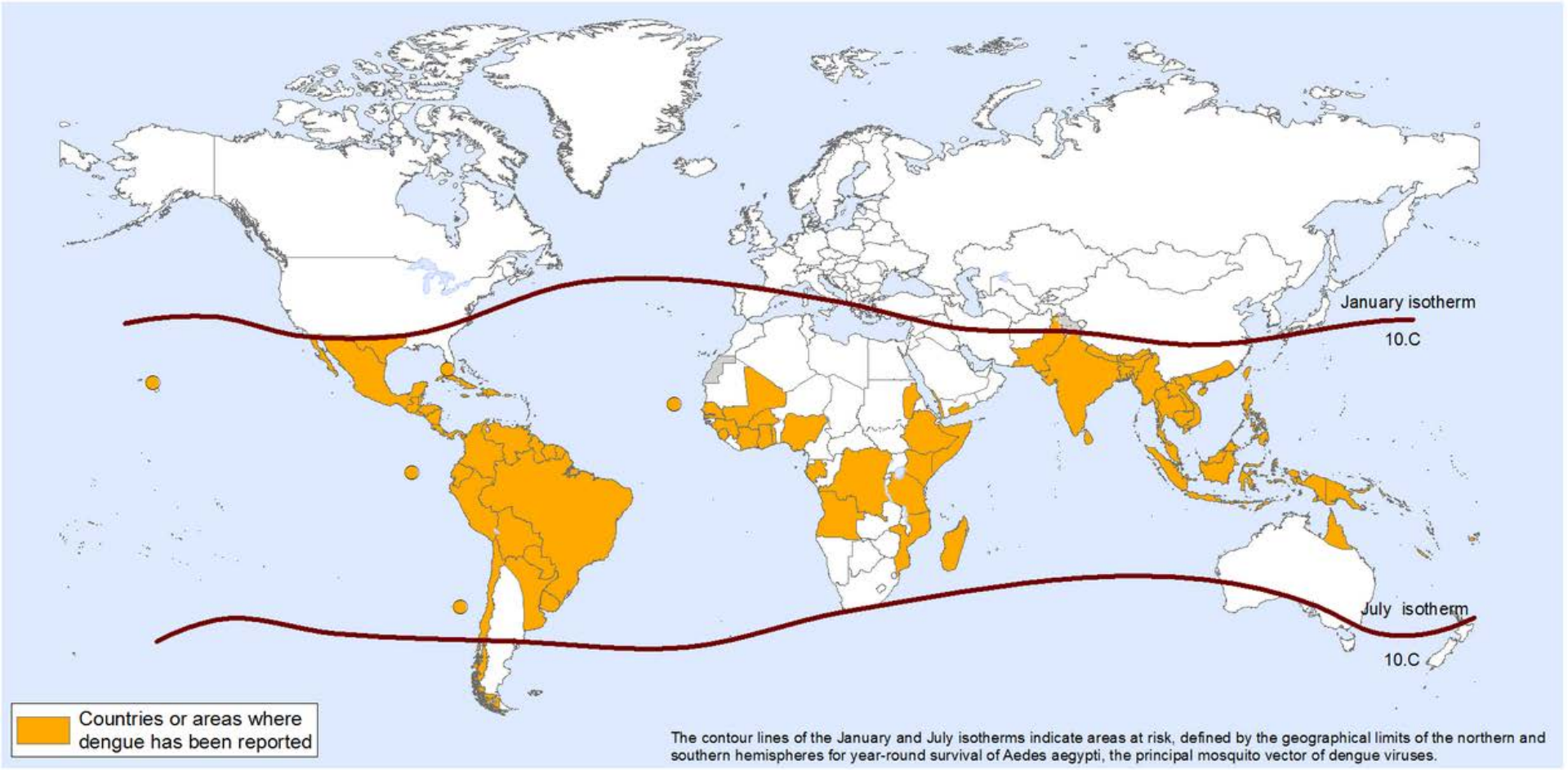
Global Burden of Dengue

- Some 2.5 billion people – two fifths of the world's population – are at risk from dengue.
- WHO estimates ~ 50 million dengue infections worldwide every year
- In 2014 there were more than 1,173,000 reported cases in the Americas
- Endemic in more than 100 countries
- Explosive outbreaks occur – In 2013, Brazil reported over 205,000 cases, in 7 weeks

Pan American Health Organization

World Health Organization

Dengue, countries or areas at risk, 2013



The contour lines of the January and July isotherms indicate areas at risk, defined by the geographical limits of the northern and southern hemispheres for year-round survival of Aedes aegypti, the principal mosquito vector of dengue viruses.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Published Date: 2013-12-09 12:31:29
Subject: PRO/EDR> Chikungunya (52): Caribbean (St Martin) alert
Archive Number: 20131209.2099940

CHIKUNGUNYA (52): CARIBBEAN (SAINT MARTIN) ALERT

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A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

Date: Fri 6 Dec 2013
Source: The Daily Herald [edited]
http://www.thedailyherald.com/index.php?option=com_content&view=article&id=44572

In St Martin, 2 cases of chikungunya [virus infection], a dengue-like sickness, have been confirmed following testing at the specialist laboratory in Marseille that returned positive results to Agence Regional de Sante (ARS [Regional Health Agency]) on 5 Dec 2013.

The disclosure was made by ARS Director-General Patrice Richard on Friday [6 Dec 2013] at a press conference in the Prefecture attended by Prefet Philippe Chopin, President of the Collectivity Aline Hanson, Dutch-side [St Maarten] Minister of Public Health Cornelius de Weever and specialist epidemiologists.

Richard said family doctors, for about 2 weeks, have been reporting cases of people showing suspected signs of chikungunya, and not dengue [virus infections]. There is no current evidence that chikungunya is on the Dutch side [of the island]. The virus can be imported by travelling from a risk country.

The 2 confirmed cases originated in French Quarter. In addition, there are currently 4 "probable" cases and 30 "suspected" cases, 15 of which are in the Oyster Pond area. In technical terms, "suspected" means just the signs are manifested while "probable" is a diagnostic test that calculates the likelihood that chikungunya [virus] has been contracted, according to epidemiologists.

ARS is awaiting more results of other cases from the Marseille laboratory.

"Chikungunya is in the Pacific islands, in Asia, in India, but never until now in the Caribbean islands," noted epidemiologist Marion Petit-Sinturel. "It's the 1st time we have located transmission here in St Martin."

ARS Director Pascal Godefroy said the situation is likely to change quickly as results come in. "This could be the beginning of an epidemic since we are already in a dengue epidemic," he said.

Minister de Weever acknowledged that "mosquitoes don't stop at the border," and assured the full cooperation of Dutch-side health authorities.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

News Scan for Sep 12, 2016

PAHO reports 510 new chikungunya cases

Countries and territories in the Americas reported only 510 new cases of chikungunya last week, raising the 2016 total to 253,020, the Pan American Health Organization (PAHO) reported late last week, while a new study notes that transmission from mothers to newborns is a concern.

Costa Rica reported the most new cases in the Sep 9 update. It had 223 new infections, bringing its 2016 total to 2,400 cases. Colombia was next with 138 new cases, and 18,697 total. Most countries, however, have not reported on their chikungunya cases for weeks, including Brazil, which has had by far the most cases this year (169,656).

The previous weekly PAHO updates included 1,428 and 290 new cases, respectively, in the Americas. PAHO reported no new deaths, keeping that number at 54.
Sep 9 PAHO report

In the study, published Sep 9 in the *International Journal of Infectious Diseases*, researchers analyzed data on 169 symptomatic newborns who had lab-confirmed chikungunya infections at four major hospitals in three Central and South American nations.

They found that the rates of transmission from mother to child ranged from 27.7% to 48.3%. Only one center reported deaths, for a case fatality rate in that hospital of 5.3%.
Sep 9 *Int J Infect Dis* study

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News Scan for Sep 19, 2016

PAHO reports about 2,000 new chikungunya cases

The Pan American Health Organization (PAHO) late last week reported 1,989 new chikungunya cases in the Americas, after 2 weeks of reporting cases below 1,000. The new cases raise the 2016 total to 255,009.

Almost all the new cases are from Panama, which had 1,788 new cases in the past month after reporting only 10 before, to bring its total this year to 1,798 cases.

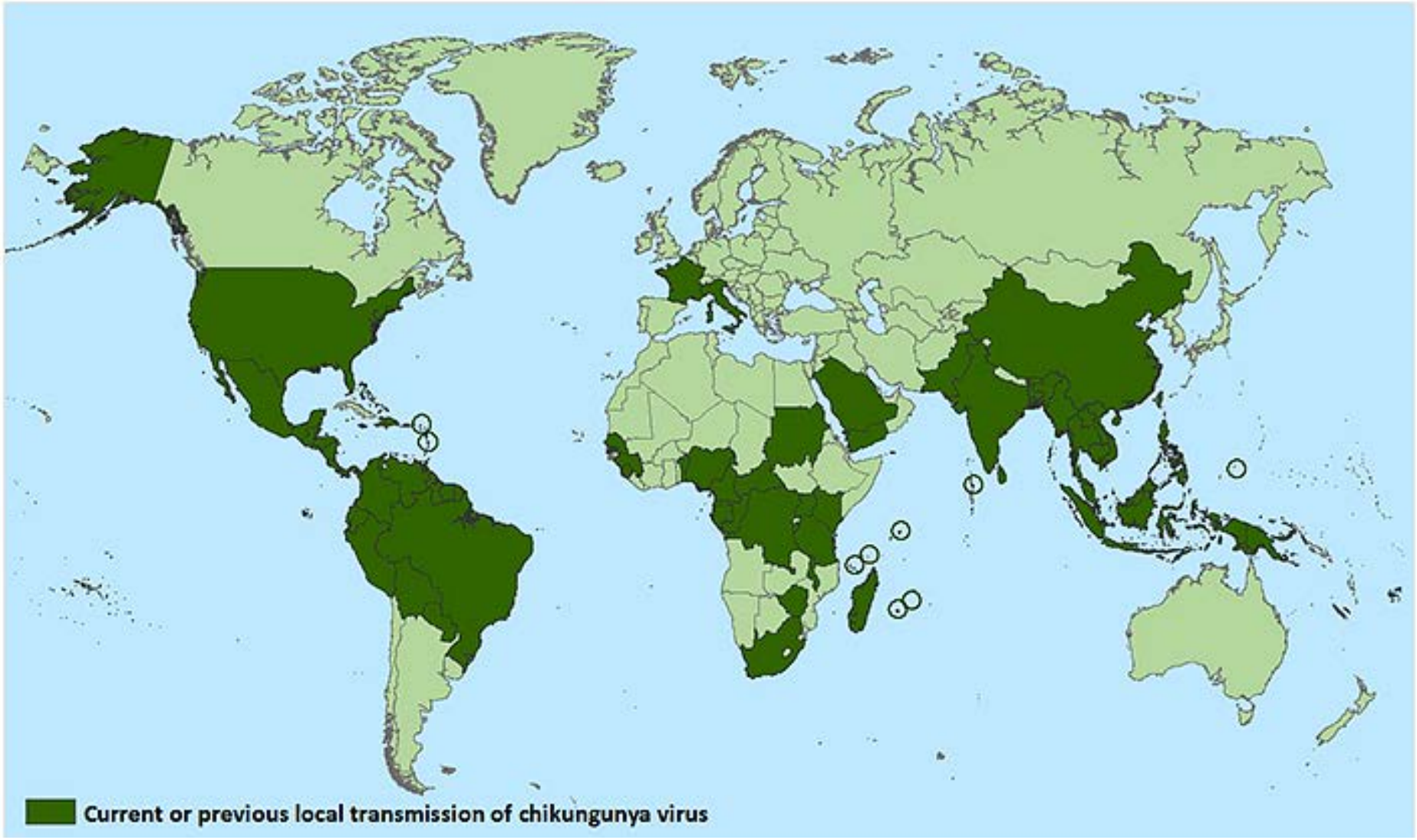
The previous weekly PAHO updates included 290 and 510 new cases, respectively. PAHO lowered the chikungunya-related death count by 1, to 53. Many countries have not reported on the disease for weeks.

The outbreak began in December 2013 on St. Martin in the Caribbean, with the first-ever cases in the Americas. Since then the region has logged 2,134,976 suspected, confirmed, and imported cases, according to PAHO statistics.

Sep 16 PAHO update

Countries and territories where chikungunya cases have been reported*

(as of October 20, 2015)



*Does not include countries or territories where only imported cases have been documented. This map is updated weekly if there are new countries or territories that report local chikungunya virus transmission.

Pan American Health Organization
World Health Organization
Americas

Epidemiological Alert

Zika virus infection

7 May 2015

The Pan American Health Organization (PAHO) / World Health Organization (WHO) recommends its Member States establish and maintain the capacity for Zika virus infection detection, clinical management and an effective public communication strategy to reduce the presence of the mosquito that transmits this disease, particularly in areas where the vector is present.

Situation summary

The Zika virus was first isolated in 1947 in Zika Forest (Uganda), in a Rhesus monkey during a study of the transmission of wild yellow fever. It was first isolated in humans in 1952 (Uganda, Tanzania).[1,2] In 1968 the virus was detected in human samples in Nigeria. [3,4]

In 2007 the first major outbreak of Zika virus fever occurred on the island of Yap (Micronesia) where 185 suspected cases were reported, of which 49 were confirmed and 59 were considered probable. The outbreak lasted 13 weeks (April to July). The probable vector was identified as being *Aedes hensilli*, however the presence of the virus in the mosquito could not be determined.

Subsequently an outbreak in French Polynesia, which began at the end of October 2013. Around 10,000 cases were registered, of which approximately 70 were severe cases, including neurological (Guillain Barré syndrome, meningoencephalitis) or autoimmune (thrombocytopenic purpura, leukopenia) complications. An investigation was carried out to determine the association between these complications and primary or secondary co-infection with other flaviviruses, especially dengue virus[5,6] The vectors responsible for transmission were *Aedes aegypti* and *Aedes polynesiensis*. In 2014, cases were also recorded in New Caledonia and in the Cook Islands.

To date, no death attributed to Zika virus infection has been reported in any of the outbreaks.

Zika virus infection

This is a disease caused by the Zika virus (ZIKAV), an arbovirus the flavivirus genus (family Flaviviridae), very close phylogenetically to viruses such as dengue, yellow fever, Japanese encephalitis, or West Nile virus.

The Zika virus is transmitted by mosquitoes of the genus Aedes, in urban areas (*A. aegypti*) as well as in the wild.

After an infected mosquito bite, the disease symptoms usually appear following an incubation period of three to twelve days.

The infection may present itself as asymptomatic or with a moderate clinical picture; no fatal cases have been detected to date.

In symptomatic cases, with **moderate disease**, the symptoms appear acutely and include fever, non-purulent conjunctivitis, headache, myalgia and arthralgia, asthenia, maculopapular rash, edema in the lower limbs and less frequently, retro-orbital pain, anorexia, vomiting, diarrhea, or abdominal pain. The symptoms last for 4-7 days and are self-limiting. Complications (neurological, autoimmune) are rare and have only been identified in the epidemic in French Polynesia.

RAPID RISK ASSESSMENT

Zika virus infection outbreak, French Polynesia

14 February 2014

Main conclusions and options for mitigation

- This is the first documented outbreak of Zika virus (ZIKAV) infection in French Polynesia and New Caledonia.
- During the course of the ZIKAV outbreak, neurological and auto-immune complications have been reported in a context of concurrent circulation of two dengue serotypes (dengue 1 and 3) since February 2013.
- Vigilance must be enhanced towards imported cases of ZIKAV infection in the EU Member States and EU overseas countries and territories and outermost regions, in particular where effective vectors are present; early detection of cases is essential to reduce the risk of autochthonous transmission.
- Clinicians and travel medicine clinics should be aware of the situation in the Pacific islands and include ZIKAV infection in their differential diagnosis. An isolated positive result for dengue IgM antibodies among travellers returning from areas affected by Zika should prompt a possible investigation for another flavivirus aetiology.
- The potential neurological and auto-immune complications might require specific healthcare capabilities and treatment (ICU) which need to be taken into account in an insular context facing a large-scale Zika outbreak.
- As an emerging pathogen, the laboratory capacity to confirm suspected Zika cases should be strengthened in the region as well as in Europe to differentiate ZIKAV infections from other arboviral dengue-like illnesses. Regional reference laboratories could provide support to confirm suspect cases.
- As many unanswered questions remain, further epidemiological and laboratory investigations could be conducted to establish:
  - evidence about eco-epidemiology of ZIKAV (viral strain genetic characteristics, transmission cycle(s), vectors and reservoir hosts) to assess its implications for public health;
  - the relationship between neurological and auto-immune complications and ZIKAV infection, notably with other aetiologies, previous infection with other infectious agents and human risk factors;
  - the performance of Zika serology and its cross-reactivity with other flaviviral infections;
  - the possibility of using urine samples for detection of the ZIKAV genome as well as other flaviviral infections.
- Blood safety authorities need to be vigilant regarding the epidemiological situation and should consider deferral of donors with travel history in line with measures defined for West Nile virus. Blood safety procedures are already in place in the Pacific region in the context of the ongoing outbreak of dengue and chikungunya and have included ZIKAV nucleic acid testing since early January 2014 in French Polynesia.

Suggested citation: European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia. 14 February 2014. Stockholm: ECDC; 2014.

The New York Times

SundayReview | OPINION

How Scared Should You Be About Zika?

By MICHAEL T. OSTERHOLM JAN. 29, 2016

Every time there is a major infectious disease outbreak that scares us — Ebola in West Africa in 2014, Middle East Respiratory Syndrome (MERS) on the Arabian Peninsula in 2012 and in South Korea in 2015, and now the Zika virus in South and Central America and the Caribbean — government leaders, the public and the news media demand explanations, guidance and predictions, and often express indignation that not enough was done to prevent it. Today everyone is asking about Zika: How did this crisis happen, and what do we need to do to make it go away? We immediately forget about the outbreak that came before it, and don't plan for the ones we know are on the horizon. Almost no one wants to talk about Ebola or MERS now, or what we have or haven't done to try to prevent an ugly recurrence.

When it comes to diseases, we have a very short attention span, and we tend to be reactive, rather than proactive. Instead of devoting ourselves to a comprehensive plan to combat microbial threats, we scramble to respond to the latest one in the headlines. There are lessons from previous infectious disease outbreaks that could and should have left us much better prepared than we are.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
February 10, 2016

Notes from the Field

Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses — Brazil, 2015

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Zika virus is a mosquito-borne flavivirus that is related to dengue virus and transmitted primarily by *Aedes aegypti* mosquitoes, with humans acting as the principal amplifying host during outbreaks. Zika virus was first reported in Brazil in May 2015 (*1*). By February 9, 2016, local transmission of infection had been reported in 26 countries or territories in the Americas.* Infection is usually asymptomatic, and, when symptoms are present, typically results in mild and self-limited illness with symptoms including fever, rash, arthralgia, and conjunctivitis. However, a surge in the number of children born with microcephaly was noted in regions of Brazil with a high prevalence of suspected Zika virus disease cases. More than 4,700 suspected cases of microcephaly were reported from mid-2015 through January 2016, although additional investigations might eventually result in a revised lower number (*2*). In response, the Brazil Ministry of Health established a task force to further investigate possible connections between the virus and brain anomalies in infants (*3*).

Since November 2015, CDC has been developing assays for Zika virus testing in formalin-fixed, paraffin-embedded (FFPE) tissue samples. In December 2015, FFPE tissues samples from two newborns (born at 36 and 38 weeks gestation) with microcephaly who died within 20 hours of birth and two miscarriages (fetal losses at 11 and 13 weeks) were submitted to CDC, from the state of Rio Grande do Norte in Brazil, for histopathologic evaluation and laboratory testing for suspected Zika virus infection. All four mothers had clinical signs of Zika virus infection, including fever and rash, during the first trimester of pregnancy, but did not have clinical signs of active infection at the time of delivery or miscarriage. The mothers were not tested for antibodies to Zika virus. Samples included brain and other autopsy tissues from the two newborns, a placenta from one of the newborns, and products of conception from the two miscarriages.

FFPE tissues were tested by Zika virus reverse transcription-polymerase chain reaction (RT-PCR) targeting the nonstructural protein 5 and envelope genes using general methods for RT-PCR (*4*), and by immunohistochemistry using a mouse polyclonal anti-Zika virus antibody, using methods previously described (*5*). Specific specimens from all four cases were positive by RT-PCR, and sequence analysis provided further evidence of Zika virus infection, revealing highest identities with Zika virus strains isolated from Brazil during 2015. In the newborns, only brain tissue was positive by RT-PCR assays. Specimens from two of the four cases were positive by immunohistochemistry: viral antigen was noted in mononuclear cells (presumed to be glial cells and neurons within the brain) of one newborn, and within the chorionic villi from one of the miscarriages. Testing for dengue virus was negative by RT-PCR in specimens from all cases.

For both newborns, significant histopathologic changes were limited to the brain, and included parenchymal calcification, microglial nodules, gliosis, and cell degeneration and necrosis. Other autopsy tissues and placenta had no significant findings. Tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV were negative in the two mothers who experienced miscarriages. Placental tissue from one miscarriage showed heterogeneous chorionic villi with calcification, fibrosis, perivillous fibrin deposition, and patchy intervillositis and focal villitis, while tissue from the other miscarriage had sparsely sampled normal-appearing chorionic villi.

* Updated information about local transmission of Zika virus is available online (http://www.cdc.gov/zika/geo/index.html).

BRIEF REPORT

Zika Virus Associated with Microcephaly

Jernej Mlakar, M.D., Misa Korva, Ph.D., Nataša Tul, M.D., Ph.D., Mara Popović, M.D., Ph.D., Mateja Poljšak-Prijatelj, Ph.D., Jerica Mraz, M.Sc., Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnaver Vipotnik, M.D., Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D., Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

SUMMARY

A widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 in South and Central America and the Caribbean. A major concern associated with this infection is the apparent increased incidence of microcephaly in fetuses born to mothers infected with ZIKV. In this report, we describe the case of an expectant mother who had a febrile illness with rash at the end of the first trimester of pregnancy while she was living in Brazil. Ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta. After the mother requested termination of the pregnancy, a fetal autopsy was performed. Micrencephaly (an abnormally small brain) was observed, with almost complete agyria, hydrocephalus, and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. ZIKV was found in the fetal brain tissue on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, with consistent findings on electron microscopy. The complete genome of ZIKV was recovered from the fetal brain.

ZIKV, AN EMERGING MOSQUITO-BORNE FLAVIVIRUS, WAS INITIALLY ISOlated from a rhesus monkey in the Zika forest in Uganda in 1947.[1] It is transmitted by various species of aedes mosquitoes. After the first human ZIKV infection, sporadic cases were reported in Southeast Asia and sub-Saharan Africa.[2] ZIKV was responsible for the outbreak in Yap Island of Micronesia in 2007 and for major epidemics in French Polynesia, New Caledonia, the Cook Islands, and Easter Island in 2013 and 2014.[3,4] In 2015, there was a dramatic increase in reports of ZIKV infection in the Americas. Brazil is the most affected country, with preliminary estimates of 440,000 to 1.3 million cases of autochthonous ZIKV infection reported through December 2015.[5]

The classic clinical picture of ZIKV infection resembles that of dengue fever and chikungunya and is manifested by fever, headache, arthralgia, myalgia, and maculopapular rash, a complex of symptoms that hampers differential diagnosis. Although the disease is self-limiting, cases of neurologic manifestations and the Guillain–Barré syndrome were described in French Polynesia and in Brazil during ZIKV epidemics.[5,6] Recent reports from the Ministry of Health of Brazil suggest that cases of microcephaly have increased by a factor of approximately 20 among newborns in the northeast region of the country, which indicates a possible association between ZIKV infection in pregnancy and fetal malformations.[5]

We present a case of vertical transmission of ZIKV in a woman who was prob-

From the Institute of Pathology, Faculty of Medicine (J. Mlakar, M. Popović, J. Mraz, A.V., J.P.), and the Institute of Microbiology and Immunology, Faculty of Medicine (M. Korva, M.P.-P., M. Kolenc, K.R.R., M. Petrovec, T.A.Z.), University of Ljubljana, and the Department of Perinatology, Division of Gynecology and Obstetrics (N.T., V.F.V.), and the Institute of Radiology (T.V.V.), University Medical Center Ljubljana — all in Ljubljana, Slovenia. Address reprint requests to Dr. Avšič Županc at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Zaloška 4, Ljubljana 1000, Slovenia, or at tatjana.avsic@mf.uni-lj.si.

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ORIGINAL ARTICLE

Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

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ABSTRACT

BACKGROUND

Zika virus (ZIKV) has been linked to neonatal microcephaly. To characterize the spectrum of ZIKV disease in pregnancy, we followed patients in Rio de Janeiro to describe clinical manifestations in mothers and repercussions of acute ZIKV infection in fetuses.

METHODS

We enrolled pregnant women in whom a rash had developed within the previous 5 days and tested blood and urine specimens for ZIKV by reverse-transcriptase–polymerase-chain-reaction assays. We followed the women prospectively and collected clinical and ultrasonographic data.

RESULTS

A total of 88 women were enrolled from September 2015 through February 2016; of these 88 women, 72 (82%) tested positive for ZIKV in blood, urine, or both. The timing of acute ZIKV infection ranged from 5 to 38 weeks of gestation. Predominant clinical features included pruritic descending macular or maculopapular rash, arthralgias, conjunctival injection, and headache; 28% had fever (short-term and low-grade). Women who were positive for ZIKV were more likely than those who were negative for the virus to have maculopapular rash (44% vs. 12%, P=0.02), conjunctival involvement (58% vs. 13%, P=0.002), and lymphadenopathy (40% vs. 7%, P=0.02). Fetal ultrasonography was performed in 42 ZIKV-positive women (58%) and in all ZIKV-negative women. Fetal abnormalities were detected by Doppler ultrasonography in 12 of the 42 ZIKV-positive women (29%) and in none of the 16 ZIKV-negative women. Adverse findings included fetal deaths at 36 and 38 weeks of gestation (2 fetuses), in utero growth restriction with or without microcephaly (5 fetuses), ventricular calcifications or other central nervous system (CNS) lesions (7 fetuses), and abnormal amniotic fluid volume or cerebral or umbilical artery flow (7 fetuses). To date, 8 of the 42 women in whom fetal ultrasonography was performed have delivered their babies, and the ultrasonographic findings have been confirmed.

CONCLUSIONS

Despite mild clinical symptoms, ZIKV infection during pregnancy appears to be associated with grave outcomes, including fetal death, placental insufficiency, fetal growth restriction, and CNS injury.

From Fundação Oswaldo Cruz, Rio de Janeiro (P.B., J.P.P.J., L.D., M.W., R.M.R.N., P.C.S., A.M.S., L.M.A.C., D.C.C., G.A.C., E.S.N., M.E.M., A.E.R.B., P.R.N.C., A.M.B.F.); Biomedical Research Institute of Southern California, Oceanside (C.R.G.); and David Geffen UCLA School of Medicine, Los Angeles (C.J., S.G.V., J.D.C., K.N.-S.). Address reprint requests to Dr. Nielsen-Saines at the Division of Pediatric Infectious Diseases, David Geffen School of Medicine at UCLA, MDCC 22-442, 10833 LeConte Ave., Los Angeles, CA 90095, or at knielsen@mednet.ucla.edu.

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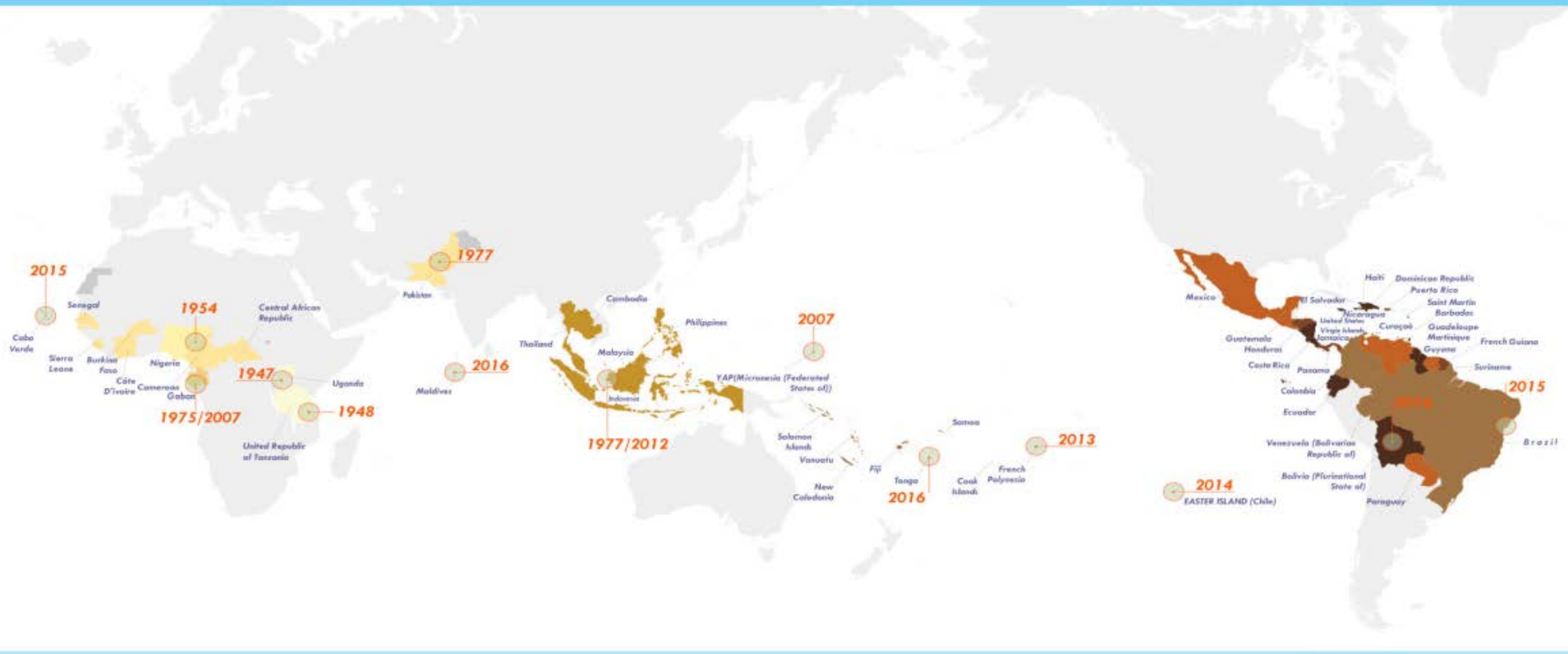
World Health Organization

Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)



European Centre for Disease Prevention and Control

Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past three months, as of 23 September 2016

ECDC

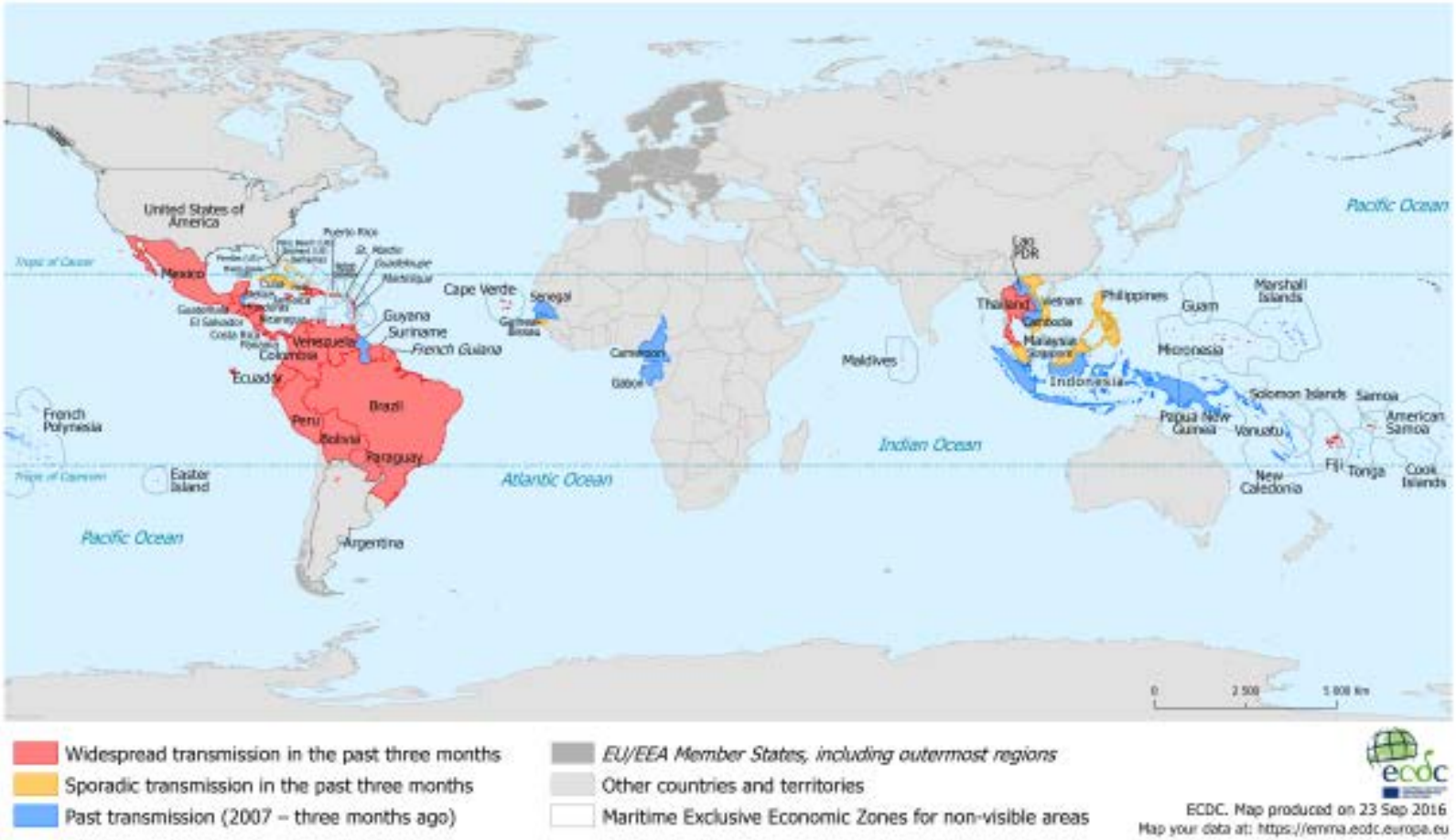
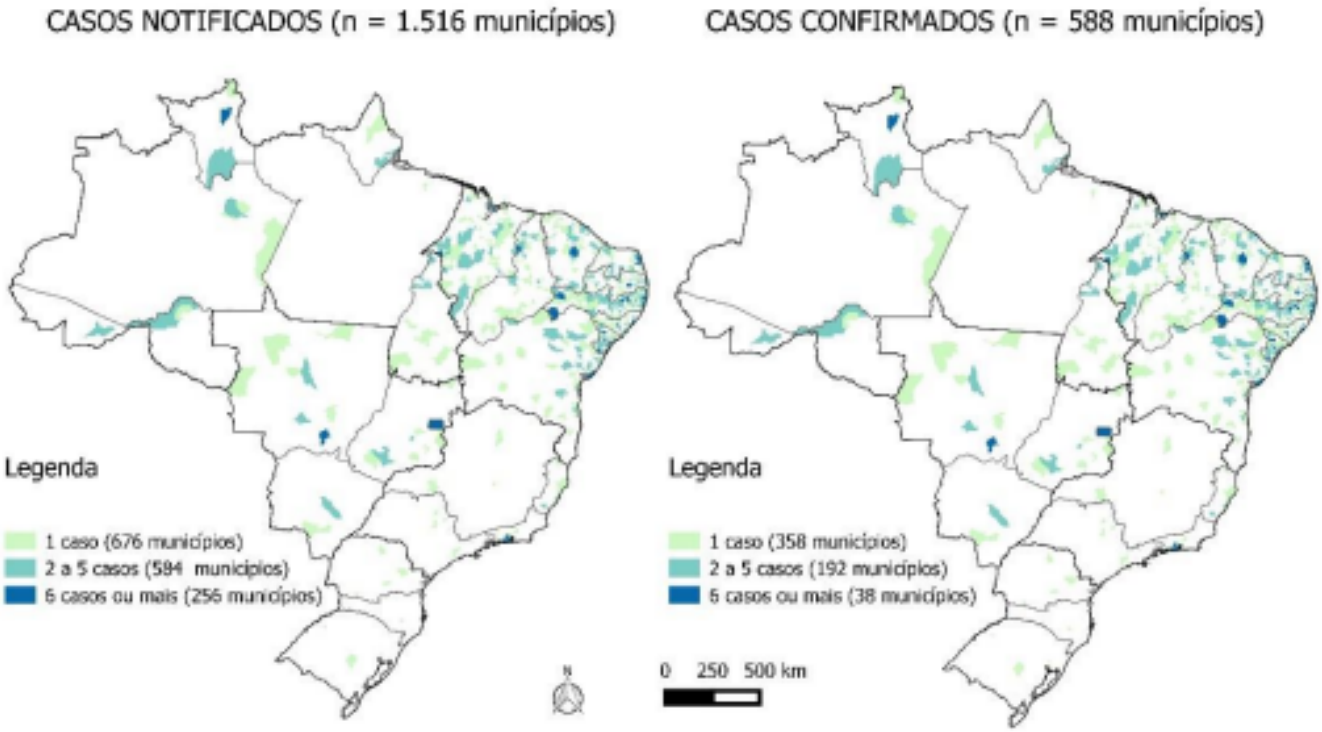


Figura 1 – Distribuição espacial com casos notificados e confirmados de microcefalia e/ou alteração do SNC, Brasil, até a SE 26/2016.



Fonte: Secretarias de Saúde dos Estados e Distrito Federal (dados atualizados até 02/07/2016).

ORIGINAL ARTICLE

Guillain–Barré Syndrome Associated with Zika Virus Infection in Colombia

Beatriz Parra, Ph.D., Jairo Lizarazo, M.D., Jorge A. Jiménez-Arango, M.D., Andrés F. Zea-Vera, M.D., Ph.D., Guillermo González-Manrique, M.D., José Vargas, M.D., Jorge A. Angarita, M.D., Gonzalo Zuñiga, M.D., Reydmar Lopez-Gonzalez, M.D., Cindy L. Beltran, M.D., Karen H. Rizcala, M.D., Maria T. Morales, M.D., Oscar Pacheco, M.D., Martha L. Ospina, M.D., Anupama Kumar, M.B., B.S., David R. Cornblath, M.D., Laura S. Muñoz, M.D., Lyda Osorio, M.D., Ph.D., Paula Barreras, M.D., and Carlos A. Pardo, M.D.

ABSTRACT

BACKGROUND

Zika virus (ZIKV) infection has been linked to the Guillain–Barré syndrome. From November 2015 through March 2016, clusters of cases of the Guillain–Barré syndrome were observed during the outbreak of ZIKV infection in Colombia. We characterized the clinical features of cases of Guillain–Barré syndrome in the context of this ZIKV infection outbreak and investigated their relationship with ZIKV infection.

METHODS

A total of 68 patients with the Guillain–Barré syndrome at six Colombian hospitals were evaluated clinically, and virologic studies were completed for 42 of the patients. We performed reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for ZIKV in blood, cerebrospinal fluid, and urine, as well as antiflavivirus antibody assays.

RESULTS

A total of 66 patients (97%) had symptoms compatible with ZIKV infection before the onset of the Guillain–Barré syndrome. The median period between the onset of symptoms of ZIKV infection and symptoms of the Guillain–Barré syndrome was 7 days (interquartile range, 3 to 10). Among the 68 patients with the Guillain–Barré syndrome, 50% were found to have bilateral facial paralysis on examination. Among 46 patients in whom nerve-conduction studies and electromyography were performed, the results in 36 patients (78%) were consistent with the acute inflammatory demyelinating polyneuropathy subtype of the Guillain–Barré syndrome. Among the 42 patients who had samples tested for ZIKV by RT-PCR, the results were positive in 17 patients (40%). Most of the positive RT-PCR results were in urine samples (in 16 of the 17 patients with positive RT-PCR results), although 3 samples of cerebrospinal fluid were also positive. In 18 of 42 patients (43%) with the Guillain–Barré syndrome who underwent laboratory testing, the presence of ZIKV infection was supported by clinical and immunologic findings. In 20 of these 42 patients (48%), the Guillain–Barré syndrome had a parainfectious onset. All patients tested were negative for dengue virus infection as assessed by RT-PCR.

CONCLUSIONS

The evidence of ZIKV infection documented by RT-PCR among patients with the Guillain–Barré syndrome during the outbreak of ZIKV infection in Colombia lends support to the role of the infection in the development of the Guillain–Barré syndrome. (Funded by the Bart McLean Fund for Neuroimmunology Research and others.)

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EDITORIAL

Zika Getting on Your Nerves? The Association with the Guillain–Barré Syndrome

Jennifer A. Frontera, M.D., and Ivan R.F. da Silva, M.D., Ph.D.

Parra and colleagues[1] report in the *Journal* the results of a prospective study of 68 Colombian patients who had a syndrome consistent with the Guillain–Barré syndrome, 66 of whom had previously had symptoms of Zika virus (ZIKV) infection. Major strengths of this study include the documentation of a temporal relationship between the Guillain–Barré syndrome and ZIKV infection (marked by a substantial increase in the incidence of the Guillain–Barré syndrome after the introduction of ZIKV, from 20 to 90 cases per month throughout Colombia), the criteria applied for the diagnosis of the Guillain–Barré syndrome, and the molecular and serologic flavivirus data from analyses of serum, cerebrospinal fluid (CSF), and urine.

However, the difficulties related to diagnosing ZIKV infection are multifold. First, the symptoms associated with ZIKV infection are similar to those caused by dengue virus (DENV) and chikungunya virus, both of which are endemic in Colombia. Second, the serologic cross-reactivity among flaviviruses (including yellow fever virus, West Nile virus, DENV, and Japanese encephalitis virus) have been well described.[2] Although the Centers for Disease Control and Prevention (CDC) recommends neutralizing antibody testing with a plaque-reduction neutralization test to distinguish among flaviviruses,[3] this testing is expensive, requires cell culture, and is also susceptible to cross-reactivity.[4] Polymerase-chain-reaction (PCR) testing can definitively identify ZIKV, but molecular studies of serum are usually sensitive only during the first week after infection. Because the Guillain–Barré syndrome has been linked to microbial pathogens through a molecular mimicry mechanism, it is typically diagnosed 1 week or longer after an infection. Indeed, Parra et al. observed that the median time to onset of the Guillain–Barré syndrome was 7 days after ZIKV infection.

The authors deal with these diagnostic dilemmas by showing that ZIKV PCR testing of other body fluids (particularly urine) may remain sensitive for a longer duration than does testing of serum. Indeed, in 13 patients, ZIKV PCR results were positive only in urine, whereas serum, CSF, or both were PCR-negative when tested in a similar time frame. IgM antibody testing of CSF for both ZIKV and DENV may be another diagnostic strategy, since the IgM pentamer is too large to cross the blood–brain barrier.[5] Therefore, CSF that is positive for ZIKV IgM and negative for DENV IgM would be suggestive of a primary central nervous system ZIKV infection. Of the patients who tested positive for ZIKV by PCR and underwent CSF IgM testing, 8 were PCR-positive but ZIKV IgM–negative in CSF, which suggested that ZIKV PCR testing of urine may be more sensitive than serologic testing of CSF.

The difficulties in diagnosing ZIKV infection are borne out in this study, as only 17 patients had definitive laboratory evidence of recent ZIKV infection. On the basis of Table S5 in the Parra et al. Supplementary Appendix, of these 17 patients, only 14 had electrophysiological data consistent with the Guillain–Barré syndrome and therefore could have met Brighton level 1 diagnostic criteria for the syndrome, although the actual number of patients meeting level 1 criteria may have been

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Zika prompts FDA to curb blood collection in Florida

Filed Under: Zika

Lisa Schnirring | News Editor | CIDRAP News | Jul 28, 2016

Based on Florida's investigation into the first possible locally acquired Zika virus cases in the continental United States, the US Food and Drug Administration (FDA) yesterday asked blood establishments in the two affected neighboring counties to immediately stop collecting blood.

vladm / iStock

In other developments, Zika infection numbers in Puerto Rico continue to rise at a fast clip, along with further increases in US travelers, including several pregnant women.

Testing, pathogen inactivation in blood

The blood collection step, which affects Broward and Miami-Dade counties, is a temporary measure to protect the blood supply until the blood groups are able to screen each unit of blood for Zika RNA or implement approved or investigational pathogen inactivation technology, the FDA said in its statement yesterday.

The Florida Department of Health (Florida Health) is investigating four suspected locally acquired Zika cases, two in each of the counties. In an update today, Florida Health reported two more travel-linked cases, both of them in pregnant women. Overall, the state has recorded 328 travel-related Zika cases, plus 55 more in pregnant women.

CORRESPONDENCE

Fatal Zika Virus Infection with Secondary Nonsexual Transmission

TO THE EDITOR: Epidemic transmission of Zika virus (ZIKV) has rapidly occurred in the Americas, with most cases limited to mild or asymptomatic disease.[1,2] To date, nine deaths from ZIKV infection that were unrelated to the Guillain–Barré syndrome have been confirmed in adults.[1] Here, we report a rapidly progressive, fatal ZIKV infection acquired outside the United States and secondary local transmission in the absence of known risk factors for ZIKV infection.

Patient 1, a 73-year-old man who had emigrated to the United States from Mexico in 2003, was admitted to a hospital in Salt Lake City with hypotension and abdominal pain. Radiation therapy for stage IIB prostate cancer had been completed 1 month earlier, and he was receiving antiandrogen therapy but was otherwise not systemically immunocompromised. Eight days before admission, he had returned from a 3-week trip to the southwest coast of Mexico, where ZIKV transmission had been reported. He was well during his trip but reported being bitten by mosquitoes. After returning home, he reported having abdominal pain, pharyngitis, and fever, which was followed by conjunctivitis, nonbloody diarrhea, and myalgias.

On the day of admission, hypotension and dyspnea had developed. The patient was alert and oriented with no fever but with tachypnea and tachycardia. He remained hypotensive after the administration of intravenous fluids, and vasopressors and broad-spectrum antibiotics were initiated. The physical examination was remarkable for marked erythematous conjunctivitis with profuse tearing and soft-palate petechiae, tachypnea, and moderate, diffuse abdominal pain with mild guarding. A tourniquet test (which is often performed in patients in whom dengue is suspected) was negative.

Laboratory testing revealed metabolic acidosis, an elevated venous lactate level, renal insufficiency, mild hypoglycemia, elevated aminotransferase levels, leukocytosis with 44% band forms, anemia, and marked thrombocytopenia. (Details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.) Testing for malaria and blood cultures were negative. A presumptive diagnosis of dengue shock syndrome was made. The patient's clinical deterioration progressed, with progressive respiratory and renal failure, metabolic acidosis, and hepatitis. On day 4 of hospitalization, the patient died shortly after care was withdrawn.

Testing was negative for dengue virus (DENV) on polymerase-chain-reaction (PCR) assay. Serologic analysis for DENV was consistent with remote infection, with a highly elevated IgG level and an equivocal IgM level. Serum testing for ZIKV on real-time PCR assay was positive, with a threshold cycle of 17 and a very high estimated viral load of 2.0×10^8 ZIKV genome copies per milliliter. High-throughput sequencing of RNA revealed the presence of a ZIKV strain that shared 99.8% of the genome sequence with a strain isolated from a mosquito in Chiapas, Mexico, in 2016 (Fig. 1). No other putative pathogen was detected by routine diagnostic testing and RNA sequencing.[3]

Five days after Patient 1 died, Patient 2, a previously healthy 38-year-old man with no known coexisting illnesses who had visited Patient 1 in the hospital, reported having conjunctivitis, fevers, myalgia, and facial maculopapular rash. The rash became generalized but resolved within 7 days. On day 7 after the onset of symptoms, urinalysis was positive for ZIKV but serum was negative on PCR assay. Serum IgM antibody to ZIKV was positive. Patient 2 reported having assisted a nurse in repositioning Patient 1 in bed without using gloves. Patient 2 also reported having wiped Patient 1's eyes during the hospitalization but reported having had no other overt contact with blood or other body fluids, including splashes or mucous membrane exposure. No health care workers who had contact with Patient 1 reported having symptomatic illness.

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Study: Zika could reach 2.6 billion people

Filed Under: Zika

Stephanie Soucheray | News Reporter | CIDRAP News | Sep 01, 2016

Two new studies published today present an alarming picture of the potential reach of Zika virus and its complex clinical presentation, while researchers reporting in the latest issue of *Eurosurveillance* said that *Culex* mosquitos aren't likely to transmit the virus.

livechina / iStock

Global at-risk populations

In a study published in the *Lancet Infectious Diseases*, researchers from the University of Toronto used modeling to identify the areas around the world most at risk for Zika virus. After considering mosquito activity, air travel data and climate information, the researchers said potentially 2.6 billion people living in low-resource parts of Africa and the Asia-Pacific region could be sickened by Zika virus.

"It's a sobering number that highlights the potential magnitude of Zika virus," said Kamran Khan, MD, MPH from St. Michael's Hospital's Li Ka Shing Knowledge Institute in Toronto. "It's not meant to be alarmist, and it may be the worst-case scenario. But Zika is a global epidemic."

The New York Times

Doctors Brace for Zika Babies

The Checkup

By PERRI KLASS, M.D. SEPT. 26, 2016

This month, the first group of babies in Puerto Rico known to have been exposed to the Zika virus in their first trimester are being born. Pediatricians do not know what to expect.

"This is not like any other outbreak or epidemic," said Dr. Fernando Ysern, a pediatrician in Caguas, Puerto Rico, who is the president of the Puerto Rico chapter of the American Academy of Pediatrics.

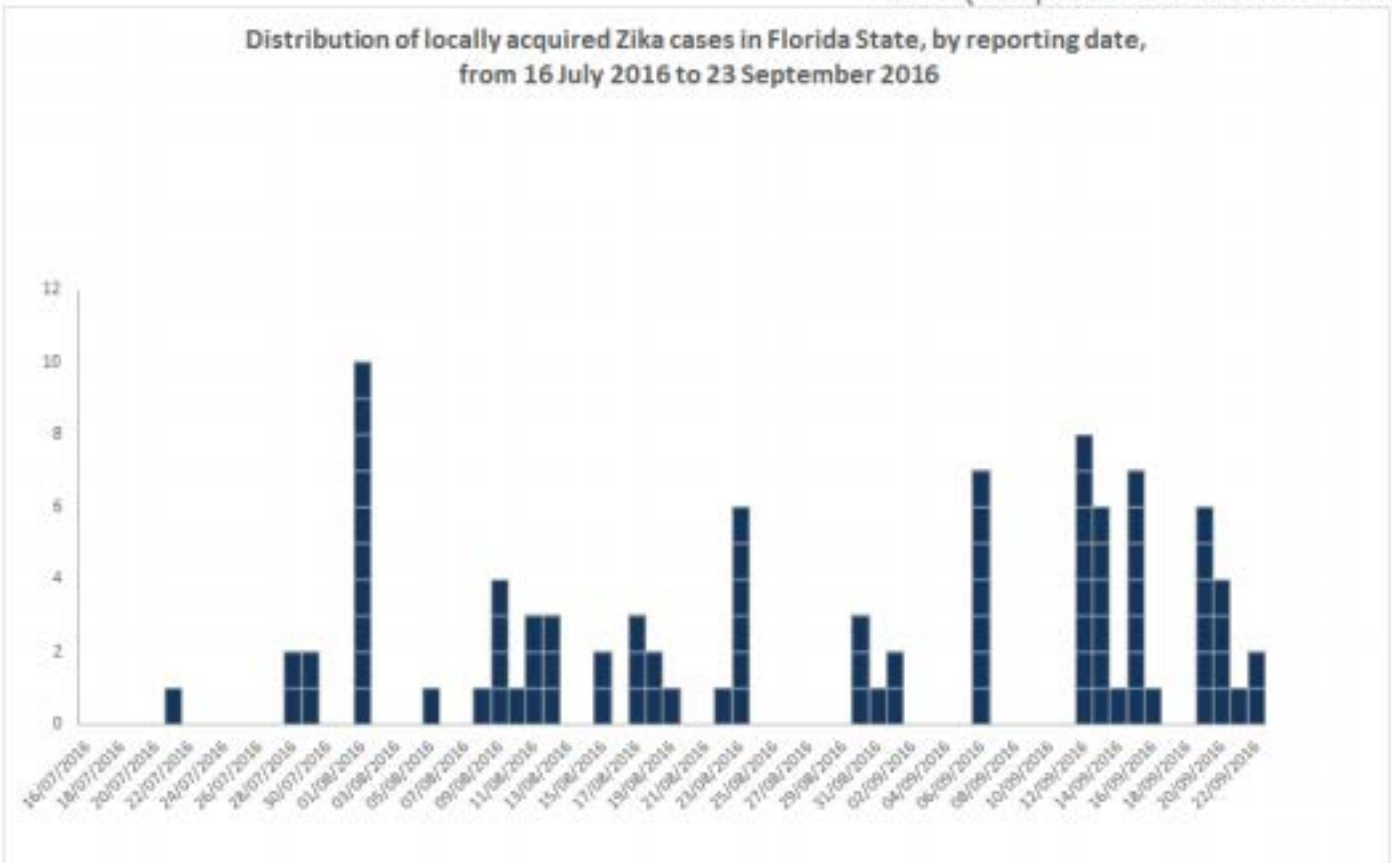
In the pediatric field, Zika looms as a kind of developmental doomsday virus, attacking the vulnerability of early brain development, striking at the neurological basis of human potential. While Puerto Rico, a United States territory, will experience the first wave of children affected by Zika, the rest of the United States is bracing for the spread of the virus.

As of Sept. 23, the Puerto Rico Department of Health reported 22,358 cases of Zika exposure, including 1,871 pregnant women. The Centers for Disease Control and Prevention's latest statistics, as of Sept. 15, list 1,348 pregnant women with "any laboratory evidence of possible Zika virus infection" in United States territories and 749 in the United States.

European Centre for Disease Prevention and Control

Distribution of locally acquired Zika cases in Florida State (US), by reporting date, from 16 July 2016 to 23 September 2016

ECDC (Adapted from Florida health departement and media)



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As one Miami area is taken off Zika advisory, another triples in size

Filed Under: Zika

Lisa Schnirring | News Editor | CIDRAP News | Sep 19, 2016

The US Centers for Disease Control and Prevention (CDC) today removed Miami's Wynwood neighborhood from its Zika travel warning while keeping in place strong cautions for pregnant women, just days after Florida officials tripled a second transmission area in Miami Beach.

Gadi Yosef / Flickr cc

In other developments, despite Senate work over the weekend, the path forward for Congress to pass a Zika funding bill is still unclear, with only 2 weeks to go until lawmakers break again until after the November election.

Wynwood cases decline, incubation periods pass

In its announcement, the CDC said no local cases have been reported in Wynwood since early August, and Director Tom Frieden, MD, MPH, said "tremendous progress" with mosquito control contributed

The New York Times

Outcry Erupts Over Miami Beach's Pesticide Spraying to Curb Zika

By LIZETTE ALVAREZ SEPT. 17, 2016

MIAMI BEACH — As Miami Beach works to blunt the spread of Zika — a virus that is taking a toll on tourism here — the city is wrestling with a separate predicament: a fast-growing outcry over the aerial spraying of naled, the pesticide used to kill adult mosquitoes.

Concerned residents and environmental protesters are coalescing around the issue of early morning naled spraying — a last-ditch approach to curb the Zika-carrying mosquitoes here — and raising concerns about its safety and efficacy. Activists are collecting accounts from residents who say the pesticide has caused rashes, headaches and nausea. It is also killing bees and some koi fish in ponds, they added.

The activists want a two-week moratorium on the spraying, which has been done twice in the last two weeks, to see if there is a decline in the number of Aedes aegypti mosquitoes, which carry the virus, with the continued use of more conventional methods. Naled, which is approved by the Environmental Protection Agency, is supplementing the hand spraying and truck spraying of a different chemical intended to kill larvae.

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Zika strain in Singapore confounds experts

Filed Under: Zika

Stephanie Soucheray | News Reporter | CIDRAP News | Sep 15, 2016

Virus mutations, rapid construction, guest workers, and dengue.

Nicolas Lannuzel / Flickr cc

The Marina One project, one of many new construction sites in Singapore.

These are a few of the theories experts are using to explain why Singapore, a city-state known for its excellent vector control programs, has seen a flurry of Zika infections in the last few weeks. Today Singapore's Ministry of Health reports there are now 356 locally acquired cases.

"Zika has been around since the 1960s. The laboratories in Ministry of Health and Ministry of Environment have been doing surveillance on this illness for several years, and we have not isolated Zika in patients or in mosquitoes [until now]," said Hoe Nam Leong, MBBS, an infectious disease specialist at Mount Elizabeth Novena Hospital in Singapore. "We think this is real."

Bloomberg

Zika Virus in Singapore Likely Evolved From Southeast Asia

by Sterling Wong

September 4, 2016 – 4:11 AM CDT

The Zika virus behind an outbreak in Singapore was not imported from South America, Singapore's Ministry of Health said in a statement Saturday.

Analysis by the National Public Health Laboratory and the Bioinformatics Institute discovered that the Zika virus found in two patients from the first cluster in the area of Aljunied Crescent and Sims Drive belongs to Asian lineage, according to the statement.

The virus in Singapore likely evolved from a strain already circulating in Southeast Asia, and was not imported from South America, where the outbreak has been linked to a condition called microcephaly, in which infants are born with abnormally small heads. The research team is expected to release more details shortly, according to the statement.

There were 26 new cases of locally transmitted Zika virus infection in Singapore on Sept. 3, the ministry confirmed. It said Sunday that it is also considering letting suspected Zika-infected patients stay home while their blood and urine samples are tested, an approach that is in line with the ministry's view on those who test positive for dengue and aren't warded in hospitals.

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Four suspected Zika microcephaly cases in Thailand

Filed Under: Zika

Stephanie Soucheray | News Reporter | CIDRAP News | Sep 26, 2016

Yesterday Thailand said authorities are investigating four microcephaly cases, while the Philippines and Singapore today reported more cases of Zika virus. Florida, meanwhile, is seeing more locally acquired cases, as well.

CDC, James Gathany

Zika-linked microcephaly in 3 infants, 1 fetus

The *Bangkok Post* reported that Thailand's Department of Disease Control is investigating three babies born with smaller-than-average heads. Another woman, who is 36 weeks pregnant, has a fetus with an abnormally small head detected on ultrasound. She is 1 of 33 pregnant women in the country's "Zika watch areas" under surveillance for any birth defects linked to the mosquito-borne disease.

Amnuay Gajeena, MD, director-general of Thailand's Department of Disease Control, said Zika is not endemic in the country, and that three to four cases of microcephaly are consistent with the 1% to 30% incidence of Zika-related microcephaly seen in other countries.

FOX NEWS Travel

MIAMI

Zika virus has many Americans rethinking fall travel to Florida

Published September 27, 2016

Florida's tourism industry is likely to take a big hit this fall as millions of Americans say they won't be traveling to the Sunshine State amid concerns over the Zika virus.

According to new analysis conducted by travel insurance provider Allianz Global Assistance, the number of people preparing to visit the state during the fall and winter seasons has dropped by almost 15 percent following highly publicized incidents of the mosquito-transmitted virus.

The drop comes after the Centers for Disease Control and Prevention (CDC) issued a travel warning in August for people heading to South Florida.

The warning for the Wynwood neighborhood of Miami-Dade County was recently lifted last week with the CDC saying it was no longer a zone of active transmission. But the agency continues to caution pregnant women about traveling to the city and surrounding areas.

The insurance provider reviewed more than 900,000 travel plans made by Americans during the month of August for the peak fall-winter vacation period, which covers travel from mid-Nov. 2016 to mid-April 2017. Compared to the same period last year the provider found that the number of travelers planning to book flights to Miami was down 29.11 percent.

REUTERS

Life | Mon Feb 8, 2016 12:11pm EST

Related: HEALTH

Race to fast-track Zika trials as 12 groups seek vaccine

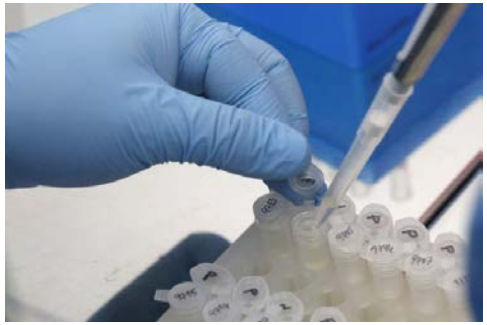
LONDON | BY BEN HIRSCHLER

At least 12 groups are now working to develop a Zika vaccine and health authorities said on Monday they were working to ensure development proceeded as rapidly as possible.

The World Health Organization said it was important to establish speedy regulatory pathways, although all the vaccines remained in early-stage development and licensed products would take "a few years" to reach the market.

With no approved Zika vaccines or medicines and none even undergoing clinical studies, scientists and drugmakers are on the starting-block in fighting the mosquito-borne disease suspected of causing a spike in birth defects in Brazil.

However, Zika is similar to dengue, yellow fever and West Nile virus, for which vaccines exist or are being developed, and the hope is to try similar approaches against the latest hazard.



The London-based European Medicines Agency (EMA) said it had established an expert task force on Zika to advise companies working on vaccines and medicines, mirroring similar action during Ebola and pandemic flu outbreak in 2009.

The NEW ENGLAND JOURNAL of MEDICINE

Fast-Track Zika Vaccine Development — Is It Possible?

Stephen J. Thomas, M.D., Maïna L'Azou, M.Sc., Alan D.T. Barrett, Ph.D., and Nicholas A.C. Jackson, Ph.D.

Studies have demonstrated that various Zika virus (ZIKV) vaccine constructs generate protective immune responses in mice and nonhuman primates,[1,2] and two DNA ZIKV vaccine candidates have entered phase 1 human safety testing (ClinicalTrials.gov numbers, NCT01099852 and NCT02840487). ZIKV vaccine development is advancing rapidly thanks to collaborations among academia, governments, and industry. Current knowledge gaps related to the properties, epidemiology, and pathology of ZIKV increase the complexity of vaccine development (see Table 1), but historical success in developing other flavivirus vaccines encourages optimism.

An ongoing epidemic in the Americas and the impact of ZIKV congenital syndrome (ZCS) necessitate rapid development of a safe, efficacious vaccine. As Ebola vaccine–development efforts taught us, conducting sequential, iterative preclinical studies followed by phase escalating human trials is suboptimal in an ongoing outbreak. Preclinical studies of ZIKV vaccine candidates need to continue in parallel with human trials, informing their design and the evolving target product profile

(TPP), including dose level and schedule, delivery method, and primary vaccinee population. Newly minted ZIKV vaccinologists need to determine which questions will inform development plans (see Table 2).

Defining the TPP of a vaccine for emergency or conditional use has been a complex exercise, and the World Health Organization (WHO) has made a proposal (www.who.int/immunization/research/development/zika/en). Considerations include indications for male and female vaccinees, a short immunization schedule, brisk induction of a protective immune response, an advantageous safety profile, and potential contraindications in pregnancy.

Though live or other replicating virus vaccine platforms would probably be less acceptable in emergencies, they might offer advantages for routine immunization, such as long-term protective immunity with minimal dosing. Given the need to protect girls before they reach childbearing age, a TPP should address vaccination starting at 9 years of age and in people of both sexes, given evidence of ZIKV in semen up to 6 months after infection.[3] This starting age would align with WHO recommendations[3] and with the precedent set by human papillomavirus vaccines (target group, girls 9 to 13 years old).

Prospective cohort studies can elucidate infection and disease attack rates, incidence of adverse pregnancy or neurologic outcomes,

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

SEPTEMBER 29, 2016

Considerations for Developing a Zika Virus Vaccine

Hilary D. Marston, M.D., M.P.H., Nicole Lurie, M.D., M.S.P.H, Luciana L. Borio, M.D., and Anthony S. Fauci, M.D.

The rapid spread of Zika virus through the Americas and its devastating consequences for pregnant women and infants have precipitated an international, multisectoral response.

Current prevention strategies focus on mosquito control, protection of the blood supply, barrier protection during sex, and other forms of contraception. When this explosive epidemic abates, Zika virus could remain endemic in many countries, where the risk to pregnant women, the general public, and travelers will persist. Therefore, a safe and effective vaccine is essential.

Development of a safe, effective Zika vaccine should be feasible. Vaccines against related flaviviruses, such as yellow fever and Japanese encephalitis, have been developed and deployed, and Zika infection appears to generate protective immunity in nonhuman primates.[1] Scientific feasibility, however, does not ensure successful development. An efficient development pathway must be delineated, including the optimal ways to evaluate the safety, immunogenicity, and effectiveness of vaccine candidates for intended target populations.

The primary goal of Zika vaccination is to prevent infection and protect against serious sequelae of the virus, particularly fetal congenital anomalies following in utero infection; however, given the relatively low frequency of these events in relation to the total number of infections, generating evidence of efficacy against these sequelae in prelicensure trials may not be feasible within a reasonable time frame. Demonstrating that vaccination averts congenital anomalies will most likely require postlicensure studies.

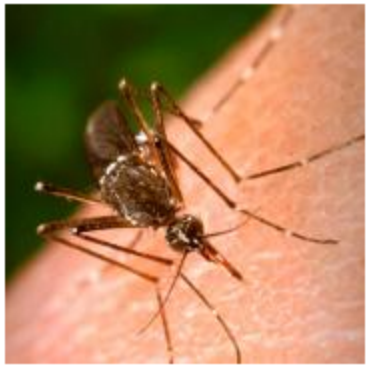
Prevention of congenital anomalies through vaccination of women during pregnancy faces several challenges. First, to protect the developing fetus, one must achieve protective immunity before the time of peak vulnerability, which is probably during the first and early second trimesters (although complications resulting from infections later in pregnancy have been reported).[2] Furthermore, many women are unaware of their pregnancies until well into the first trimester. Although replicating live-virus vaccines may be protective after a single dose, these are generally not good candidates for vaccines administered during pregnancy. Inactivated, recombinant subunit, and other nonreplicating vaccines, more appropriate for use during pregnancy, usually require multiple doses to achieve protec-

Zika

Resources

Jump to Selected Reading

Last updated Sep 22, 2016



Latest Cases & General Information

Zika virus (CDC landing page)
Latest Zika situation reports (WHO)
Zika virus infections and complications called Public Health Emergency of International Concern (WHO, Feb 1, 2016)
Zika virus disease, frequently asked questions about Zika virus (WHO Emergencies Preparedness, Response)
Zika virus infection (PAHO/WHO landing page)

Maps

2016 Zika outbreak timeline map (HealthMap)
Pacific Disaster Center maps (updated periodically)
Zika in the United States, explained in 9 maps (Vox, Aug 4, 2016)
Zika cases in the United States (*New York Times*, Jul 29, 2016)
Maps predict possible Zika hot spots (*USA Today*, Apr 28, 2016)
Mapping global environmental suitability for Zika virus (*eLife* study, Apr 19, 2016)

Agents of Concern

- Diseases with pandemic potential
  - Influenza
  - Antimicrobial resistance
- **Diseases resulting in outbreaks of regional critical importance**
  - Ebola
  - MERS
  - Dengue, Chikungunya and Zika
  - **Yellow fever**

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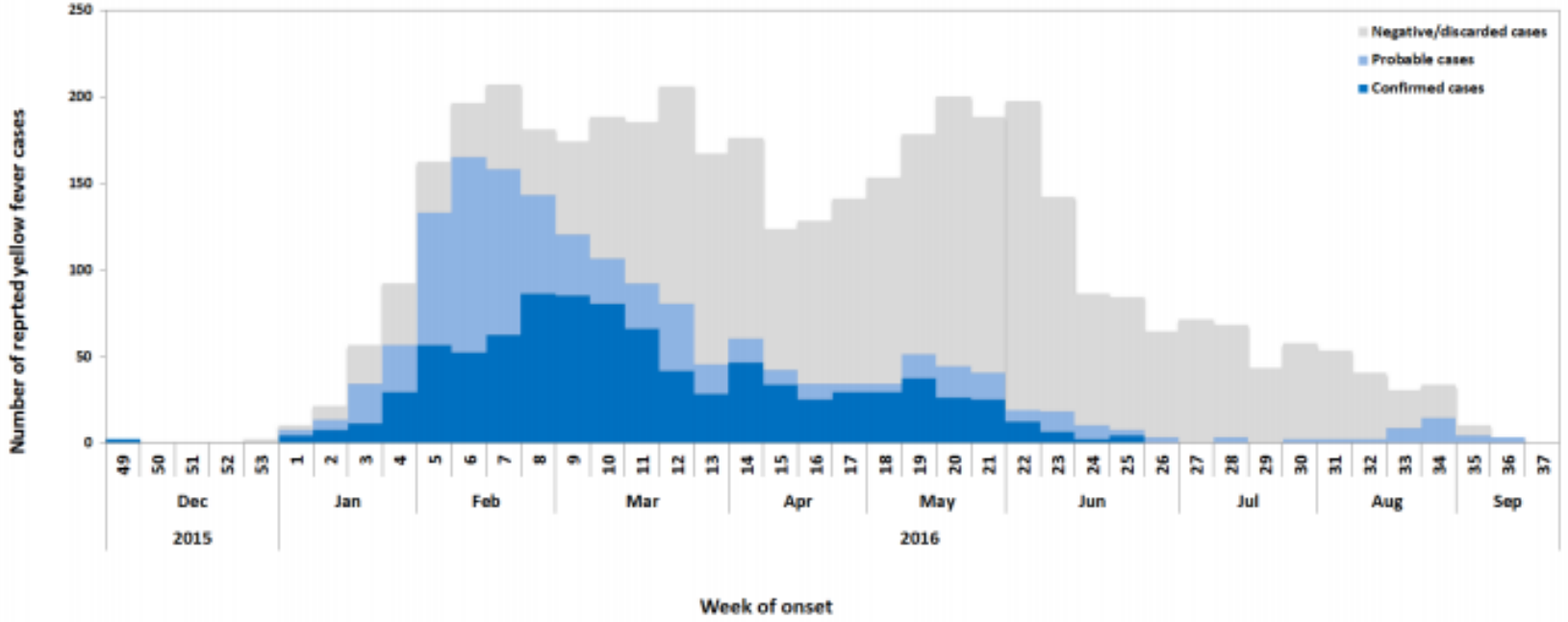
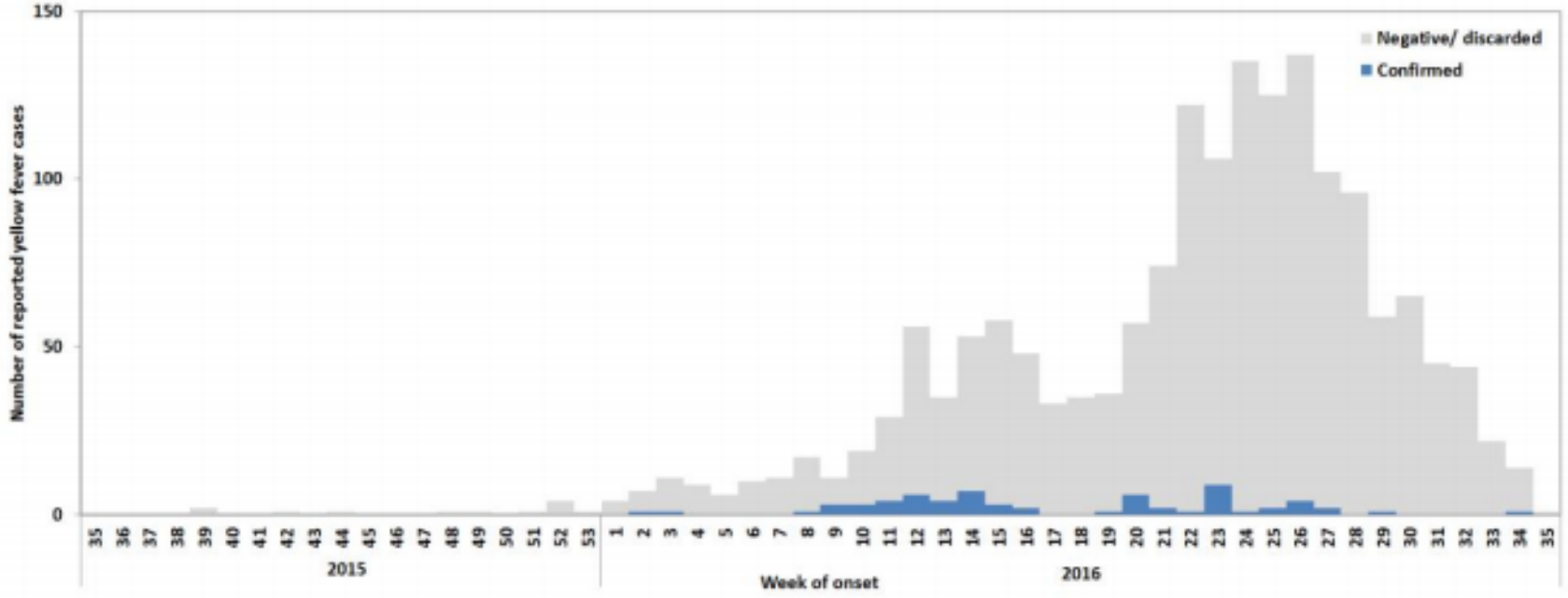
Figure 1. National weekly number of confirmed, probable and negative yellow fever cases in Angola, 5 December 2015 to 15 September 2016



Data source: Data as of 15 September 2016. Data for the past four weeks are subject to revision pending ongoing investigation and reclassification.

Figure 2. National weekly number of confirmed and negative yellow fever cases in DRC, 24 August 2015 to 11 September 2016*



*Data source: DRC yellow fever data as of 11 September. Data are subject to revision pending ongoing investigation and reclassification. *Data where date of onset is unknown are not shown.*

World Health Organization

YELLOW FEVER OUTBREAK IN ANGOLA

INCIDENT MANAGEMENT

Vol: 9 -02

SITUATION REPORT W36, 11 Sept 2016

I. Key Highlights

- The last vaccination Campaign round was implemented from 15th to 26th August ; 2,218, 966 persons were vaccinated and mop up vaccination continued until a coverage rate of 95% was achieved.
- The Ministry of Health is planning a next phase of vaccination from 30 September to 09 October 2016 that include 12 municipalities with a target population of 2,136,225. The vaccine from the ICG is expected to arrive in the country in the coming days.
- A total of 26 national and international health professionals from the Ministry of Health and partners in the Incident Management team; three drivers are ready to be deployed to support the preparation of the next phase of vaccination in 9 targeted provinces.

II. Epidemiological Situation as of 11 September 2016

⇒ **Week 36 statistics (5—11 September 2016)**:

- Of **35** suspected cases reported and tested by the National Laboratory, four samples were positive at laboratory: two of these cases had vaccination antecedent and were discarded as yellow fever cases. The two other cases are under investigation; both cases are coming from already vaccinated districts.
- **One(1)** death was reported among the suspected cases during this period.
- Eighteen (18) districts in 8 provinces reported suspected cases of yellow fever. **No** district reported new confirmed local transmission.

⇒ **Cumulative statistics since 05 December 2015:**

- A total of **884 laboratory confirmed cases** have been reported out of **4 100** suspected cases and **3 577** laboratory samples tested
- Overall, **373 (CFR = 9.2%)** deaths were reported among suspected cases and **121 (CFR 13.7%)** among confirmed cases
- Laboratory confirmed cases have been reported for **16** out of **18** provinces in **80** out of **134** districts.
- The last confirmed cases had a date of onset on 23 June 2016 from Cunene and Cuanza Norte provinces
- Vaccination campaigns have been completed in 73 districts with a cumulative number of 16,002,820 people vaccinated (95%) of the target population.

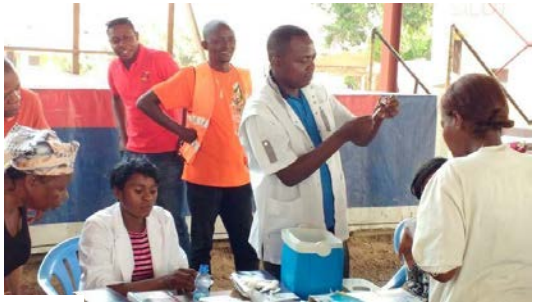
Table 1: National Summary of Yellow Fever Outbreak

Yellow Fever Outbreak Summary 05 — 11 Sep 2016, (W36)	
Reported cases	35
Samples tested	35
Confirmed cases	0
Total Deaths	1
Total provinces that reported cases	8
New provinces with confirmed cases	0
Total districts with reported cases	18
New districts with confirmed cases	0
New districts with documented local transmission	0
Yellow Fever Outbreak Summary from 5 Dec 2015— 11 Sep 2016	
Total cases reported to central level	4,100
Total Samples Tested	3,577
Total confirmed cases	884
Total deaths	373
Total deaths among confirmed cases	121
Total provinces that have reported cases	18
Total provinces with confirmed cases	16
Total districts that have reported cases	134
Total districts with confirmed cases	80
Total provinces with documented local transmission	12
Total districts with documented local transmission	45
Total number of provinces in Angola	18
Total number of districts in Angola	166

REUTERS

HEALTH NEWS | Tue Sep 13, 2016 | 10:09am EDT

WHO says Angola, Congo yellow fever outbreak under control



By **Tom Miles** | GENEVA

A yellow fever outbreak in Angola and Congo has been brought under control by a major vaccination campaign, the World Health Organization's director of infectious hazard management Sylvie Briand said on Tuesday.

"One (piece of) good news is that this outbreak is under control now. We haven't had any new cases in Angola since June 23, and since July 12 in DRC (Democratic Republic of Congo)," Briand told a regular U.N. briefing in Geneva.

The entire Congolese capital of Kinshasa, 7.7 million people, had been vaccinated in less than 10 days, as well as 3 million in border areas to prevent transmission from Angola, and another 3 million on the Angolan side of the border, where a second phase of vaccinations would be carried out soon.

"So far in Angola more than 15 million people (have been vaccinated), this represents 65 percent of the population. So we still have to protect certain districts and provinces but the risk of a major outbreak I think is now over," she said.

But there were still 32 endemic countries in Africa, so further outbreaks could not be ruled out, including in the parts of Congo that had not been vaccinated recently, she said.

World Health Organization

Media centre

Millions protected in Africa's largest-ever emergency yellow fever vaccination campaign

News release

2 SEPTEMBER 2016 | GENEVA - A major part of the largest emergency vaccination campaign against yellow fever ever attempted in Africa has been completed, with more than 7.7 million people vaccinated in record time in the city of Kinshasa, Democratic Republic of Congo (DRC). This has been accomplished through an extraordinary network of partnerships and collaborations.

In less than two weeks, the campaign successfully reached the targeted population of Kinshasa, most of them (7.3 million people) using an emergency vaccine – one fifth of the full dose of yellow fever vaccine. This dose sparing strategy was recommended by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) as a short-term emergency measure to reach as many people as possible given limited supplies of the vaccine.

"WHO commends the Government of the DRC for this significant achievement to roll out such a complex campaign in such a short period of time," said Dr Yokouide Allarangar, WHO Representative in the DRC.

Planning a mass vaccination campaign on this scale usually takes up to 6 months. This complex and ambitious emergency campaign was put in place in a matter of weeks to end transmission of yellow fever before the rainy season starts in September.

Eurosurveillance 20 years 1996–2016
Europe's journal on infectious disease epidemiology, prevention and control

Announcements

EUROSURVEILLANCE IN OPEN ACCESS DIRECTORIES
Eurosurveillance remains in the updated list of the Directory of Open Access Journals (DOAJ). It was first added to the DOAJ on 9 September 2004. Eurosurveillance is also listed in the Securing a Hybrid Environment for Research Preservation and Access / Rights MEtadata for Open archiving (SHERPA/RoMEO) [2], a database which uses a colour-coding scheme to classify publishers according to their self-archiving policy and to show the copyright and open access self-archiving policies of academic journals. Eurosurveillance is listed there as a 'green' journal, which means that authors can archive pre-print (i.e. pre-refereeing),

Eurosurveillance, Volume 21, Issue 39, 29 September 2016

Rapid communication

FRENCH *AEDES ALBOPICTUS* ARE ABLE TO TRANSMIT YELLOW FEVER VIRUS

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We assessed the ability of a French population of *Aedes albopictus* to transmit yellow fever virus (YFV). Batches of 30 to 40 female mosquitoes were analysed at 7, 14 and 21 days post-exposure (dpe). Bodies, heads and saliva were screened for YFV. Infectious viral particles were detected in bodies and heads at 7, 14 and 21 dpe whereas the virus was found in saliva only from 14 dpe. Our results showed that *Ae. albopictus* can potentially transmit YFV.

We assessed the vector competence of *Aedes albopictus* collected in France for a West African strain of yellow fever virus (YFV). Our results show that this temperate population of *Ae. albopictus* was able to deliver virus through saliva 14 days after receiving an infectious blood-meal.

Experimental infection of mosquitoes

A YFV S79-P4 strain isolated in 1979 from a human case in Senegal [1] was passaged twice on newborn mice and two times on C6/36 *Ae. albopictus* cells. Viral stocks were produced on C6/36 *Ae. albopictus* cells.

Science AAAS

Angolan yellow fever outbreak highlights dangerous vaccine shortage

By Kai Kupferschmidt | Apr. 4, 2016 , 3:30 PM

The three people dressed in baby blue plastic suits and goggles form a human conveyor belt for chicken embryos. The first takes a tray of eggs that were injected with a yellow fever vaccine virus, then left to incubate for 4 days, and cuts the top off each egg. The second tweezes the embryos out of the eggs and deposits them in a large bottle. The last person adds some liquid, then blends the embryos into a rich, red broth that contains millions of weakened virus particles.

The end result of this procedure, repeated dozens of times every week at the **Pasteur Institute of Dakar**, is a highly effective vaccine that offers lifelong protection against yellow fever. But the 80-year-old process is decidedly low-tech and hard to scale up—and that's become a problem, because a big yellow fever outbreak that started in December 2015 in Luanda, Angola's capital, has emptied the world's strategic reserves of the vaccine.

Opportunities for Success

- The infectious disease problems of the 21th century need to be understood from the “new world order” in which we live
- We must integrate creative imagination and scientific data
- We have to fix the business model of public health, particularly in the areas of vaccine and anti-infective R&D through effective use
- Tell the truth or find a different line of work; my kids and grandkids lives depend on it!

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

“It’s no use saying, ‘We’re doing our best.’ You have got to succeed in doing what is necessary.”

Sir Winston Churchill

“If you don’t know where you’re going, any road will get you there.”

- Lewis Carroll

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

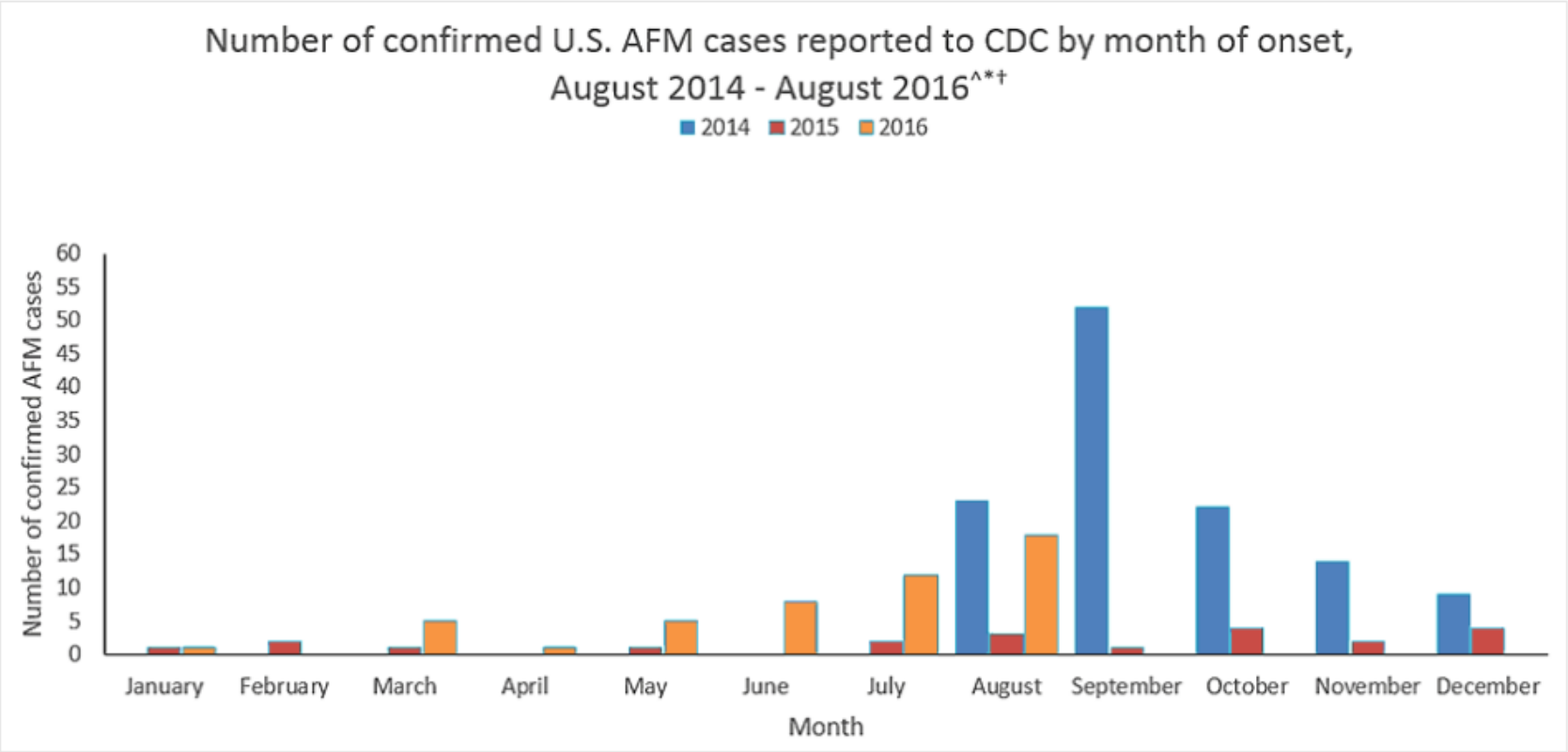
“Are these the shadows of the things that Will be, or are they shadows of things that May be, only?“

Ebenezer Scrooge

AFM in the United States

Acute flaccid myelitis (AFM) is a rare illness that anyone can get. It affects a person's nervous system, specifically the spinal cord. AFM can result from a variety of causes, including viral infections.

Beginning in August 2014, CDC received an increase in reports of people across the United States with AFM for which no cause could be found. Since then, CDC has been actively investigating this illness. We continue to receive reports of sporadic cases of AFM. From January 1 to August 31, 2016, a total of 50 people in 24 states across the country were confirmed to have AFM.



Updated October 3, 2016