Infectious Diseases in the 21st Century: The Need for a New Brand of Public Health Leadership

Michael T. Osterholm, PhD, MPH

Regents Professor

McKnight Presidential Endowed Chair in Public Health

Director, Center for Infectious Disease Research & Policy

Distinguished University Teaching Professor, Division of Environmental Health Sciences, School of Public Health

Professor, Technological Leadership Institute College of Science and Engineering

Adjunct Professor, Medical School

University of Minnesota

CIDRAP

Center for Infectious Disease Research & Policy

University of Minnesota

Infectious Diseases and Public Health Leadership

- Communicable diseases and public health in the 20th century
- The 21st century "New World Order"
- The challenges of infectious diseases in the 21st century
- The opportunities for success

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Infectious Diseases and Public Health Leadership

- **Communicable diseases and public health in the 20th century**
- The 21st century "New World Order"
- The challenges of infectious diseases in the 21st century
- The opportunities for success

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

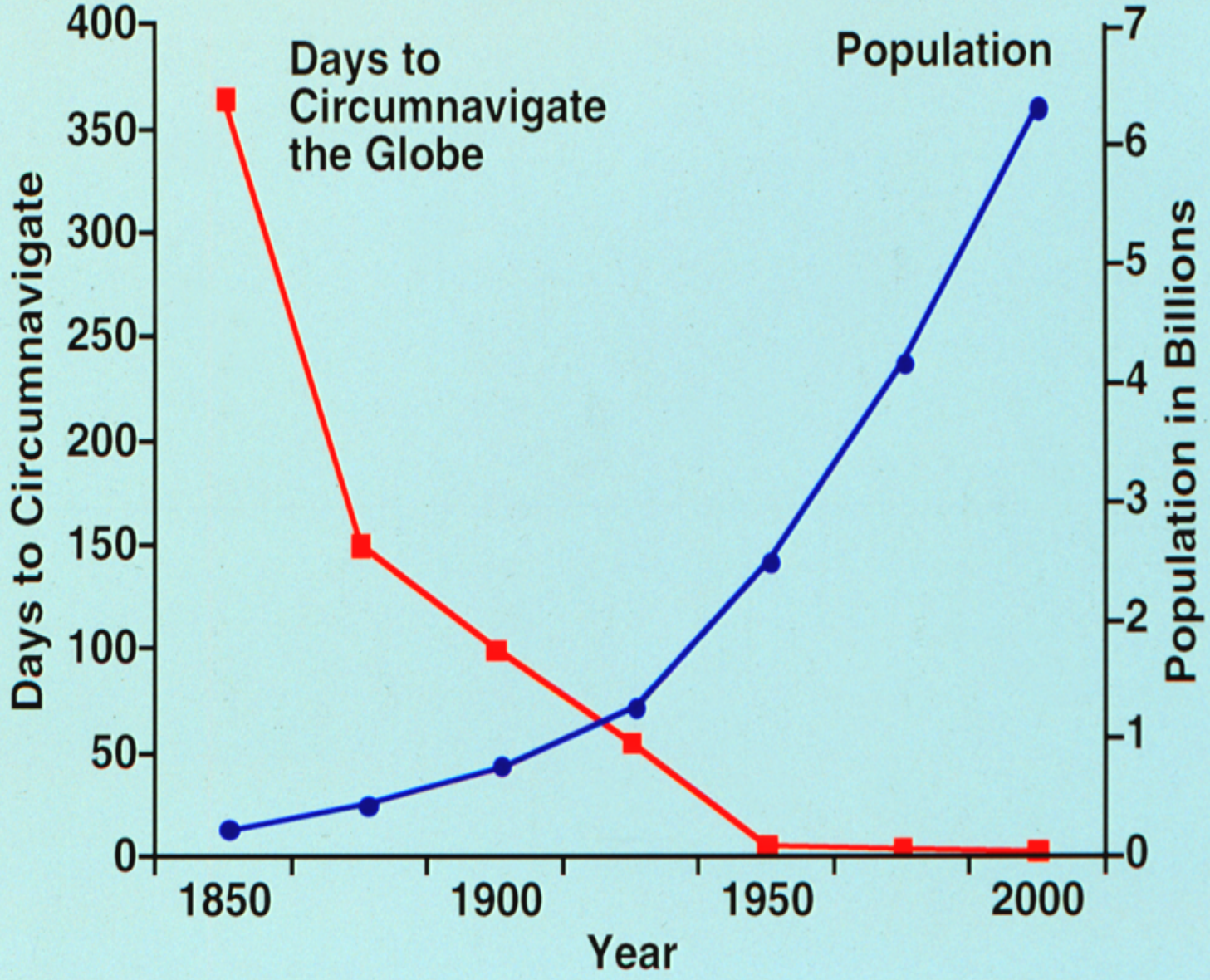
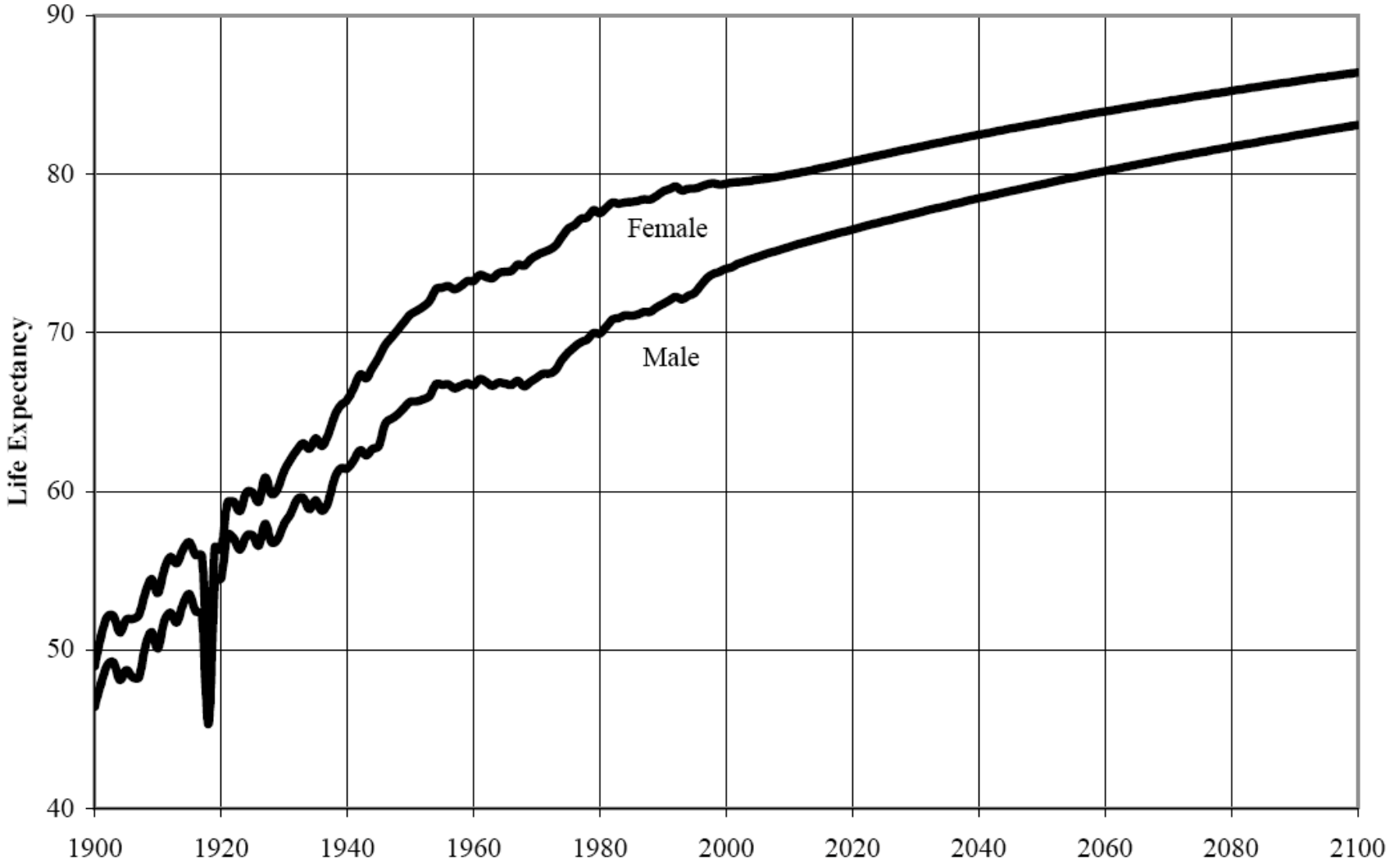
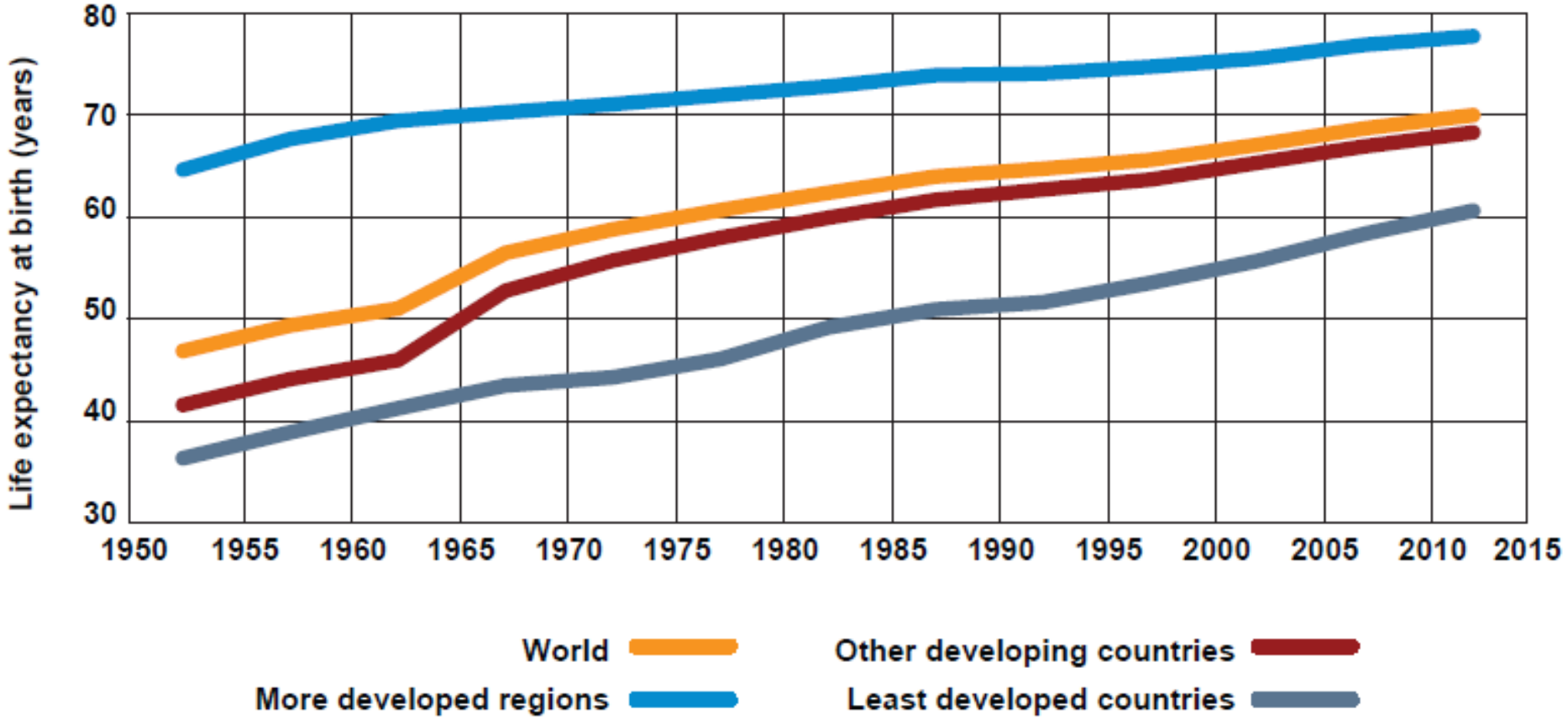

Days to Circumnavigate the Globe
Population
Days to Circumnavigate
Population in Billions
Year
400
350
300
250
200
150
100
50
0
7
6
5
4
3
2
1
0
1850
1900
1950
2000

Figure 2a—Life Expectancy at age 0
by Sex and Calendar Year
(Based on Period Tables)



Countries at all levels of development have achieved gains in life expectancy at birth since 1950, but the least developed countries continue to lag behind the other countries in the less developed regions and those in the more developed regions

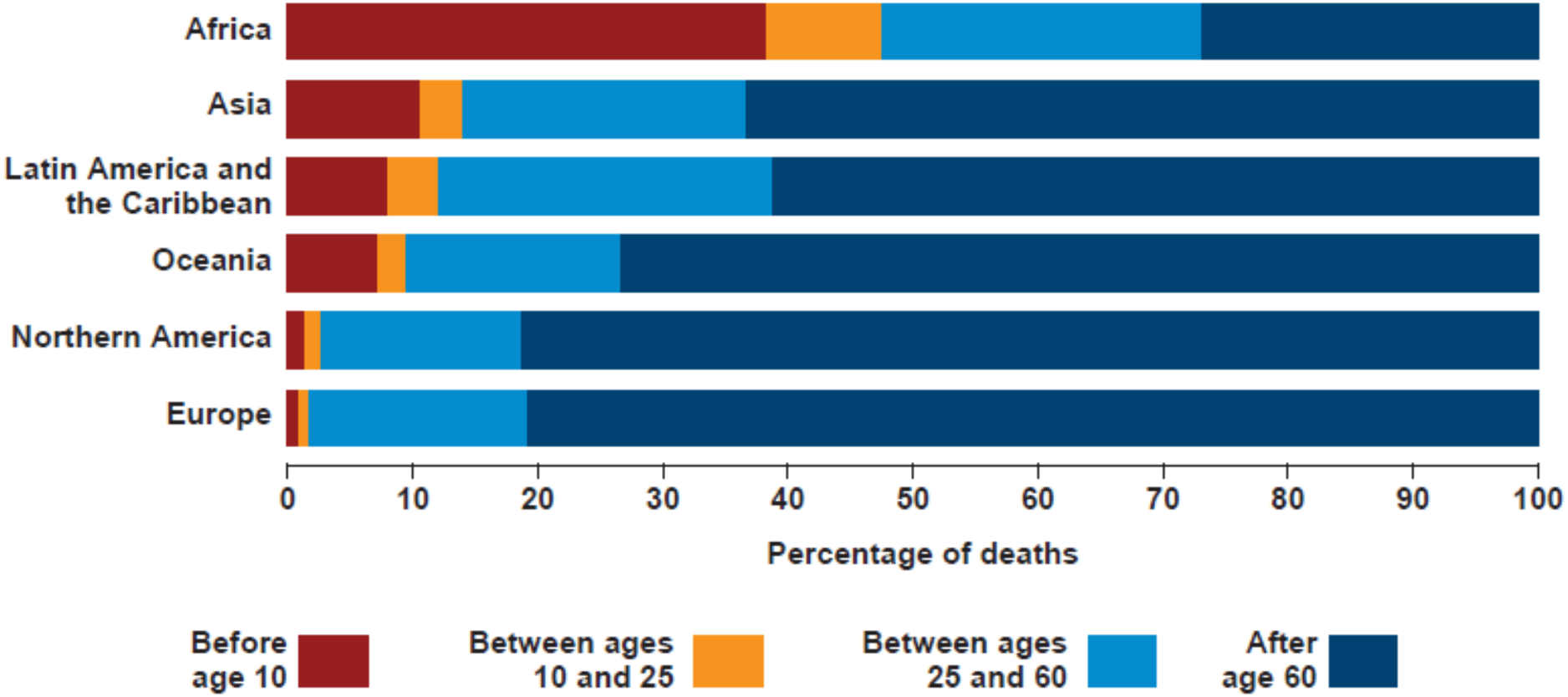


United Nations • Department of Economic and Social Affairs • Population Division

World Mortality 2013

www.unpopulation.org

In countries in the early stages of the demographic tranistion a large proportion of deaths occur among children. In the later stages of the transition the vast majority of deaths occur among older adults



United Nations • Department of Economic and Social Affairs • Population Division

World Mortality 2013

www.unpopulation.org

THE LOCAL fr

Why has life expectancy in France taken a historic drop?

Published: 19 Jan 2016 15:43 GMT+01:00

New figures show that France's life expectancy has taken a drop, after the country was plagued by extreme weather and a vicious flu virus.

- Population of France to pass 70 million by 2050 (02 Oct 13)

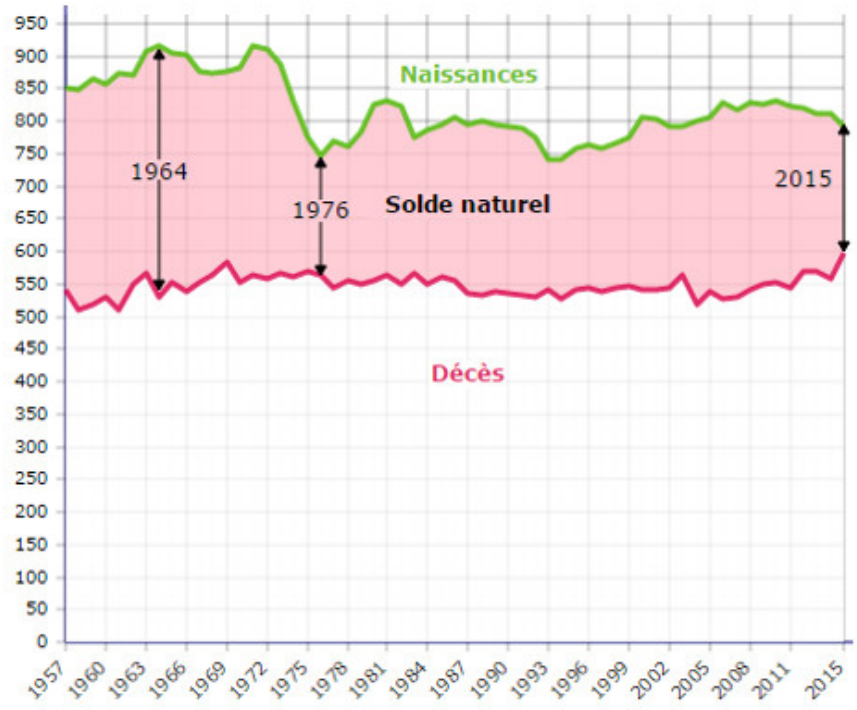
The typical Frenchman will live to be 78.9 years old, while French women live to 85, according to fresh figures from national statistics office INSEE.

While this may be a healthy longevity compared to many other countries, France's figures took a considerable dip in 2015.

The average age of death was down 0.4 years for men and 0.3 years for women, compared to 2014.

France also recorded an extra 41,000 deaths compared to in 2014, and 19,000 fewer births, meaning the average French woman gives birth to 1.96 children, after a previous average of over two.

The difference between birth rate and death rate, as a result, was the lowest it had been since 1976. The graph below shows France's total number of births (in green) and deaths (in pink), both measured in the thousands, since 1957.



Graph: Insee

Mortality and Years of Life Lost

Globally, years of life lost:

- **51%** communicable diseases
- **34%** non-communicable diseases
- **14%** injuries for 14%

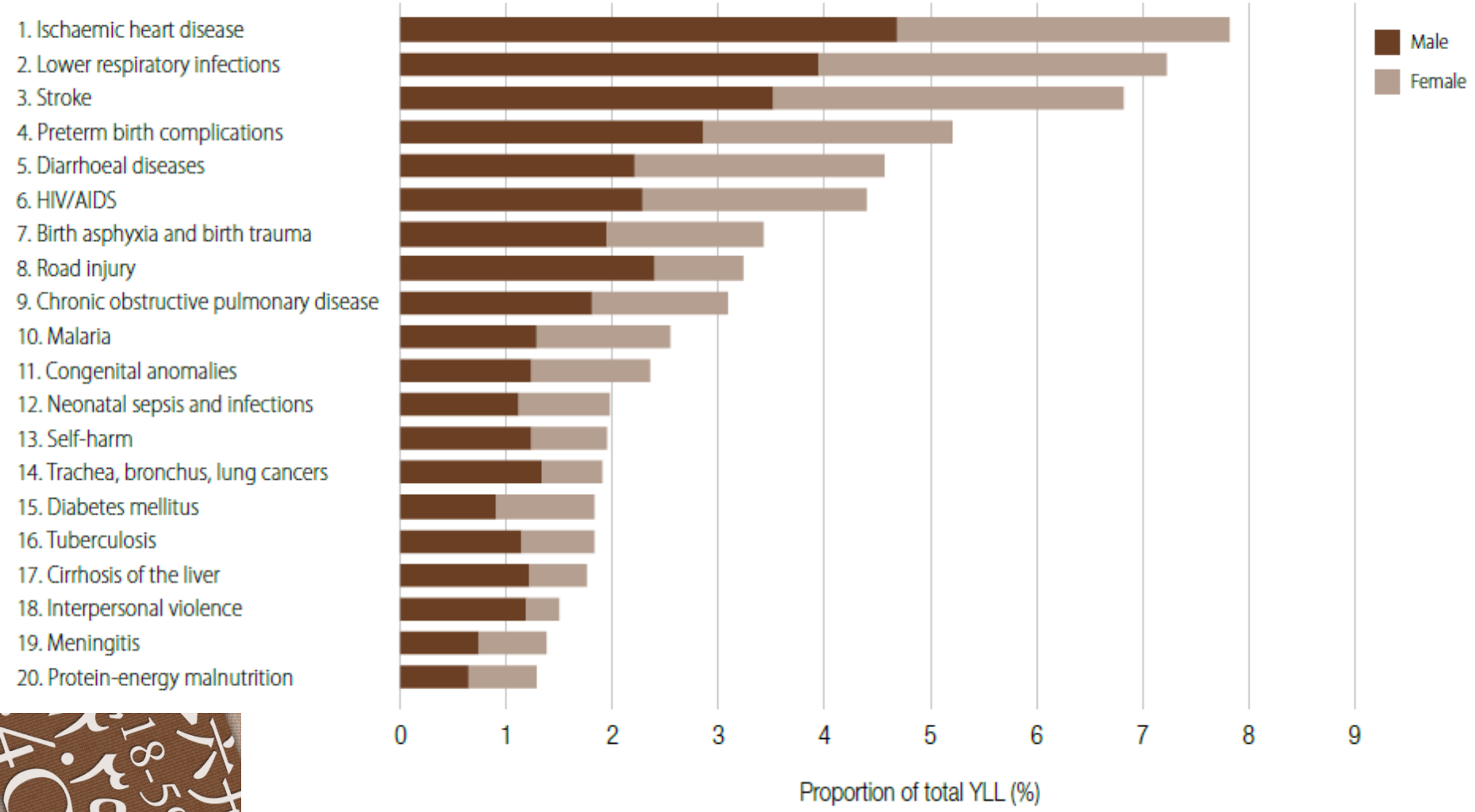
Regional variations:

In high-income countries, communicable diseases account for only **8%** of years of life lost, compared with **68%** in low-income countries.

World Health Statistics 2009, WHO

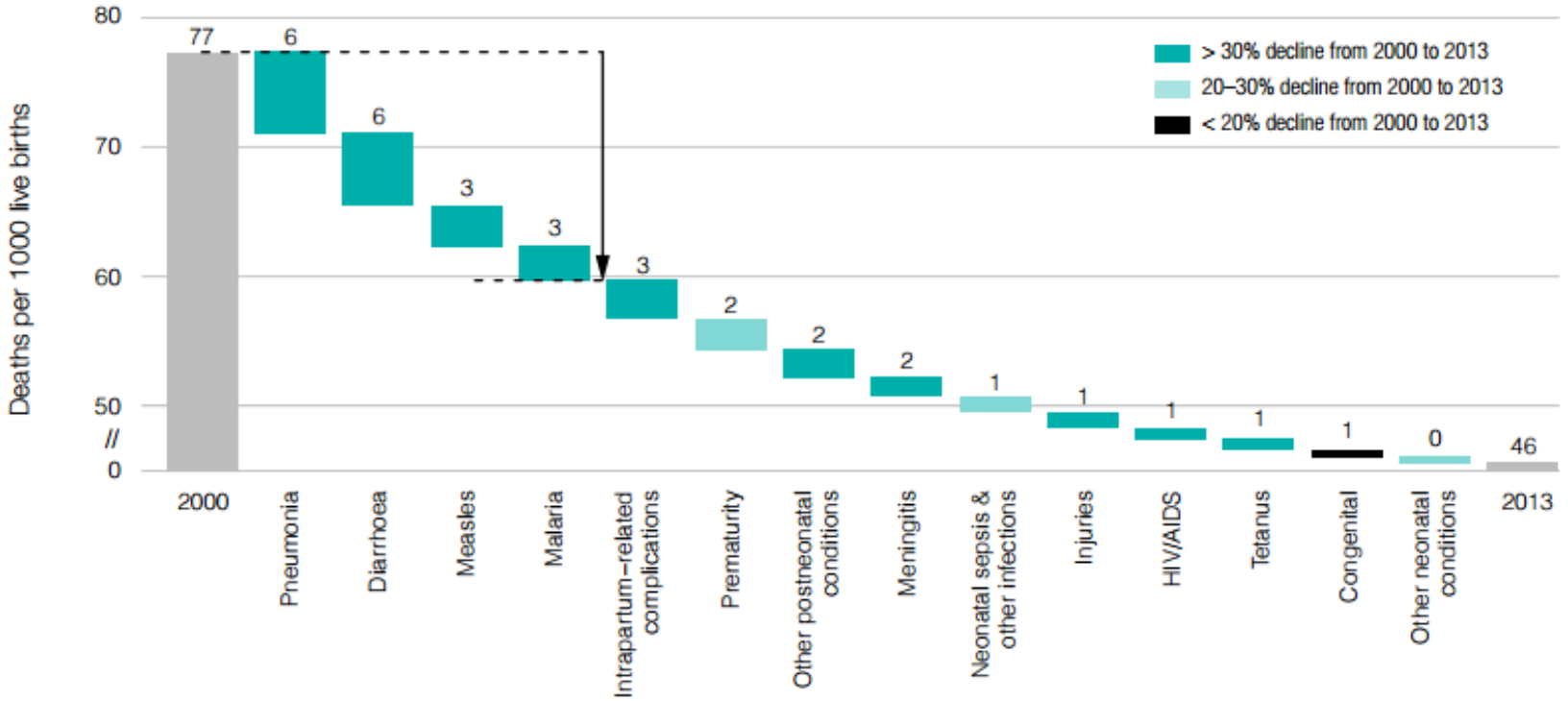
World Health Organization

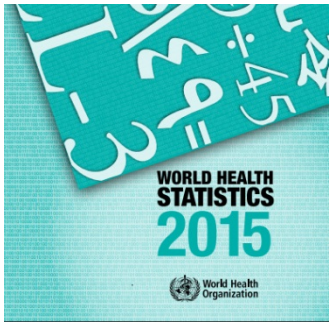
Figure 15. The 20 leading causes of YLL – globally, 2012



Health-related Millennium Development Goals

Figure 2. Global trends in cause-specific mortality rates among children under 5 years of age, 2000–2013

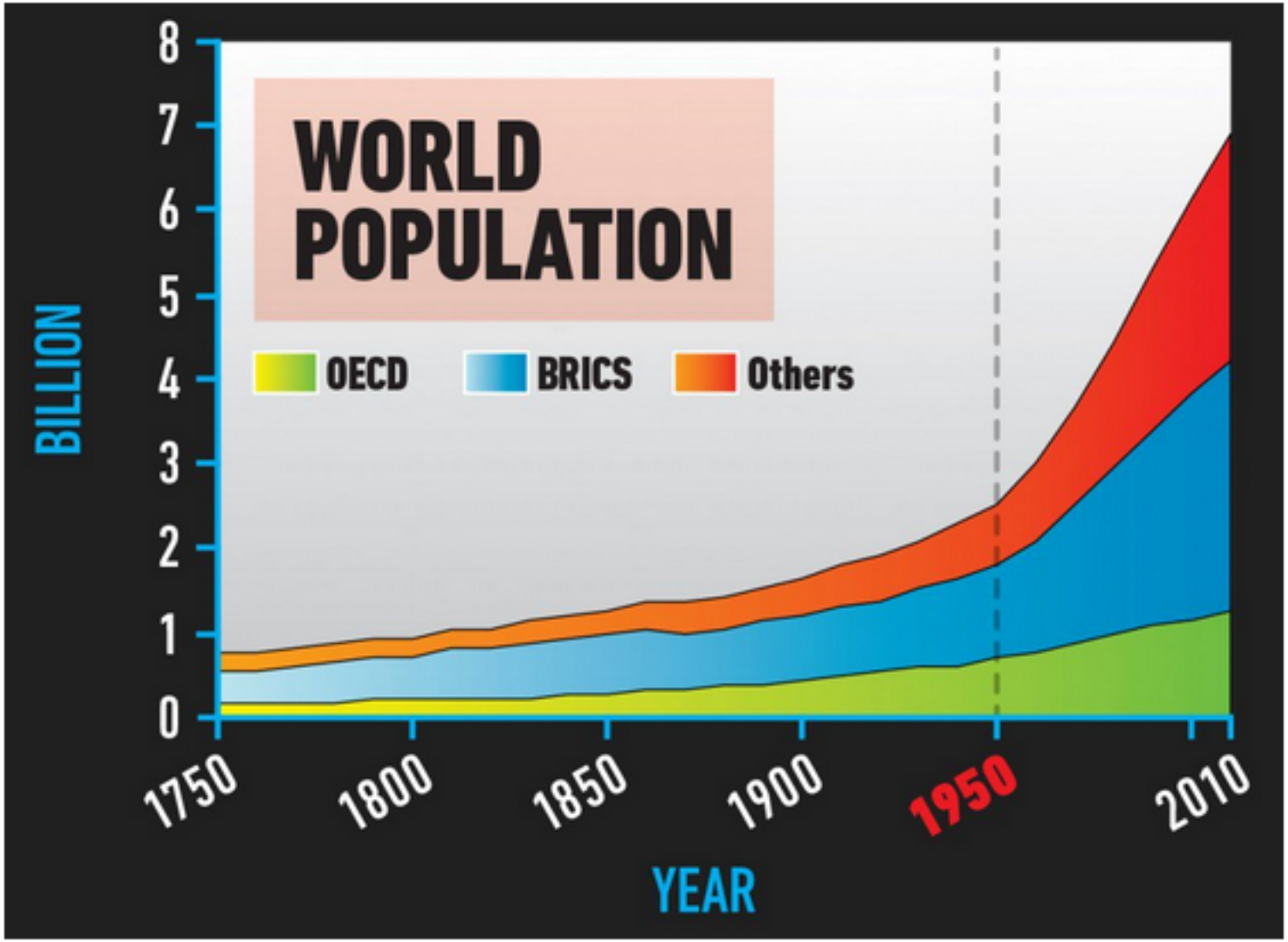




Infectious Diseases and Public Health Leadership

- Communicable diseases and public health in the 20th century
- **The 21st century "New World Order"**
- The challenges of infectious diseases in the 21st century
- The opportunities for success

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

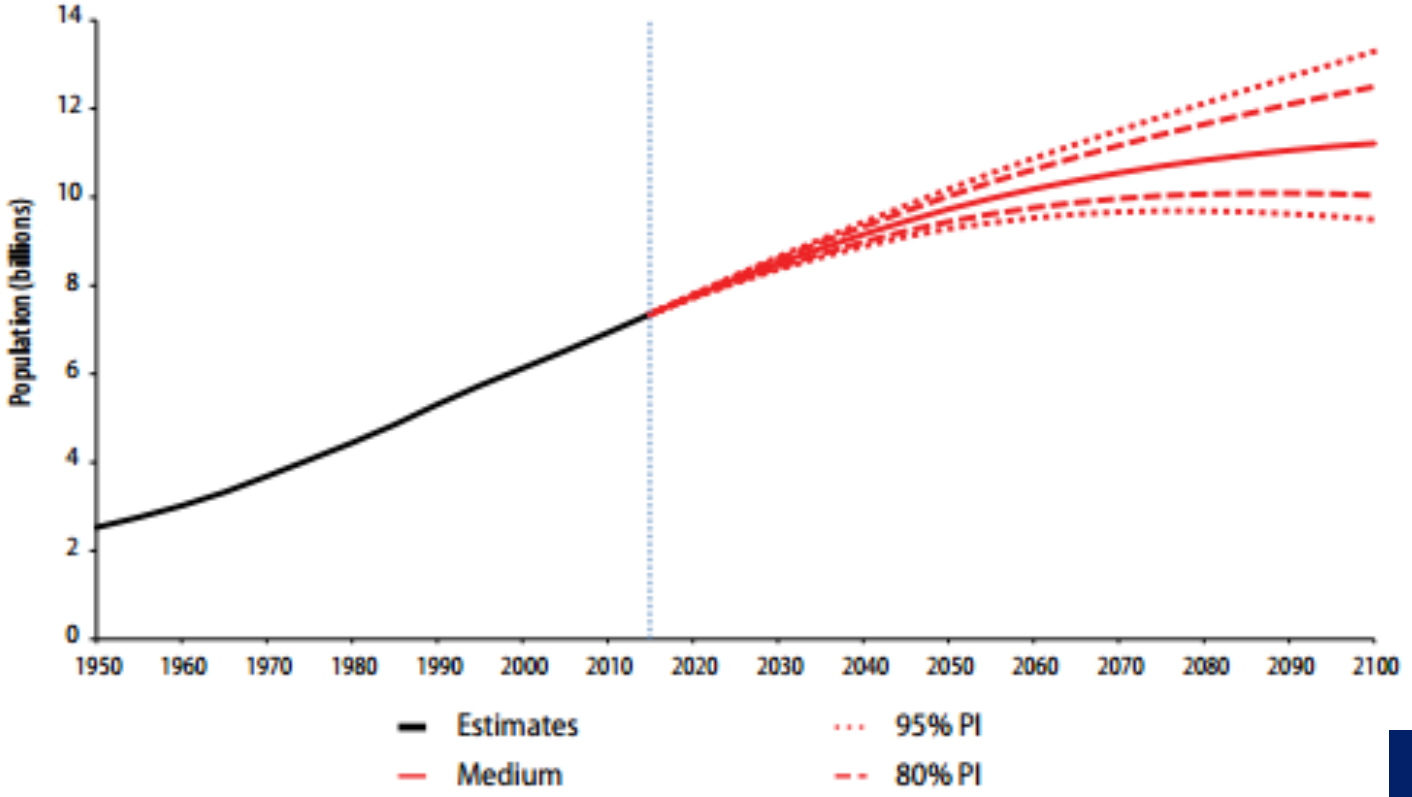


(Steffen et al 2014) Global population data according to the HYDE (History Database of the Global Environment) database. Data before 1950 are modelled. Data are plotted as decadal points.

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

Global population projected to reach 9.7 billion in 2050, 11.2 billion in 2100

Population of the world: estimates, 1950-2015, medium-variant projection and 80 and 95 per cent prediction intervals, 2015-2100



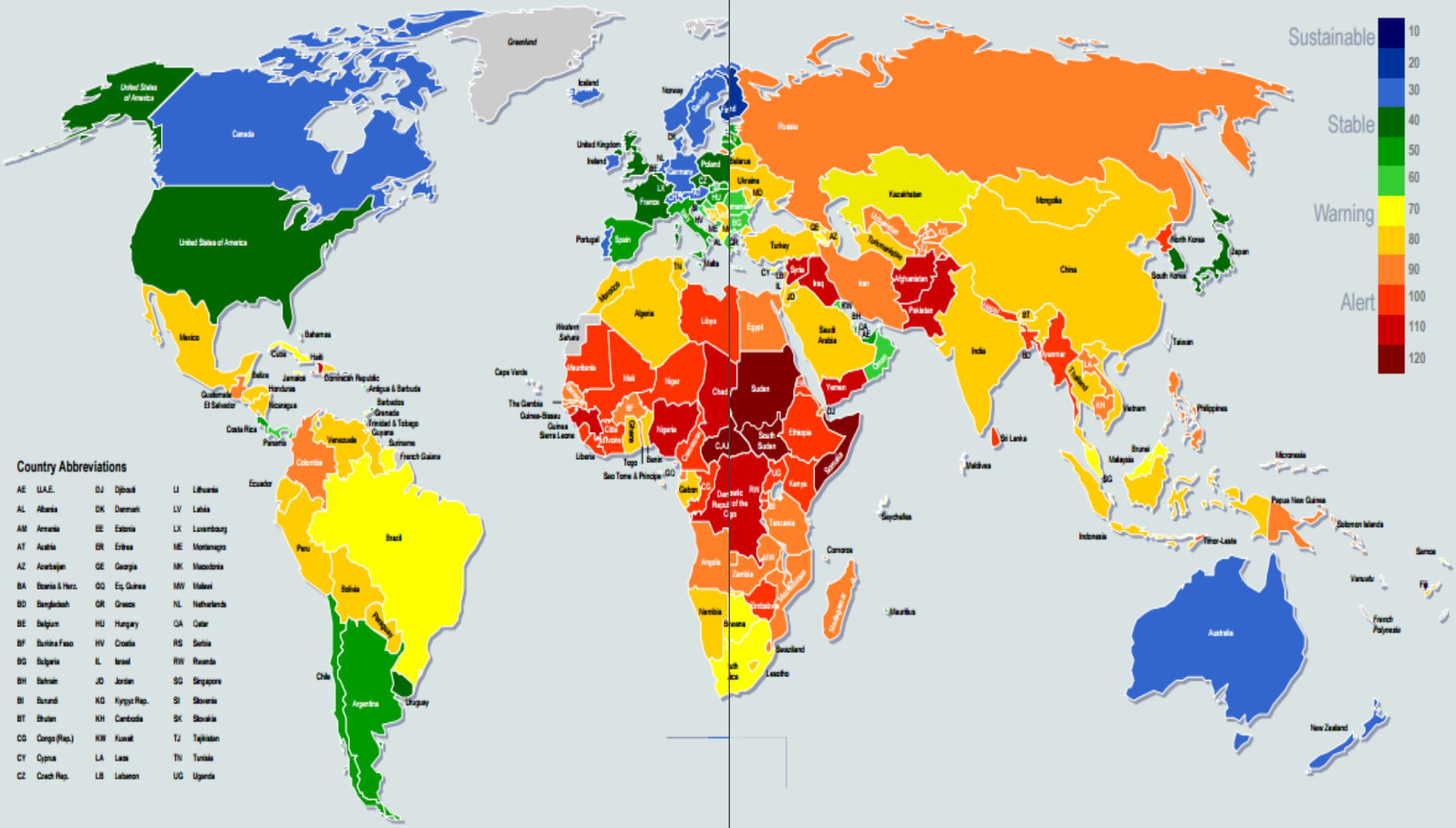
United Nations

FRAGILE STATES INDEX 2015

FFP

THE FUND FOR PEACE

Fragile States Index:
Fragility in the World 2015



Report of the

Ebola Interim Assessment Panel

World Health Organization


The Neglected Dimension of Global Security
A Framework to Counter Infectious Disease Crises
Commission on a Global Health Risk Framework for the Future

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

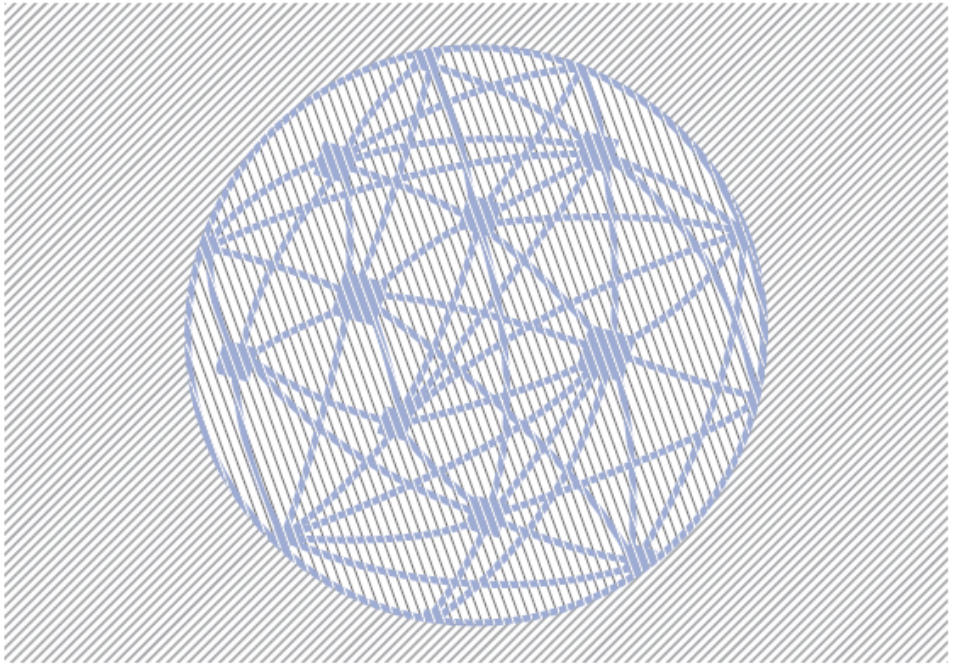
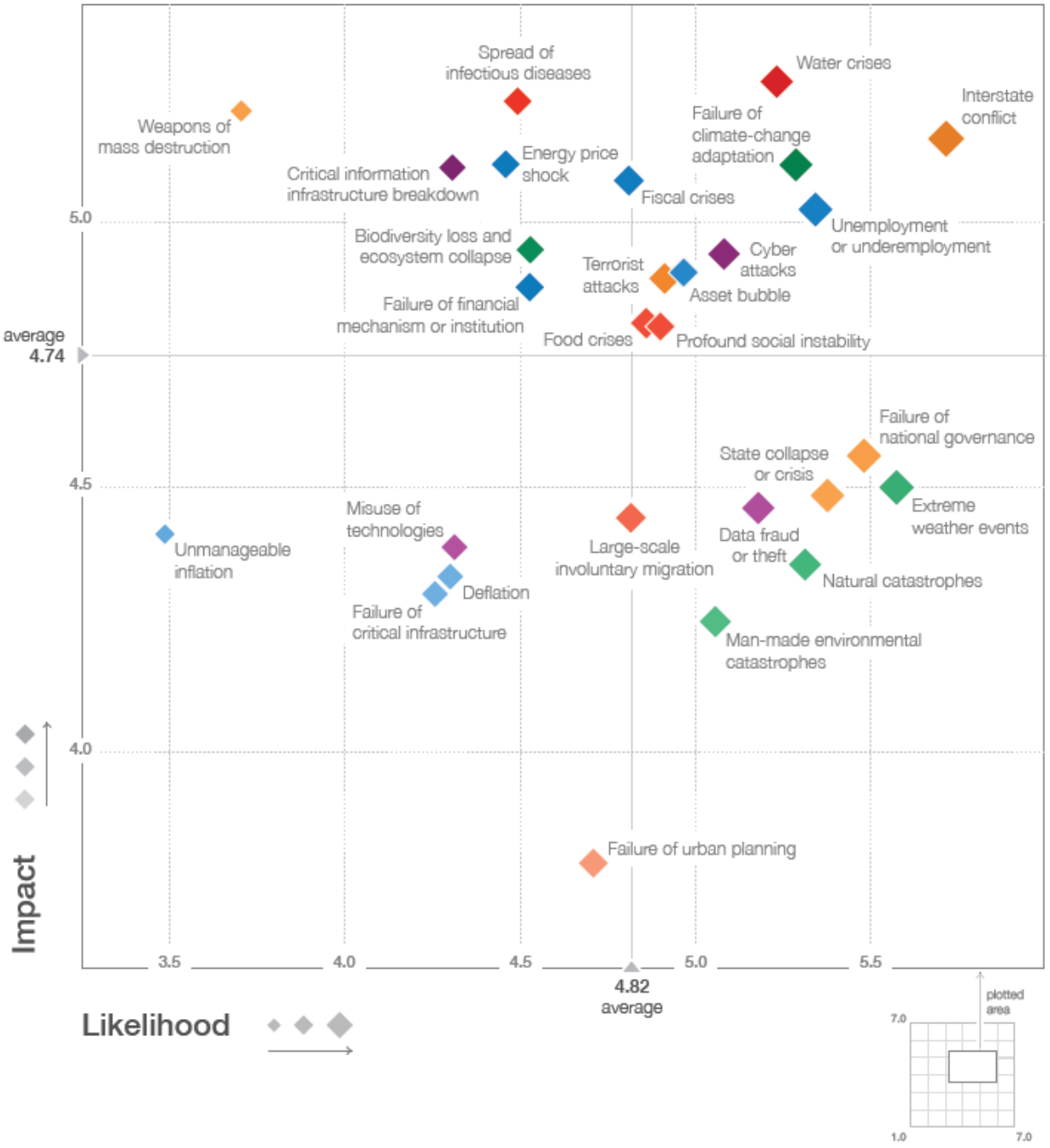


Figure 1: The Global Risks Landscape 2015



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

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

The Washington Post

The Post's View

More pandemics are inevitable, and the U.S. is grossly underprepared

By Editorial Board January 21 at 8:21 PM Follow @postopinions

Female Aedes aegypti mosquitoes are kept in a container in Sao Paulo, Brazil. The Aedes aegypti is a vector for transmitting the Zika virus. (Andre Penner/Associated Press)

WHILE IT has not gained much attention in the United States, Brazil has been struck in recent months with an outbreak of Zika virus that has infected hundreds of thousands of people. Most of the time the symptoms are mild and flu-like, but in some cases health officials say the virus has led to birth defects in babies born to women who were infected in pregnancy. The virus is spread by small insects such as mosquitoes or fleas, and there is no known vaccine to prevent infection.

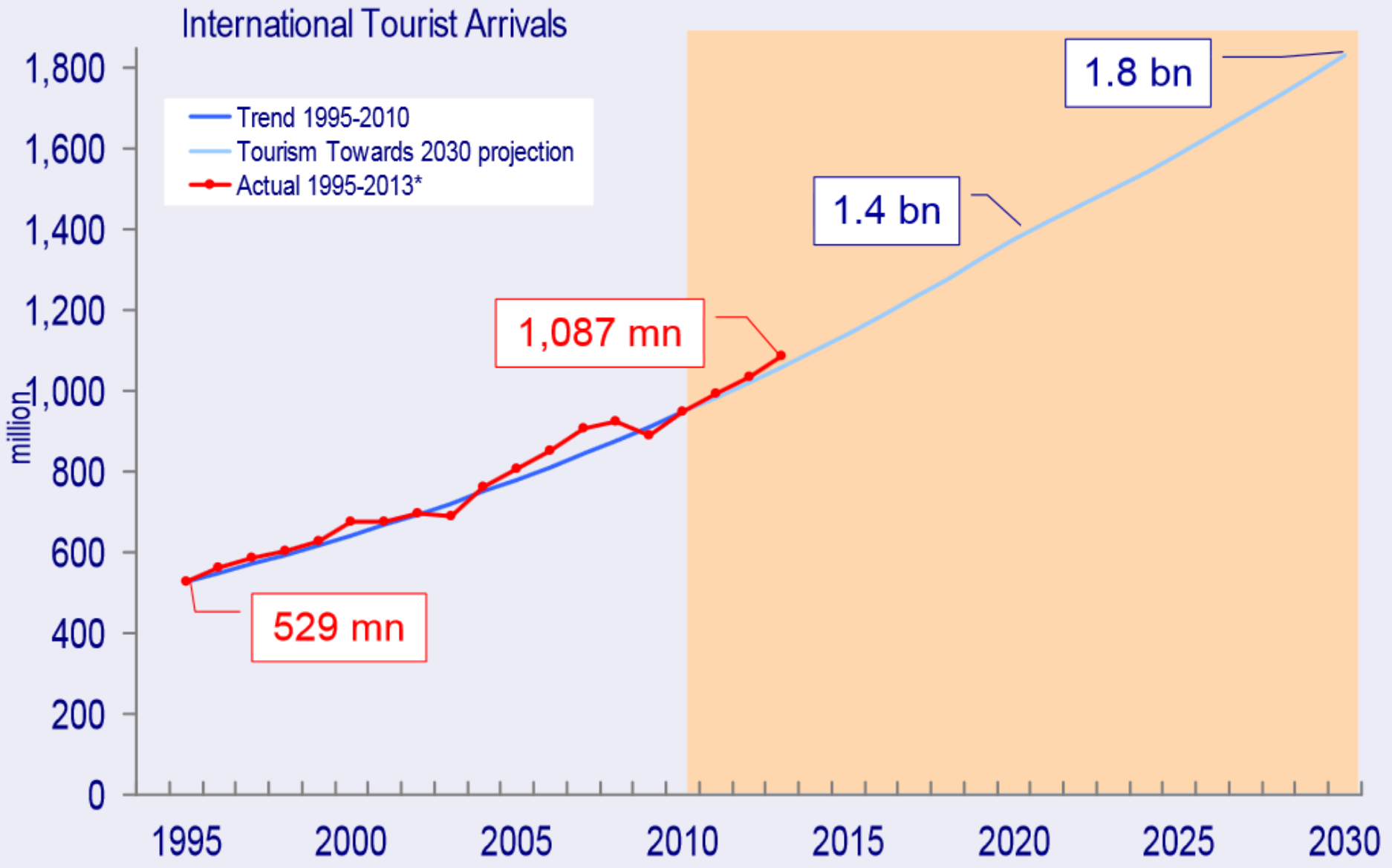
The Zika story might seem easy to dismiss if one is not living in Brazil. Is this just another unpleasant headline about misery far away?

Not quite. In the aftermath of the mishandled and tardy reaction to the Ebola epidemic in West Africa in which more than 11,000 people died, an independent and authoritative commission was set up in the United States to look ahead and draw lessons from this and other recent waves of infectious disease. The 17-member Commission on a Global Health Risk Framework for the Future issued its final report on Jan. 13, and the panel's conclusions are a wake-up call about the threat of pandemic disease that could originate almost anywhere and spread everywhere. Despite all the advances of science, "the

Peri-urban Slum: Mumbai, India

http://www.theguardian.com/world/ng-interactive/2014/aviation-100-years

Actual Trend vs. Tourism Towards 2030 projection World



Source: World Tourism Organization (UNWTO)

World container ship traffic has doubled since 1997

Ship Traffic Worldwide: Thursday, **Feb 11, 2016, 3:50 PM UTC**

Infectious Diseases and Public Health Leadership

- Communicable diseases and public health in the 20th century
- The 21st century "New World Order"
- **The challenges of infectious diseases in the 21st century**
- The opportunities for success

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Infectious Diseases and Global Impact

- The number of deaths or the disability-adjusted life years (DALY) often don't tell the actual story of the societal impact of an infectious disease in the 21st century
- What kills us, versus what hurts us, versus what worries us, versus what scares us is often very different!!!!

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Infectious Diseases Requiring a New Public Health Leadership Approach

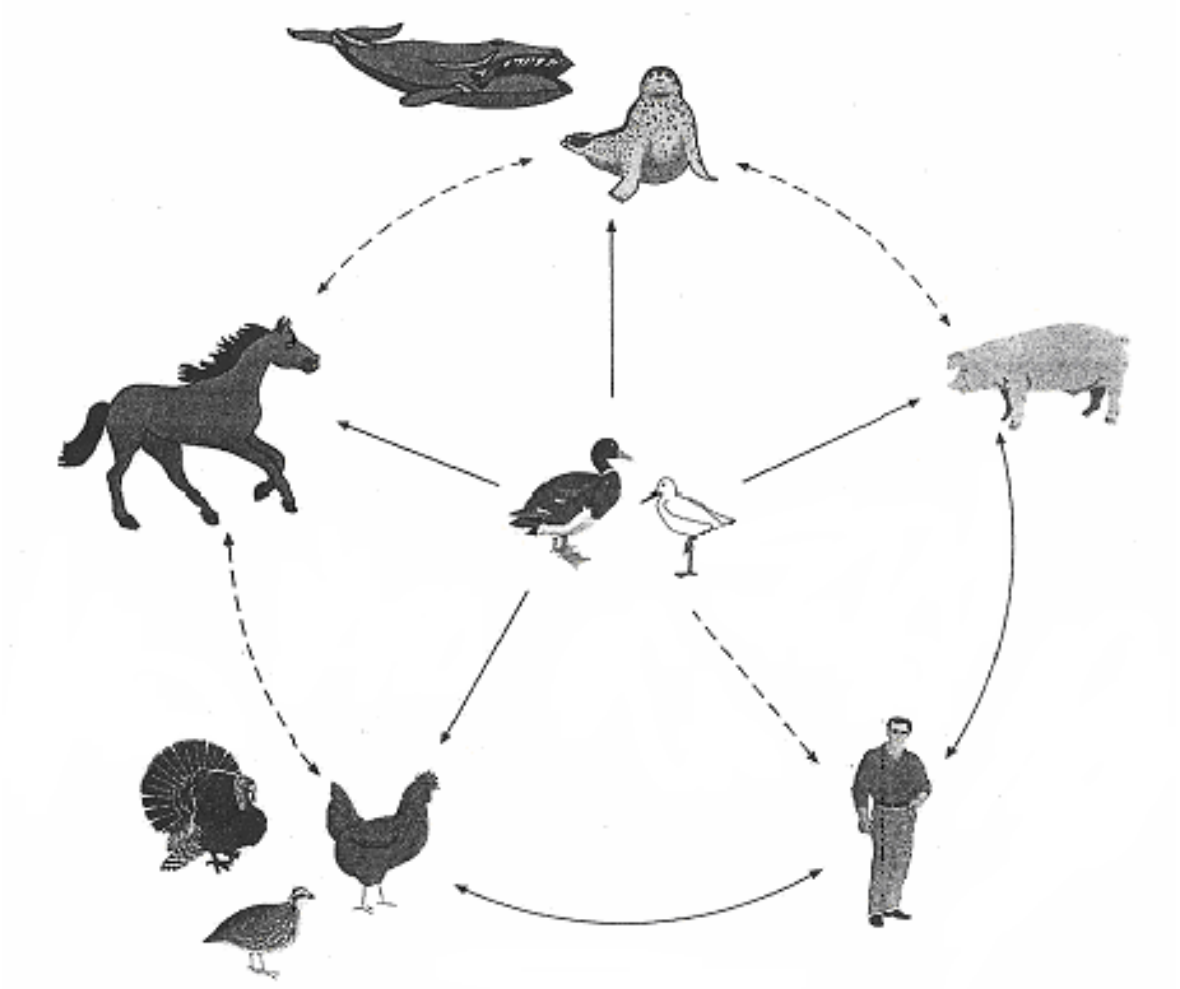
- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - Smallpox
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

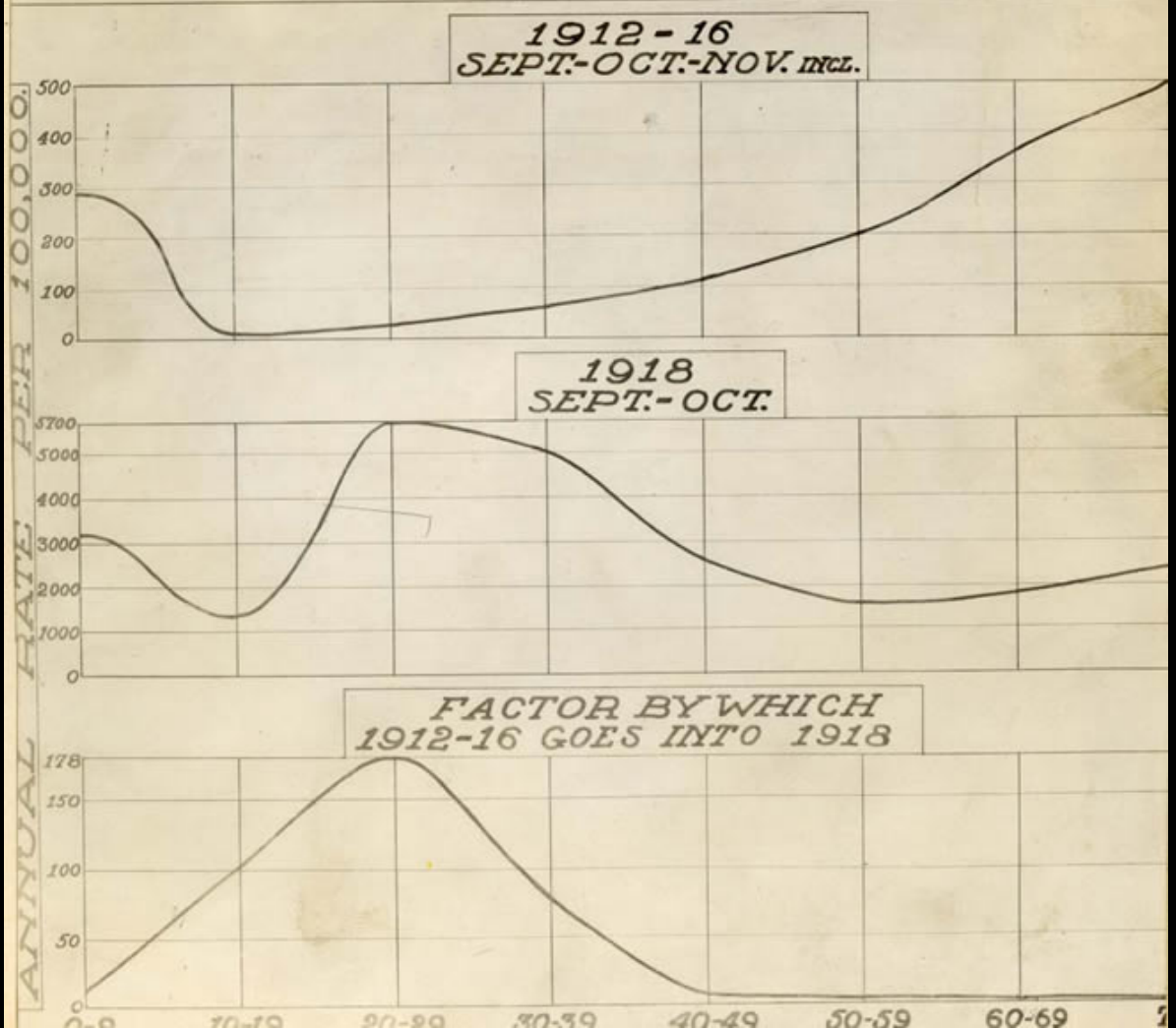
Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - **Influenza**
  - Gain of function-related agents
  - Smallpox
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota



AGE DISTRIBUTION OF DEATHS FROM INFLUENZA AND PNEUMONIA AT BOSTON




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

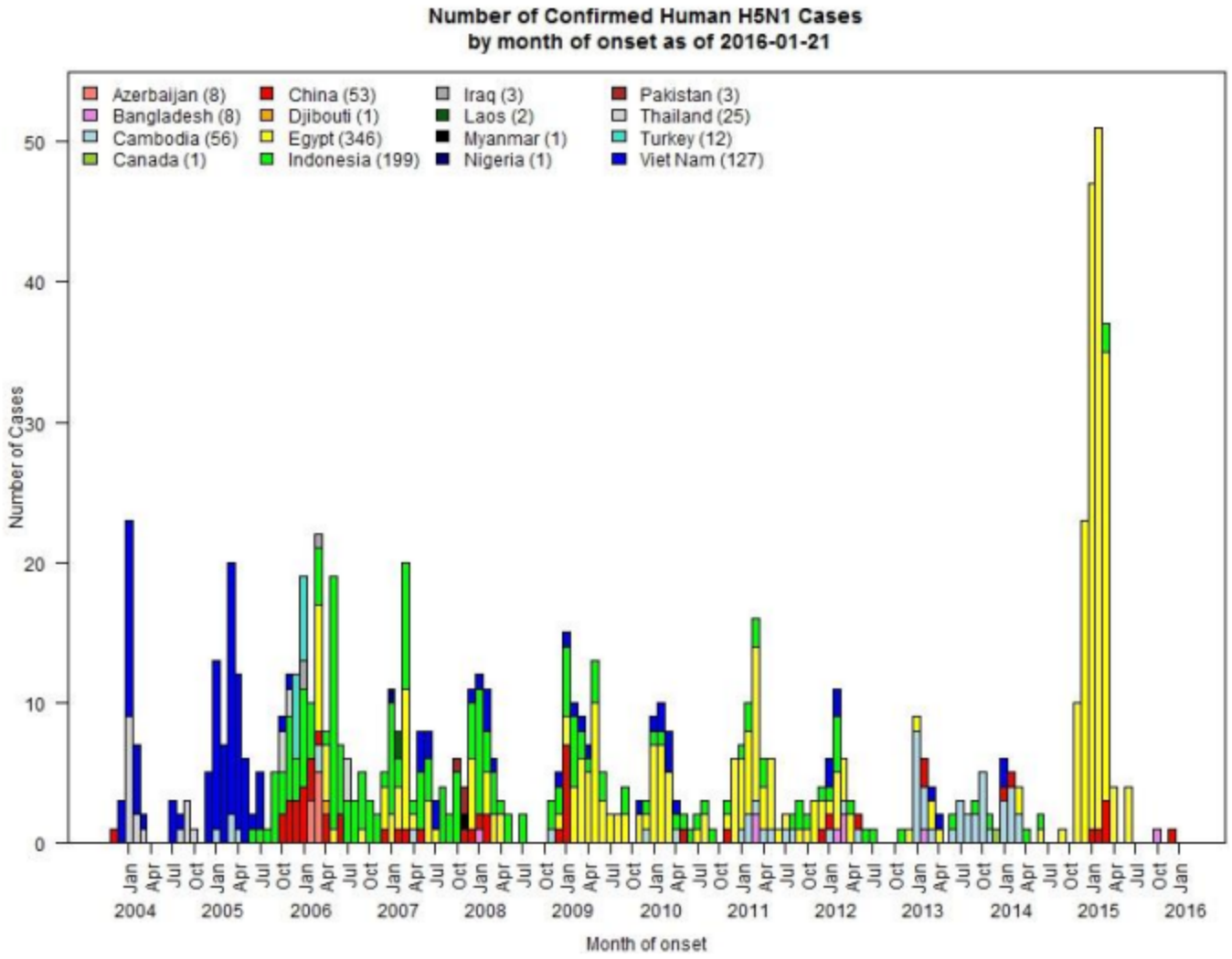
Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

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

World Health Organization

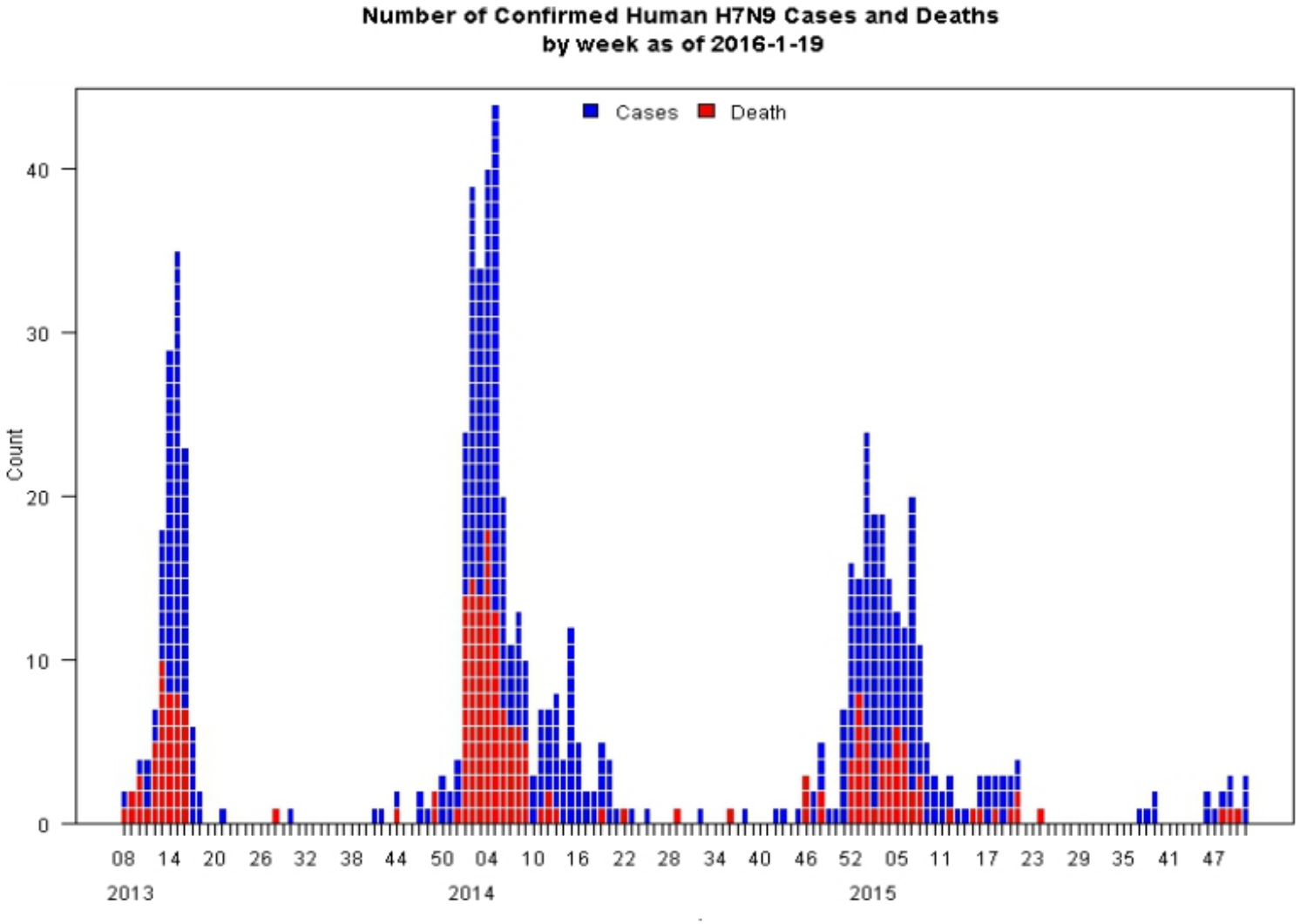
World Health Organization

Figure 1: Epidemiological curve of avian influenza A(H5N1) cases in humans by week of onset, 2004-2016



World Health Organization

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



World Health Organization

Human infection with avian influenza A(H7N9) virus – China

Disease outbreak news
10 February 2016

On 5 February 2016, the National Health and Family Planning Commission (NHFPC) of China notified WHO of 28 additional laboratory-confirmed cases of human infection with avian influenza A (H7N9) virus, including five deaths.

Onset dates ranged from 21 December 2015 to 25 January 2016. Cases ranged in age from 14 to 91 years, with a median age of 58 years. Of these 28 cases, 18 (64%) were male. The majority (25 cases, 89%) reported exposure to live poultry or live poultry markets; the exposure history of three cases is unknown or no clear exposure to poultry. No clusters were reported. Cases were reported from six provinces and municipalities: Zhejiang (13), Jiangsu (5), Guangdong (4), Fujian (3), Shanghai (2) and Hunan (1). See attachment for individual case information.

Detailed information concerning these cases can be found in a separate document (see related links).

Public health response

The Chinese Government has taken the following surveillance and control measures:

- strengthening outbreak surveillance and situation analysis;
- reinforcing all efforts on medical treatment; and
- conducting risk communication with the public and dissemination of information.

WHO risk assessment

WHO is assessing the epidemiological situation and conducting further risk assessment based on the latest information. Based on the information received thus far, the overall public health risk from avian influenza A(H7N9) viruses has not changed.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Probable Hospital Cluster of H7N9 Influenza Infection

N Engl J Med 2016; 374:596-598 | February 11, 2016 | DOI: 10.1056/NEJMc1505359

Article

To the Editor:

Avian influenza A (H7N9) virus emerged in eastern China in the spring of 2013,[1] with 698 cases and 281 deaths reported as of January 10, 2016.[2] Human H7N9 infections appear to be acquired through zoonotic transmission, although clusters of human-to-human household transmission have occurred.[3,4] We report here a hospital cluster of H7N9 infections that took place from January to February 2015. This study was approved by the ethics committee at Shantou University Medical College.

A 28-year-old man (index patient), with repeated exposure to live poultry, presented with respiratory infection and was admitted to the respiratory department, where his condition worsened. Laboratory investigation of serum and sputum samples obtained later in the course of illness showed that he was positive for H7N9 by serologic testing and polymerase-chain-reaction (PCR) assay. Seven days after admission of the index patient, influenza-like illness developed in a 33-year-old male physician (Doctor 1) who attended the index patient. The acute respiratory distress syndrome later developed in this physician. Four days after the onset of symptoms in Doctor 1, influenza-like illness and bronchial pneumonia developed in a second attending physician (Doctor 2), a 35-year-old man, in the same department (Figure 1A). He too had close contact with the index patient. Although standard infection-control practices, including the wearing of personal protective equipment, are hospital policy when caring for patients with H7N9 infection, the use of these practices by the attending physicians while caring for the index patient could not be verified. No other common epidemiologic link among these three persons was identified, and all are unrelated.

FIGURE 1

Clinical Events and Phylogenetic Analysis of the H7N9 Influenza Cluster.

With the use of real-time reverse-transcriptase–PCR assay, seroconversion (hemagglutination-inhibition assay and microneutralization antibody assay), and viral isolation (methods detailed in the Supplementary Appendix, available with the full text of this letter at NEJM.org), H7N9 infection was confirmed in all three persons; they recovered from their illness and were discharged from the hospital (Figure 1A, and Fig. S1, Table S1, Table S2, and case reports in the Supplementary Appendix). Even though the index patient appeared to be convalescent at the time of discharge, he continued to shed H7N9 virus 42 days after the initial onset of symptoms.

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

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.

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.

Funding Alfred P Sloan Foundation.

Published Online
October 26, 2011
DOI:10.1016/S1473-3099(11)70295-X

See Online/Comment
DOI:10.1016/S1473-3099(11)70389-4

Center for Infectious Disease Research and Policy, University of Minnesota, MN, USA (Prof M T Osterholm PhD, N S Kelley PhD); **Department of International Health, and the Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA** (Prof A Sommer MD); **and Epidemiology Research Center, Marshfield Clinic Research Foundation, Marshfield, WI, USA** (EA Belongia MD)

Correspondence to:
Prof Michael Osterholm, Center for Infectious Disease Research and Policy, University of Minnesota, MN 55455, USA
mtoz@umn.edu

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

University of Minnesota
CIDRAP Center for Infectious Disease Research and Policy

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.

n vaccine
related to the
he H3N2

PUBLIC HEALTH

Rethinking Influenza

We have already learned a great deal about fighting influenza, but we need to move from a reactive to a proactive and sustainable stance.

Rino Rappuoli,[1]* Giuseppe Del Giudice,[1] Gary J. Nabel,[2] Albert D. M. E. Osterhaus,[3] Robin Robinson,[4] David Salisbury,[5] Klaus Stöhr,[6] John J. Treanor[7]

Today, we are better prepared to face the H1N1 influenza A 2009 virus than we were for any other previous pandemic. Although the present manufacturing capacity is unlikely to have all the vaccines needed before the peak of the next wave of cases, the potential output of vaccine manufacturing has increased from 400 to 900 million (*1*). A vaccine will be produced in Europe with modern cell culture technology instead of eggs. A large facility for cell culture production under construction in the United States is expected to improve the current limited production capacity. Although vaccines against avian H5N1 are not highly immunogenic, this shortcoming can be overcome by using adjuvants or reverting to using whole-virus vaccines (*2*–*5*).

Adjuvants based on oil-in-water emulsions, such as MF59 and AS03, are licensed in Europe and, although their approval in the United States is still a work in progress, they can be used under the Emergency Use Application legislation. MF59 has already been used in vaccination of more than 45 million people. Although yields may be lower than those of seasonal vaccines, preliminary data from clinical trials suggest that protection against H1N1 may be achieved with only one vaccine dose (*6*, *7*). On 13 July, the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) advised that priority should be given to maintaining the infrastructure by vaccinating health workers, then to reducing deaths by vaccinating pregnant women and people with chronic medical conditions, followed by vaccination of children and young people to reduce transmission (*8*). H1N1 vaccinations should be monitored to provide information on vaccine and adjuvant safety on a large scale. It will be necessary to establish the background rates of death, miscarriages, Guillain-Barré syndrome, and so on, in populations to be vaccinated in order to see whether changes in rates occur after vaccination.

The current approach of responding to influenza outbreaks in a reactive rather than anticipatory mode is not optimal, but because most of our knowledge of influenza virus is based on data accumulated in developed countries, we have an incomplete, and sometimes inaccurate, view of virus spread and its global impacts. For example, in many low-income and tropical regions, influenza is not markedly seasonal; it persists year-round and often manifests itself as pneumonia. In the few developing countries where studies have been performed, influenza has been associated with an unexpectedly high mortality rate among infants and children (*9*, *10*). Therefore, improved influenza surveillance in developing countries is needed, and it seems appropriate to add influenza to the vaccines recommended by the Expanded Program for Immunization (EPI). Potential sources for funding could derive from one of the existing models such as the Advanced Market Commitment. The increase in vaccination would be based on the excess manufacturing capacity for seasonal vaccines now and would encourage both international and local vaccine manufacturers to invest in additional capacity, so as to sustain the surge capacity that is necessary in case of a pandemic. Pediatric vaccination remains a problem in developed countries. At present, only the United States, Finland, and Mexico recommend vaccination of children, and implementation is low. To improve implementation, studies are required that analyze differences in seasonal patterns of the disease, whether yearly pediatric vaccination is necessary (especially in the absence of strong antigenic drift), and whether adjuvants promote multiyear protection. Vaccination during pregnancy and/or linking influenza to vaccines that target clinically important infections, such as *Streptococcus pneumoniae*, also need investigation.

Finally, a definitive solution to influenza cannot be achieved without addressing the development of additional antiviral drugs and the gaps in knowledge about the virus, including the role in protection of antibodies, T cells, and immune memory, as well as the determinants of transmissibility and disease susceptibility. Epidemiological studies need to include developing countries, humans, their livestock, and wild animals to be able to map the diversity and circulation of the virus.

Until H1N1, the scientific community believed that a pandemic strain could only arise from a strain that had not previously been widely disseminated in humans. However, the H1N1 virus has shown that human varieties characterized by different hemagglutinin (HA) molecules may follow separate lines of evolution and may generate potentially pandemic strains within an existing human HA type. Hence, it is essential to develop methods for estimating how many antigenically different subtypes may reside within each HA type.

Research toward development of a universal vaccine should be accelerated by testing adjuvants to increase cross-protection, conserved antigens (such as M2 and NP), or different vaccine platforms (such as the live attenuated vaccines) (*11*), and alternative approaches to vaccine delivery. In conclusion, although the H1N1 pandemic has the potential to cause a social and economic emergency, it also provides an opportunity to rethink our approach to influenza virus disease and to develop more effective vaccines and economically sustainable solutions for developing and developed countries.

[1]Novartis Vaccines and Diagnostics Srl, 53100 Siena, Italy. [2]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD 20892–3005, USA. [3]Erasmus University, 3015E Rotterdam, Netherlands. [4]U.S. Department of Health and Human Services (HHS), Washington, DC 20201, USA. [5]World Health Organization (WHO), Strategic Advisory Group of Experts (SAGE) on Immunization, 1211 Geneva 27, Switzerland. [6]Novartis Vaccines and Diagnostics, Inc., Cambridge, MA 02139, USA. [7]University of Rochester, Rochester, NY 14642, USA.

*Author for correspondence. E-mail: rino.rappuoli@novartis.com

References and Notes

1. International Federation of Pharmaceutical and Manufacturers & Associations, presentation at Influenza Vaccines for the World (IVW) 2009, Cannes, France, 27 to 30 April 2009; www.ifpma.org/influenza/content/pdfs/Presentations/2009_04_27_Bridging_the_Gap_Cannes.pdf.
2. J. J. Treanor, J. D. Campbell, K. M. Zangwill, T. Rowe, M. Wolff, *N. Engl. J. Med.* **354**, 1343 (2006).
3. I. Leroux-Roels *et al.*, *Lancet* **370**, 580 (2007).
4. G. Galli *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 7962 (2009).
5. H. J. Ehrlich *et al.*, *N. Engl. J. Med.* **358**, 2573 (2008).
6. H. B. Greenberg *et al.*, *N. Engl. J. Med.* (2009).
7. T. W. Clark *et al.*, *N. Engl. J. Med.* (2009).
8. WHO, "Update on A(H1N1) pandemic and seasonal vaccine availability" (WHO, Geneva, 2009), www.who.int/immunization/sage/8_MPK-SAGE_7_July.pdf.
9. W. Abdullah Brooks *et al.*, *Emerg. Infect. Dis.* **13**, 1507 (2007).
10. K. Zaman *et al.*, *N. Engl. J. Med.* **359**, 1555 (2008).
11. Live attenuated vaccines for seasonal vaccination are approved for immunization of individuals 2 to 49 years of age and do not cover the elderly and infants below 2 years of age.
12. The views expressed represent those of the authors, but do not necessarily reflect those of their institutions. They also do not constitute an endorsement of a specific commercial product.

10.1126/science.1179475

POLICYFORUM

PUBLIC HEALTH

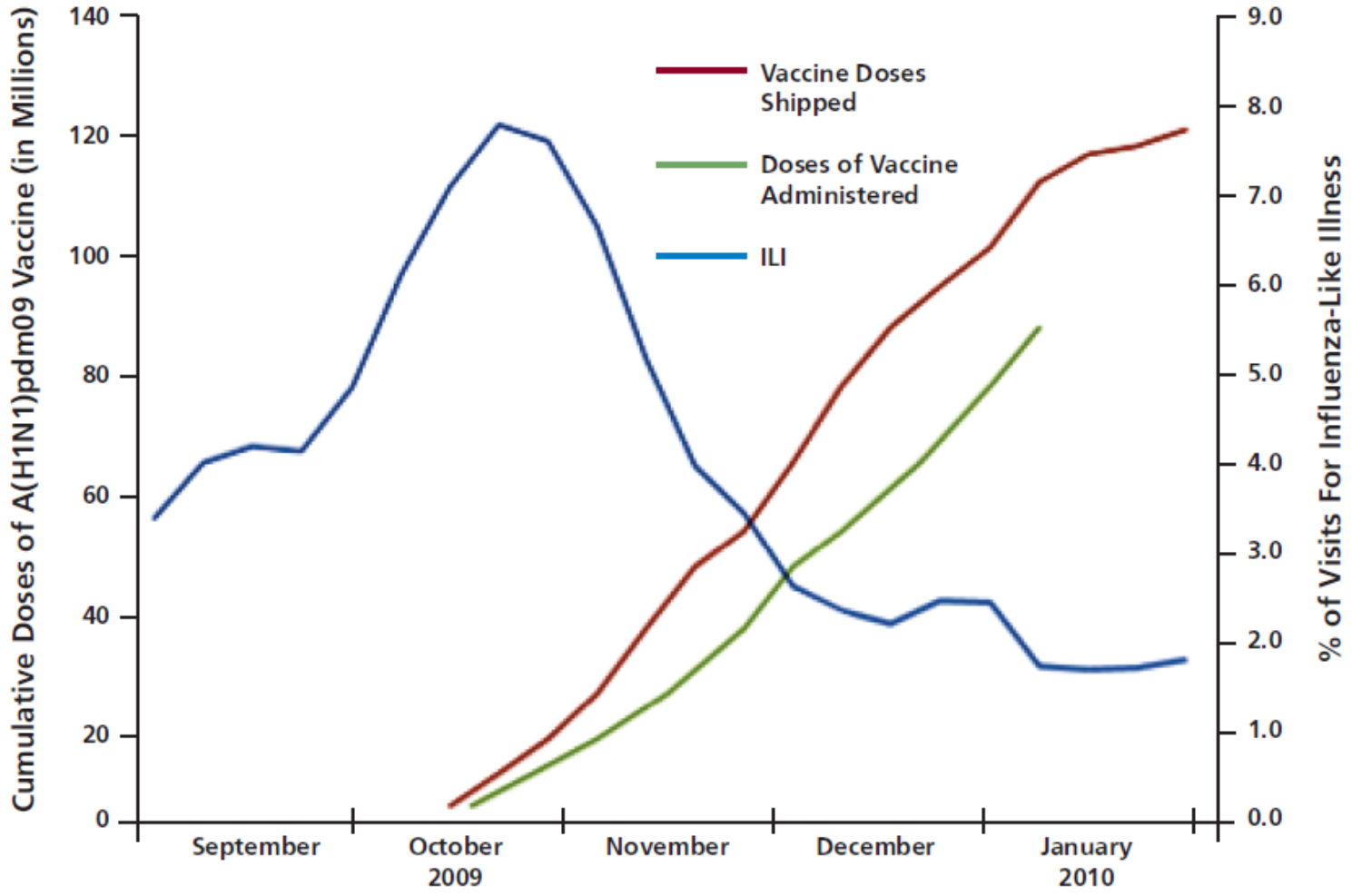
Rethinking Influenza

Rino Rappuoli,[1]* Giuseppe Del Giudice,[1] Gary J. Nabel,[2] Albert D. M. E. Osterhaus,[3] Robin Robinson,[4] David Salisbury,[5] Klaus Stöhr,[6] John J. Treanor[7]

2 OCTOBER 2009 VOL 326 SCIENCE

Today, we are better prepared to face the H1N1 influenza A 2009 virus than we were for any other previous pandemic. Although the present manufacturing capacity is unlikely to have all the vaccines needed before the peak of the next wave of cases, the potential output of vaccine manufacturing has increased from 400 to 900 million (*1*). A vaccine will be produced in Europe with modern cell culture technology instead of eggs. A large facility for cell culture production under construction in the United States is expected to improve the current limited production capacity. Although vaccines against avian H5N1 are not highly immunogenic, this shortcoming can be overcome by using adjuvants or reverting to using whole-virus vaccines (*2*–*5*).

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.

Prospects for Broadly Protective Influenza Vaccines

John Jay Treanor

The development of vaccines that could provide broad protection against antigenically variant influenza viruses has long been the ultimate prize in influenza research. Recent developments have pushed us closer to this goal, and such vaccines may now be within reach. This brief review outlines the current approaches to broadly protective vaccines, and the probable hurdles and roadblocks to achieving this goal.

(Am J Prev Med 2015;49(6S4):S355–S363)

Introduction

It was only a few years after the discovery of influenza virus as the cause of the disease, that it was shown that injection of animals with a preparation of inactivated virus could protect them against subsequent exposure to influenza.[1] These observations were rapidly extended to humans, with controlled clinical trials demonstrating the protective efficacy of inactivated influenza vaccine in healthy adults as early as 1943,[2] and licensing of influenza vaccine in the U.S. in 1945. However, the conquest of influenza was dealt a severe blow in 1949 with the failure of the vaccine to prevent disease due to a new variant of influenza, A/Fort Monmouth/49.[3] This new virus was antigenically very different from preceding influenza viruses, which were subsequently denoted as influenza A_0, while the new variant was called influenza A' (we now recognize all of these viruses as H1N1 viruses).[4] The realization that effective vaccination against influenza might require continual reformulation of the vaccine to match antigenic changes to the virus was felt by some at the time to mean that control of influenza through vaccination was impractical.

After 70 years, nothing much has really changed. Reformulation of the vaccine is still required almost every year, putting enormous pressure on manufacturers and regulatory authorities to make decisions about formulations and have the appropriate vaccine ready in time. The complexity of the vaccine has increased, from two strains to three strains in the late 1970s, and more recently, from three strains to four strains. And, the development and stockpiling of vaccines that might provide protection against pandemic influenza A viruses with novel surface antigens, such as H5N1, H7N9, H9N2, and the like, remains a formidable challenge. Influenza vaccines that could potentially provide protection against multiple antigenic variants within a hemagluttinin subtype (heterovariant immunity), between subtypes (heterosubtypic immunity) or against both influenza type A and B viruses (heterotypic immunity) remains a very important but elusive goal, sometimes referred to as the "holy grail" of influenza vaccinology. However, recent observations on the immune response to influenza infection may be leading to a pathway toward such "universal" vaccines. This brief review will discuss the basic strategy used for current vaccines and the potential targets that have been identified as strategies for more broadly protective vaccination.

Current Influenza Vaccines

Current inactivated vaccines are designed to induce serum antibody directed at the globular head, or HA1 domain, of the viral hemagglutinin (HA). Antibody to the globular head region of the HA interferes with the ability of the virus to bind to its cellular receptor(s), and is reflected in assays that measure inhibition of agglutination of red blood cells by the virus (hemagglutination-inhibition, or HAI) and viral neutralization in vitro. Inactivated influenza vaccines are standardized for content based on the amount of immunologically reactive HA protein they contain, and new inactivated vaccines can receive provisional licensure based on their ability to induce specific titers of HAI antibody.

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, Box 689, 601 Elmwood Avenue, Rochester, NY 14642, United States

Address correspondence to: Tel.: +1 585 275 5871; fax: +1 585 442 9328. E-mail: john_treanor@urmc.rochester.edu.

0749-3797/$36.00
http://dx.doi.org/10.1016/j.amepre.2015.09.012

GIZMODO

Scientists Create a Blueprint For the First Universal Flu Vaccine

Adam Clark Estes

9/23/13 11:40am · Filed to: SCIENCE

A team of British scientists just took a major stride forward in the quest to develop a universal flu vaccine. Using data gathered after the 2009 swine flu outbreak, the team from the Imperial College London have a game plan to develop a vaccine that stands to save as many as half a million lives every year.

The key to the latest flu research can be found in immune cells known as CD8 T cells. Research showed those of the 341 subjects in the swine flu study, those who had more CD8 T cells in their blood experienced less severe symptoms or no symptoms at all. A new vaccine would simply instruct the body to produce more of these types of cells.

"It's a blueprint for a vaccine. We know the exact subgroup of the immune system and we've identified the key fragments in the internal core of the virus," Professor Ajit Lalvani, who led the study, told the BBC. "In truth, in this case it is about five years [away from a vaccine]. We have the know-how, we know what needs to be in the vaccine and we can just get on and do it."

So now comes the fun part: Actually developing the vaccine. Those currently working on it say that some vaccines in use are better at increasing the T cell count, but they only work in children. Now the challenge will be to develop a universal vaccine that will work on anybody. [BBC]

Sciencexpress Research Articles

A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen

Antonietta Impagliazzo,[1*†] Fin Milder,[1‡§] Harmjan Kuipers,[1‡§] Michelle Wagner,[2‡||] Xueyong Zhu,[3‡] Ryan M. B. Hoffman,[3‡] Ruud van Meersbergen,[1§] Jeroen Huizingh,[1§] Patrick Wanningen,[1§] Johan Verspuij,[1§] Martijn de Man,[1§] Zhaoqing Ding,[2||] Adrian Apetri,[1†] Başak Kükrer,[1†] Eveline Sneekes-Vriese,[1] Danuta Tomkiewicz,[1†] Nick S. Laursen,[3¶] Peter S. Lee,[3] Anna Zakrzewska,[1§] Liesbeth Dekking,[1§] Jeroen Tolboom,[1§] Lisanne Tettero,[1§] Sander van Meerten,[1§] Wenli Yu,[3] Wouter Koudstaal,[1†] Jaap Goudsmit,[1†] Andrew B. Ward,[3] Wim Meijberg,[1§] Ian A. Wilson,[3*] Katarina Radošević[1#]

[1]Crucell Vaccine Institute, Janssen Center of Excellence for Immunoprophylaxis, Archimedesweg 4-6, 2301 CA Leiden, Netherlands. [2]Crucell Vaccine Institute, Janssen Center of Excellence for Immunoprophylaxis, 3210 Merryfield Row, San Diego, CA 92121, USA. [3]Department of Integrative Structural and Computational Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

*Corresponding author. E-mail: aimpagli@its.jnj.com (A.I.); wilson@scripps.edu (I.A.W.)

†Present address: Janssen Prevention Center, Janssen Pharmaceutical Companies of Johnson & Johnson, Archimedesweg 4-6, 2301 CA Leiden, Netherlands.

‡These authors contributed equally to this work.

influenza viruses (*1*–*7*) has raised hopes that a broadly protective vaccine may indeed be feasible (*8*–*12*). The majority of these bnAbs are directed toward highly conserved conformational epitopes in the HA stem (*1*, *2*, *4*, *5*, *7*) suggesting that this region may have the potential to induce broad protective immunity, provided it is well exposed and properly presented. Various strategies to enhance exposure of the HA stem to the immune system are being explored, including presentation on self-assembling nanoparticles (*13*), chimeric HAs (*14*, *15*), epitope transplantation on a virus-like particle (VLP) (*16*), and immune refocusing (*17*). Yet another approach involves removal of the HA head while stabilizing the HA stem. A prerequisite for generating a broadly protective soluble HA stem immunogen is

nature medicine

Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection

Hadi M Yassine[1,6], Jeffrey C Boyington[1,6], Patrick M McTamney[1,5,6], Chih-Jen Wei[1,5,6], Masaru Kanekiyo[1], Wing-Pui Kong[1], John R Gallagher[2], Lingshu Wang[1], Yi Zhang[1], M Gordon Joyce[1], Daniel Lingwood[1,5], Syed M Moin[1], Hanne Andersen[3], Yoshinobu Okuno[4], Srinivas S Rao[1,5], Audray K Harris[2], Peter D Kwong[1], John R Mascola[1], Gary J Nabel[1,5] & Barney S Graham[1]

The antibody response to influenza is primarily focused on the head region of the hemagglutinin (HA) glycoprotein, which in turn undergoes antigenic drift, thus necessitating annual updates of influenza vaccines. In contrast, the immunogenically subdominant stem region of HA is highly conserved and recognized by antibodies capable of binding multiple HA subtypes[1–6]. Here we report the structure-based development of an H1 HA stem–only immunogen that confers heterosubtypic protection in mice and ferrets. Six iterative cycles of structure-based design (Gen1–Gen6) yielded successive H1 HA stabilized-stem (HA–SS) immunogens that lack the immunodominant head domain. Antigenic characterization, determination of two HA–SS crystal structures in complex with stem-specific monoclonal antibodies and cryo-electron microscopy analysis of HA–SS on ferritin nanoparticles (H1–SS–np) confirmed the preservation

(HA–SS) glycoproteins that lack the immunodominant HA head region (**Fig. 1** and **Supplementary Fig. 1**).

We used the ectodomain of H1N1 A/New Caledonia/20/1999 (H1 1999 NC) HA, the crystal structures of H1N1 A/South Carolina/1/1918 (H1 1918 SC) HA (PDB 3GBN)[2] and a foldon trimerization domain (PDB 1RFO) as design templates and evaluated each generation of HA–SS variant for expression as soluble trimers and for antigenicity on the basis of reactivity to stem-specific monoclonal antibodies (mAbs). The first four generations of HA–SS designs entailed the successive replacement of the HA head region with a short linker (Gen1 HA–SS), replacement of the membrane-distal region of HA2 with a thermostable HIV-1 glycoprotein 41 (gp41) trimerization domain[7] (Gen2 HA–SS), further truncation of membrane-distal HA1 and HA2 regions of the stem (Gen3 HA–SS) and mutations in the linker between HA and gp41 (Gen4 HA–SS) (**Fig. 1**, **Supplementary**

J&J Researchers Move Closer to Developing Universal Flu Vaccine

by Cynthia Koons

August 24, 2015 — 10:00 AM CDT

Researchers at Johnson & Johnson are getting closer to developing a universal flu vaccine that could work against a number of strains of the virus, a holy grail for the medical field that could eliminate the need to formulate a new vaccine every year.

A study conducted by the Scripps Research Institute and J&J's Janssen Pharmaceutical unit showed that, in mice and monkeys, a molecule designed in the lab to mimic a key part of the flu virus's attack could protect against multiple influenza strains, not just one.

The findings, published online Monday by the journal Science, are just a "proof of principle," and much work is left to be done to make a vaccine that works in humans.

THE COMPELLING NEED FOR GAME-CHANGING INFLUENZA VACCINES

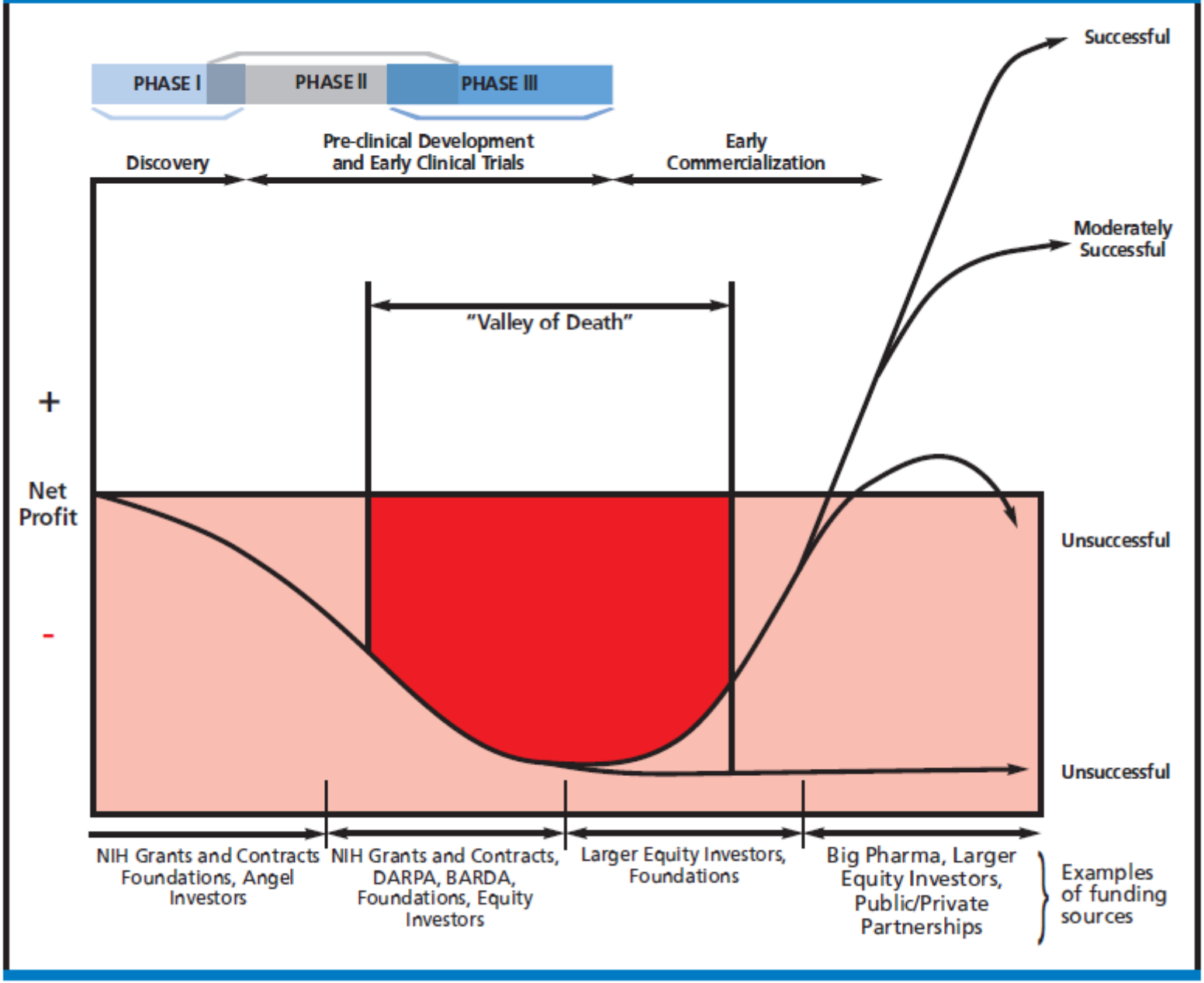
AN ANALYSIS OF THE INFLUENZA VACCINE ENTERPRISE AND RECOMMENDATIONS FOR THE FUTURE

OCTOBER 2012

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Contents

FIGURE 12-1. Market Dynamics for Developing Novel-Antigen Game-Changing Influenza Vaccines



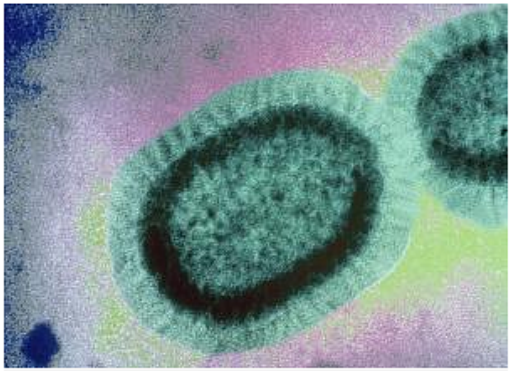
University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

BARDA: Recent 'universal' flu vaccine proposals fell short

Filed Under: **Avian Influenza (Bird Flu)**; **Business Preparedness**; **Pandemic Influenza**

Robert Roos | News Editor | CIDRAP News | Jul 23, 2015



Sanof Pasteur / Flickr cc

The quest for a broadly protective or "universal" influenza vaccine suffered a setback recently when the US Biomedical Research and Development Authority (BARDA) determined that industry plans submitted in response to a formal request for proposals (RFP) fell short of the government's requirements, according to BARDA Director Robin Robinson, PhD.

"From the RFP we had a number of proposals and unfortunately none of those met our minimum mandatory requirements. Some of them were maybe 6 months away from meeting our requirements," Robinson told CIDRAP News in an interview about BARDA's pandemic flu preparedness programs.

Robinson said BARDA, which is part of the Department of Health and Human Services (HHS), plans to issue a "broad agency announcement" in October to renew the call for proposals for advanced development of broadly protective flu vaccines. He expects that some of the proposals that didn't meet the requirements will be more mature by then.

In other comments, Robinson said BARDA is supporting development of two vaccines for the H5N8 avian flu virus and hopes to develop a vaccine for the H5N2 virus, in case either of those evolves into a human pathogen. He also voiced concern about the agency's future pandemic flu funding, as bills now in Congress would provide far less than the $170 million the Obama administration has requested for fiscal year 2016.

STAT | Reporting from the frontiers of health and medicine

HEALTH

Flu hearing turns tense as Congress questions progress on vaccines

BALCE CENETA/AP

By SHEILA KAPLAN NOVEMBER 19, 2015

WASHINGTON — Lawmakers fiercely questioned federal officials at a congressional hearing Thursday on US preparedness for seasonal influenza, demanding to know why the flu remains a serious threat to public health.

The atmosphere at the hearing, held by the House Energy and Commerce Committee Oversight and Investigations subcommittee, quickly turned tense as members of Congress challenged witnesses from the the nation's public health agencies to explain why more progress has not been made in developing effective flu vaccines and treatments.

Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - Influenza
  - **Gain of function-related agents**
  - Smallpox
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

PUBLIC HEALTH AND BIOSECURITY

Adaptations of Avian Flu Virus Are a Cause for Concern

Members of the National Science Advisory Board for Biosecurity explain its recommendations on the communication of experimental work on H5N1 influenza.

Kenneth L. Berns,[1*] Arturo Casadevall,[2] Murray L. Cohen,[3] Susan A. Ehrlich,[4] Lynn W. Enquist,[5] J. Patrick Fitch,[6] David R. Franz,[7] Claire M. Fraser-Liggett,[8] Christine M. Grant,[9] Michael J. Imperiale,[10] Joseph Kanabrocki,[11] Paul S. Keim,[12†] Stanley M. Lemon,[13] Stuart B. Levy,[14] John R. Lumpkin,[15] Jeffery E. Miller,[16] Randall Murch,[17] Mark E. Nance,[18] Michael T. Osterholm,[19] David A. Relman,[20] James A. Roth,[21] Anne K. Vidaver[22]

We are in the midst of a revolutionary period in the life sciences. Technological capabilities have dramatically expanded, we have a much improved understanding of the complex biology of selected microorganisms, and we have a much improved ability to manipulate microbial genomes. With this has come unprecedented potential for better control of infectious diseases and significant societal benefit. However, there is also a growing risk that the same science will be deliberately misused and that the consequences could be catastrophic. Efforts to describe or define life-sciences research of particular concern have focused on the possibility that knowledge or products derived from such research, or new technologies, could be directly misapplied with a sufficiently broad scope to affect national or global security. Research that might greatly enhance the harm caused by microbial pathogens has been of special concern (*1*–*3*). Until now, these efforts have suffered from a lack of specificity and a paucity of concrete examples of "dual use research of concern" (*3*). Dual use is defined as research that could be used for good or bad purposes. We are now confronted by a potent, real-world example.

Highly pathogenic avian influenza A/H5N1 infection of humans has been a serious public health concern since its identification in 1997 in Asia. This virus rarely infects humans, but when it does, it causes severe disease with case fatality rates of 59% (*4*). To date, the transmission of influenza A/H5N1 virus from human to human has been rare, and no human pandemic has occurred. If influenza A/H5N1 virus acquired the capacity for human-to-human spread and retained its current virulence, we could face an epidemic of substantial proportions. Historically, epidemics or pandemics with high mortalities have been documented when humans interact with new agents for which they have no immunity, such as with *Yersinia pestis* (plague) in the Middle Ages and the introduction of smallpox and measles into the Americas after the arrival of Europeans.

Recently, several scientific research teams have achieved some success in isolating influenza A/H5N1 viruses that are transmitted efficiently between mammals, in one instance with maintenance of high pathogenicity. This information is very important because, before these experiments were done, it was uncertain whether avian influenza A/H5N1 could ever acquire the capacity for mammal-to-mammal transmission. Now that this information is known, society can take steps globally to prepare for when nature might generate such a virus spontaneously. At the same time, these scientific results also represent a grave concern for global biosecurity, biosafety, and public health. Could this knowledge, in the hands of malevolent individuals, organizations, or governments, allow construction of a genetically altered influenza virus capable of causing a pandemic with mortality exceeding that of the "Spanish flu" epidemic of 1918? The research teams that performed this work did so in a well-intended effort to discover evolutionary routes by which avian influenza A/H5N1 viruses might adapt to humans. Such knowledge may be valuable for improving the public health response to a looming natural threat. And, to their credit and that of the peer reviewers selected by the journals *Science* and *Nature*, the journals themselves, as well as the U.S. government, it was recognized before their publication that these experiments had dual use of concern potential.

"Communication … should be greatly limited in terms of the experimental details and results."

The U.S. government asked the National Science Advisory Board for Biosecurity (NSABB) (*5*), to assess the dual-use research implications of two as-yet-unpublished manuscripts on the avian influenza A/H5N1 virus, to consider the risks and benefits of communicating the research results, and to provide findings and recommendations regarding the responsible communication of this research.

Risk assessment of public harm is challenging because it necessitates consideration of the intent and capability of those who wish to do harm, as well as the vulnerability of the public and the status of public health preparedness for both deliberate and accidental events. We found the potential risk of public harm to be of unusually high magnitude. In formulating our recommendations to the government, scientific journals, and the broader scientific community, we tried to balance the great risks against the benefits that could come from making the details of this research known. Because the NSABB found that there was significant potential for harm in fully publishing these results and that the harm exceeded the benefits of publication, we therefore recommended that the work not be fully communicated in an open forum. The

[1]Genetics Institute, University of Florida, Gainesville, FL 32611, USA. [2]Albert Einstein School of Medicine, Bronx, NY 10461, USA. [3]Frontline Healthcare Workers Safety Foundation, Ltd., Atlanta, GA 30338, USA. [4]University of Texas Medical Branch, Galveston, TX 77555, USA. [5]Princeton University, Princeton, NJ 08544, USA. [6]Battelle National Biodefense Institute, LLC, Frederick, MD 21702, USA. [7]MRI Global, Frederick, MD 21702, USA. [8]University of Maryland School of Medicine, Baltimore, MD 21201, USA. [9]InfecDetect Rapid Diagnostic Tests, LLC, Princeton, NJ 08540, USA. [10]University of Michigan Medical School, Ann Arbor, MI 48109, USA. [11]University of Chicago, Chicago, IL 60637, USA. [12]Northern Arizona University, Flagstaff, AZ 86011, and Translational Genomics Research Institute, Phoenix, AZ 85004, USA. [13]University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA. [14]Tufts University School of Medicine, Boston, MA 02111, USA. [15]The Robert Wood Johnson Foundation, Princeton, NJ 08540, USA. [16]University of California–Los Angeles, Los Angeles, CA 90095, USA. [17]Virginia Polytechnic Institute and State University–Virginia Tech Resource Center, Arlington, VA 22203, USA. [18]GE Healthcare, Princeton, NJ 08540, USA. [19]University of Minnesota, Minneapolis, MN 55455, USA. [20]Stanford University School of Medicine, Stanford, CA 94305, USA. [21]Center for Food Security and Public Health, Iowa State University, Ames, IA 50011, USA. [22]University of Nebraska, Lincoln, NE 68588, USA.

*The authors are members of the U.S. National Science Advisory Board for Biosecurity. †Author for correspondence. E-mail: Paul.Keim@nau.edu

Life Sciences at a Crossroads: Respiratory Transmissible H5N1

Release of details of recent research on affecting influenza transmissibility poses far more risk than any good that might occur.

Michael T. Osterholm* and Donald A. Henderson

Two recently submitted manuscripts to *Science* and *Nature* report success in creating mutant isolates of influenza A/H5N1 that are able to be transmitted by respiratory droplet or aerosol between mammals (ferrets). The studies imply that human-to-human transmission could be possible as well. Shortly after the submission of the papers to the journals, the National Science Advisory Board for Biosecurity (NSABB) was asked by the U.S. government to address this question. The NSABB recommended that the papers not be fully published; rather, the basic results of the studies should be communicated without methods or detailed results but in sufficient detail to maximize the benefits to society of the studies' findings. In turn, these recommendations were accepted by the U.S. government and shared with the authors and the editors of *Science* and *Nature*.

Some have asserted that these recommendations represent unwarranted censorship of scientific research and that the sharing of the results, particularly the specific viral mutations, is necessary to protect global public health. They argue that sharing the virus mutation information with global influenza surveillance organizations would result in the rapid identification of a potential H5N1 pandemic virus in birds or humans. This early information might permit health authorities to quash an emerging human influenza pandemic. In addition, they believe that knowledge of the mutations could enhance H5N1 vaccine research and manufacturing.

While considering the possible merits of a wider dissemination of more complete information regarding mutational changes of the newly created H5N1 strains, one fact must be kept in mind. The current circulating strains of influenza A/H5N1, with their human case-fatality rate of 30 to 80%, place this pathogen in the category of causing one of the most virulent known human infectious diseases.

Disseminating the entirety of the methods and results of the two H5N1 studies in the general scientific literature will not materially increase our ability to protect the public's health from a future H5N1 pandemic.

Moreover, detecting an emerging pandemic virus in animals before the occurrence of a human pandemic is unrealistic; rather, the pandemic virus documentation will be "an after-the-fact record of what just happened." For example, in the six countries of the world where highly pathogenic avian influenza H5N1 is endemic (Bangladesh, Cambodia, China, Egypt, Indonesia, and Viet Nam), the quality of public and private veterinary and animal production services is variable and low in some places (*1*). These countries are not often able to detect and respond to influenza A/H5N1 infections in birds. When H5N1 isolates are obtained, little to no gene sequencing is conducted, meaning that a mutation map of possible prepandemic viruses will not be generally available. Even if such laboratory support were readily available and samples from ill birds were processed in a timely manner, these countries lack the commitment to deal vigorously with H5N1. This conclusion was recently highlighted by the United Nations Food and Agriculture Organization (*1*, *2*).

The World Health Organization (WHO) is also well aware of the magnitude of the challenge of identifying an emerging human influenza pandemic and stopping it before it spreads globally. Experiences with pan-

[1]Center for Infectious Disease Research and Division of Environmental Health Sciences, Medical School, University of Minnesota, Minneapolis, MN 55455, USA. [2]Center for Biosecurity of UPMC, University of Pittsburgh, Pittsburgh, PA 15213, USA.

*Author for correspondence. E-mail: mto@umn.edu.

Creating a Mammalian-Transmissible A/H5N1 Influenza Virus: Social Contracts, Prudence, and Alternative Perspectives

Michael T. Osterholm[1,2,3] and David A. Relman[4,5]

[1]Center for Infectious Disease Research and Policy, [2]Division of Environmental Health Sciences, School of Public Health, and [3]School of Medicine, University of Minnesota, Minneapolis; [4]Division of Infectious Diseases, Department of Medicine, and [5]Department of Microbiology and Immunology, Stanford University School of Medicine, Palo Alto, California

(See the editorial commentary by Hirsch, on pages 1621, the perspectives by Herfst, on pages 1628–31 and Bouvier, on pages 1632–5.)

Much has been written about 2 unpublished manuscripts submitted to *Science* and *Nature* that describe research studies in which mutant derivative strains of highly-pathogenic influenza A/H5N1 virus were created that can be transmitted by respiratory droplets or aerosols between mammals (specifically, ferrets) [1–23]. These manuscripts were referred by the US government to the National Science Advisory Board for Biosecurity (NSABB) for assessment of the dual-use research implications of this work and to make recommendations regarding the responsible communication of the work. The results of the NSABB risk-benefit review process and the subsequent recommendation that neither manuscript be fully communicated in an open forum are well-known to the international life sciences community.

We propose to address this critical issue from both a historical perspective, the view through the rearview mirror, and from a future perspective, the view forward through the windshield. From the rearview mirror perspective, we review critical guidance from the life sciences community that predates the formation of the NSABB but clearly provides a relevant framework for our deliberations regarding the recent A/H5N1 virus research. We also consider existing work that the NSABB had completed prior to this recent research. From the windshield perspective, we consider 3 issues involving social and ethical principles that these 2 studies and any other future research efforts must address. We do not cover issues related to the A/H5N1 case-fatality rates or the potential benefits in sharing the entire research record of these studies for purposes of improving A/H5N1 infection surveillance or countermeasure production. We posit that the case-fatality rates associated with A/H5N1 virus infection are worrisome and that the potential benefits at present are limited, but we suggest that other important matters deserve treatment here [8, 19].

The concept of dual-use research of concern (DURC) is not a new issue in science. It was recognized in the early days of atomic physics that scientific research can be used to bring both benefit and harm to society (originally framed as research with both civilian and military applications) [24]. While the post–World War II threat of biowarfare was a serious concern, it rarely involved international life sciences research communities in the academic or private sectors. Much of the work in this area was classified and was conducted in government research laboratories, where public dissemination of the methods or results of the studies was never intended. And then the events of 9/11 and the subsequent anthrax attacks in the United States changed the worldview about the willingness of individuals to sacrifice themselves in order to harm many others and about the methods that they might be willing to use to do so. Meanwhile, the revolution in the life sciences continued to unfold [25, 26].

In 2004, the National Research Council (NRC) published a seminal report, commonly known as the Fink Report, after Gerald Fink, the chairman of the committee that composed the report [27]. The charge to the committee was to consider ways of minimizing threats from biological warfare and bioterrorism without hindering the progress of biotechnology, the latter of which is essential for improving global health. The report summarized the work of experts mostly from the academic community and, thus, reflected the response of the life sciences community to increased concerns about bioterrorism. It concluded that DURC should not

Received and accepted 13 March 2011; electronically published 27 March 2012.

Correspondence: Michael T. Osterholm, PhD, MPH, Center for Infectious Disease Research and Policy, University of Minnesota, Academic Health Center, 420 Delaware St SE, MMC 263, Minneapolis, MN 55455 (mtoster@umn.edu).

The Journal of Infectious Diseases 2012;205:1636–8

DOI: 10.1093/infdis/jis258

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

Gain-of-function debate focuses on clarity, global perspective

Filed Under: Biosecurity Issues; Dual-Use Research

Lisa Schnirring and Jim Wappes | Staff Writers | CIDRAP News | Jan 08, 2016

A federal advisory group today wrapped up its 2-day discussion of issues aimed at clarifying how the government assesses and funds gain-of-function (GOF) studies on H5N1 avian flu viruses and other disease threats, which came with requests to make policies as clear as possible and to reflect a more global perspective.

CDC / Dr. Scott Smith

The meeting is part of the process put in place by the Obama administration in October 2014 to reevaluate federal GOF funding policies in light of controversial work on H5N1 viruses. The White House had asked the National Science Advisory Board for Biosecurity (NSABB) to put together recommendations.

The centerpiece of today's panel discussion was the NSABB working group's draft report and recommendations. Yesterday the main topics were a risk-benefit assessment and an ethics white paper commissioned to help the NSABB with finalizing its report.

GOF research involves studies that enhance the pathogenicity, transmissibility, or host range of a pathogen to better understand it.

Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - **Smallpox**
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - MERS
  - Zika

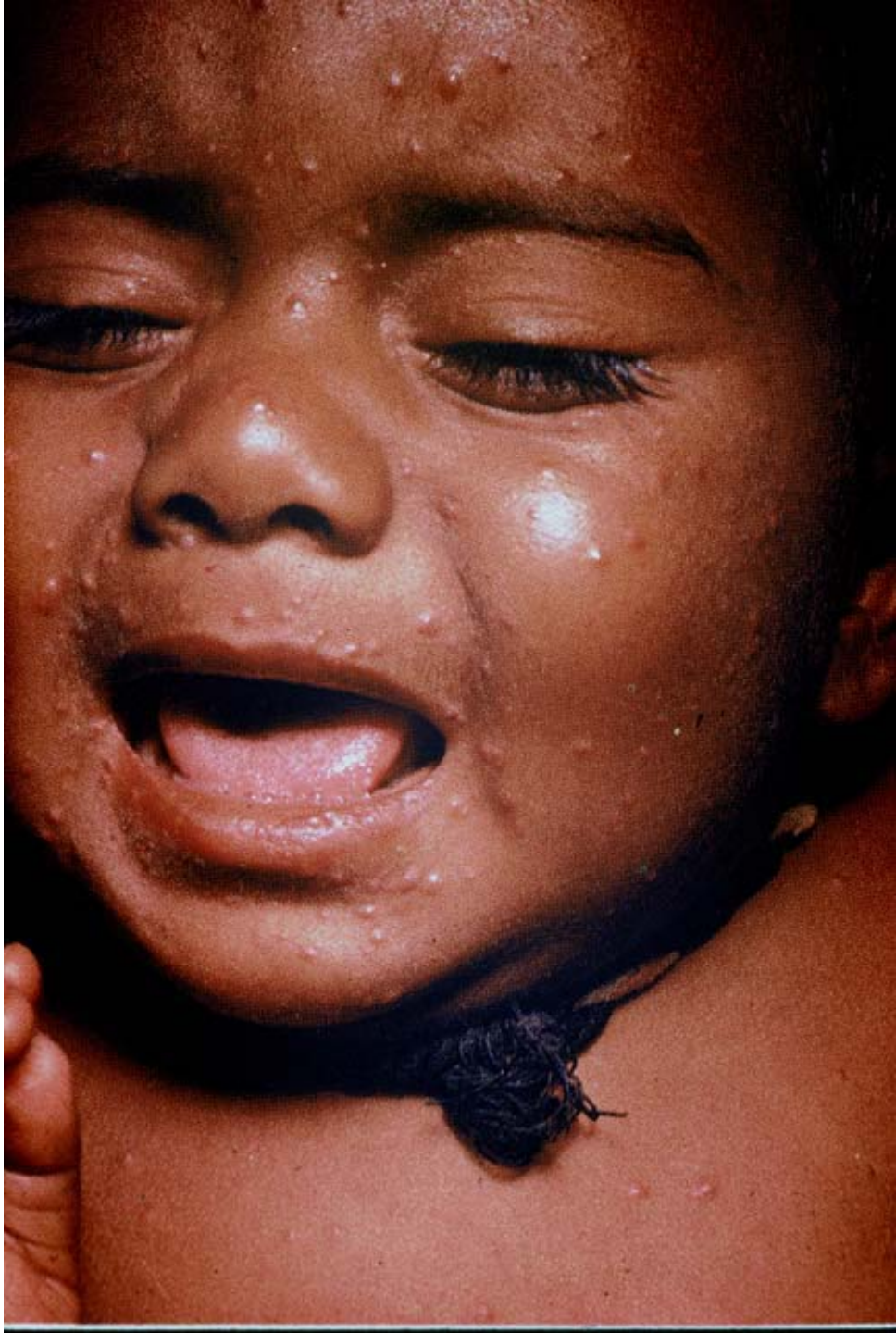
CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Smallpox

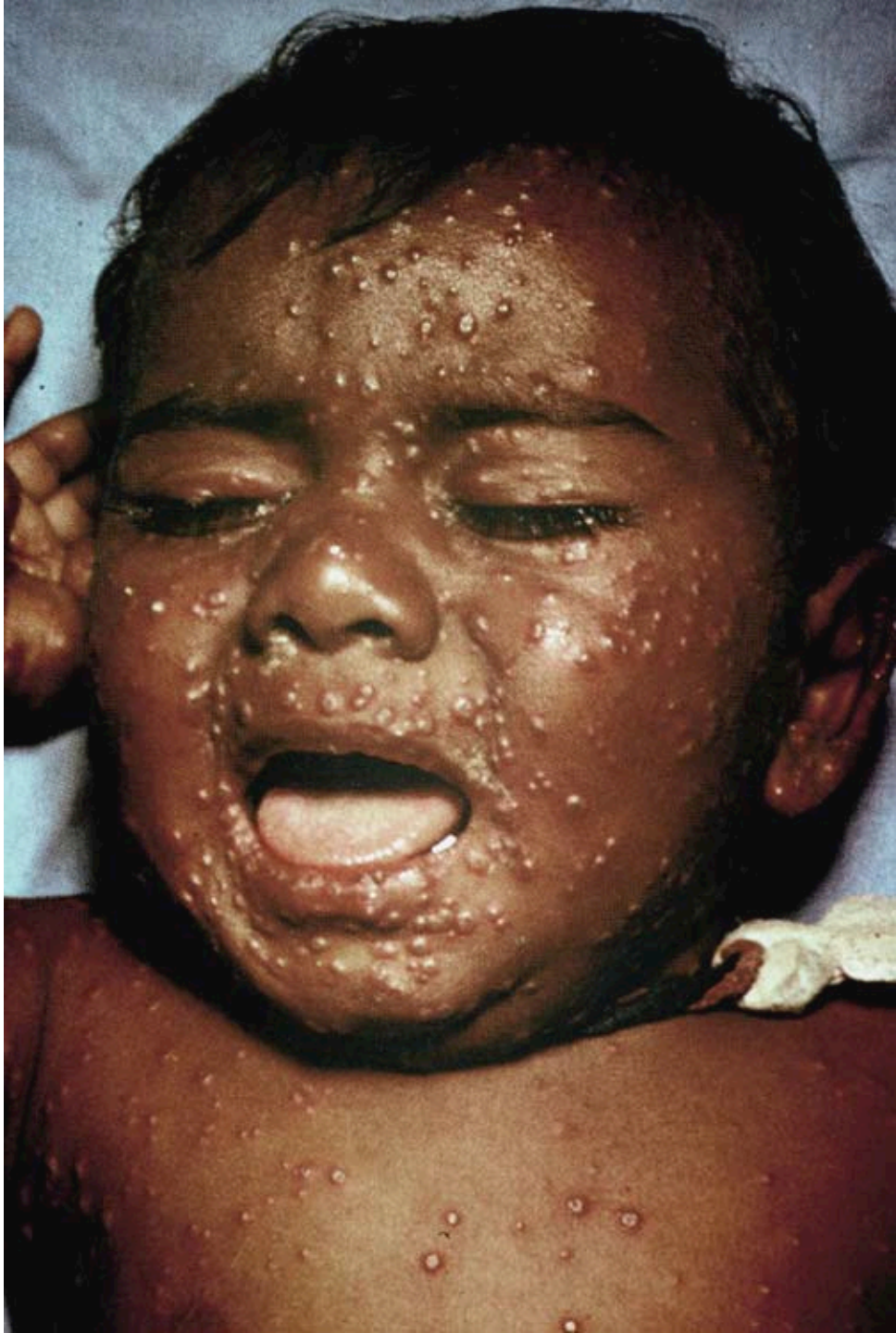
- Along with pandemic influenza, smallpox WAS the Lion King of human infectious diseases for centuries
- *"There has been no greater medical--or humanitarian—miracle in modern times than the eradication of smallpox"*

  David Oshinsky, historian
- During the 20th century alone, an estimated 200 million people died from smallpox

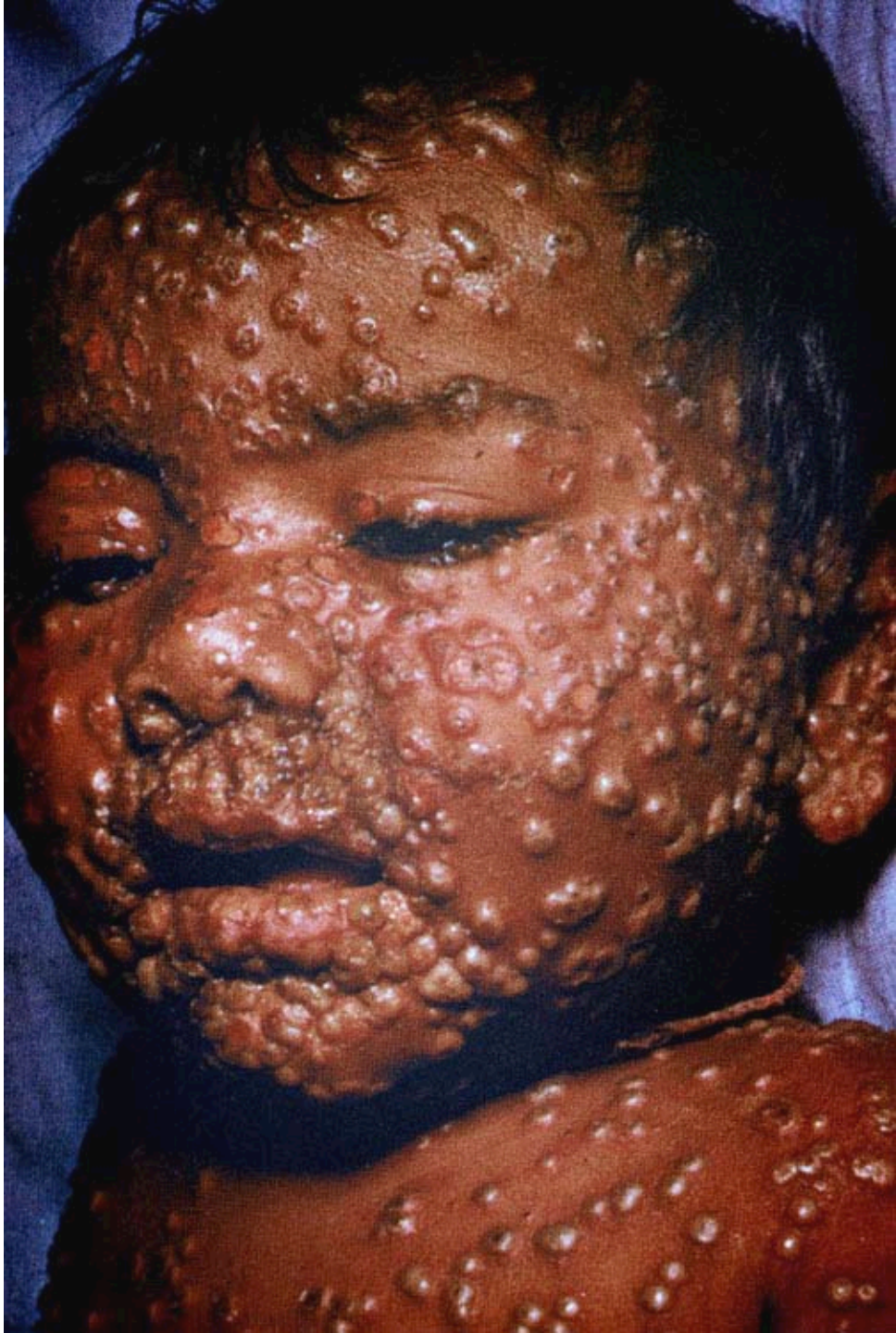
Day 3



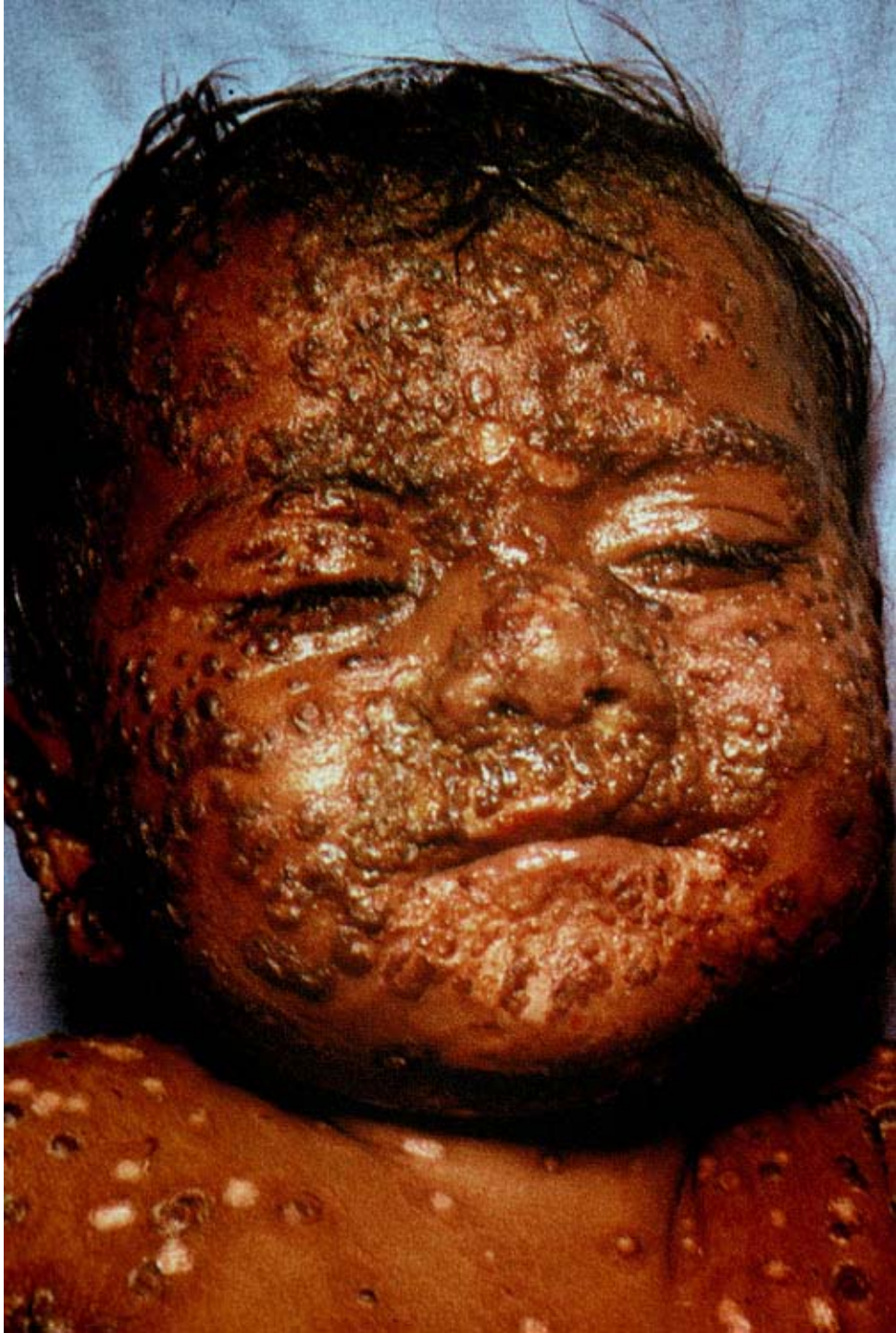
Day 5

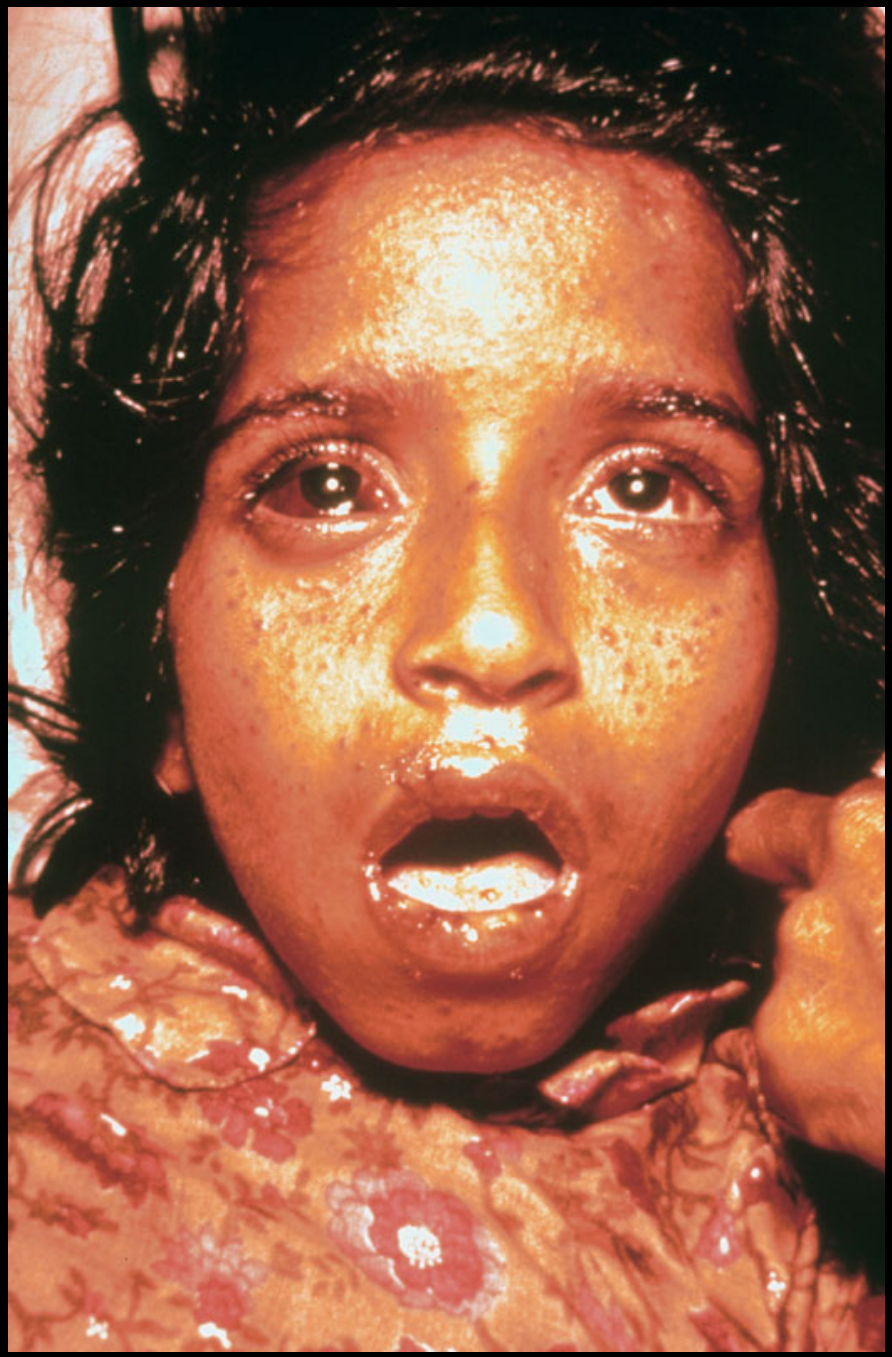


Day 9



Day 13





VIROLOGY 201, 215–240 (1994)

Analysis of the Complete Genome of Smallpox Variola Major Virus Strain Bangladesh-1975

ROBERT F. MASSUNG,* LI-ING LIU,†‡ JIN QI,* JANICE C. KNIGHT,* THOMAS E. YURAN,*
ANTHONY R. KERLAVAGE,†‡ JOSEPH M. PARSONS,* J. CRAIG VENTER,†‡
AND JOSEPH J. ESPOSITO*,[1]

*Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; †National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892; and ‡The Institute for Genomic Research, Gaithersburg, Maryland 20878

Received December 6, 1993; accepted February 17, 1994

We analyzed the 186,102 base pairs (bp) that constitute the entire DNA genome of a highly virulent variola virus isolated from Bangladesh in 1975. The linear, double-stranded molecule has relatively small (725 bp) inverted terminal repeat (ITR) sequences containing three 69-bp direct repeat elements, a 54-bp partial repeat element, and a 105-base telomeric end-loop that can be maximally base-paired to contain 17 mismatches. Proximal to the right-end ITR sequences are another seven 69-bp elements and a 53- and a 27-bp partial element. Sequence analysis showed 187 closely spaced open reading frames specifying putative major proteins containing ≥65 amino acids. Most of the virus proteins correspond to proteins in current databases, including 150 proteins that have >90% identity to major gene products encoded by vaccinia virus, the smallpox vaccine. Variola virus has a group of proteins that are truncated compared with vaccinia virus counterparts and a smaller group of proteins that are elongated. The terminal regions encode several novel proteins and variants of other poxvirus proteins that potentially augment variola virus transmissibility and virulence for its only natural host, humans.

INTRODUCTION

The poxviruses are a family of large DNA viruses that replicate in a temporally regulated manner in the cytoplasm of infected cells of insects (*Entomopoxvirinae*) and vertebrates (*Chordopoxvirinae*). Four of the eight vertebrate poxvirus genera contain human pathogens, but by far the most significant poxvirus disease of humans was smallpox, which was caused by the orthopoxvirus variola virus. Variola virus was a strictly human pathogen transmitted by aerosol or contact, producing a systemic infection manifested by virus growth in lymphoid organs, viremia, generalized rash, and fever with toxemia and complications that led to fatality rates ranging to 40% for variola major strains in unvaccinated populations. Variola minor strains, which consist of alastrim viruses and apparently attenuated variants of variola major virus, usually produced discrete, ordinary smallpox with generally milder disease and fatality rates of <1%. The eradication of smallpox was declared in 1979 after the last naturally occurring case in Somalia in 1977, ending an historically unparalleled worldwide conquest of disease (Fenner *et al.*, 1988; Dumbell and Huq, 1986). The only known samples of variola virus are currently held by the Centers for Disease Control and Prevention, Atlanta, Georgia, and the Research Institute for Viral Preparations, Moscow, Russia.

Except for cloning and mapping of DNA restriction fragments, work with variola virus virtually ceased after certification of eradication was sanctioned in May 1980 by the World Health Assembly. Important contributions toward understanding poxvirus-encoded gene products have been made using other poxvirus species, especially vaccinia virus, the smallpox vaccine virus. Many of the enzymes, structural components, transcriptional regulators, and other elements that augment poxvirus reproduction have been identified along with some of the factors that likely contribute to host-range and pathogenicity (reviewed by Moyer and Turner, 1990; Fenner *et al.*, 1989; Buller and Palumbo, 1991; Smith, 1993). Resolving the features and understanding the mechanism of action of corresponding components of variola virus will further unravel the complexity and the concerted roles of such elements in virulence and host-range, and will further define the origins and evolutionary trends of such genes with particular relevance to the emergence of virulent new poxviruses. Toward these goals, we determined the complete genome DNA sequence of a highly virulent Asian variola major virus from Bangladesh (VAR-BSH; Massung *et al.*, 1993). This report provides a detailed analysis of that sequence. Most of the VAR-BSH putative proteins that we discuss have correlates in vaccinia strain Western Reserve (VAC-WR), which has been exten-

Sequence data from this article have been deposited with the EMBL/GenBank Libraries under Accession No. L22579.

[1] To whom correspondence and reprint requests should be addressed.

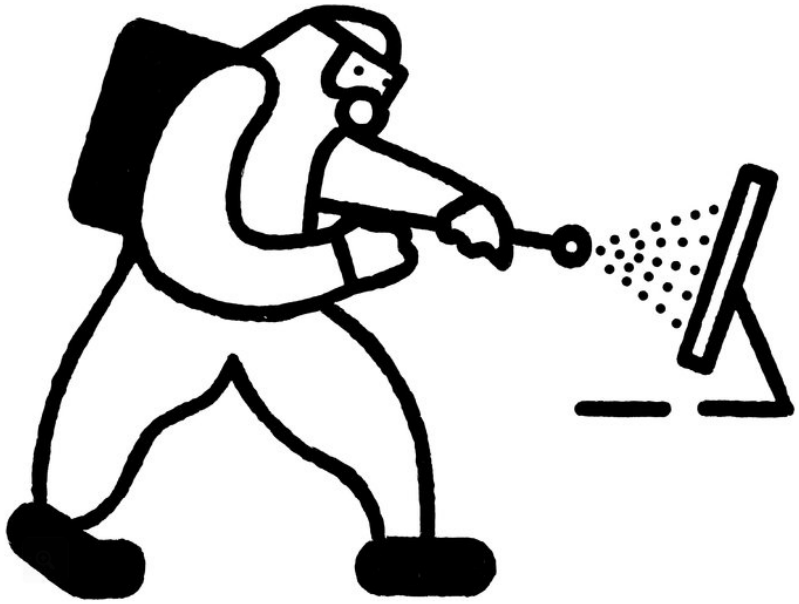
0042-6822/94 $6.00

The New York Times

Resurrecting Smallpox? Easier Than You Think

By LEONARD ADLEMAN OCT. 15, 2014

LOS ANGELES — ON Oct. 16, 1975, 3-year-old Rahima Banu of Bangladesh became the last human infected with naturally occurring smallpox (variola major). When her immune system killed the last smallpox virus in her body, it also killed the last such smallpox virus in humans. In what is arguably mankind's greatest achievement, smallpox was eradicated.



Jan Bajtlik

Our war with this smallpox virus was brutal. It appears likely that the virus killed about one billion of us. Initially, our only defense was our immune system, but eventually we developed new tools, including vaccination. In the late 1950s, the World Health Organization began responding to outbreaks by vaccinating everyone in the surrounding area to prevent the virus from spreading. By 1975, we had won.

The smallpox virus had only a single host species: us. Other viruses have multiple hosts. For example, some strains of flu live in both humans and pigs, hence "swine flu." If smallpox had had a second host, eradicating it in humans would have been of little value, since it would have thrived in its second host and later re-emerged in humans.

A few samples of the virus are still kept in special labs: one in the United States and one in Russia. We don't bother vaccinating against smallpox anymore; if the virus escapes from one of these labs, the war will begin again. Currently, there is debate about whether these samples should be destroyed or kept for scientific purposes.

Outbreak News Today

Suspected monkeypox outbreak reported in DRC

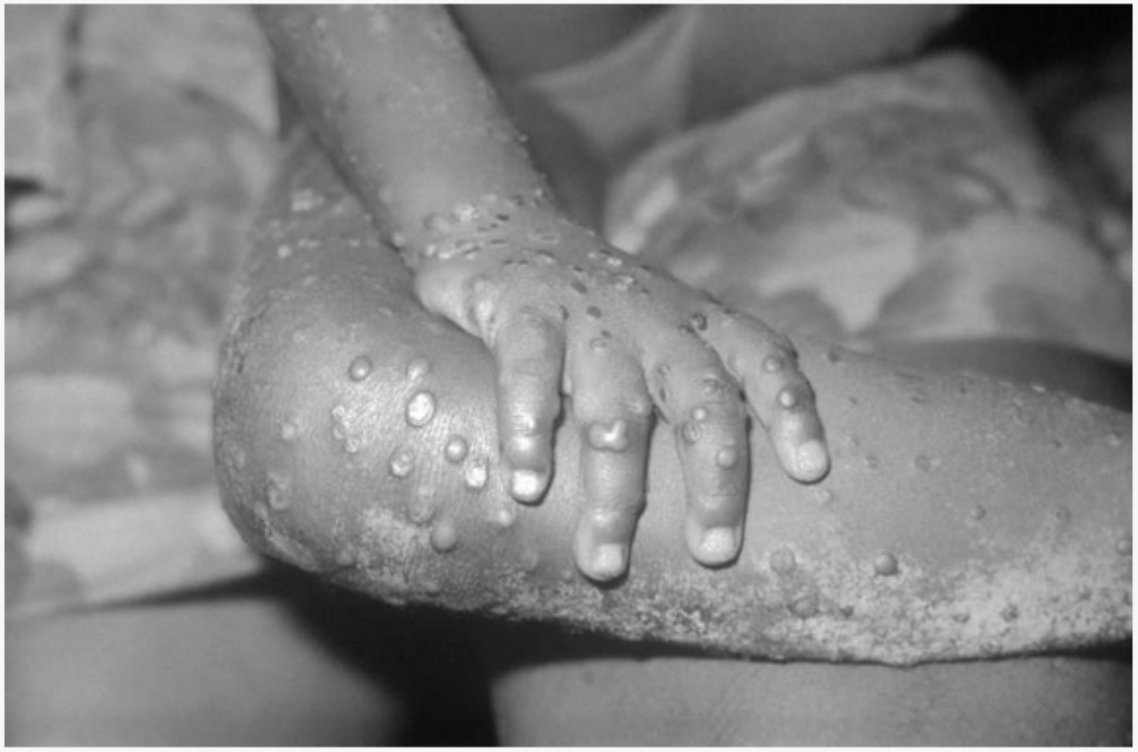
Posted by Robert Herriman on September 11, 2015 // 2 Comments

At least 20 suspected monkeypox cases have been reported since the beginning of the week in Tshuapa district, Democratic Republic of the Congo, according to a Radio Okapi report today (computer translated).

Sources say that 18 of the suspect cases are hospitalized at a hospital in the town of Ikela. Despite not being laboratory confirmed, the Chief Health officer in the Mbamba health area, Dr Jean-Pierre Inonga said they are calling the cases monkeypox based of several telltale symptoms presented– fever, scabs and generalized skin rash .

Confirmation testing is being performed at the National Institute of Biomedical Research (INRB) in Kinshasa as of this writing.

The resurgence of the viral disease is believed to be due to consumption of game animals found dead in the forest by the public.



Monkeypox/CDC

Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - Smallpox
- **Diseases resulting in outbreaks of regional critical importance**
  - Ebola
  - MERS
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - Smallpox
- Diseases resulting in outbreaks of regional critical importance
  - **Ebola**
  - MERS
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Ebolavirus Ecology

Enzootic Cycle

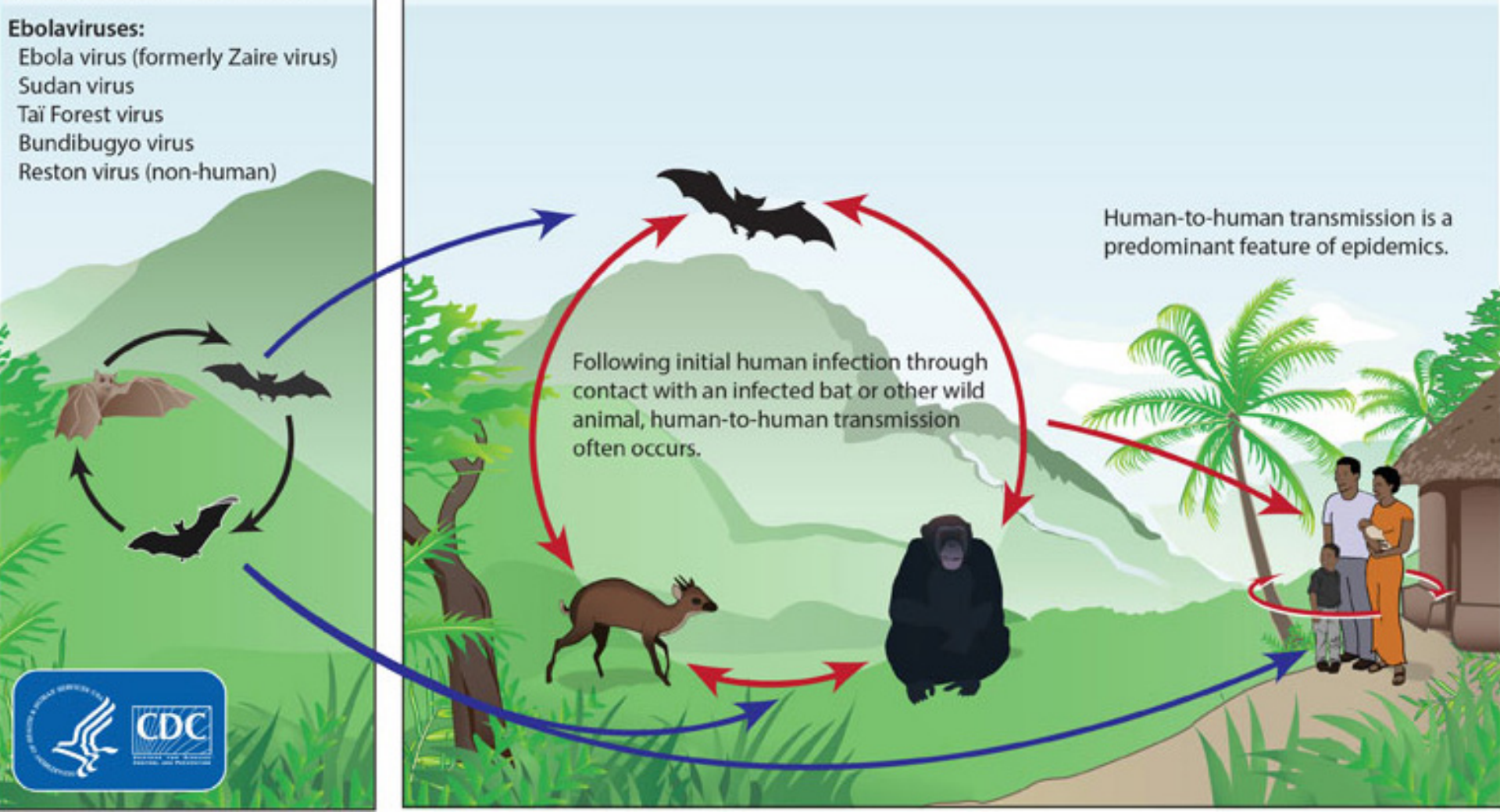
New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintainance and transmission of the virus within bat populations remain unknown.

Ebolaviruses:

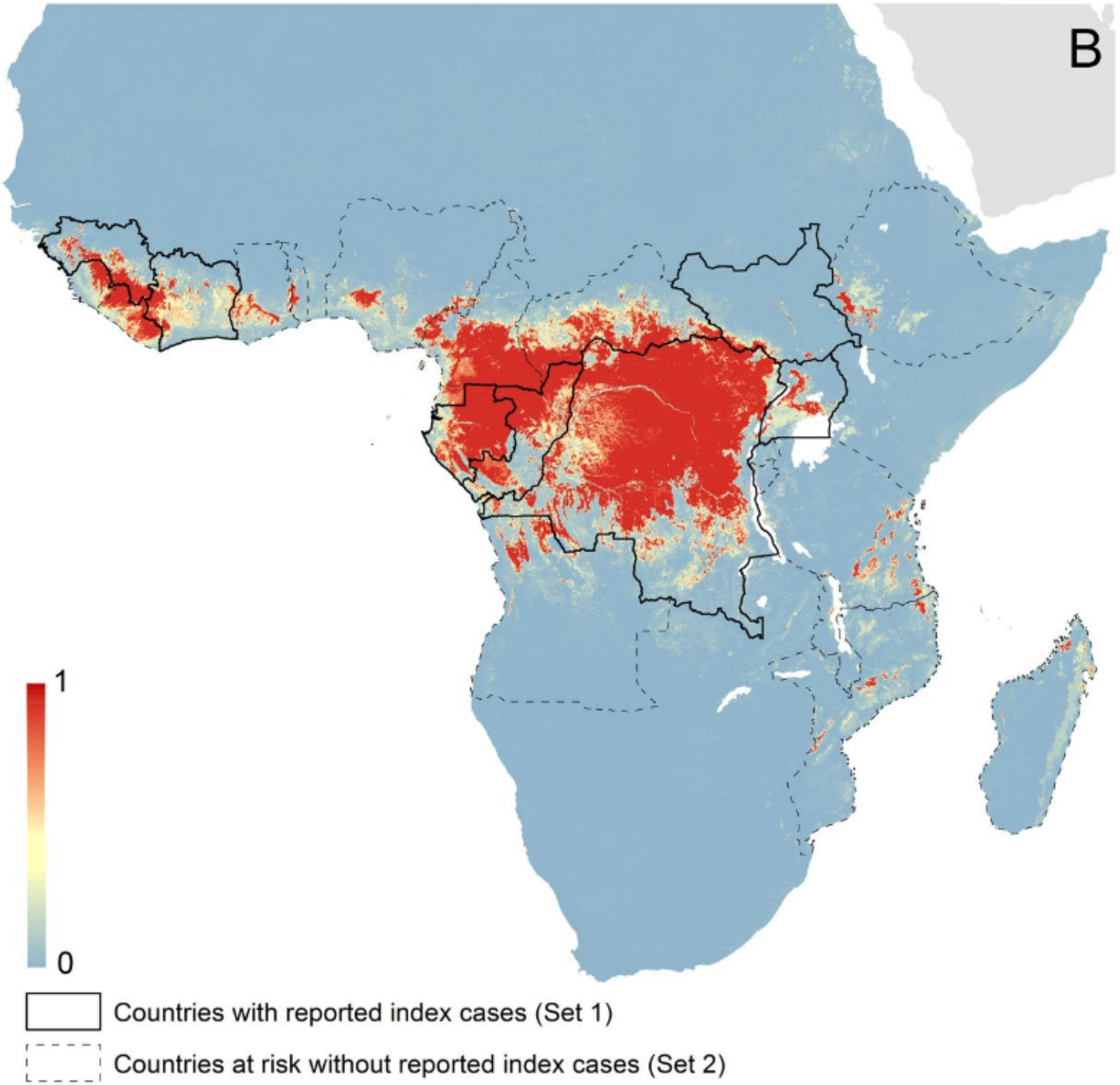
Ebola virus (formerly Zaire virus)
Sudan virus
Taï Forest virus
Bundibugyo virus
Reston virus (non-human)

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



Transmission of Ebola Viruses: What We Know and What We Do Not Know

Michael T. Osterholm,[a] Kristine A. Moore,[a] Nicholas S. Kelley,[a] Lisa M. Brosseau,[b] Gary Wong,[c] Frederick A. Murphy,[d] Clarence J. Peters,[d] James W. LeDuc,[d] Phillip K. Russell,[e] Michel Van Herp,[f] Jimmy Kapetshi,[g] Jean-Jacques T. Muyembe,[g] Benoit Kebela Ilunga,[h] James E. Strong,[c] Allen Grolla,[c] Anja Wolz,[f] Brima Kargbo,[i] David K. Kargbo,[i] Pierre Formenty,[j] David Avram Sanders,[k] Gary P. Kobinger[c]

Center for Infectious Disease Research and Policy, University of Minnesota, Minneapolis, Minnesota, USA[a]; Division of Environmental and Occupational Health Sciences, University of Illinois at Chicago, Chicago, Illinois, USA[b]; National Laboratory for Zoonotic Diseases and Special Pathogens, Public Health Agency of Canada, Winnipeg, Canada[c]; The Galveston National Laboratory, University of Texas Medical Branch, Galveston, Texas, USA[d]; Sabin Vaccine Institute, Washington, DC, USA[e]; Medical Department Unit, Médecins sans Frontières, Brussels, Belgium[f]; Institut National de Recherche Biomédicale, Kinshasa, Democratic Republic of the Congo[g]; Ministry of Health, Kinshasa, Democratic Republic of the Congo[h]; Ministry of Health and Sanitation, Freetown, Sierra Leone[i]; Department of Epidemic and Pandemic Alert and Response, World Health Organization, Geneva, Switzerland[j]; Department of Biological Sciences, Purdue University, Lafayette, Indiana, USA[k]

ABSTRACT **Available evidence demonstrates that direct patient contact and contact with infectious body fluids are the primary modes for Ebola virus transmission, but this is based on a limited number of studies. Key areas requiring further study include (i) the role of aerosol transmission (either via large droplets or small particles in the vicinity of source patients), (ii) the role of environmental contamination and fomite transmission, (iii) the degree to which minimally or mildly ill persons transmit infection, (iv) how long clinically relevant infectiousness persists, (v) the role that "superspreading events" may play in driving transmission dynamics, (vi) whether strain differences or repeated serial passage in outbreak settings can impact virus transmission, and (vii) what role sylvatic or domestic animals could play in outbreak propagation, particularly during major epidemics such as the 2013–2015 West Africa situation. In this review, we address what we know and what we do not know about Ebola virus transmission. We also hypothesize that Ebola viruses have the potential to be respiratory pathogens with primary respiratory spread.**

PAST EBOLA OUTBREAKS

Between the first recognized outbreak of Ebola virus disease (EVD) in 1976 and the onset of the 2013–2015 Ebola epidemic in West Africa, 24 outbreaks of EVD involving approximately 2,400 reported cases had been recognized by the World Health Organization (WHO) (1). One additional outbreak involving 69 cases occurred in the Democratic Republic of the Congo (DRC) between July and October 2014 (2). To date, five species of Ebola viruses have been identified; four from Africa (Zaire, Sudan, Bundibugyo, and Tai Forest) and one from the Philippines (Reston) (1, 3, 4). Most pre-2013 outbreaks were caused by Zaire Ebola virus (EBOV) (14 outbreaks) or Sudan virus (SUDV) (7 outbreaks); Bundibugyo virus (BDBV) caused two outbreaks, and Tai Forest virus (TAFV) was identified in a single case from Côte d'Ivoire (1). Outbreaks caused by Reston virus (RESTV) have occurred in nonhuman primates and pigs, with associated asymptomatic human infections (5).

Only seven outbreaks involved more than 100 reported cases. The maximum number of generations of human-to-human transmission for these outbreaks is unknown but is likely relatively low. One report estimated 15 generations of viral transmission during a 1976 SUDV outbreak (284 cases), which was the most that were identified (6). Investigators recorded four generations of spread during the EBOV outbreak in Kikwit, DRC (315 cases) (7).

Many experts have concluded that the extensive transmission documented in the 2013–2015 West Africa epidemic is due to societal factors (poverty, urban density, population migration patterns, and poor health care and public health infrastructure) rather than unique biological characteristics of the agent (8, 9). Limited data are available, however, regarding virus genomics (affecting phenotype/pathotype), patient viral loads, and certain epidemiological features for this unique EBOV strain. Furthermore, information about Ebola virus transmission in humans remains incomplete, given the relatively small number of outbreak investigations and cases recognized before 2013; as a result, additional questions remain (10). In this review, we explore what we know—and what we do not know—about Ebola virus transmission.

WHAT WE KNOW ABOUT EBOLA VIRUS TRANSMISSION IN HUMANS

Past outbreaks provide opportunities to examine human-to-human transmission of Ebola viruses. Spread within hospitals has been documented repeatedly, and outbreak amplification has occurred in health care settings for both EBOV and SUDV (6, 7, 11). Early outbreak investigations demonstrated the importance of parenteral transmission via nonsterile needles, although this has not been noted more recently (6, 11). In addition, investigators have shown that health care workers are at particularly high risk (6, 7, 11, 12). Use of barrier protection

Published 19 February 2015

Citation Osterholm MT, Moore KA, Kelley NS, Brosseau LM, Wong G, Murphy FA, Peters CJ, LeDuc JW, Russell PK, Van Herp M, Kapetshi J, Muyembe J-JT, Ilunga BK, Strong JE, Grolla A, Wolz A, Kargbo B, Kargbo DK, Formenty P, Sanders DA, Kobinger GP. 2015. Transmission of Ebola viruses: what we know and what we do not know. mBio 6(2): e00137-15. doi:10.1128/mBio.00137-15.

Editor Michael J. Imperiale, University of Michigan

Address correspondence to Michael T. Osterholm, mto@umn.edu.

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.

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

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.

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.

Ebola Vaccine Team B

- Formed nine working groups;
  - Research and development
  - Manufacturing
  - Safety
  - Efficacy/effectiveness determination
  - Regulatory pathways
  - Ethics
  - Vaccination strategy
  - Community engagement
  - Funding

February 2015

Recommendations for Accelerating the Development of Ebola Vaccines

REPORT & ANALYSIS

wellcome trust

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

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

Published Online
October 29, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00416-8

*Members listed at the end of the paper
Center for Infectious Disease Research and Policy, University of Minnesota, Minneapolis, MN, USA (M Osterholm PhD, K Moore MD, J Ostrowsky MSc, K Kimball-Baker BA); and the Wellcome Trust, London, UK (J Farrar, FRS FRCP)

Correspondence to:
Dr Michael Osterholm, Center for Infectious Disease Research and Policy, C315 Mayo Memorial Building, MMC 263, 420 Delaware Street, SE, Minneapolis, MN 55455, USA
mto@umn.edu

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

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

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

Gavi, Merck ink Ebola vaccine purchase agreement

Filed Under: Ebola; VHF

Lisa Schnirring | News Editor | CIDRAP News | Jan 20, 2016

Gavi, the Vaccine Alliance, and Merck have signed a purchase agreement worth $5 million to push the VSV-EBOV Ebola vaccine through initial licensing and to stockpile enough for clinical trials and emergency use.

UNAMID / Albert Gonzalez Farran / Flickr cc

The agreement between Gavi and Merck, which licensed the vaccine in 2014 to improve its chances of reaching clinical trials and of production ramp-up, was announced today at the World Economic Forum in Davos, Switzerland. The deal is unusual, because it signals Gavi's first such support for an unlicensed vaccine.

VSV-EBOV, one of several vaccines under development, is furthest along in clinical trials and after showing good effectiveness in a phase 3 trial has been used in ring vaccination strategies in the outbreak region. Developed by Canadian scientists, VSV-EBOV was licensed by NewLink Genetics along with Merck.

Path to licensing, stockpiling

As part of the deal, Merck will submit the vaccine for licensing by the end of 2017, and once it's approved, Gavi will start buying the vaccine to build a stockpile for future outbreaks. Also, Merck will ensure 300,000 doses of the vaccine are available as of May to use in expanded clinical trials or for emergency use.

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.

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

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

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.

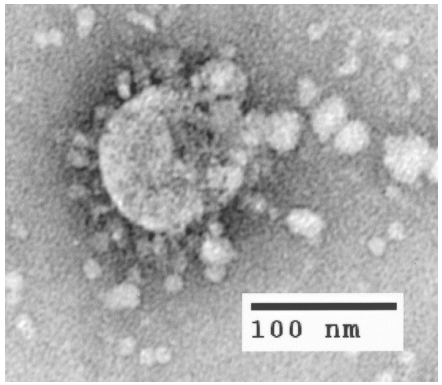
The WHO guidance comes after flare-ups of Ebola virus disease (EVD) in West Africa, some tied to sexual transmission of the virus, and after a high-profile relapse in a nurse survivor in the United Kingdom. Issues with survivors include the ability of the Ebola virus to survive for long periods in some 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.

Infectious Diseases Requiring a New Public Health Leadership Approach

- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - Smallpox
- Diseases resulting in outbreaks of regional critical importance
  - Ebola
  - **MERS**
  - Zika

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota



THE LANCET PUBLISHING GROUP

THE LANCET | The Journal | Protocol Reviews | eResearch Archive | Info for Authors | Profile | Help | Feedback

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.

Global SARS Figures*

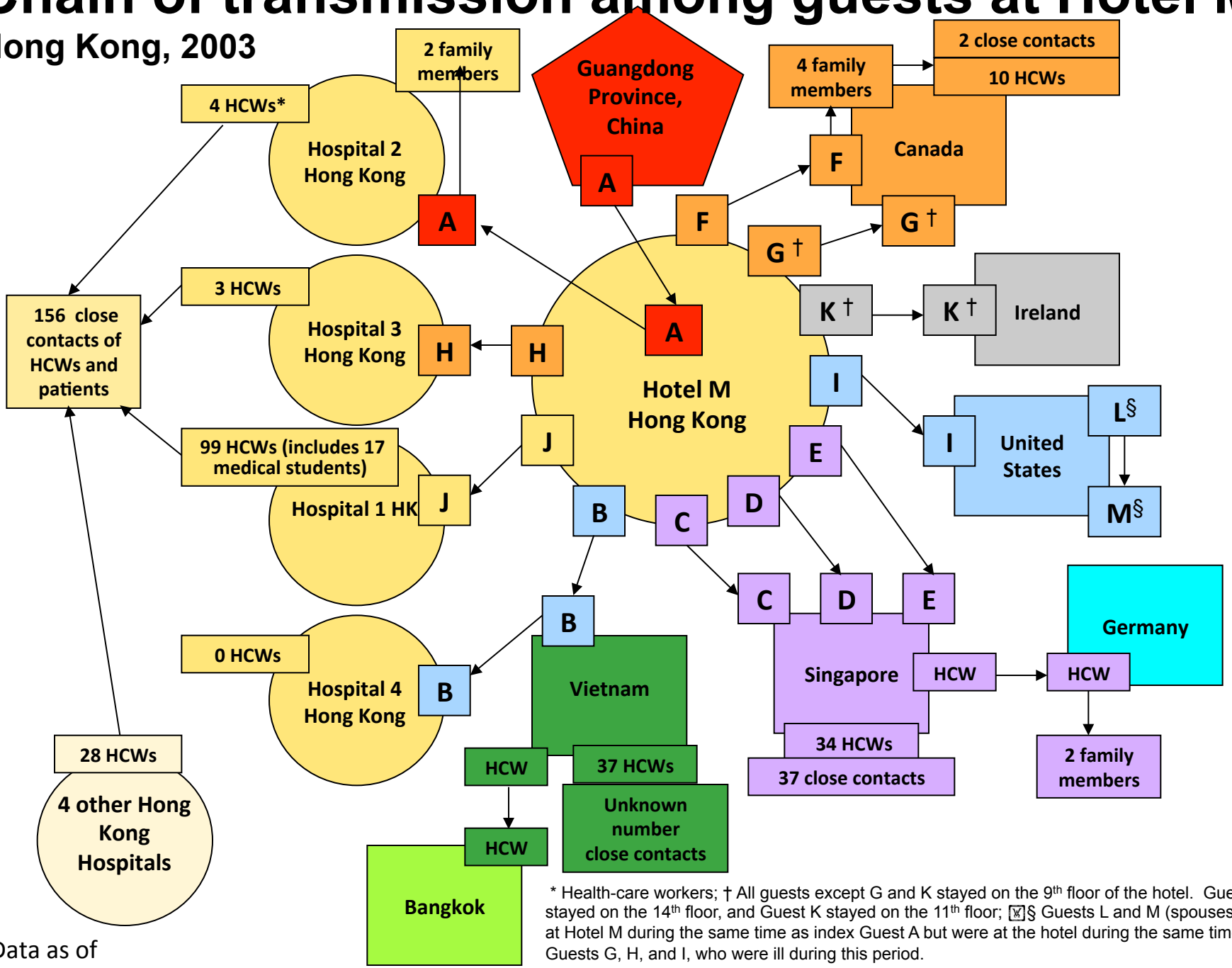
Country	Cases (% total)	Deaths
China	5,327 (65)	349
Hong Kong	1,755 (22)	299
Taiwan	346 (4)	37
Canada	251 (3)	43
Singapore	238 (3)	33
Other	182 (2)	13
Total	8,098	774

✉Source: WHO, data through Sept. 26, 2003

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

Chain of transmission among guests at Hotel M

Hong Kong, 2003



* Health-care workers; † All guests except G and K stayed on the 9th floor of the hotel. Guest G stayed on the 14th floor, and Guest K stayed on the 11th floor; § Guests L and M (spouses) were not at Hotel M during the same time as index Guest A but were at the hotel during the same times as Guests G, H, and I, who were ill during this period.

Data as of

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]

1. Institute of Virology, University of Bonn Medical Centre, Bonn, Germany
2. German Centre for Infection Research (DZIF), Germany
3. Virology Laboratory, Dr Soliman Fakeeh Hospital, Jeddah
4. TibMolbiol, Berlin, Germany
5. Department of Virology and Virosciences, Erasmus Medical Centre, Rotterdam, The Netherlands
6. Health Protection Agency (HPA), London, United Kingdom

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

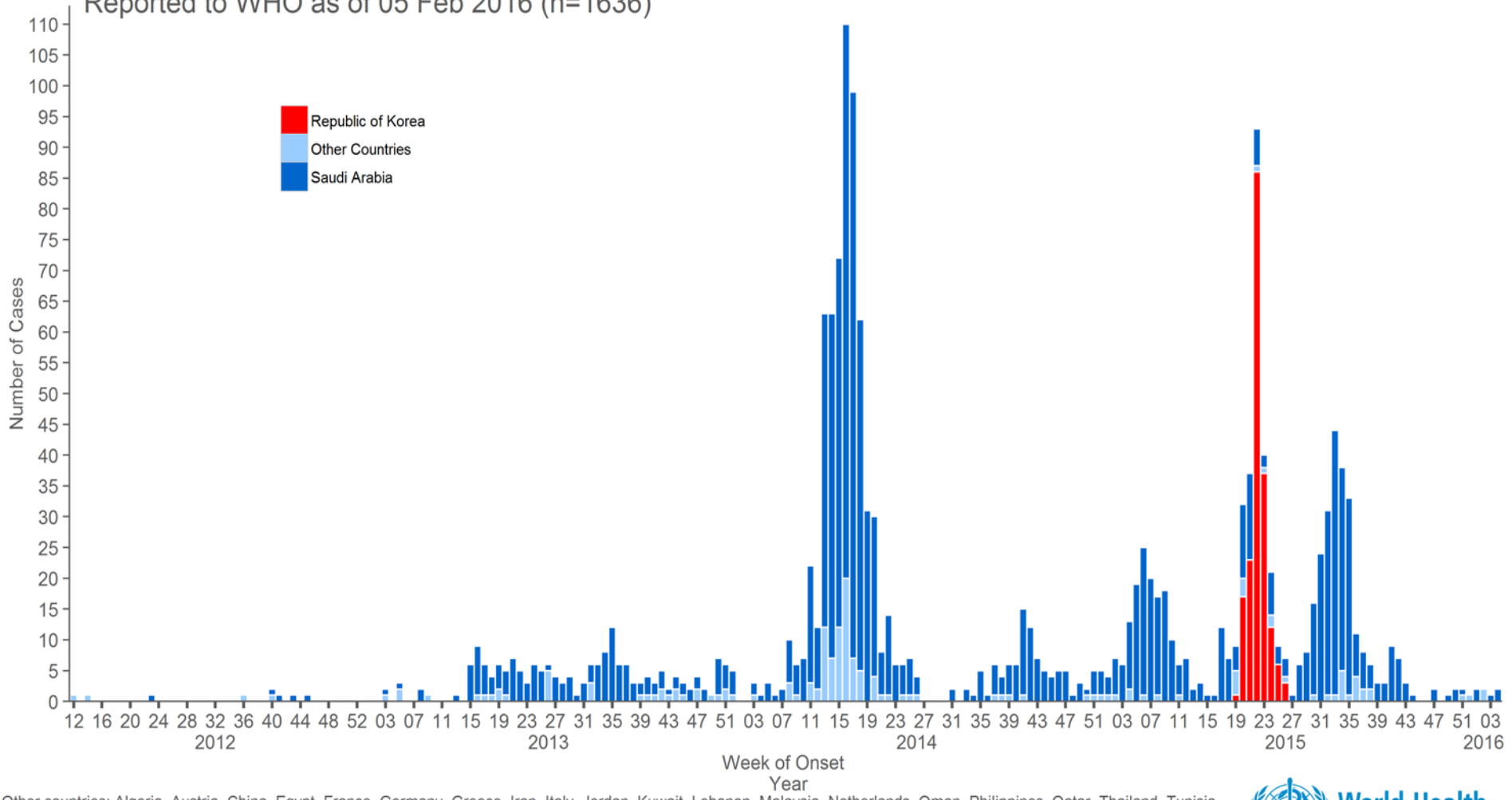
Template for design of assays

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 05 Feb 2016 (n=1636)



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 Feb 03, 2016

Saudi Arabia confirms MERS case in man who had camel contact

Saudi Arabia's Ministry of Health (MOH) today reported a new MERS-CoV infection in a man who had contact with camels, the second case in 3 days, and agriculture officials said 85% of camels recently tested at a market in Jeddah harbored the virus.

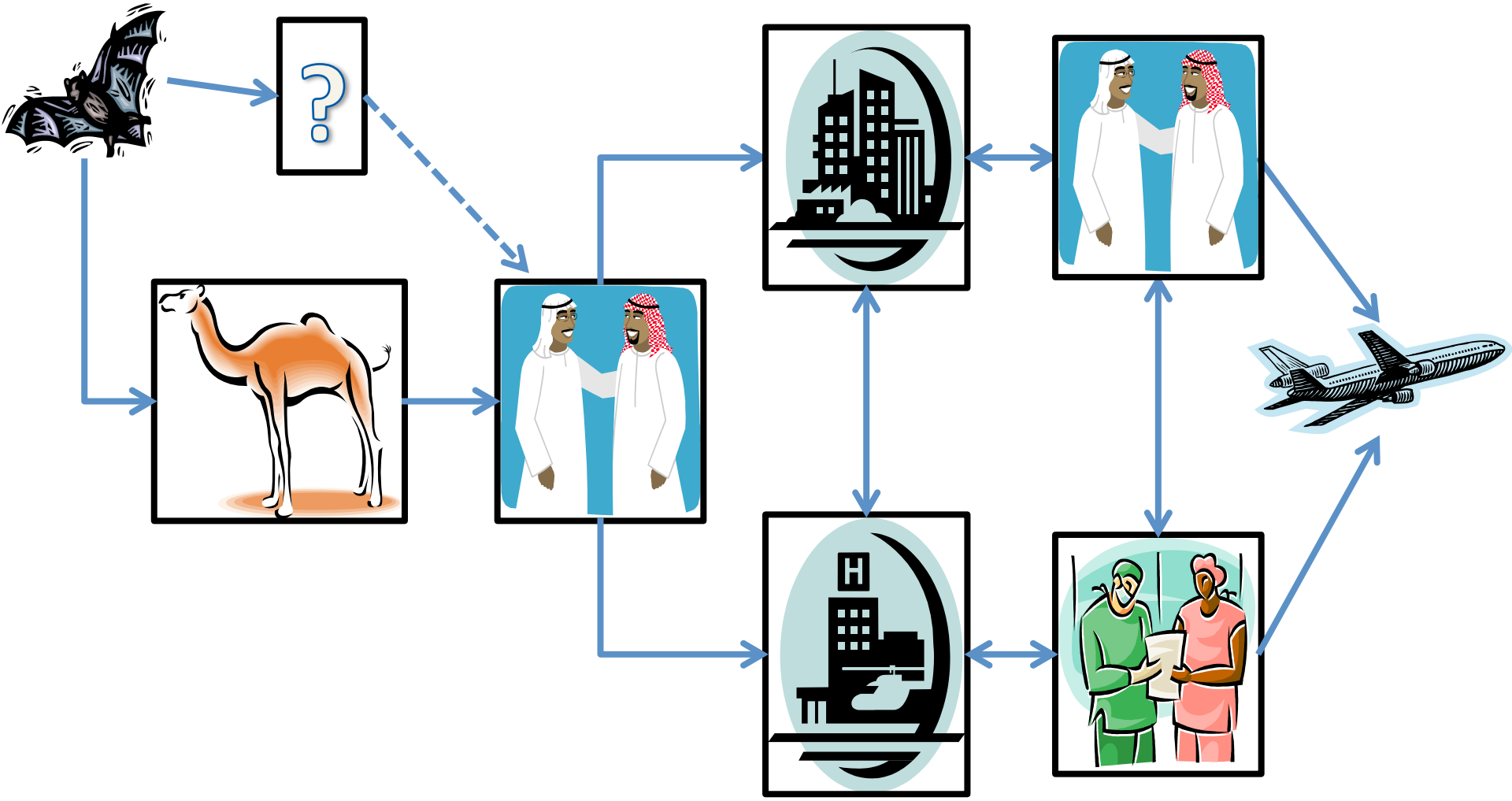
The new case of MERS-CoV (Middle East respiratory syndrome coronavirus) infection involves a 78-year-old Saudi man in Taif in southwestern Saudi Arabia, the MOH reported. He is hospitalized in stable condition and is not a healthcare worker. The agency said he had contact with camels, a known risk factor.

The country's previous case was in a 43-year-old man in Riyadh whose probable cause of infection was still being investigated when his case was confirmed on Feb 1. Today's case brings the country's MERS total to 1,290, of which 551 proved fatal, the MOH said. Six patients are still being treated.

The animal testing, meanwhile, involved 112 camels at the Al-Inam Central Market in Jeddah, Arab News reported today. Of 112 camels tested in an Agriculture Ministry study, 85% were found to carry MERS-CoV. Undersecretary for animal resources Habed bin Abdulaziz Al-Batshaan said preventive measures must continue to be taken by camel dealers, with mandatory use of masks and gloves.

Feb 3 MOH update
Feb 1 CIDRAP News scan on previous case
Feb 3 *Arab News* story

The MERS Transmission Model



University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

WHO Saudi MERS mission finds progress, urges more steps

Filed Under: MERS-CoV

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

A joint mission led by the World Health Organization (WHO) to assess Saudi Arabia's efforts against MERS-CoV said today that the country has made progress and is ready to take the next proactive steps, such as better surveillance in camels.

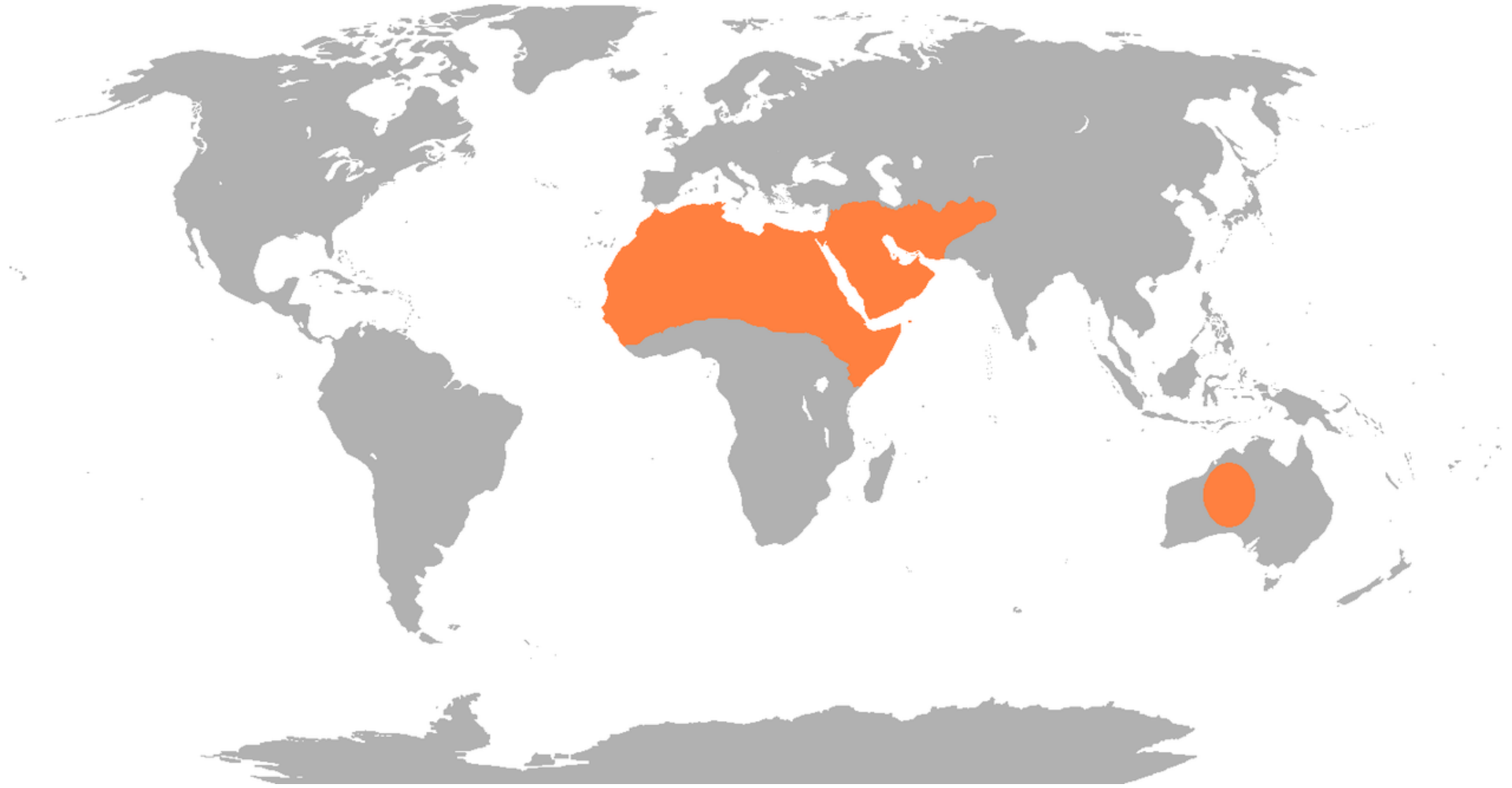
The WHO today also released new details about 4 of Saudi Arabia's recent cases, plus 2 in the United Arab Emirates (UAE). Of the 6 MERS-CoV (Middle East respiratory syndrome coronavirus) cases, 5 patients had a history of contact with camels, while 1 case involves an asymptomatic contact.

darren baker / iStock

Progress and remaining challenges

The WHO joint mission to Saudi Arabia took place from Jan 11 through 14 and included visits to health and agriculture ministries, hospitals in Riyadh and Hofuf, labs, a camel research facility, and a camel slaughterhouse and market in Hofuf, according to a report posted by the WHO Eastern Mediterranean regional office.

The event marked the third recent joint MERS mission to the country. The previous one came in



THE CONVERSATION

18 OCTOBER 2015

Africa: Studying African Camels Is Key to Learning More About the MERS Virus

Tagged: Africa • Environment • Health • Science • Sustainable Development • Wildlife

ANALYSIS

By Eric Fèvre, University of Liverpool

African camels could hold important clues to controlling the potential spread of a respiratory disease transmitted by the animals.

For many years African camels have lived with the disease and the risk of it spreading to humans is still low. But more research is necessary to understand the disease better. This is even more important given the confirmation that the chains of transmission of the human Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection originated from contact with camels. MERS was first recognised in 2012.

Camels are an extremely important source of livelihood, nutrition and income in Africa. They are especially common in arid and semi-arid areas of the continent, particularly in East Africa. But having these animals around may not be risk-free for humans.

However there have been no human case of MERS diagnosed in Africa. This could be because of limited clinical or epidemiological surveillance for the virus where infections have gone unrecognised. It could also be because there is simply no zoonotic, human infective virus circulating in sub-Saharan Africa, or indeed because risk factors for transmission differ in the two regions.

Geographic Distribution of MERS Coronavirus among Dromedary Camels, Africa

Chantal B.E.M. Reusken,[1] Lilia Messadi,[1] Ashenafi Feyisa,[1] Hussaini Ularamu,[1] Gert-Jan Godeke, Agom Danmarwa, Fufa Dawo, Mohamed Jemli, Simenew Melaku, David Shamaki, Yusuf Woma, Yiltawe Wungak, Endrias Zewdu Gebremedhin, Ilse Zutt, Berend-Jan Bosch, Bart L. Haagmans, and Marion P.G. Koopmans

We found serologic evidence for the circulation of Middle East respiratory syndrome coronavirus among dromedary camels in Nigeria, Tunisia, and Ethiopia. Circulation of the virus among dromedaries across broad areas of Africa may indicate that this disease is currently underdiagnosed in humans outside the Arabian Peninsula.

A novel betacoronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), was identified as the cause of severe respiratory disease in humans during 2012 (*1*). In August 2013, dromedary camels (*Camelus dromedarius*) were implicated for the first time as a possible source for human infection on the basis of the presence of MERS-CoV neutralizing antibodies in dromedaries from Oman and the Canary Islands of Spain (*2*). Since then, the presence of MERS-CoV antibodies in dromedaries has been reported in Jordan (*3*), Egypt (*4*,*5*), the United Arab Emirates (*6*,*7*), and Saudi Arabia (*8*,*9*). In October 2013, analysis of an outbreak associated with 1 barn in Qatar (*10*) found dromedaries and humans to be infected with nearly identical strains of MERS-CoV. Further proof of widespread circulation of MERS-CoV among dromedaries was provided by studies from Egypt and Saudi Arabia (*5*,*9*). These findings have raised questions about the geographic distribution of MERS-CoV among camel populations elsewhere. Here, we report our assessment of the geographic distribution of MERS-CoV circulation among dromedaries in Africa by serologic investigation of convenience samples from these animals in Nigeria, Tunisia, and Ethiopia.

The Study

In Nigeria, serum samples from 358 dromedaries that were raised for meat production were collected at abattoirs in 4 provinces (Kano, n = 245; Sokoto, n = 51; Borno, n = 51; and Adamawa, n = 11; Figure 1, panel A) during 2010–2011 for testing for peste des petits ruminants virus. The ages of the animals ranged from 4 to 15 years. The abattoirs also served the neighboring countries of Chad, Niger, and the Central African Republic. In Tunisia, serum samples from 204 dromedaries that were 1 to 16 years of age were collected in 3 provinces in 2009 and 2013 (Figure 1, panel B). Samples were collected from 155 dromedaries in Sidi Bouzid Province from 27 herds that were kept for meat production and from 39 dromedaries in Kebili Province from 16 herds that were kept for tourist rides; samples from both provinces had originally been collected for a study investigating the presence of *Anaplasma phagocytophilum*. Samples were collected from 10 dromedaries from Sousse Province that were kept for meat production because they were suspected of being infected with *Trypanosoma evansi*. In Ethiopia, samples from 188 dromedaries, 1 to 13 years of age, were collected as part of a study evaluating the presence of toxoplasmosis and respiratory tract diseases in 3 provinces (Afar, n = 118; Somalia, n = 11; and Oromia, n = 59; Figure 1, panel C) during 2011–2013. All samples were taken by jugular vein puncture according to local laws, and serum samples were stored at –20°C until testing. All serum samples were shipped to the Erasmus MC laboratory in the Netherlands in agreement with Dutch import regulations.

The serum samples were tested for the presence of IgG antibodies reactive with S1 antigens against MERS-CoV (residues 1–747), severe acute respiratory syndrome CoV (residues 1–676), and human CoV OC43 (residues 1–760) by using extensively validated protein-microarray technology, as described (*2*,*3*,*6*,*11*). Results were expressed as relative mean fluorescent intensity (RFU) for each set of quadruplicate spots of antigen, with a cutoff of 4,000 RFU as used by Meyer et al. (*6*). Human CoV OC43 S1 was used as a proxy for bovine coronavirus (BCoV), the latter of which is known to circulate commonly in dromedaries (*7*,*12*). High percentages of animals seropositive

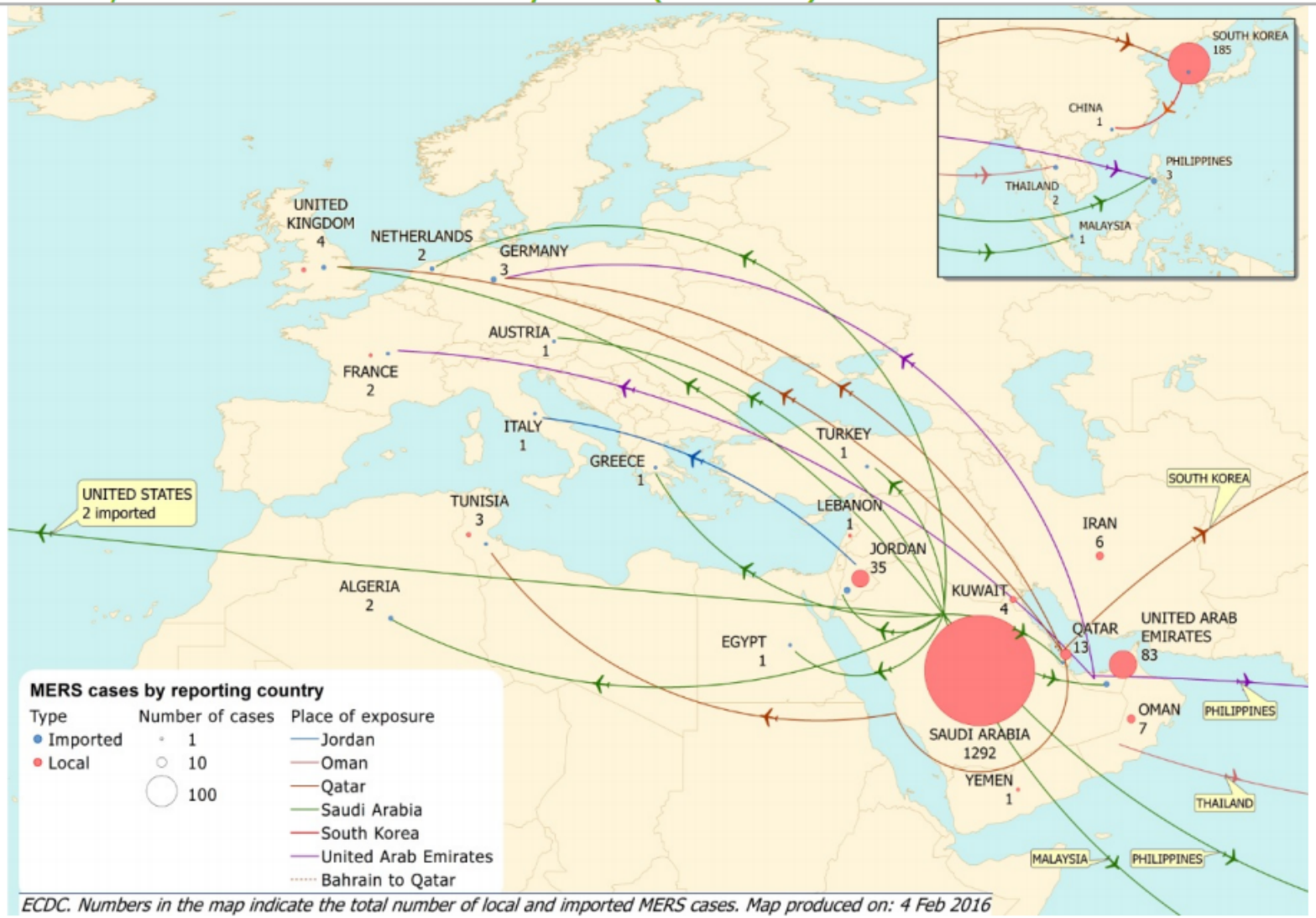
Author affiliations: Netherlands Centre for Infectious Disease Control, Bilthoven, the Netherlands (C.B.E.M. Reusken, G.-J. Godeke, I. Zutt, M.P.G. Koopmans); Erasmus Medical Center, Rotterdam, the Netherlands (C.B.E.M. Reusken, B.L. Haagmans, M.P.G. Koopmans); National Veterinary Medicine School, University of La Manouba, Sidi Thabet, Tunisia (L. Messadi, M. Jemli); Addis Ababa University College of Veterinary Medicine and Agriculture, Bishoftu, Ethiopia (A. Feyisa, F. Dawo, S. Melaku, E. Z. Gebremedhin); National Veterinary Research Institute, Vom, Nigeria (H. Ularamu, A. Danmarwa, D. Shamaki, Y. Woma, Y. Wungak) and Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands (B.-J. Bosch)

DOI: http://dx.doi.org/10.3201/eid2008.140590

[1]These authors contributed equally to this article.

European Centre for Disease Prevention and Control

Distribution of confirmed cases of MERS-CoV by first available date, and probable place of infection, March 2012 – 4 February 2016 (n=1 657)



ECDC. Numbers in the map indicate the total number of local and imported MERS cases. Map produced on: 4 Feb 2016

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

Thailand reports imported MERS case; Saudi Arabia notes 2

Filed Under: MERS-CoV

Lisa Schnirring | News Editor | CIDRAP News | Jan 25, 2016

Thailand's health ministry yesterday confirmed a MERS-CoV infection in a man who had traveled from Oman, the second such case in the past 7 months, while Saudi Arabian health officials announced a pair of new cases, both in men who had direct contact with camels.

ruchos / iStock

Though most MERS-CoV (Middle East respiratory syndrome coronavirus) cases have been reported from Saudi Arabia, the dribble of exported cases is worrisome, given that unsuspected and undetected cases have the potential to trigger large outbreaks, as occurred in South Korea last summer.

Meanwhile, the cases in Saudi Arabia are the latest in a spate of camel-linked MERS illnesses in that country.

Morbidity and Mortality Weekly Report (*MMWR*)

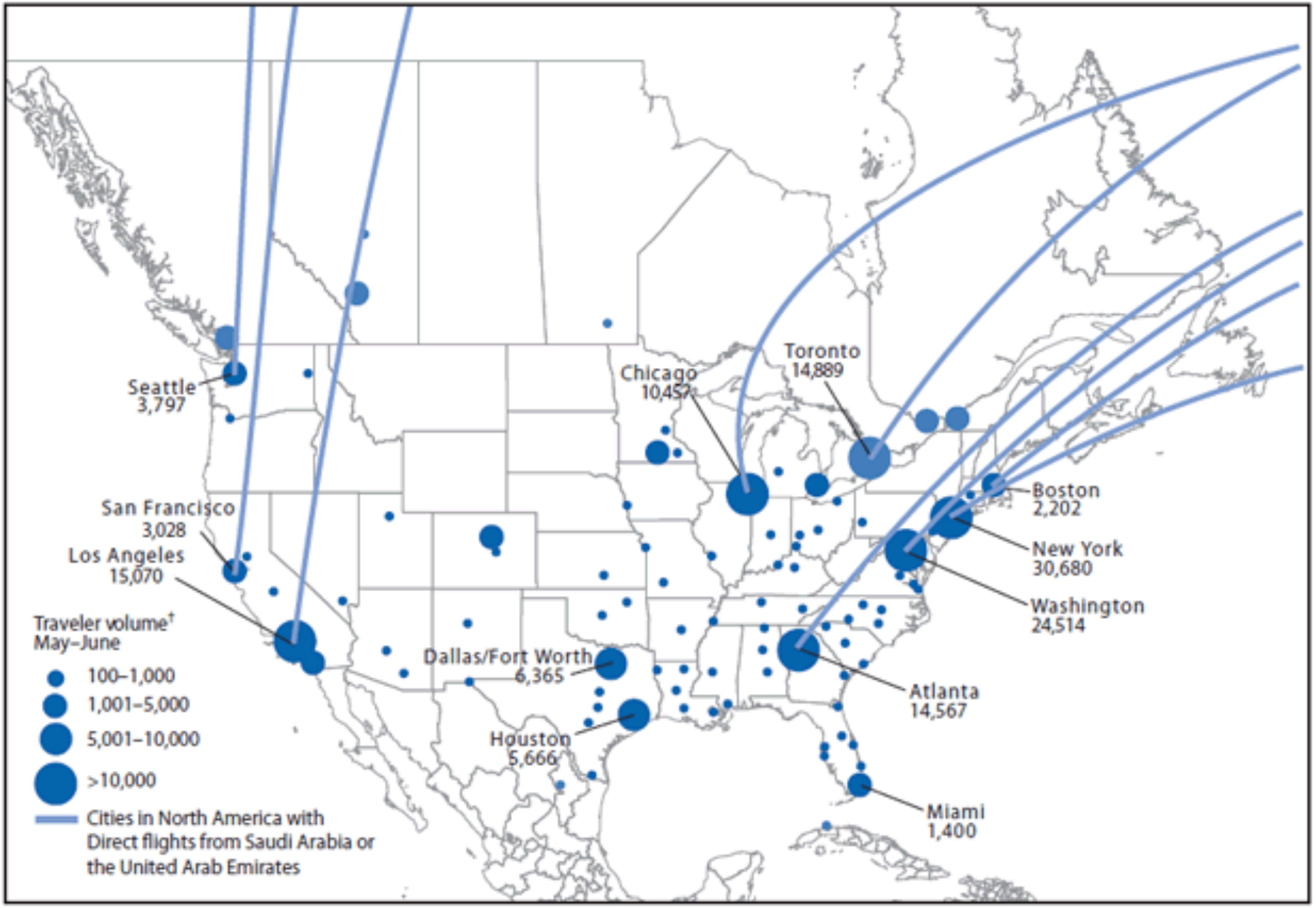
MMWR

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

Stephanie R. Bialek, MD[1], Donna Allen, MS[2], Francisco Alvarado-Ramy, MD[3], Ray Arthur, PhD[4], Arunmozhi Balajee, PhD[4], David Bell, MD[1], Susan Best, DO[5], Carina Blackmore, DVM, PhD[6], Lucy Breakwell, PhD[7,8], Andrew Cannons, PhD[6], Clive Brown, MD[3], Martin Cetron, MD[3], Nora Chea, MD[7,9], Christina Chommanard, MPH[1], Nicole Cohen, MD[3], Craig Conover, MD[10], Antonio Crespo, MD[11], Jeanean Creviston[5], Aaron T. Curns, MPH[1], Rebecca Dahl, MPH[1], Stephanie Dearth, MS[2], Alfred DeMaria, Jr, MD[12], Fred Echols, MD[2], Dean D. Erdman, DrPH[1], Daniel Feikin, MD[1], Mabel Frias, MPH[13], Susan I. Gerber, MD[1], Reena Gulati, MD[3], Christa Hale, DVM[3], Lia M. Haynes, PhD[1], Lea Heberlein-Larson, MPH[6], Kelly Holton[3], Kashef Ijaz, MD[4], Minal Kapoor, MD[14], Katrin Kohl, MD[3], David T. Kuhar, MD[9], Alan M. Kumar, MD[14], Marianne Kundich[5], Susan Lippold, MD[3], Lixia Liu, PhD[2], Judith C. Lovchik, PhD[2], Larry Madoff, MD[12], Sandra Martell, DNP[13], Sarah Matthews, MPH[15], Jessica Moore, MPH[1], Linda R. Murray, MD[13], Shauna Onofrey, MPH[12], Mark A. Pallansch, PhD[1], Nicki Pesik, MD[3], Huong Pham, MPH[1], Satish Pillai, MD[16], Pam Pontones, MA[2], Sarah Poser[1], Kimberly Pringle, MD[1,7], Scott Pritchard, MPH[6], Sonja Rasmussen, MD[17], Shawn Richards[2], Michelle Sandoval, MPH[2,18], Eileen Schneider, MD[1], Anne Schuchat, MD[19], Kristine Sheedy, PhD[19], Kevin Sherin, MD[15], David L. Swerdlow, MD[19], Jordan W. Tappero, MD[4], Michael O. Vernon, DrPH[12], Sharon Watkins, PhD[6], John Watson, MD[1] (Author affiliations at end of text)


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

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.

University of Minnesota

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

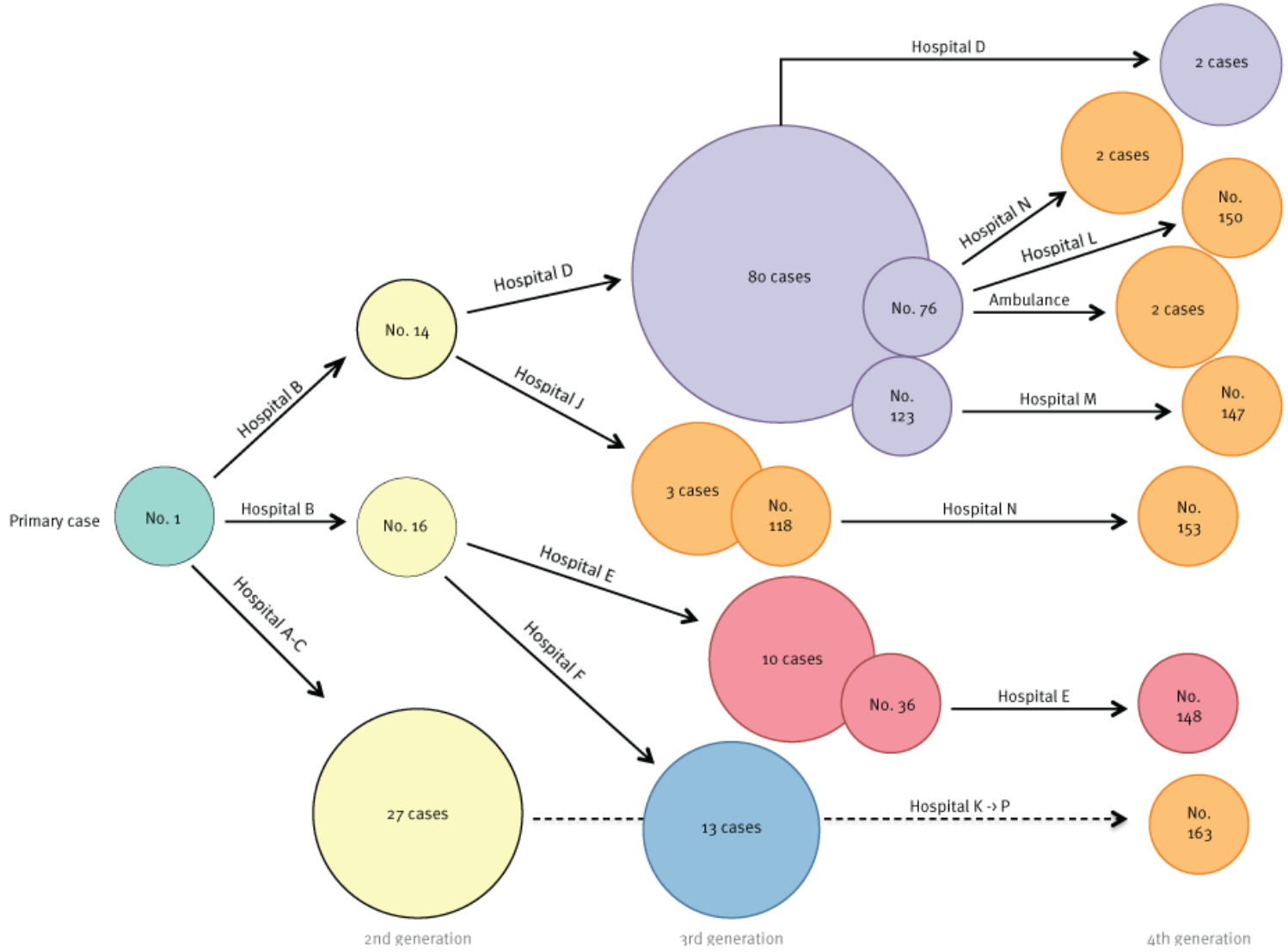
Major role of super-spreaders

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.

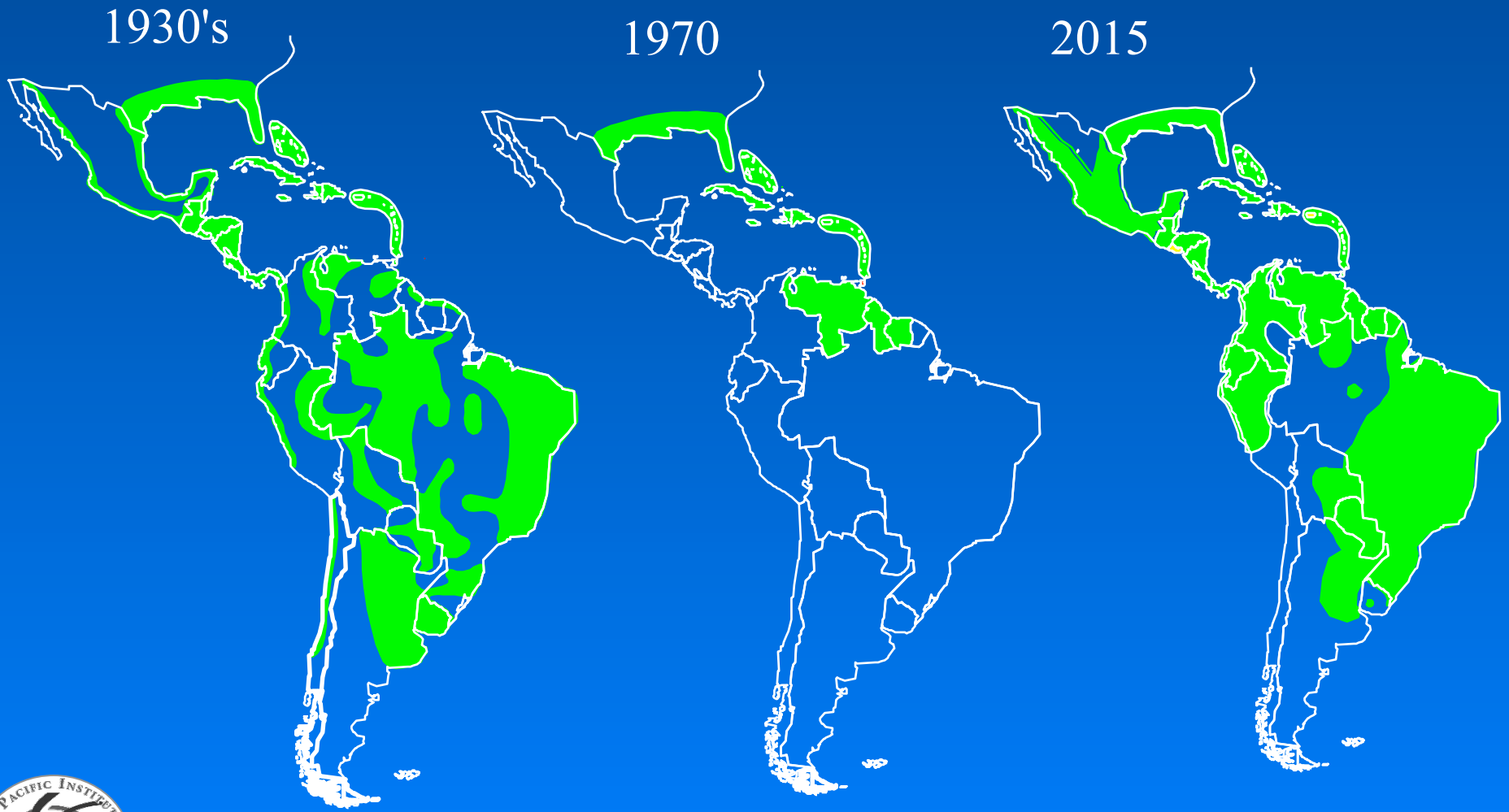
Preparedness and Vaccines

- Diseases with pandemic potential
  - Influenza
  - Gain of function-related agents
  - Smallpox
- **Diseases resulting in outbreaks of regional critical importance**
  - Ebola
  - MERS
  - **Zika**

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

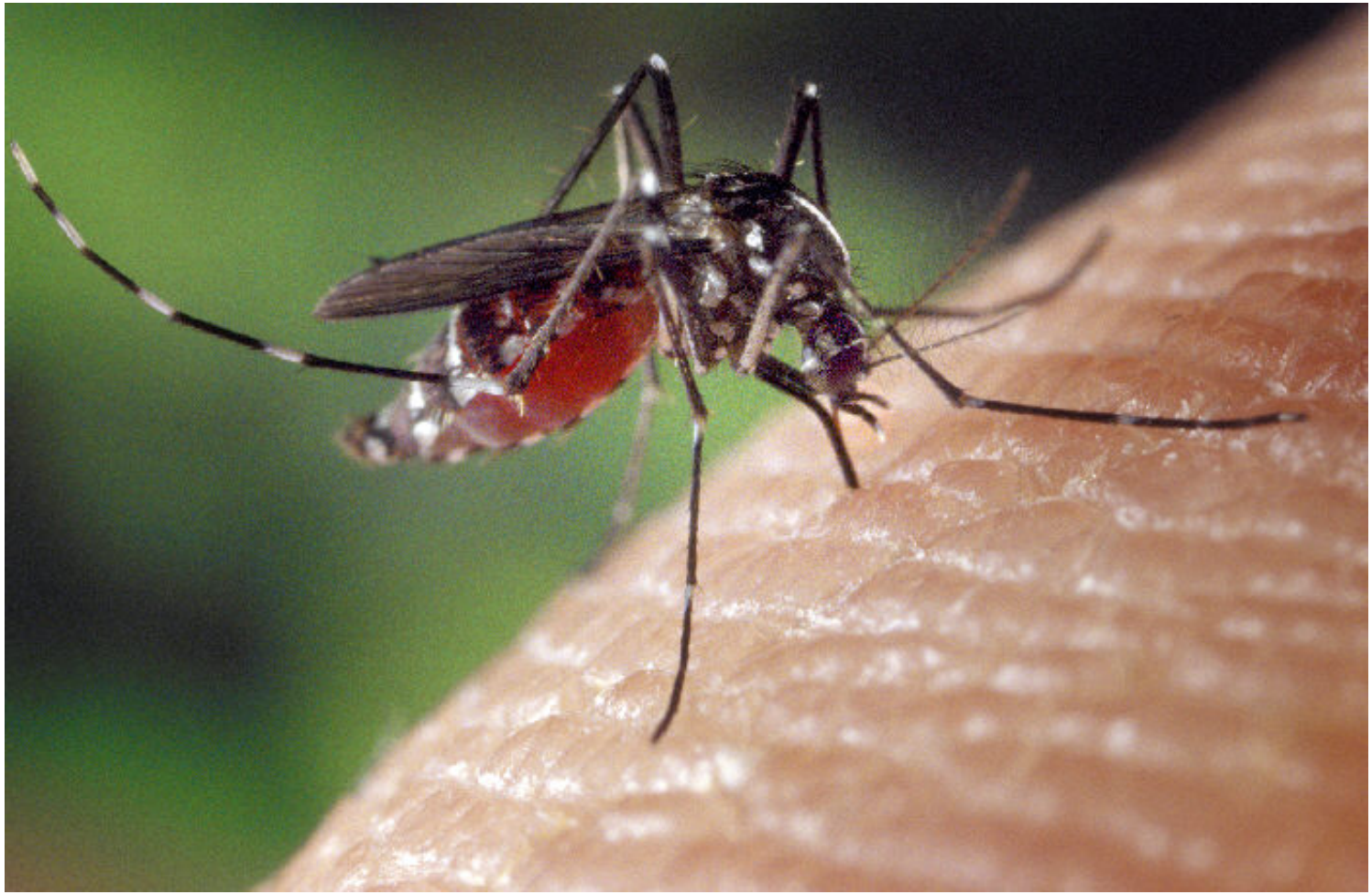
Aedes aegypti

Aedes aegypti Distribution in the Americas

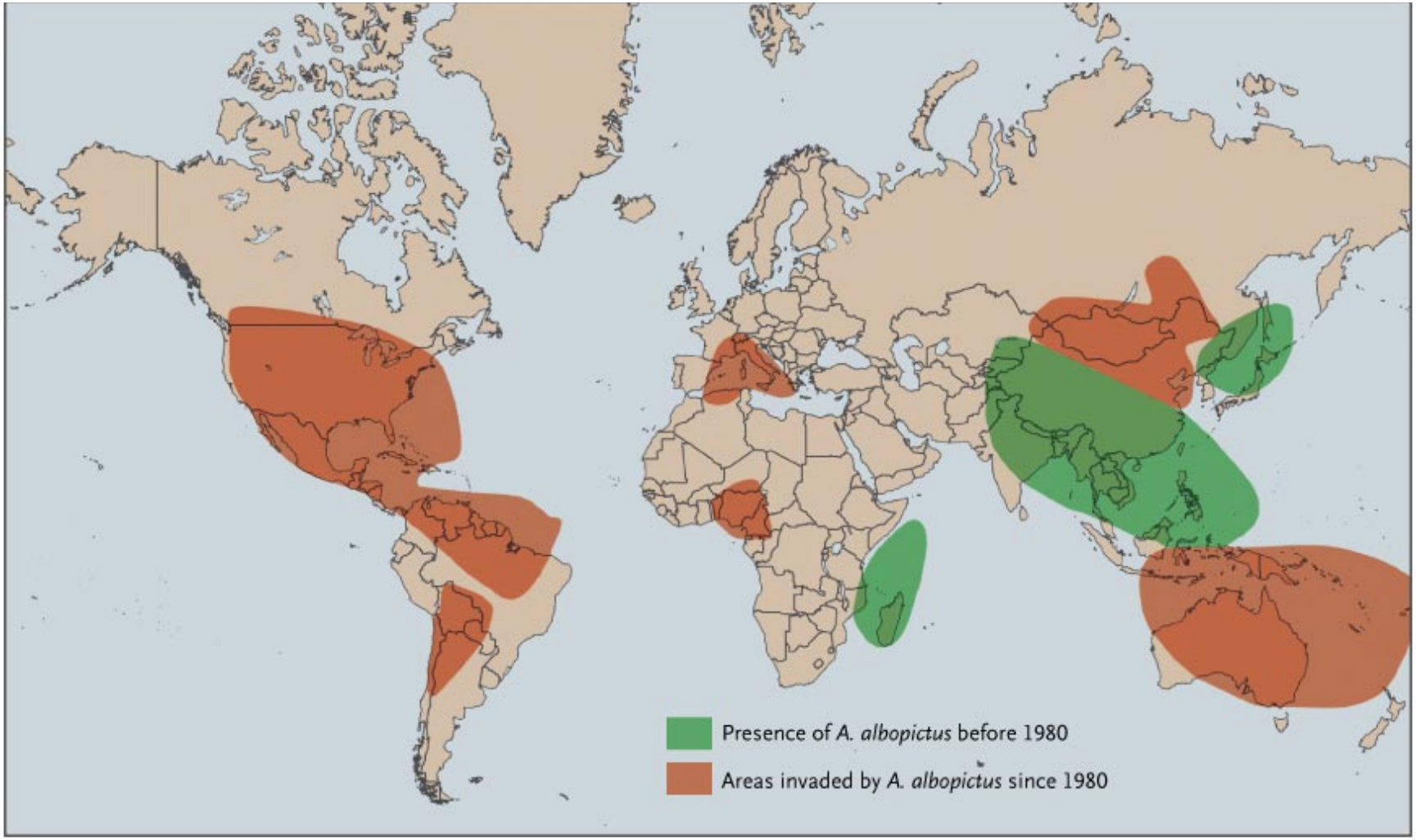


Adapted from Gubler, 1998

Aedes albopictus Female



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

REUTERS

Hawaii's Big Island declares emergency over dengue fever infections

The mayor of Hawaii's Big Island declared a state of emergency on Monday to deal with a growing outbreak of dengue fever, spread by infected mosquitoes, with 250 cases confirmed over the past four months.

As a result of Hawaii County Mayor Billy Kenoi's order people on the Big Island will be allowed to resume disposing of old tires in landfills, since tires which are left lying around are a known breeding spot for mosquitoes.

There have been 250 confirmed cases of dengue fever on the island since Oct. 29, making it the largest outbreak in the state since the 1940s, according to the mayor's declaration and Hawaii health officials.

Dengue fever causes flu-like symptoms and can develop into the deadly dengue hemorrhagic fever.

Hawaii Governor David Ige said in a statement he supported the efforts on the Big Island but would not issue a statewide emergency declaration unless the outbreak spread to other islands or expanded to include other diseases, such as the Zika virus.

Zika is spreading rapidly in South and Central America and the Caribbean and has been linked to severe birth defects in Brazil.


Metro
vodafone Sol
CASA DE DIEGO
DIEGO
PARAGUAS
ABANICOS
COMPRO ORO
LOTERIA SOL
CHANGE
www.sonyh
blow


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

The global burden of dengue: an analysis from the Global Burden of Disease Study 2013

Jeffrey D Stanaway, Donald S Shepard, Eduardo A Undurraga, Yara A Halasa, Luc E Coffeng, Oliver J Brady, Simon I Hay, Neeraj Bedi, Isabela M Bensenor, Carlos A Castañeda-Orjuela, Ting-Wu Chuang, Katherine B Gibney, Ziad A Memish, Anwar Rafay, Kingsley N Ukwaja, Naohiro Yonemoto, Christopher J L Murray

Summary

Background Dengue is the most common arbovirus infection globally, but its burden is poorly quantified. We estimated dengue mortality, incidence, and burden for the Global Burden of Disease Study 2013.

Methods We modelled mortality from vital registration, verbal autopsy, and surveillance data using the Cause of Death Ensemble Modelling tool. We modelled incidence from officially reported cases, and adjusted our raw estimates for under-reporting based on published estimates of expansion factors. In total, we had 1780 country-years of mortality data from 130 countries, 1636 country-years of dengue case reports from 76 countries, and expansion factor estimates for 14 countries.

Findings We estimated an average of 9221 dengue deaths per year between 1990 and 2013, increasing from a low of 8277 (95% uncertainty estimate 5353–10 649) in 1992, to a peak of 11 302 (6790–13 722) in 2010. This yielded a total of 576 900 (330 000–701 200) years of life lost to premature mortality attributable to dengue in 2013. The incidence of dengue increased greatly between 1990 and 2013, with the number of cases more than doubling every decade, from 8·3 million (3·3 million–17·2 million) apparent cases in 1990, to 58·4 million (23·6 million–121·9 million) apparent cases in 2013. When accounting for disability from moderate and severe acute dengue, and post-dengue chronic fatigue, 566 000 (186 000–1 415 000) years lived with disability were attributable to dengue in 2013. Considering fatal and non-fatal outcomes together, dengue was responsible for 1·14 million (0·73 million–1·98 million) disability-adjusted life-years in 2013.

Interpretation Although lower than other estimates, our results offer more evidence that the true symptomatic incidence of dengue probably falls within the commonly cited range of 50 million to 100 million cases per year. Our mortality estimates are lower than those presented elsewhere and should be considered in light of the totality of evidence suggesting that dengue mortality might, in fact, be substantially higher.

Funding Bill & Melinda Gates Foundation.

Lancet Infect Dis 2016

Published Online February 10, 2016 http://dx.doi.org/10.1016/S1473-3099(16)00026-8

See Online/Comment http://dx.doi.org/10.1016/S1473-3099(16)00076-1

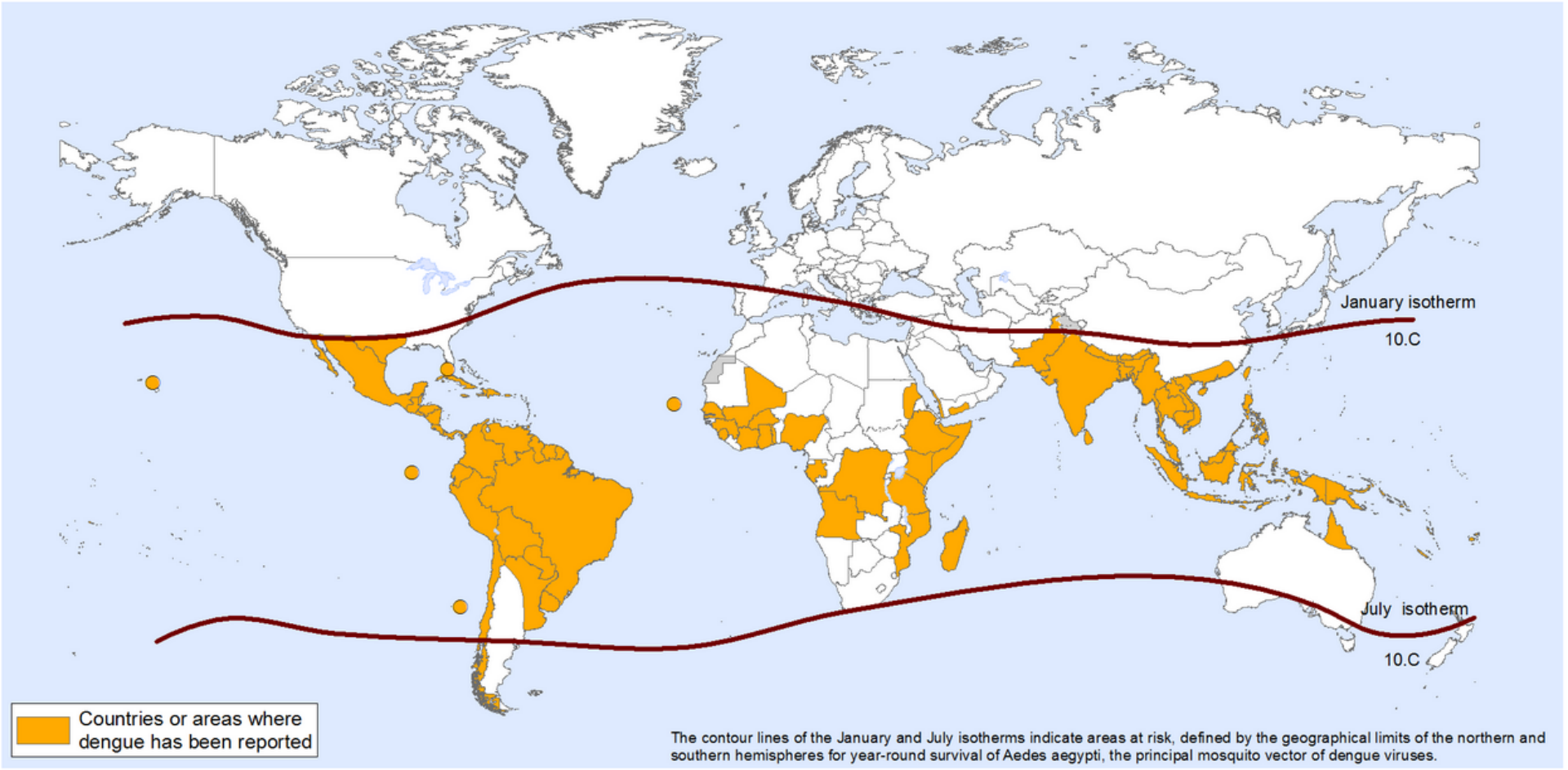
Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA (J D Stanaway PhD, Prof S I Hay DSc, Prof C J L Murray DPhil); Schneider Institutes for Health Policy, Heller School for Social Policy and Management, Brandeis University, Waltham, MA, USA (Prof D S Shepard PhD, E A Undurraga PhD, Y A Halasa DDS); Department of Public Health, Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands (L E Coffeng PhD); Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK (O J Brady DPhil, S I Hay); Fogarty International Center, National Institutes of Health, Bethesda, MD, USA (S I Hay); College of Public Health and Tropical Medicine, Jazan University, Jazan, Saudi Arabia (Prof N Bedi MD); University of São Paulo, Hospital Universitário, São Paulo, Brazil (I M Bensenor PhD); Colombian National Health Observatory, Bogotá, DC, Colombia (C A Castañeda-Orjuela MD); Epidemiology and Public Health Evaluation Group, Public Health Department, Universidades Nacional de Colombia, Ciudad Universitaria, Facultad de Medicina, Bogotá, Colombia (C A Castañeda-Orjuela); Taipei Medical University, Taipei City, Taiwan (T-W Chuang PhD); Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia (K B Gibney FRACP); Melbourne Health, Victorian Infectious Diseases Service, The Royal

Introduction

Dengue is the most common arbovirus infection globally, with transmission occurring in at least 128 countries and almost 4 billion people at risk.[1] The number of dengue cases reported to WHO has increased steadily from an average of less than a thousand cases per year globally in the 1950s to more than 3 million cases in 2013.[2–4] These reports, however, greatly understate the problem and estimates of the true number of annual apparent infections range from 50 million to 200 million, where apparent infections are defined as all symptomatic infections, including those that are undetected by reporting systems. The most commonly cited range, including by WHO, is 50 million to 100 million apparent cases per year.[4,7] Although estimates of dengue deaths are less often reported, the most commonly cited number is around 20 000 deaths per year.[8] To our knowledge, these estimates seem largely to be based on expert opinion. The Global Burden of Disease Study 2010—providing the most recent data-driven estimate of dengue deaths—estimated that more than 14 000 people died from dengue in 2010.[9]

The disparity between the number of reported cases and estimates of the number of actual cases stems from under-recognition and under-reporting of dengue. Symptomatic dengue infections have a broad range of severity and as many as 70% of patients choose to not seek treatment or treat themselves.[7] Even for those who are seen by a health-care professional, the clinical presentation of dengue shares similarities with up to 12 major pathogens, making misdiagnosis common, particularly in areas with a high incidence of febrile illnesses.[10] Population-based cohort studies[11,12] have consistently found dengue cases to be greatly under-reported through official passive surveillance and reporting systems. Several studies have attempted to quantify the degree of under-reporting by comparing incidence rates derived from active febrile-illness surveillance with comparable incidence rates derived from official reports. The ratio of these rates is referred to as the expansion factor, and it represents the number by which one would multiply the number of reported cases to derive the number of true apparent dengue infections in a given population. That said, the degree to which dengue is under-reported varies by orders of magnitude across time

Dengue, countries or areas at risk, 2013

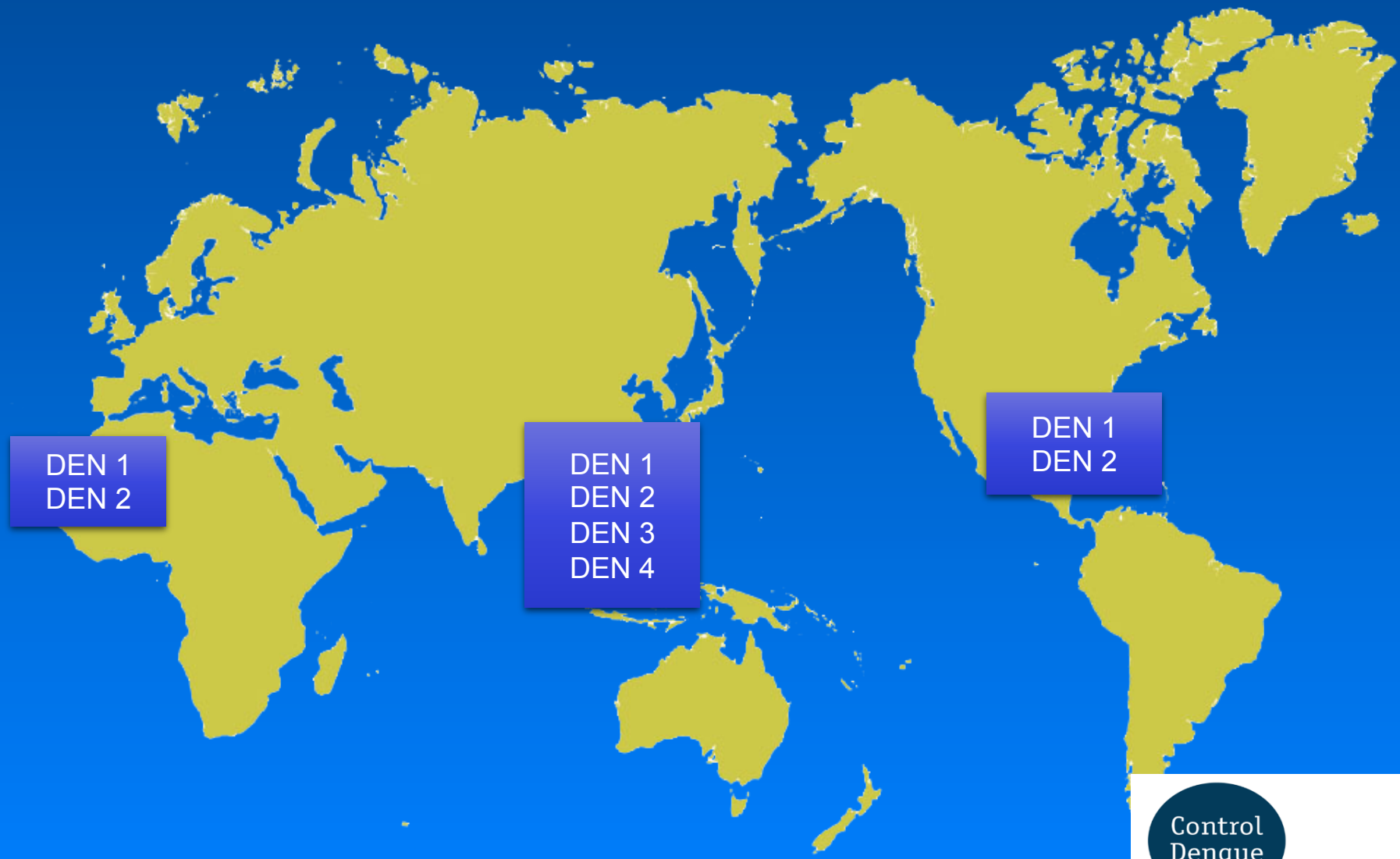


The contour lines of the January and July isotherms indicate areas at risk, defined by the geographical limits of the northern and southern hemispheres for year-round survival of Aedes aegypti, the principal mosquito vector of dengue viruses.

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

World Health Organization

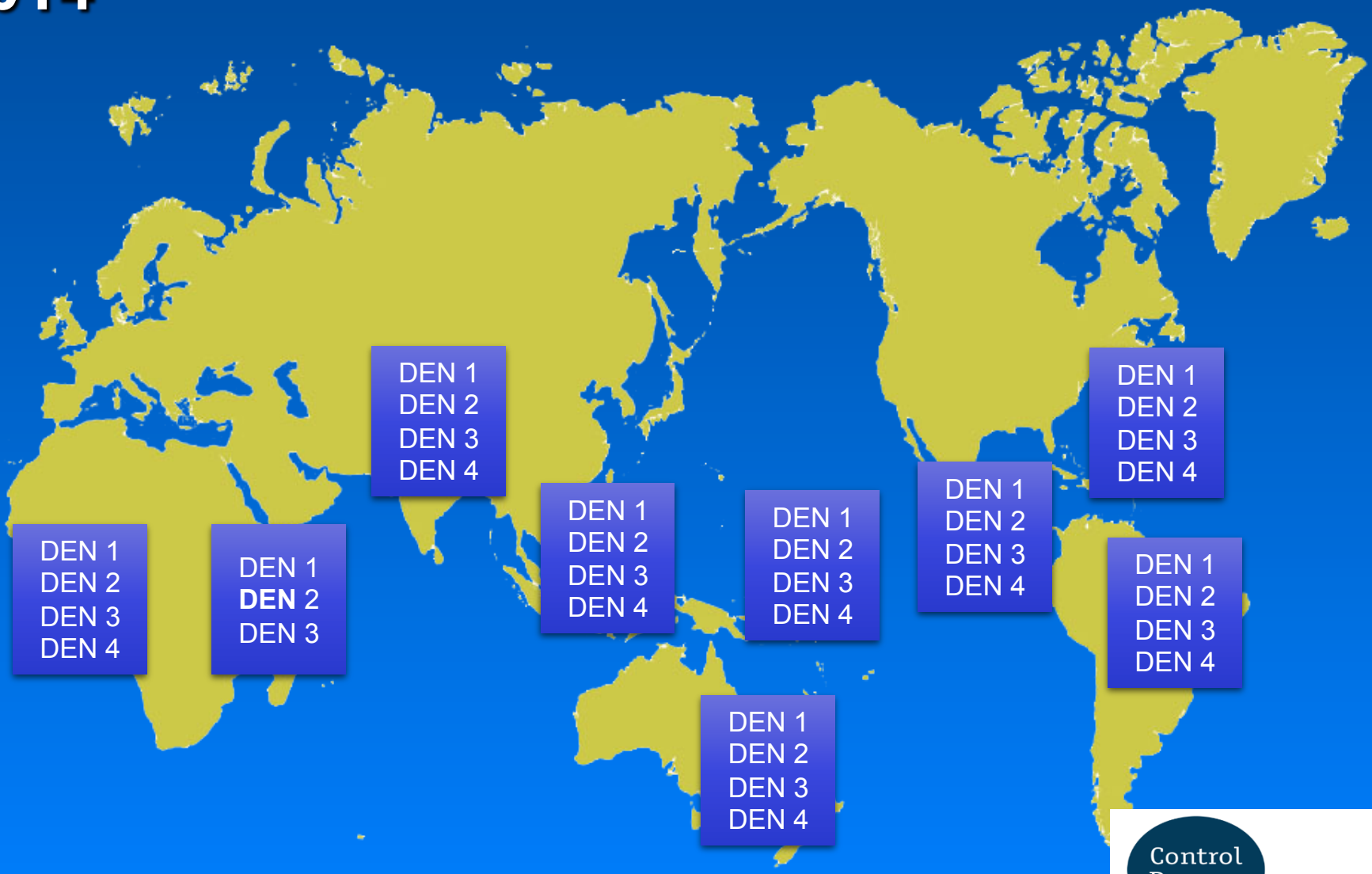
Global distribution of dengue virus serotypes, 1970



Control Dengue

PDC Partnership

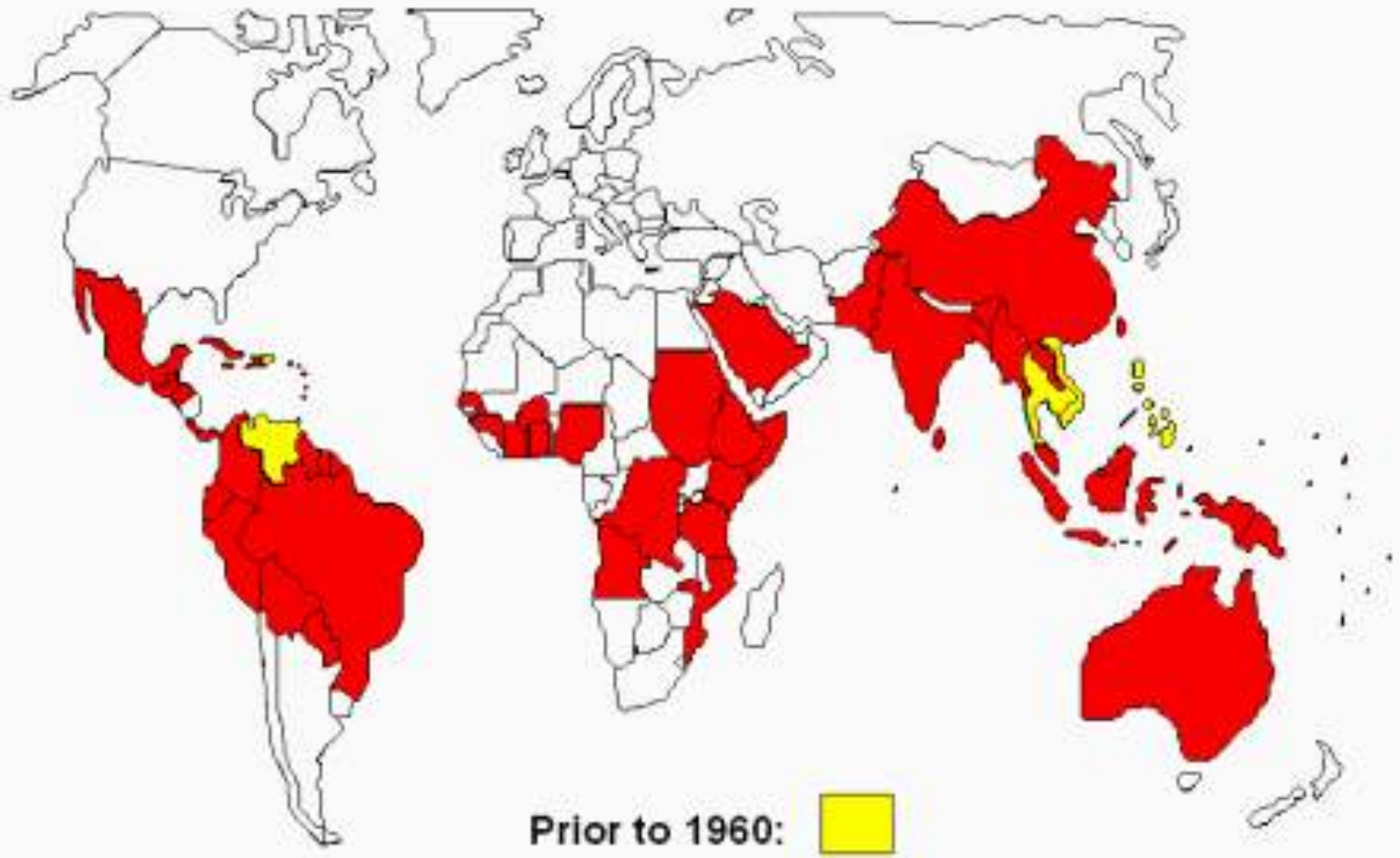
Global distribution of dengue virus serotypes, 2014



Control Dengue

PDC Partnership

Emergence of Dengue and Dengue Hemorrhagic Fever



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

****

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.

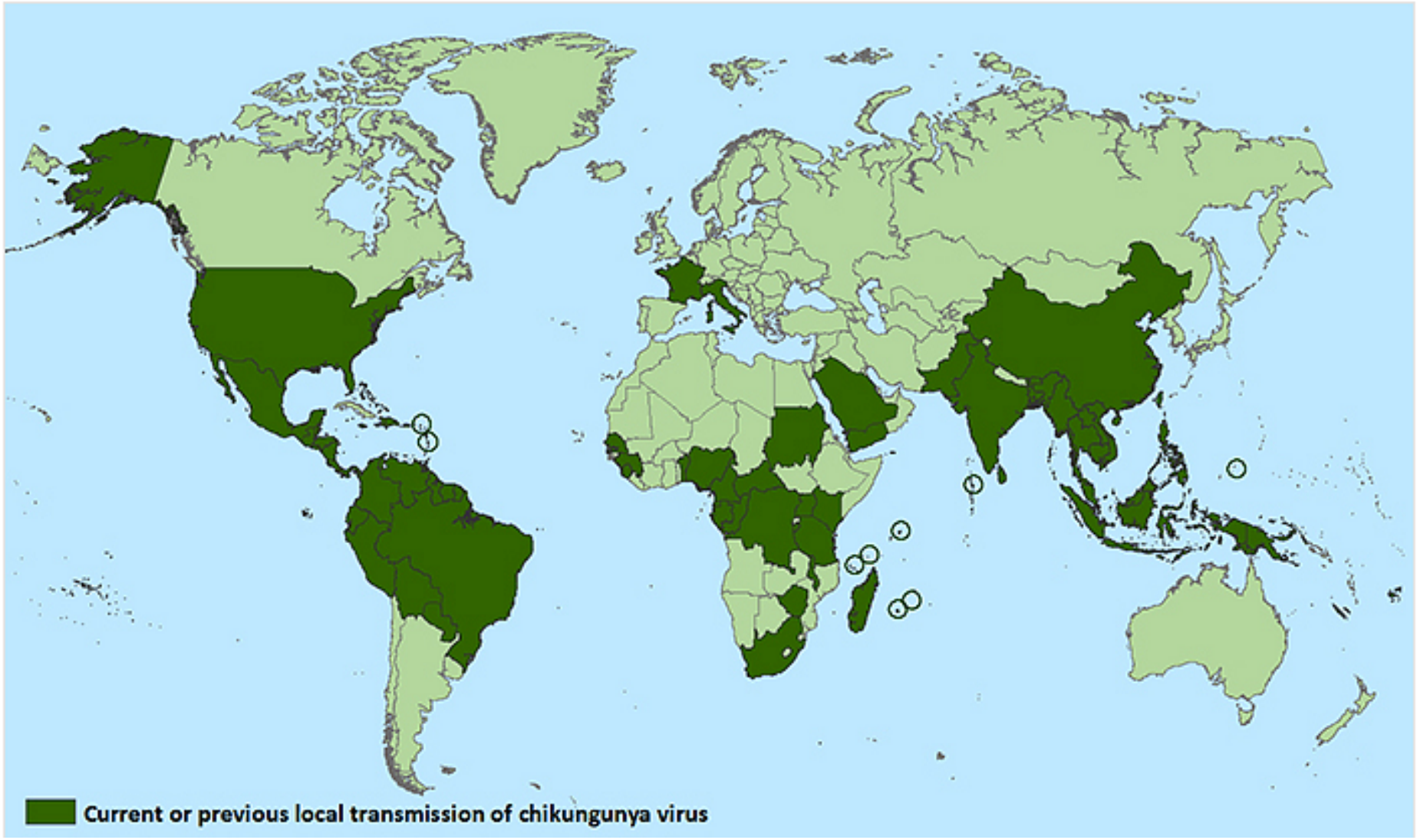
Chikungunya, countries or areas at risk

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

World Health Organization

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
Regional Office for the Americas

Number of Reported Cases of Chikungunya Fever in the Americas, by Country or Territory
2016 (to week noted)
Cumulative cases
Epidemiological Week / EW1 (Updated as of 8 January 2016)

Country/Territory	Epidemiological Week[a]	Autochthonous transmission cases[b]		Imported cases	Incidence Rate[c]	Deaths[d]	Population[e] X 1000
		Suspected	Confirmed				
North America							
Bermuda	Week 17			3			70
Canada	Week 36			85			35,871
Mexico	Week 51		11,468	20	9.2		125,235
United States of America[f]	Week 50			653			325,127
Subtotal		*0*	*11,468*	*761*	*2.4*	*0*	*486,303*
Central American Isthmus							
Belize	Week				0.0		347
Costa Rica	Week 20		142		2.8		5,001
El Salvador	Week 35	39,704	17		618.1	0	6,426
Guatemala	Week 48	27,759	1,998		183.1	5	16,255
Honduras	Week 45	82,003	5		973.6	1	8,423
Nicaragua	Week 51	68,945	5,117		1,183.9	1	6,256
Panama	Week 51	123	36	19			3,987
Subtotal		*218,534*	*7,315*	*19*	*483.7*	*7*	*46,695*
Latin Caribbean							
Cuba	Week				0.0		11,248
Dominican Republic	Week 28	67			0.6		10,652
French Guiana	Week 47	6,960	1,759		3,340.6	2	261
Guadaloupe	Week 46	157			33.4		470
Haiti	Week						10,603
Martinique	Week 46	341			84.2		405
Puerto Rico[f]	Week 51	801	214		27.6	1	3,680
Saint Barthelemy	Week 18	317			3,561.8		9
Saint Martin (French part)	Week 46	602			1,686.7		36
Subtotal		*9,245*	*1,973*	*0*	*30.0*	*3*	*37,364*
Andean Area							
Bolivia	Week 13	143	916	1	9.6		11,024
Colombia	Week 51	355,175	3,192		723.5	70	49,529
Ecuador	Week 51	29,350	4,173	21	206.6	2	16,225
Peru	Week 48	85	100	77	0.6		31,161
Venezuela	Week 51	15,839	355	0	51.8	0	31,292
Subtotal		*400.592*	*8.736*	*99*	*294.0*	*72*	*139.231*
TOTAL		653,249	31,543	935	69.1	82	991,134

Chikungunya virus–associated encephalitis

A cohort study on La Réunion Island, 2005–2009

Patrick Gérardin, MD, PhD
Thérèse Couderc, PhD
Marc Bintner, MD
Patrice Tournebize, MD
Michel Renouil, MD
Jérome Lémant, MD
Véronique Boisson, MD
Gianandrea Borgherini, MD
Frédérik Staikowsky, MD, PhD
Frédéric Schramm, MD, PhD
Marc Lecuit, MD, PhD
Alain Michault, PharmD†
On behalf of the Encephalchik Study Group

Correspondence to Dr. Gérardin: patrick.gerardin@chu-reunion.fr

ABSTRACT

Objective: To estimate the cumulative incidence rate (CIR) of Chikungunya virus (CHIKV)-associated CNS disease during the La Réunion outbreak, and assess the disease burden and patient outcome after 3 years.

Methods: CHIKV-associated CNS disease was characterized retrospectively in a cohort of patients with positive CHIKV reverse transcriptase PCR or anti-CHIKV immunoglobulin M antibodies in the CSF and fulfilling International Encephalitis Consortium criteria for encephalitis or encephalopathy. Neurologic sequelae were assessed after 3 years.

Results: Between September 2005 and June 2006, 57 patients were diagnosed with CHIKV-associated CNS disease, including 24 with CHIKV-associated encephalitis, the latter corresponding to a CIR of 8.6 per 100,000 persons. Patients with encephalitis were observed at both extremes of age categories. CIR per 100,000 persons were 187 and 37 in patients below 1 year and over 65 years, respectively, both far superior to those of cumulated causes of encephalitis in the United States in these age categories. The case-fatality rate of CHIKV-associated encephalitis was 16.6% and the proportion of children discharged with persistent disabilities estimated between 30% and 45%. Beyond the neonatal period, the clinical presentation and outcomes were less severe in infants than in adults.

Conclusions: In the context of a large outbreak, CHIKV is a significant cause of CNS disease. As with other etiologies, CHIKV-associated encephalitis case distribution by age follows a U-shaped parabolic curve. *Neurology*® 2016;86:94–102

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **CHIKV** = Chikungunya virus; **CFR** = case-fatality rate; **CIR** = cumulative incidence rate; **DQ** = development quotient; **DWI** = diffusion-weighted imaging; **ECSA** = East Central South African; **IEC** = International Encephalitis Consortium; **IgM** = immunoglobulin M; **LP** = lumbar puncture; **NECACD** = nonencephalitic Chikungunya virus–associated CNS disease; **WNV** = West Nile virus.

Chikungunya virus (CHIKV) is a re-emerging alphavirus.[1] Alphaviruses are divided into arthritogenic viruses (old world) and encephalitogenic viruses (new world) including equine encephalitis viruses.[2]

Until its reemergence in the Indian Ocean in 2004 and the worldwide spread that followed, beyond the burden of arthritis, known for lasting weeks to years,[3] Chikungunya was considered as a nonfatal disease with spontaneous resolution, not causing lifelong disabilities, even though rare cases of CNS disease had been reported.[4,5]

The major outbreaks that have occurred since 2005 in the Indian Ocean islands were attributable to a new Indian Ocean lineage that evolved from the East Central South African (ECSA) lineage and selected the mutation E1-A226V, which favors transmission by *Aedes albopictus*.[6,7]

Supplemental data at Neurology.org

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.

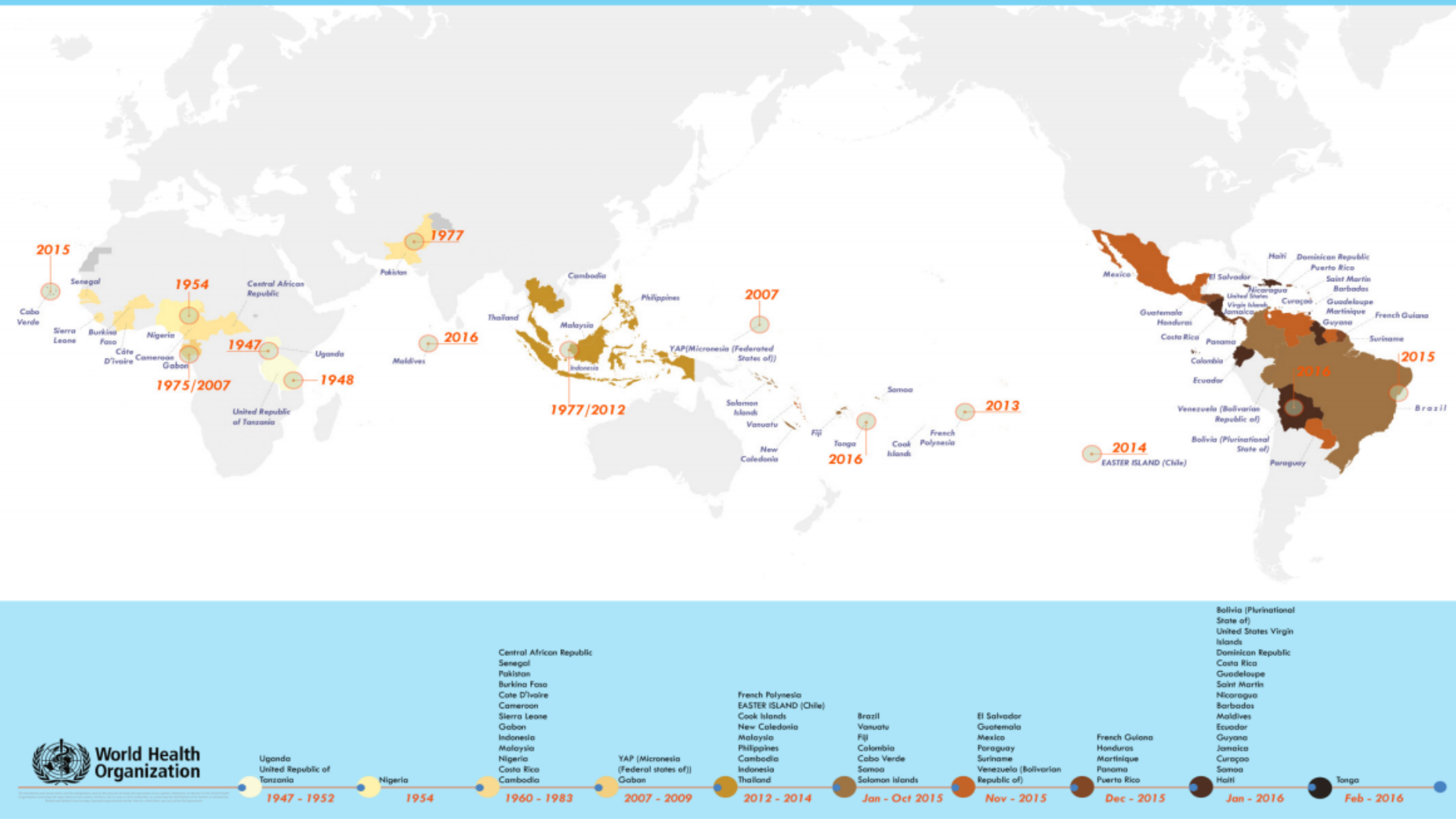
After an infected mosquito bite, the disease symptoms usually appear following an incubation period of three to twelve days.

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.

World Health Organization

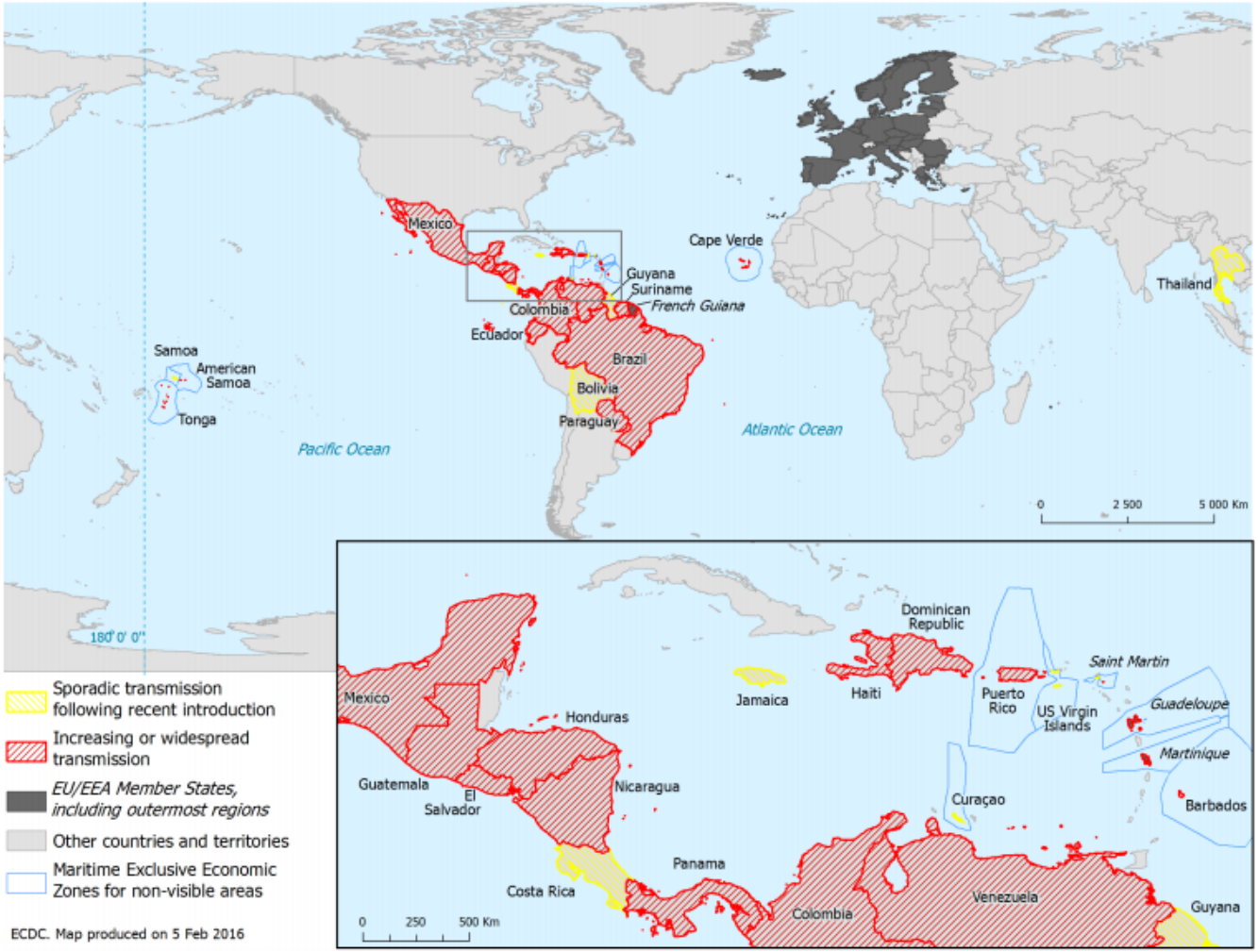
Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)



European Centre for Disease Prevention and Control

Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past two months, as of 5 February 2016

ECDC



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

Roosecelis Brasil Martines, MD, PhD[1]; Julu Bhatnagar, PhD[1]; M. Kelly Keating, DVM[1]; Luciana Silva-Flannery, PhD[1]; Atis Muehlenbachs, MD, PhD[1]; Joy Gary, DVM, PhD[1]; Cynthia Goldsmith, MS[1]; Gillian Hale, MD[1]; Jana Ritter, DVM[1]; Dominique Rollin, MD[1]; Wun-Ju Shieh, MD, PhD[1]; Kleber G. Luz, MD, PhD[2]; Ana Maria de Oliveira Ramos, MD, PhD[3]; Helaine Pompeia Freire Davi, MD, PhD[4]; Wanderson Kleber de Oliveria, MD[5]; Robert Lanciotti, PhD[6]; Amy Lambert, PhD[6]; Sherif Zaki, MD, PhD[1]

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.

This article was published on February 10, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1600651

Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans

Caio César de Melo Freire[1], Atila Iamarino[1], Daniel Ferreira de Lima Neto[1], Amadou Alpha Sall[2], and Paolo Marinho de Andrade Zanotto[1*]

[1]**Laboratory of Molecular Evolution and Bioinformatics, Department of Microbiology, Biomedical Sciences Institute, University of Sao Paulo, Sao Paulo, Brazil.**
[2]**Institut Pasteur de Dakar, Dakar, Senegal.**
[*]**Corresponding author: pzanotto@usp.br.**

ABSTRACT

Zika virus (ZIKV) infections were more common in the zoonotic cycle until the end of the 20th century with few human cases in Africa and Southeastern Asia. Recently, the Asian lineage of ZIKV is spreading along human-to-human chains of transmission in the Pacific Islands and in South America. To better understand its recent urban expansion, we compared genetic differences among the lineages. Herein we show that the recent Asian lineage spread is associated with significant NS1 codon usage adaptation to human housekeeping genes, which could facilitate viral replication and increase viral titers. These findings were supported by a significant correlation with growth in Malthusian fitness. Furthermore, we predicted several epitopes in the NS1 protein that are shared between ZIKV and Dengue. Our results imply in a significant dependence of the recent human ZIKV spread on NS1 translational selection.

Keywords: Zika virus, emerging diseases, molecular evolution, codon usage adaptation, NS1

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.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

CDC notes Zika-microcephaly link, ponders travel alert

Filed Under: Chikungunya; Dengue; Meningitis; Zika

Jim Wappes | Editorial Director | CIDRAP News | Jan 14, 2016

The US Centers for Disease Control and Prevention (CDC) yesterday presented perhaps its most compelling evidence for a link between Zika virus infection and microcephaly, a condition of small heads and brains that has risen 10-fold in Brazil as Zika infections there have spiked, according to media reports.

CDC / James Gathany

The CDC is also considering warning pregnant women not to travel to Zika-affected countries, officials said.

And in related news, two National Institutes of Health (NIH) experts wrote in the *New England Journal of Medicine* (*NEJM*) yesterday that the disease presents yet another facet of the growing threat of mosquito-borne diseases to North America.

Zika detection in infants, moms

Lyle Peterson, MD, MPH, the director of the CDC's Division of Vector-Borne Diseases, said yesterday that CDC lab tests have confirmed Zika virus in the brains of two Brazilian newborns who died and in the placentas of two women who miscarried, the Associated Press (AP) reported today. All four cases involved microcephaly.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

CDC releases Zika guidance on pregnant patients

Filed Under: Zika

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

quintanilla / iStock

The US Centers for Disease Control and Prevention (CDC) today released interim guidance on Zika virus for clinicians with pregnant patients returning from or considering visiting countries where it is circulating, a move that comes on the heels of its Jan 15 travel advice for pregnant women and those trying to conceive.

The CDC's warning a few days ago—urging pregnant women and those planning pregnancies to temporarily shelve their travel plans—was underscored by an announcement only hours later of a microcephaly case in a baby born in Hawaii.

Today's guidance for clinicians and the stepped-up travel advisory from a few days ago come during the winter vacation travel season to tropical climates and ahead of Brazil's pre-Lenten Carnival celebrations next month and the Summer Olympics that get under way in August.

Meanwhile, the Pan American Health Organization (PAHO) said the mosquito-borne virus has expanded its reach, which came with a request for countries to look for unusual rises in cases of Guillain-Barre syndrome (GBS), and officials in Brazil announced funding to fast-forward vaccine development.

Health provider guidance

The CDC published its interim guidance today in an early-release report in *Morbidity and Mortality Weekly Report (MMWR)*. Health providers should ask all pregnant women about recent travel, and

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

News Scan for Jan 20, 2016

US Zika cases in pregnancy; H5N1 outbreaks in Nigeria; Lassa fever in Nigeria

Filed Under: Lassa; Zika; Avian Influenza (Bird Flu); VHF

Illinois reports 2 pregnancy-related Zika cases as affected nations mount

Shortly after the Centers for Disease Control and Prevention (CDC) released guidance on Zika virus infection and pregnancy yesterday, Illinois officials reported two imported cases in pregnant women, a potential risk for birth defects.

And in related news, the World Health Organization (WHO) today confirmed that Guyana, Barbados, Ecuador, and Bolivia have joined the ever-growing list of countries affected by the mosquito-borne disease.

The Illinois Department of Public Health (IDPH) said the two pregnant Illinois residents had recently traveled to Zika-affected countries and have tested positive for the virus. "Physicians are monitoring their health and pregnancies," the agency said in a press release.

"There is virtually no risk to Illinois residents since you cannot contract Zika virus from another person, but only through the bite of an infected mosquito," said IDPH Director Nirav D. Shah, MD, JD. "But . . . we are urging residents, especially pregnant women, to take preventive measures when traveling in affected countries and check health travel advisories."

The concern is over microcephaly in infants born to infected mothers—an underdeveloped head that is often associated with cognitive defects. Brazil has now reported 3,893 suspected microcephaly cases, including 363 new ones, according to a post today on Avian Flu Diary, an infectious disease blog. Recent testing has shown a possible link between Zika and the condition.

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

RAPID RISK ASSESSMENT

Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome (first update)

21 January 2016

Main conclusions

The spread of the Zika virus epidemic in the Americas is likely to continue as the competent vectors *Aedes aegypti* and *Aedes albopictus* mosquitoes are widely distributed there. There is also a significant increase in the number of babies born with microcephaly in the north-eastern states of Brazil, however, the magnitude and geographical spread of the increase have not yet been well characterised. Despite growing evidence of a link between intra-uterine Zika virus infection and adverse pregnancy outcomes, a causal link between these events has not yet been confirmed.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

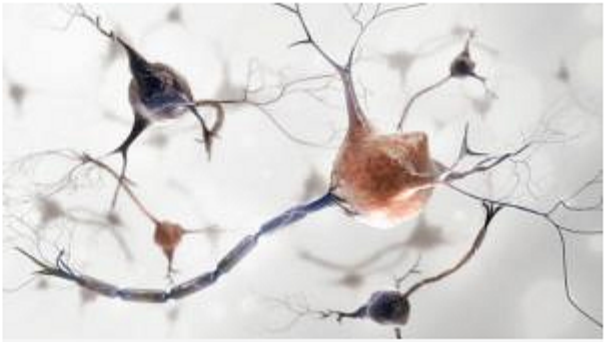
WHO reports more local Zika confirmations, GBS spike

Filed Under: Zika

Lisa Schnirring | News Editor | CIDRAP News | Jan 21, 2016

In Zika virus developments today, the World Health Organization (WHO) said El Salvador is investigating an unusual spike in Guillain-Barre syndrome (GBS) that may be linked its recent surge of infections and confirmed the first locally transmitted cases in two French Caribbean territories, St. Martin and Guadeloupe.

Also, Brazilian scientists reported Zika virus in placental tissue, shedding a little more light on the possible link between maternal infections and microcephaly—or smaller-than-normal heads—in babies.



muzon / iStock

Thought to be an autoimmune disorder that damages nerve cells, GBS causes muscle weakness and sometimes paralysis.

GBS reports hint at acute illness complications

Though the main threat surrounding the Zika virus epidemic has been a heart-wrenching rise in microcephaly cases, new questions are swirling about other complications in what is typically a fairly mild illness. Thought to be an autoimmune disorder that damages nerve cells, GBS causes muscle weakness and sometimes paralysis. Most people recover, but some have lingering nerve damage.

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

CDC adds countries to interim travel guidance related to Zika virus

Media Statement

For Immediate Release: Friday, January 22, 2016

Contact: Media Relations,
(404) 639-3286

CDC is working with other public health officials to monitor for ongoing Zika virus transmission. Today, CDC added the following destinations to the Zika virus travel alerts: Barbados, Bolivia, Ecuador, Guadeloupe, Saint Martin, Guyana, Cape Verde, and Samoa. On January 15, CDC issued a travel alert (Level 2-Practice Enhanced Precautions) for people traveling to regions and certain countries where Zika virus transmission is ongoing: the Commonwealth of Puerto Rico, a U.S. territory; Brazil; Colombia; El Salvador; French Guiana; Guatemala; Haiti; Honduras; Martinique; Mexico; Panama; Paraguay; Suriname; and Venezuela. Specific areas where Zika virus transmission is ongoing are often difficult to determine and are likely to continue to change over time.

As more information becomes available, CDC travel alerts will be updated. Travelers to areas where cases of Zika virus infection have been recently confirmed are at risk of being infected with the Zika virus. Travelers to these areas may also be at risk of being infected with dengue or chikungunya viruses. Mosquitoes that spread Zika, chikungunya, and dengue are aggressive daytime biters, prefer to bite people, and live indoors and outdoors near people. There is no vaccine or medicine available for Zika virus. The best way to avoid Zika virus infection is to prevent mosquito bites.

Some travelers to areas with ongoing Zika virus transmission will become infected while traveling but will not become sick until they return home. Symptoms include fever, rash, joint pain, and red eyes. Other commonly reported symptoms include muscle pain, headache, and pain behind the eyes. The illness is usually mild with symptoms lasting from several days to a week. Severe disease requiring hospitalization is uncommon and case fatality is low. Travelers to these areas should monitor for symptoms or illness upon return. If they become ill, they should tell their healthcare professional where they have traveled and when.

telesur

Zika Virus: Despite Lack of Evidence, El Salvador Warns Against Pregnancy for 2 Years

A man carries his son as health workers fumigates the Altos del Cerro neighbourhood to combat the Zika virus in Soyapango, El Salvador Jan. 21, 2016. | Photo: Reuters

Published 22 January 2016

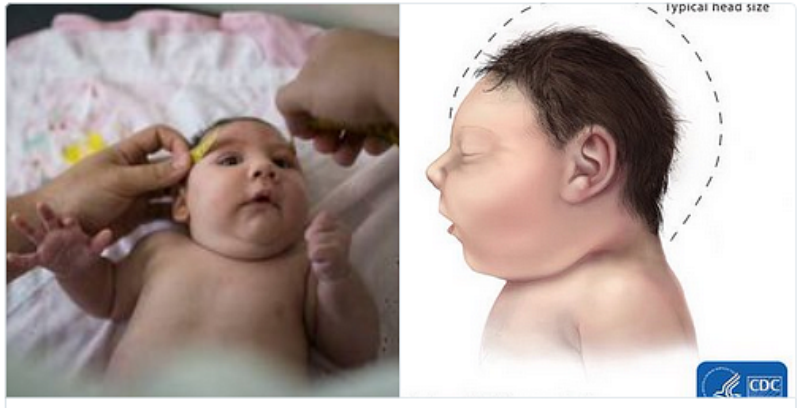
Although there is still no evidence that the Zika virus is responsible for microcephaly in babies, health officials in the Central American nation have warned women against falling pregnant.

Health officials in El Salvador have advised women to delay pregnancy until 2018 amid fears that the spreading Zika virus causes birth defects in newborns.

The mosquito-borne virus is suspected to cause a rare brain defect in babies, known as microcephaly, which causes abnormally small heads, leading to severe developmental issues, brain damage and sometimes death.

Speaking Thursday, El Salvador's vice minister for public health, Eduardo Espinoza, warned women from the central American country to avoid having babies for the next two years to avoid passing on potential negative effects of the Zika virus.

"We'd like to suggest to all the women of fertile age that they take steps to plan their pregnancies, and avoid getting pregnant between this year and next," he said.



UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

WHO convenes emergency panel over Zika virus

Filed Under: Zika

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

World Health Organization (WHO) Director-General Margaret Chan, MD, MPH, today announced she has convened an emergency committee to discuss the growing Zika virus threat in the Americas that has been strongly associated with microcephaly and other neurologic complications.

Committee to meet Feb 1

Chan's announcement came during her opening statement before a special briefing on the virus before the WHO's executive board, which is meeting in Geneva this week to hammer out the agenda and resolutions for the World Health Assembly in May. Chan said the committee will meet on Feb 1 in Geneva to discuss whether the developments warrant a public health emergency of international concern (PHEIC) declaration under the International Health Regulations.

Besides assessing the need for an emergency declaration, WHO emergency committees also draw attention to emerging global health issues and lay out a set of recommendations to assist member countries.

Juan Manuel Herrera, OAS / Flickr cc

WHO Director-General Margaret Chan.

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

Zika outbreak alters Red Cross blood donor protocol

Filed Under: Zika

Lisa Schnirring | News Editor | CIDRAP News | Feb 03, 2016

The American Red Cross today said it is closely monitoring the spread of Zika virus and as a precaution is implementing a self-deferral policy for blood donors who have traveled to Mexico, the Caribbean, or Central or South America within 28 days of donating.

Jarek Joepera / iStock

In other Zika virus developments, the US Centers for Disease Control and Prevention (CDC) added two more destinations—Jamaica and Tonga—to its Zika-related travel advisory for pregnant women, Brazil's microcephaly totals have increased, and an India company detailed two new vaccine candidates.

Potential impact on blood supply

In its statement today, the American Red Cross also asks those who develop symptoms of Zika virus infection within 14 days of donation to immediately notify the Red Cross so it can quarantine the blood.

The group said it and other blood collection agencies are working with the US Food and Drug Administration (FDA), the CDC, and state health departments to track the virus and update donor eligibility criteria as needed.

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

CDC advises on Zika-related sexual spread, pregnancy care

Filed Under: Guillain-Barre Syndrome; Zika

Lisa Schnirring | News Editor | CIDRAP News | Feb 05, 2016

Just days after Dallas officials announced a sexually transmitted Zika virus case, the Centers for Disease Control and Prevention (CDC) today released interim guidance on preventing such cases and at the same time updated its guidance for health providers caring for pregnant women who may have been exposed.

EmiliaU/ iStock

Both sets of advice focus tightly on the threat to pregnant women and their babies, given the suspected link between Zika virus and microcephaly, which the CDC said is becoming stronger. The CDC published both documents as early reports on its *Morbidity and Mortality Weekly Report (MMWR)* portal.

At a media briefing today, CDC Director Tom Frieden, MD, MPH, said mosquito bites are still the primary way Zika virus transmits, but he also fielded questions about two more routes revealed by Brazilian scientists today: saliva and urine. He said so far the CDC has no data on the virus in saliva and urine, so the risk of transmission through those routes isn't clear.

"We're quite literally discovering more about it each and every day," he said, also acknowledging reports this week of blood-transfusion transmission. "We take all reports seriously, but back to the bottom line: This is a mosquito-borne disease."

University of Minnesota

CIDRAP Center for Infectious Disease Research and Policy

Companies announce new Zika vaccine initiatives

Filed Under: Zika

Jim Wappes | Editorial Director | CIDRAP News | Feb 02, 2016

Two vaccine makers, Sanofi Pasteur and NewLink Genetics, today announced efforts to develop vaccines against Zika virus infection that will springboard off existing technologies.

zilli / iStock

In related news, Honduras yesterday declared a national emergency over an expanding Zika virus infection outbreak, while Thailand confirmed its first locally acquired case.

Building on flavivirus vaccine experience

Sanofi Pasteur, the vaccines division of Sanofi, based in Lyon, France, already has licensed vaccines for dengue, yellow fever, and Japanese encephalitis, which, like Zika virus (ZIKV) infection, are mosquito-borne diseases caused by flaviviruses, the company said in a news release.

Sanofi officials emphasized the company's dengue vaccine, which was approved for use in Mexico and Brazil in December. "Sanofi Pasteur's expertise and established R&D and industrial infrastructure for the newly licensed vaccine for dengue, Dengvaxia, can be rapidly leveraged to help understand the spread of ZIKV and potentially speed identification of a vaccine candidate for further clinical development," the company said in the release.

REUTERS

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

Related: HEALTH

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

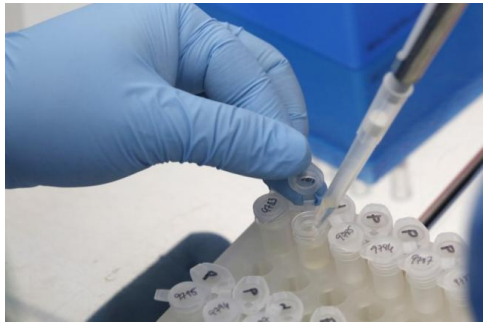
LONDON | BY BEN HIRSCHLER

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.

UNIVERSITY OF MINNESOTA

CIDRAP Center for Infectious Disease Research and Policy

Obama seeks $1.8 billion for Zika response; CDC ups emergency level

Filed Under: Zika

Lisa Schnirring | News Editor | CIDRAP News | Feb 08, 2016

The Obama administration announced today that it will ask Congress for $1.8 billion in emergency funding to help prepare for and respond to the Zika virus threat, as the US Centers for Disease Control and Prevention (CDC) stepped up its emergency response to its highest level.

Greg Knobloch / CDC

In a White House statement today the Obama administration said it has been aggressively working on Zika virus response since late 2015 and that it would make a formal request for the $1.8 billion in emergency funding shortly.

"As spring and summer approach, bringing with them larger and more active mosquito populations, we must be fully prepared to mitigate and quickly address local transmission within the continental U.S., particularly in the Southern United States," the statement said.

Proposed funding breakdown

The largest chunk of the funds—$1.48 billion—would go to the Department of Health and Human Services (HHS), and within it, the CDC. Funding is targeted, for example, to improving mosquito control efforts, improving surveillance, boosting lab capacity and infrastructure, establishing rapid response teams if clusters are detected in the United States, and monitoring for pregnancy and Guillain-Barre syndrome (GBS) risks.

STAT | Reporting from the frontiers of health and medicine

POLITICS

Abortion politics threatens to derail Zika funding in Congress

By SHEILA KAPLAN @bySheilaKaplan

FEBRUARY 10, 2016

WASHINGTON — Two Republican lawmakers leading a congressional hearing on the Zika virus Wednesday said they hope pregnant women who become infected will not have abortions to avoid giving birth to children with a birth defect.

By linking abortion politics to the Zika virus, Representatives Jeff Duncan of South Carolina and Christopher Smith of New Jersey raised a prospect that worries public health advocates: that President Barack Obama's request for $1.8 billion in emergency funds to fight the virus could get derailed by battles over whether the money could be used for abortions.

According to the Centers for Disease Control and Prevention, the mosquito-borne virus is strongly associated with microcephaly, a congenital abnormality in which babies are born with undersized heads, and sometimes, small brains and a range of of health and cognitive difficulties.

Testifying at the hearing, CDC Director Dr. Thomas Frieden said new research has provided more evidence of a link between Zika and microcephaly, but said it is still not definitive. The hearing was held by two subcommittees of the House Foreign Affairs Committee.

CDC Director Dr. Thomas Frieden assured Congress that Obama's Zika budget request doesn't include money for abortions.

The New York Times

AMERICAS

Brazilians Shrug Off Zika Fears to Revel in Carnival Fun

By ANDREW JACOBS FEB. 10, 2016

Performers from a samba school paraded during carnival celebrations in Rio de Janeiro on Tuesday.
Silvia Izquierdo/Associated Press

SALVADOR, Brazil — From a mosquito's point of view, the sweaty, minimally clothed multitudes thronging the streets of this northeastern city on Monday night must have looked especially delectable.

Drunk on beer and preoccupied by the prodigious carnal possibilities, young men and women danced their way along Avenida Oceânica as Brazilian pop icons performing atop giant motorized stages exhorted them to jump, party and celebrate life.

Momentarily distracted from the bacchanal, Mariana Souza, 26, rolled her eyes when asked about Zika, the mosquito-borne virus that is raging across the nation and much of Latin America. "Do I look worried?" Ms. Souza, a shop clerk dressed in short-shorts and a stringy halter top, shouted above the din. "Ask me next week, after Carnival is over."

Despite deepening fear and worry across the Americas since the World Health Organization declared that Zika is a global emergency, millions of Brazilians this week offered a collective shrug and took to the streets to celebrate Carnival. Such dispassion has alarmed public health officials, who are scrambling to curb the outbreak among a population that has long lived with mosquitoes — and which seldom takes precautions to avoid bites, especially those too poor to afford repellent, window screens or air-conditioning.

University of Minnesota

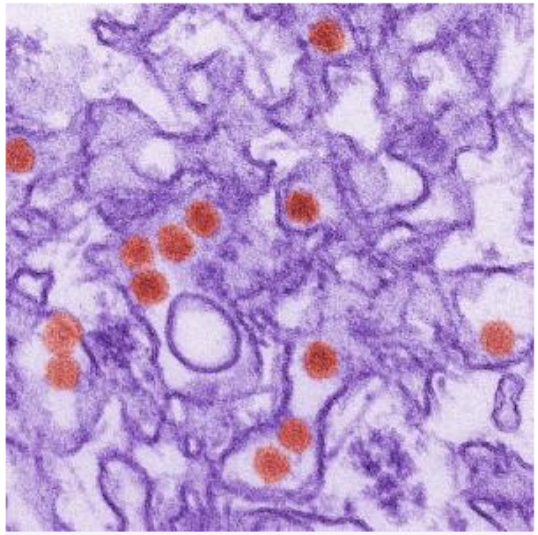
CIDRAP Center for Infectious Disease Research and Policy

WHO: Local Zika cases in 33 nations as GBS numbers climb

Filed Under: Zika

Jim Wappes | Editorial Director | CIDRAP News | Feb 05, 2016

Countries and territories reporting local transmission of Zika virus now number 33, with 6 more showing indication of such transmission and 7 experiencing a parallel rise in cases of microcephaly (small heads in infants) or the neurologic condition called Guillain-Barre syndrome (GBS), the World Health Organization (WHO) said in an update today



CDC

Electron microscope view of Zika virus.

And the European Centre for Disease Prevention and Control (ECDC) published a Zika virus epidemiologic update that noted imported cases to France and New Zealand involving neurologic complications. The public health emergency declared by the WHO on Feb 1 focused on the potential link of microcephaly and GBS to Zika infection.

Further geographic spread likely

The WHO noted that 26 countries in the Americas have reported locally transmitted Zika virus disease, which the Pan American Health Organization has already noted. The WHO also listed local Zika cases in Cape Verde, the Maldives, Fiji, Tonga, Samoa, the Solomon Islands, and Vanuatu.

Zika

Resources

Jump to Selected Reading

Last updated Feb 5, 2016

Latest Cases & General Information

Zika Virus (CDC landing page)
Zika virus (WHO fact sheet, January 2016)
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)
Zika virus threatens U.S. from abroad (*Scientific American*, Jan 26, 2016)
Everything you need to know about Zika virus (STAT News, Jan 14, 2016)
What is the Zika virus? Your questions answered (NBC News, Jan 28, 2106)
Zika virus (Virology Blog, Jan 28, 2016)
What you should know about the birth defect tied to Zika virus (STAT News, Jan 27, 2016)The Zika questions that science needs to answer (STAT News, Feb 2, 2016)
Concern over Zika virus grips the world (*Lancet* special report, Feb 2, 2016)
Microcephaly, spotlighted by Zika virus, has long afflicted and mystified (*New York Times*, Feb 2, 2106)
The past, present, and future of Zika (*The Atlantic*, Feb 3, 2016)
How much harm can the Zika virus really do? (NPR, Feb 2, 2016)
5 questions everyone still has about Zika (NBC News, Feb 3, 2016)
Zika virus's other looming threat (CNN commentary on Guillain-Barre syndrome, Feb 4, 2016)
2016 Zika outbreak timeline map (HealthMap)
Pregnant? The CDC says these are the Zika-affected areas to avoid (STAT map, Feb 2, 2016)
Here are all the known cases of Zika virus in the world (*Popular Science* map)

Zika

RECENT NEWS | RESOURCES & LITERATURE

FEB 10, 2016

WHO addresses Zika fears as more microcephaly findings surface

Lisa Schnirring | News Editor | CIDRAP News | Feb 10, 2016

Also today, two new microcephaly studies documented Zika virus in fetal tissue, strengthening a possible link between the two conditions.

FEB 09, 2016

News Scan for Feb 09, 2016

- Global leishmaniasis burden
- More H5N1 in Nigeria
- Eye problems and Zika-linked microcephaly

FEB 08, 2016

Obama seeks $1.8 billion for Zika response; CDC ups emergency level

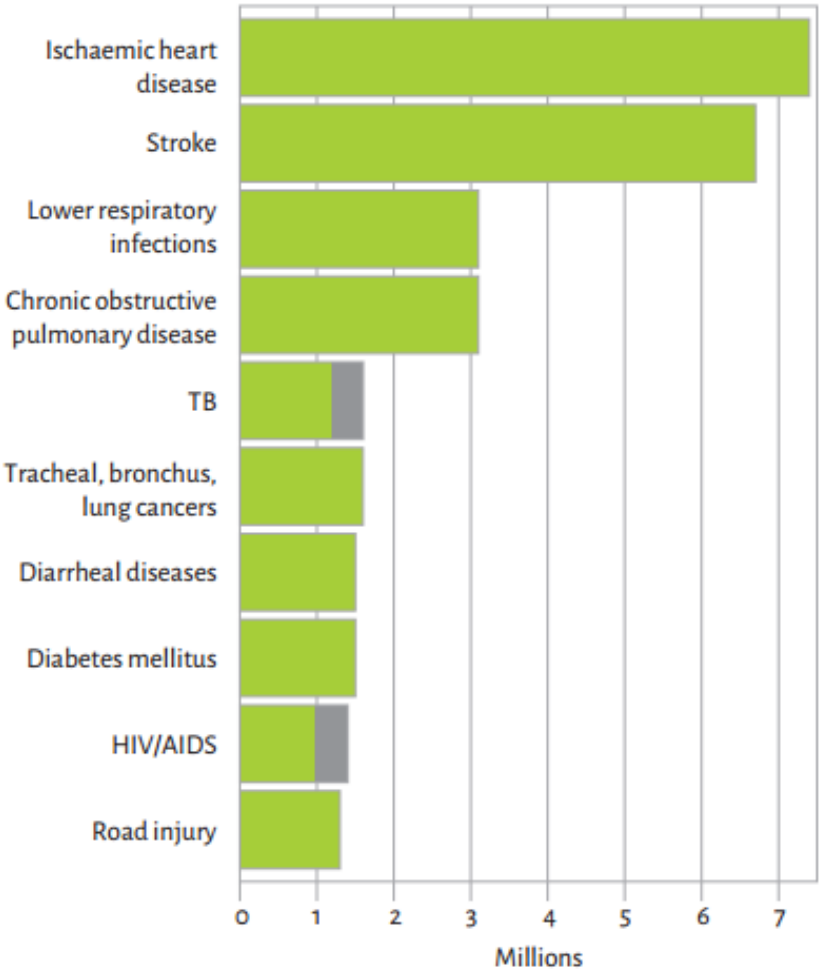
Lisa Schnirring | News Editor | CIDRAP News | Feb 08, 2016

The administration's request covers both domestic and international actions, with CDC's EOC at a level to speed up and coordinate the response.

World Health Organization

FIGURE 2.16a

Top causes of death worldwide in 2012.[a,b] Deaths from TB among HIV-positive people are shown in grey.[c]



The Future of Antibiotics and Resistance

Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D.

In its recent annual report on global risks, the World Economic Forum (WEF) concluded that "arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall."[1]

Traditional practices in infection control, antibiotic stewardship, and new antibiotic development are cornerstones of society's approach to combating resistance and must be continued. But the WEF report underscores the facts that antibiotic resistance and the collapse of the antibiotic research-and-development pipeline continue to worsen despite our ongoing efforts on all these fronts. If we're to develop countermeasures that have lasting effects, new ideas that complement traditional approaches will be needed.

New ideas are often based on the recognition of old truths. Prokaryotes (bacteria) "invented" antibiotics billions of years ago, and resistance is primarily the result of bacterial adaptation to eons of antibiotic exposure. What are the fundamental implications of this reality? First, in addition to antibiotics' curative power, their use naturally selects for preexisting resistant populations of bacteria in nature. Second, it is not just "inappropriate" antibiotic use that selects for resistance. Rather, the speed with which resistance spreads is driven by micro-

Bioterrorism

- Anthrax
- Smallpox
- Plague
- Botulism
- Viral Hemorrhagic Fever
- Tularemia

CIDRAP
Center for Infectious
Disease Research & Policy
University of Minnesota

Infectious Diseases and Public Health Leadership

- Communicable diseases and public health in the 20th century
- The 21st century "New World Order"
- The challenges of infectious diseases in the 21st century
- **The opportunities for success**

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota

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

CIDRAP
Center for Infectious Disease Research & Policy
University of Minnesota