LA PREVENZIONE VACCINALE
UNO STRUMENTO DI SOSTENIBILITÀ

2019 MOTORE SANITÀ
Gestire il Cambiamento

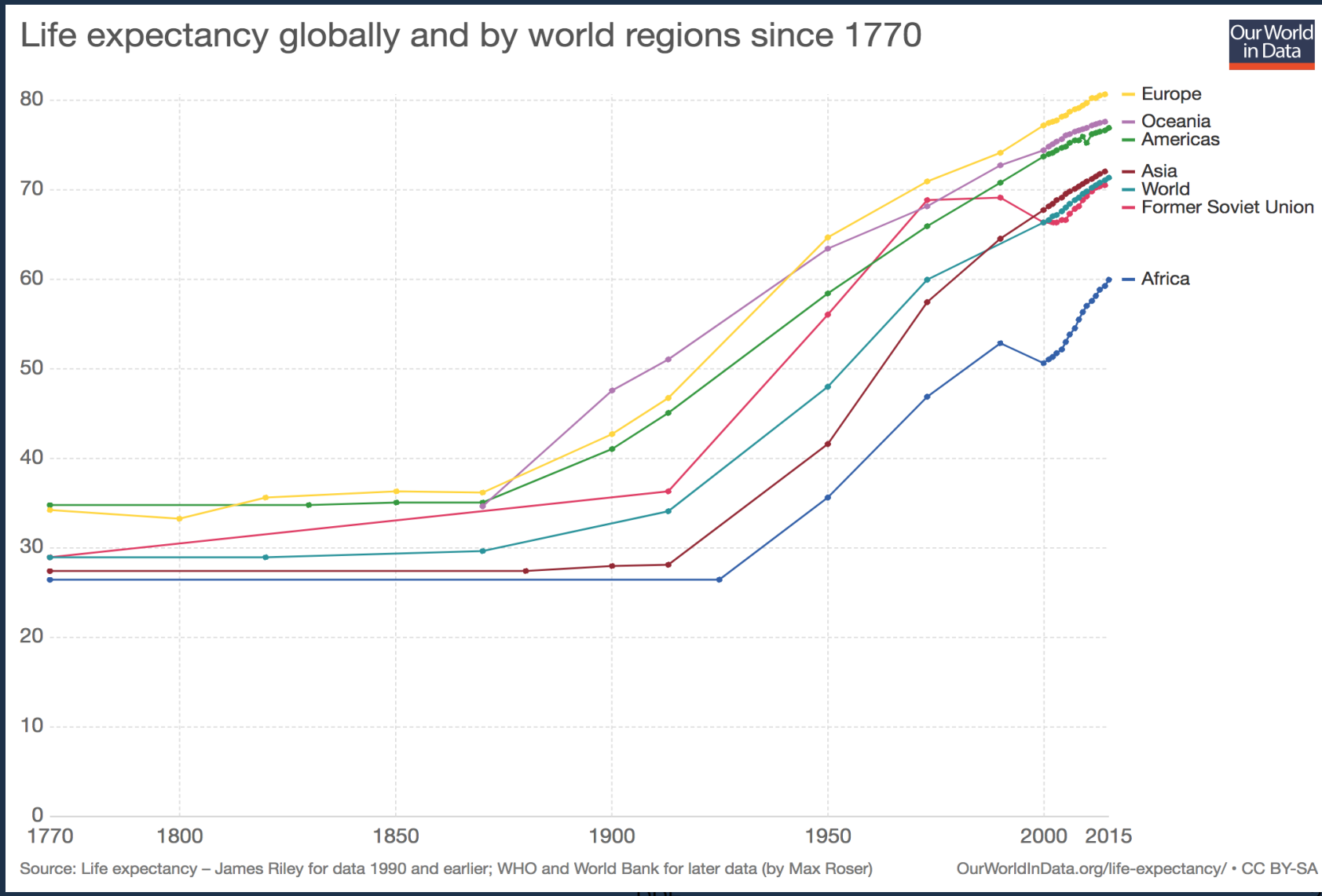
Quando i vaccini non c'erano (o non sono disponibili…..)

Stefano Vella MD

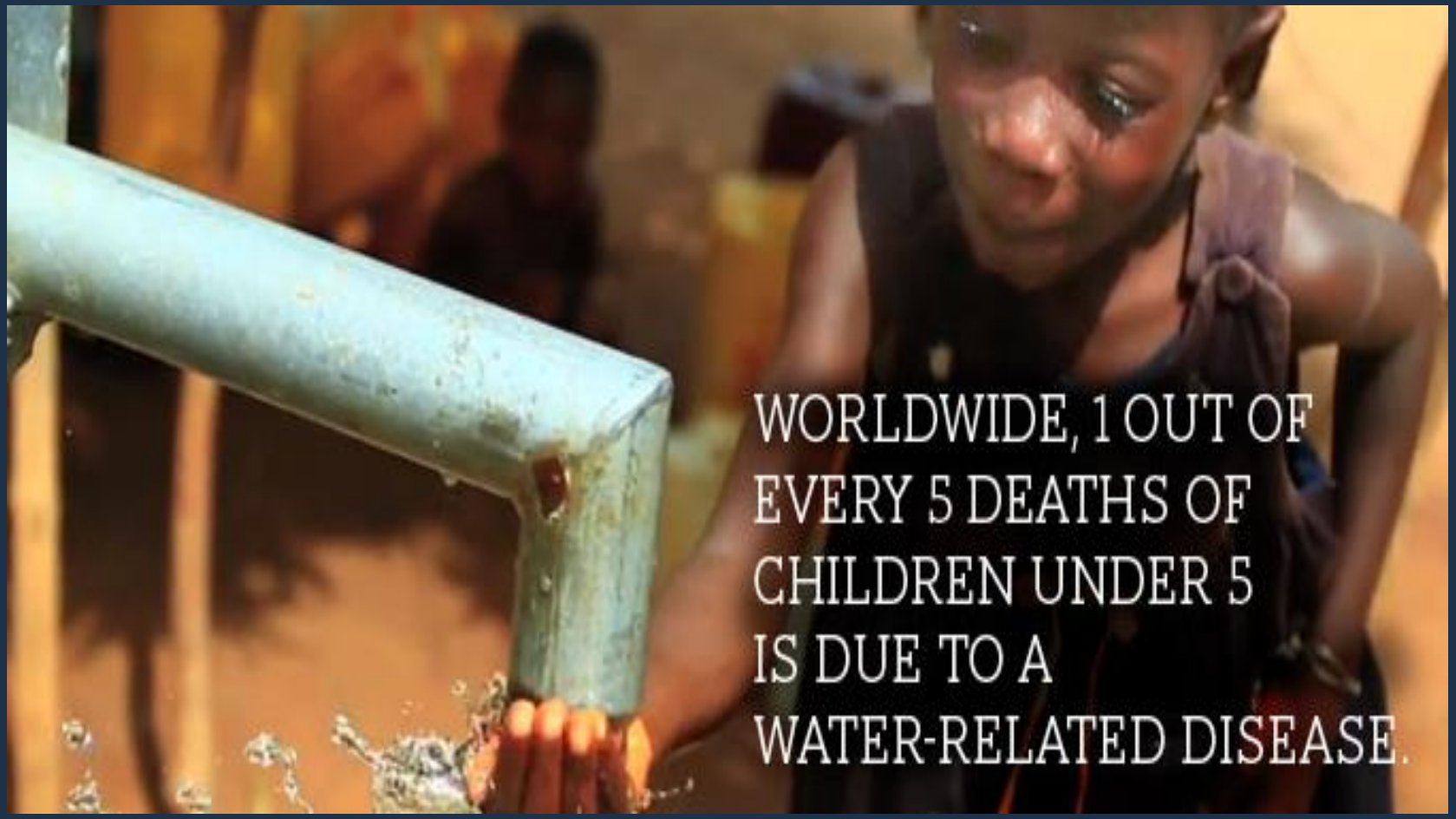
Global Health

Università Cattolica del Sacro Cuore (UCSC) - Roma

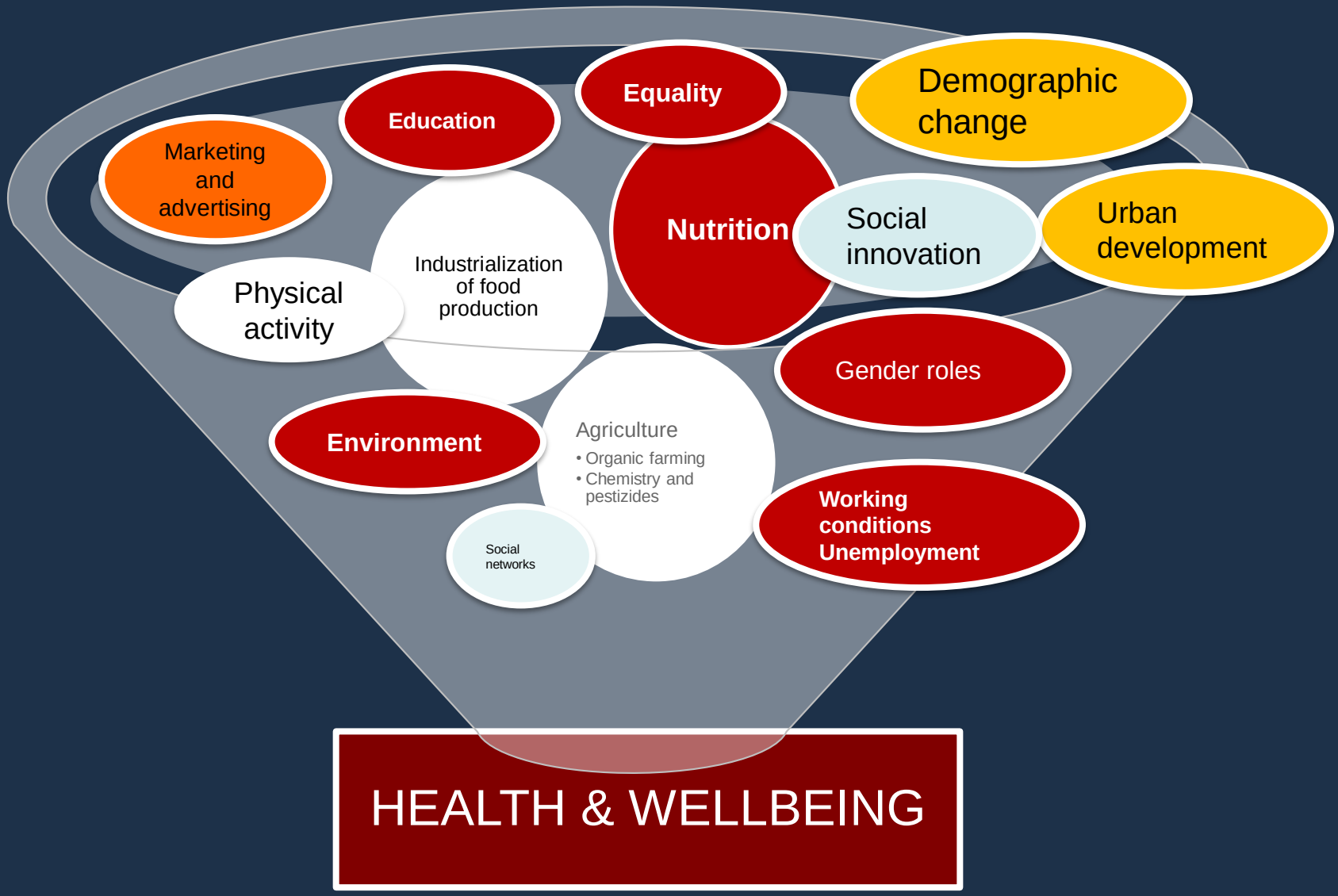
THE RISE OF LIFE EXPECTANCY



THE DRIVERS.....1. CLEAN WATER



THE DRIVERS.....**2. SOCIAL DETERMINANTS**

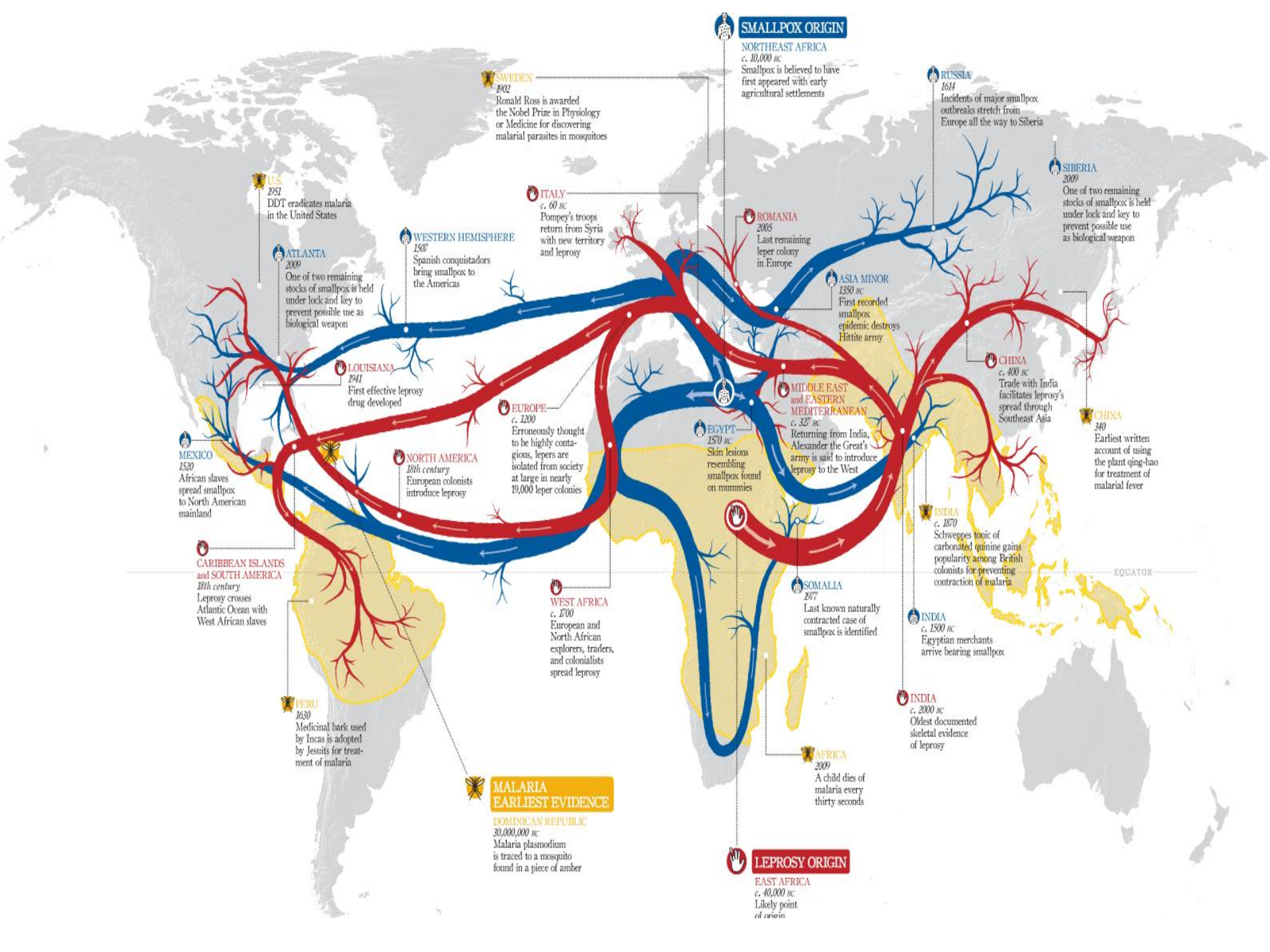


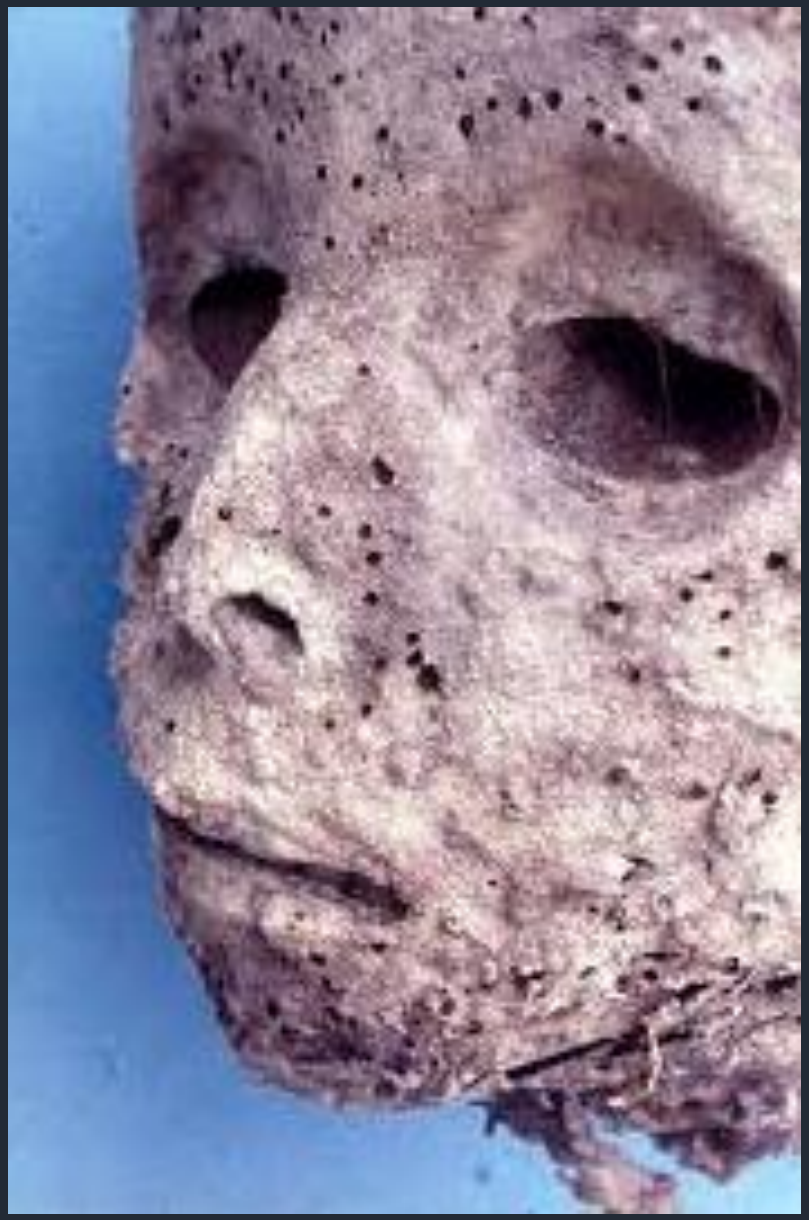
THE DRIVERS.....**3. ADVANCES OF MEDICINE**

1796

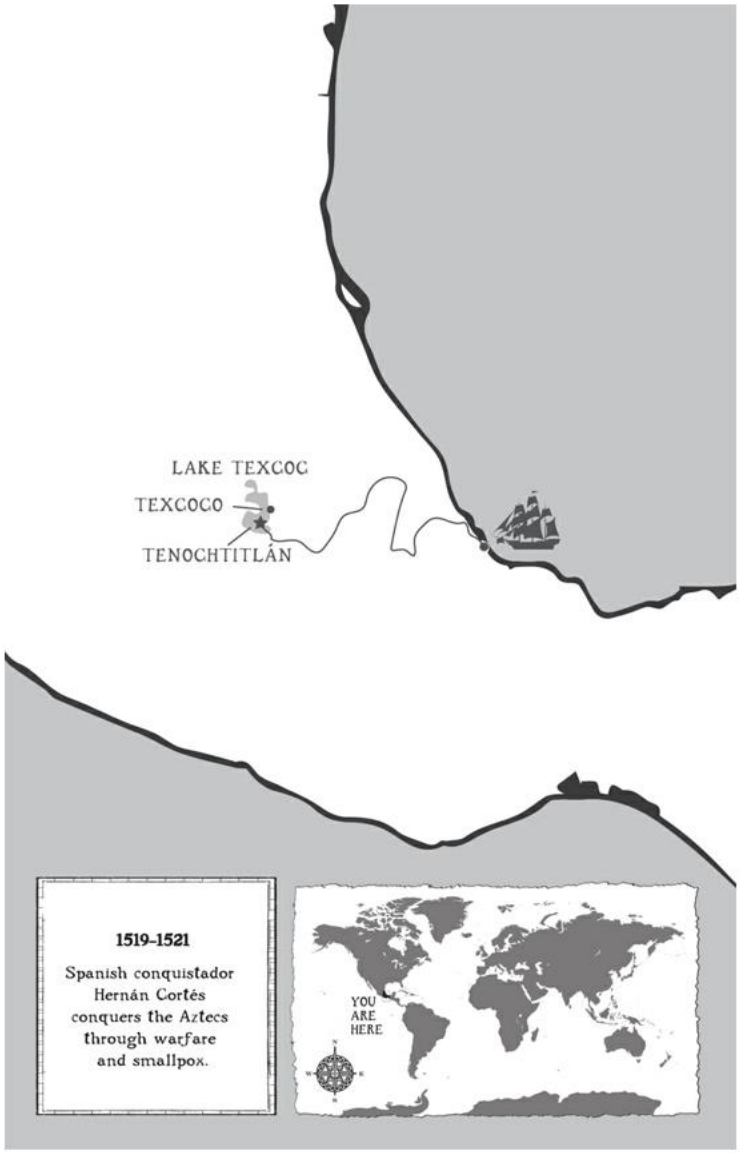
Tre storie

- Vaiolo
- Polio
- Ebola


SMALLPOX ORIGIN
NORTHEAST AFRICA
c. 10,000 BC
Smallpox is believed to have first appeared with early agricultural settlements
SWEDEN
1902
Ronald Ross is awarded the Nobel Prize in Physiology or Medicine for discovering malarial parasites in mosquitoes
RUSSIA
1614
Incidents of major smallpox outbreaks stretch from Europe all the way to Siberia
SIBERIA
2009
One of two remaining stocks of smallpox is held under lock and key to prevent possible use as biological weapon
U.S.
1951
DDT eradicates malaria in the United States
ITALY
c. 60 BC
Pompey's troops return from Syria with new territory and leprosy
ROMANIA
2005
Last remaining leper colony in Europe
WESTERN HEMISPHERE
1507
Spanish conquistadors bring smallpox to the Americas
ATLANTA
2009
One of two remaining stocks of smallpox is held under lock and key to prevent possible use as biological weapon
ASIA MINOR
1350 BC
First recorded smallpox epidemic destroys Hittite army
LOUISIANA
1941
First effective leprosy drug developed
CHINA
c. 400 BC
Trade with India facilitates leprosy's spread through Southeast Asia
EUROPE
c. 1200
Erroneously thought to be highly contagious, lepers are isolated from society at large in nearly 19,000 leper colonies
MIDDLE EAST and EASTERN MEDITERRANEAN
c. 327 BC
Returning from India, Alexander the Great's army is said to introduce leprosy to the West
CHINA
340
Earliest written account of using the plant qing-hao for treatment of malarial fever
EGYPT
1570 BC
Skin lesions resembling smallpox found on mummies
MEXICO
1520
African slaves spread smallpox to North American mainland
NORTH AMERICA
18th century
European colonists introduce leprosy
INDIA
c. 1870
Schweppes tonic of carbonated quinine gains popularity among British colonists for preventing contraction of malaria
EQUATOR
CARIBBEAN ISLANDS and SOUTH AMERICA
18th century
Leprosy crosses Atlantic Ocean with West African slaves
SOMALIA
1977
Last known naturally contracted case of smallpox is identified
WEST AFRICA
c. 1700
European and North African explorers, traders, and colonialists spread leprosy
INDIA
c. 1500 BC
Egyptian merchants arrive bearing smallpox
INDIA
c. 2000 BC
Oldest documented skeletal evidence of leprosy
PERU
1630
Medicinal bark used by Incas is adopted by Jesuits for treatment of malaria
AFRICA
2009
A child dies of malaria every thirty seconds
MALARIA EARLIEST EVIDENCE
DOMINICAN REPUBLIC
30,000,000 BC
Malaria plasmodium is traced to a mosquito found in a piece of amber
LEPROSY ORIGIN
EAST AFRICA
c. 40,000 BC
Likely point of origin



La decimazione del popolo azteco



OUTBREAK

Deadliest Pandemics in History

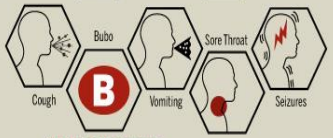
Because a virus doesn't care about state lines or national borders, it can wipe out millions and span multiple continents rapidly. Here is a look at the infectious diseases the world has battled throughout history.

What is a Pandemic?

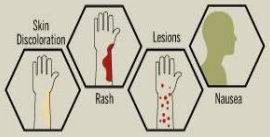
Derived from the Greek word *pandemos* meaning "pertaining to all people," a pandemic is a widespread disease that affects humans over a wide geographic area.

Key:

PANDEMIC YEAR	DEATH TOLL



A bubo is an abnormal swelling of the lymph nodes.



MEASLES
7th Century BC - 1963
200 million

HIV / AIDS
1981 - TODAY
25+ million

PLAGUE of JUSTINIAN
541 - 750
25 million

SMALLPOX
10,000 BC - 1979
300+ million

Bigpox?
In terms of an estimated death toll, smallpox is the deadliest pandemic in history. The highly contagious, rash-inducing infection has killed more than 500 million people. Some believe that 90 percent of the native population of the New World was wiped out by the disease.

SPANISH FLU
1918 - 1919
50-100 million

BLACK DEATH
1340 - 1771
75 million

Ring Around the Rosie, a Pocket Full of Plague
Legend says the Black Death plague inspired the children's rhyme "Ring Around The Rosy," which alluded to the rash-like rings and ashes of the deceased victims.

THIRD PANDEMIC
1855
12 million

TYPHUS
430 BC - TODAY
4 million

CHOLERA
1817 - TODAY
3 million

HONG KONG FLU
1968 - 1969
1 million

Honorable Mentions

Although the following viruses do not have a figure for total amount of lives claimed, they continue to terrorize various areas around the world.

MALARIA 1600 - Today

Common Symptoms

Chills, Headache, Fever, Jaundice, Muscle Pain, Nausea, Vomiting, Seizures

Death Toll

According to the World Health Organization's 2010 "World Malaria Report," an estimated 781,000 people are killed by the virus every year.

TUBERCULOSIS 700 BC - Today

Common Symptoms

Chest Pain, Cough, Fever, Chills, Fatigue

Death Toll

There are almost 2 million tuberculosis-related deaths worldwide every year.

YELLOW FEVER 16th Century - Today

Common Symptoms

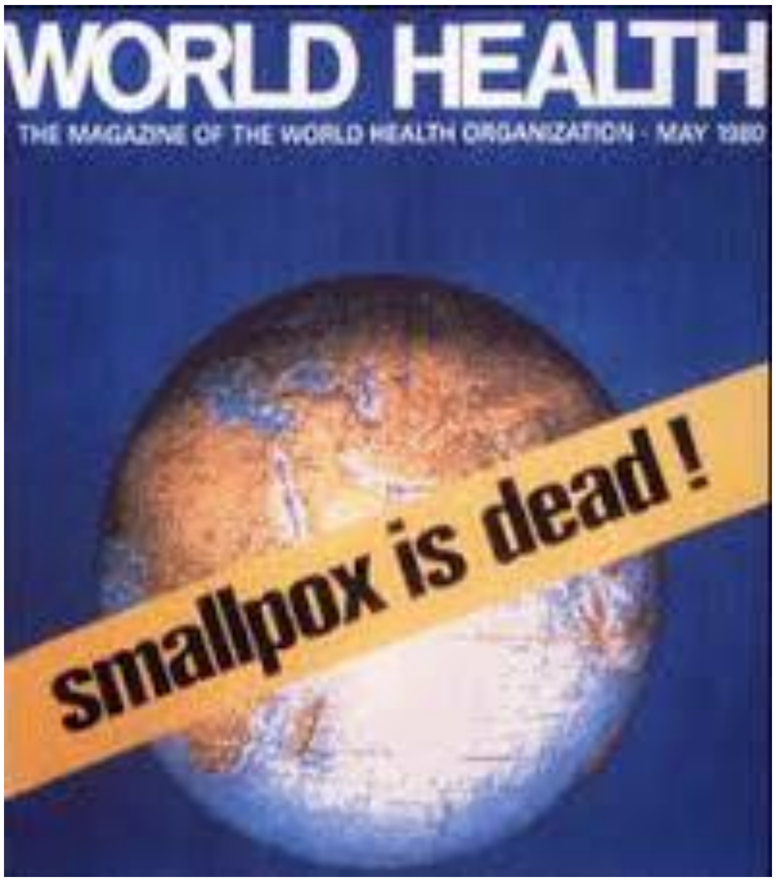
Bleeding, Fever, Nausea, Vomiting, Delirium, Seizures, Jaundice

Death Toll

Worldwide, 30,000 deaths are caused by the infection every year.


1796

Ottobre 1977



نحن أعضاء اللجنة العالمية للإشهاد الرسمى باستئصال
الجدرى نشهد بأنه قد تم إستئصال الجدرى من العالم .

WE, THE MEMBERS OF THE GLOBAL COMMISSION FOR THE CERTIFICATION OF SMALLPOX ERADICATION, CERTIFY THAT SMALLPOX HAS BEEN ERADICATED FROM THE WORLD.

NOUS, MEMBRES DE LA COMMISSION MONDIALE POUR LA CERTIFICATION DE L'ÉRADICATION DE LA VARIOLE, CERTIFIONS QUE L'ÉRADICATION DE LA VARIOLE A ÉTÉ RÉALISÉE DANS LE MONDE ENTIER.

我们，全球扑灭天花证实委员会委员，
证实扑灭天花已经在全世界实现。

МЫ, ЧЛЕНЫ ГЛОБАЛЬНОЙ КОМИССИИ ПО СЕРТИФИКАЦИИ ЛИКВИДАЦИИ ОСПЫ, НАСТОЯЩИМ ПОДТВЕРЖДАЕМ, ЧТО ОСПЫ В МИРЕ БОЛЬШЕ НЕТ.

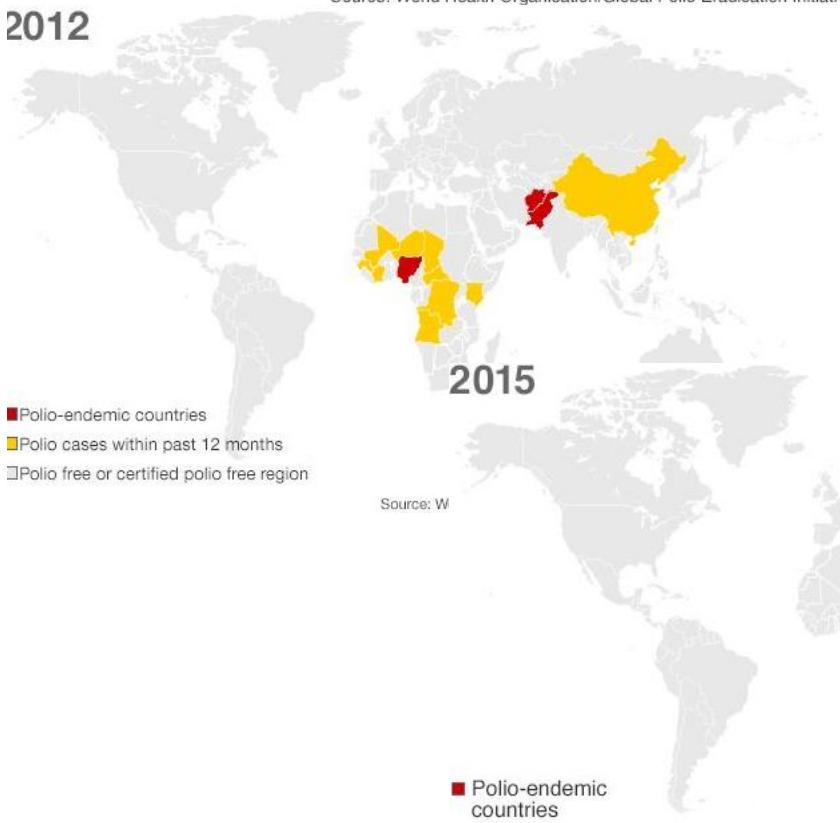
NOSOTROS, MIEMBROS DE LA COMISION MUNDIAL PARA LA CERTIFICACION DE LA ERRADICACION DE LA VIRUELA, CERTIFICAMOS QUE LA VIRUELA HA SIDO ERRADICADA EN TODO EL MUNDO.

Genève, le 9 décembre 1979

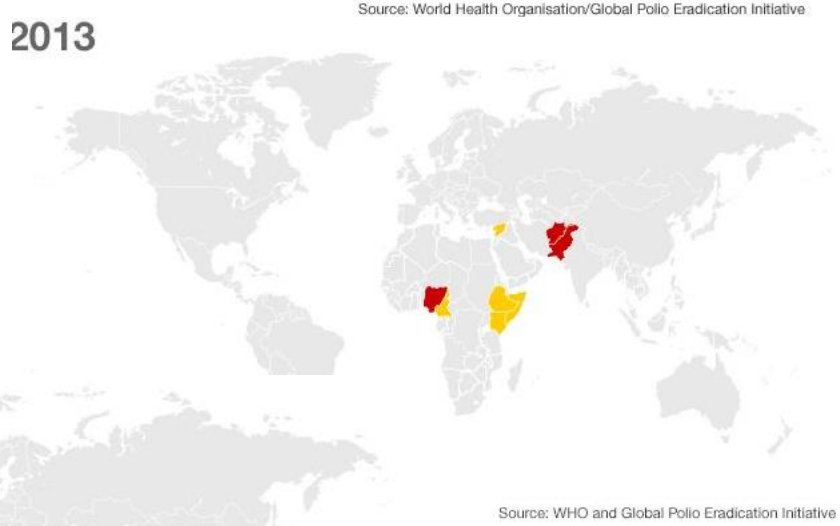
The history of polio

Source: World Health Organisation/Global Polio Eradication Initiative

Source: World Health Organisation/Global Polio Eradication Initiative



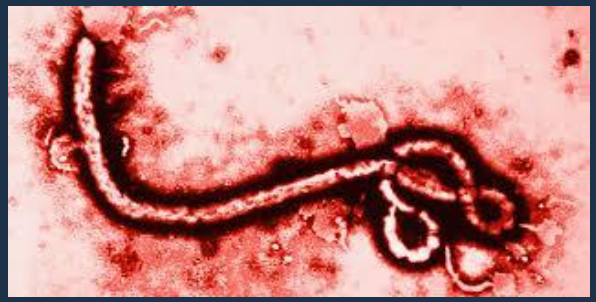
Source: W



Source: WHO and Global Polio Eradication Initiative

Source: World Health Organisation/Global Polio Eradication Initiative

EBOLA



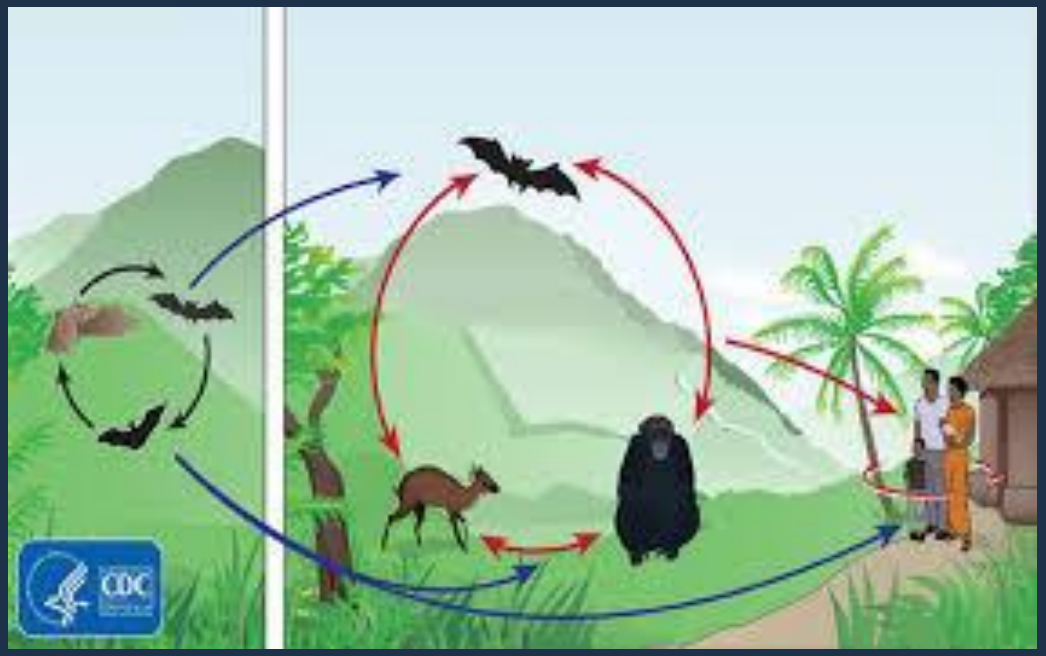


Fig 2 - Map of Ebola virus outbreaks 1976-2014 (Centers for Disease Control and Prevention).

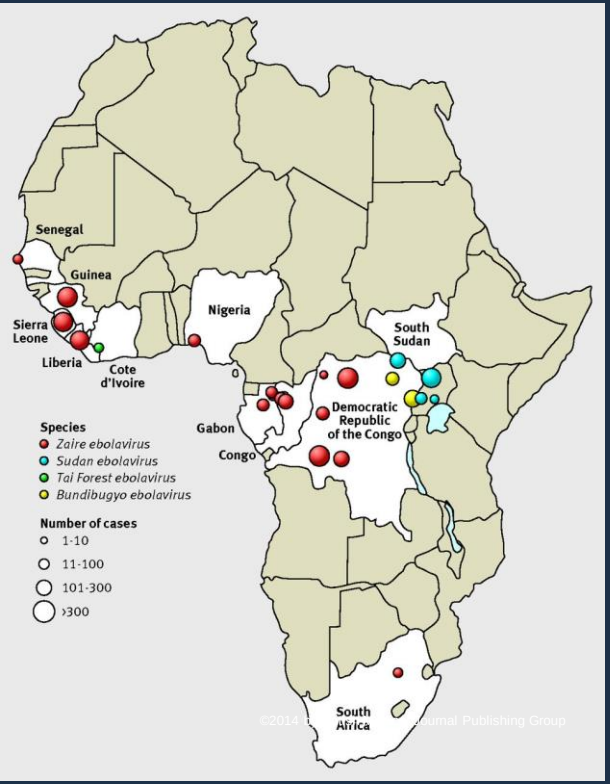


Fig 3 - Healthcare worker in personal protective equipment at an Ebola treatment centre in Sierra Leone, 2014 (with permission from Chris Lane, Public Health England/WHO).

Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéïta, Souleymane Kone, Eewa Kuisma, Myron M Levine, Sema Mandal, Thomas Mauget, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Røttingen*, Marie-Paule Kieny*

Summary

Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, west Africa.

Methods We did an open-label, cluster-randomised ring vaccination trial (Ebola ça Suffit!) in the communities of Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea, and in Tomkolili and Bombali in Sierra Leone. We assessed the efficacy of a single intramuscular dose of rVSV-ZEBOV (2×10^7 plaque-forming units administered in the deltoid muscle) in the prevention of laboratory confirmed Ebola virus disease. After confirmation of a case of Ebola virus disease, we definitively enumerated on a list a ring (cluster) of all their contacts and contacts of contacts including named contacts and contacts of contacts who were absent at the time of the trial team visit. The list was archived, then we randomly assigned clusters (1:1) to either immediate vaccination or delayed vaccination (21 days later) of all eligible individuals (eg, those aged ≥18 years and not pregnant, breastfeeding, or severely ill). An independent statistician generated the assignment sequence using block randomisation with randomly varying blocks, stratified by location (urban *vs* rural) and size of rings (≤20 individuals *vs* >20 individuals). Ebola response teams and laboratory workers were unaware of assignments. After a recommendation by an independent data and safety monitoring board, randomisation was stopped and immediate vaccination was also offered to children aged 6–17 years and all identified rings. The prespecified primary outcome was a laboratory confirmed case of Ebola virus disease with onset 10 days or more from randomisation. The primary analysis compared the incidence of Ebola virus disease in eligible and vaccinated individuals assigned to immediate vaccination versus eligible contacts and contacts of contacts assigned to delayed vaccination. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Findings In the randomised part of the trial we identified 4539 contacts and contacts of contacts in 51 clusters randomly assigned to immediate vaccination (of whom 3232 were eligible, 2151 consented, and 2119 were immediately vaccinated) and 4557 contacts and contacts of contacts in 47 clusters randomly assigned to delayed vaccination (of whom 3096 were eligible, 2539 consented, and 2041 were vaccinated 21 days after randomisation). No cases of Ebola virus disease occurred 10 days or more after randomisation among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters. Vaccine efficacy was 100% (95% CI 68·9–100·0, p=0·0045), and the calculated intraclass correlation coefficient was 0·035. Additionally, we defined 19 non-randomised clusters in which we enumerated 2745 contacts and contacts of contacts, 2006 of whom were eligible and 1677 were immediately vaccinated, including 194 children. The evidence from all 117 clusters showed that no cases of Ebola virus disease occurred 10 days or more after randomisation among all immediately vaccinated contacts and contacts of contacts versus 23 cases (11 clusters affected) among all eligible contacts and contacts of contacts in delayed plus all eligible contacts and contacts of contacts never vaccinated in immediate clusters. The estimated vaccine efficacy here was 100% (95% CI 79·3–100·0, p=0·0033). 52% of contacts and contacts of contacts assigned to immediate vaccination and in non-randomised clusters received the vaccine immediately; vaccination protected both vaccinated and unvaccinated people in those clusters. 5837 individuals in total received the vaccine (5643 adults and 194 children), and all vaccinees were followed up for 84 days. 3149 (53·9%) of 5837 individuals reported at least one adverse event in the 14 days after vaccination; these were typically mild (87·5% of all 7211 adverse events). Headache (1832 [25·4%]), fatigue (1361 [18·9%]), and muscle pain (942 [13·1%]) were the most commonly reported adverse events in this period across all age groups. 80 serious adverse events were identified, of which two were judged to be

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See Comment page 479

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In Congo outbreak, Ebola vaccine faces reality tests

Friday, May 18, 2018 6:16 a.m. EDT

FILE PHOTO: Congolese Health Ministry officials carry the first batch of experimental Ebola vaccines in Kinshasa, Democratic Republic of Con

By Kate Kelland

LONDON (Reuters) - An experimental Ebola vaccine to be deployed in an outbreak in Democratic Republic of Congo has conquered some major scientific hurdles in giving high protection, but it now faces extreme real-world tests including heat, humidity, language barriers and lack of roads.

Because it is not yet licensed, the Merck & Co vaccine has been offered to Congo under a "compassionate use" protocol agreed by national and international health and ethics authorities.

This means fully informed, signed consent is needed from every person who wants the shot. And in the current Ebola outbreak, that makes logistical, cultural and language barriers the ultimate challenges, global health specialists say.

The hurdles illustrate how hard it can be to move from laboratory to real life, especially in remote communities with no functioning health systems. The Congo outbreak is a chance to reality-test a vaccine against a disease epidemic that can't be replicated in controlled environments.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

First vaccine to protect against Ebola

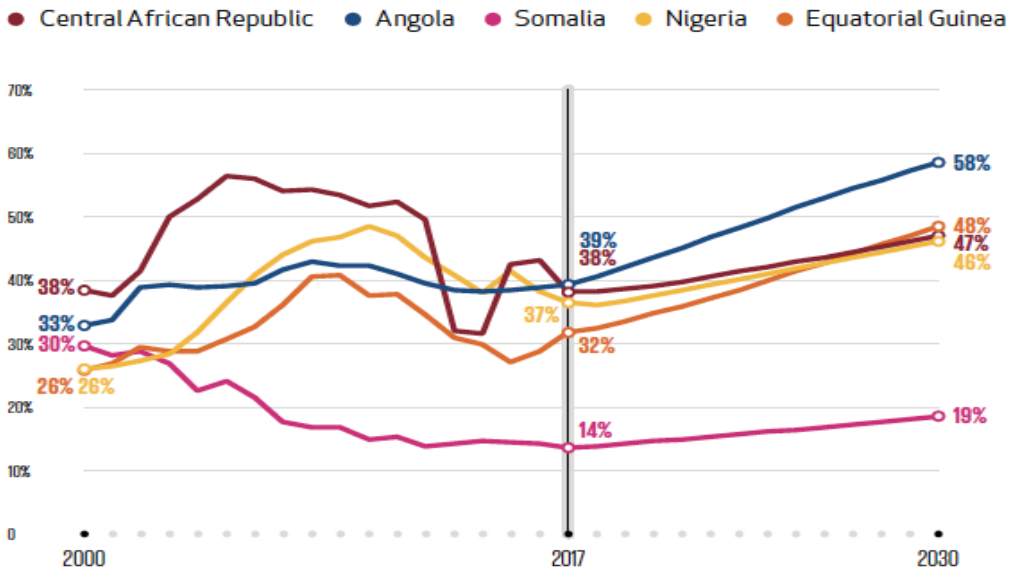
Press release 18/10/2019

EMA's human medicines committee (CHMP) has recommended granting a conditional marketing authorisation in the European Union for Ervebo (rVSVΔG-ZEBOV-GP), the first vaccine for active immunisation of individuals aged 18 years and older at risk of infection with the Ebola virus.

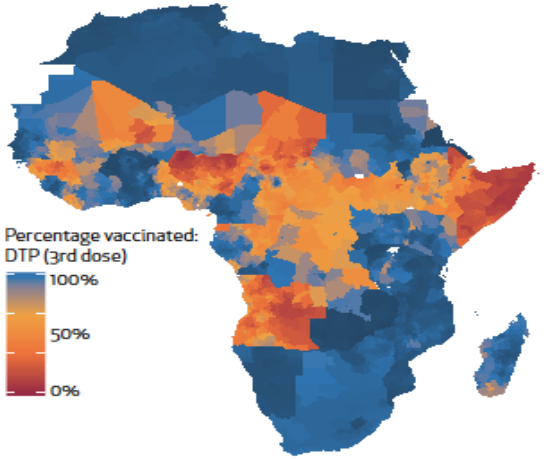
"This is an important step towards relieving the burden of this deadly disease," said Guido Rasi, EMA's Executive Director. "The CHMP's recommendation is the result of many years of collaborative global efforts to find and develop new medicines and vaccines against Ebola. Public health authorities in countries affected by Ebola need safe and efficacious medicines to be able to respond effectively to outbreaks and save lives."

I vaccini
non accessibili

NATIONAL DTP3 COVERAGE



SUB-NATIONAL DTP3 COVERAGE 2016



60 percent through 2030. Dramatic improvements are needed to increase coverage and avoid leaving children behind in these settings.

The heatmap shows that even within countries that may be doing well, certain areas can be neglected. More than half of children haven't received the necessary three doses of DTP in 26 percent of districts in sub-Saharan Africa.

The priority now is replicating successful strategies in the most challenging places so that all people everywhere receive lifesaving vaccines.

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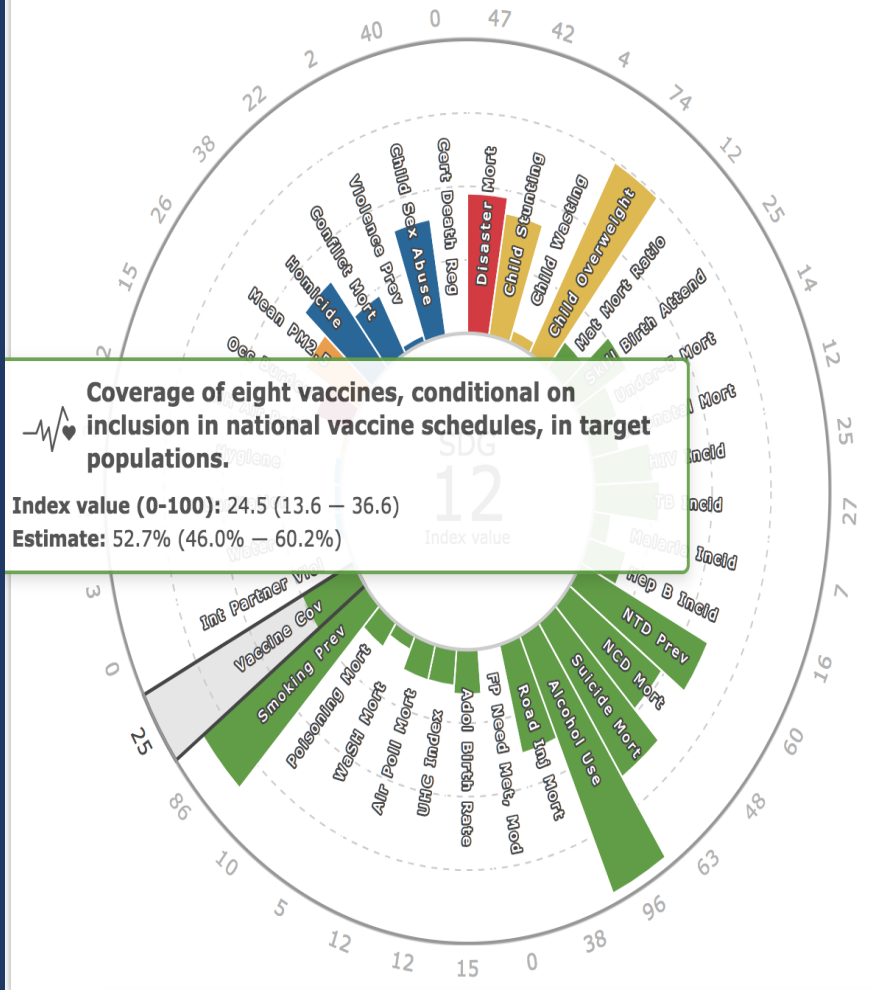
Health-related SDGs | Viz Hub

Visualizations ▾ | Help ▾ | Share | Download

View: Country | Map | Scatter | Line — Health-related index: SDG | MDG | Non-MDG — Uncertainty: Off — Lock scale: Off

Location: South Sudan — Indicator: 3.b.1: Coverage of eight vaccines in target po... — Year: 2016 — Labels: On

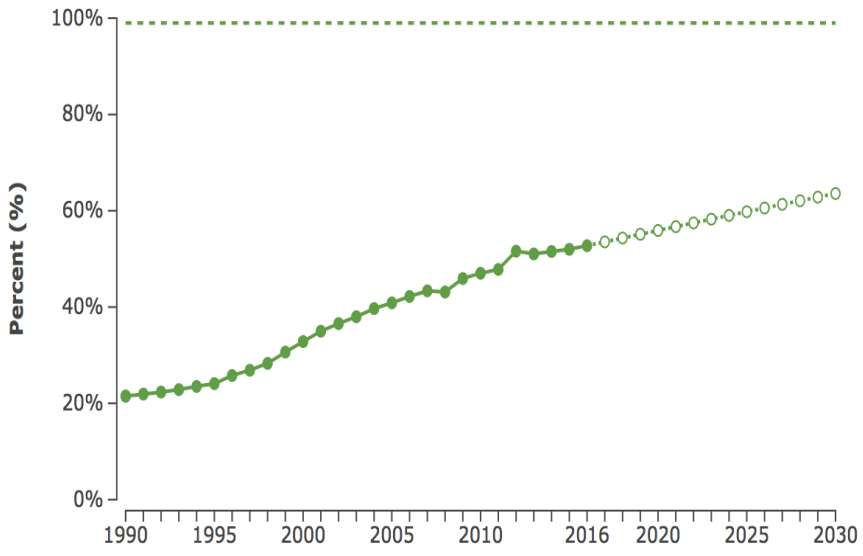
South Sudan, 2016



Coverage of eight vaccines, conditional on inclusion in national vaccine schedules, in target populations.

Index value (0-100): 24.5 (13.6 — 36.6)
Estimate: 52.7% (46.0% — 60.2%)

Coverage of eight vaccines in target populations, South Sudan



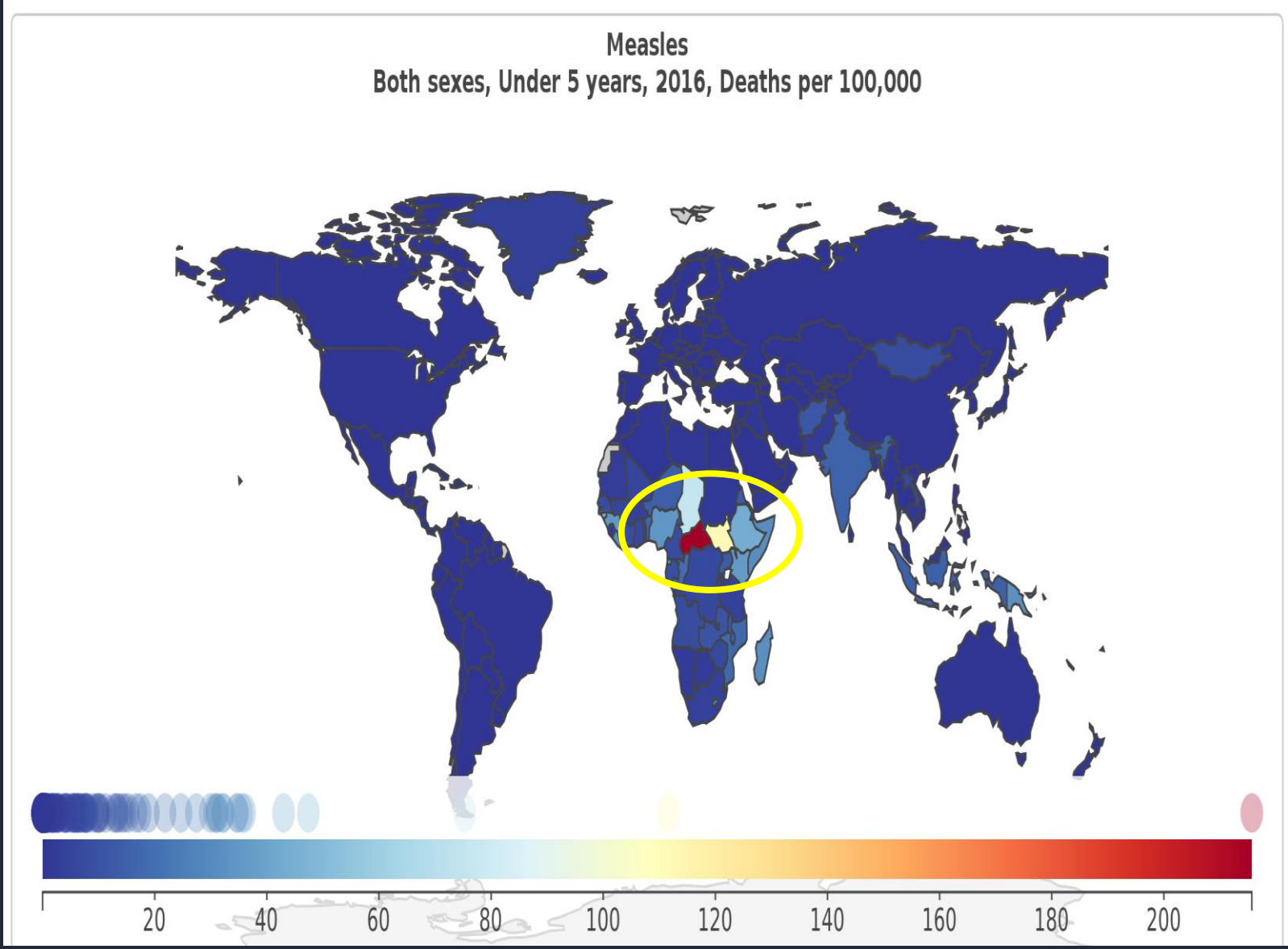
Indicator 3.b.1: Coverage of eight vaccines, conditional on inclusion in national vaccine schedules, in target populations.

Target 3.b: Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, and, in particular, provide access to medicines for all.

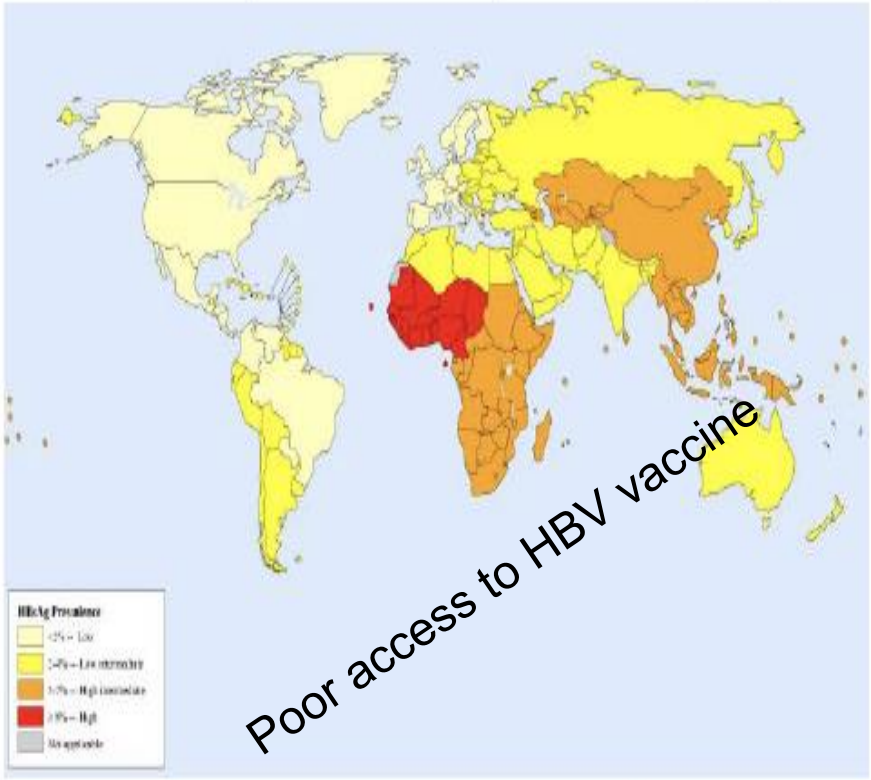
Goal 3: Ensure healthy lives and promote well-being for all at all ages.

Measles immunization coverage
(% of children ages 12-23 months) (2016)

Measles mortality

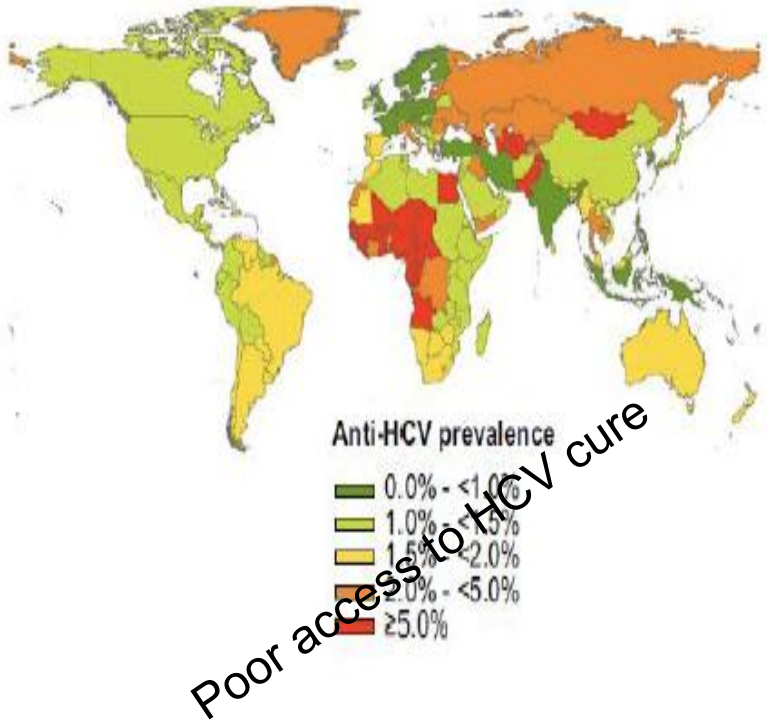


Prevalence of hepatitis B infection, adults 19-89 years, 2005



Ott, J. J., G. A. Stevens, J. Groeger, and S. T. Wiersma. "Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity." *Vaccine* 30, no. 12 (2012): 2212-2219.

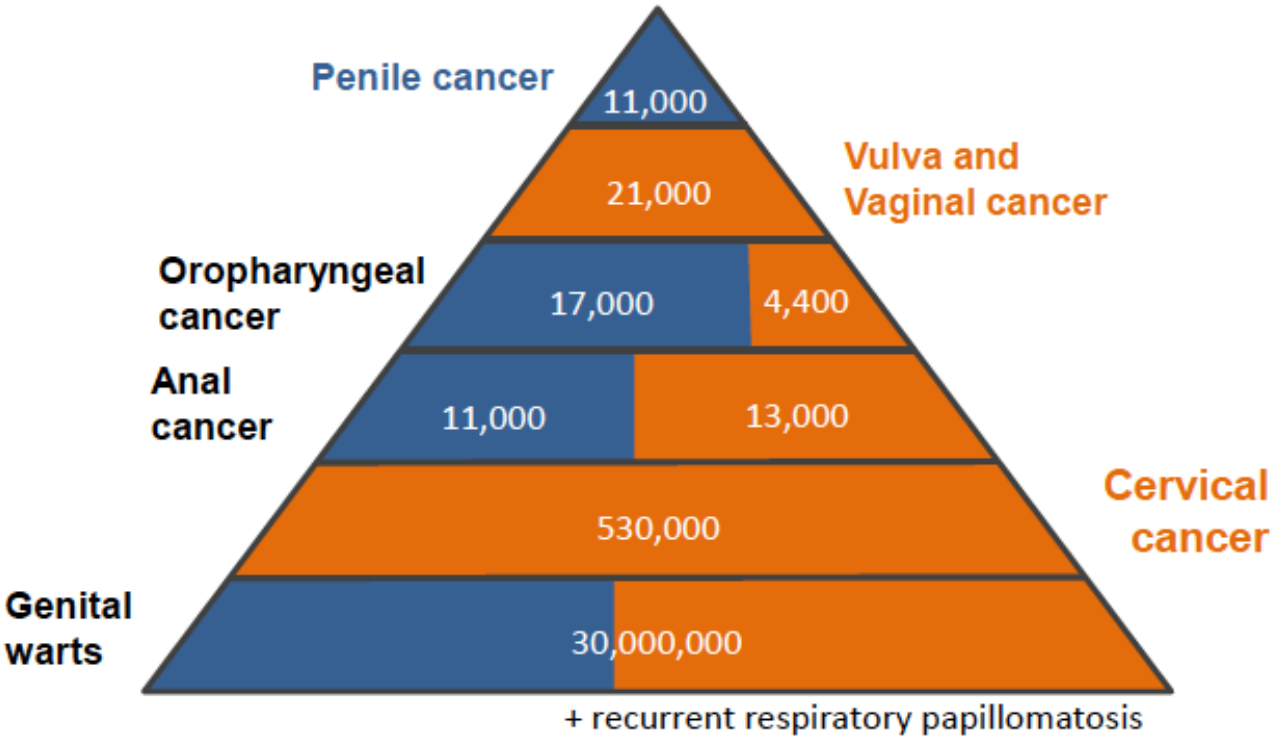
Prevalence of anti-hepatitis C virus

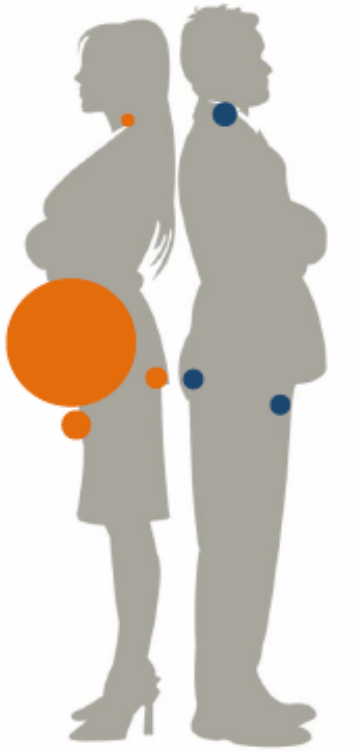


Gower, E., Estes, C., Blach, S., Razavi-Shearer, K., & Razavi, H. (2014). Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of hepatology, 61(1), S45-S57.

2008 Global HPV-related burden:

607,000 annual cancer cases





*Circles proportional to annual burden

International Agency for Research on Cancer

World Health Organization

De Martel et al. 2012 Lancet Oncol (cancers) and Dillner et al. 2010 BMJ (genital warts)

I vaccini
che mancano

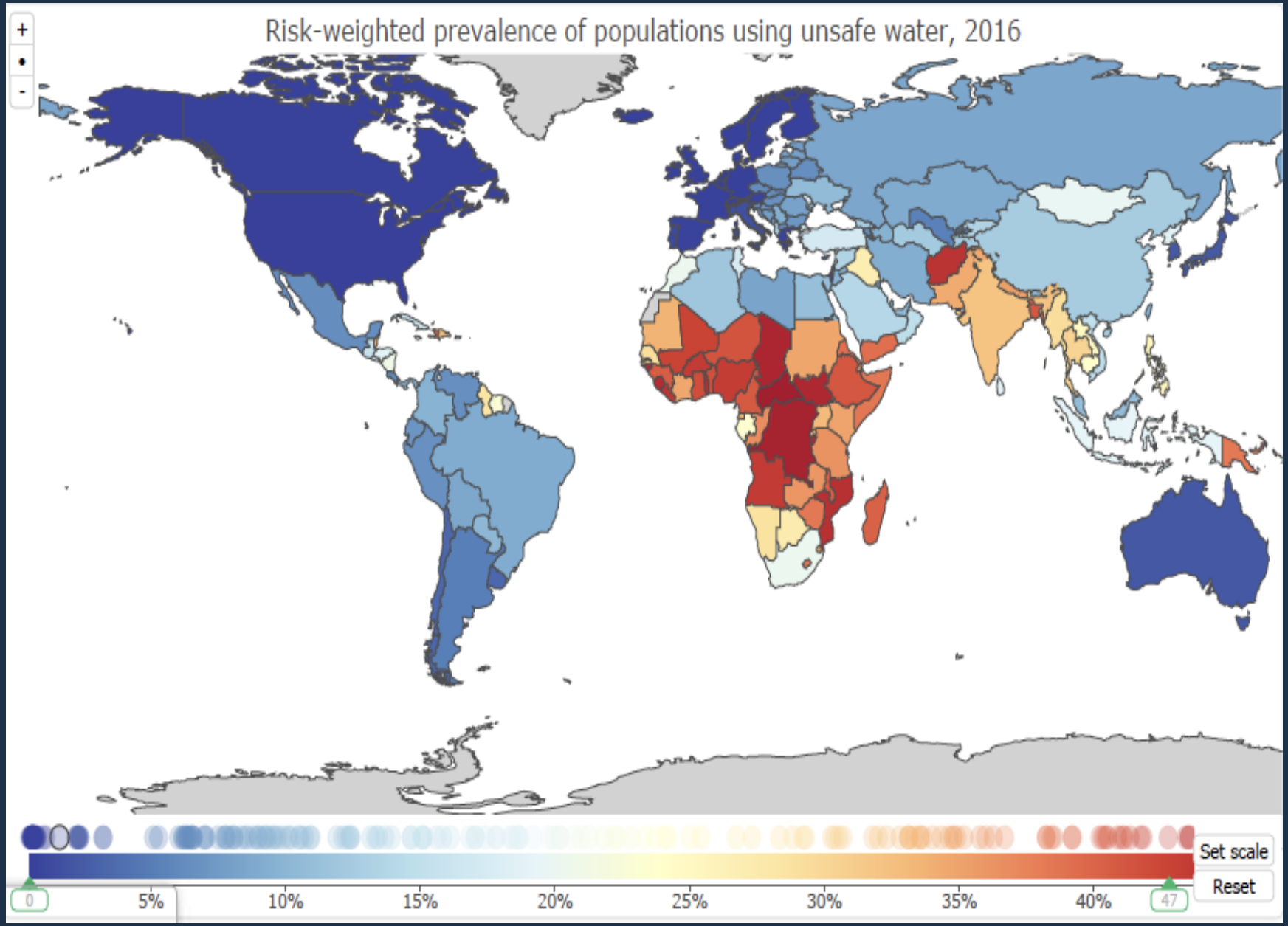

Risk-weighted prevalence of populations using unsafe water, 2016
+
•
-
0
5%
10%
15%
20%
25%
30%
35%
40%
47
Set scale
Reset

Fig. 3.4
Countries reporting cholera deaths and imported cases, 2016

Efficacy of a single-dose regimen of inactivated whole-cell oral cholera vaccine: results from 2 years of follow-up of a randomised trial

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See Comment page 591

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Summary

Background A single-dose regimen of inactivated whole-cell oral cholera vaccine (OCV) is attractive because it reduces logistical challenges for vaccination and could enable more people to be vaccinated. Previously, we reported the efficacy of a single dose of an OCV vaccine during the 6 months following dosing. Herein, we report the results of 2 years of follow-up.

Methods In this placebo-controlled, double-blind trial done in Dhaka, Bangladesh, individuals aged 1 year or older with no history of receipt of OCV were randomly assigned to receive a single dose of inactivated OCV or oral placebo. The primary endpoint was a confirmed episode of non-bloody diarrhoea for which the onset was at least 7 days after dosing and a faecal culture was positive for *Vibrio cholerae* O1 or O139. Passive surveillance for diarrhoea was done in 13 hospitals or major clinics located in or near the study area for 2 years after the last administered dose. We assessed the protective efficacy of the OCV against culture-confirmed cholera occurring 7–730 days after dosing with both crude and multivariable per-protocol analyses. This trial is registered at ClinicalTrials.gov, number NCT02027207.

Findings Between Jan 10, 2014, and Feb 4, 2014, 205 513 people were randomly assigned to receive either vaccine or placebo, of whom 204 700 (102 552 vaccine recipients and 102 148 placebo recipients) were included in the per-protocol analysis. 287 first episodes of cholera (109 among vaccine recipients and 178 among placebo recipients) were detected during the 2-year follow-up; 138 of these episodes (46 in vaccine recipients and 92 in placebo recipients) were associated with severe dehydration. The overall incidence rates of initial cholera episodes were 0·22 (95% CI 0·18 to 0·27) per 100 000 person-days in vaccine recipients versus 0·36 (0·31 to 0·42) per 100 000 person-days in placebo recipients (adjusted protective efficacy 39%, 95% CI 23 to 52). The overall incidence of severe cholera was 0·09 (0·07 to 0·12) per 100 000 person-days versus 0·19 (0·15 to 0·23; adjusted protective efficacy 50%, 29 to 65). Vaccine protective efficacy was 52% (8 to 75) against all cholera episodes and 71% (27 to 88) against severe cholera episodes in participants aged 5 years to younger than 15 years. For participants aged 15 years or older, vaccine protective efficacy was 59% (42 to 71) against all cholera episodes and 59% (35 to 74) against severe cholera. The protection in the older age groups was sustained throughout the 2-year follow-up. In participants younger than 5 years, the vaccine did not show protection against either all cholera episodes (protective efficacy −13%, −68 to 25) or severe cholera episodes (−44%, −220 to 35).

Interpretation A single dose of the inactivated whole-cell OCV offered protection to older children and adults that was sustained for at least 2 years. The absence of protection of young children might reflect a lesser degree of pre-existing natural immunity in this age group.

Funding Bill & Melinda Gates Foundation to the International Vaccine Institute.

Introduction

Despite progress in understanding of the epidemiology, pathogenesis, and treatment of cholera, and in providing access to clean water and adequate sanitation, *Vibrio cholerae* O1 continues to cause large outbreaks and remains endemic in many parts of the world, especially in the least privileged populations.[1–3] A major advance to address this persisting problem was the development and creation of a global stockpile of inexpensive, safe, and effective inactivated whole-cell oral cholera vaccines (OCVs). These OCVs are given as a two-dose regimen and confer protection against cholera for at least 5 years after dosing.[4] To date, two such vaccines, identical in composition but produced under different trade names (Shanchol by Shantha Biotechnics, Hyderabad, India, and Euvichol by Eubiologics, Seoul, South Korea) have been used in the stockpile. They have been deployed to control cholera in humanitarian crises, outbreaks, and

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Use of Vibrio cholerae vaccine in an outbreak in Guinea.

Luquero FJ[1], Grout L, Ciglenecki I, Sakoba K, Traore B, Heile M, Diallo AA, Itama C, Page AL, Quilici ML, Mengel MA, Eiros JM, Serafini M, Legros D, Grais RF.

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Abstract

BACKGROUND: The use of vaccines to prevent and control cholera is currently under debate. Shanchol is one of the two oral cholera vaccines prequalified by the World Health Organization; however, its effectiveness under field conditions and the protection it confers in the first months after administration remain unknown. The main objective of this study was to estimate the short-term effectiveness of two doses of Shanchol used as a part of the integrated response to a cholera outbreak in Africa.

METHODS: We conducted a matched case-control study in Guinea between May 20 and October 19, 2012. Suspected cholera cases were confirmed by means of a rapid test, and controls were selected among neighbors of the same age and sex as the case patients. The odds of vaccination were compared between case patients and controls in bivariate and adjusted conditional logistic-regression models. Vaccine effectiveness was calculated as (1-odds ratio)×100.

RESULTS: Between June 8 and October 19, 2012, we enrolled 40 case patients and 160 controls in the study for the primary analysis. After adjustment for potentially confounding variables, vaccination with two complete doses was associated with significant protection against cholera (effectiveness, 86.6%; 95% confidence interval, 56.7 to 95.8; P=0.001).

CONCLUSIONS: In this study, Shanchol was effective when used in response to a cholera outbreak in Guinea. This study provides evidence supporting the addition of vaccination as part of the response to an outbreak. It also supports the ongoing efforts to establish a cholera vaccine

Lessons learnt from 12 oral cholera vaccine campaigns in resource-poor settings

Amber Hsiao,[a] Sachin N Desai,[a] Vittal Mogasale,[b] Jean-Louis Excler[c] & Laura Digilio[a]

Abstract Improving water and sanitation is the preferred choice for cholera control in the long-term. Nevertheless, vaccination is an available tool that has been shown to be a cost-effective option for cholera prevention in endemic countries or during outbreaks. In 2011 the first low-cost oral cholera vaccine for international use was given prequalification by the World Health Organization (WHO). To increase and prioritize use of the vaccine, WHO created a global stockpile in 2013 from which countries may request oral cholera vaccine for reactive campaigns. WHO has issued specific guidelines for applying for the vaccine, which was previously in short supply (despite prequalification for a second oral vaccine in 2015). The addition of a third WHO-prequalified oral cholera vaccine in 2016 is expected to increase the global stockpile considerably and alleviate supply issues. However, prioritization and best use of the vaccine (e.g. how, when and where to use) will remain challenges. We describe 12 past oral cholera vaccine campaigns, conducted in settings with varying burdens of cholera. These case studies illustrate three key challenges faced in the use of the oral cholera vaccines: regulatory hurdles, cold chain logistics and vaccine coverage and uptake. To pave the way for the introduction of current and future oral cholera vaccines, we discuss operational challenges and make recommendations for future research with respect to each of these challenges.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

The World Health Organization (WHO) estimates that there are 1.3 to 4.0 million cholera cases annually and that 21 000 to 143 000 of them result in death.[1] Additionally, in cholera-endemic countries, 1.3 billion people are at risk of cholera.[2] The high morbidity and consequent mortality caused by cholera is attributable to several factors, including lack of access to safe drinking water, poor sanitation and poor hygiene practices (WASH).[3] Recent estimates suggest that cholera is endemic in 69 countries, with sub-Saharan Africa accounting for the majority of cases between 2008 and 2012 (7.0 of 11.6 million; 60%), followed by South East Asia (3.4 of 11.6 million; 29%).[2]

Improving water and sanitation is the preferred choice for cholera control in the long-term. Although progress has been made towards providing universal access to piped water and water treatment,[4] 663 million people worldwide still do not use improved drinking water sources that can reduce the spread of contaminants such as fecal matter.[4] Sanitation is likewise lacking for 2.4 billion people, 950 million of whom still practise open defecation.[5]

Vaccination has been shown to be a cost–effective, more immediate option for cholera control and prevention.[6–8] Two oral cholera vaccines have been available for years, but have not been widely used due to either cost or licensing restrictions. With the availability of lower-cost options, cholera vaccine is increasingly being considered for use in endemic countries or during outbreaks. Table 1 provides an overview of oral cholera vaccines that are currently, or soon to be, available on the market. Current vaccines are two-dose inactivated vaccines. Several live oral cholera vaccines, including a single-dose vaccine that was recently approved by the United States Food and Drug Administration,[9] are currently under consideration for future vaccination policy. A single-dose regimen would have great potential for use in emergency or epidemic situations.

In 2011 the first low-cost oral cholera vaccine obtained prequalification by WHO for international use.[10] Prequalification certifies the acceptability of a vaccine for purchase by the United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies; the main vaccine procurers for low-income countries.[11] In 2013, Gavi, the Vaccine Alliance approved financing of a stockpile of an oral cholera vaccine for use in endemic and epidemic settings. Although the financing (115 million United States dollars) could support a stockpile of 20 million doses over the following 5 years, full capacity could not be achieved due to a short supply of vaccine. Thus, vaccine deployment was low, despite demand for the vaccine.[12] To help overcome anticipated supply constraints, the International Vaccine Institute facilitated the transfer of the vaccine technology to a second manufacturer, which led to WHO prequalification of a second affordable oral cholera vaccine for global use in December 2015 (Table 1). This has already begun contributing to the global stockpile of oral cholera vaccines[12] and is projected to increase the supply significantly in 2017.[13] The same manufacturing technology for the vaccine was transferred to a third manufacturer, who is expected to begin production of the first-ever oral cholera vaccine registered and licensed for use in Bangladesh – one of the countries most affected by cholera – in the near future.[14,15]

As demonstrated by the creation of the stockpile, global interest in cholera control has increased,[16] which should help pave the way to global use, availability and distribution of the vaccine, particularly in low-income countries through the UNICEF and Gavi procurement mechanisms. It is still not known, however, what the demand would be for oral cholera vaccines. Based on experiences from other vaccines, even

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(Submitted: 2 September 2016 – Revised version received: 24 January 2017 – Accepted: 30 January 2017 – Published online: 21 February 2017)

Table 1

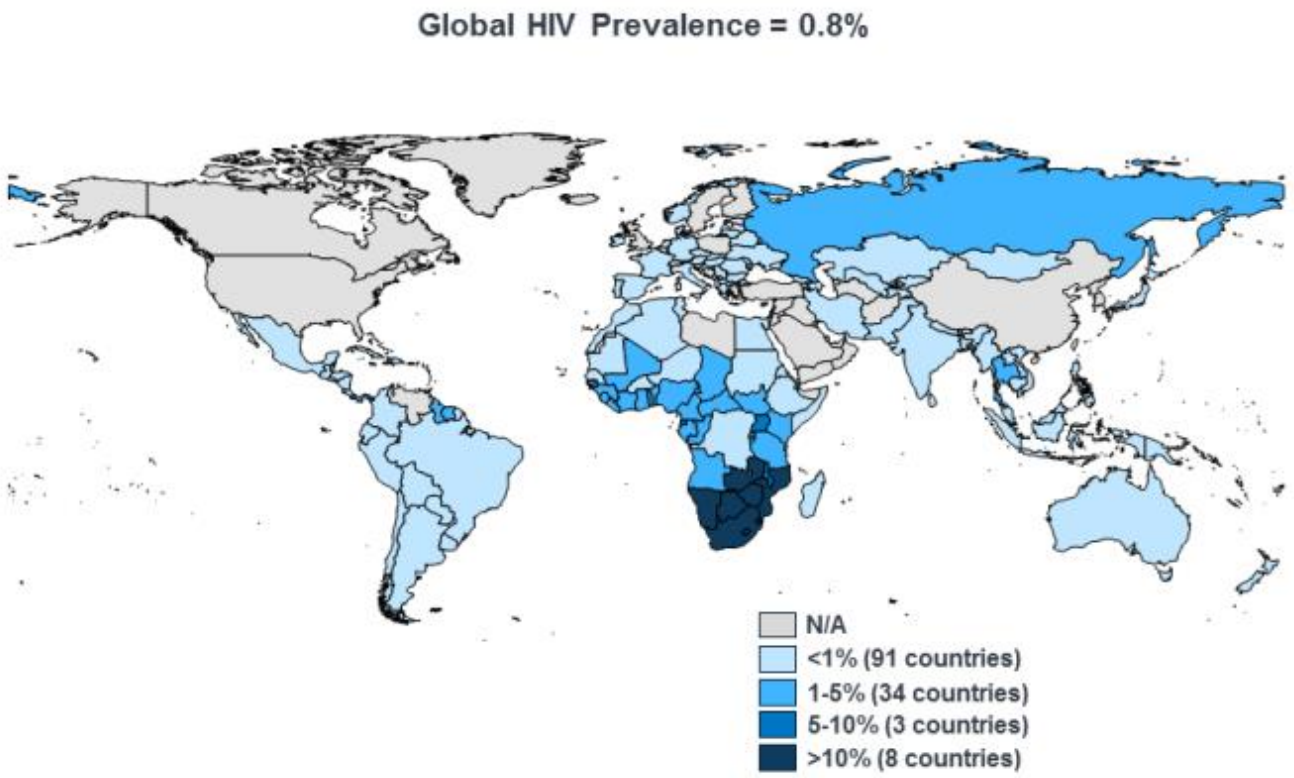
Characteristics of oral cholera vaccines currently licensed or pending licensing

Vaccine	Dukoral®[a]	ORC-Vax and mORC-Vax[b]	Shanchol[b]	Euvichol®[b]	Vaxchora	Cholvax®[b]
Place of initial licensing (date)	Sweden (1991)	Viet Nam (1997, 2009)	India (2009)	Republic of Korea (2015)	United States (2016)	Bangladesh (pending)
WHO pre-qualification (date)	Yes (2001)	No	Yes (2011)	Yes (2015)	No	No
Manufacturer	Developed by SBL Vaccine (Solna, Sweden); now Valneva (Montreal, Canada)	VabioTech (Hanoi, Viet Nam)	Developed by Shantha Biotechnics (Hyderabad, India); now Sanofi Pasteur India (Mumbai, India)	Eubiologics (Seoul, Republic of Korea)	Paxvax (Redwood City, United States)	Incepta (Dhaka, Bangladesh)
Additional notes	Requires buffer for administration. Difficult to use in emergency situations. Has not been widely used apart from traveller's market. Two-dose (≥ 6 years of age) and three-dose (2–5 years of age) inactivated vaccine	Only available for Viet Nam market. Two-dose inactivated vaccine	First low-cost oral cholera vaccine with WHO prequalification for international use. Two-dose inactivated vaccine	Two-dose inactivated vaccine	First live-attenuated oral cholera vaccine composed of *Vibrio cholerae O1 (Inaba)*. Currently indicated as a single-dose regimen for ages 18–64 years	Only available for Bangladesh market. Two-dose inactivated vaccine

WHO: World Health Organization.

Figure 1

Adult HIV Prevalence, 2017

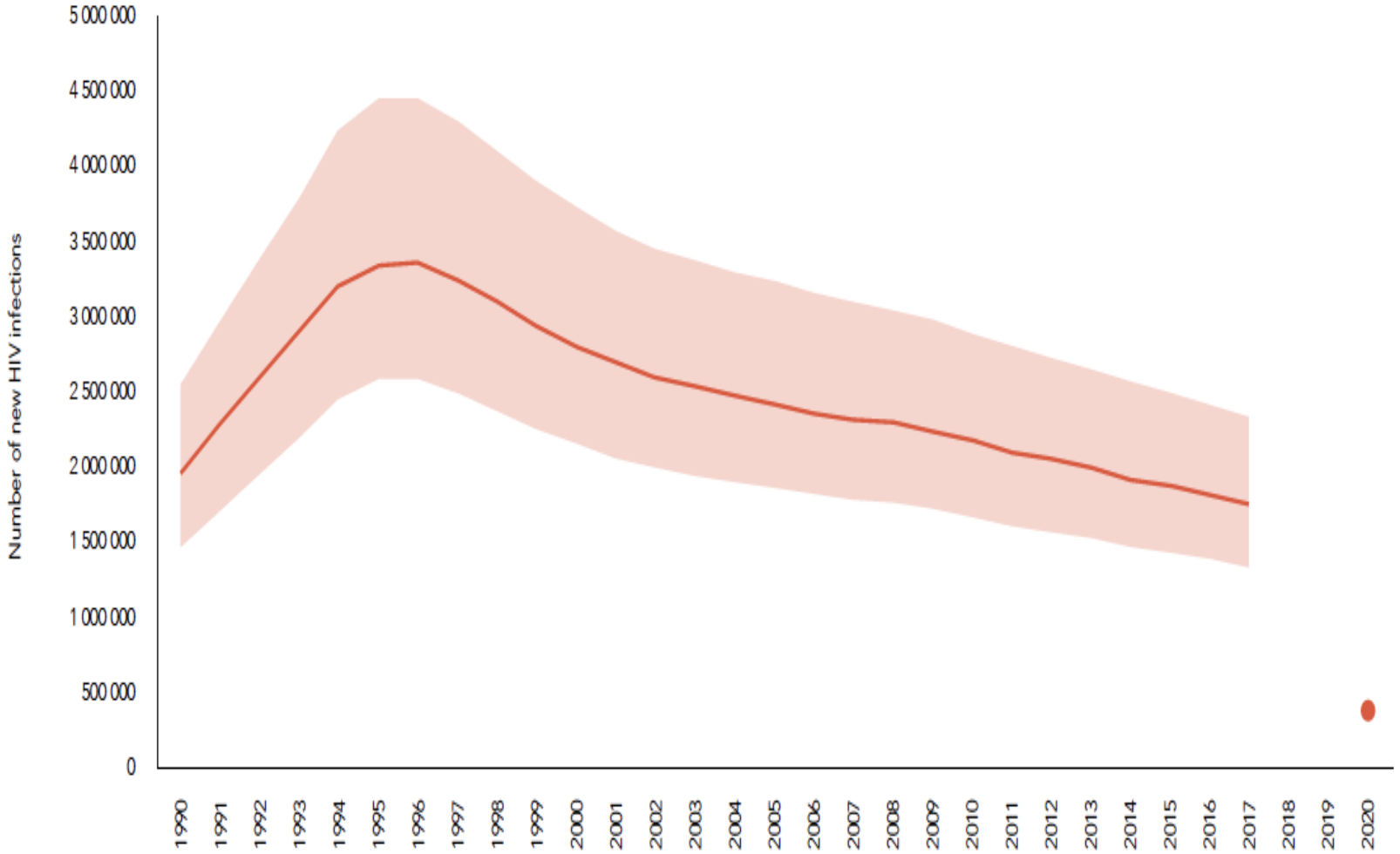


NOTES: Data are estimates. Prevalence includes adults ages 15-49.
SOURCES: Kaiser Family Foundation, based on UNAIDS, AIDSinfo, Accessed July 2018

KFF

FIGURE 2.3 **Insufficient progress on prevention**

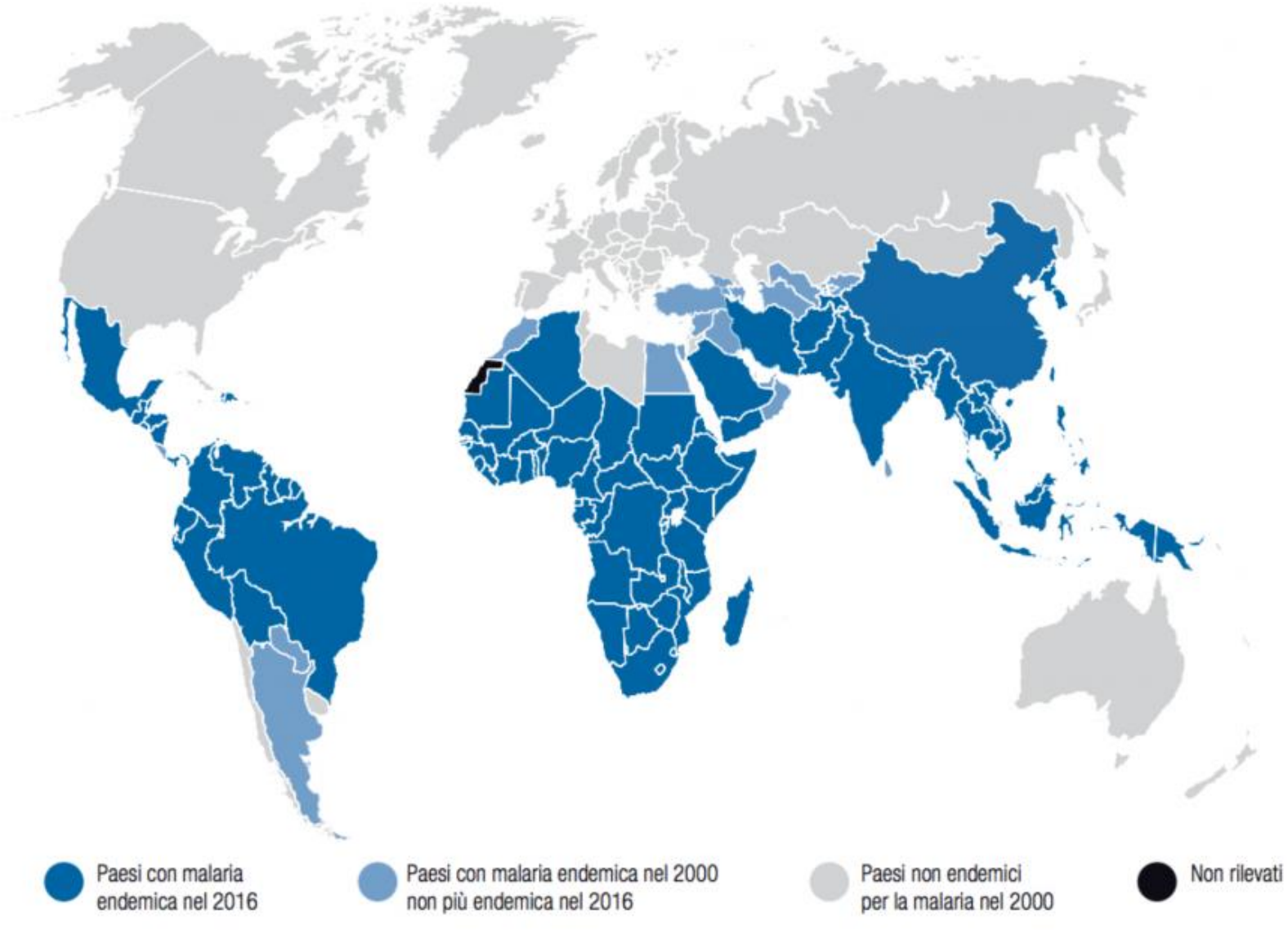
Number of new HIV infections, global, 1990–2017 and 2020 target



"We have never ended a global epidemic without a vaccine or a cure and HIV will not be an exception"

Vella S. Wilson D. From Durban to Durban: end of AIDS further than hoped. **Lancet HIV**, Vol 3, September 2016, e403-405.

Figura 1. Paesi a endemia malarica: confronto anni 2000-2016. Fonte: WHO, 2016.



World Health Organization

Credits

Malaria vaccine pilot launched in Malawi

Country first of three in Africa to roll out landmark vaccine

23 April 2019 | News release | Geneva

WHO welcomes the Government of Malawi's launch of the world's first malaria vaccine today in a landmark pilot programme. The country is the first of three in Africa in which the vaccine, known as RTS,S, will be made available to children up to 2 years of age; Ghana and Kenya will introduce the vaccine in the coming weeks.

Malaria remains one of the world's leading killers, claiming the life of one child every two minutes. Most of these deaths are in Africa, where more than 250 000 children die from the disease every year. Children under 5 are at greatest risk of its life-threatening complications. Worldwide, malaria kills 435 000 people a year, most of them children.

An innovation milestone, three decades in development

Thirty years in the making, RTS,S is the first, and to date the only, vaccine that has demonstrated it can significantly reduce malaria in children. In clinical trials, the vaccine was found to prevent approximately 4 in 10 malaria cases, including 3 in 10 cases of life-threatening severe malaria

"Malaria is a constant threat in the African communities where this vaccine will be given. The poorest children suffer the most and are at highest risk of death," said Dr Matshidiso Moeti, WHO Regional Director for Africa. "We know the power of vaccines to prevent killer diseases and reach children, including those who may not have immediate access to the doctors, nurses and health facilities they need to save them when severe illness comes."

"This is a day to celebrate as we begin to learn more about what this tool can do to change the trajectory of malaria through childhood vaccination," she added.

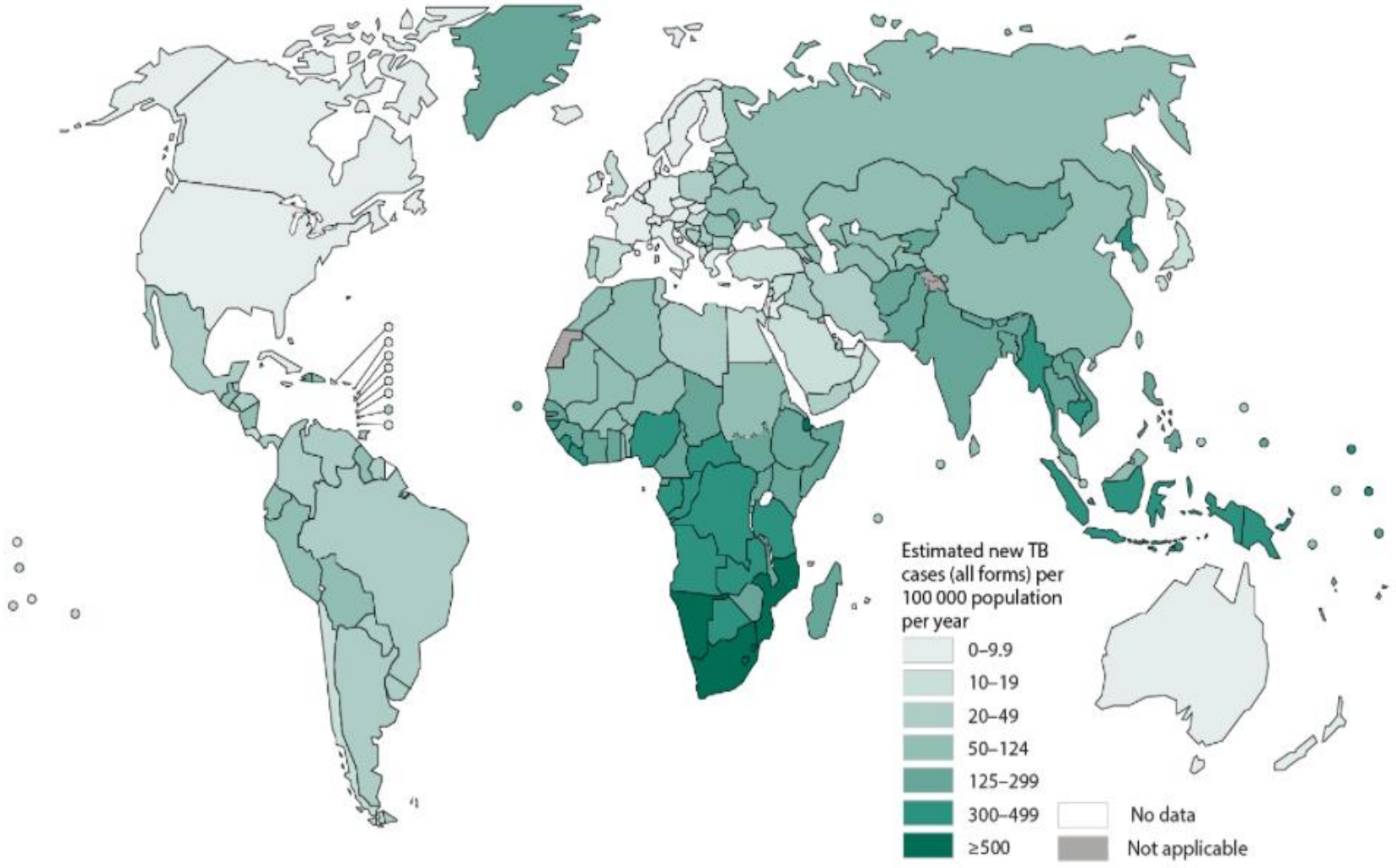
The pilot programme is designed to generate evidence and experience to inform WHO policy recommendations on the broader use of the RTS,S malaria vaccine. It will look at reductions in child deaths; vaccine uptake, including whether parents bring their children on time for the four required doses; and vaccine safety in the context of routine use.

The vaccine is a complementary malaria control tool – to be added to the core package of WHO-recommended measures for malaria prevention, including the routine use of insecticide-treated bed nets, indoor spraying with insecticides, and the timely use of malaria testing and treatment.

A model public-private partnership

The WHO-coordinated pilot programme is a collaborative effort with ministries of health in Ghana, Kenya and Malawi and a range of in-country and international partners, including PATH, a non-profit organization, and GSK, the vaccine developer and manufacturer, which is donating up to 10 million vaccine doses for this pilot.

Estimated TB incidence rates, 2014



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

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ABSTRACT

BACKGROUND

A vaccine to interrupt the transmission of tuberculosis is needed.

METHODS

We conducted a randomized, double-blind, placebo-controlled, phase 2b trial of the M72/AS01$_E$ tuberculosis vaccine in Kenya, South Africa, and Zambia. Human immunodeficiency virus (HIV)–negative adults 18 to 50 years of age with latent *M. tuberculosis* infection (by interferon-γ release assay) were randomly assigned (in a 1:1 ratio) to receive two doses of either M72/AS01$_E$ or placebo intramuscularly 1 month apart. Most participants had previously received the bacille Calmette–Guérin vaccine. We assessed the safety of M72/AS01$_E$ and its efficacy against progression to bacteriologically confirmed active pulmonary tuberculosis disease. Clinical suspicion of tuberculosis was confirmed with sputum by means of a polymerase-chain-reaction test, mycobacterial culture, or both.

RESULTS

We report the primary analysis (conducted after a mean of 2.3 years of follow-up) of the ongoing trial. A total of 1786 participants received M72/AS01$_E$ and 1787 received placebo, and 1623 and 1660 participants in the respective groups were included in the according-to-protocol efficacy cohort. A total of 10 participants in the M72/AS01$_E$ group met the primary case definition (bacteriologically confirmed active pulmonary tuberculosis, with confirmation before treatment), as compared with 22 participants in the placebo group (incidence, 0.3 cases vs. 0.6 cases per 100 person-years). The vaccine efficacy was 54.0% (90% confidence interval [CI], 13.9 to 75.4; 95% CI, 2.9 to 78.2; P=0.04). Results for the total vaccinated efficacy cohort were similar (vaccine efficacy, 57.0%; 90% CI, 19.9 to 76.9; 95% CI, 9.7 to 79.5; P=0.03). There were more unsolicited reports of adverse events in the M72/AS01$_E$ group (67.4%) than in the placebo group (45.4%) within 30 days after injection, with the difference attributed mainly to injection-site reactions and influenza-like symptoms. Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two groups.

CONCLUSIONS

M72/AS01$_E$ provided 54.0% protection for *M. tuberculosis*–infected adults against active pulmonary tuberculosis disease, without evident safety concerns. (Funded by GlaxoSmithKline Biologicals and Aeras; ClinicalTrials.gov number, NCT01755598.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Van Der Meeren at GlaxoSmithKline, 20 Fleming Ave., 1300 Wavre, Belgium, or at olivier.x.van-der-meeren@gsk.com.

Drs. Van Der Meeren and Hatherill and Drs. Gillard and Tait contributed equally to this article.

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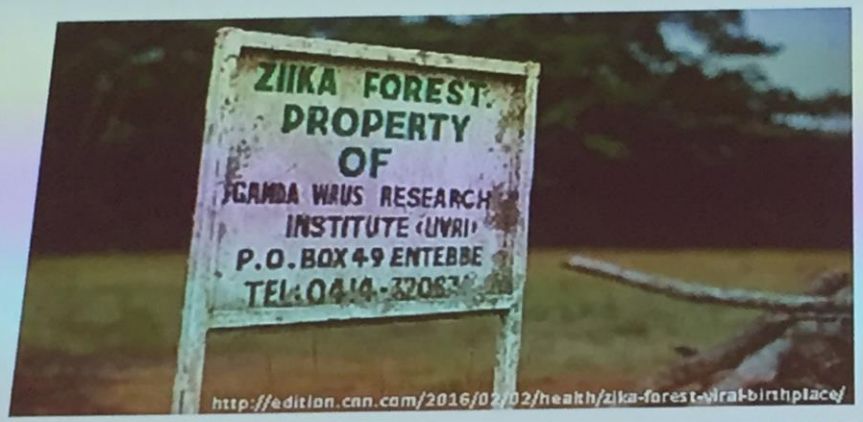
DOI: 10.1056/NEJMoa1803484

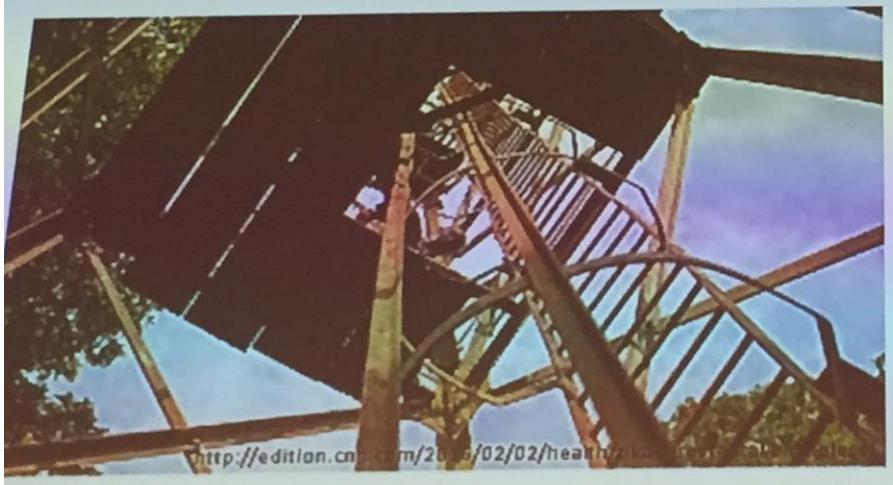
ZIKA

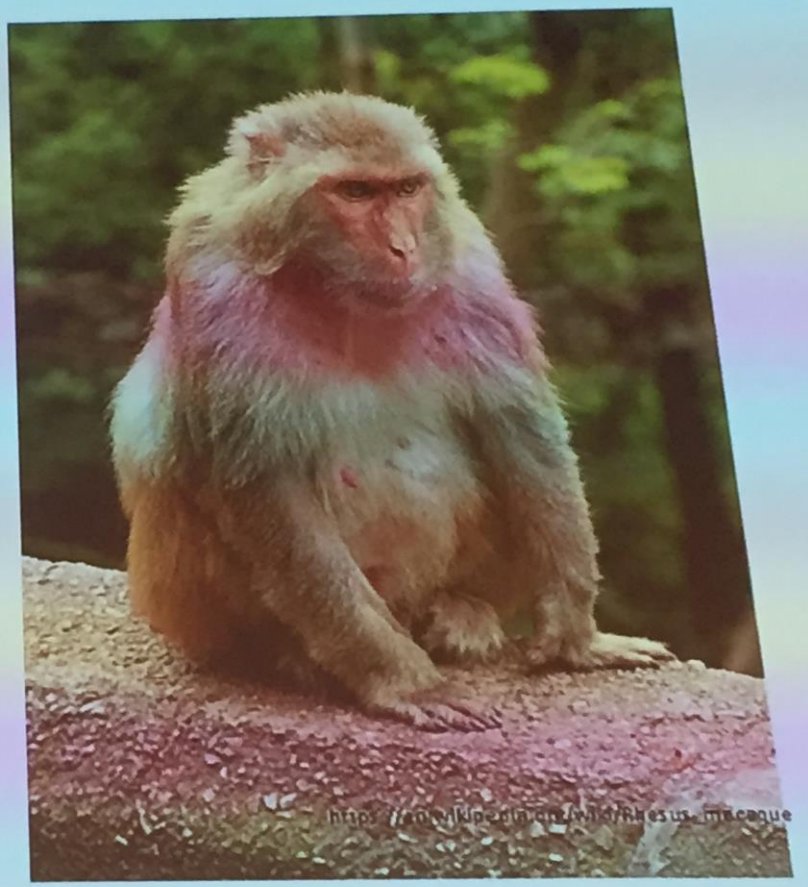
1947 — Uganda

First description: Uganda 1947

Zika forest

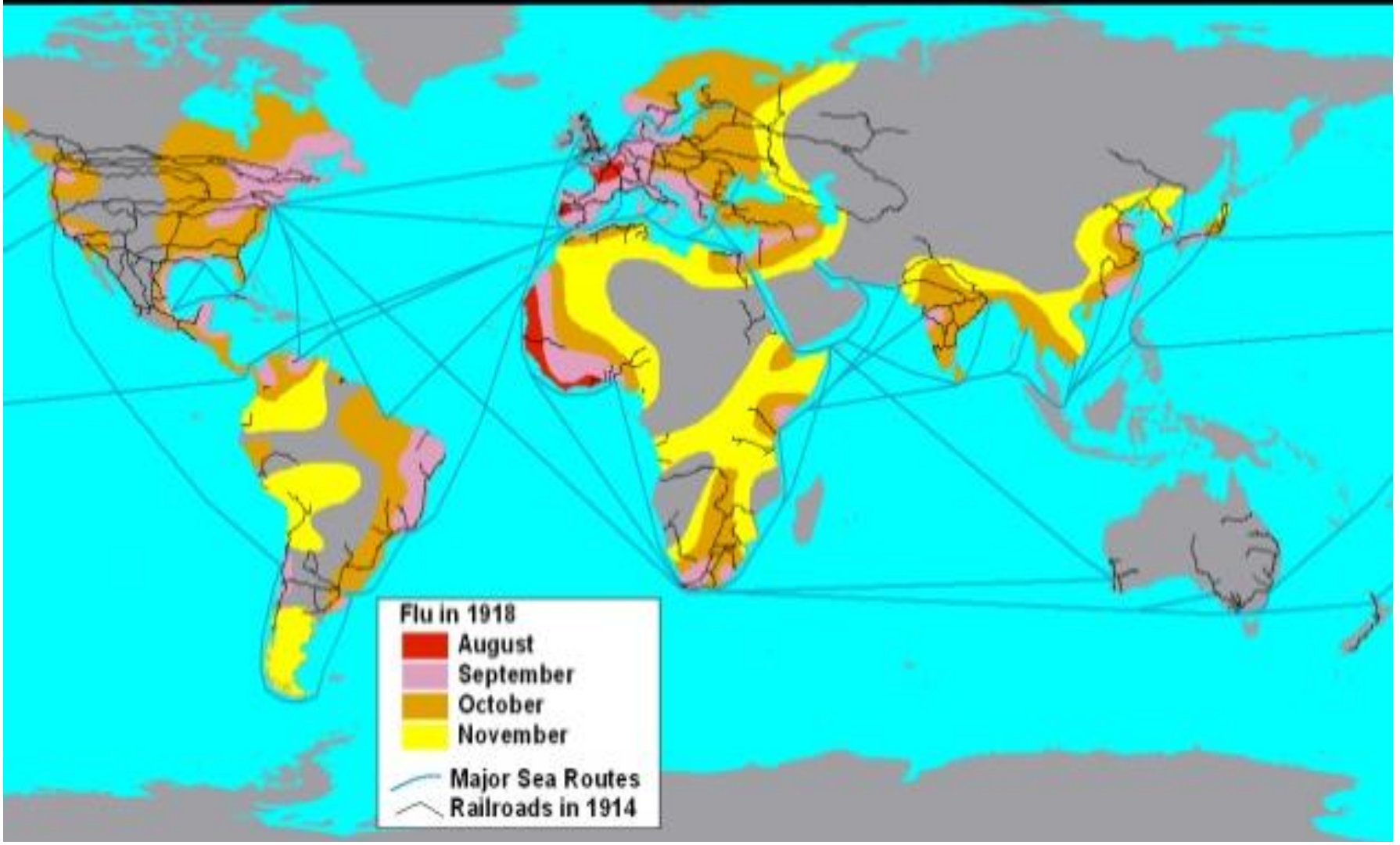




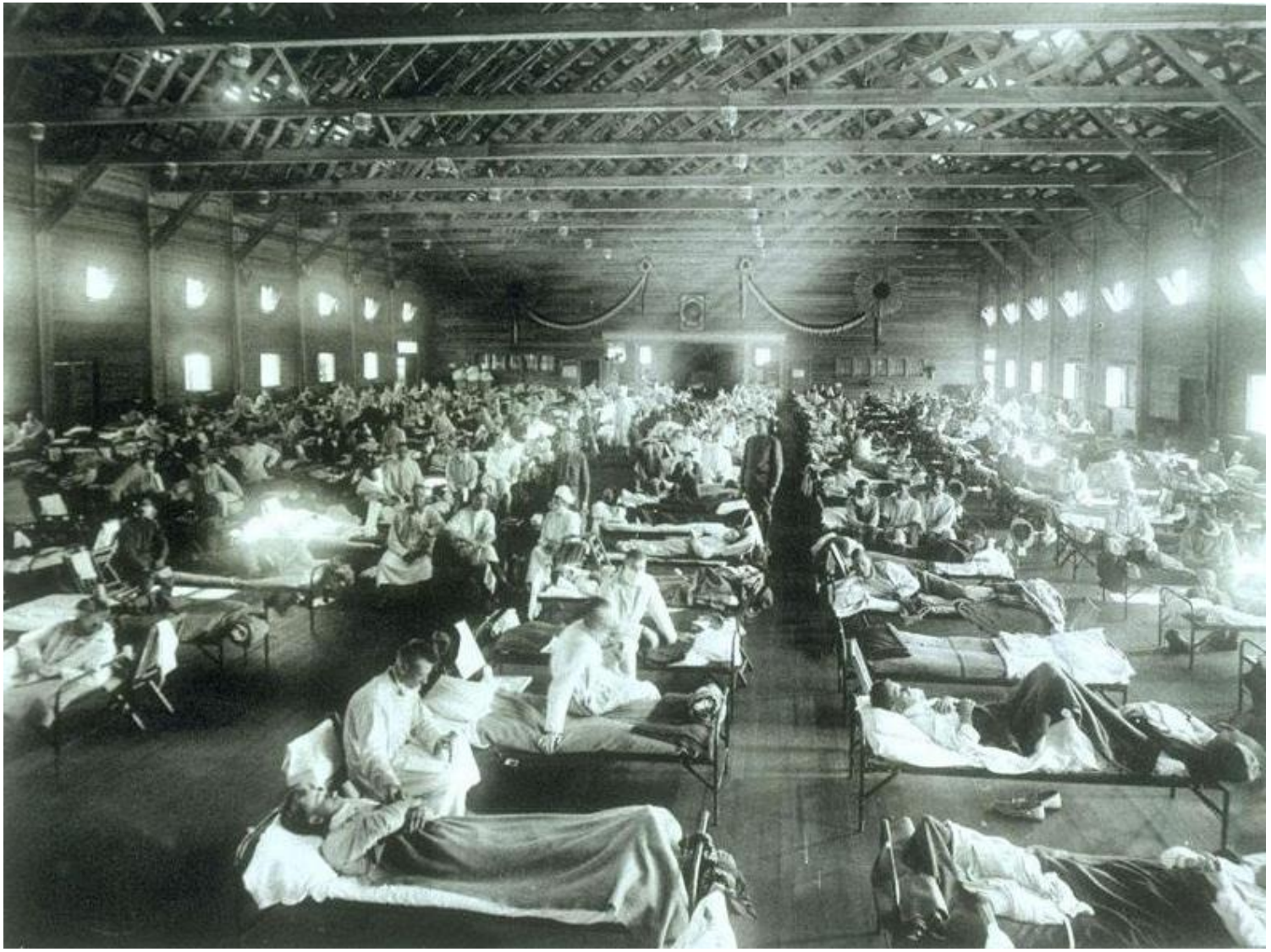


Rhesus monkey (*Macaca mulatta*)

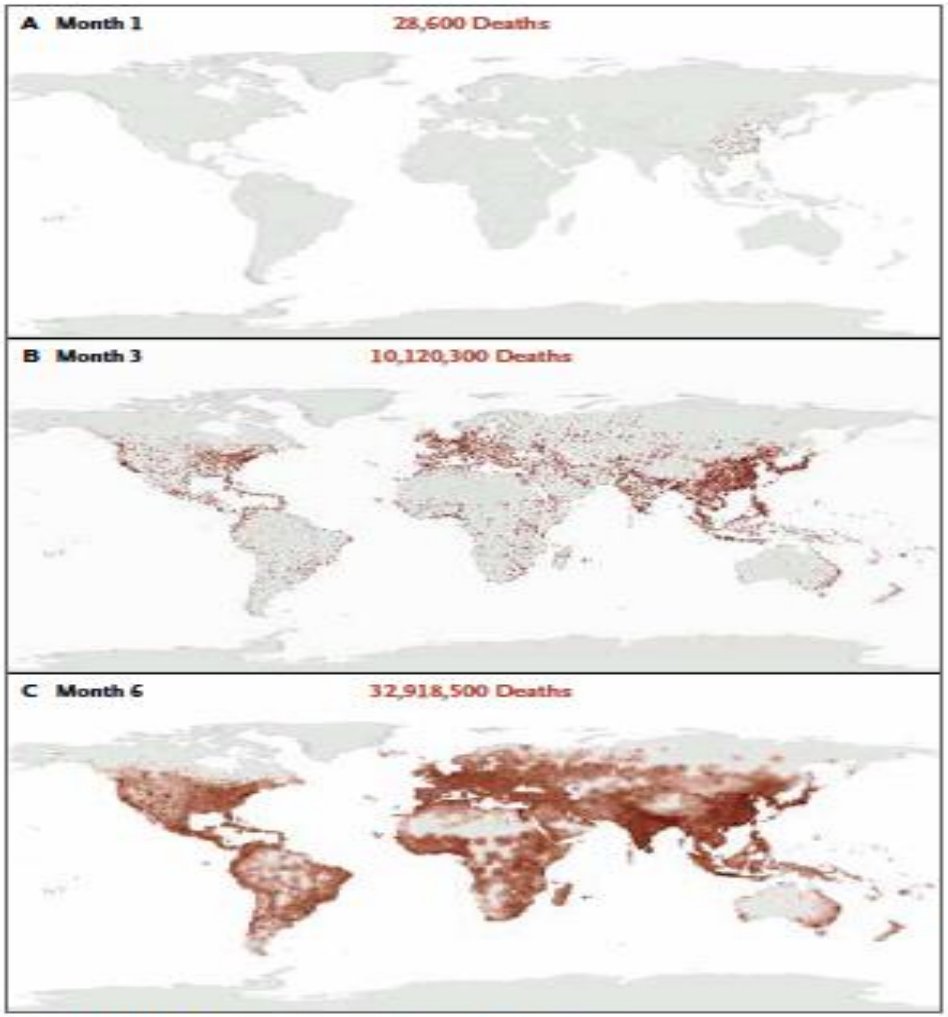
Flu Pandemic of 1918



The 1918-1919 influenza pandemic: 30 million deaths



The need for a universal flu vaccine



Simulation of a Modern-Day Global Influenza Pandemic.

After 1 month (Panel A), there would be a total of approximately 28,600 deaths; after 3 months (Panel B), 10,120,300 deaths; and after 6 months (Panel C), 32,918,500 deaths worldwide. From the Institute for Disease Modeling. An animated map is available with the full text of this article at NEJM.org.

the chance to put the world on a more prosperous, fair, and sustainable path and ensure that economic growth is also socially just and environmentally sustainable.

500 million people worldwide lack health care including access to essential medicines, vaccines, diagnostics, medical devices, and health technologies that prevent and treat diseases

The concept of “public good”

non exclusive: anyone can use them

non competitive: their use will not limit others to use them

The concept of “public good”

Vaccines shall be considered as global public goods and shall be accessible to all human beings living on our planet

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