

Beyond effectiveness: research on vaccines seen as a continuum

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Chair, Strategic Advisory Group of Experts (SAGE) on Immunization
World Health Organization

Global Vaccine and Immunization Research Forum (GVIRF) 20-22 March 2018 Bangkok, Thailand

Acknowledgements

- Joachim Hombach
- Martin Friede
- Malin Finkernagel
- Jon Abramson
- Susan Wang
- James Goodson
- Firdausi Qadri
- Ian Shepherd

Definition of RESEARCH

1: careful or diligent search

2: studious inquiry or examination; *especially* : investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws

3: the collecting of information about a particular subject

Merriam-Webster

Definition of RESEARCH

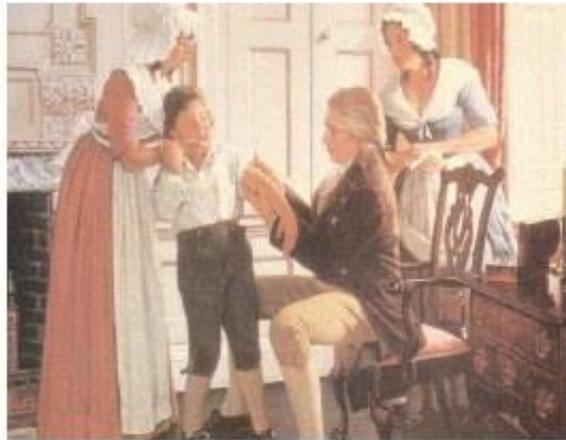
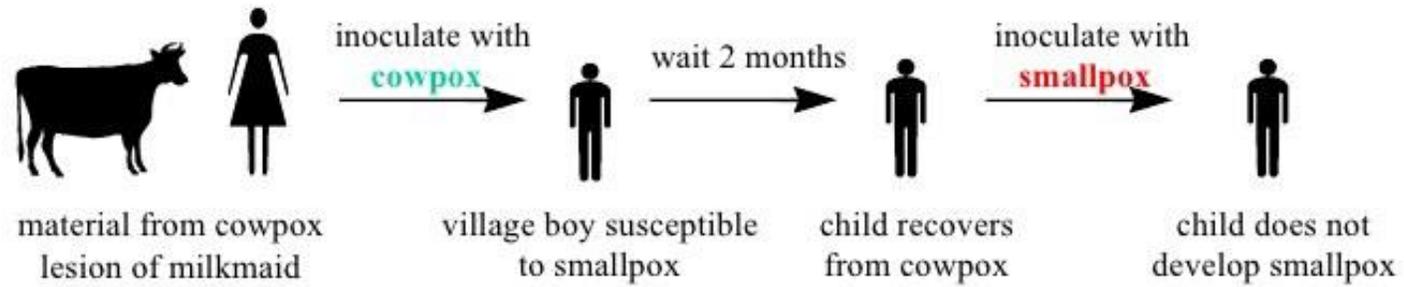
1: careful or diligent search

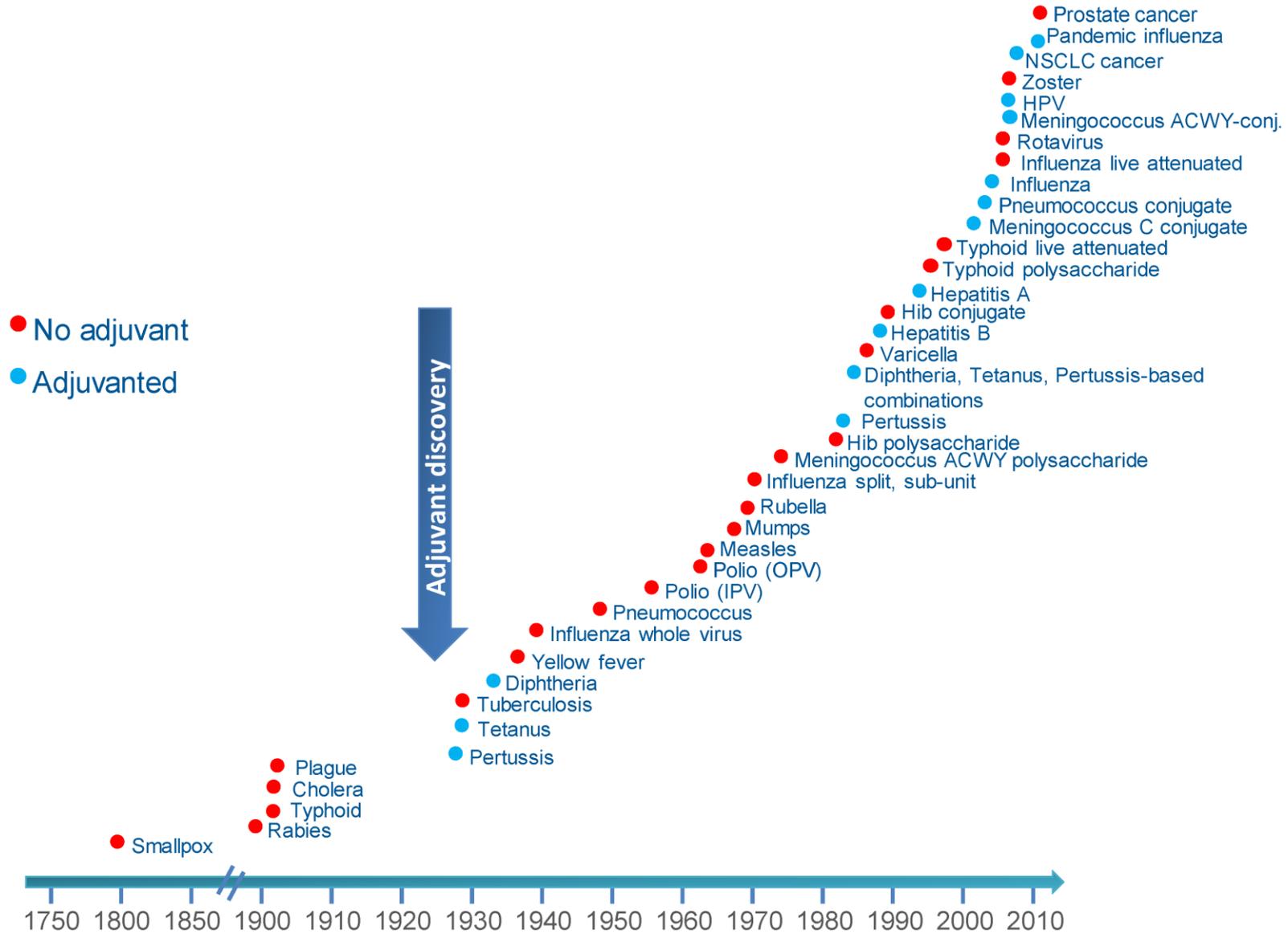
2: studious inquiry or examination; *especially* : investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, **or practical application of such new or revised theories or laws**

3: the collecting of information about a particular subject

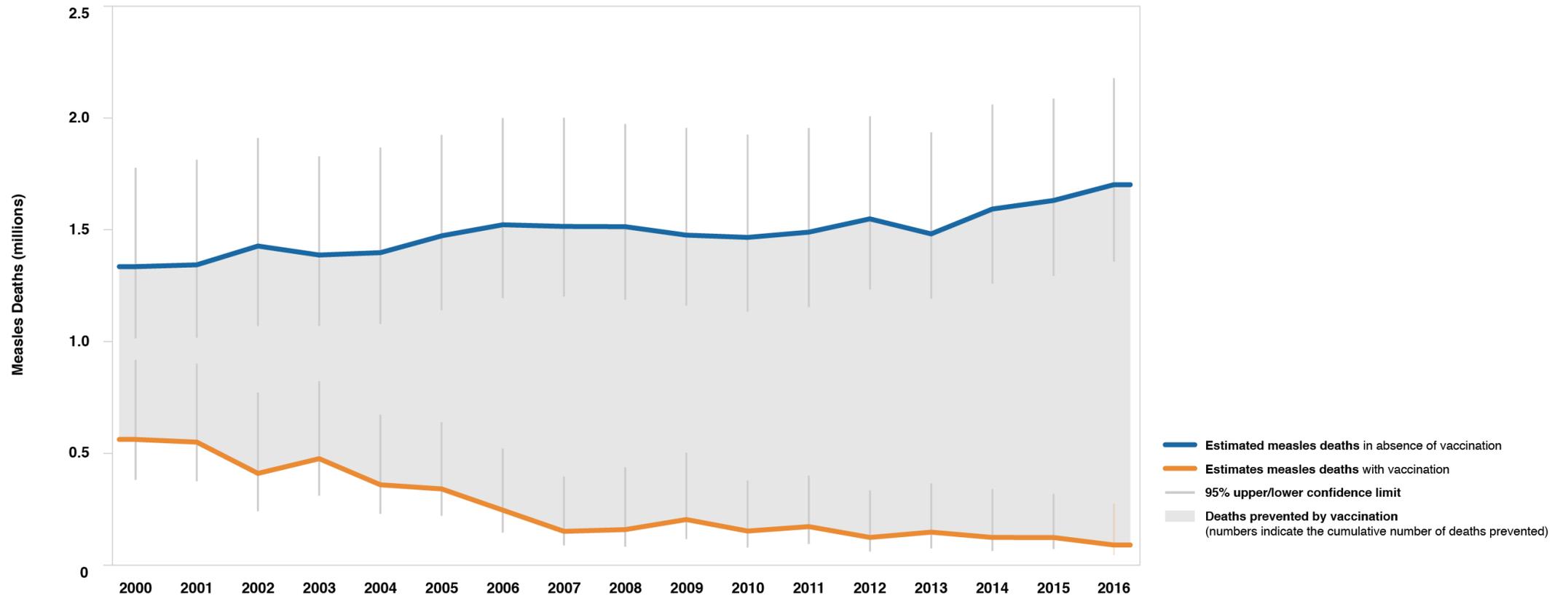
Merriam-Webster

Edward Jenner's experiment (1796)



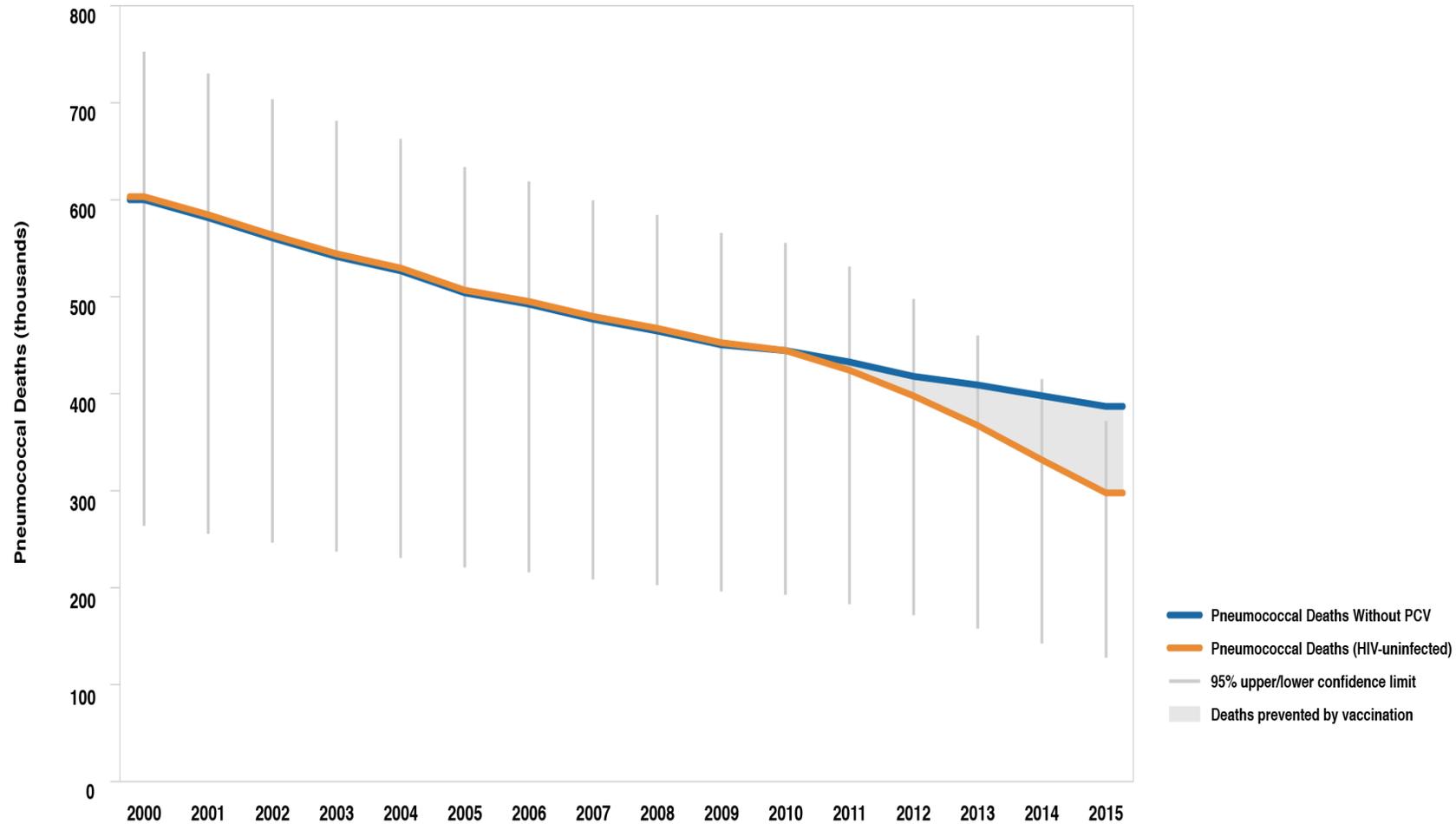


Measles vaccination averted 20 million measles deaths between 2000 and 2016

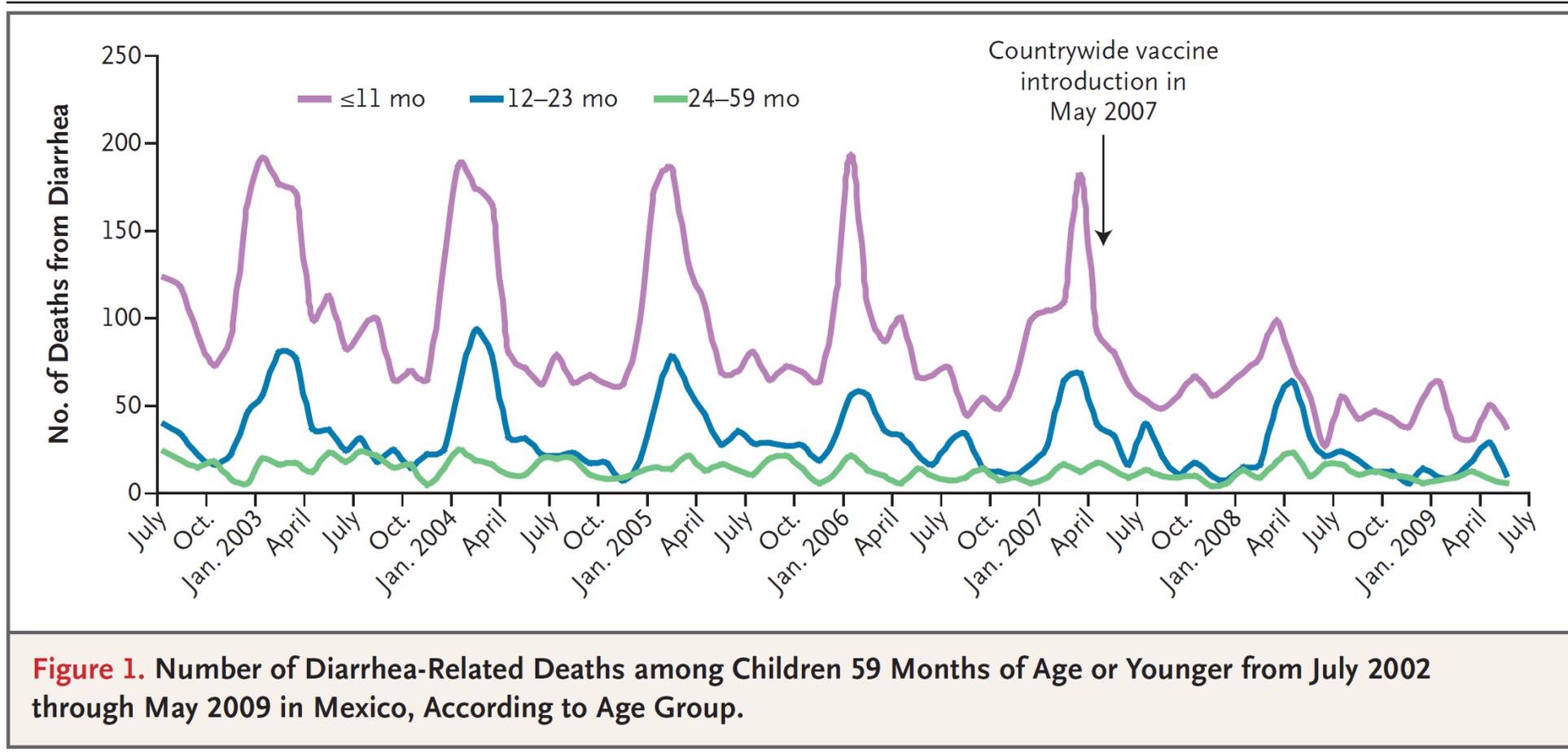


• Source: Progress Toward Regional Measles Elimination — Worldwide, 2000–2016. *MMWR* 2017 10 27; in press. EMBARGOED

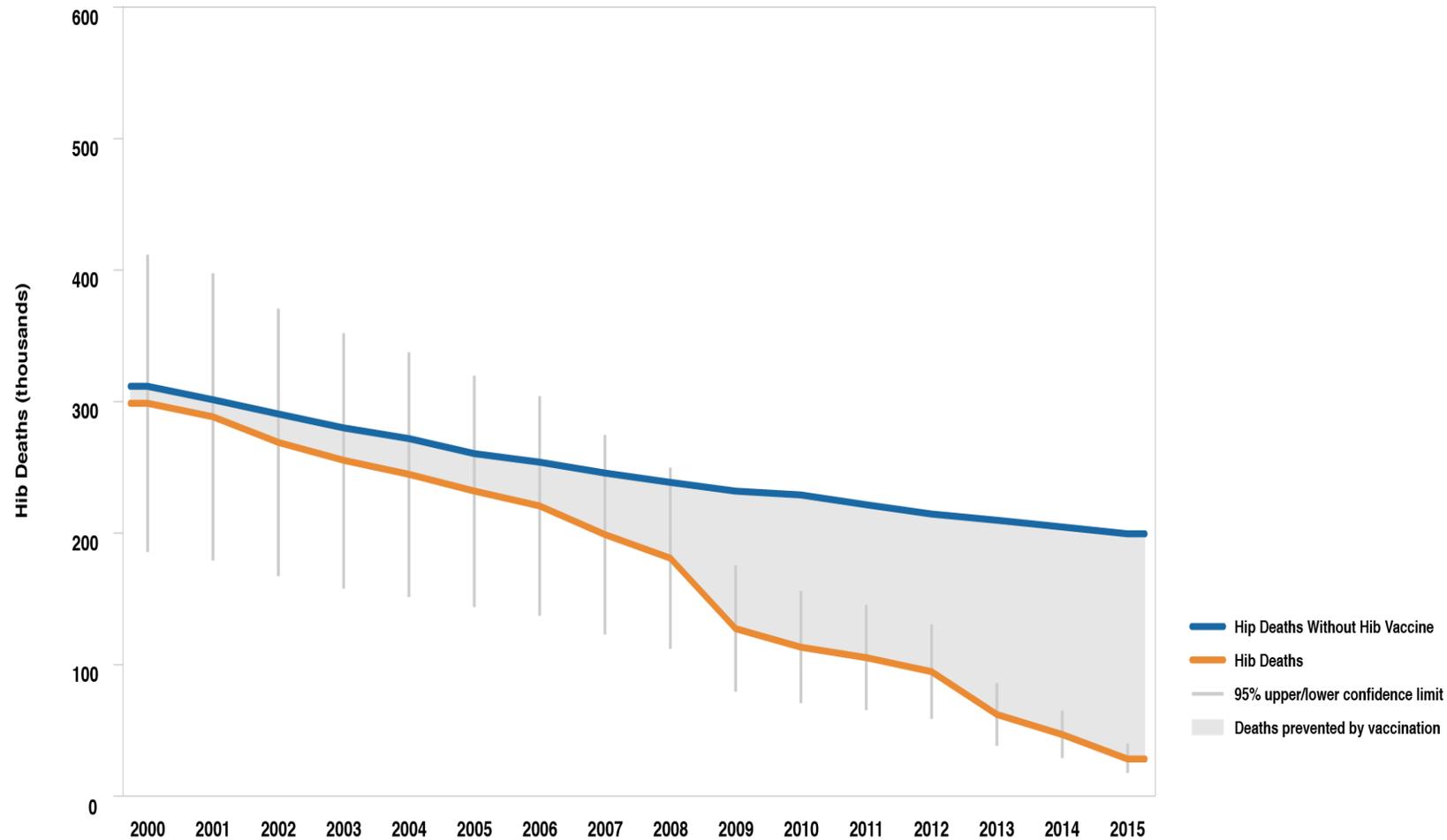
PCV uptake has accelerated and is now preventing almost 100,000 deaths per year. Since introduction, 190,000 deaths have been averted



Source: John's Hopkins University, JHSPH/IVAC

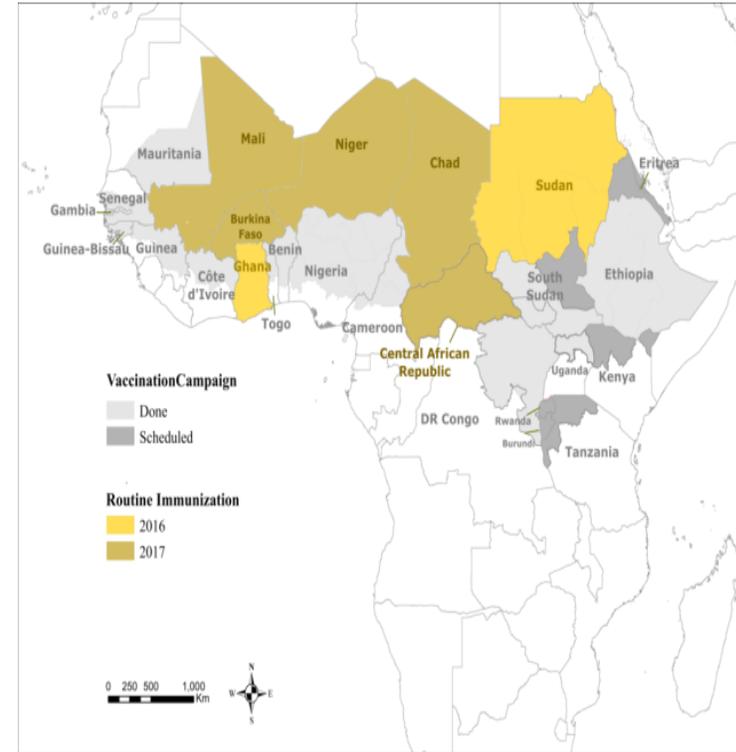
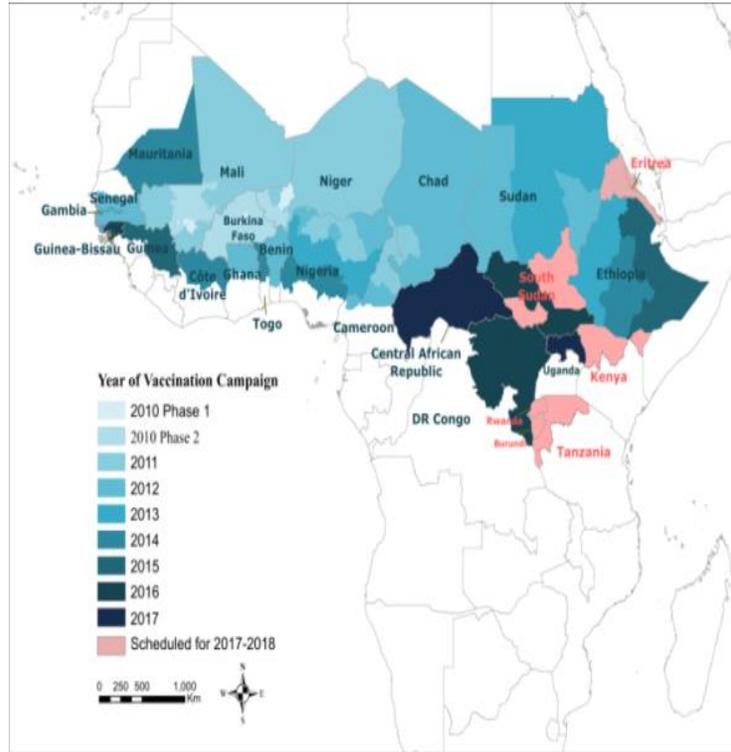


Introduction of Hib vaccine averted 1.2m deaths since 2000



Source: John's Hopkins University, JHSPH/IVAC

Meningitis A: 30,000 deaths averted since 2010 in the African Meningitis belt

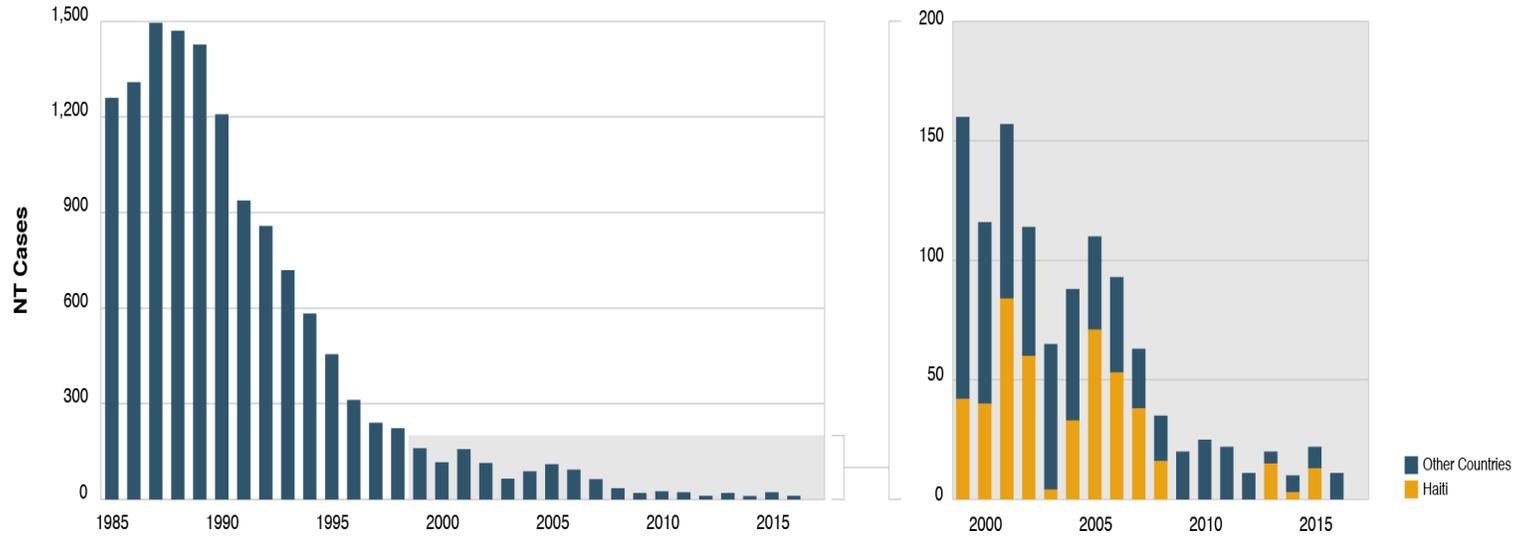


300,000,000
vaccinated

300,000 cases
averted

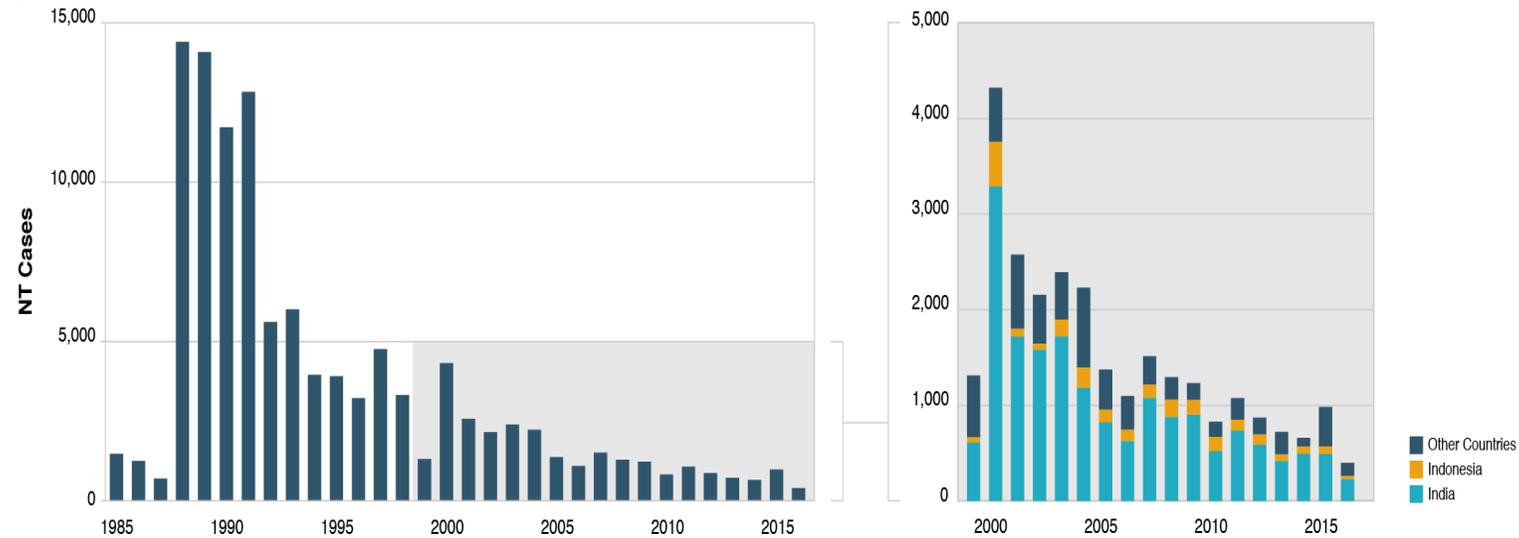
30,000 deaths
averted

The region of the Americas achieved Neonatal Tetanus Elimination



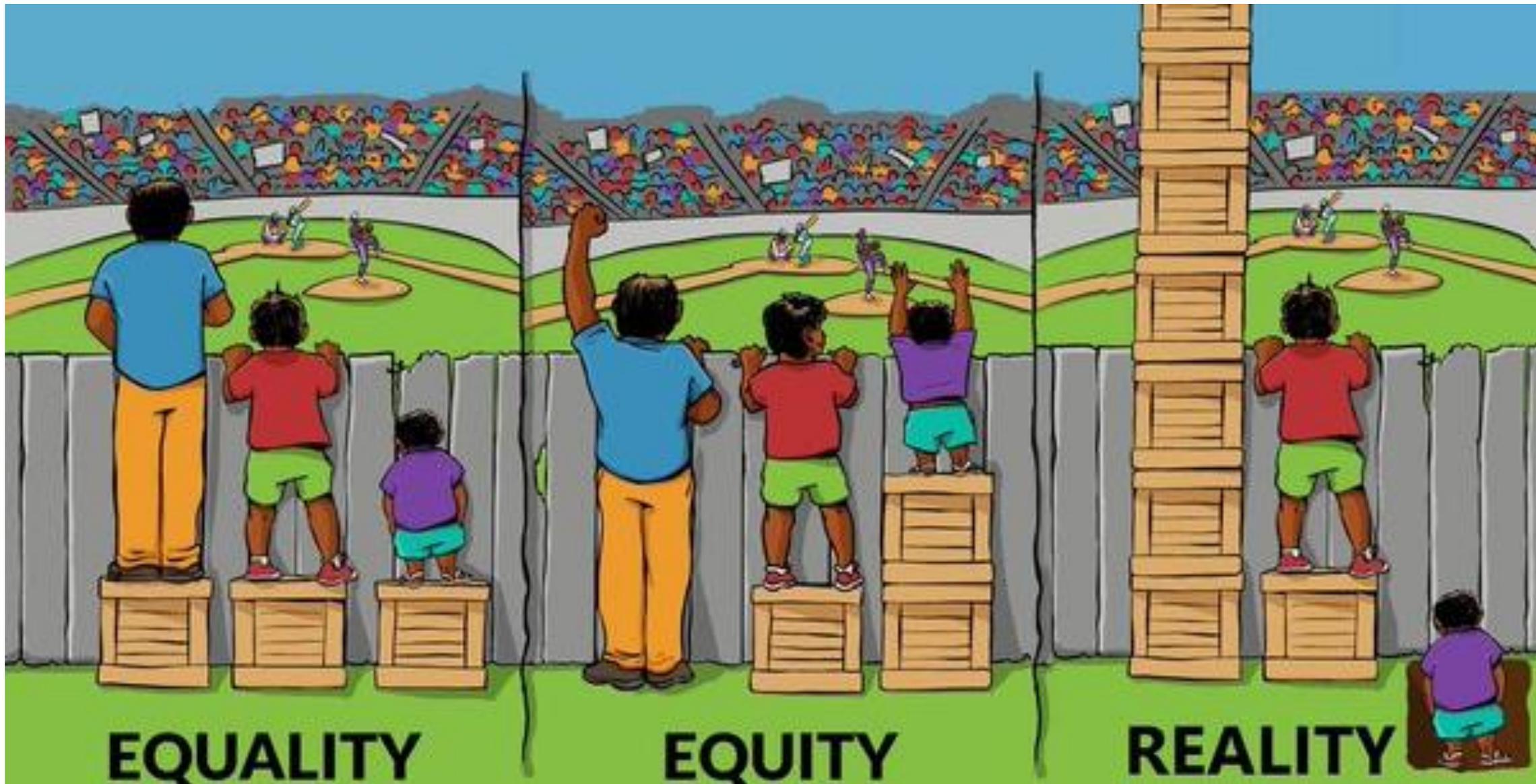
Source: WHO/UNICEF Joint Reporting Form (JRF)

The South East Asia Region achieved Maternal & Neonatal Tetanus Elimination in 2016



Year MNTTE validated:

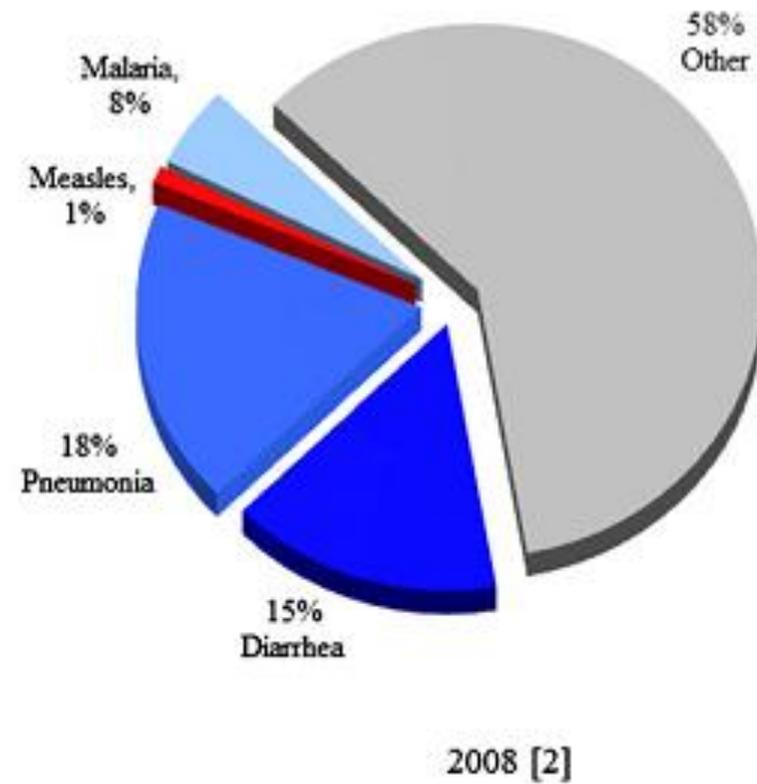
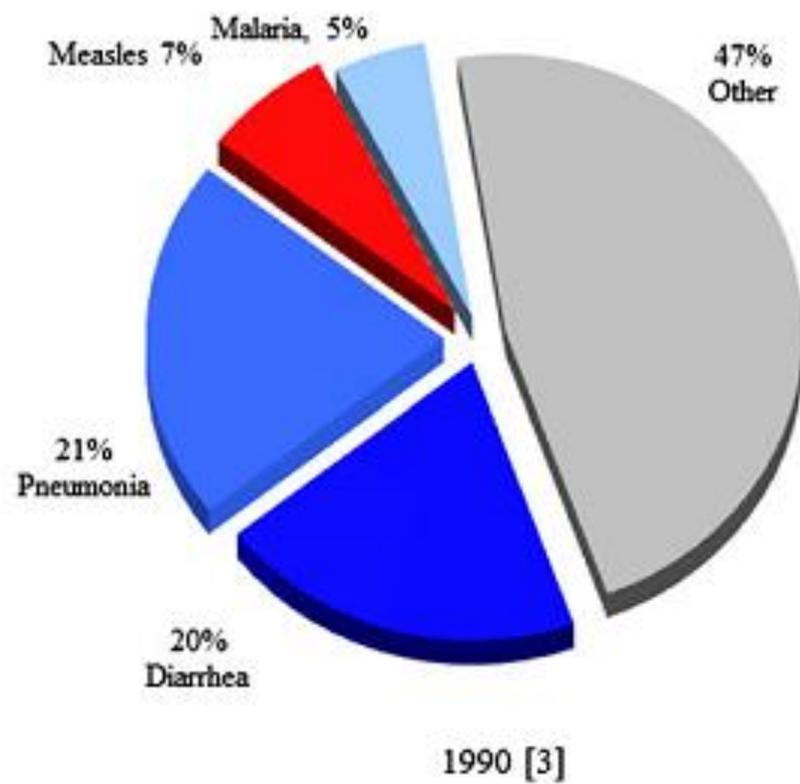
- Nepal 2005
- Bangladesh 2008
- Myanmar 2010
- Timor Leste 2012
- India phased manner 2003-15
- Indonesia phased manner 2010-16
- **Regional MNTTE goal achieved May 2016**
- Other countries succeeded prior to 2000



EQUALITY

EQUITY

REALITY



Cause-specific proportionate mortality worldwide among children <5 years of age in 1990 [3] and 2008 [2].

Maya M. V. X. van den Ent,¹

Numbers of deaths and cases of medical impoverishment averted by vaccines to be administered in 41 low- and middle-income countries, 2016–30

ANTIGEN	DEATHS AVERTED ('000s)	NUMBER OF DEATHS AVERTED (PER MILLION PEOPLE VACCINATED)	MEDICAL IMPOVERISHMENT CASES AVERTED ('000s)
Measles	22,204	11,339	4,787
Hepatitis B	6,639	10,751	14,034
Human papillomavirus	2,522	11,990	112
Yellow Fever	1,804	4,551	835
<i>Hemophilus influenzae</i> type b	1,242	1,998	1,054
<i>Streptococcus pneumoniae</i>	782	1,337	248
Rotavirus	454	819	242
Rubella	355	897	141
<i>Neisseria meningitidis</i> serogroup A	137	81	2,684
Japanese encephalitis	13	35	8



SUSTAINABLE DEVELOPMENT GOALS

1 NO POVERTY

2 ZERO HUNGER

3 GOOD HEALTH AND WELL-BEING

4 QUALITY EDUCATION

5 GENDER EQUALITY

6 CLEAN WATER AND SANITATION

7 AFFORDABLE AND CLEAN ENERGY

8 DECENT WORK AND ECONOMIC GROWTH

9 INDUSTRY, INNOVATION AND INFRASTRUCTURE

10 REDUCED INEQUALITIES

11 SUSTAINABLE CITIES AND COMMUNITIES

12 RESPONSIBLE CONSUMPTION AND PRODUCTION

13 CLIMATE ACTION

14 LIFE BELOW WATER

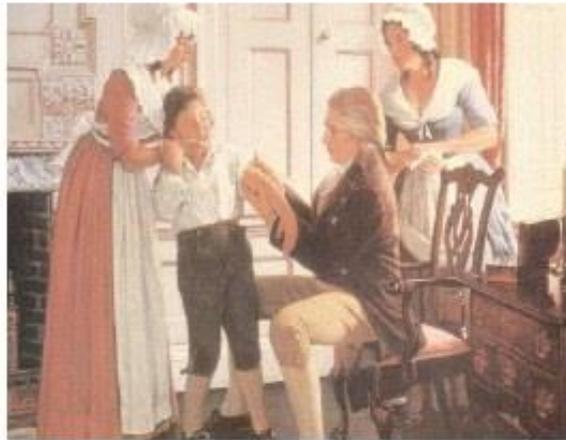
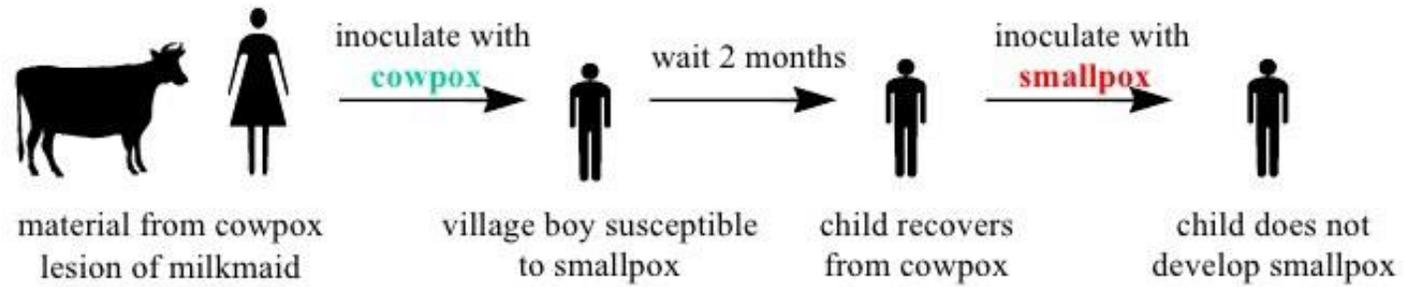
15 LIFE ON LAND

16 PEACE, JUSTICE AND STRONG INSTITUTIONS

17 PARTNERSHIPS FOR THE GOALS

SUSTAINABLE DEVELOPMENT GOALS

Edward Jenner's experiment (1796)



AN
INQUIRY
INTO
THE CAUSES AND EFFECTS
OF
THE VARIOLÆ VACCINÆ,
A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,
PARTICULARLY
GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF
THE COW POX.

BY EDWARD JENNER, M. D. F. R. S. &c.

— QUID NOBIS CERTIUS IPSIS
SERRIUS ERIT POTEST, QUO VERA AC FALSA NOVERIMUS.

LUCRETIVS.

London:

PRINTED, FOR THE AUTHOR,

BY SAMPSON LOW, N^o. 7, BIRWICK STREET, SOHO:

AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.



EL D^o EDUARDO JENNER
Descubridor de la Vacunación

TRATADO
HISTORICO Y PRACTICO
DE LA VACUNA,

Que contiene en compendio el origen y los resultados de las observaciones y experimentos sobre la vacuna, con un exámen imparcial de sus ventajas, y de las objeciones que se le han puesto, con todo lo demas que concierne á la práctica del nuevo modo de inocular.

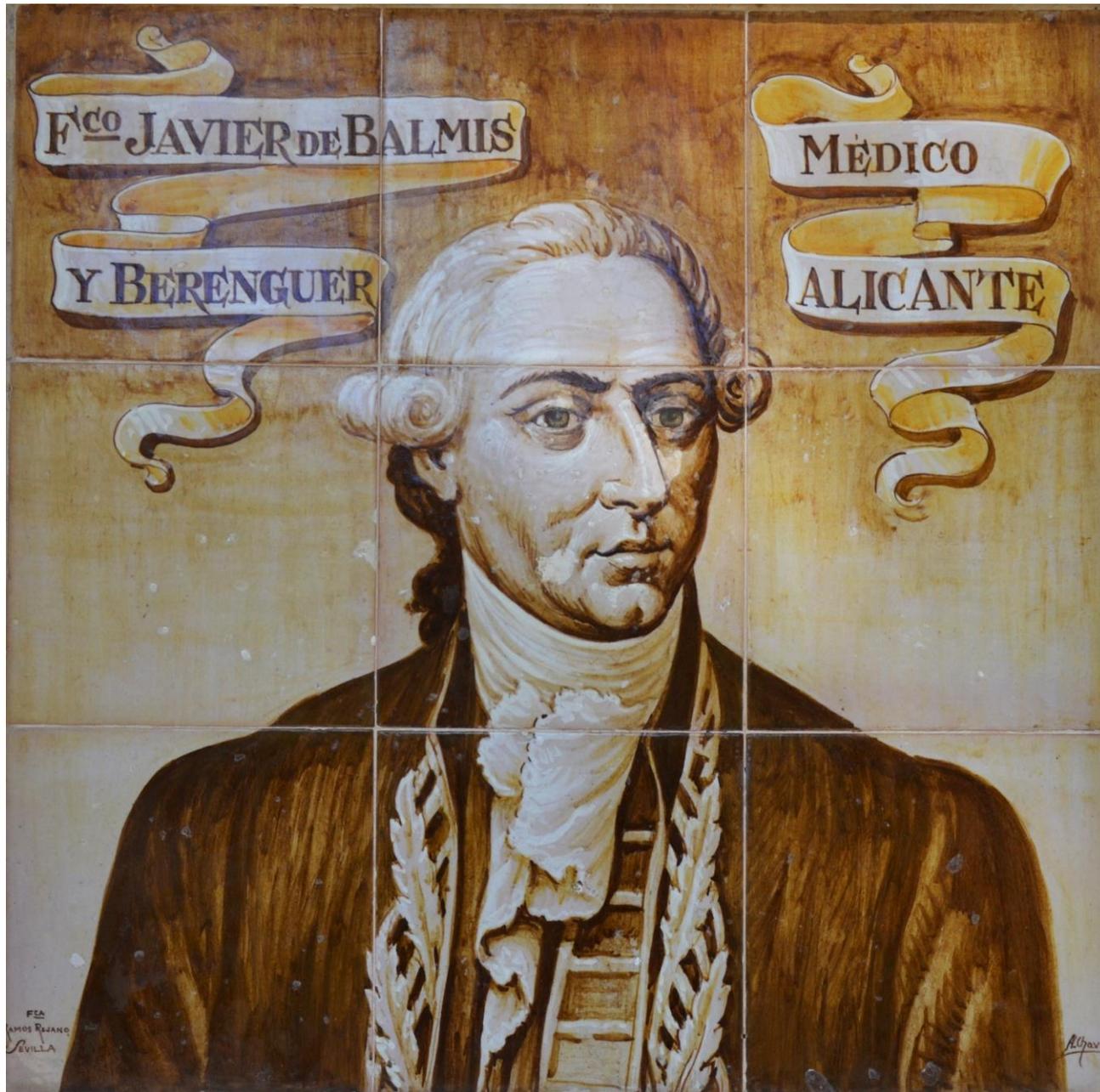
POR J. L. MOREAU (DE LA SARTHE),
Profesor de Medicina, segundo Bibliotecario de la Escuela Médica de París, Catedrático de Higiene en el Liceo republicano, individuo de la Junta comisionada para observar la vacuna en el Louvre, de las Sociedades de Medicina, de la Medicinal de Emulación, de la Filomática de los observadores del hombre, y Miembro correspondiente de la Sociedad Médica de Burdeos, de la de Emulación de Abbeville y de Poitiers, y de la Sociedad de Ciencias y Artes de Mars.

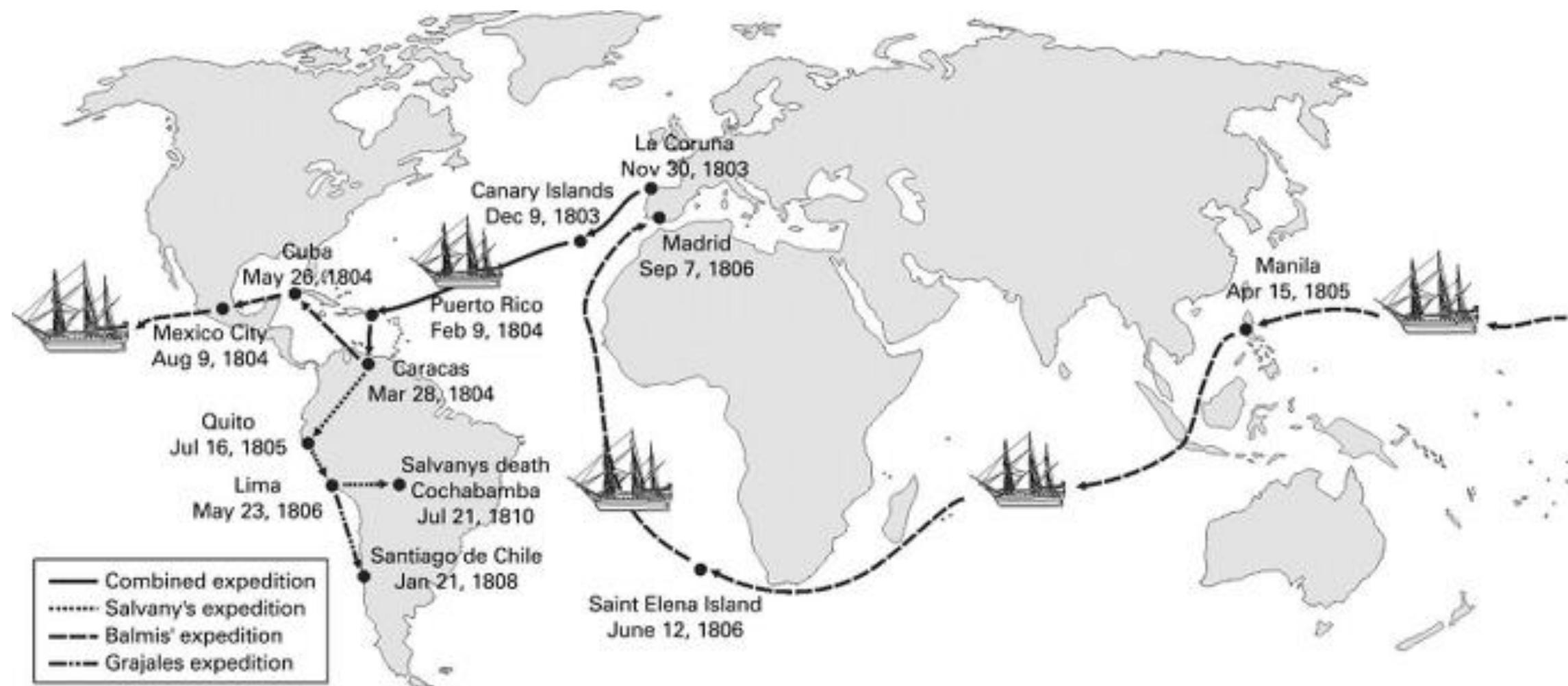
TRADUCIDO

POR EL Dr. D. FRANCISCO XAVIER DE BALBUENA,
Fiscal de Cámara de S. M., Honorario Consultor de Cirugía de las Reales Exércitos, Profesor de Medicina, y Socio correspondiente de la Real Academia Médica de Madrid.

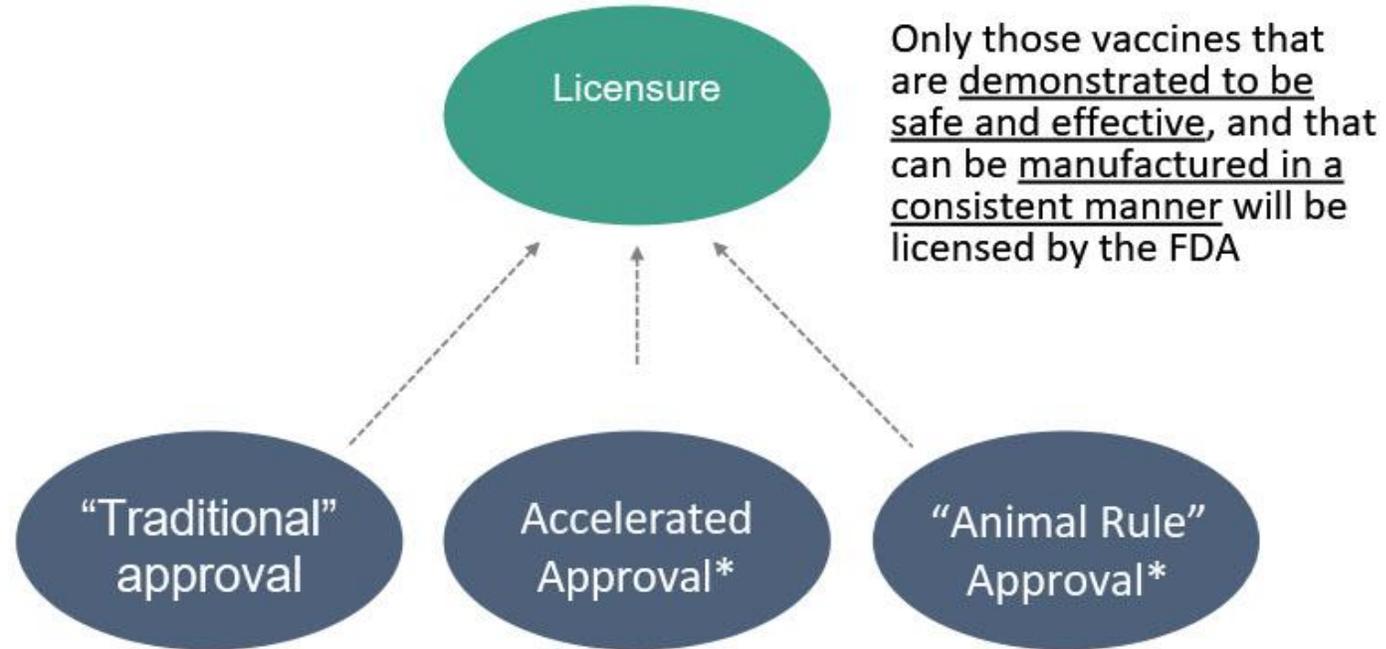
MADRID EN LA IMPRENTA REAL
AÑO DE 1809.



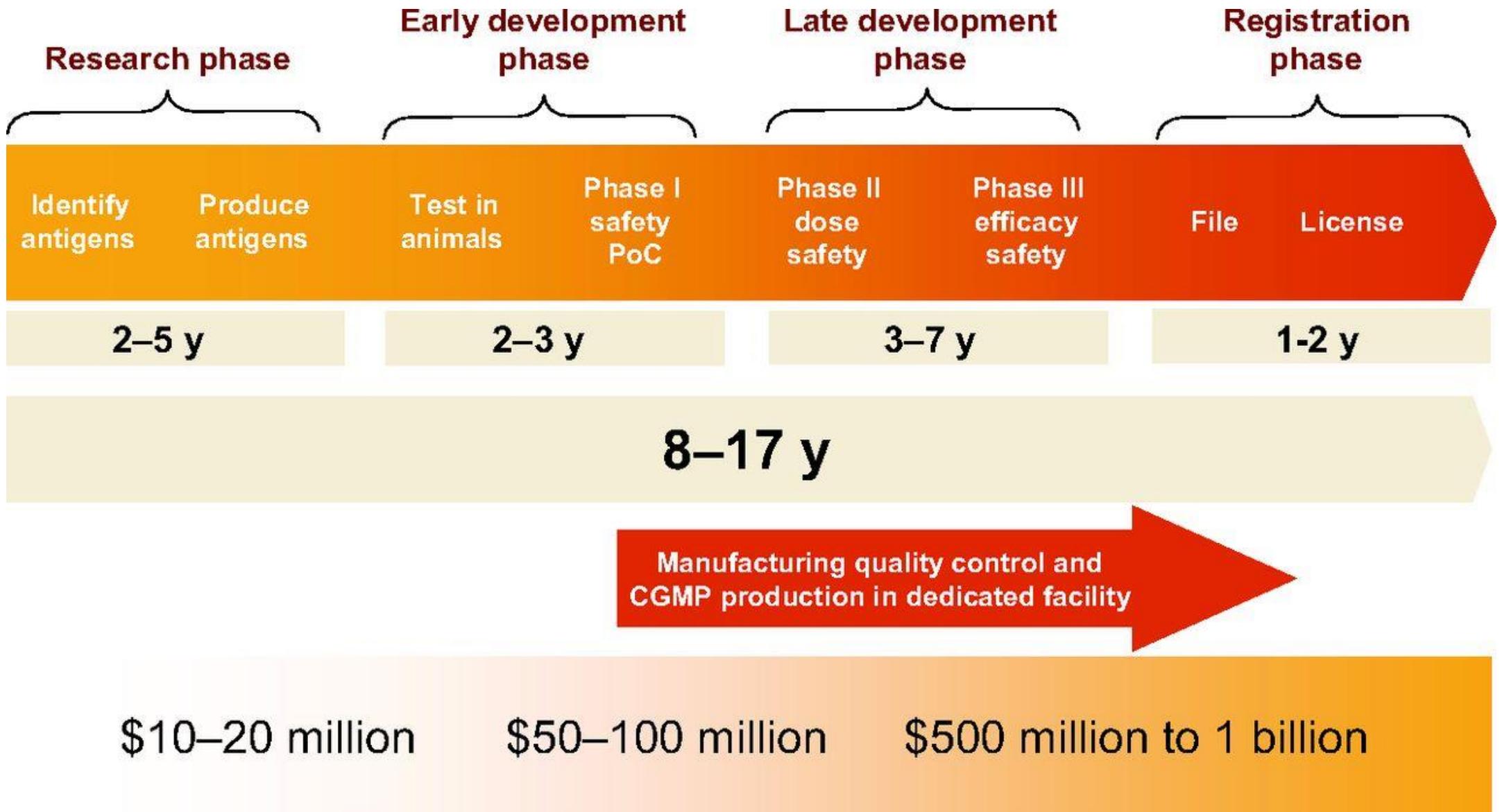




U.S. Licensure Pathways



- Demonstration of clinical safety is required for all pathways.
- Demonstration of effectiveness is required for all pathways, there are differences in approach among pathways.
- *Accelerated Approval and Animal Rule have specific “eligibility” criteria and associated requirements.



Efficacy and effectiveness

- **Vaccine efficacy:** vaccine efficacy measures direct protection (that is, protection induced by vaccination in the vaccinated population sample).
 - a measure of the proportionate reduction in disease attack rate (AR) between the control group that did not receive vaccination against the infectious disease under study (ARU) and the vaccinated (ARV) group(s).
- **Vaccine effectiveness:** vaccine effectiveness is an estimate of the protection conferred by vaccination.
 - usually obtained by monitoring the disease to be prevented by the vaccine during routine use in a specific population.

Demonstration of Safety & Effectiveness of Preventive Vaccines

- Effectiveness:
 - “...all indications [e.g., prevention of disease]...must be supported by **substantial evidence** of effectiveness.”
- Demonstration of effectiveness is based on **adequate and well-controlled clinical studies** using a product that is
 - standardized as to identity, strength, quality, purity and dosage form.

Safety database considerations:

- Characteristics of the vaccine
- Safety signals or theoretical safety concerns
- Target population/ Intended use
- Seriousness of disease targeted for prevention

Dukoral (rBS-WC)



Shanchol and Euvichol (WC-only)



- Currently the vaccines available through the stockpile
- Used in mass vaccination campaigns
- Targeting people at risk age 1+

Now Approved!



Vaxchora™

Cholera Vaccine, Live, Oral

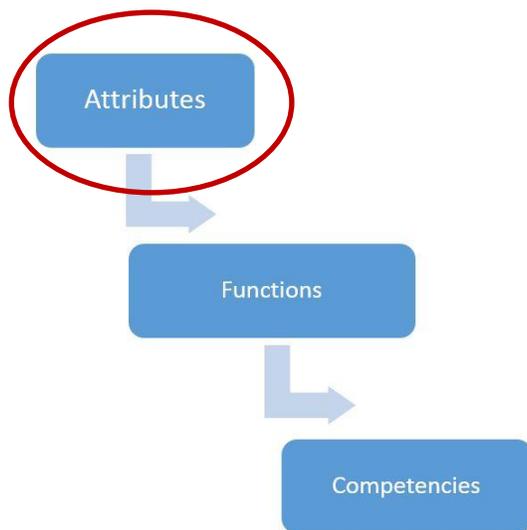
The only cholera vaccine
licensed for use in the US



Implementation research

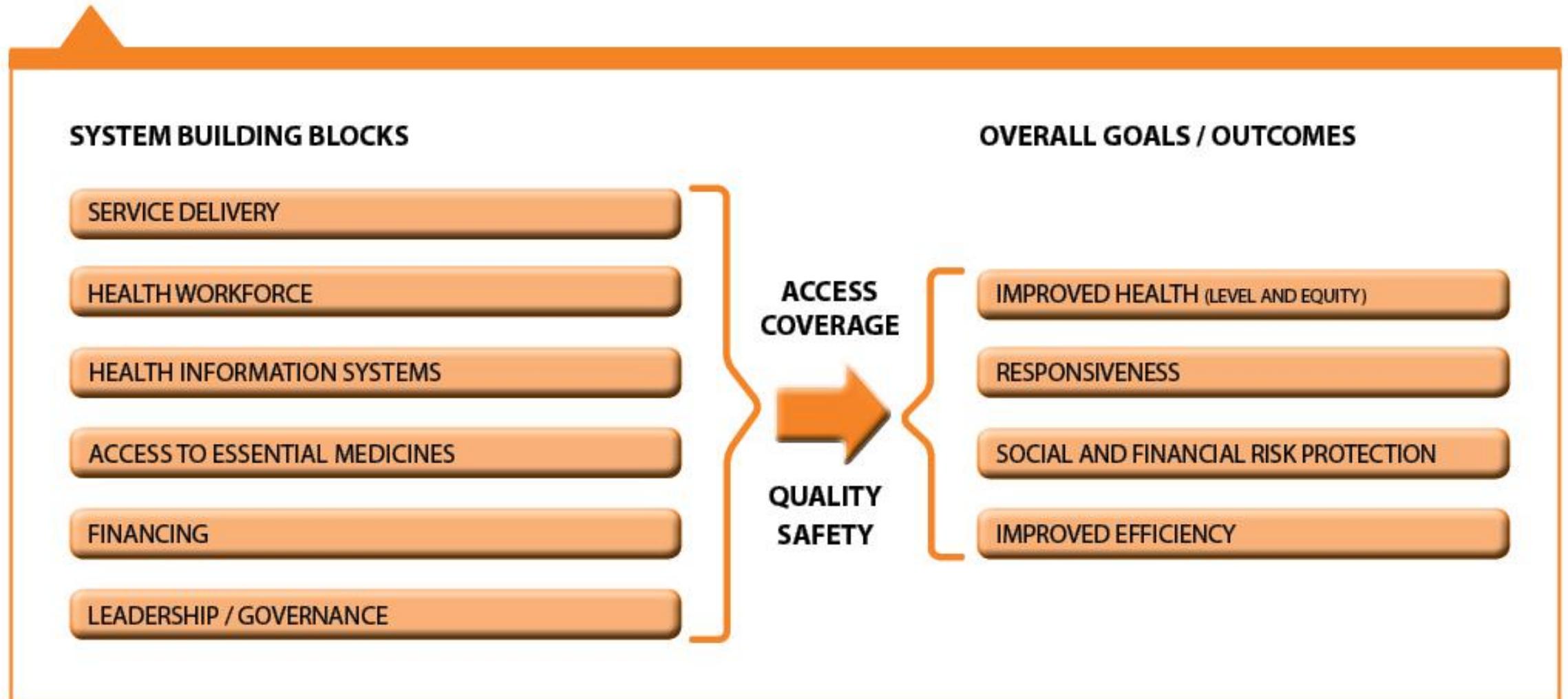
The Attributes of a Strong Immunization Program

The core functions and competencies are encompassed in 7 main technical and management areas:



Domain
1. Policy, Planning and Finance
2. Communications /Advocacy
3. Human Resources and Performance Management
4. Vaccines, supplies & logistics
5. Immunization and Injection Safety
6. Disease Surveillance and Response
7. Monitoring, Evaluation and Data Use

Figure 1. The WHO Health Systems Framework



Source: Reference c

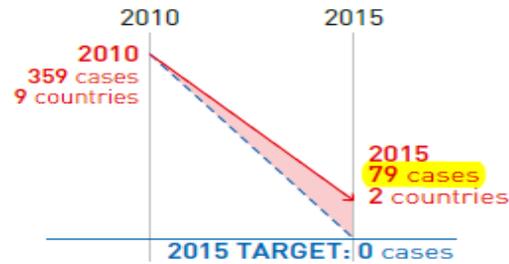


GVAP mid-term report: some progress, but too slow to achieve goals

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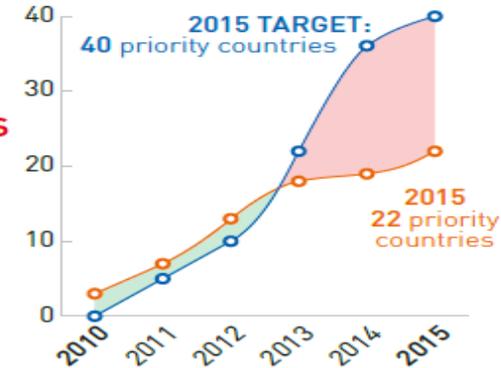
POLIO:

Number of new cases of paralytic poliomyelitis due to wild poliovirus



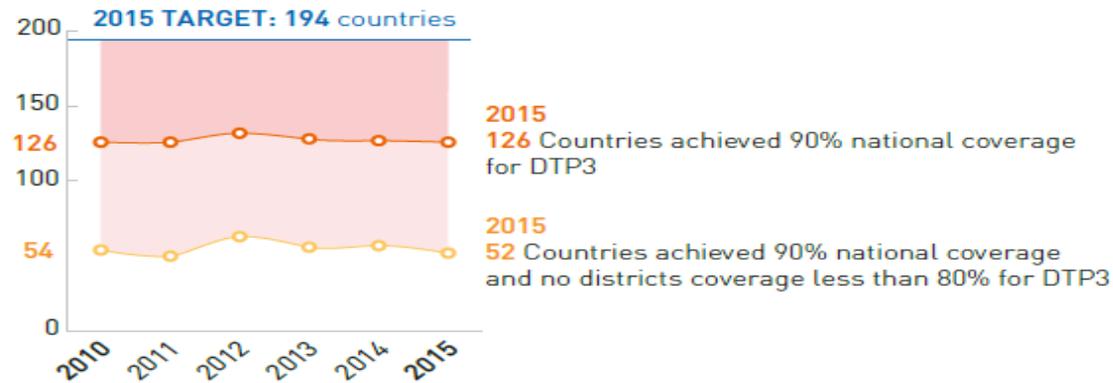
MATERNAL AND NEONATAL TETANUS ELIMINATION:

Number of countries verified for elimination



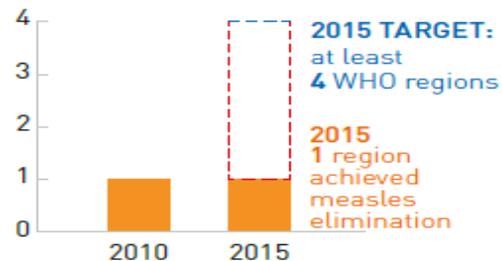
COVERAGE AND EQUITY:

Number of countries with national vaccination coverage of 90%, with no district's coverage less than 80%



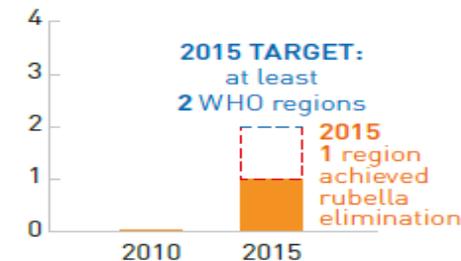
MEASLES:

Number of WHO regions to achieve measles elimination

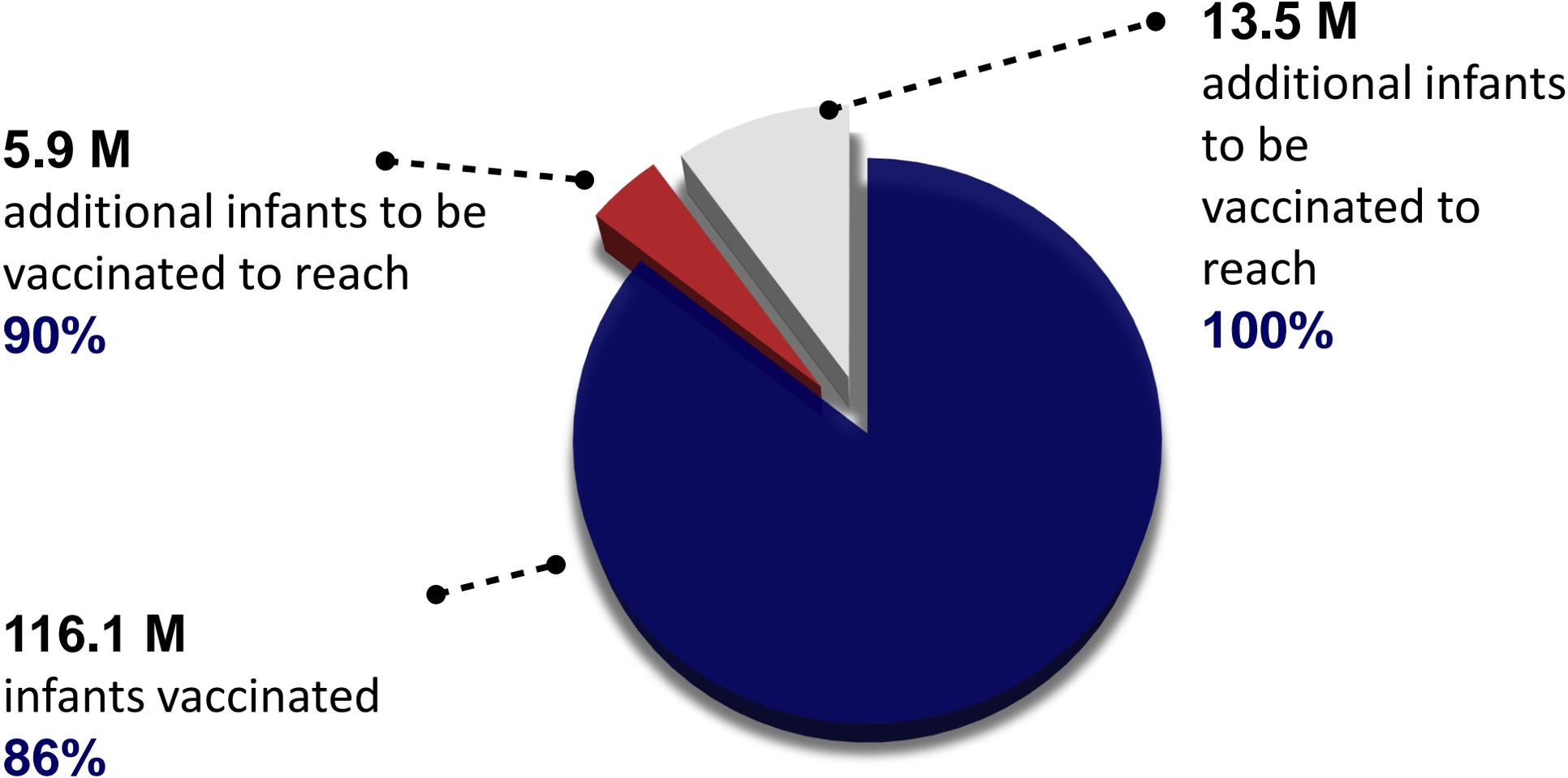


RUBELLA:

Number of WHO regions verified for rubella and CRS elimination



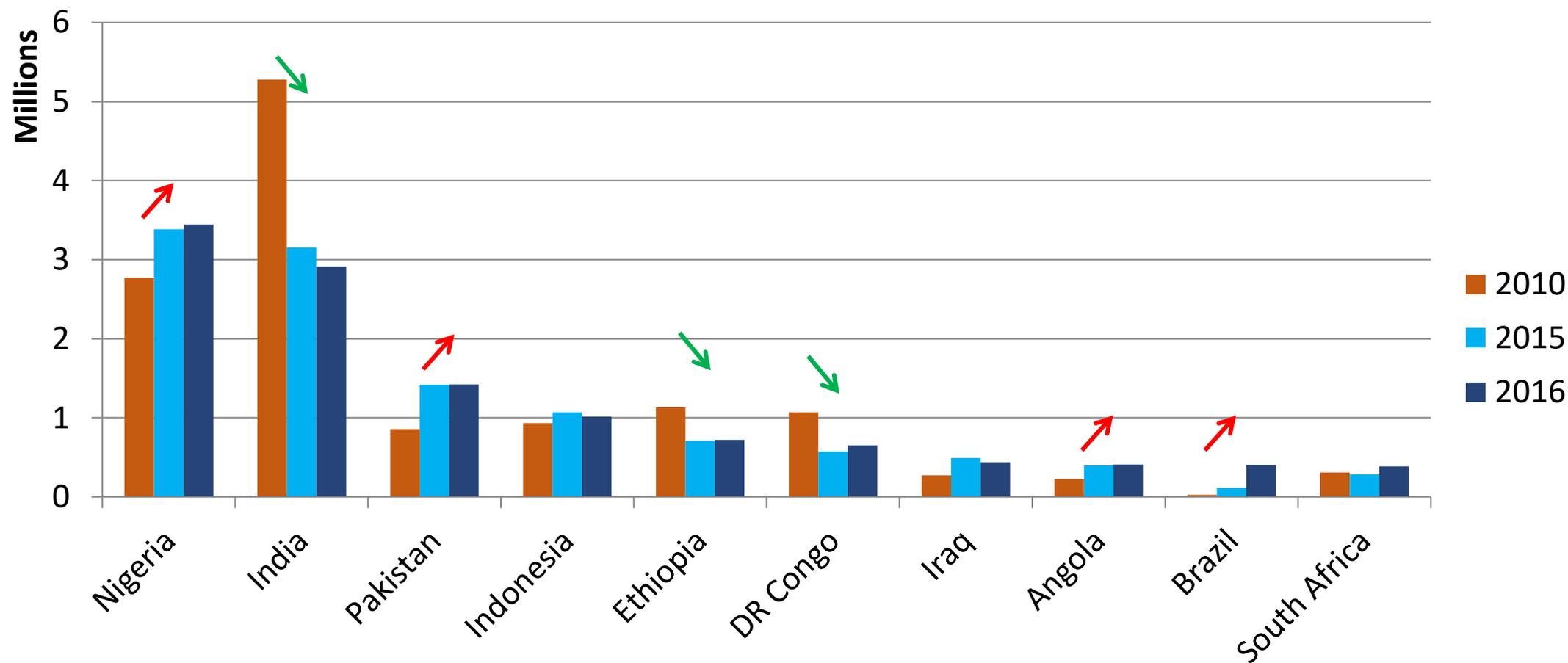
Infants in the world according to their DTP3 vaccination status, 2015



Source: JRF 194 WHO Member States. Updated on 18 July 2016

THE NUMBERS OF UNVACCINATED CHILDREN ARE FALLING IN SOME BUT NOT ALL LARGE COUNTRIES

Number of DTP3 unvaccinated children, top 10 countries



Mapping under-5 and neonatal mortality in Africa, 2000–15: a baseline analysis for the Sustainable Development Goals



Nick Golding, Roy Burstein*, Joshua Longbottom, Annie J Browne, Nancy Fullman, Aaron Osgood-Zimmerman, Lucas Earl, Samir Bhatt, Ewan Cameron, Daniel C Casey, Laura Dwyer-Lindgren, Tamer H Farag, Abraham D Flaxman, Maya S Fraser, Peter W Gething, Harry S Gibson, Nicholas Graetz, L Kendall Krause, Xie Rachel Kulikoff, Stephen S Lim, Bonnie Mappin, Chloe Morozoff, Robert C Reiner Jr, Amber Sligar, David L Smith, Haidong Wang, Daniel J Weiss, Christopher J L Murray, Catherine L Moyes, Simon I Hay*



Summary

Background During the Millennium Development Goal (MDG) era, many countries in Africa achieved marked reductions in under-5 and neonatal mortality. Yet the pace of progress toward these goals substantially varied at the national level, demonstrating an essential need for tracking even more local trends in child mortality. With the adoption of the Sustainable Development Goals (SDGs) in 2015, which established ambitious targets for improving child survival by 2030, optimal intervention planning and targeting will require understanding of trends and rates of progress at a higher spatial resolution. In this study, we aimed to generate high-resolution estimates of under-5 and neonatal all-cause mortality across 46 countries in Africa.

Lancet 2017; 390: 2171–82

Published Online

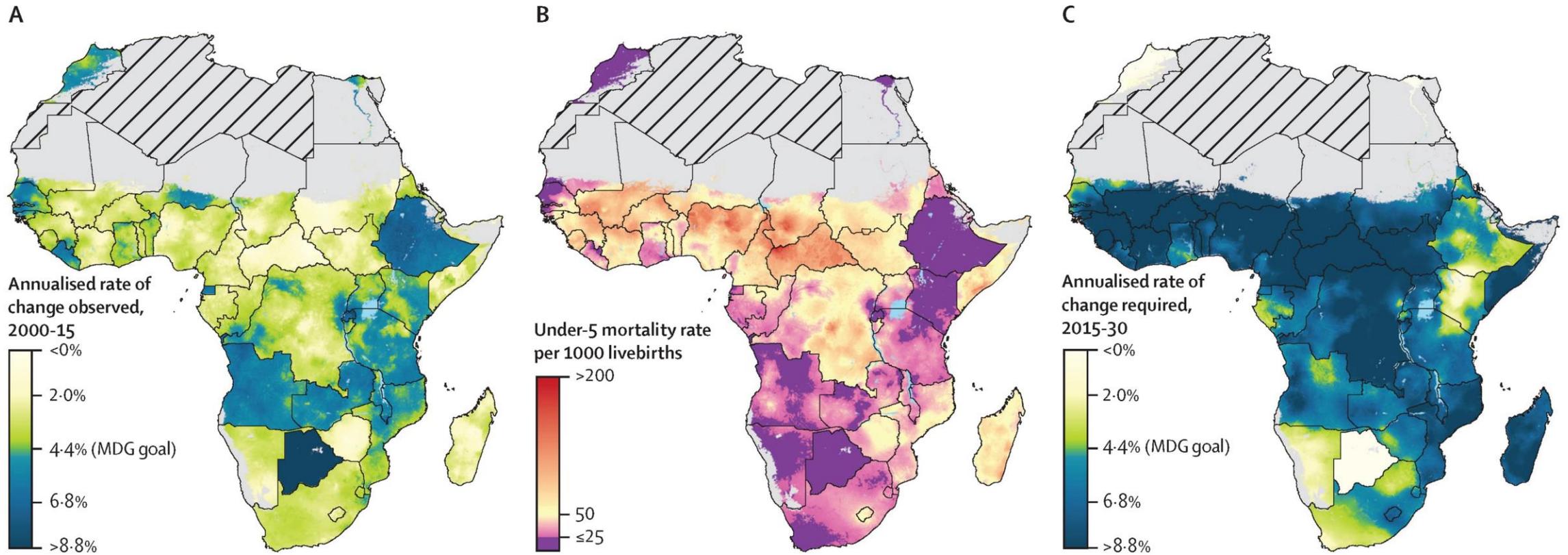
September 25, 2017

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S0140-6736(17)31758-0)

[S0140-6736\(17\)31758-0](http://dx.doi.org/10.1016/S0140-6736(17)31758-0)

See [Comment](#) page 2126

*These authors contributed equally

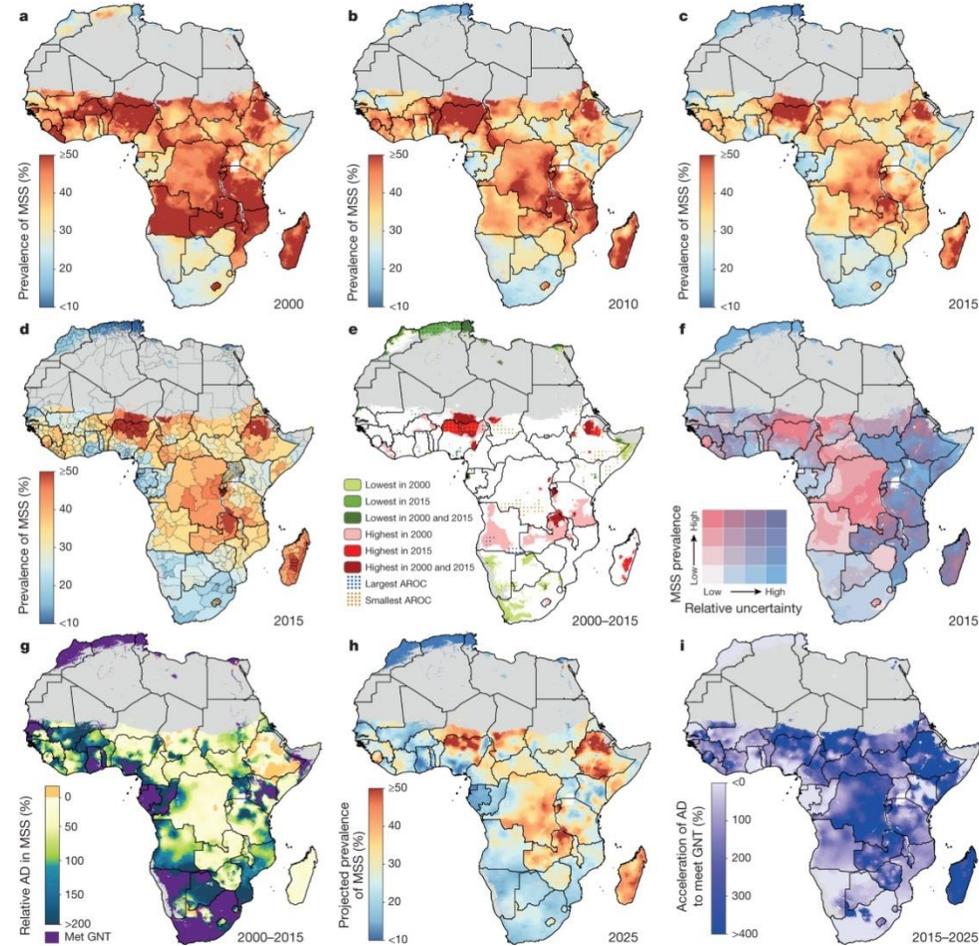


The Lancet 2017 390, 2171-2182 DOI: (10.1016/S0140-6736(17)31758-0)

Mapping child growth failure in Africa between 2000 and 2015

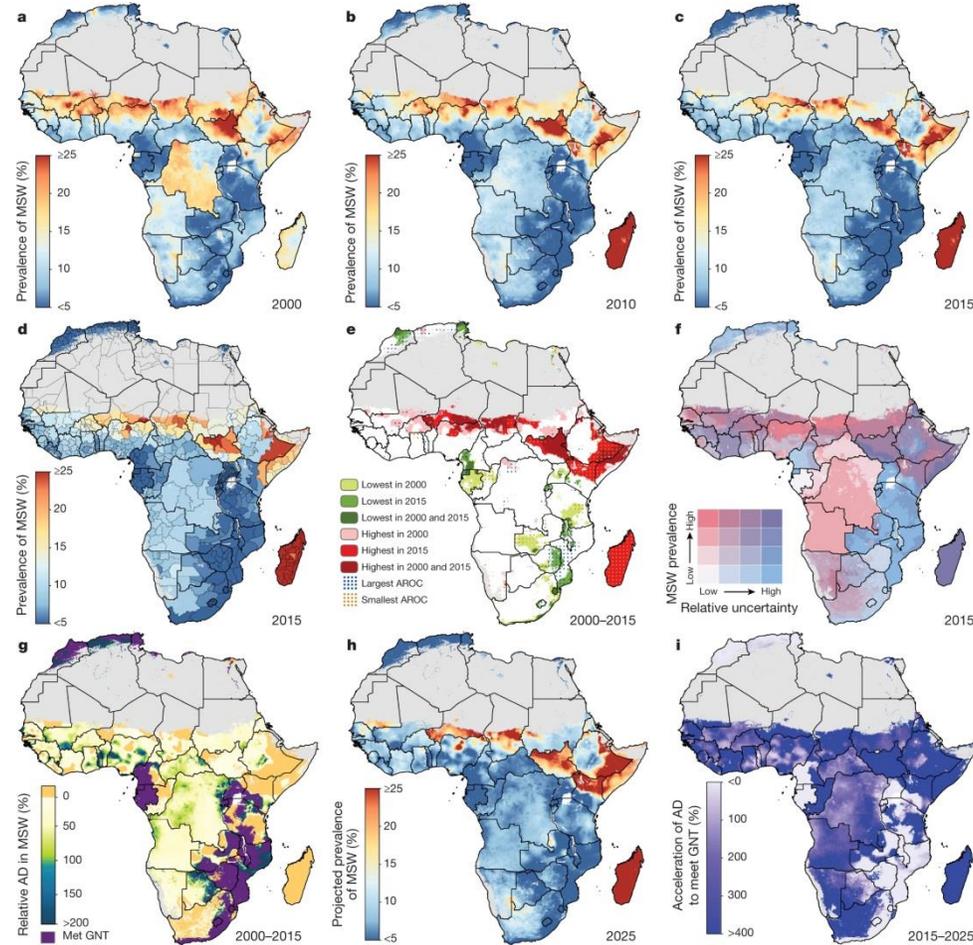
Aaron Osgood-Zimmerman^{1*}, Anoushka I. Millea^{1*}, Rebecca W. Stubbs¹, Chloe Shields¹, Brandon V. Pickering¹, Lucas Earl¹, Nicholas Graetz¹, Damaris K. Kinyoki¹, Sarah E. Ray¹, Samir Bhatt², Annie J. Browne³, Roy Burstein¹, Ewan Cameron³, Daniel C. Casey¹, Aniruddha Deshpande¹, Nancy Fullman¹, Peter W. Gething³, Harry S. Gibson³, Nathaniel J. Henry¹, Mario Herrero⁴, L. Kendall Krause⁵, Ian D. Letourneau¹, Aubrey J. Levine¹, Patrick Y. Liu¹, Joshua Longbottom³, Benjamin K. Mayala¹, Jonathan F. Mosser¹, Abdisalan M. Noor^{6,7}, David M. Pigott¹, Ellen G. Piwoz⁵, Puja Rao¹, Rahul Rawat⁵, Robert C. Reiner Jr¹, David L. Smith¹, Daniel J. Weiss³, Kirsten E. Wiens¹, Ali H. Mokdad¹, Stephen S. Lim¹, Christopher J. L. Murray¹, Nicholas J. Kassebaum^{1,8§} & Simon I. Hay^{1,3§}

Prevalence of stunting (2000–2015) in children under five and progress towards 2025



A Osgood-Zimmerman *et al. Nature* **555**, 41–47 (2018) doi:10.1038/nature25760

Wasting prevalence (2000–2015) in children under five and progress towards 2025



A Osgood-Zimmerman *et al. Nature* **555**, 41–47 (2018) doi:10.1038/nature25760



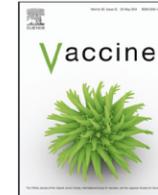




Contents lists available at [ScienceDirect](#)

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



The oral cholera vaccine Shanchol™ when stored at elevated temperatures maintains the safety and immunogenicity profile in Bangladeshi participants

Amit Saha^{a,b}, Arifuzzaman Khan^a, Umme Salma^a, Nusrat Jahan^a,
Taufiqur Rahman Bhuiyan^a, Fahima Chowdhury^a, Ashrafur Islam Khan^a,
Farhana Khanam^a, Sundaram Muruganandham^e, Sreeramulu Reddy Kandukuri^e,
Mandeep Singh Dhingra^e, John D. Clemens^{a,d}, Alejandro Cravioto^c, Firdausi Qadri^{a,*}



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Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh [☆]



Ashraful Islam Khan ^a, Mohammad Ali ^b, Fahima Chowdhury ^a, Amit Saha ^a, Iqbal Ansary Khan ^a, Arifuzzaman Khan ^a, Afroza Akter ^a, Muhammad Asaduzzaman ^a, Md. Taufiqul Islam ^a, Alamgir Kabir ^a, Young Ae You ^c, Nirod Chandra Saha ^a, Alejandro Cravioto ^d, John D. Clemens ^a, Firdausi Qadri ^{a,*}



Technical feasibility of microarray patch delivery of inactivated poliovirus, MR, HPV, pentavalent, pneumococcal, and rotavirus vaccines

Submitted to the Bill & Melinda Gates Foundation

August 7, 2017

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Seattle, WA 98109
USA

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Suite 200
Seattle, WA, USA

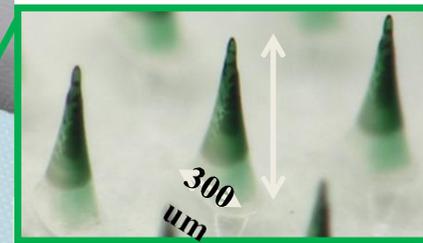
TEL: 206.285.3500
FAX: 206.285.6619
www.path.org



Emerging Vaccine Delivery Technology – Vaccine Patch



James L. Goodson, Centers for Disease Control and Prevention, Global Immunization Division



Potential game changer for Measles/Rubella elimination and eventual eradication





The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial

Nadine G Roupael, Michele Paine, Regina Mosley, Sebastien Henry, Devin V McAllister, Haripriya Kalluri, Winston Pewin, Paula M Frew, Tianwei Yu, Natalie J Thornburg, Sarah Kabbani, Lilin Lai, Elena V Vassilieva, Ioanna Skountzou, Richard W Compans, Mark J Mulligan, Mark R Prausnitz*, for the TIV-MNP 2015 Study Group†*

Summary

Background Microneedle patches provide an alternative to conventional needle-and-syringe immunisation, and potentially offer improved immunogenicity, simplicity, cost-effectiveness, acceptability, and safety. We describe safety, immunogenicity, and acceptability of the first-in-man study on single, dissolvable microneedle patch vaccination against influenza.

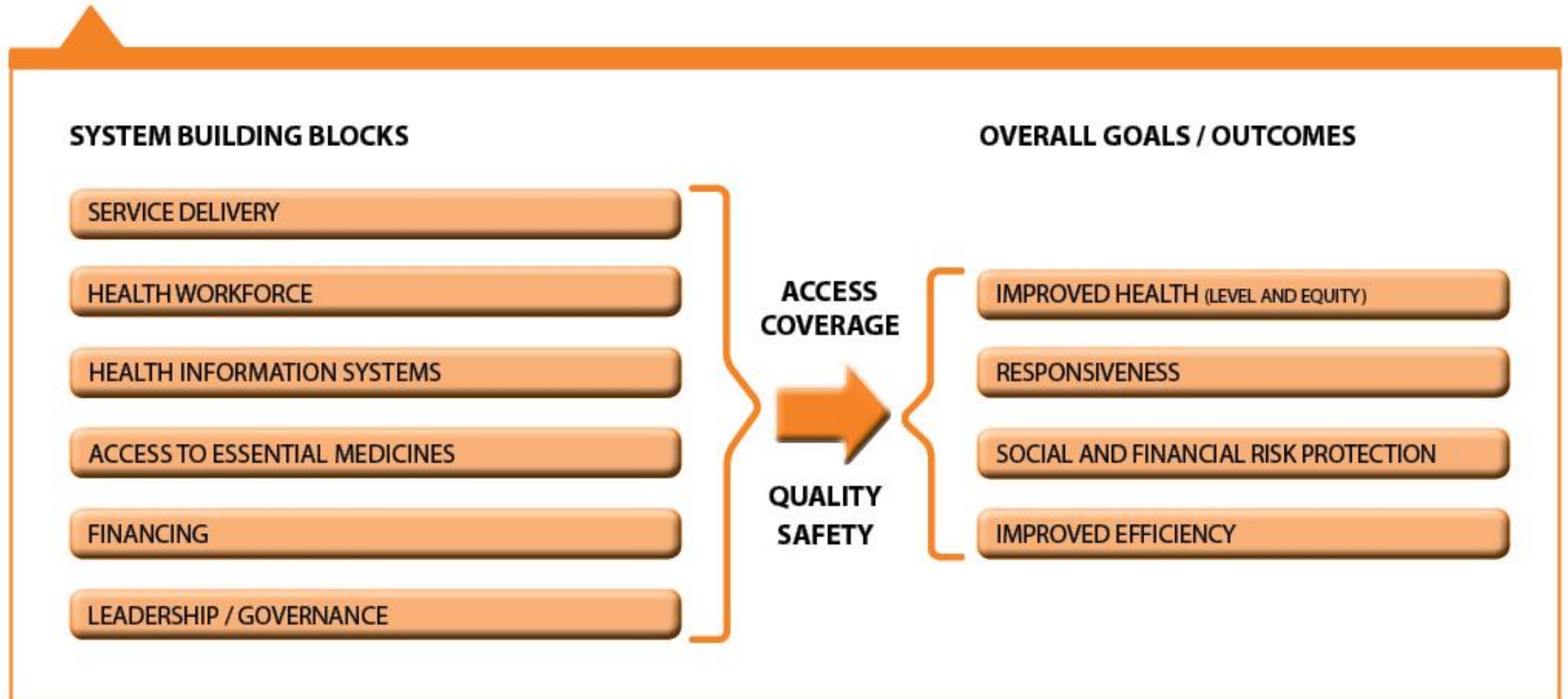
Published Online

June 27, 2017

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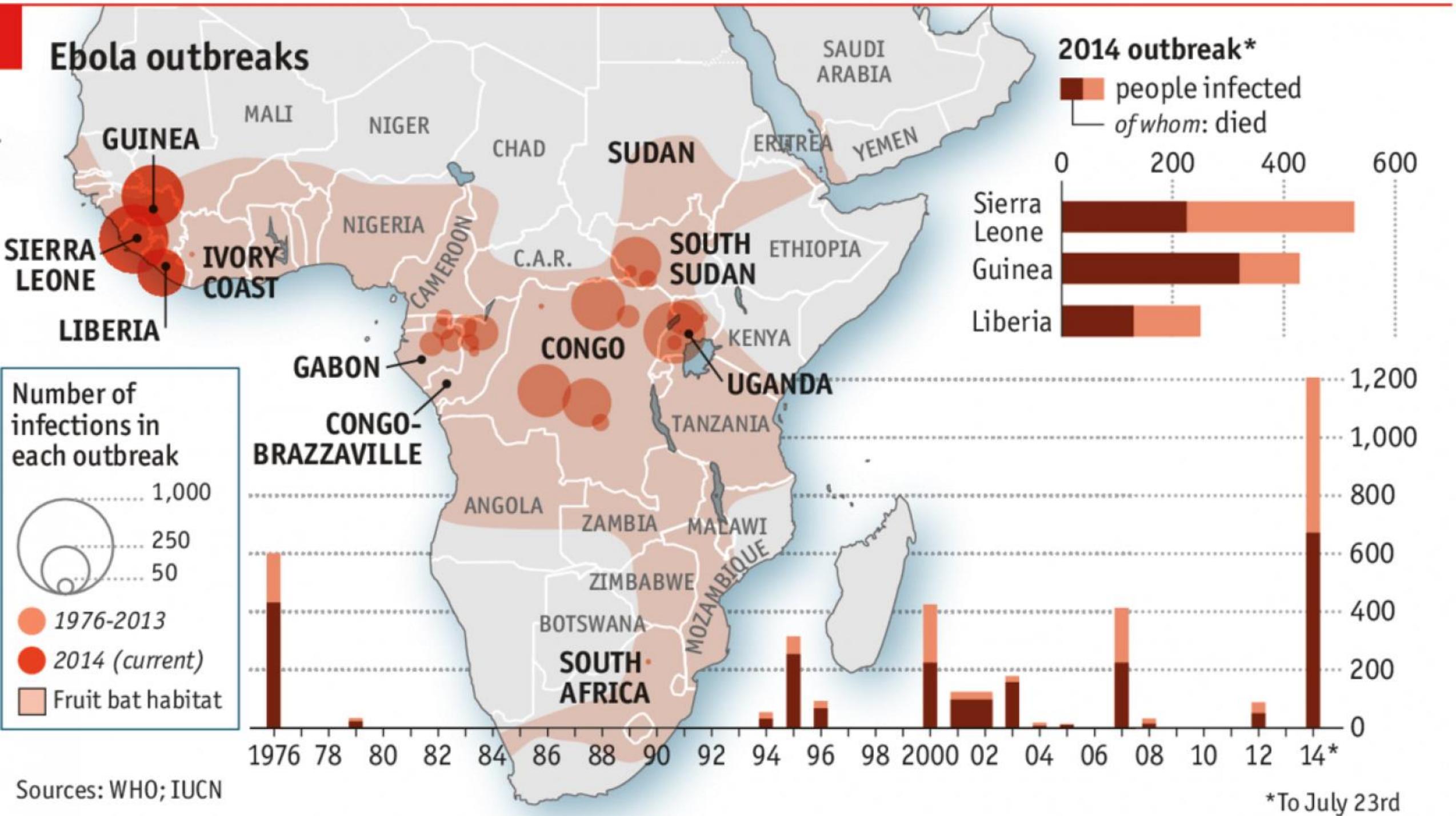
[See Online/Comment](#)

Figure 1. The WHO Health Systems Framework



Source: Reference c

Ebola outbreaks



Sources: WHO; IUCN

*To July 23rd



 World Health Organization
Organisation mondiale de la Santé

Our Children, da our Future
Vaccines help give children a
healthy start in life
ALL VACCINES are FREE and SAFE

LIBERIA
CRUSADERS FOR PEI

 World Health Organization
Organisation mondiale de la Santé





Mapping the burden of cholera in sub-Saharan Africa and implications for control: an analysis of data across geographical scales



Justin Lessler, Sean M Moore*, Francisco J Luquero, Heather S McKay, Rebecca Grais, Myriam Henkens, Martin Mengel, Jessica Dunoyer, Maurice M'bangombe, Elizabeth C Lee, Mamoudou Harouna Djingarey, Bertrand Sudre, Didier Bompangue, Robert S M Fraser, Abdinasir Abubakar, William Perea, Dominique Legros, Andrew S Azman*



Summary

Background Cholera remains a persistent health problem in sub-Saharan Africa and worldwide. Cholera can be controlled through appropriate water and sanitation, or by oral cholera vaccination, which provides transient (~3 years) protection, although vaccine supplies remain scarce. We aimed to map cholera burden in sub-Saharan Africa and assess how geographical targeting could lead to more efficient interventions.

Published **Online**

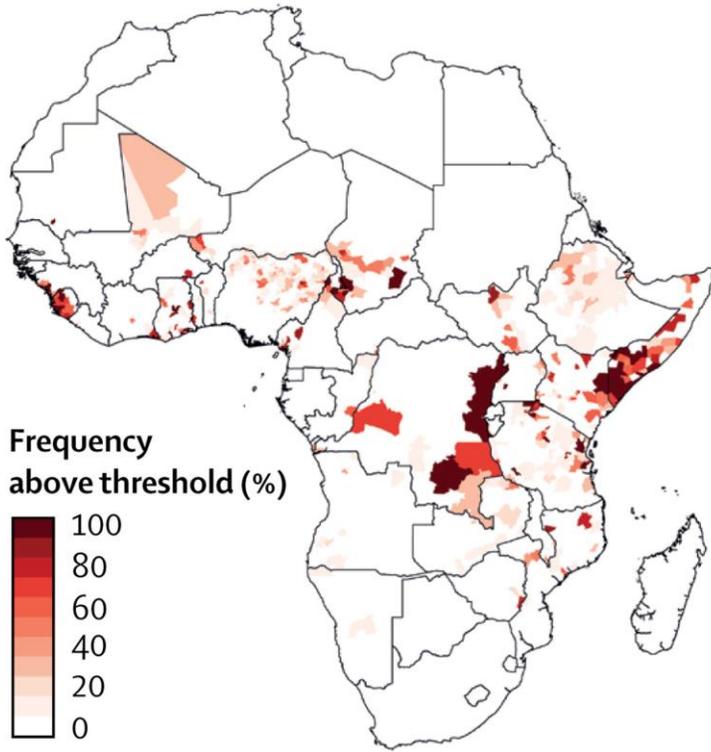
March 1, 2018

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S0140-6736(17)33050-7)

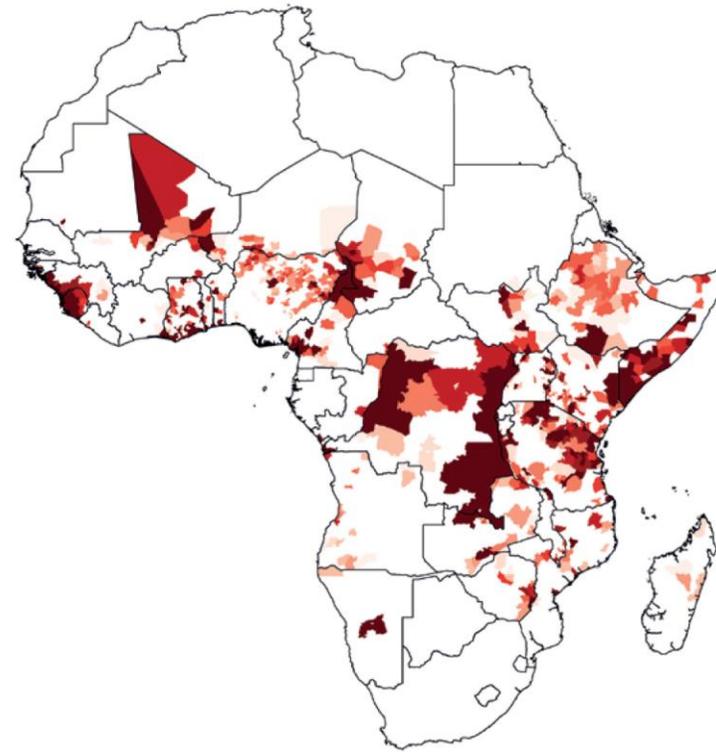
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[See Online/Comment](#)

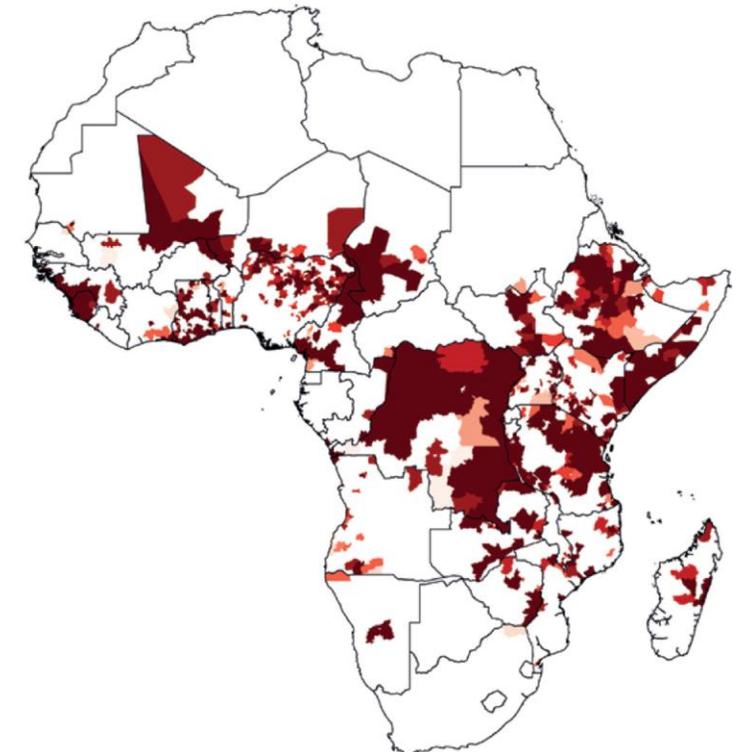
A Annual incidence >1 case per 1000 people



B Annual incidence >1 case per 10000 people

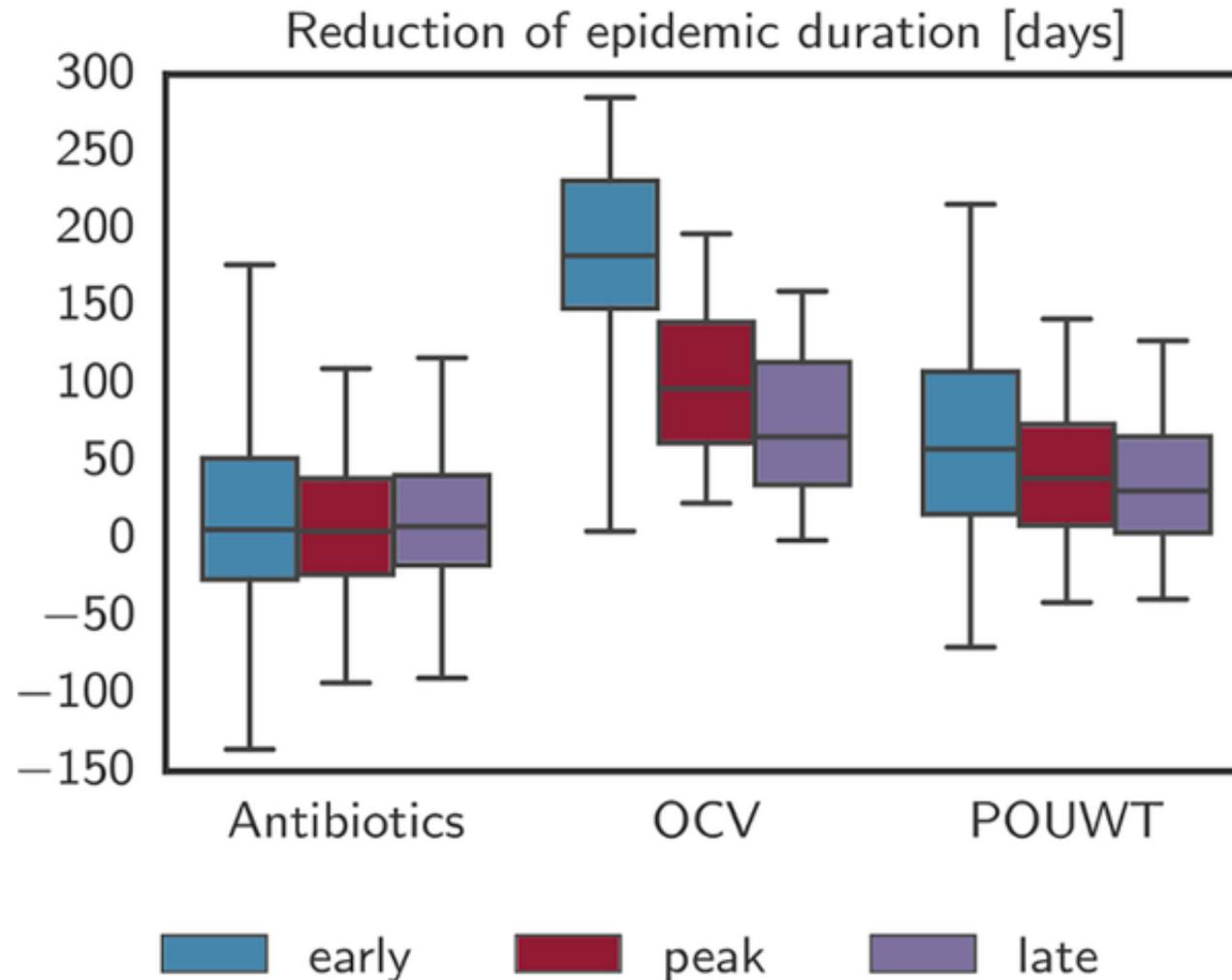


C Annual incidence >1 case per 100000 people

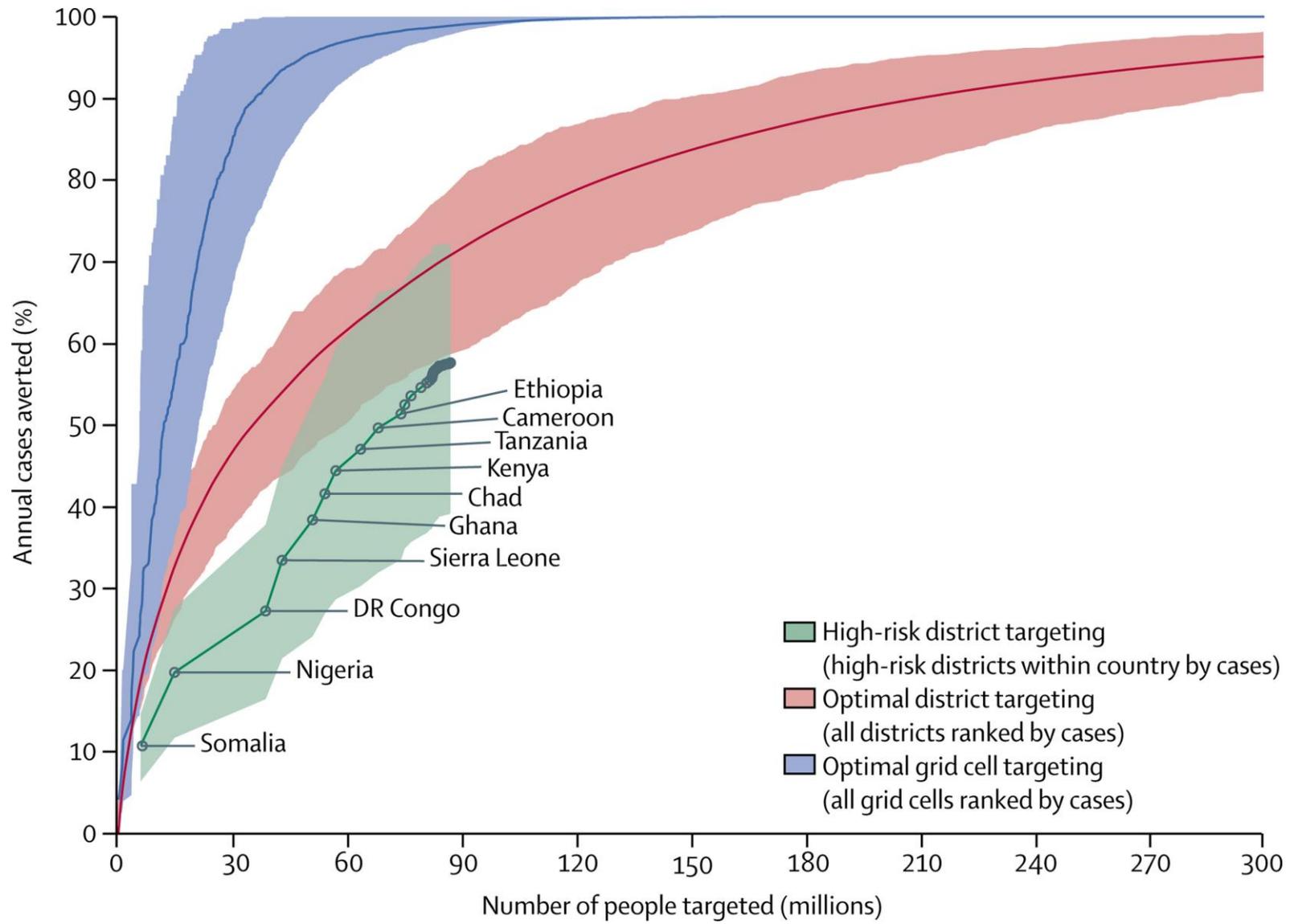


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Fig 4. Reduction of epidemic duration with case-area targeted interventions.



Finger F, Bertuzzo E, Luquero FJ, Naibei N, Touré B, et al. (2018) The potential impact of case-area targeted interventions in response to cholera outbreaks: A modeling study. *PLOS Medicine* 15(2): e1002509. <https://doi.org/10.1371/journal.pmed.1002509>
<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002509>



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Conference report

Estimating the full public health value of vaccination

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The brick wall: Moving from vaccines to vaccination

The brick wall

Traditional approach

- Candidate vaccines
- Clinical trial (phase III/IV)
- Efficacy
- Risk/safety (individual)
- Suitability (target population, regional variation, etc.)
- Cost-benefit analysis
- **Researchers/regulators**



The other side: FPHV of vaccination

- Post-licensure studies (safety, efficacy, effectiveness)
- Reduce disease incidence directly and indirectly by reducing transmission in population
- Reduce frequency and size of outbreaks
- Stabilize health systems
- Programmatic and health system impact
- Social and economic benefits
- Equity, access, affordability, acceptance
- **Recipients/communities**



