Beyond effectiveness: research on vaccines seen as a continuum

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Facultad de Medicina, Universidad Nacional Autónoma de México
Chair, Strategic Advisory Group of Experts (SAGE) on Immunization
World Health Organization

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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
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Merriam-Webster
Edward Jenner’s experiment (1796)

- Inoculate with cowpox
- Wait 2 months
- Inoculate with smallpox

Material from cowpox lesion of milkmaid

Village boy susceptible to smallpox

Child recovers from cowpox

Child does not develop smallpox
Measles vaccination averted 20 million measles deaths between 2000 and 2016

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
Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.
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

Source: Meningitis Vaccine Project
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 MNTE validated:
- Nepal 2005
- Bangladesh 2008
- Myanmar 2010
- Timor Leste 2012
- India phased manner 2003-15
- Indonesia phased manner 2010-16

Regional MNTE goal achieved May 2016
- Other countries succeeded prior to 2000

Source: WHO/UNICEF Joint Reporting Form (JRF)

Maya M. V. X. van den Ent.
### Numbers of deaths and cases of medical impoverishment averted by vaccines to be administered in 41 low- and middle-income countries, 2016–30

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

Edward Jenner’s experiment (1796)

- Material from cowpox lesion of milkmaid
- Inoculate with cowpox
- Village boy susceptible to smallpox
- Wait 2 months
- Child recovers from cowpox
- Inoculate with smallpox
- Child does not develop smallpox
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.

LONDON:

PRINTED, FOR THE AUTHOR,

BY SAMPHON LOW, NO. 7, BIRWICK STREET, S.DO;

AND SOLD BY LAW, AVEN-SAIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.
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 examen imparcial de sus ventajas, y de las objeciones que se le han puesto, con todo lo demás que concierne a 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 constituida 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 corresponsal de la Sociedad Médica de Burdeos, de la de Emulación de Abbeville y de Póltres, y de la Sociedad de Ciencias y Artes de Muna.

TRADUCIDO
POR EL DR. D. FRANCISCO XAVIER DE BALMES,
Fílósofo de Cámara de S. M., Historiador Consultor de Criología de las Reales Entidades, Profesor de Medicina, y Sube corresponsal de la Real Academia Médica de Madrid.

MADRID EN LA IMPRENTA REAL
AÑO DE 1803.
U.S. Licensure Pathways

Licensure

- Only those vaccines that are demonstrated to be safe and effective, and that can be manufactured in a consistent manner will be licensed by the FDA.

- “Traditional” approval
- Accelerated Approval*
- “Animal Rule” Approval*

- 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.
The process of developing a vaccine can be divided into several phases:

- **Research phase**: Identify antigens, produce antigens
  - Duration: 2–5 years

- **Early development phase**: Test in animals, Phase I safety PoC
  - Duration: 2–3 years

- **Late development phase**: Phase II dose safety, Phase III efficacy safety
  - Duration: 3–7 years

- **Registration phase**: File, License
  - Duration: 1–2 years

The total time from the start of research to the registration phase can range from 8 to 17 years.

- **Manufacturing quality control and CGMP production in dedicated facility**

The costs associated with each phase are as follows:

- Research phase: $10–20 million
- Early development phase: $50–100 million
- Late development phase: $500 million to 1 billion
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)

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

Shanchol and Euvichol (WC-only)

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

Vaxchora™ Cholera Vaccine, Live, Oral

Now Approved!
Implementation research
National immunization programme management: functions and competencies

The Attributes of a Strong Immunization Program

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

<table>
<thead>
<tr>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Policy, Planning and Finance</td>
</tr>
<tr>
<td>2. Communications / Advocacy</td>
</tr>
<tr>
<td>3. Human Resources and Performance Management</td>
</tr>
<tr>
<td>4. Vaccines, supplies &amp; logistics</td>
</tr>
<tr>
<td>5. Immunization and Injection Safety</td>
</tr>
<tr>
<td>6. Disease Surveillance and Response</td>
</tr>
<tr>
<td>7. Monitoring, Evaluation and Data Use</td>
</tr>
</tbody>
</table>
Figure 1. The WHO Health Systems Framework

SYSTEM BUILDING BLOCKS
- Service Delivery
- Health Workforce
- Health Information Systems
- Access to Essential Medicines
- Financing
- Leadership / Governance

OVERALL GOALS / OUTCOMES
- Improved Health (Level and Equity)
- Responsiveness
- Social and Financial Risk Protection
- Improved Efficiency

Source: Reference c
GVAP mid-term report: some progress, but too slow to achieve goals
Infants in the world according to their DTP3 vaccination status, 2015

- **116.1 M** infants vaccinated, 86%
- **5.9 M** additional infants to be vaccinated to reach 90%
- **13.5 M** additional infants to be vaccinated to reach 100%

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


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.

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Lancet 2017; 390: 2171–82

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September 25, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31758-0
See Comment page 2126

* These authors contributed equally
Mapping child growth failure in Africa between 2000 and 2015


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

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

Amit Saha¹,², Arifuzzaman Khan³, Umme Salma³, Nusrat Jahan³, Taufiqur Rahman Bhuiyan⁴, Fahima Chowdhury⁴, Ashraful Islam Khan⁴, Farhana Khanam⁴, Sundaram Muruganandham⁵, Sreeramulu Reddy Kandukuri⁵, Mandeep Singh Dhingra⁵, John D. Clemens¹,⁴, Alejandro Cravioto⁵, Firdausi Qadri¹,⁶
Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh

Ashraful Islam Khan, Mohammad Ali, Fahima Chowdhury, Amit Saha, Iqbal Ansary Khan, Arifuzzaman Khan, Afroza Akter, Muhammad Asaduzzaman, Md. Taufiquil Islam, Alamgir Kabir, Young Ae You, Nirod Chandra Saha, Alejandro Cravioto, John D. Clemens, Firdausi Qadri
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
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


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.
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**OVERALL GOALS / OUTCOMES**
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- Responsiveness
- Social and Financial Risk Protection
- Improved Efficiency

**Access Coverage**

**Quality Safety**

Source: Reference c
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.
Fig 4. Reduction of epidemic duration with case-area targeted interventions.

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002509
Conference report

Estimating the full public health value of vaccination

Bradford D. Gessner a,*,1,2, David Kaslow b, Jacques Louis c, Kathleen Neuzil d, Katherine L. O'Brien e, Valentina Picot c, Tikki Pang f, Umesh D. Parashar g, Mitra Saadatian-Elahi h, Christopher B. Nelson i

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iSanofi Pasteur, Vaccination Policy Department, 2 Avenue du Pont Pasteur, 69367 Lyon cedex 07, France
The brick wall: Moving from vaccines to vaccination

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

Source: Vaccine 35 (2017) 6255-6263
Thank you