CELEBRATING VACCINE VICTORIES

EPI AT 50

JOIN THE INTERNATIONAL VACCINE ACCESS CENTER (IVAC) FOR A WEBINAR WITH AN EXPERT PANEL DISCUSSING THE PAST, PRESENT AND FUTURE OF THE ESSENTIAL PROGRAMME ON IMMUNIZATION (EPI). A MODERATED Q&A SESSION WILL FOLLOW.

📅 25 April 2024
11am – 12pm ET

REGISTER NOW! bit.ly/3PJMJnVe
A Brief History of The Expanded Program on Immunization (EPI)*

Neal A. Halsey

* 2024: Essential Programme on Immunization
EPI was Established Because of the Successful Smallpox Eradication Program
Measles and Smallpox Eradication
Ghana 1970s

AL Rosenbloom. Used with permission.
Ralph (Rafe) Henderson
First Director of EPI

- Established:
  - Global management
  - Standardized assessments of coverage
  - Recommended schedule
  - Programs in all countries

DTP is the Backbone
EPI Founded in 1974

• WHO initially supported programs and personnel
• Estimated coverage DTP3 by 12 months
  • 1974: no good measure (~5%?)
  • 1980 ~20%
  • 1984 ~41%
  • 1989 ~75%

### EPI Immunization Schedule

**Established 1984**

<table>
<thead>
<tr>
<th>Age</th>
<th>Immunization(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>BCG, OPV (Endemic countries)</td>
</tr>
<tr>
<td>6 wks</td>
<td>DTP, OPV</td>
</tr>
<tr>
<td>10 wks</td>
<td>DTP, OPV</td>
</tr>
<tr>
<td>14 wks</td>
<td>DTP, OPV</td>
</tr>
<tr>
<td>9 months</td>
<td>Measles (Yellow Fever)</td>
</tr>
<tr>
<td>Women of Childbearing age</td>
<td>Tetanus Toxoid</td>
</tr>
</tbody>
</table>

Logistical issues in establishing EPI Clinics
Large Scale Transportation and Storage Issues Overcome

www.msf.ca

WHO EPI
Some Areas are Hard to Reach
Himalayan Region Pakistan

Aamir Khan
Adding Vaccines to EPI Programs

1976
1. TB (BCG)
2. Diphtheria
3. Tetanus
4. Pertussis
5. Polio - OPV
6. Measles
7. (Yellow Fever)

2024
1. Hepatitis B
2. *H. influenzae* type b (Hib)
3. Pneumococcal
4. Influenza-pregnant women
5. Polio-IPV
6. Rotavirus
7. HPV
8. Pneumococcal
9. (Rubella, Mumps)
10. (Meningococcal)
11. COVID-19
Coverage with DTP3 containing vaccines, by country income levels, 1980-2017


Income classification not available for: Cook Islands and Niue

Immunization Vaccines and Biologicals, (IVB), World Health Organization.
Global Vaccination coverage trendline

DTP-containing vaccine, 1st dose

89%

https://immunizationdata.who.int/
Adding Vaccines Creates New Challenges

*H. influenzae* type b (Hib)

Hib, 3rd dose

76%
Before Hib Initiative

IVAC Hib Initiative

Countries Using Hib Vaccine in their National Immunization Program (2014)

Routine Hib Implementation Status, March 2014

Yes
No

*Widespread coverage through the private market (≥50%)

Sources:
GAVI Alliance:
http://www.gavialliance.org/support/nvs/pentavalent/#
Combination Vaccines Have Helped

- DTP/Hib
- DTP/Hep B/Hib
- DTP/Hib/IPV
- Measles/Rubella
- Measles/Mumps/Rubella
Infants are Protected by Passively Acquired Tetanus Antibodies from Immune Mothers

2 doses TT in pregnancy

www.nlm.nih.gov
Neonatal Tetanus

Neonatal tetanus 2,098

Reported cases

2000 2022
17,935 2,098
All EPI Vaccines Save Lives

- Deaths averted and projected per year

Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world 2021; 10: e67635
Lives Saved From EPI Vaccines 2000–2030 in 112 Countries

- Estimated 50 million deaths averted between 2000 and 2019
- Projected 97 million deaths could be averted 2000–2030

Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world 2021; 10: e67635
EPI Became a Platform for Delivering Vitamin A Supplementation

Bednets to Prevent malaria
Kate O'Brien is the Director of the Department of Immunization, Vaccines and Biologicals at the World Health Organization (WHO). Previously she was the Executive Director of the International Vaccine Access Center (IVAC), and Professor of International Health and Epidemiology, at the Johns Hopkins Bloomberg School of Public Health. Dr O'Brien served on the WHO Strategic Advisory Group of Experts on Immunization (SAGE) committee from 2012 to 2018. Prior to joining IVAC, she served as the Director of Infectious Disease in the Johns Hopkins Center for American Indian Health. She also served as an Epidemic Intelligence Officer, in the Respiratory Diseases Branch, at the CDC, Atlanta (USA).

Dr O'Brien earned her BSc in Chemistry from the University of Toronto (Canada), her MD (Medicinae Doctorem) from McGill University, Montreal (Canada), and her Master of Public Health from Johns Hopkins Bloomberg School of Public Health, Baltimore (USA). She completed her paediatric and infectious disease clinical training at Johns Hopkins Medical Institutions, Baltimore (USA).
Rotavirus Vaccines

Dr. Mathuram Santosham
Professor, Departments of International Health & Pediatrics
Johns Hopkins University
## Etiology of gastroenteritis, Melbourne 1970s

### Table 1  Etiological gastroenteritis in children admitted to Royal Children’s Hospital, Melbourne

<table>
<thead>
<tr>
<th></th>
<th>1972</th>
<th>1974</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total admissions</td>
<td>539</td>
<td>378</td>
</tr>
<tr>
<td><em>Salmonella</em> sp.</td>
<td>39 (7.2%)</td>
<td>40 (10%)</td>
</tr>
<tr>
<td><em>Shigella</em> sp.</td>
<td>2 (0.4%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Pathogenic <em>E. coli</em></td>
<td>23 (4.3%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>475 (88%)</td>
<td>102 (29%)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>not tested</td>
<td>197 (52%)</td>
</tr>
<tr>
<td>Enteric adenovirus</td>
<td>not tested</td>
<td>27 (7%)</td>
</tr>
</tbody>
</table>

Causes of severe acute gastroenteritis among children <5 years before rotavirus vaccines

- Developed Countries
  - Rotavirus
  - Unknown
  - Bacterial
  - Other

- Developing Countries
  - Rotavirus
  - Unknown
  - Bacterial
  - Other

A. Kapikian, Fields Virology 2003
# Timeline of rotavirus vaccine development

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>RIT</td>
<td>Single bovine strain</td>
</tr>
<tr>
<td>1986</td>
<td>RRV</td>
<td>Single simian strain</td>
</tr>
<tr>
<td>1991</td>
<td>TRRV</td>
<td>Simian/human reassortant G₁ G₂ G₃ G₄</td>
</tr>
<tr>
<td>1999</td>
<td>Withdrawn</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Rotarix</td>
<td>Single human strain G₁ P(8)</td>
</tr>
<tr>
<td>2000</td>
<td>RotaTeq</td>
<td>Bovine/human reassortants G₁ G₂ G₃ G₄ P(8)</td>
</tr>
</tbody>
</table>

Rotavirus is a leading cause of death due to diarrhea in young children, and the leading cause among infants.

In the absence of vaccination, nearly every child is infected—rotavirus kills ~200,000 children and hospitalizes hundreds of thousands more each year.

- Number of children dying from rotavirus every day: >500
- Percent of under-5 diarrhea hospitalizations due to rotavirus, globally (2013): ~37%
- Percent of under-5 rotavirus deaths occurring in Gavi-eligible low-income countries (2013): >90%

Tate, CID, 2016. Slide courtesy of Molly Sauer.
Economic burden of rotavirus

Treating rotavirus diarrhea is expensive for families and countries

Inpatient admission for one episode of severe rotavirus diarrhea costs **10%** of the average family’s monthly income

Treating one episode of rotavirus diarrhea can amount to **85%** of the average family’s monthly income

Rotavirus hospitalization costs more than **25%** of the average family’s monthly income
Health system burden of rotavirus

Rotavirus hospitalizations can overwhelm health systems and facilities

1 in 8 admissions was due to AGE

54% of AGE admissions were due to rotavirus

Largest pediatric hospital in Bangladesh


1 in 4 cases requiring hospitalization was refused because of bed shortages

Rotavirus vaccines

First generation vaccines
- “Jennerian” approach
  - Naturally attenuated animal strains (bovine, rhesus)
- Variable performance
  - 80% efficacy in Finland but 0-30% efficacy in developing countries
- Best efficacy of rhesus vaccine (serotype G3) seen in Venezuela during G3 outbreak

Second generation vaccines
- “Modified Jennerian” approach
- Naturally attenuated animal strain as backbone
- Insertion of genes coding human G types by reassortment in cell culture
Intussusception (IS)

Intussusception

The telescoping of the intestine onto itself usually at the ileal-cecal junction, leading to reversible repair or entrapment with edema, necrosis and perforation.
Final chapter for Rotashield®

- US withdrew recommendation
- Without efficacy data from Asia and Africa, clinical trials needed
- Trials considered ethical, but political challenges of testing tainted vaccine
- Vaccine manufacture stopped
- Abrupt demise of first vaccine licensed after 20 years of research
# Today’s WHO-prequalified rotavirus vaccines

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Manufacturer</th>
<th>Dosing schedule</th>
<th>Formulation options</th>
<th>Efficacy against severe rotavirus gastroenteritis in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq®</td>
<td>Merck &amp; Co.</td>
<td>3 doses (same as DTP/penta 1, DTP/penta 2, DTP/penta 3)</td>
<td>Liquid ready-to-use</td>
<td>HIC / UMIC: 98-100%&lt;sup&gt;1,2&lt;/sup&gt; LMIC / LIC: 43-64%&lt;sup&gt;3,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>ROTARIX®</td>
<td>GSK</td>
<td>2 doses (same as DTP/penta 1, DTP/penta 2)</td>
<td>Liquid ready-to-use</td>
<td>HIC / UMIC: 85-96%&lt;sup&gt;5,6&lt;/sup&gt; LMIC / LIC: 49-77%&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>ROTAVAC® / ROTAVAC5D®</td>
<td>Bharat Biotech</td>
<td>3 doses (same as DTP/penta 1, DTP/penta 2, DTP/penta 3)</td>
<td>(1) Frozen (2) Liquid ready-to-use</td>
<td>No data</td>
</tr>
<tr>
<td>ROTASIIL®</td>
<td>Serum Institute of India</td>
<td>3 doses (same as DTP/penta 1, DTP/penta 2, DTP/penta 3)</td>
<td>(1) Lyophilized (2) Liquid ready-to-use</td>
<td>No data</td>
</tr>
</tbody>
</table>
# Impact of rotavirus vaccines

**Rotavirus diarrhea hospitalizations declined with routine rotavirus vaccine use**

<table>
<thead>
<tr>
<th>Country income level</th>
<th>Percent efficacious</th>
<th>Case prevented per 100 vaccinated infants</th>
</tr>
</thead>
</table>
| Low                  | 50%                 | ![Rotavirus positives in 4 countries with vaccine](chart)
| Middle               | 75%                 | ![Rotavirus positives in 3 countries without vaccine](chart)

Vaccines prevent more hospitalizations and deaths per population in low-income countries than they do in middle- and high-income countries.


Brazil and Mexico: Vaccination benefit versus risk

<table>
<thead>
<tr>
<th></th>
<th>Admissions per year</th>
<th>Deaths per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus events averted by</td>
<td>- 81,123</td>
<td>- 1,303</td>
</tr>
<tr>
<td>vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intussusception events</td>
<td>+ 118</td>
<td>+ 5</td>
</tr>
<tr>
<td>caused by vaccination*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit to risk comparison</td>
<td>687 to 1</td>
<td>261 to 1</td>
</tr>
</tbody>
</table>

* Source of background IS rates: Patel et al. Exp Rev Vacc; 2009; 8(11); assumes Rotarix coverage at current DTP3 rates; risk estimates from current study for week 1 after vaccination; with assumption of 5% case-fatality
“Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high rotavirus gastroenteritis-associated fatality rates, such as in South and South-eastern Asia and sub-Saharan Africa. …

The use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases with the scaling up of both prevention (promotion of early and exclusive breastfeeding, handwashing, improved water supply and sanitation) and treatment packages packages (low osmolarity ORS and zinc).”
Rotavirus Organization of Technical Allies (ROTA Council)

MISSION
To accelerate the introduction of rotavirus vaccines through the use of evidence and strategic communications targeting policymakers and other key decision makers.
Expert members and advisors

24 members from 16+ countries
The role of ROTA Council

- **Communicating** the burden of rotavirus and need for prevention
- **Delivering** accurate information on vaccine safety and efficacy, underscoring the availability, affordability and life-saving, health-improving potential of vaccines
- **Serving** as an independent body for the latest evidence on rotavirus vaccines
- **Working** to ensure that vaccines are seen as part of a comprehensive approach to addressing all of diarrhea’s causes
Rotavirus vaccine coverage (2010)
Rotavirus vaccine coverage (2012)
Rotavirus vaccine coverage (2022)
Progress, challenges, and opportunities

- RVV landscape has drastically expanded from just 7 years ago when just two vaccines were available to countries.

- Interchangeability and vaccine switches
  - Elective switches may improve suitability for a specific context and reduce costs.
  - Compulsory switches can interrupt RVV programs, strain resources, and may not necessarily be best-suited options for the specific setting.

- 120+ countries use RVV in their national immunization programs yet 36.2 million children still lack access to RVV.

- 140,000 deaths prevented from 2006 to 2019.

- Global supply challenges and withdrawals lead to stockouts, missed doses, and coverage gaps disproportionately affecting Gavi-eligible countries.

- Prioritizing rotavirus vaccines in the remaining countries — and sustaining existing programs — remains critical.
Rota team over the years

Tyler Best, Amelia Gerste, Kelly Healy, Kirthini Muralidharan, Nicole Obe, Debora Sandiford, Molly Sauer, Rose Weeks
April 25, 2024

Success Story: Pneumococcal Conjugate Vaccines

Maria Deloria Knoll, PhD
Research Professor
Pneumococcal Disease

Pneumococcus causes severe pneumonia, meningitis and sepsis

Responsible for 37% of child pneumonia deaths (pre-vaccine era)

Annually >600,000 deaths and >5 million cases in children <5 years of age globally (pre-vaccine)

100+ different strains (serotypes) but most (~80%) severe disease is caused by <20 serotypes
Pneumococcal Conjugate Vaccine (PCV)

First PCVs licensed in high-income country in 2000 - highly effective & very safe

Protected against 7 of 100+ serotypes responsible for 50-80% of severe disease

10- and 13-valent PCVs licensed in 2009/10 (protect against 70-90% of disease)

15- and 20-valent PCVs licensed in 2023/24
PCVs prevented 90% of invasive pneumococcal disease (IPD) in children <5 years old, USA

Pneumococcal Conjugate Vaccine (PCV) prevented 310,000 cases & 22,000 deaths between 2000-2016 in USA

Source: CDC, Emerging Infections Program, Active Bacterial Core surveillance, https://www.cdc.gov/pneumococcal/surveillance.html
Low-income countries had access to PCV decades sooner

IVAC’s PneumoADIP project (funded by Gavi) accelerated access to PCV in low-income countries

Source: www.VIEW-Hub.org
Low-income countries had access to PCV before some high-income countries

IVAC’s PneumoADIP project (funded by Gavi) accelerated access to PCV in low-income countries

Source: www.VIEW-Hub.org
Currently all Gavi countries and 93% of countries worldwide have introduced PCV or are planning introduction.
Global impact of PCV on invasive pneumococcal disease (IPD)

PCV10-type IPD in Children <5 years

Incidence Rate Ratio

Pre-PCV Rate
96% decline

Year since PCV10/13 introduction

PCV10/13 Intro

PCV10/13 Impact

Substantial
Moderate
No use

Post-PCV10/13 IPD

73% Non-vaccine-type

All IPD declined 58-74%

Source: PSERENADE
40 country study
Bennett & Deloria
Knoll, et al. Lancet PREPRINT 2024
Infant PCV program reduced invasive pneumococcal disease (IPD) in all ages

PCV10-type IPD in Adults 65+ Years

54-96% decline

PCV10/13

Adults 65+ years

PCV13

PCV10

PCV7 Impact

- Substantial
- Moderate
- No use

Source: PSERENADE
40 country study
Bennett & Deloria Knoll, et al. Lancet PREPRINT 2024
New PCVs coming to address much remaining pneumococcal disease

Serotypes covered by current and anticipated new PCVs

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>PRODUCT</th>
<th>SEROTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed PCV7 (7v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV10 (10v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV13 (13v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV15 (15v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV20 (20v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV24 (24v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV25 (25v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licensed PCV21 (21v)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coming PCV26 (26v)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCV7 replaced by PCV13

Remaining IPD covered by current and anticipated new PCVs in children <5 years

Post-PCV10/13 IPD

73% Non-PCV10/13-type

Source: PSERENADE 40 country study

Garcia Quesada, et al. Lancet PREPRINT 2024
Remaining challenges

Global WUENIC coverage 2022

Other challenges:
- 20% of children in countries without access
- Remaining non-vaccine type IPD, which increased (“replacement disease”)
- Limited suppliers for low-income markets
- Some higher valency PCVs not affordable for LMICs
Most countries have introduced PCVs → disease declining

PCVs reduce transmission → prevent disease in unvaccinated children & adults

Multiple vaccine manufacturers, including DCVM → good supply

New PCVs could prevent even more disease, but increasing coverage more impactful

LMICs need access to higher valency PCVs
HPV vaccines and impact (introduction into the EPI schedule, and IVAC’s role)

Presented by Dr. Chizoba Wonodi, MBBS, MPH, DrPH,
The Human Papillomavirus (HPV)

- HPV infection is a common sexually transmitted infection in men and women.
- There are over 100 types of HPV, 12 of these are high risk (cancer causing).
- HPV infection resolves spontaneously in most people.
- However, in some people, persistent infection can lead to skin and oral warts and orogenital cancers in both men and women.
- HPV causes nearly all cervical cancers.
Cervical cancers is a major public health and equity challenge

Age-standardized (World) incidence and mortality rates of cervical cancer, both sexes, per region

- Huge regional disparity in burden
  - (>40 per 100,000)
  - (<3 per 100,000)

About 4.5% of all cancers worldwide (630,000 new cancer cases per year) are attributable to HPV: 8.6% in women and 0.8% in men

- About 90% of deaths from cervical cancer occurred in low- and middle-income countries [1].

The WHO Strategy for cervical cancer elimination

By 2030, 90% of girls should be fully vaccinated with HPV vaccine at 15 years of age.

70% of women should be screened using a high-performance test by age 35, and again by age 45.

90% of those identified with cervical disease should receive appropriate treatment.
WHO position paper on HPV vaccinations

- Six licensed HPV vaccines: three bivalent, two quadrivalent, and one nonavalent vaccine.
- All vaccines are highly efficacious in preventing infection with virus types 16 and 18, which are together responsible for approximately 70% of cervical cancer cases globally.
- Highly efficacious in preventing precancerous cervical lesions caused by these virus types.
- The quadrivalent vaccine is also highly efficacious in preventing anogenital warts, a common genital disease which is virtually always caused by infection with HPV types 6 and 11.
- The nonavalent provides additional protection against HPV types 31, 33, 45, 52 and 58.
- Data from clinical trials and initial post-marketing surveillance conducted in several continents show HPV vaccines to be safe.
- The primary target group in most of the countries recommending HPV vaccination is young adolescent girls, aged 9-14. For all vaccines, the vaccination schedule depends on the age of the vaccine recipient.

HPV vaccines is one of the most cost-effective vaccines


Global introduction map

WHO recommended schedule

Girls 9-14 years
• One or two dose schedule

Girls 15-20 years
• One or two dose schedule

Women older than 21 years
• Two doses with a 6-month interval

A minimum of 2 doses and when feasible 3-doses remain necessary for those known to be immunocompromised and/or HIV-infected.
HPV Revitalization Programs- Global focus

• Gavi alongside other stakeholders are working to
  * accelerate quality HPV vaccine introductions; (2)
  * rapidly improve global and national coverage; and
  * generate long-term programmatic sustainability through integration and optimizing whole-of-family services.
IVAC is supporting the HPV vaccine roll out in Nigeria

The Johns Hopkins International Vaccine Access Centre (IVAC) with funding from Gavi, is working with Direct Consulting and Logistics (DCL) to support the Nigeria with the HPV vaccine roll out in Nigeria.

IVAC has trained and equipped > 200 CSOs and young people across 37 states to support demand generation for the HPV vaccine introduction.

The CSOs and youths have in turn activated more than 2,000 community-based vaccine champions.

IVAC is a member of the national HPV technical working group and provides technical assistance.
HPV Vaccination Rate Using MAC Campaign Targets (80% of TP). Data as of Feb 6th

Cumulative Coverage By Age Cohort

Source: NPHCDA
In summary

• HPV is a major cause of cervical and other anogenital cancers globally, with 90% of deaths occurring in low- and middle-income countries.

• Despite the vaccine's introduction in over 137 countries, global coverage stands at 21%. Efforts to optimize coverage include school-based campaigns and catch-up initiatives.

• Challenges include access, affordability, and misinformation.

• IVAC supports countries with technical assistance, advocacy, and capacity building to improve coverage and address challenges.
Thank you