Vaccines for Adults and the Elderly: Antinomy and Apologia

Gregory A. Poland, MD, MACP
Mary Lowell Leary Emeritus Professor of Medicine
Distinguished Mayo Investigator
Director, Mayo Vaccine Research Group
Editor-in-Chief, VACCINE
Mayo Clinic, Rochester, MN
The Charge

• Review specific childhood vaccines that can be recommended for adults and the elderly
  • Varicella, DTP, MMR, shingles
  • Exclude influenza, pneum, RSV, Hib, Hep A/B

• Review vaccine performance in this age group

• Review available data from LMICs

• Identify critical data gaps

“Language is conceived in sin and science is its redemption”
(Willard van Orman Quine)
FIGURE 1: Number of Elderly, as a Percent of the Population

<table>
<thead>
<tr>
<th>Country</th>
<th>2000</th>
<th>2040</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>16.3%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Australia</td>
<td>16.6%</td>
<td>30.1%</td>
</tr>
<tr>
<td>Canada</td>
<td>17.0%</td>
<td>33.3%</td>
</tr>
<tr>
<td>UK</td>
<td>20.8%</td>
<td>33.9%</td>
</tr>
<tr>
<td>France</td>
<td>20.6%</td>
<td>35.0%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>18.5%</td>
<td>35.5%</td>
</tr>
<tr>
<td>Belgium</td>
<td>22.2%</td>
<td>36.1%</td>
</tr>
<tr>
<td>Germany</td>
<td>23.5%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Sweden</td>
<td>22.8%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Japan</td>
<td>23.9%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Spain</td>
<td>22.0%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Italy</td>
<td>24.4%</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

Elderly are aged 60 and over
Silver Tsunami – India

- Population of persons > 60 y/o in India alone:
  - Year          Numbers > 60 y/o
  - 2021          133 million
  - 2031          179 million
  - 2041          236 million
  - 2051          301 million

Ministry of Statistics and Programme Implementation, Government of India, 2011
Vaccination – Economic Impact

• Clean water, sanitation and vaccines have substantially improved human health and longevity (CDC)

• The common childhood vaccines are generally very cost–effective, often with CE ratios in the 1:5 – 1:21 range

• Far fewer data for CE in adults, fewer–no data for adults in LMICs
Benefits/Impact of Vaccines

• Health–related benefits
  • Health gains (reduction in M&M)
  • Health care savings (reduction in health care costs)

• Productivity–related benefit
  • Short– and long–term
  • Household behavior

• Community–related benefits
  • Ecological effects (indirect protection)
  • Financial benefits
  • Macroeconomic impact (across generations, across nations, etc.)
Economics, Briefly

- MMR, DPT are “1st wave” vaccines that are low cost (<$1/dose), cost-saving, avert M&M and costs associated with treatment
- Varicella, HZ are more expensive and less obviously “cost-saving” depending upon a number of considerations
- 3 companies have 70% of the global vaccine market, with > $24B in sales*

*Angelmar R et al. Vaccine Marketing 2014; Springer
Adult Immunization—Our Antinomy

- Competition with childhood programs
- Little in the way of any adult vaccine financing systems in LMICs
- A rapidly approaching “silver tsunami”
- Inadequate vaccines in the setting of immunosenescence
- The tyranny of the “status quo” and the trap of premature cognitive narrowing
Significant Research and Data Gaps

- Varying vaccine types and preparations
- Varying national and sub-national public health epi infrastructure
- Varying disease reporting requirements
- Varying criteria for disease diagnosis
- Varying vaccine programs, schedules, and recommendations
- Inadequate data on burden of disease in LMICs – especially in adults
- Inadequate CE studies in LMICs – essentially none for adults
- Scant data on use of *childhood* vaccines in adults
4 Vaccines – 8 Diseases

- DTP
- MMR
- Chickenpox
- Shingles

The above diseases are occurring in a highly dynamic politico-social setting of trans-national immigration and human mobility unprecedented in human history – nearly all from countries with suboptimal vaccination rates.
Diphtheria

- *Corynebacterium diphtheriae*
  - Membraneous nasopharyngitis
  - Obstructive laryngotracheitis
  - Cutaneous, vaginal, conjunctival, otic infections
  - Myocarditis
  - Peripheral neuropathy

- CFR as high as 10%, but higher in those >40 y/o

- Preventing disease in adults
  - Decennial Td dose
Diphtheria– Tetanus – Pertussis

- DTwP
- DTaP
  - Diphtheria Lf units 7–10x than TdaP
  - PT content 4–10x higher than TdaP
  - Somewhat higher FH and Pct content than TdaP
- TdaP
- DT (< 6 yrs) 10x the Diph content compared to Td
- Td (> 7 yrs)
- In healthy people, a primary series induces essentially 100% develop protective Ab levels
Baseline Diph and Tet Ab – Spain

- Seroprevalence study 1995–1998
  - Adults 18–30 y/o (n=201)
    - Tetanus Ab: 90.5%
    - Diphtheria Ab: 38.3%
  - Adults > 45 y/o (n=147)
    - Tetanus Ab: 30.6%
    - Diphtheria Ab: 19.0%
- Finding: *high levels of disease susceptibility*

Epidemiol Infect 2001;127:451-460
Diphtheria

- Seroepidemiology study – age 1 mo – 85 yrs throughout Poland (n=1,387)
- Seroprevalence of non-protective Ab levels:
  - > 18 y/o: 40.5%
  - 56% had borderline protective levels of Ab
  - 67% of persons > 60 y/o were seronegative

BMC Infect Dis 2013;13:551
Seroepidemiology – Tajikistan

• 2010 study – stratified random cluster study – age 1–24 yrs (n=2,582)

• Results:
  • 51.4% seroprotective Ab for diphtheria
  • 79% seroprotective Ab for tetanus
  • Among persons 15–19 y/o:
    • Tetanus Ab – 65.3%
    • Diphtheria Ab – 70.1%

Vaccine 2013;31:4917-4922
Vaccine Efficacy – Diphtheria

• No controlled clinical efficacy trial ever done

• Multiple observational studies demonstrating excellent immunogenicity and effectiveness for 3 or more doses

• No study has demonstrated 100% effectiveness (54% – 98% in field studies)

• Herd immunity important

• Primary series, booster at school entry, and boosters every 10 years throughout life appear to be necessary
Data Gaps

- Surveillance for disease burden
- Surveillance studies for circulating toxigenic strains
- Frequency of boosters in different settings
  - Low circulation of toxigenic strains
  - High circulation of toxigenic strains
- Cost–benefit studies in adults, elderly and in LMIC’s missing
Tetanus – “The Inexcusable Disease”

- *Clostridium tetani*
  - Generalized tetanus
  - Neonatal tetanus
  - Localized tetanus
  - Cephalic tetanus

- CFR approx. 10% – morbidity a major problem

- Preventing disease in adults
  - 3 dose primary series, then decennial boosters
  - Booster for dirty wounds if >5 yrs since booster
Tetanus – Elderly – Australia

- Surveillance health data bases – nationwide (n=58 cases)
- 1993–2002 (adults >65 y/o)
  - 62% of cases
  - 44% of hospitalizations
  - 83% of deaths

Vaccine 2007;25:1304-1309
Tetanus – Italy

• Nationwide health databases 2001–2010

• Results
  • 594 cases – all but 3 in adults; 80% in persons > 64 y/o
  • Only 10% of cases had received any dose of tetanus vaccine
  • CFR 16.5%

• Seroprevalence Ab study (n=3,604)
  • 45–64 y/o: 43%
  • 65–74 y/o: 27%
  • 75–84 y/o: 28%
  • ≥ 85 y/o: 17%

Vaccine 2014;32:639-644
Tetanus – Adults – Delhi, India

- 219 cases from 1998–2000 – Lok Nayak Hospital

Characteristics:
- Mean age 36 yrs
- 62% were 20 – 60 y/o
- 11% > 60 y/o
- “Inadequately immunized status”
Tetanus – Global

• Global Burden of Disease Study: Vital registration, mortality surveillance covering 12,534 site–years from 1980–2014

• Results:
  • 56,743 tetanus deaths in 2015 (95% uncertainty level: 48,199–80,042)
  • 38,806 of these deaths occurred in older children and adults (95%: 29,452–61,481)
  • Highest rates of mortality (after the neonatal period) observed in Somalia, South Sudan, Kenya

BMC Public Health 2017;17:179
Global Age Distribution–Tetanus Deaths, 2015
Vaccine Efficacy

• If administered properly, if cold chain appropriate, in a normal host; efficacy is essentially 100%

• The vaccine is inexpensive and readily produced and available
Data Gaps – Tetanus

- Reporting efficiency low in many LMICs
- Non-neonatal tetanus reporting low
- Cold-chain monitoring (repeated freezing)
- How often should booster doses be given in adults (after a primary series) based on the epidemiological setting?
- Efficacy in setting of HIV infection and other immunocompromising diseases?
Pertussis

• *Bordetella pertussis*
  • Whooping cough
  • Seizures, pneumonia, encephalopathy

• Preventing disease in adults (US)
  • Single lifetime dose of TdaP
  • A dose of TdaP with every pregnancy

• Clinical trial studies performed in Germany, Sweden, and Italy revealed wP VE ranging from 60% – 83% for 3 doses and up to 94% after 4 doses – similar ranges for aP studies over the short-term
Number of cases and costs for (US):

A. Persons age > 50

- Herpes Zoster (≥50): 937,773 (9%)
- Pertussis (≥50): 387,809 (4%)
- Pneumococcal (≥50): 603,337 (6%)
- Influenza (≥50): 8,101,104 (81%)

B. Persons age > 65

- Herpes Zoster (≥65): 555,989 (11%)
- Pertussis (≥65): 207,241 (4%)
- Pneumococcal (≥65): 440,187 (8%)
- Influenza (≥65): 4,019,759 (77%)

J Prim Prevent 2015;36:259-277
Burden of Disease

- Pertussis is endemic worldwide
- WHO 2015 global modeling estimates
  - 56,700 deaths in children < 5 y/o
    - 50% of these deaths in Africa
  - Overall, despite significant circulating disease in LMIC’s, no significant burden of severe disease/death in infants identified
    - Implication: maternal immunity levels high
- Caveat – inadequate epi systems, lab dx, clinical dx and reporting, etc.

Clin Infect Dis 2016;63:S123-S133
aP Vaccine

- In US, move from wP to aP in 1996

- California epidemic of 2010
  - VE 41% (age 2–10 yrs)
  - VE 24% (age 8–12 yrs)
  - Odds of acquiring pertussis increased 42% for every year following the 5th dose of DTaP
  - Children who got 4 doses of DTwP were 6x less likely to get pertussis

- Reason
  - Waning immunity
  - ? B. pertussis adaptation under selective pressure – pertactin–deficient strains

NEJM 2012;367:1012-1019
OR Pertussis By Year Since Last Dose

Circle=5 doses, Triangle=3 doses

- Klein et al
- Misegades et al
- Tartof (MN)
- Tartof (OR)
- Zepp et al
- Zinke et al
- Esposito et al 2001
- Esposito et al 2002
- Gustafsson et al
- Lacombe et al
- Olin et al
- Salmaso et al (SB)
- Salmaso et al (CB)

Odds Ratio of Pertussis

Years Since Last DTaP

Ped 2015;135:331-343
Cold Chain and Vaccine Failure

• OIG study: “76% of pertussis–containing vaccines were stored improperly resulting in freezing or heating of vaccine”

• Either freezing or heating of the vaccine diminishes immunogenicity and therefore vaccine effectiveness and efficacy

Data Gaps – Pertussis

- Legion...
- The disease is not adequately controlled anywhere...despite sustained high vaccine coverage rates in some locales...
- Duration of immunity in different settings
- Correlates of protection
- Efficacy in outbreak setting
- Strain changes under vaccine pressure?
- Induction of Th2 vs Th1 immunity and implications
- Better vaccines needed...
COVERAGE WITH DTP3 HAS REMAINED RELATIVELY UNCHANGED SINCE 2010

MMR: 1 Vaccine – 3 Diseases

• Vaccine licensure:
  • Live attenuated measles vaccine – 1963
  • Live attenuated mumps vaccine – 1967
  • Live attenuated rubella vaccine – 1969
  • MMR 1971
  • MMR–II – 1979

• MR, MMR

• Preventing disease in adults (US)
  • 2 dose series
MMR Issues

- Requires cold chain
- Contraindications (live virus)
- Interference by maternal antibody
- Variable efficacy by antigen
  - Primary failure
  - Secondary failure (waning)
MMR

- Vaccine available and inexpensive
- Increased M&M as age increases from childhood to adulthood – but large-scale data – esp. in LMIC’s missing
- Because of widespread disease in persons born prior to 1950’s, no longitudinal studies of long-term efficacy in “immunized-only” persons living in highly immunized settings where no wild virus boosting occurs
Measles

• Complications
  • Diarrhea, otitis media, bronchopneumonia
  • Encephalitis (1/1,000)
  • Death (1–2/1,000)
  • SSPE (1/10,000–100,000)
  • Immunosuppression (essentially 100%)

• Developing countries – disease generally worse, with CFR as high as 25% (vitamin A deficiency, malnutrition, immunosuppression, etc.)

• Primary and secondary vaccine failure
MMR – Primary Failure Rates

- Estimated among young healthy children at 3+% after 2 doses – some studies as high as 10%
- Inadequate data in LMIC settings and in patients with various immunocompromising diseases (malnutrition, HCV, chronic infectious disease burden, etc.)
MMR – Secondary Failure Rates

- Harder to estimate – insufficient data
- Only 90–95% or less of healthy children age–appropriately immunized have detectable MV antibody 10–15 years later
- The majority of subjects do not have markers of MV–CMI 15 years after a second dose, nor are these boosted by a 3rd dose
- M&M less than with primary failure
Contribution (%) to global measles mortality

India: 31
Nigeria: 13
Ethiopia: 9

Measles – FSM

- 393 cases of measles Feb–Aug 2014
- 2/3’s of cases among adults
- Of those adults with vaccination records:
  - 96% had documentation of at least one dose of MMR
  - 70% had documentation of at least 2 doses of MMR
- 124 subjects hospitalized – 1 death
- Genotype B3
- Vaccine cold chain generally good
- Vaccine failure played a major role

MMWR, Oct 2, 2015;64:1088-1091
Measles – FSM

• VE study of MV (household study)

• VE:
  • 1 dose: 23.1%
  • 2 dose: 63.4%
  • 3 doses: 95.9%

• VE for doses prior to 2010 = 51–57%

• VE for second doses received after 2010 = 84%

• Likely waning immunity and perhaps cold chain issues for older doses?
>800 cases despite vaccine coverage rates >80–90%
  - 90% of cases had received 1 dose of MMR
  - 68% had received ≥ 2 doses
  - 36% of cases in those ≥ 15 y/0

VE for 1 dose: 92%

VE for 2 doses: 95%

Clin Infect Dis 2006;42:315-319
• 1,480 adults from all regions of the world (2006)

• Tested for MMR susceptibility
  • Measles: 3–12% (based on region of the world)
  • Mumps: 16–33%
  • Rubella: 6–24%

• 22–54% susceptible to at least one disease (F>M)

Ann Int Med 2007;146:20-24
Measles Susceptibility – Malawi

- Large outbreak – 2010 – >134,000 cases and 304 deaths
- VE
  - First dose: 83.9%
  - Second dose: 90.5%
- 28% of cases > 19 y/o
- Assessment – accumulation of susceptibles

Measles – China – HCWs

• 2015 outbreak: 50/60 measles patients age 20–40 yrs, all HCWs (hospital–based)

• Cases:
  • One dose of vaccine: 44/60 (73.3%)
  • Two doses of vaccine: 1/60 (1.67%)

Canadian J Inf Dis and Med Micro 2016
<table>
<thead>
<tr>
<th>No. (%) of Students Immunized of 2,000</th>
<th>No. of Students Immune Because of Vaccine†</th>
<th>No. of Students Susceptible Who Get Disease When Exposed (% of Students)‡</th>
<th>% of All Measles Cases That Will Occur in Immunized Students◊</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0)</td>
<td>0</td>
<td>2,000 (100)</td>
<td>0</td>
</tr>
<tr>
<td>500 (25)</td>
<td>475</td>
<td>1,525 (76)</td>
<td>1.6</td>
</tr>
<tr>
<td>1,000 (50)</td>
<td>950</td>
<td>1,050 (53)</td>
<td>5</td>
</tr>
<tr>
<td>1,500 (75)</td>
<td>1,425</td>
<td>575 (29)</td>
<td>13</td>
</tr>
<tr>
<td>1,800 (90)</td>
<td>1,710</td>
<td>290 (15)</td>
<td>31</td>
</tr>
<tr>
<td>1,900 (95)</td>
<td>1,805</td>
<td>195 (10)</td>
<td>49</td>
</tr>
<tr>
<td>1,960 (98)</td>
<td>1,862</td>
<td>138 (7)</td>
<td>71</td>
</tr>
<tr>
<td>1,980 (99)</td>
<td>1,892</td>
<td>108 (5.4)</td>
<td>94</td>
</tr>
<tr>
<td>2,000 (100)</td>
<td>1,900</td>
<td>100 (5)</td>
<td>100</td>
</tr>
</tbody>
</table>

*Assumes a school size of 2,000 students and an overall vaccine efficacy of 95%.
† Number of students immunized times 0.95.
‡ Number of students not immunized plus number of vaccine failures.
◊ \[\frac{\text{No. of vaccine failures}}{\text{No. of students susceptible}}\] \times 100. This assumes that all susceptible students develop measles when exposed.

Poland et. al. Arch Int Med 1994;154:1815-20
<table>
<thead>
<tr>
<th>Source, year</th>
<th>No. of Students*</th>
<th>No. of Measles Cases (% of Students)</th>
<th>% of School Immunized</th>
<th>% of Cases Immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shasby et al., 1977</td>
<td>NR</td>
<td>33</td>
<td>&gt;95</td>
<td>91</td>
</tr>
<tr>
<td>Hull et al., 1985</td>
<td>8,187</td>
<td>76 (0.93)</td>
<td>98</td>
<td>98.7</td>
</tr>
<tr>
<td>Davis et al., 1987</td>
<td>1,731</td>
<td>82 (4.7)</td>
<td>98.7</td>
<td>63</td>
</tr>
<tr>
<td>Gustavson et al., 1987</td>
<td>2,937</td>
<td>26 (0.89)</td>
<td>99</td>
<td>NR</td>
</tr>
<tr>
<td>Nkowane et al., 1987</td>
<td>2,098</td>
<td>24 (1.1)</td>
<td>98</td>
<td>70</td>
</tr>
<tr>
<td>Chen et al., 1989</td>
<td>1,873</td>
<td>69 (3.7)</td>
<td>99.7</td>
<td>49</td>
</tr>
<tr>
<td>Edmonson et al., 1990</td>
<td>NR</td>
<td>186</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Hutchins et al., 1990</td>
<td>22,692</td>
<td>211 (0.93)</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Hersh et al., 1991</td>
<td>3,555</td>
<td>84 (2.4)</td>
<td>99</td>
<td>83</td>
</tr>
<tr>
<td>McCombie et al., 1988</td>
<td>4,136</td>
<td>112 (2.7)</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Guasparini et al., 1988</td>
<td>50,353</td>
<td>109 (0.22)</td>
<td>91 (overall)†</td>
<td>73</td>
</tr>
<tr>
<td>Mast et al., 1990</td>
<td>18, 189</td>
<td>185 (1)</td>
<td>96 (estimated)</td>
<td>85</td>
</tr>
<tr>
<td>Birkhead et al., 1991</td>
<td>&gt; 53,000</td>
<td>91 (0.17)</td>
<td>NR</td>
<td>87</td>
</tr>
<tr>
<td>Veit et al., 1991</td>
<td>368</td>
<td>3 (0.8)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Judelsohn et al., 1980</td>
<td>1,462</td>
<td>56 (4)</td>
<td>99.8</td>
<td>79</td>
</tr>
<tr>
<td>Centers for Disease Control, 1985</td>
<td>NR</td>
<td>47</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Narian and Farrell, 1989</td>
<td>1,522</td>
<td>10 (0.7)</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Osterman and Melnychuk, 1992</td>
<td>19, 439</td>
<td>88 (0.45)</td>
<td>71–98.2</td>
<td>55</td>
</tr>
</tbody>
</table>

*NR indicates not reported.
†Refers to multiple schools reported as a single group.
Table 1: Recent Measles Cases in US as of September 15, 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Infected</th>
<th>Unknown Vaccine Status</th>
<th>No Doses of Measles Vaccine</th>
<th>Received Only 1 Dose</th>
<th>Having Received 2 Doses</th>
<th>Any Dose where Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>66</td>
<td>8</td>
<td>50</td>
<td>7</td>
<td>1</td>
<td>13.8%</td>
</tr>
<tr>
<td>2006</td>
<td>55</td>
<td>15</td>
<td>25</td>
<td>12</td>
<td>3</td>
<td>37.5%</td>
</tr>
<tr>
<td>2007</td>
<td>43</td>
<td>10</td>
<td>25</td>
<td>4</td>
<td>4</td>
<td>24.2%</td>
</tr>
<tr>
<td>2008</td>
<td>140</td>
<td>21</td>
<td>108</td>
<td>6</td>
<td>5</td>
<td>9.2%</td>
</tr>
<tr>
<td>2009</td>
<td>71</td>
<td>15</td>
<td>49</td>
<td>6</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>2010</td>
<td>63</td>
<td>20</td>
<td>37</td>
<td>2</td>
<td>4</td>
<td>14.0%</td>
</tr>
<tr>
<td>2011</td>
<td>211</td>
<td>48</td>
<td>134</td>
<td>16</td>
<td>13</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

Source: Div Viral Diseases, Epi Branch, Natl Ctr Immunization & Resp Dis, CDC, Sep. 21, 2011
REPORTED MEASLES INCIDENCE RATE (JAN TO DEC 2013)
REPORTED MEASLES CASES IN 15 LARGEST OUTBREAKS SINCE JANUARY 2012

*Rate per 1'000'000 population
Outbreaks represent cases reported to WHO through end Jan 2014 except where noted
†: DRC through 31 Dec 2013
Pakistan through end July 2013
Somalia through 20 Oct 2013

Measles Rubella Initiative, Annual Report 2013
Data Gaps – Measles

- Surveillance and reporting
- Number of doses needed based on setting and CE
- Mechanisms of primary and secondary vaccine failure
- New vaccines without heat lability or contraindications (immunocompromised, etc.)
- Mechanisms of extreme transmissibility
Mumps

• Complications
  • Parotitis (usually subclinical in adults)
  • Orchitis (30% of adult males)
  • Oophoritis (5% of adult females)
  • Aseptic meningitis (asymptomatic–50%, symptomatic–10%)
  • Encephalitis (0.1%)
  • Sensorineural deafness (1/20,000)

• Multiple large outbreaks in persons with prior receipt of 2 doses of MMR (US)
  • Multistate, 7,000 cases – 2006
  • New York, 3,500 cases – 2010
Mumps

• In healthy children, VE is:
  • 48% after one dose
  • 60–88% after two doses in young adults

• Outbreaks among highly vaccinated persons have occurred in the US, France, Ireland, Moldova, Netherlands, England, Wales, Serbia, etc.)

• France, 2013, 15 clusters of cases*
  • 72% had received 2 doses of MMR
  • Odds of mumps increased by 10% for every year since 2nd dose of MMR

*Eurosurveillance 2016;21:1-8
Mumps Vaccine Performance

• Marked waning of detectable Ab levels after 5+ years

• Vaccine effectiveness estimated at approx. 80% (Urabe and JL strains) – lower VE for other vaccine strains where studied

• Field effectiveness*:
  • 1 dose: 48%
  • 2 doses: 62–85%

*Emerg Inf Dis 2007;13:12-17
Data Gaps – Mumps

- Mechanism for poorly immunogenic vaccines
- Mechanism for primary and secondary vaccine failure
- No CE studies in LMICs
Rubella

• 25–50% of infections asymptomatic
• Arthritis (60% adult females)
• CRS
  • Maternal–neonatal transmission almost 100% in 1st trimester
  • Fetopathy rare with maternal infection in the 3rd trimester
Rubella, CRS Cost–Effectiveness

- Incorporating rubella vaccine into national programs is both cost–beneficial and cost–effective

  - Barbados
    - Lifetime cost of a CRS case: $50,000 (2002)

  - Guyana
    - Lifetime cost of a CRS case: $64,000 (2002)

  - Cost of incorporating rubella vaccine into (MR or MMR) is $0.31 and $1.37 per 10 dose vial

Bull World Health Organ 2002;80:264-70
Vaccine Performance – Rubella

• Highly immunogenic
  • >95% develop protective titers
  • Ab persist at least 15 years in >90%

• High effectiveness and efficacy

• Durable and persistent vaccine–induced immunity
Data Gaps – Rubella

• Active surveillance for burden of disease
• Weak reporting infrastructure
• Otherwise as for measles
Varicella

- **Complications**
  - Bacterial infections (GABHS)
  - Otitis media, pneumonia, bacteremia, osteomyelitis, septic arthritis, endocarditis, necrotizing fasciitis, TSS
  - CNS complications (ataxia, Reye’s)
  - Congenital varicella syndrome (1% of pregnancies with infection within 1–2 trimester)

- **Adults with more severe disease and higher complication rates**
  - 1% admitted to hospital
  - CFR 25–174x higher than children
  - While only 5% of the cases, 35% of deaths occur in adults
Complications in adults

- Dehydration
- Pneumonia
- Bleeding, DIC
- Hepatitis
- Infection/inflammation of the brain
- CNS complications
- TSS
- Bone/joint infections
- Death
Varicella Susceptibility – Adults

- Lack of seroepidemiological data from LMICs for adults
- Latin American – 1.7%\(^1\)
- Tamil – 75%\(^2\)

\(^1\)Infect Dis Poverty 2016;6:41  
Varicella Vaccine Performance

- Licensed 1995
- 2\textsuperscript{nd} dose recommendation – 2007
- Waning immunity over time (US)*
  - 10 yr study of active surveillance – sentinel population of 350,000 subjects
    - 9.5\% breakthrough disease
  - Annual rate of breakthrough disease:
    - 1.6/1,000 after 1 year
    - 9/1,000 at 5 yrs
    - 58.2/1,000 at 9 yrs

*NEJM 2007;356:1121-1129
1 vs. 2–Dose Programs

• Deterministic realistic age–structured dynamic model in Canada

• Assumes 90% coverage and healthy population – benefits over 80 years
  • 1 dose program:
    • Reduce varicella by 64% (14–94%)
    • Reduce zoster by 5% (−2 – 22%)
  • 2 dose program
    • Reduce varicella by additional 22% (0–82%)
    • Reduce zoster by additional 6% (0–14%)

Vaccine 2010;28:3385-3397
Varicella Data Gaps

- CE studies in LMICs
- Issues of shifting disease into older age groups if childhood immunization programs don’t reach 85–90% of younger children
- How many life–time doses in the presence/absence of subclinical boosting?
Incidence of Herpes Zoster

- Estimated 1 million cases in the US annually\(^1\)
  - 0.74 – 5 cases per 1,000 persons per year in immunocompetent adults younger than age 60\(^2\)
  - 10.79 – 11.50 per 1,000 persons per year in immunocompetent adults age 60 and older\(^1\)
- Lifetime risk ~ 20%, 50% of those living to age 85
- PHN, the most common and debilitating complication, occurs in up to one third of patients with herpes zoster\(^3\)

Number of cases and costs for (US):
A. Persons age > 50
B. Persons age > 65

J Prim Prevent 2015;36:259-277
Herpes Zoster Incidence

Annual incidence (per 10,000 person-yrs)

- Canada (Manitoba) - Brisson
- UK - Hope-Simpson
- UK (RCGP) - Brisson
- Netherlands - de Melker
- US (Olmsted) - Yawn
- US (Medstat) - Insinga
Hospital Burden of VZV – England

- 2004–2013 – hospital episode statistics database (averages reported)

- Incidence of admissions:
  - Varicella: 7.6/100,000 [93% immunocompetent]
  - HZ: 8.8/100,000 [82% immunocompetent]

- Hospital Days:
  - Varicella: 10,748
  - HZ: 41,780

- Deaths:
  - Varicella: 18.5
  - HZ: 160

J Infect 2016;73:241-253
Mean hospitalization rates of cases of herpes zoster increase above age 60\textsuperscript{1}

Mean hospitalization costs per patient for herpes zoster is $15,583 (1995 US Dollars)\textsuperscript{2}

Zoster Vaccine

• **Efficacy:** Shingles Prevention Trial

• The use of the vaccine (VE) was associated overall with:
  • A 51% reduction in the incidence of zoster (p<0.001)
  • A 66% reduction in the incidence of postherpetic neuralgia
  • A 61% reduction in the burden of illness due to zoster

Immunosenscencence – HZ Vaccine

• SPS Trial VE in adults > 60 y/o:
  • HZ: 51.3%
  • PHN: 66.7%

• F/U 7–11 years after ZV receipt, VE:
  • HZ: 21.1%
  • PHN: 35.4%
Vaccination Reduces Long–Term Incidence of Herpes Zoster

Vaccination Reduces Incidence of Postherpetic Neuralgia

Cumulative incidence of PHN (%)

Years of follow-up

Placebo

Zoster vaccine

Placebo: n=19,247
Zoster vaccine: n=19,254

P < .001

No. at Risk

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</table>

Issues with Current HZ Vaccine

• Current shingles vaccine (Zostavax–Merck):
  • Single dose
  • Cold chain required
  • Expensive
  • Live, attenuated virus – significant contraindications for the age group intended
  • Declining effectiveness with time – just as risk dramatically increases
Declining Effectiveness of HZ Vaccine

- 176,078 vaccinated persons > 60 y/o, and 528,234 unvaccinated at KPSC

- Vaccine effectiveness:
  - Year 1: 69%
  - Year 2: 39%
  - Year 3: 35%
  - Year 4: 37%
  - Year 5: 33%
  - Year 6: 16.5%
  - Year 7: 4.2%
New HZ Vaccine

- Investigational vaccine (GSK)
- Subunit vaccine (VZV glycoprotein E and ASO1B (HZ/su))
- Requires 2 doses
- High levels of efficacy reported (97.2%)*

*NEJM 2015;372:2087-96
**ZOE–70 Trial**

- Randomized, placebo-controlled phase 3 trial in 18 countries, adults > 70 y/o (13,900 participants, 1:1 ratio)
- F/U for 3.7 years
- Results:
  - VE for HZ: 89.8%
  - VE for PHN: 88.8%
  - No difference in VE for > 70 y/o in ZOE–50 vs. ZOE–70

NEJM 2016;375:1019-1032
HZ/su – Immunopersistence

- 129 subjects 60–84 y/o (Sweden, Netherlands, Germany, Czech)
- Two doses of vaccine (2 mos apart)baseline
- Results:
  - 6 years later, gE–specific CD4 cells 3.8x higher than baseline

Vaccine 2016;34:863-868
Data Gaps – Zoster Vaccines

• CMI correlate of protection
• Define rates and mechanisms of primary and secondary vaccine failure
• How many life–time doses?
• Sequencing of vaccine type for optimal efficacy? Need vaccines without need for cold chain or with contraindications (immunocompromised, etc.)
• CE studies in LMICs
• Others
Other Issues – Varicella/Zoster Vaccines

• Implementation and use in LMIC’s will be difficult:
  • Cost of goods
  • Cold chain requirement
  • Need for 1–2 or more doses
  • Low cost–effectiveness ratios (> $100,000 for 2nd dose in the US) [for varicella vaccine]
  • Higher priority of other diseases with higher M&M
Apologia

Latin; defense, answers
UN Sustainable Development Goal

“Ensure healthy lives and promote well-being for all ages”

Invest in sustainably expanding routine vaccination schedules to cover people’s entire lives.
2.3.1. Decade of Vaccines Vision and GVAP Mission

The Decade of Vaccines (2011–2020) vision is:

A world in which all individuals and communities enjoy lives free from vaccine-preventable diseases.

The GVAP mission is:

To extend, by 2020 and beyond, the full benefit of immunization to all people, regardless of where they are born, who they are or where they live, and what age they are...
Global Health 2035: Mission Grand Convergence

- Global Burden of Disease 2010
  - 6,800,000 deaths due to infectious diseases
  - 91% of these deaths occur in LMIC’s
  - 60% of infectious disease deaths is from diseases for which there are no vaccines

Vaccine 2017;35:A16-A19
“Every system is perfectly designed to achieve exactly the results it gets.”

Don Berwick, MD
Adult Immunization: The Architecture of Success
The Architecture of Adult Immunization

- System to Acquire, Store, Distribute
- System to Finance
- System of Administration
- System of Record-Keeping
- System to Assess Burden of Disease – and therefore reduction in disease
- System to Monitor Vaccine Safety
- System of Education
- System of Partnership
• For LMIC’s the single most efficient change that could occur is to utilize existing systems and platforms to broaden immunization programs from a singular focus on children, to a “whole-life” program

• PAHO has started this process
Nine Transformative Investments:
1. National Team
2. Strategies to Reach
3. Planning Cycle
4. Funding Flow
5. Vaccinator Capacity
6. Adequate Supply
7. Monitoring Systems
8. Beyond Infancy Vaccination
9. Community Involvement
Thank you!

poland.gregory@mayo.edu
Papers to commend:

1. What vaccine product attributes do immunization stakeholders value? Results from interviews in six low- and middle-income countries. (Vaccine 2016;34:6236-6242)

2. Overcoming economic barriers to the optimal use of vaccines. (Health Affairs 2005;24:666-679)

3. Vaccines for low-income countries. (Sem in Immunology 2013:25:114-123)

4. Prioritizing vaccines for developing world diseases (Vaccine 2017;35:A16-19)
**GRISP: Global Routine Immunization Strategies and Practices**

**Coordinating Actions to Achieve Disease Prevention for All**

The GRISP framework outlines the specific strategies and activities required to ensure the lifesaving power of routine immunization is accessible to all—regardless of who they are or where they live. To equip routine immunization programs for success in every country, GRISP recommends that national governments, global partners, and donors focus and invest in the following nine areas:

- **Operational level funding**
  Assurance that sufficient and adequately appropriated funds reach the operational level of the programme regularly.

- **Vaccinator and manager skills**
  Regular and systematic capacity building, skills development and supportive supervision for vaccinators and district managers.

- **Modern vaccine supply chain**
  Modernized vaccine supply chains and management to ensure the correct amounts of the right potent vaccines are available at each vaccination session.

- **Strategic and operational plans**
  Strategic multiyear plans and operational annual plans outlining and coordinating strategies and activities, monitored quarterly.

- **Strategies to reach**
  Tailored strategies that identify undervaccinated and unvaccinated persons and regularly provide them with the vaccines they need.

- **National team**
  The most important factor for all other eight investments to succeed: A capable national team—supplied with sufficient resources and authority—to excellently manage each country’s national immunization program.

- **Accurate information system**
  An information system that identifies and tracks each person’s vaccination status.

- **Life course vaccination**
  Expanded routine immunization schedules that cover people’s entire lives.

- **Community support**
  Shared responsibility for immunization delivery between communities and the immunization programme to reach uniformly high coverage through high demand and quality services.
Vaccine Financing

- UNICEF
- WHA–EPI (1974)
- GAVI (2000)
- BMGF–Decade of Vaccines (2010)
- UN Millennium Development Goals (4 and 5)
- ProVac Initiative and the Gates Reference Case for Economic Evaluation
- Others

**MAXIMIZE REACH**
- Detect and reach the unreached
- Design services to reach all equitably
- Build capacity of vaccinators and managers
- Ensure vaccine quality and availability
- Create synergy with special vaccination efforts
- Integrate immunization services

**MANAGE the PROGRAMME**
- Secure political commitment and partnerships
- Plan, budget and mobilize resources
- Ensure excellence in national leadership
- Set programme policy and guidance

**MOBILIZE PEOPLE**
- Engage communities and create demand
- Mobilize and communicate for vaccination
- Address vaccine hesitancy & false perceptions

**MONITOR PROGRESS**
- Monitor programme performance & disease occurrence
- Evaluate the programme through surveys & reviews
GVAP TARGETS FOR 2015 WERE MISSED IN ALL BUT ONE CATEGORY

VACCINE INTRODUCTION:
Number of low- or middle-income countries (LMIC) to have introduced one or more new or under-utilized vaccine since 2010

2010: 0 LMICs
2015: 99 LMICs
2015 TARGET: 90 LMICs

EXCEEDED

POLIO:
Number of new cases of paralytic poliomyelitis due to wild poliovirus

2010
359 cases
9 countries

2015
74 cases
2 countries

2015 TARGET: 0 cases

MISSED

MATERNAL AND NEONATAL TETANUS ELIMINATION:
Number of countries verified for elimination

2015 TARGET: 40 priority countries

2015
22 priority countries
**MEASLES:**
Number of WHO regions to achieve measles elimination

- 2015 Target: at least 4 WHO regions
- 2015: 1 region achieved measles elimination

**RUBELLA:**
Number of WHO regions verified for rubella and CRS elimination

- 2015 Target: at least 2 WHO regions
- 2015: 1 region achieved rubella elimination

<table>
<thead>
<tr>
<th>GROUP</th>
<th>VACCINE</th>
<th>NO. OF FUTURE DEATHS Averted&lt;sup&gt;ab&lt;/sup&gt;</th>
</tr>
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</table>
| Original Expanded Programme on Immunization vaccine<sup>c</sup> | Measles 1st dose  
Measles 2nd dose  
Measles supplementary immunization activities | 10.6M  
0.4M  
3.1M |
| New or underutilized vaccines | Hepatitis B<sup>d</sup>  
Haemophilus influenzae type b  
Pneumococcus  
Rotavirus  
Human papillomavirus  
Yellow fever<sup>a</sup>  
Meningococcal A meningitis<sup>f</sup>  
Japanese encephalitis<sup>g</sup>  
Rubella | 5.3–6.0M  
1.4–1.7M  
1.6–1.8M  
0.8–0.9M  
0.5M  
0.03–0.04M  
0.07M  
0.4M |
| TOTAL (2011–2020)                          |                                                                        | 24.6–25.8M |
Relation between the number of WHO Member States using hepatitis B vaccine and the UNICEF weighted average price for the monovalent vaccine

Source: WHO: based on programme data received from WHO Member States and UNICEF weighted average price for monovalent hepatitis B vaccine
Figure 1. Estimated global immunization coverage, DTPc3 vaccine, 1980-2014
Reported Measles and Rubella Cases, The Americas, 1980-2010*

*Data until EW 27/2010. Aruba and Netherland Antilles not reporting.

Source: EPI tables (1999-2003) and country reports to PAHO/WHO (since 2004).

Vaccine 2011:29S:D91-96