Overview of the Impact of Vaccines in the US and Globally

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Wake Forest Medical School
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Immediate-past Chair of the WHO Strategic Advisory Group of Experts on Immunizations (SAGE)
## Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>20th Century Annual Morbidity†</th>
<th>2016 Reported Cases † †</th>
<th>Percent Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>69</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>5,311</td>
<td>97%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>15,737</td>
<td>92%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>5</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>152</td>
<td>1</td>
<td>99%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>33</td>
<td>94%</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>20,000</td>
<td>22*</td>
<td>&gt; 99%</td>
</tr>
</tbody>
</table>

† JAMA. 2007;298(18):2155-2163
† † CDC. MMWR January 6, 2017/ 65(52);ND-924 – ND-941. (MMWR 2016 week 52 provisional data)
* Haemophilus influenzae type b (Hib) < 5 years of age. An additional 11 cases of Hib are estimated to have occurred among the 222 reports of Hi (< 5 years of age) with unknown serotype.
**Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Vaccine Era Annual Estimate</th>
<th>2015 Estimate (unless otherwise specified)</th>
<th>Percent Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>117,333 †</td>
<td>2,500 *</td>
<td>98%</td>
</tr>
<tr>
<td>Hepatitis B (acute)</td>
<td>66,232 †</td>
<td>19,200 *</td>
<td>71%</td>
</tr>
<tr>
<td>Pneumococcus (invasive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ages</td>
<td>63,067 †</td>
<td>29,000 #</td>
<td>54%</td>
</tr>
<tr>
<td>&lt; 5 years of age</td>
<td>16,069 †</td>
<td>1,800 #</td>
<td>89%</td>
</tr>
<tr>
<td>Rotavirus (hospitalizations,</td>
<td>62,500 † †</td>
<td>11,250 ##</td>
<td>82%</td>
</tr>
<tr>
<td>&lt; 3 years of age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella (Chickenpox)</td>
<td>4,085,120 †</td>
<td>126,639 ###</td>
<td>97%</td>
</tr>
</tbody>
</table>

† JAMA. 2007;298(18):2155-2163
†† CDC. MMWR. February 6, 2009 / 58(RR02);1-25
* CDC. Viral Hepatitis Surveillance - United States, 2014
# CDC. Unpublished, Active Bacterial Core Surveillance, 2015
## New Vaccine Surveillance Network 2015 data (unpublished); U.S. rotavirus disease now has biennial pattern
### CDC. MMWR. November 25, 2016 / 65(46);1306-1321 (2015 final data)
A highly susceptible population in which a transmitting case is likely to come in contact with a susceptible person leading to a chain of person-to-person transmission. (B) A highly immune population in which a transmitting case is unlikely to come in contact with a susceptible person, thereby breaking the chain of transmission and achieving indirect protection of remaining susceptible because they are not exposed. (Oreinstein WA, Amed R. Simply put: Vaccinations save lives. PNAS. doi: 10.1073/pnas.1704507114)
Impact of Vaccines in US

- A recent analysis estimated that of the routinely recommended vaccines used to protect against 13 diseases in each US birth cohort of 4,000,000 infants:
  - ~20 million cases of vaccine-preventable diseases were prevented
  - >40,000 deaths were avoided.

- In addition to saving the lives of our children, vaccination has resulted in net economic benefits to society amounting to almost $69 billion in the US.*

Vaccines have been contributors to the global reduction of under 5 mortality

number of estimated deaths in thousands

Source: WHO
Figure 2: Global trends in cause-specific mortality rates in neonates and children aged 1-59 months, 2000-15

*About 61% of the reduction comes from pneumonia, diarrhoea, malaria, and measles among 1-59-month olds and neonatal intrapartum related events.
Global Impact of Vaccines

Achievements

• From 1990 to 2015 the mortality rate in low income countries was reduced from ~83/100 to 40/1000 in children <5 yrs of age (53%) in large part due to expanded use of vaccines.
  – Global deaths have decreased from ~12.2M to 5.9M annually
  – ~17,000 fewer children <5 yrs died every day in 2015 than in 1990

• Life expectancy this century has increased by 5 yrs globally and 10 yrs in Africa mainly due to the decrease in deaths of children <5 yrs of age.

• An economic analysis of 10 vaccines for 94 low and middle income countries estimated that an investment of $34 billion for the immunization programs resulted in savings of $586 billion in reducing costs of illness and $1.53 trillion when broader economic benefits were included.*

Global Impact of Vaccines
Much Remains to be Accomplished

• Many of the deaths in low income countries in children <5 yrs of age continue to be due to vaccine preventable diseases.
  – ~16,000 children <5 yrs still die every day
  – Almost 50% of these deaths now occur in the neonatal period.
The Global Vaccine Action Plan (GVAP)

• GVAP was created to provide a pathway for achieving the goals of the Decade of Vaccines.
  – The Gates Foundation has donated $10 billion dollars in support of this effort.

• GVAP has 5 main goals to achieve and only one is currently on target
Goals for the Decade of Vaccines

- Achieve a world free of poliomyelitis
- Meet global and regional elimination targets
- Meet vaccination coverage targets in every region, country, and community
- Develop and introduce new and improved vaccines and technologies
- Exceed the Millennium Development Goal 4 target for reducing child mortality
2016 SAGE Assessment of GVAP Progress in Achieving Decade of Vaccine Goals

**Coverage:** All countries DTP3 >90% national coverage, and >80% in every district by end 2015.
OFF TRACK

**Polio:** transmission stopped by end 2014. OFF TRACK

**Maternal and neonatal tetanus:** eliminated by 2015. OFF TRACK

**Measles/Rubella:** eliminated in 4 and 2 regions by end-2015, respectively. OFF TRACK

**Introduction of under-utilized vaccines:** At least 90 LMIC have introduced one or more such vaccines by 2015. ON TRACK

**2020**

**Coverage:** all vaccines in national programs: >90% national coverage, and >80% in every district by end 2020

**Polio:** eradicated by end 2018

Maternal and neonatal tetanus:
Eliminate before 2020

**Measles/Rubella:** eliminated in 5 regions by end-2020
Number of unimmunized children is now $\sim 18.7$ m - progress has stagnated during the past five years.
# GVAP Target- Polio
Global Polio Eradication Status

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated</th>
<th>Recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>350,000</td>
<td>35,251</td>
</tr>
<tr>
<td>1993</td>
<td>100,000</td>
<td>10,487</td>
</tr>
<tr>
<td>1995</td>
<td>—</td>
<td>7,035</td>
</tr>
<tr>
<td>2000</td>
<td>—</td>
<td>719</td>
</tr>
<tr>
<td>2005</td>
<td>—</td>
<td>1,979</td>
</tr>
<tr>
<td>2010</td>
<td>—</td>
<td>1,352</td>
</tr>
<tr>
<td>2011</td>
<td>—</td>
<td>650</td>
</tr>
<tr>
<td>2012</td>
<td>—</td>
<td>223</td>
</tr>
<tr>
<td>2013</td>
<td>—</td>
<td>416</td>
</tr>
<tr>
<td>2014</td>
<td>—</td>
<td>359</td>
</tr>
<tr>
<td>2015</td>
<td>—</td>
<td>74</td>
</tr>
<tr>
<td>2016</td>
<td>—</td>
<td>37</td>
</tr>
<tr>
<td>2017 (through June 2017)</td>
<td>—</td>
<td>12</td>
</tr>
</tbody>
</table>

Modification of WHO Table: 1988 to 2016
## GVAP Target

### Maternal and Neonatal Tetanus (MNT)

24 Countries Yet to Achieve Elimination in 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Guinea</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>India</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Mauritania</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Philippines</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Chad</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Haiti</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Kenya</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Niger</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Drastically behind despite relatively stable political situation</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Sudan</td>
<td>Set back by political instability</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Mali</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Somalia</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>South Sudan</td>
<td>Close to elimination</td>
</tr>
<tr>
<td>Yemen</td>
<td>Close to elimination</td>
</tr>
</tbody>
</table>

**10 Countries Close to Elimination**

**8 Countries Are Drastically Behind Despite Relatively Stable Political Situation**

**6 Countries Are Being Set Back by Political Instability**
GVAP Target
Maternal and Neonatal Tetanus Elimination-

• Progress
  – As of 2016 MNT has been eliminated from all but 19 countries

• Concerns
  – MNT still kills ~49,000 babies and a substantial number of women annually.
# GVAP Target - Measles

**Countries with Largest Number of Reported Measles Cases (as of mid 2015)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>50,878</td>
</tr>
<tr>
<td>DR Congo</td>
<td>47,492</td>
</tr>
<tr>
<td>India</td>
<td>24,977</td>
</tr>
<tr>
<td>Philippines</td>
<td>19,773</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>14,923</td>
</tr>
<tr>
<td>Somalia</td>
<td>12,691</td>
</tr>
<tr>
<td>Angola</td>
<td>8,527</td>
</tr>
<tr>
<td>Indonesia</td>
<td>6,959</td>
</tr>
<tr>
<td>Vietnam</td>
<td>3,946</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3,376</td>
</tr>
<tr>
<td>Georgia</td>
<td>2,387</td>
</tr>
</tbody>
</table>
US Measles Burden

- Measles was declared eliminated from the US in 2000 due to a highly effective vaccination program and other control measures.

- However, measles remains present in many other countries and can be brought into the United States by unvaccinated travelers (Americans or foreign visitors).

- Since 2000, the annual number of reported measles cases ranged from 37 people in 2004 to 667 people in 2014.
Measles cases, United States, 2001-2014*

*Source: Morbidity and Mortality Weekly Report (MMWR), Notifiable Diseases and Mortality Tables
GVAP Target
Rates of Measles Severity and Complications in the US*

• Hospitalization: 1 out of 4 cases

• Encephalitis (brain inflammation): 1 per 1,000 cases

• Deaths: 1-2 per 1,000 cases

• Complications are more common in children < 5 yrs and adults >20 yrs.

*Source: www.cdc.gov/measles/about/complications.html
## Emerging Infections in Humans During Impacting the US During the Last 25 Years

<table>
<thead>
<tr>
<th>Infection</th>
<th>Year</th>
<th>Person to Person Transmission</th>
<th>Zoonosis</th>
<th>Mosquito Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya</td>
<td>2013</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Dengue</td>
<td>2010-2013</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ebola</td>
<td>2013</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>1993</td>
<td>Rarely</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>H1N1 flu pandemic</td>
<td>2009</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>2000-2006</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Zika</td>
<td>2016</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Zika Virus Infection
Overview

• The Zika virus likely entered into the Americas in 2013
  – In 2014 clinical cases detected in Brazil
• Most cases asymptomatic or mild.
• Zika mainly spread via mosquitoes.
• Vaccines are currently available
Probable Origin of ZIKA Virus Infection

- **1947** - Discovered in the sentinel rhesus monkey population in Uganda
- **1948** – ZIKA recovered from *Aedes africanus* Zika Forest
- **1952** – First human cases in Uganda and United Republic of Tanzania
Countries with Zika Virus
(as of 4/18/17)
Zika Virus Infections
Most Recent Emerging Infection Impacting the Americas

- >70 countries and territories reporting transmission

- Majority in countries with no prior circulation of Zika virus and are experiencing their initial outbreak
  - >100,000 confirmed cases
  - Low number of deaths

- Major impact is on pregnant women and their infants
  - >2000 cases of microcephaly
Cases of ZIKA Infection in the USA Mainland & Territories (as of April 26, 2017)

• USA mainland population
  – locally acquired mosquito-borne cases reported: 224

• USA travel-associated cases reported: 5,264
  – Guillain-Barré syndrome: 13
  – Sexually transmitted: 46
  – Laboratory acquired: 1
  – Congenital (USA): 29
  – Guillain-Barré syndrome: 50

• Cases in USA Territories: 36,575
ZIKA Virus

Modes of Transmission

• Bite from an infected mosquito

• Maternal-fetal
  – Intrauterine
  – Perinatal

• Sexual transmission from an infected person to his or her partners (oral, vaginal, anal sex)

• Laboratory exposure
Zika Virus
Clinical Manifestations

• The majority (~80%) of persons infected with Zika virus infections have no illness or only mild symptoms.

• For people with symptoms, the most common symptoms are:
  – Fever
  – Rash
  – Joint pain
  – Conjunctivitis (red eyes)
  – Muscle pain
  – Headache
  – Symptoms last several days to a week.

• People usually don’t get sick enough to need hospitalization.
  – Very low mortality.
Zika Virus
Guillain- Barré Syndrome (GBS)

• GBS is an uncommon disease of the nervous system in which a person’s own immune system damages the nerve cells, causing muscle weakness and sometimes paralysis.

• GBS is strongly associated with Zika but only a small proportion of people with recent Zika infection get GBS.
Zika Virus Infection
Impact on Pregnancy

• Zika virus can pass from a pregnant woman to her fetus during pregnancy or around the time of birth.
  – Infections of infants during pregnancy occur in all three trimesters

• Zika infection in pregnancy can cause microcephaly and other major neurologic defects.
  – It is not known exactly how often this happens, but a recent study in Brazil found significant abnormalities in ~50% of infants born to infected mothers.

• Other problems linked to Zika infection before birth include
  – Miscarriage, stillbirth, absent or poorly developed brain structures, eye defects, hearing deficits, limb abnormalities, and impaired growth
  – No evidence that past infection will affect future pregnancies once the virus has cleared the body.
Fetal Ultrasound Findings in 87 Infected Infants in Brazil*

*Clin Infect Dis May 15 2017
# Zika Virus

**CDC Recommendations to Prevent Sexual Transmission in Couples w/ Travel Exposure or Residence in Area with Active Transmission**

<table>
<thead>
<tr>
<th>Specific scenarios for couples</th>
<th>Guidance to prevent sexual transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Woman is pregnant</strong></td>
<td><strong>Condoms vs abstain duration pregnancy</strong></td>
</tr>
<tr>
<td><strong>Not pregnant w/ no plans:</strong></td>
<td><strong>Condoms vs abstain</strong></td>
</tr>
<tr>
<td>partner w/ confirmed Zika virus infection or clinical illness consistent</td>
<td>at least 6 months after onset of illness men and 8 weeks women</td>
</tr>
<tr>
<td>partner traveled to an area w/ active Zika virus transmission has NO symptoms</td>
<td>for at least 8 weeks after departure from the area</td>
</tr>
<tr>
<td>Partner resides in an area with active Zika virus transmission but has NO symptoms</td>
<td><strong>might consider condoms vs abstaining while active transmission persists.</strong></td>
</tr>
</tbody>
</table>
Zika Virus
Vaccines Under Development

• ~40 different Zika virus vaccines are currently under development.

• WHO is giving highest priority to an inactivated vaccine with no adjuvants since it would be easier to use in pregnant women.
  – Attenuated live virus, recombinant and DNA vaccines are also being developed against Zika, The NIH is giving DNA vaccines a lot attention.
  – Could have a vaccine in 2 - 3 years
VSV-based vaccine vectors
exploiting useful properties of vesicular stomatitis virus to develop new vaccines

Douglas S. Lyles, Ph.D.
Department of Biochemistry
Wake Forest School of Medicine
Vaccine vector, defined

- Vaccine that uses weakened (attenuated) viruses or bacteria to deliver pieces of a pathogenic organism (foreign antigen) to stimulate an immune response against the pathogen
1984: First report of successful vaccination using a live virus vaccine vector strategy

- Live vaccinia virus (smallpox vaccine) engineered to produce surface antigen from hepatitis B virus (HBVsAg) was protective against HBV infection in animals

- Why is this important?
  - Hepatitis B virus does not grow in tissue culture
  - Producing virus and viral proteins for construction of vaccines is difficult and expensive
  - Engineering HBVsAg gene into a virus vector to deliver the antigen to the immune system is one solution to the problem of making an HBV vaccine

Recombinant VSVs As Vaccine Vectors

- **Vesicular stomatitis virus vaccine vectors**: live, recombinant VSVs that produce foreign antigens
- Highly effective at inducing B cell and T cell-mediated immunity in vaccinated animals and humans
- VSV vaccine vectors are highly attenuated to reduce the risk of potential adverse effects.
What is VSV?
Vesicular stomatitis virus (VSV) is an arthropod borne virus.

Transmitted to domestic livestock by several insect species.
VSV Infects Epithelial Cells and Neurons

• VSV infects epithelial cells
  • In cattle and horses, infects mucous membranes of the mouth and lips, and cells of the coronary band of the hooves.

• VSV belongs to the family Rhabdoviridae, related to rabies virus
  • Rarely pathogenic in humans
VSV is a small bullet-shaped RNA virus that has only 5 genes.

- 5 proteins encoded by the VSV genome are all that the virus needs to make copies of itself in mammalian host cells:
  - N – nucleocapsid protein
  - P – phosphoprotein
  - L – large polymerase protein
  - M – matrix protein
  - G – glycoprotein

Lichty et al., *Trends in Molecular Medicine* 2004
Other viruses can also be vaccine vectors, but VSV has some advantages

• 50+ years of research: much of what we understand about the immune system comes from studying the immune response to VSV

Peter Doherty

Rolf Zinkernagel

1996 Nobel prize in Physiology or Medicine “for their studies concerning the specificity of the cell-mediated immune defense”
More advantages of VSV as a vaccine vector

• Unlike some viruses, VSV is not picky: it infects almost all types of cells, which helps to activate the immune system.

• VSV is typically not harmful to humans, and there are multiple strategies to further weaken the virus to ensure safety, while retaining its ability to produce foreign antigens.

• VSV accepts extra genetic material fairly readily without compromising its ability to induce an immune response.
Recombinant VSV Vaccine Vectors: attenuation by multiple strategies

Wild-type VSV

Prototype vaccine vector

Attenuated vaccine vector that “scrambles” the genome, mutates proteins M and G, and encodes a foreign antigen (e.g., HIV-gag)

M51R
The current Ebola vaccine is VSV engineered to produce Ebola G protein. VSV G protein is replaced with Ebola virus G protein. This attenuates VSV but still allows it to infect cells and make Ebola G protein which is highly immunogenic.
Years of research and testing, and millions of dollars ensure that vaccines are safe and effective.
VSV as a vector for emerging and established diseases: in development

- Ebola
- HIV
- Influenza
- Zika
- SARS
- MERS
- Cancer
Thank you for your attention
Influenza: development of a safe flu vaccine for neonates and the elderly

NACBR Workshop on Vaccines
July 13, 2017
The seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States from 2005 through 2014.
While babies and the elderly can demonstrate amazing acts of strength and agility……
their immune system cannot......

http://www.everydayfamily.com/blog/dont-touch-my-baby-its-flu-season/

The Facts

**INFANTS**
- Infants <6 months of age are particularly vulnerable to development of severe disease and the highest risk of death is present in the first years of life
- The influenza vaccine is not approved for use in infants under 6 months
- Studies of vaccine responsiveness in human infants show
  - Antibody production in infants between 3-5 months old is virtually nonexistent after one administration of the trivalent inactivated influenza vaccine

**ELDERLY**
- more than 90% of the 36,000 influenza-related annual deaths occur in those age 65 years or older
- Response to current vaccine is one quarter of that observed in younger adults
- Rates in those ≥75 years of age are especially impaired
Challenges to generating a protective influenza vaccine for neonates & the elderly

- The current flu vaccine must be re-designed each year because the molecules recognized by the immune system keep changing.
- The immune cells from these groups are dampened in their sensitivity/responsiveness.
How can we make a better vaccine against influenza?
The ultimate goal—a universal vaccine

Focus the immune response on a conserved portion of the viral protein

Heads, stalks and everything else: how can antibodies eradicate influenza as a human disease?
Curr. Opin. Immunol. 42:48
How can we make it work in infants and the elderly?

Add adjuvants, e.g. agents that increase the stimulatory capacity of the vaccine for the immune system.
TLR agonists as adjuvants to overcome these defects

TLR act as innate sensors of pathogens: promotes activation of immune cells

Adapted from http://labs.mmg.pitt.edu/sarkar/Signaling.htm
Targets of TLR7/8 agonist R848 action

Adapted from http://www.uta.edu/chagas/html/biolImmu.html#1st_back
What is the best way to identify a promising vaccine?

With models that reproduce our immune response/function as closely as possible
There is no substitute for animal models to do initial assessment of safety and effectiveness......
Why are nonhuman primates so useful?

• The distribution and responsiveness of TLR in the mouse and human differ, while there is a high degree of similarity between nonhuman primates and humans.

• Mice are immunologically less mature at birth than are humans and have a highly abbreviated neonatal period.
How is it going?

• We have identified a novel vaccine that is capable of inducing potent antibody and T cell responses in newborn nonhuman primates.

• These immune responses provide increased protection from disease when infants are exposed to influenza virus.

• A second generation vaccine appears to have even greater potential for stimulating the immune system.

• We have plans to test this vaccine in elderly animals to see if it can overcome the immune defects present in the aging immune system.
HPV: virus and vaccine

David Ornelles, Ph.D.
Microbiology and Immunology

Avinash K. Shetty, MD
Chief, Pediatric Infectious Diseases
Associate Dean, Office of Global Health
What is HPV

- Human papillomavirus
- Over 100 types that infect skin and mucosal surfaces
- About 80 million Americans are infected with some type of HPV
- HPV is **the most common** sexually transmitted infection
Does HPV cause health problems?

- Innocuous warts in the skin
- Less innocuous warts in the genital region or in the throat and mouth
- **Cancer**
  - Cervical
  - Vulvar, Vaginal, Penile, Anal
  - Oropharynx
What is cancer?

• Cancer is a genetic disease
• Cancer results from changes in genes that control the way our cells grow and divide
• Sometimes these changes are inherited or the result of random chance
• Often these changes are caused by eternal factors such as cigarette smoke and viruses
How does HPV cause cancer?

The mythical Jackalope?
How does HPV cause cancer?

A grain of truth behind the myth
How does HPV cause cancer?

- Material in the “horn” caused warts in some rabbits but fatal cancer in others.
- Richard Shope and Peyton Rous discovered a cancer-causing virus.
- This virus is a papillomavirus.
How much cancer does HPV cause?

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Percent cases due to HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>100</td>
</tr>
<tr>
<td>Vulva cancer</td>
<td>40</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>70</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>50</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>85</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>35</td>
</tr>
</tbody>
</table>

About 5% of the worldwide cancer burden, 4th most common in women
Progression of cervical cancer
How can I avoid HPV diseases?

- Abstinence
  - mutually monogamous sexual relationship

- Latex condoms
  - HPV can infect areas not covered by a condom

- Cervical cancer screen
  - women aged 21 to 65 years

- Vaccine
  - prevents but cannot treat HPV infection
Folk remedies for warts

“Cut a slice from a potato, rub the white part on the wart, then go bury the potato in the yard”

Google, *The Internet*
More folk remedies for warts

“Split a bean. Cut the wart so as to get some blood and put the blood on one piece of the bean. Bury that half in a hole 'bout midnight in the dark of the moon and then burn up the rest of the bean.”

“Take your dead cat into the graveyard after somebody that was wicked has been buried. Round midnight when the devils come to take that wicked fellow away, heave your cat after 'em and say, 'Devil follow corpse, cat follow devil, warts follow cat, I'm done with ye!'”

Mark Twain, *The Adventures of Huckleberry Finn*
Sometimes the immune system will eliminate warts (HPV infection)

- Most infections clear spontaneously
- Persistent infection is due to HPV’s ability to evade the immune system
- **Vaccines** educate the immune system to prevent infection
What is the HPV vaccine?

- The vaccines for HPV are made of the viral proteins that have been produced in yeast cells or in insect cells
- No viral genes
- No infectious material

3D-printable model of HPV, instructions available from https://3dprint.nih.gov/
Who should get the vaccine?

• All boys and girls ages 11 or 12 years
• Two doses at least six months apart  
  - ages 9 to 14
• Three doses for teens and young adults  
  - ages 15 through 26

• Gardasil 9 protects against greater than 90% of cancer-causing human papillomaviruses

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil</td>
<td>6, 11, 16, 18</td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
</tr>
</tbody>
</table>
In just a little bit more time than it took for this talk, another person in the United States developed cancer because of HPV.

Most of these cancers can be prevented by the HPV vaccine.
Objectives

To understand:

• Why vaccination matters?
• Impact of community immunity
Change in U.S. Morbidity from 1900 to 2015

MMWR 2015;64(43):ND763-ND778
How were these accomplishments achieved?

- Consistent, high levels of vaccine coverage
- Intensive surveillance
- Effective public health disease control measures
So how does herd immunity work?

Herd Immunity: How It Works

- Percent Vaccinated: 0%
- Percent Vaccinated: 25%
- Percent Vaccinated: 50%
- Percent Vaccinated: 75%
- Percent Vaccinated: 90%
- Percent Vaccinated: 95%

- Infected • Unvaccinated • Vaccinated

Wake Forest Baptist Medical Center
So how does herd immunity work?
2015 Measles Outbreak

- January 5th: 1 child in California diagnosed
- January 5th: 2 children in Utah diagnosed
- January 7th: 7 children in California diagnosed
Measles Outbreak 2015 Disneyland

MMWR 2015;64(06):153-154
Community immunity: 80% vaccinated
Pertussis (Whooping Cough)
15,207 Pertussis Cases in 2015

D.C.  
- <200
- 201-400
- 401-600
- 601+

MMWR 2015;64(43):ND763-ND778
Pertussis in Alamance County

• Dec 14, 2011: 8 y/o tested positive for pertussis 21 days after illness onset and attending school
• Investigation initiated next day
• 700 children/adults screened
  • 4 tested positive
  • 21 persons with cough and exposure
  • 20 probable cases
• Antibiotic treatment for cases and exposed
Pertussis in Alamance County

• Early January: 2\textsuperscript{nd} case at 2\textsuperscript{nd} school identified
• Investigation expanded
• Schools had 110 (74\%) of 148 cases
  • 12 elementary
  • 6 middle schools
  • 2 high schools
  • 3 private schools
  • 3 child care centers
  • 2 colleges
Pertussis in Alamance County

- All cases 3-12 y/o were appropriately immunized

- Key intervention: Over 3,000 doses of Tdap administered to eligible persons for free
  - Particularly caregivers of infants
  - Of infants with pertussis and known source, 80% are infected by household contact
Reported pertussis cases, by year – United States, 1922-2004


Wake Forest Baptist Medical Center
Measles 2016

- NC 1 case
- US 70 cases (108 cases by mid-June 2017)

- NC MMR coverage: 94%
  national coverage: 92% (range 87%-98%)

https://www.cdc.gov/measles/cases-outbreaks.html
Pertussis 2016

• 300 NC cases
• 20,762 US cases

• NC childhood DTaP coverage: 89%
  national coverage: 90% (range 83%-97%)

• NC teen Tdap coverage: 93%
  national coverage: 86% (range 70%-94%)
Change in U.S. Morbidity from 1900 to 2015

Annual Cases

Years

1900 2015

Vaccine coverage:
- 90% DTaP
- 94% IPV
- 92% MMR
- 93% Hib

MMWR 2015;64(43):ND763-ND778
Pneumococcal vaccines

Karen M. Haas, PhD
Department of Microbiology and Immunology
Wake Forest School of Medicine
Streptococcus pneumoniae

- Pneumococcal disease is caused by a Gram+ bacterium called *Streptococcus pneumoniae* (pneumococcus)

- The leading cause of vaccine-preventable illness and death in the U.S.

- Causes >2.5 million deaths worldwide per year (most in children under the age of 5 and elderly).

- Increasing antibiotic resistance
Streptococcus pneumoniae

• >90 known serotypes – each serotype has a unique polysaccharide (sugar-containing) capsule.

• Polysaccharide capsule shields the bacteria from immune attack and phagocytosis and is therefore an important virulence factor.
Transmission

- Pneumococcus is found in many people’s noses and throats (carriers)

- Spread by coughing, sneezing or via contact with respiratory secretions.
Pneumococcal Disease

Pneumococcus can lead to serious infections of the
covering of the brain (meningitis)
blood (bacteremia)
lungs (pneumonia)
as well as ear infections and conjunctivitis
Pneumococcal Disease Mortality Rates

- **Pneumonia**: 1 in 20 deaths
- **Bacteremia**: 1 in 5 deaths
- **Meningitis**: 3 in 10 deaths
Streptococcus pneumoniae

- >90 known serotypes – each serotype has a unique polysaccharide (sugar-containing) capsule.

Vaccines are composed of polysaccharides isolated from different serotypes
Streptococcus pneumoniae

• How do we achieve protection?
  Through vaccines that cause the immune system to produce soluble proteins called antibodies that bind to pneumococcal polysaccharides.
Effector mechanisms involved in clearance of extracellular bacteria:
Antibody and complement

*S. pneumoniae*

Ab + complement

Phagocytosis and clearance

Complement and Fc receptor engagement

Lysis
Antibody Responses to Protein Antigens
B cells and T cells work together

B cell Antigen Receptor (BCR)

Antibody

Instructive Signals

MHC II

Isotype Switching
Affinity Maturation
Full differentiation to PC
Memory B cells
Antibody Production in Response to Carbohydrate Antigens (Pneumovax-23)

T cell help is lacking

Regulatory Signals?
Native polysaccharide and protein-conjugated polysaccharide vaccines

**Pneumovax-23**
- Adults (>65)
- *No adjuvant*

**Prevnar-13**
- Children (4 doses)
- *Aluminum phosphate*
Pneumococcal Polysaccharide Vaccine

- Pneumovax - purified pneumococcal polysaccharide (23 types)

- **60%-70% efficacy against invasive disease**

- **Less effective in preventing pneumococcal pneumonia**

How can we make it even better?
B cells express an inhibitory protein after they encounter polysaccharides

Proliferation
Differentiation to antibody producing cell

Polysaccharide vaccine

B cell

BCR

PD-1

Antibodies

Pneumovax

Pneumococcus
Blocking inhibitory proteins on B cells improves Pneumovax vaccine responses in mice

Polysaccharide vaccine

BCR

Proliferation
Differentiation to ASC

Pneumovax

PD-1 block

Pneumococcus

antibodies
PD-1 block following Pneumovax vaccination provides mice significantly increased protection against *S. pneumoniae* infection
Take home messages

- *Streptococcus pneumoniae* is a serious threat to human health (especially the very young and the elderly)
- Emerging antibiotic resistance has left people unprotected
- Vaccines consisting of pneumococcal capsule polysaccharides provide significant (but not complete) protection
- More research is needed to improve these vaccines
Get vaccinated!