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Vaccines—Impact, Questions, and Challenges

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Infectious disease prevention with the safest vaccines possible

Epidemiological studies of vaccine-preventable diseases and phase I, II, and III vaccine trials of hepatitis A and B, inactivated polio virus, pertussis, *Haemophilus influenzae* type B, tetanus, Lyme disease, rotavirus, Argentina hemorrhagic fever, and influenzae vaccine viruses

Control of measles has been a particular focus of interest
Section A

Background and History
The Most Effective Tool

- Vaccines are the most effective tool we have to control infectious diseases

Reported Measles in the United States

- Vaccine licensed
- First elimination goal announced
- Second elimination goal announced
- Third elimination goal announced

Reported Cases (in Thousands)

Year

60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 00 02 04
Reported Measles in the United States

- **Vaccine Licensed**
- First elimination goal announced
- Second elimination goal announced
- Third elimination goal announced

One dose is ~95% effective.

Second dose recommended
Measles cases and weighted average of routine measles vaccination coverage, Southern African countries

Mumps Cases Linked to Multi-State Outbreak

- Number of reported mumps cases linked to multi-state outbreak, January 1 to May 2, 2006

Mumps Cases Linked to Multi-State Outbreak

Number of reported mumps cases linked to multi-state outbreak, January 1 to May 2, 2006

N = 2,597

† 3 cases related to the outbreak

§ 12 cases related to the outbreak

Number of Reported Mumps Cases, U.S., 1980–2006

Questions

1. How did scientists figure out how to make vaccines?
2. Why aren’t some vaccines more effective?
3. Why can’t we eradicate more disease?
4. What new vaccines might be approved in the future?
5. What diseases other than infections might be prevented with vaccines?
6. Why do we have so many misunderstandings about vaccine safety?
1879 Laboratory Attenuation

1. Chicken cholera culture exposed to air over a holiday
2. Infected chickens
3. Chickens protected from challenge
4. “Induced immunity”
Edmonston B Measles Vaccine

Wild type virus

1954

24 passages human kidney tissue

28 passages primary human amnion tissue

6 passages chick embryos

Chick embryo cells

Edmonston B Vaccine

1963
1890s: Killed Typhoid Vaccines

- Richard Pfeiffer, Wilhelm Kolle (Germany)
- Almoth Wright (England)
- 1899 Boer War—mass immunization in military
  - Great opposition, dumped vaccine overboard
  - 58,000 cases, 9,000 deaths in military
How Are Vaccines Made?

- **Attenuate (live)**
  - Serial passage

- **Inactivated**
  - Disrupt
  - Purify

- **Extract DNA**
  - Insert in yeast or bacteria
  - Express antigen
  - Purify

  - Insert DNA into vector

- **Cold adapted “parent”**

- **Attenuated**
- **Killed**
- **Subunit**
- **Recombinant vaccine**
- **Vectored**
- **Naked DNA**
- **Reassortant**
### Routine Vaccines in U.S. and Developing Country EPI Programs

Vaccines for Routine Use in U.S. and in Developing Country Expanded Programme on Immunization (EPI) Programs

#### U.S.

1. Diphtheria
2. Tetanus
3. Pertussis
4. Polio (IPV)
5. Hepatitis B
6. *H. influenzae* type b
7. *S. pneumoniae*
8. *N. meningitidis*
9. Measles
10. Mumps
11. Rubella
12. Varicella
13. Rotavirus
14. Influenza
15. HPV

#### EPI

1. BCG
2. Diphtheria
3. Tetanus
4. Pertussis
5. Polio (OPV)
6. Measles
7. (Yellow Fever)
8. Hepatitis B
9. (H. influenzae type b)
10. (Rubella)
Vaccines for Selective Populations

- Smallpox
- Anthrax
- Argentine hemorrhagic fever
- Typhoid fever
- Rabies
- Japanese encephalitis
- Plague
- Clostridium perfringens “pig bell”
Section B

Modern Vaccine Issues
Needed Vaccines

Viruses
- Herpes simplex
- Dengue
- HIV
- RSV
- Hepatitis C
- Cytomegalovirus
- EBV
- West Nile
- Parainfluenza

Bacteria
- Syphilis
- Gonorrhea
- *E. coli*
- Lyme disease
- *C. trachomatis*
- Group A streptococci
- Oral streptococci

Parasites
- Malaria
- Helminths
- Schistosomes

Under development
1.7 Million Childhood Deaths

- 1.7 million childhood deaths due to vaccine-preventable diseases in 2000 (not including influenza, pneumococcal, and meningococcal diseases)

Why Do We Still Have So Much Preventable Disease?

1. Failure of delivery systems
2. Incomplete protection from some vaccines
3. Financing
Why Aren’t Some Vaccines More Effective?

- Influenza: rapid evolution of new strains
- Human variability: genetic differences
  - Hepatitis B, measles (1 dose): ~95–98%
- Incomplete immunity
  - Pertussis: 70–90% (June 2005—booster at 11–12 years for U.S.)
  - Varicella (1 dose): 70–90% (2 doses 2006)
- Errors in storage or administration
- Evasion of the immune system
  - HCV, HIV, parasites
Anticipated Supply of Flu Vaccine for U.S. Is Abruptly Cut in Half

By: Denise Gamlin and Melissa Healy, Times Staff Writers

U.S. public health officials warned Tuesday of serious flu vaccine shortages after the plant makes Chiron's entire

All of Chiron's flu vaccine deemed unsafe; FDA checks firm's plant, says no doses can be salvaged

BYLINE: Sabah Burrell

British and American drug regulators have found additional contaminated lots of influenza vaccine. FDA investigators and Chiron's legal team are searching for a potential cause of a batch.

Vaccine gap shows faults in supply system; $85 vial may cost $600 amid shortage in U.S.

BY: M. William Salganik

To David Webster, an industry consultant, flu is a disease that affects the flu of a vaccine with a normal price tag of $85. A
Why Can’t We Eradicate More Diseases?

- Tetanus: animal reservoirs
- Pneumococcal disease: too many types
- Varicella and hepatitis B: viral persistent infections and transmissions
Varicella zoster virus persists in dorsal root ganglia of sensory nerves.
Herpes Zoster and Presence of Children in Household

Rate of herpes zoster by presence of children in household

Incidence Ratio
0.75 (0.632-0.89)

Adapted from Brisson et al. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine. 2002;20:2500-2507
Incidence of Postherpetic Neuralgia and Herpes Zoster following Zoster Vaccine (5-6 X Potency of Varicella Vaccine)

Postherpetic neuralgia
66.5% efficacy

Herpes zoster
61.1% efficacy

p<0.001

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Cervical Cancer

- Age-standardized incidence rate per 100,000


29
Burden of Cervical Cancer

- 400,000–500,000 cases and 230,000 deaths from cervical cancer each year
- Second leading cause of cancer-related deaths among women worldwide
HPV Types and Cervical Cancer Worldwide

- HPV types in cases of cervical cancer from different regions of the world

Cumulative incidence of HPV infection from time of first sexual intercourse, female college students, U.S.

## Vaccines That Prevent Cervical Cancer

- Types 16 and 18 cause ~70% of cancer
- Types 6 and 11 cause 90% of genital warts

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>GARDASIL™ (Merck)</td>
<td>6, 11, 16, 18</td>
</tr>
<tr>
<td>Cervarix (GSK)</td>
<td>16, 18</td>
</tr>
</tbody>
</table>
### Infectious Causes of Cancer

<table>
<thead>
<tr>
<th>1. Hepatitis B</th>
<th>Liver cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. HPV</td>
<td>Cervical, penile, anal</td>
</tr>
<tr>
<td>3. EBV</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>4. HTLV-I</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>5. HHV-8</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>6. <em>H. pylori</em></td>
<td>Gastric carcinoma</td>
</tr>
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</tbody>
</table>
All Vaccines Cause Adverse Events

1. Pain
2. Local reactions
3. Fever
4. Allergic reactions
5. Unchecked replication (immune deficient)
6. Adverse immune responses
Vaccine-Associated Paralytic Poliomyelitis

- Oral polio vaccine can cause vaccine-associated paralytic poliomyelitis
  1. Similar to wild type paralysis
  2. Risk ~ 1 per 760,000 children vaccinated
Diseases Once Common in the U.S.

- Measles
- Mumps
- Congenital rubella
- Diphtheria
- Tetanus
- Smallpox
Current Vaccine Dilemmas

1. How do we maintain high acceptance in absence of disease?
2. Causal assessment: science vs. legal?
3. Vaccines to treat chronic infections (hep B)
4. Criteria to stop vaccinating (polio)?
5. Who should receive vaccines for bioterrorism agents?
6. How do we get new expensive vaccines introduced and sustained in developing countries?