SP.718 Special Topics at Edgerton Center: D-Lab Health: Medical Technologies for the Developing World
Spring 2009

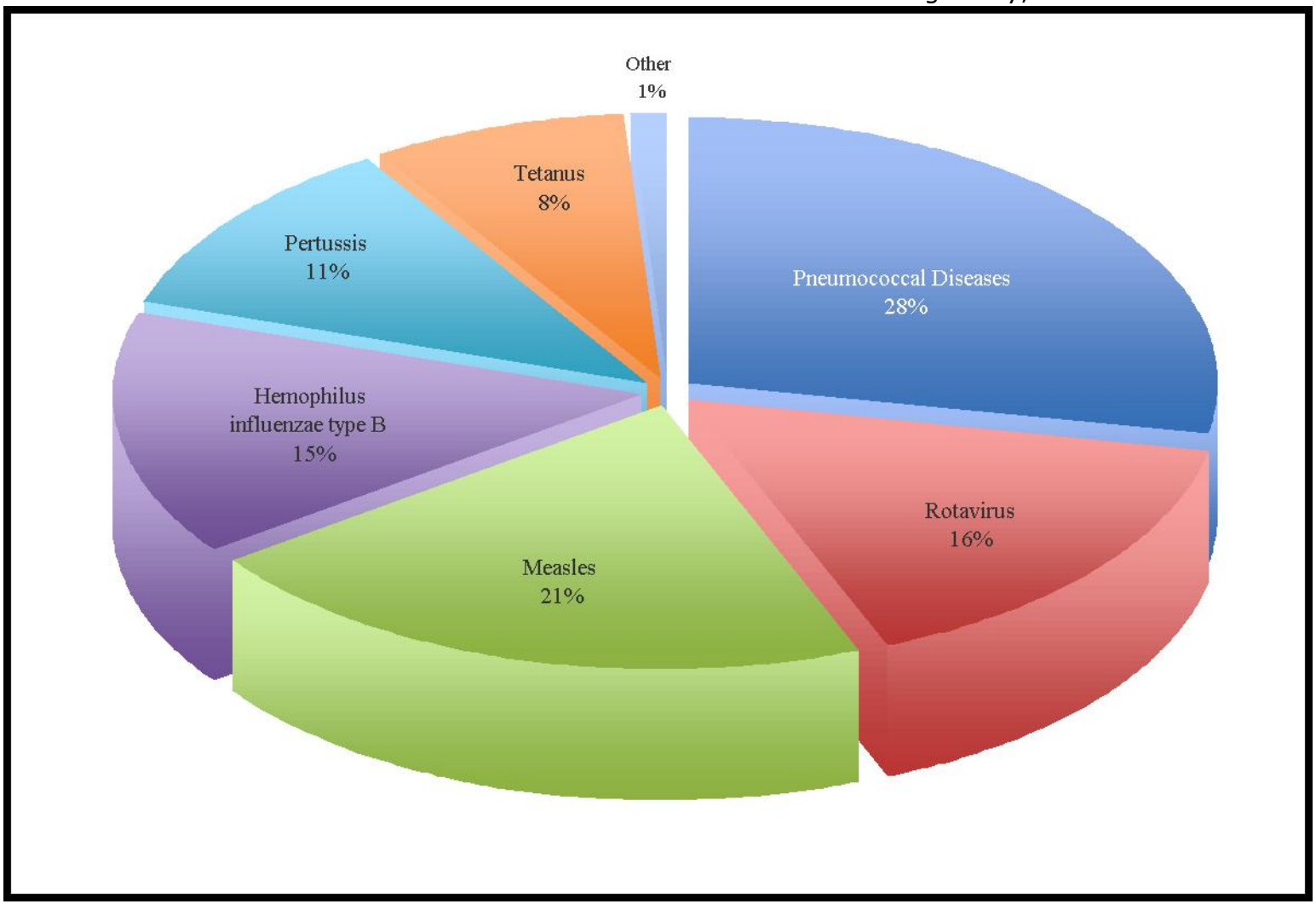
Massachusetts Institute of Technology

D-LAB HEALTH
sp 718/755

Amit Srivastava
Jose Gomez-Marquez

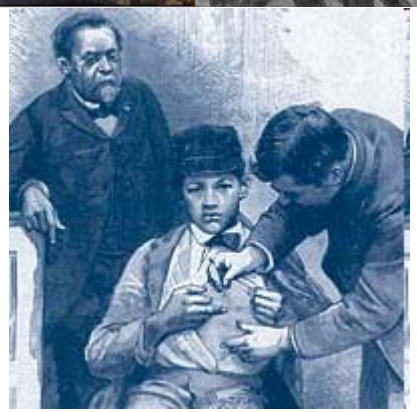
Vaccine Preventable Diseases

Causes of 2.5 million child deaths out of 10.5 million child deaths globally, 2002



Source: WHO *Wkly Epidemiol Rec.* (2006) 81:189-196.

Immunization - A Brief History



1780 Edward Jenner discovers Smallpox vaccine

1885 Pasteur discovers Rabies vaccine

1920s Diphtheria and Tetanus

1934 Pertusis (Whooping Cough)

1955 Salk Polio

1960s Measles, Mumps and Rubella
Sabin Polio

1985 Haemophilus

1990s Hepatitis, Varicella

Rationale for Immunization or Vaccination

- Prevention of life-threatening and prevalent disease
- Reduction of carriage
- Reduction of disease transmission
- Reduction of antibiotic resistance
- Retention of antibiotic effectiveness

Active imunization: induces immediate protective immunity and stable immunological memory

- Selective Immunization
- Universal Immunization

Universal Immunization Schedule

Image removed due to copyright restrictions.
"Recommended childhood immunization schedule in the United States, 2002."
Table 18-3 in Goldsby, R. A. *Immunology*. 5th edition. New York, NY: Macmillian, 2003. p. 417.
See http://books.google.com/books?id=8281_jkbdhoC&pg=RA1-PA417

Effect of Polio Vaccination

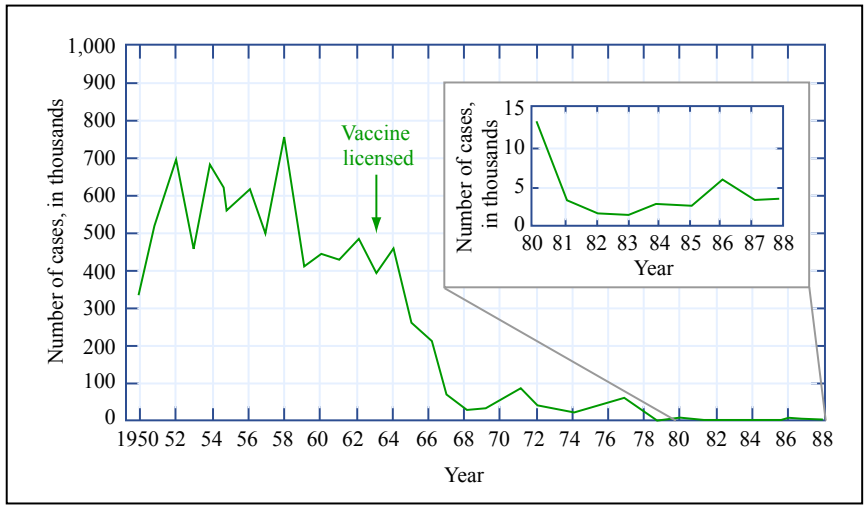


Figure by MIT OpenCourseWare.

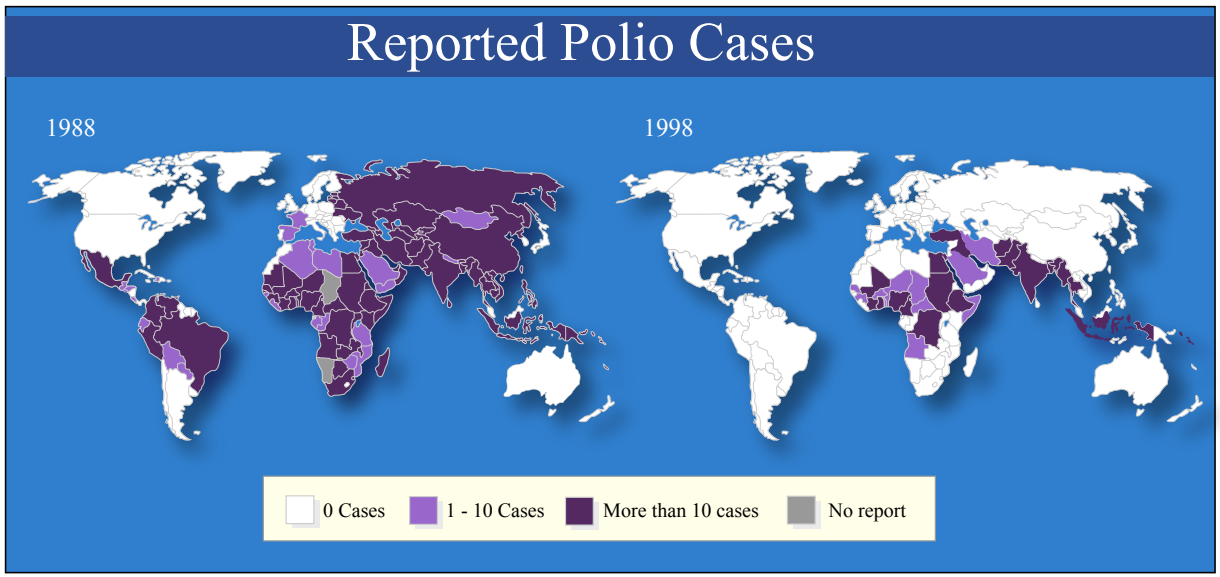


Figure by MIT OpenCourseWare.

Vaccination

Properties of an Ideal Vaccine

- Effective protection against all forms of the disease
- Strong and durable immunological memory
- Easy administration
- Easy transport *i.e.*, refrigeration, clean needles and syringes *etc*
- Affordable

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

- Attenuated bacteria and viruses, e.g. BCG for tuberculosis, Sabin polio vaccine

  Advantages: transient growth favors cell-mediated response and therefore a single vaccination is sufficient

  Disadvantages: reversion and induction of disease-like symptoms

- Inactivated/killed pathogens, e.g. Salk polio vaccine.

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

- Bacterial polysaccharide capsules, e.g. *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Hemophilus influenzae*. Conjugation with carrier ensures cell-mediated response
- Toxoids, e.g. Diphtheria and Tetanus toxin
- Recombinant proteins, e.g. Hepatitis B surface antigen

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

Genes encoding major antigens carried by benign or attenuated viruses or bacteria, e.g.

Canarypox virus, BCG strain of *Mycobacterium*.

- Vaccinia virus, is able to carry several foreign genes. Easy administration.
- Attenuated *Salmonella typhimurium* is used to carry antigens from Cholera and Gonorrhea causing bacteria

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

Plasmid DNA encoding antigenic proteins injected directly into muscle. Uptake by dendritic cells elicits protective immune response.

Advantages

- Native antigen that triggers both humoral and cell mediated immunity and immunological memory
- Stable vaccine, easily delivered and multiplexing is possible

Disadvantages

- Cannot be used for non-protein antigens

Vaccine Design and Development

Vaccines that elicit protective immunity and stable immunological memory

1. Whole organism vaccines
2. Purified macromolecules
3. Recombinant vector vaccines
4. DNA vaccines
5. Multivalent subunit vaccines

Synthetic carriers that contain immunodominant B and T cell epitopes

- Solid Matrix Antibody Antigen (SMAA)
- Immunostimulatory complexes (ISCOMs)

Focus Areas for Designing Solutions

- Development of new effective vaccines
- Formulation
- Delivery

The Cold Chain for Vaccines

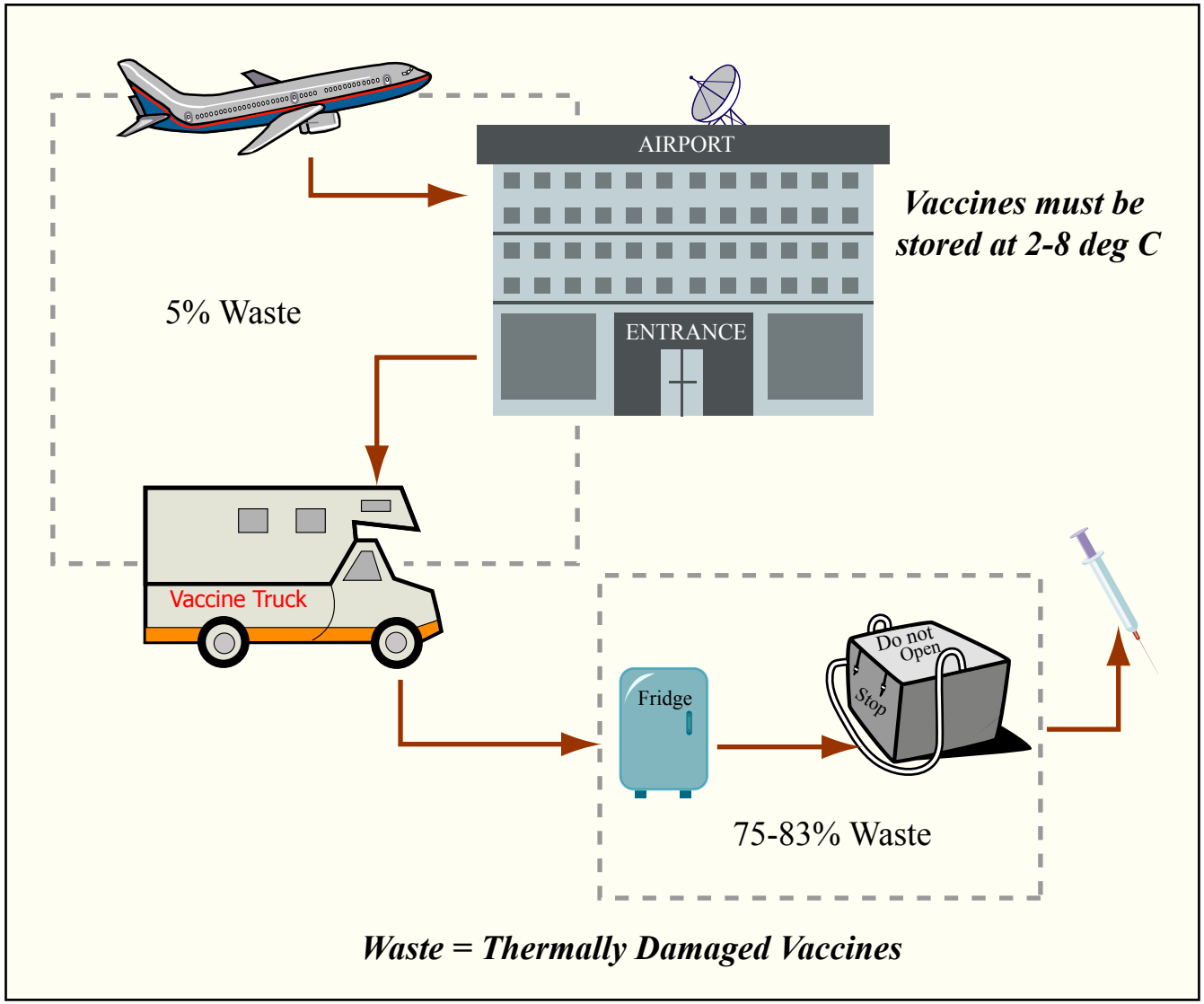
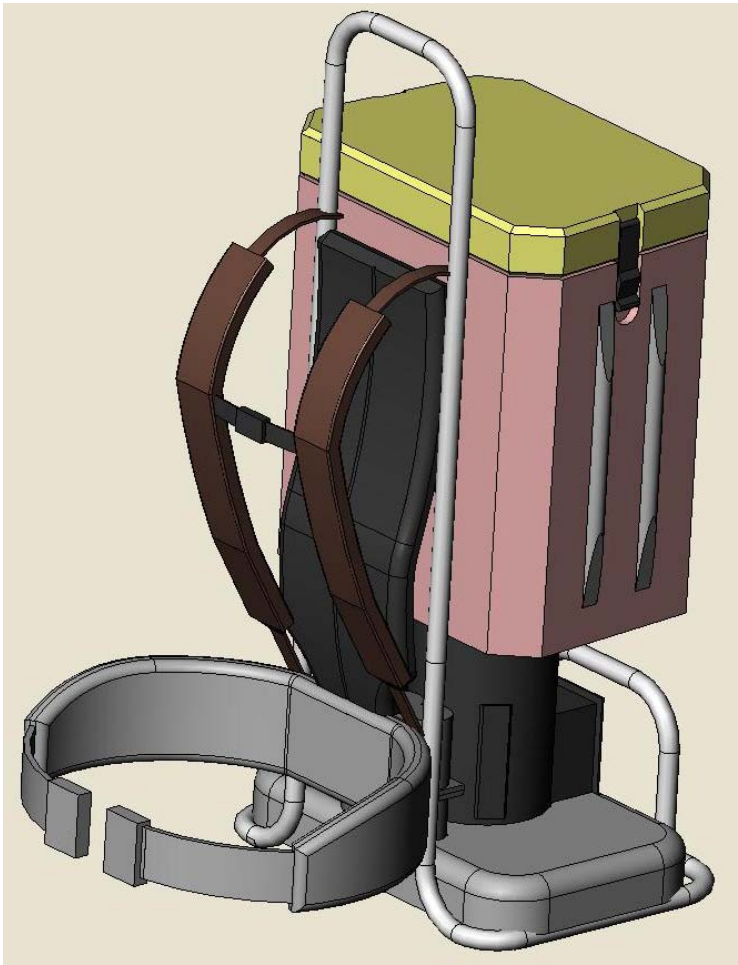


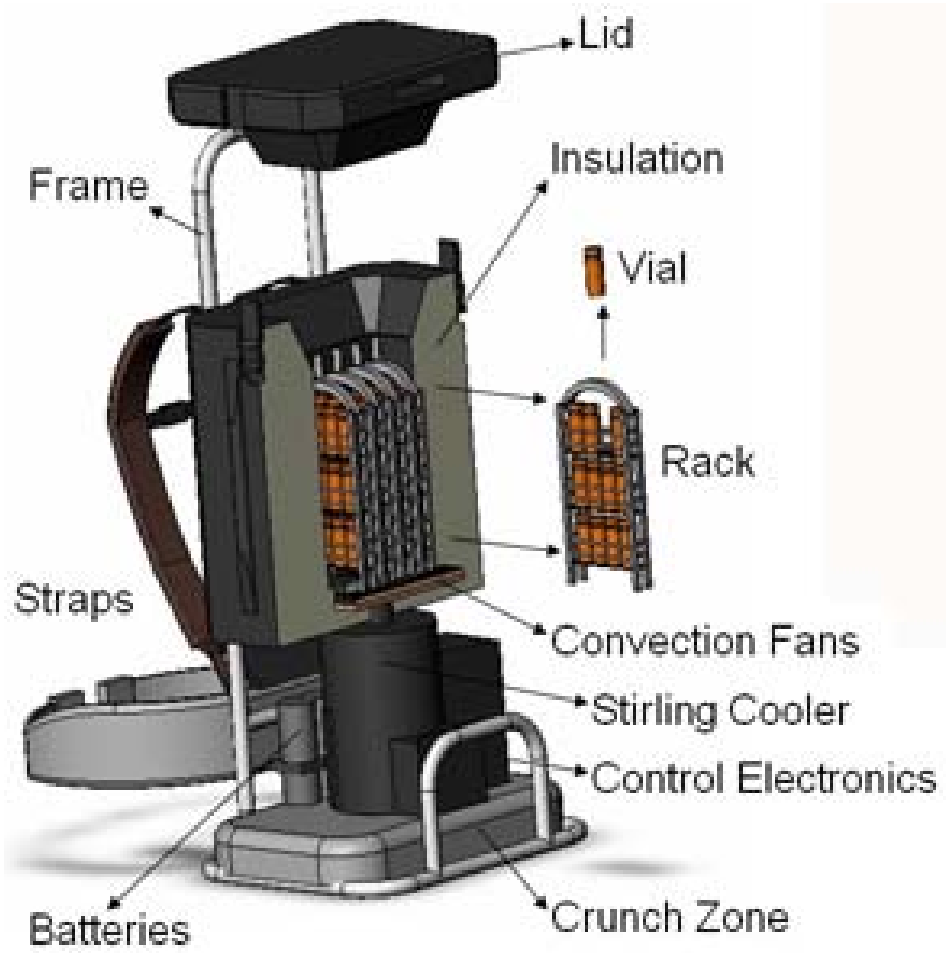
Figure by MIT OpenCourseWare.

one world medical devices

Vaccine Pack

making bridges to a healthy world

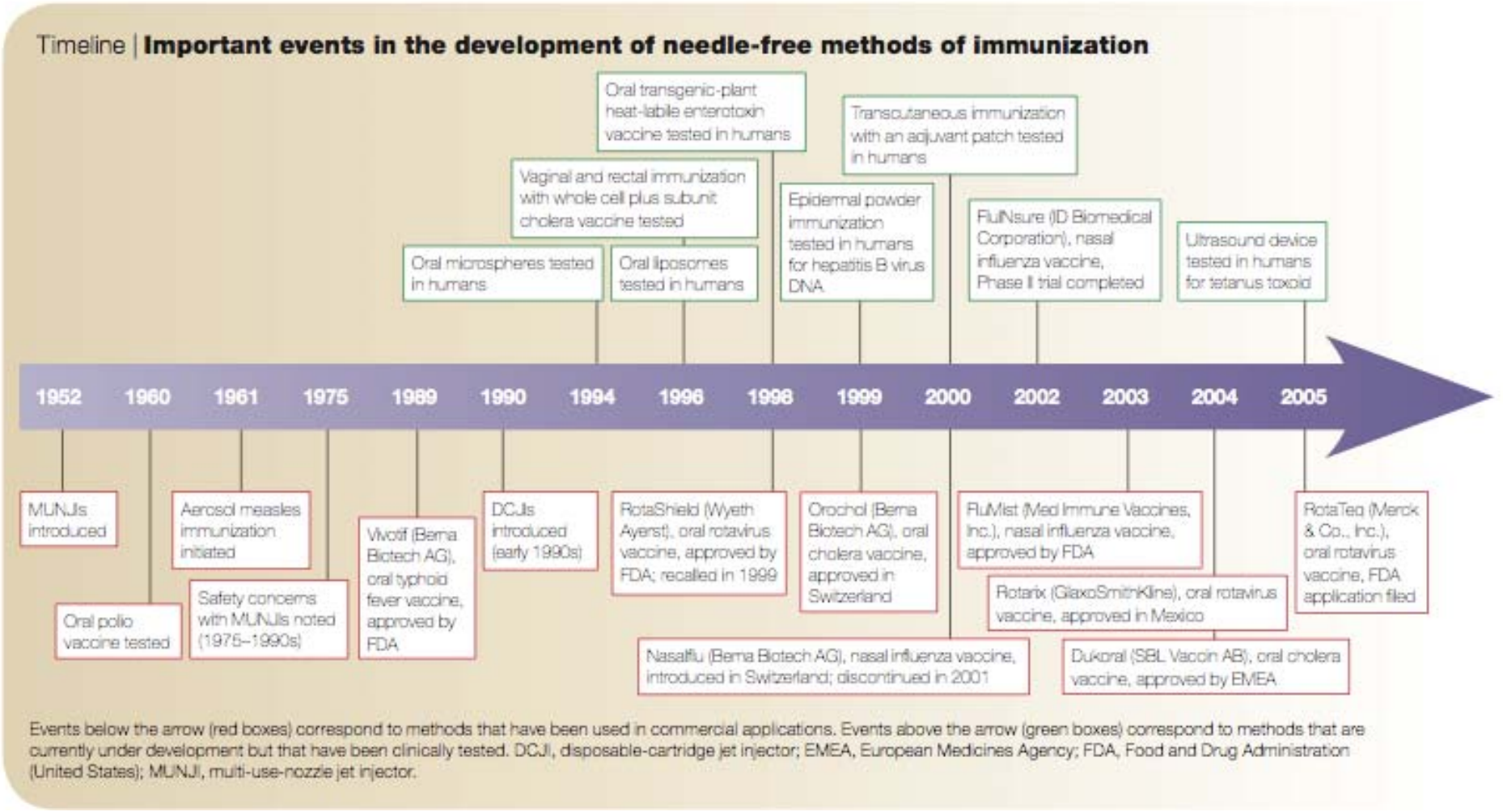




Currently administered Vaccines

Disease/Pathogen	Vaccine type		Administration
Hepatitis A	Inactivated virus		Injection
Hepatitis B	Protein	Hep B surface antigen	Injection
Rotavirus	Live, attenuated virus	5 Human-bovine reassortant viruses	Injection
Polio	Live, attenuated virus		Oral
Varicella	Live, attenuated virus		Injection
Influenza	Inactivated virus		Injection
MMR	Live, attenuated viruses	Measles, mumps, rubella	Injection
Diptheria	Protein	Diptheria toxoid	Injection
Tetanus	Protein	Tetanus toxoid	Injection
Pertussis	Protein	Viral hemaglutinins	Injection
Pneumococcus	Polysaccharide-protein conjugat	Capsular polysaccharide	Injection
Meningococcus	Polysaccharide	Capsular polysaccharide	Injection
Hemolphilus influenzae	Polysaccharide	Capsular polysaccharide	Injection

Needle-free Vaccination



Courtesy of Samir Mitragotri. Used with permission.

Needle-free Vaccination Sites

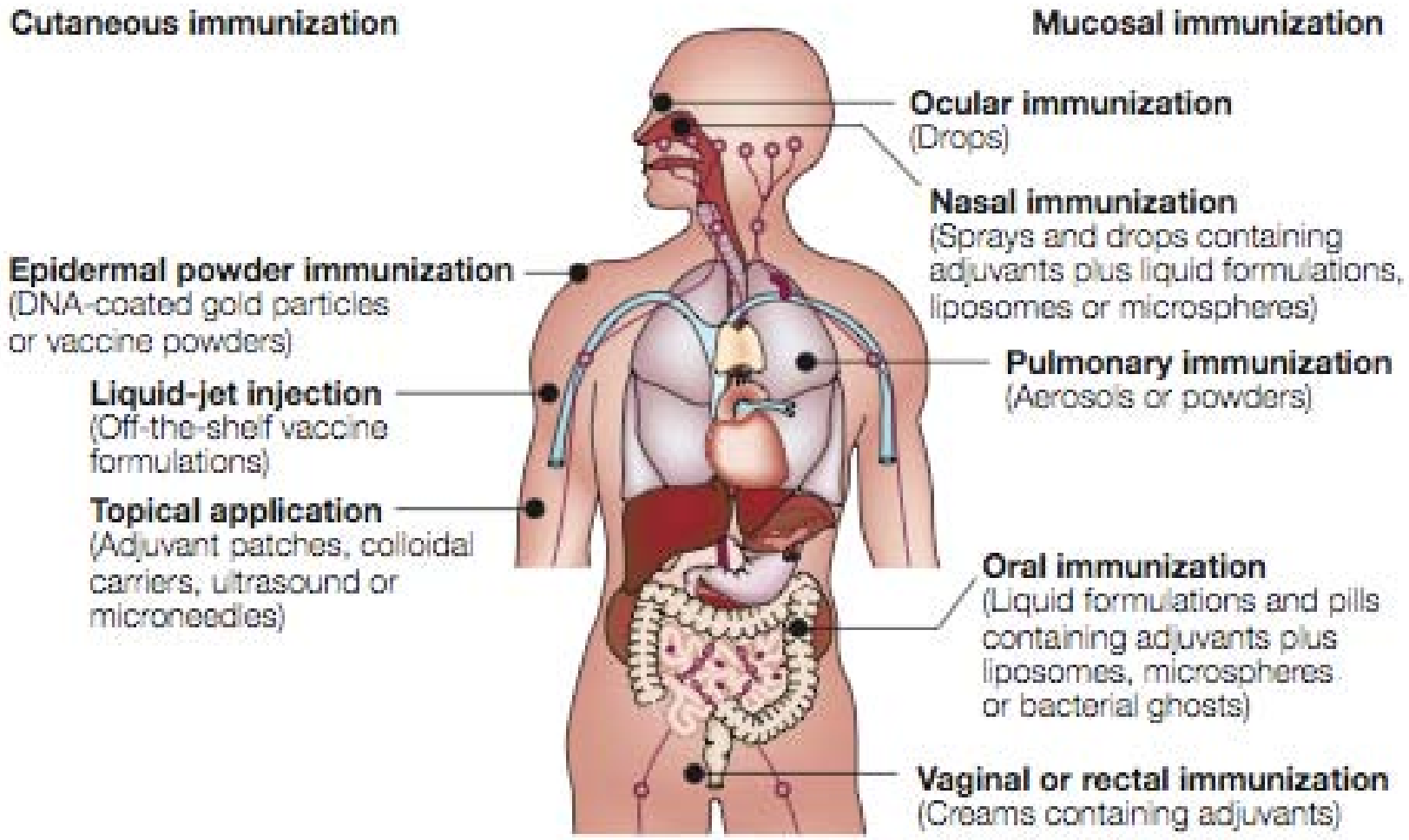


Figure 1 | **Schematic representation of various methods of needle-free immunization.**

DNA Vaccine Delivery by Propulsion into Skin via a "Gene Gun"

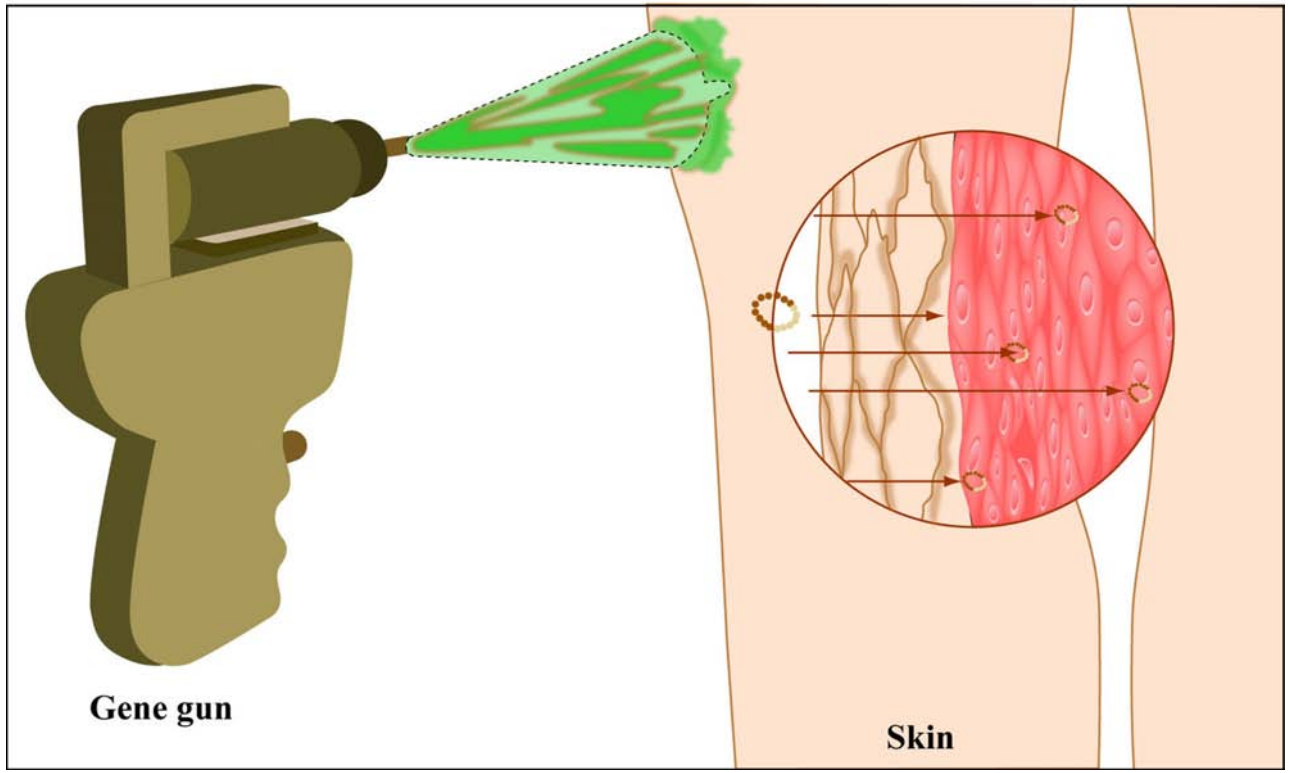


Figure by MIT OpenCourseWare.

Allows rapid delivery of a vaccine to large populations without the requirement of huge supplies of sterile needle and syringes

Two images removed due to copyright restrictions.
"How to Make an Edible Vaccine" and
"How Edible Vaccines Provide Protection."
Source: Langridge, W. H. R. "Edible Vaccines." *Scientific American*.
September 2000.

Standard Immunization Team

DRUG PREPARATION

DOCTOR GIVES SHOT

PATIENT REGISTRATION

BIOHAZARD DISPOSAL

6 *PHYSICIANS AND AIDES*

200 *PATIENTS IN-CLINIC*

70 *PATIENTS IN THE FIELD*

Sources: USAID, Becton Dickinson

Aerovax Man

1 *LOW SKILLED VOLUNTEER*

650 *PATIENTS IN THE FIELD*

62% *SAVINGS*

Sources: Aerovax, MIT Analysis

Dry Powder Vaccines

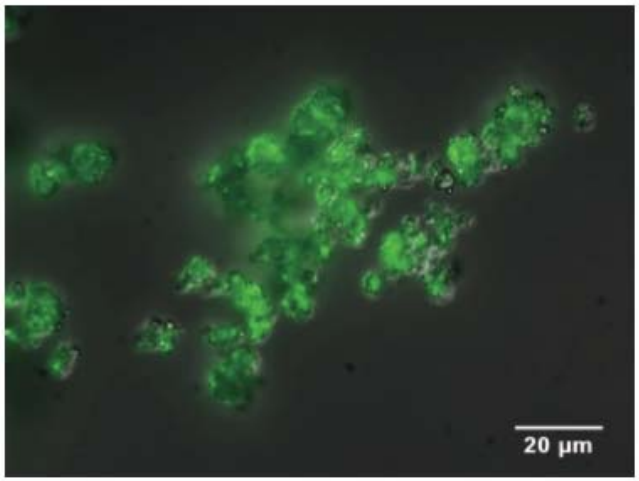
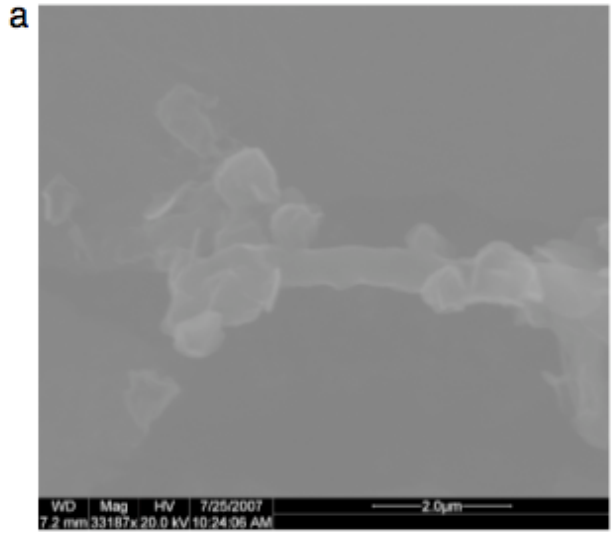
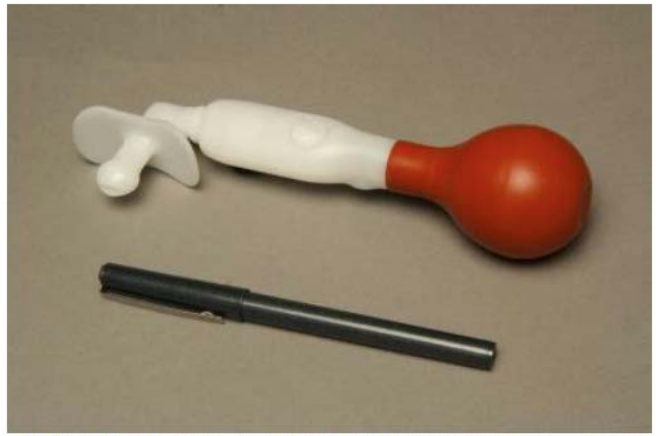


Fig. 3. Electron micrograph of GFP-labeled *M. smegmatis* spray dried with leucine.





SI Fig 5. Newborn dry powder inhaler device with squeeze actuation.

Sources: Left: Wong, Y-L, et al. "Drying a tuberculosis vaccine without freezing." *Proc Natl Acad Sci USA* (2007) 104, no. 8: 2591-2595. Right: Garcia-Contreras, L, et al. "Immunization by a bacterial aerosol." *Proc Natl Acad Sci USA* (2008) 105 (12): 4656-4660. Courtesy of National Academy of Sciences, U. S. A. Used with permission. Copyright © 2007, 2008 National Academy of Sciences, U.S.A.

Focus Areas for Designing Solutions

- Transcutaneous delivery of vaccines – Iomai/Intercell Inc Technology

- See videos at http://www.iomai.com/content/view/23/37/

Pneumococcal Vaccines …

- Wyeth: 7-valent Prevnar/Prevenar™ licensed in >70 countries.
- Wyeth: 13-valent expected licensure in late 2009/early 2010.
- Glaxo Smith-Kline: 10-valent expected licensure in Q4 2008.
- Some protein-based vaccines in development.

pneumoADIP

…and Global Health Issues

- Cost - Prevnar™ ≈ $300 for a 3-4 dose regimen.
- Administered by needles, requiring qualified medical personnel.
- Absolute cold chain requirement.
- Only modest effect on nasopharyngeal colonization.
- Limited number of capsular serotypes included causes concerns of serotype replacement - non vaccine-type invasive disease has increased following universal immunization with conjugate vaccines.

Streptococcus pneumoniae (Pneumococcus)

- A major cause of morbidity and mortality worldwide
  - Over 1 million deaths annually due to pneumonia[1]
- Incidence of infection varies globally
- Age groups at highest risk for disease:
  - Infants and children < 2 years of age
  - Adults > 65 years of age
- Pneumococcal disease frequently observed in children up to 5 years of age
- Causes pneumonia, bacteremia, meningitis, otitis media, sinusitis

WHO. "Pneumococcal vaccines."
Wkly Epidemiol Rec. (1999) 74:177-184.

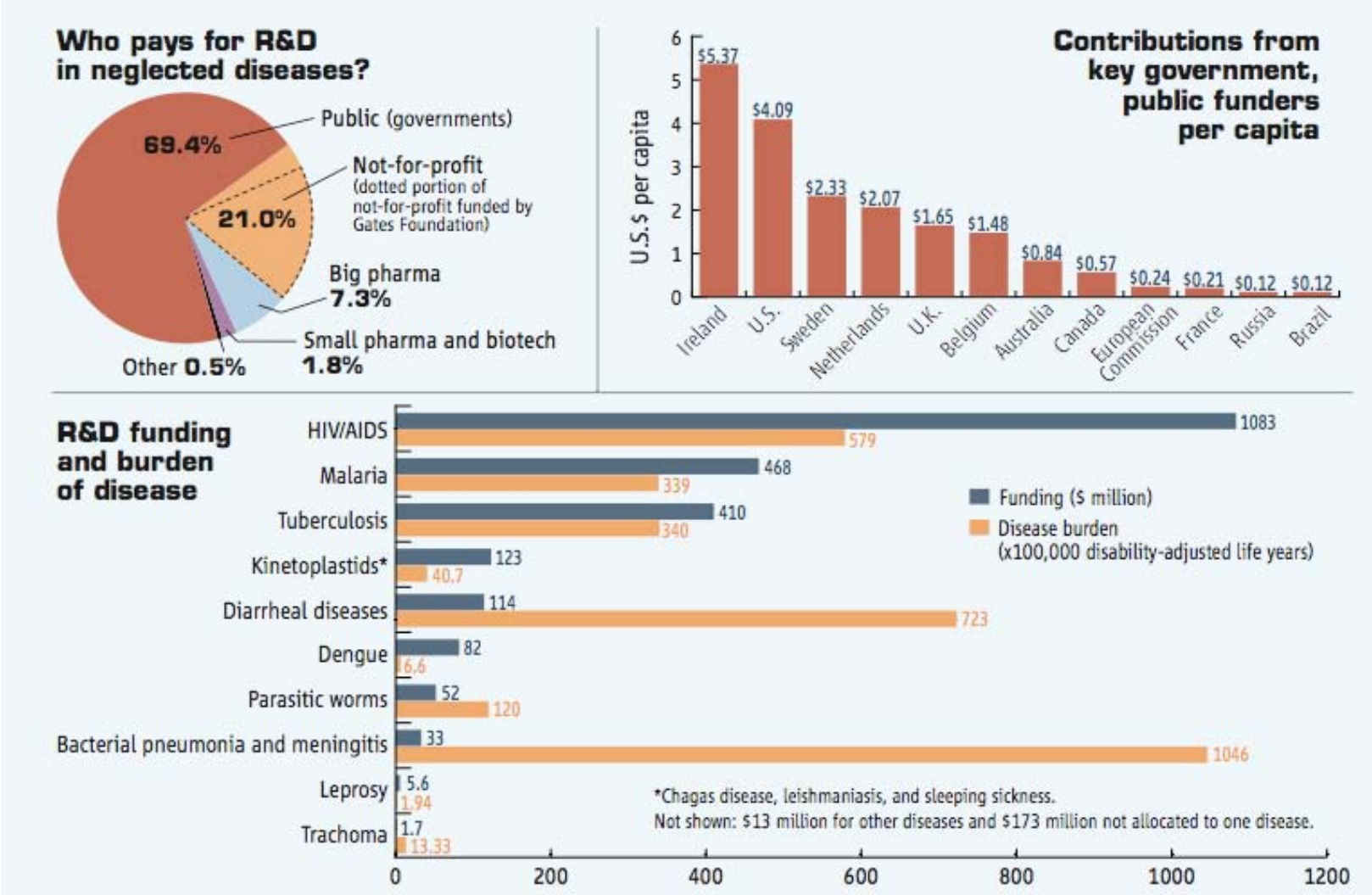
Photos of pneumococcus removed due to copyright restrictions. See Fig. 3 in Hammerschmidt, S. et al. "Illustration of Pneumococcal Polysaccharide Capsule during Adherence and Invasion of Epithelial Cells." *Infection and Immunity* 73, no. 8 (2005): 4653-4667.

Whole Cell Vaccine Against *S. pneumoniae*

- Ethanol killed whole pneumoccal bacteria
- Simple manufacture
- Easy and inexpensive to prepare
- Stable
- Administered intrnasally at a non-sterile site
- Inexpensive to administer

- Institutions
  - Children's Hospital Boston
  - Göteborg University
  - Harvard School of Public Health
  - Instituto Butantan
  - PATH

Some Neglected Diseases Are More Neglected Than Others



Moran M, Guzman J, Ropars AL, McDonald A, Jameson N, et al." Neglected Disease Research and Development: How Much Are We Really Spending?" *PLoS Medicine Vol. 6, No. 2, e30 doi:10.1371/journal.pmed.1000030*. Licensed CC – by.

Global Health Innovation Compass

Inexpensive / Appropriate

Expensive / Appropriate

Figure by MIT OpenCourseWare.

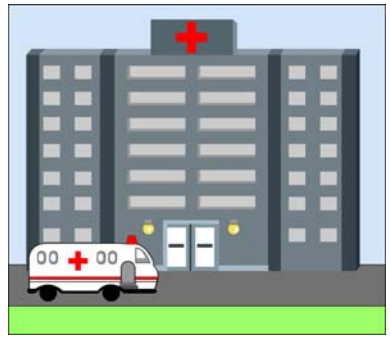


Figure by MIT OpenCourseWare.

Inexpensive / Not Very Appropriate

Expensive / Not Very Appropriate

Program Goal X Level of Pushing the Status Quo

Net Resources Expended (Time & Money – Resulting Impact)