Vaccines: Past, Present, and Future

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About the Speaker

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- **Scientific interests: gene therapy, microbial pathogenesis, immunology**
- **A full time medical translator since 2007 (English-Finnish)**

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Folkhälsoinnstitutet
National Public Health Institute
Publications of the National Public Health Institute A 3 / 1997

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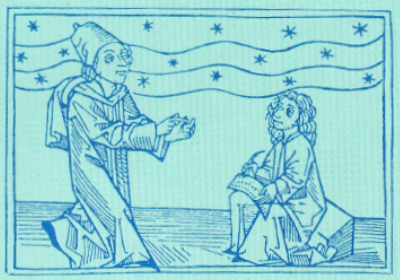
REGULATION OF INTERFERON-INDUCIBLE ANTIVIRAL GENE EXPRESSION IN HUMAN CELLS



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Contents of This Talk

- History of vaccination
- Immunological memory
- Classification of vaccines
- Case studies in vaccine development
- Regulatory affairs and vaccine safety
- Vaccine safety and herd immunity
- Future challenges

History of Vaccination

A Greek historian Thucydides noted that those who survived the plague epidemic in ancient Athens (430 BC) did not fall ill twice.

Indeed, the recovered individuals were considered "exempt from " the disease -- they became "immune."

Latin: immunis "exempt, free"

History of Vaccination (cont'd)

- In medieval times, Chinese used "variolation" to protect against smallpox
- Skin material from patient given to healthy recipient
- Dangerous but popular
- The real cause of smallpox not understood

History of Vaccination (cont'd)

- **Until 19th century, Europeans believed that "miasma" (bad air) caused epidemics of plague etc.**
- **Variolation adopted by Turks, and from them by English**
- **Edward Jenner developed the cowpox *vaccine* based on his observations of milkmaids and their immunity from smallpox**
- **Latin: vaccinus ("from cows")**

Edward Jenner (1749-1823)

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Painting by James Northcote. National Portrait Gallery, London.

History of Vaccination (cont'd)

- **Foundation of Germ Theory: microscope invented by a Dutch scientist Antonie van Leeuwenhoek (1632-1732)**
- **Magnification of up to 250x**
- **First person to see single-celled organisms (micro-organisms)**

History of Vaccination (cont'd)

- **Germ Theory of Disease was firmly established in the 19th century by Louis Pasteur and Robert Koch**
- **Pathogenic microbes were now isolated and studied systematically**

Louis Pasteur (1822-1895)

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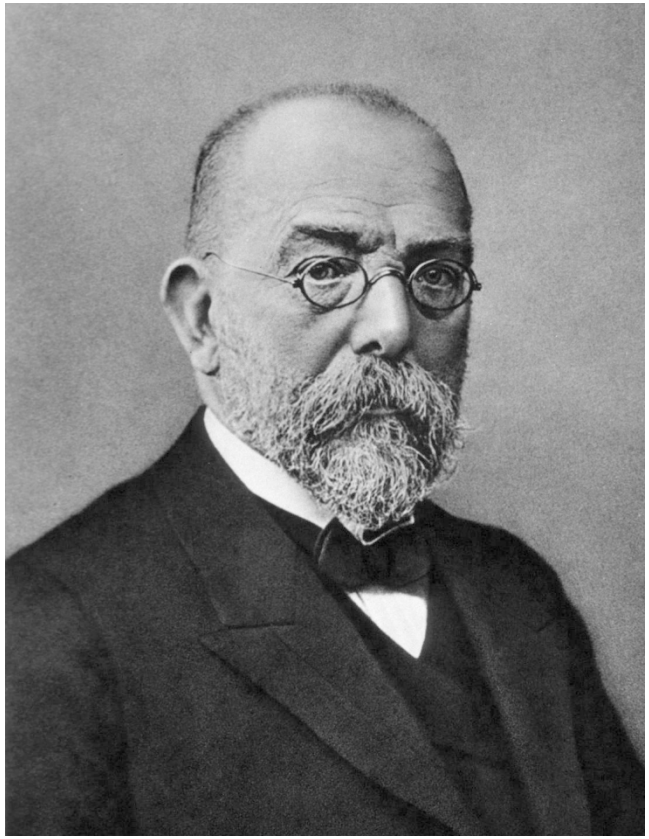
Robert Koch (1843–1910)



Public Domain image. https://en.wikipedia.org/wiki/Robert_Koch

The First Golden Age of Vaccines

- **Attenuated and inactivated pathogens, inactivated toxins**
- **Cell cultures – study of viruses in vitro**
- **Vaccines against polio, mumps, rubella, measles, and others**

Eradication of Smallpox

- Old scourge of mankind
- Infectious disease caused by Variola virus
- Mortality rate 20-60% (and over 80% of infected children)
- Systematic vaccination campaigns led to global eradication of smallpox in 1979
  - No animal host for Variola

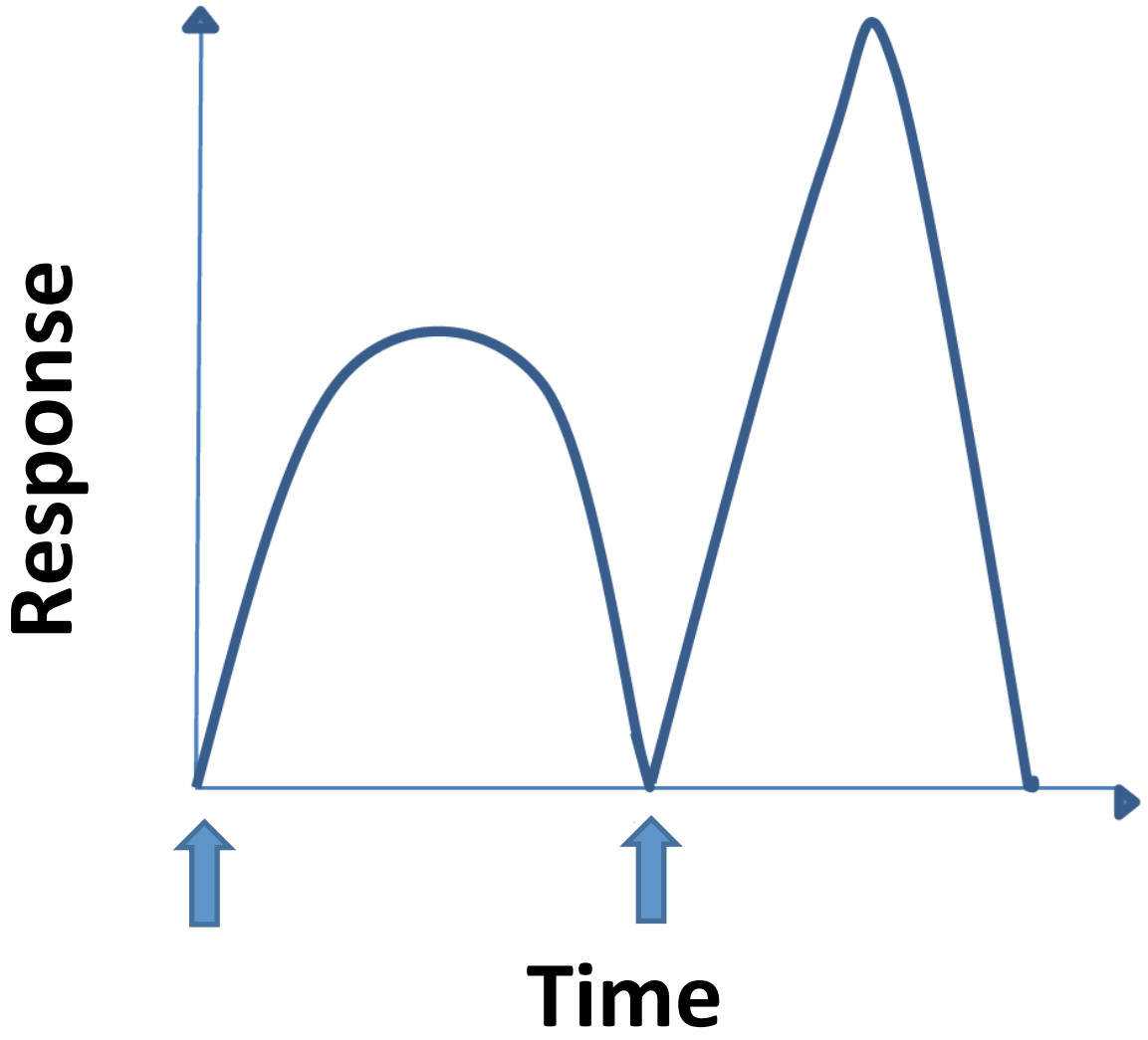
Eradication of Rinderpest

- Infectious viral disease of cattle
- High mortality (up to 100%)
- Widespread eradication efforts since the early 1900s
- Global Rinderpest Eradication Programme 1994->, last confirmed case in Kenya in 2001
- Declared eradicated in 2011

Immunological Memory

- **Rapid, innate response (macrophages and other innate immune cells)**
- **Slower, acquired response (B and T cells)**
  - **B cells make antibodies**
  - **T cells kill infected host cells**
- **Acquired response has a memory**

Immunological Memory (cont'd)



Efficacy and Safety

- **Vaccination is based on immunological memory**
- **Sufficient immunogenicity -> *efficacy***
  - **Adjuvants as needed**
  - **Antigen selection**
  - **Both innate and adaptive immunity activated**
- **Purity, formulation -> *safety***

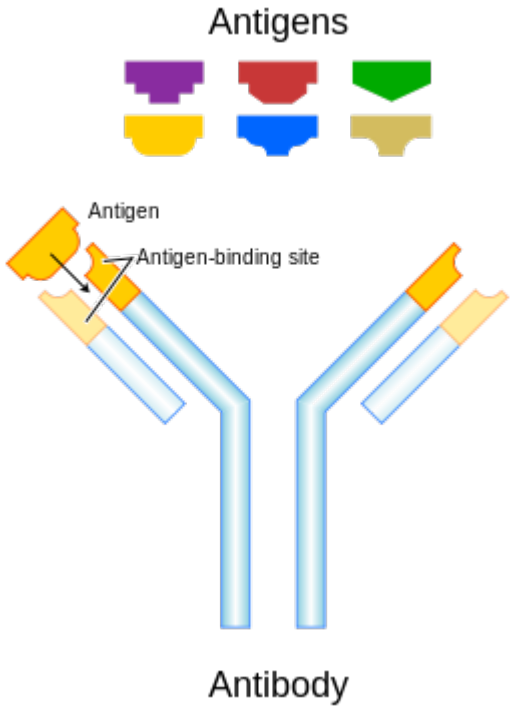
Key Concepts

- **Antigen: any molecular structure capable of generating an immune response**
- **Antibody: soluble protein from B cells, able to bind to antigen**
- **Adjuvant: substance in vaccine that enhances its ability to induce protection against infection**
  - **Alum only or Alum combined with lipid**

Key Concepts (cont'd)

- **Prime: immune system is primed to a target antigen using vaccine 1**
- **Boost: immune response is enhanced by a second vaccination with vaccine 2**
  - **Vaccine 2 may be the same as vaccine 1 or different**

Antibody with Antigens



Public Domain image. https://en.wikipedia.org/wiki/Antibody

Classification of Vaccines

- Live, attenuated vaccines
- Inactivated vaccines
- Toxoid vaccines
- Subunit vaccines
- Nucleic acid vaccines
- Recombinant vector vaccines

Live, Attenuated Vaccines

- **Viruses or bacteria that have been weakened by repeated growth cycles (in case of viruses) or by chemical methods (in case of bacteria)**
  - **Example: Bacillus Calmette-Guerin (BCG)**
- **Easier to attenuate viruses**
- **Robust immunity**
- **Reversion may sometimes be an issue**
  Example: *Sabin polio vaccine*

Inactivated Vaccines

- **Microbes rendered noninfectious by chemical or thermal treatment, or by radiation**
- **No reversion**
- **More stable in storage**
- **May be less immunogenic**
- **Example: *Salk polio vaccine***

Toxoid Vaccines

- **Contain bacterial toxins rendered harmless by formalin treatment**
- **Still antigenic and can generate an immune response**
- **Example: vaccines against diphteria and tetanus**

Subunit Vaccines

- **Contain only a subunit / subunits of the pathogenic micro-organism**
- **Safe and effective (if subunits immunogenic)**
- **Fewer adverse effects (*vaccine reactions*)**
- **Usually protein subunits, sometimes carbohydrates**
- **Example: vaccine against *Haemophilus influenzae type b (Hib)***

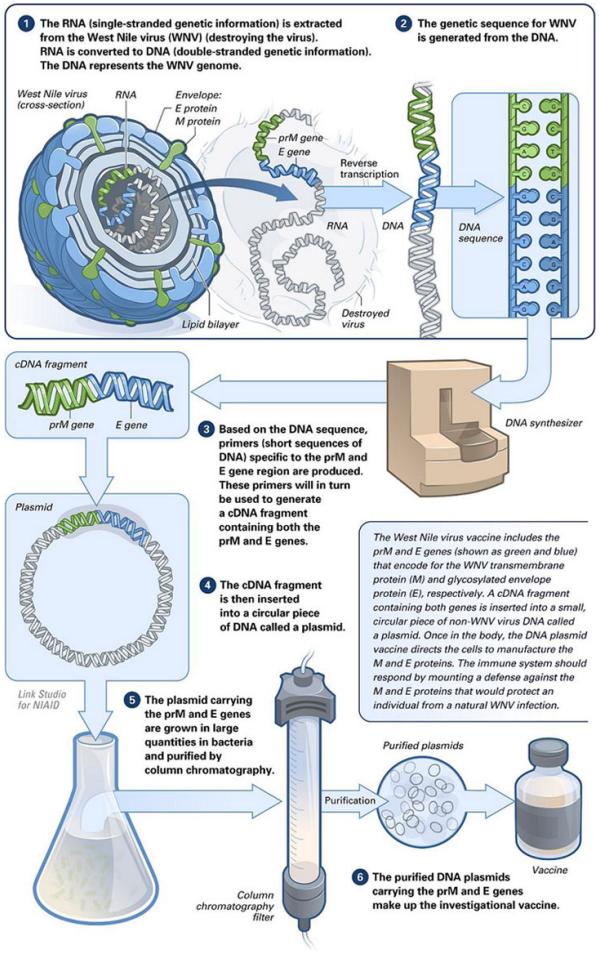
Nucleic Acid Vaccines

- **Still experimental but show great promise**
- **Instead of heat labile, complex formulations, DNA or RNA given to recipient's muscle**
- **Cheap to make and deliver**
- **Suitable adjuvants necessary**
- **DNA antibodies? Insertion mutagenesis?**

Nucleic Acid Vaccines (cont'd)

- RNA vaccines are in development
- RNA into cells -> translated to protein
- Self replicating RNA constructs
- RNA active in cytoplasm (no nuclear safety concerns)
- RNA itself highly immunogenic -> innate immunity activation
- No concerns with DNA antibodies

Nucleic Acid Vaccines (cont'd)

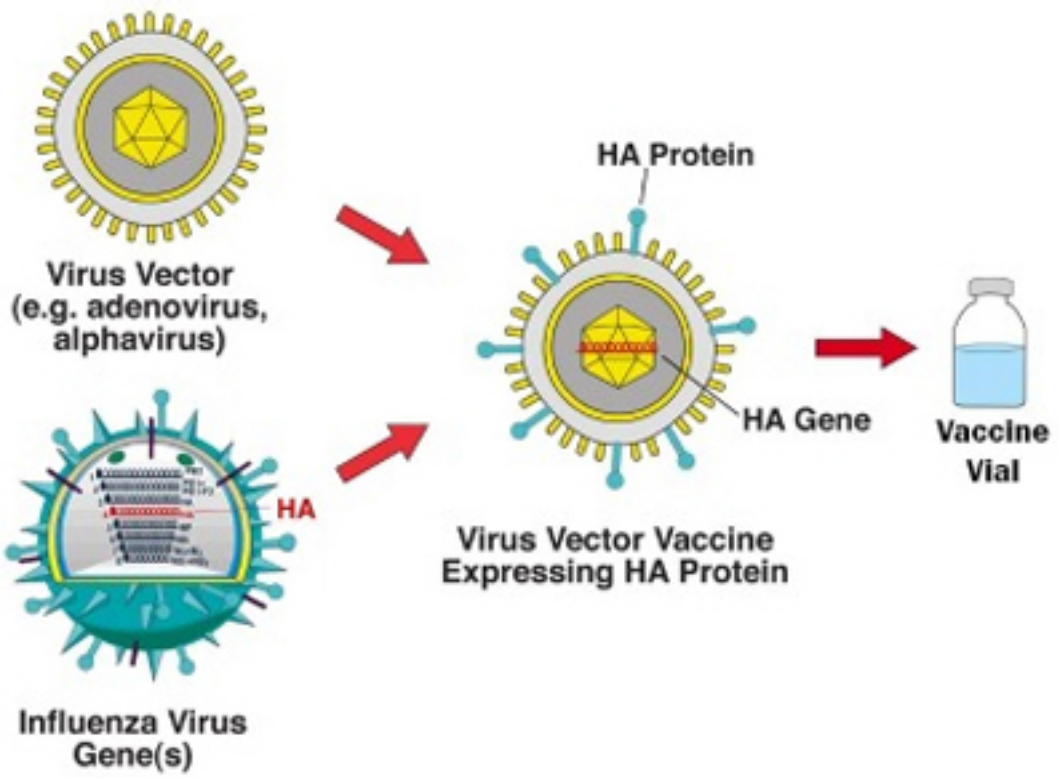


Courtesy: National Institute of Allergy and Infectious Diseases

Recombinant Vector Vaccines

- **Hybrid viruses (or bacteria)**
- **Harmless microbe (vector) combined with antigen of interest**
- **For example: VSV vector**
- **Vectors well understood and safe**
- **As living microbes, they give long challenge to the immune system**

Recombinant Vector Vaccines (cont'd)



Courtesy: National Institute of Allergy and Infectious Diseases

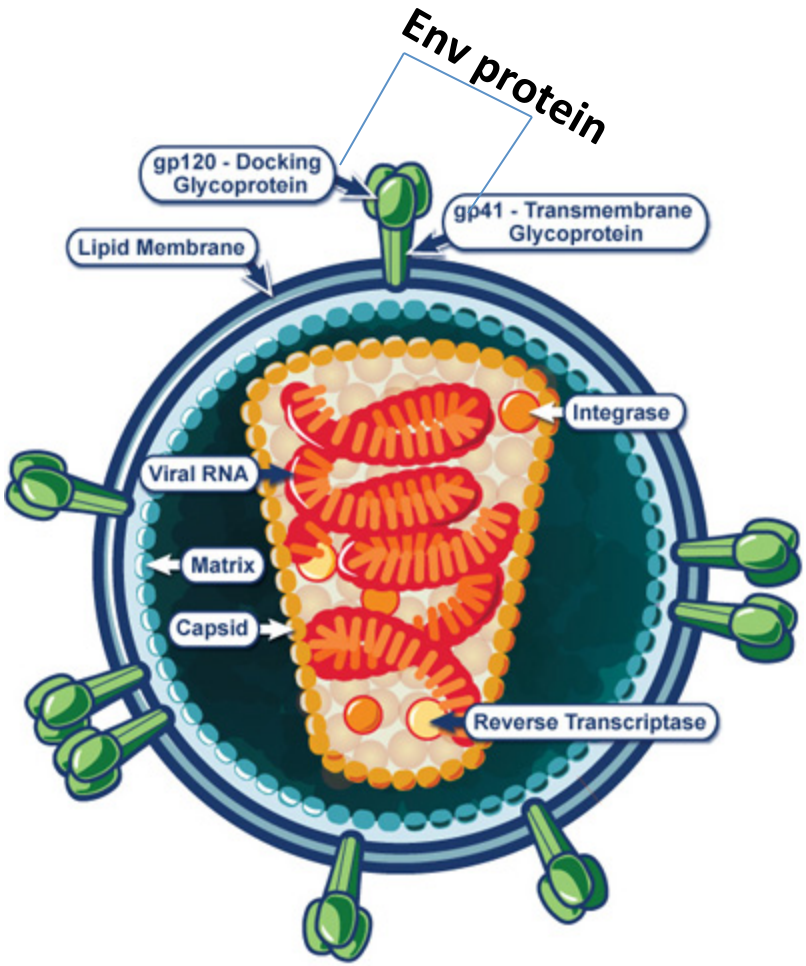
Case Studies in Vaccine Development

- **Good protective vaccination urgently needed for some important diseases, such as HIV/AIDS, tuberculosis, malaria, and hepatitis C**
- **Often the problem is poor antigenicity or high variability of the pathogen**
- **Three case studies: HIV/AIDS, tuberculosis, Ebola**

Case 1: HIV/AIDS

- **HIV is a complex retrovirus that causes AIDS**
- **Highly variable virus antigens**
- **Virus can stay latent inside host genome for years**
- **Goal: identify antigenic structures on the HIV surface that would provide broad immunity against different HIV strains**

Structure of HIV



Courtesy: National Institute of Allergy and Infectious Diseases

Case 1: HIV/AIDS (cont'd)

- **HIV is a complex retrovirus that causes AIDS**
- **Highly variable virus antigens**
- **Virus can stay latent inside host genome for years**
- **Killed HIV not antigenic; weakened HIV unsafe**
- **Goal: identify antigenic structures on the HIV surface that would provide broad immunity against different HIV strains**

Case 1: HIV/AIDS (cont'd)

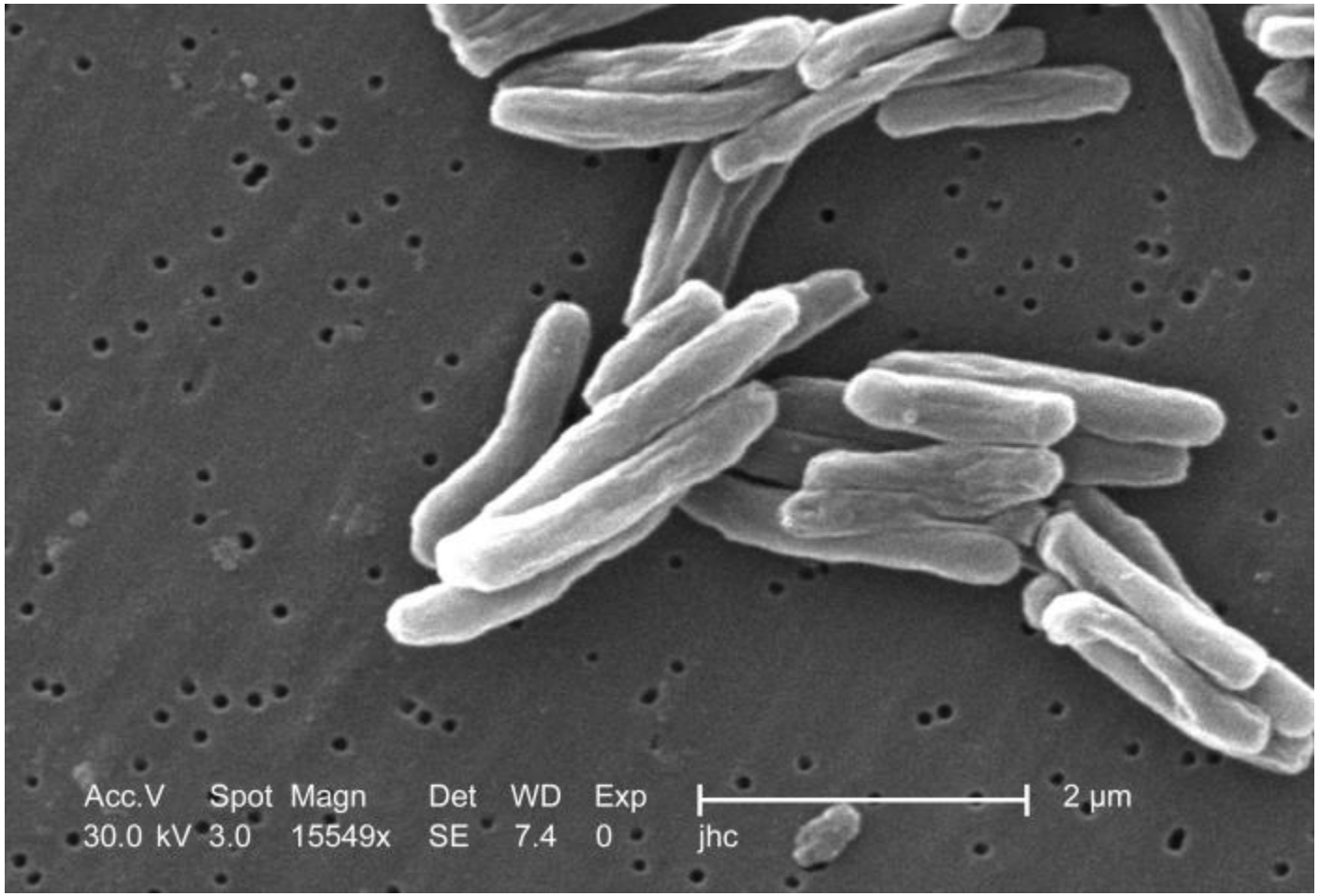
- **Many vaccine trials have been disappointing**
- **Thai vaccine study used two recombinant vectors as prime / boost combination**
- **Efficacy 31% (in preventing HIV infection) among 16 thousand participants**
- **Next goal: efficacy >50%**
  - **Enough for licensing?**

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al.
Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand.
N Engl J Med. 2009 Dec 3;361(23):2209-20

Case 2: Tuberculosis

- **Major public health problem in developing countries**
- **Predominantly lung disease caused by *Mycobacterium tuberculosis***
- **BCG vaccine inefficient in adults**
- **Slow infection – efficacy?**
- **Multivalent vaccines in development**

Mycobacterium tuberculosis

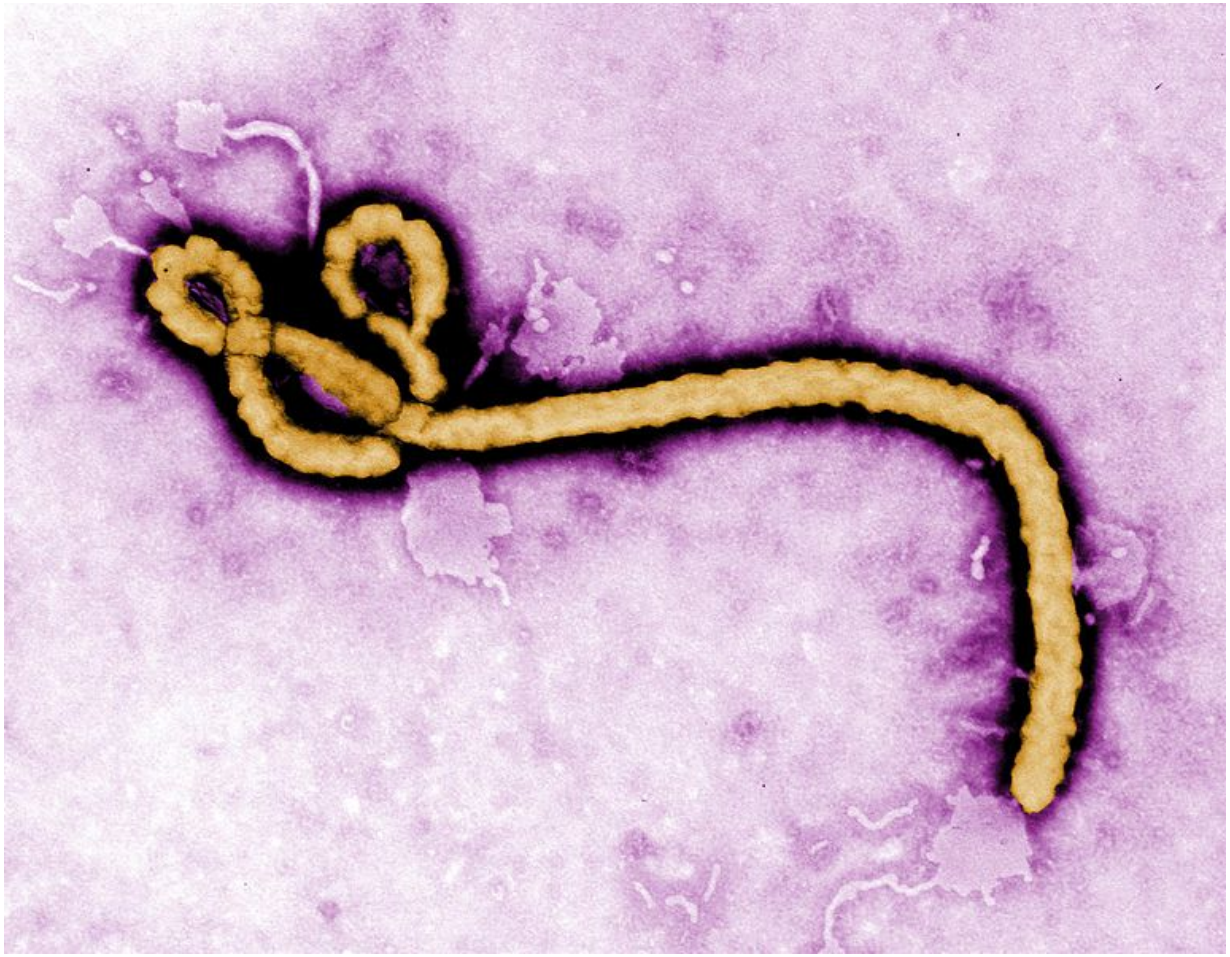


Courtesy: Centers for Disease Control and Prevention.

Case 3: Ebola

- **Deadly viral hemorrhagic fever caused by a filovirus**
- **Primary host not human (fruit bat?)**
- **Mortality rate over 50%**
- **Recent epidemic prompted intense vaccine development efforts**

Case 3: Ebola (cont'd)



Courtesy: Centers for Disease Control and Prevention. Image by Frederick A. Murphy.

Case 3: Ebola (cont'd)

Active outbreak still in 2015 in Liberia, Guinea, and Sierra Leone

Public Domain Image

Case 3: Ebola (cont'd)

- **Recent paper in Lancet detailed a vaccine trial in Guinea where vaccination was safe and 100% effective**
- **VSV vector with Ebola glycoprotein antigen**
- **Due to ethical concerns, the control group got delayed vaccination instead of placebo**

Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015 Aug 29;386(9996):857-66

Regulatory Framework for Vaccines

- **Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER)**
  - **Investigational New Drug (IND) application for any clinical trial**
  - **If all trial phases successful, submit Biologics License Application (BLA)**
  - **Approved BLA -> marketing launch**
  - **VAERS system to monitor adverse events**
- **In Europe: European Medicines Agency, CHMP**

Vaccine Safety and Herd Immunity

- **The benefit/risk balance of current vaccines is good**
- **However, some recipients unsuitable (immunocompromised or allergic persons)**
- **Claimed link between vaccinations and autism has been thoroughly debunked**

Vaccine Safety and Herd Immunity (cont'd)

- **It is not necessary to be able to vaccinate 100% of the target population to stop infectious diseases.**
- **A concept called *herd immunity* protects the unvaccinated individuals in the target population as long as the vaccination coverage is adequate (WHO recommends coverage of 95%).**
- **Measles epidemic of 2015 in US is an example of what can happened if vaccination coverage is inadequate (189 cases)**

Future Challenges

- **Cold chain in developing countries**
- **Highly variable microbes (influenza, HIV)**
- **Many pediatric vaccines not affordable to people in poorest countries**
  - **Global Vaccine Alliance**

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Thank you!

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