Vaccines

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Who Is Bruce Scharschmidt & Why Is He Giving This Talk?

UCSF Faculty from 1977 – 1996 (Chief of GI)

- Editor of JCI and President of Am Society for Clinical Investigation
- With Colleagues in Surgery & Medicine (e.g. Drs. Ascher, Bass) started liver transplant program

Left Academic For Industry in 1996

- Headed clinical development of therapeutics and vaccines at Chiron
- VP in Novartis Vaccines Division from 2006-2008 after its acquisition of Chiron
- Joined Hyperion as Chief Medical Officer in 2008

Thinks Vaccine Development is a Terrific Field

- Also underserved
- Hopes one person comes away intrigued by vaccines

Conflict of Interest: Novartis Shareholder

Severe Hereditary Sensorineural Hearing Loss

- Don’t hesitate to ask questions – I’ve got an interpreter

Outline

High Altitude View

- What is a vaccine
- Immunization launched the modern medical era
- Vaccines play on a world stage
- Establishing safety and efficacy
- Vaccines from a business perspective

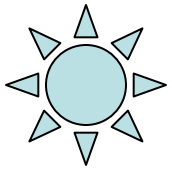
Ground Level View

- Safety: How would we prove a vaccine doesn't cause Sudden Infant Death?
- Efficacy Endpoints: Immunogenicity vs. Field

Real Case Studies

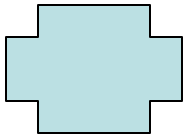
- Meningococcus A,C,W,Y (Menveo)
- Meningococcus B & discovery of new antigens using 'reverse vaccinology'
- Group B Strep – Reverse vaccinology & serendipity
- Influenza/pendemic influenza & adjuvants
- *H. pylori* & where it has taken me

The Basics: Vaccine = Antigen +/- Adjuvant



Antigen

- Mimics a microbe -> immune stimulation
- Traditional: killed pathogen, purified pathogen subunit
- Recombinant proteins: HBV was the forerunner
- New approach to discovery: ‘Reverse vaccinology’ (Will discuss this later in relation to MenB & Group B Strep)



Adjuvant

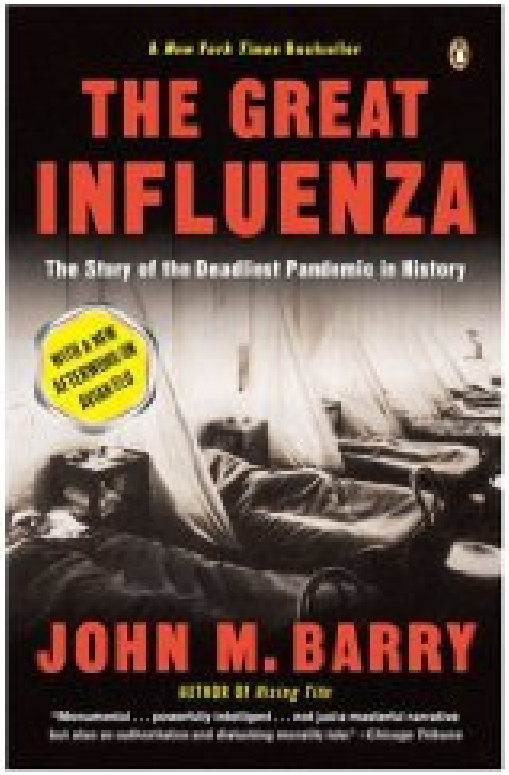
- Many vaccines have none (e.g. seasonal flu in US)
- Pace of development slow (‘only’ Alum for decades)
- Emerging ‘smarter antigens’: pattern recognition receptors (Will discuss later in relation to seasonal, pandemic influenza)

Live Attenuated Vaccines

- Similar pathogen which induces protection but not disease
  - o Cowpox and smallpox

- Altered/attenuated version of the original pathogen
  - o Grown under altered conditions (e.g. Sabin's polio vaccine, or MMR (measles, mumps and rubella)

The Great Influenza by John Barry

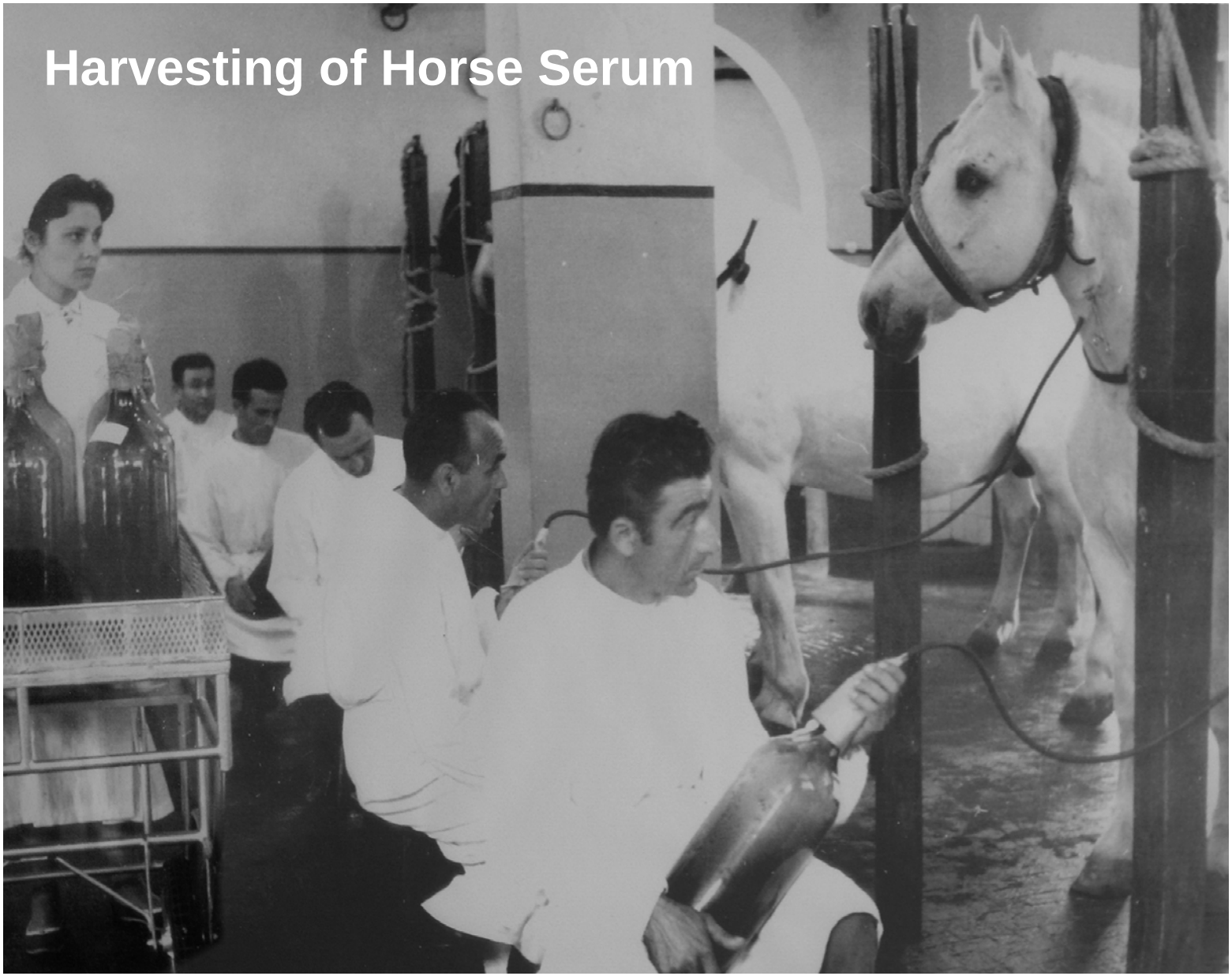


- Begins with the sorry state of American medicine at the turn of the century
- Only a minority of states required MDs to be licensed, the presumption being it was largely quackery
- Immunotherapy changed perceptions. In 1901, Emil von Behring was awarded the first Nobel Prize in Medicine for serum therapy for diphtheria.
- Led to foundation of Behringwerke – subsequently part of Chiron & now Novartis Vaccines.
- Similar work on anthrax by Achilles Sclavo, in Siena Italy, resulted in founding of ‘Sclavo’ that is now also Research Headquarters for Novartis Vaccines.

- Passive immunotherapy evolved into vaccination
- The 1918 pandemic, killed up to 50M worldwide, was a tough lesson on protection

From Sclavo Archives

(Now Novartis Vaccines in Siena Italy)



Steps to the Research Center

The Deep & Shallow Steps Were Made For Horses

Vaccines ‘Push & Pull’

PUSH

Multinational & Non-governmental organizations

GAVI, IVI, IAVI, Gates Foundation

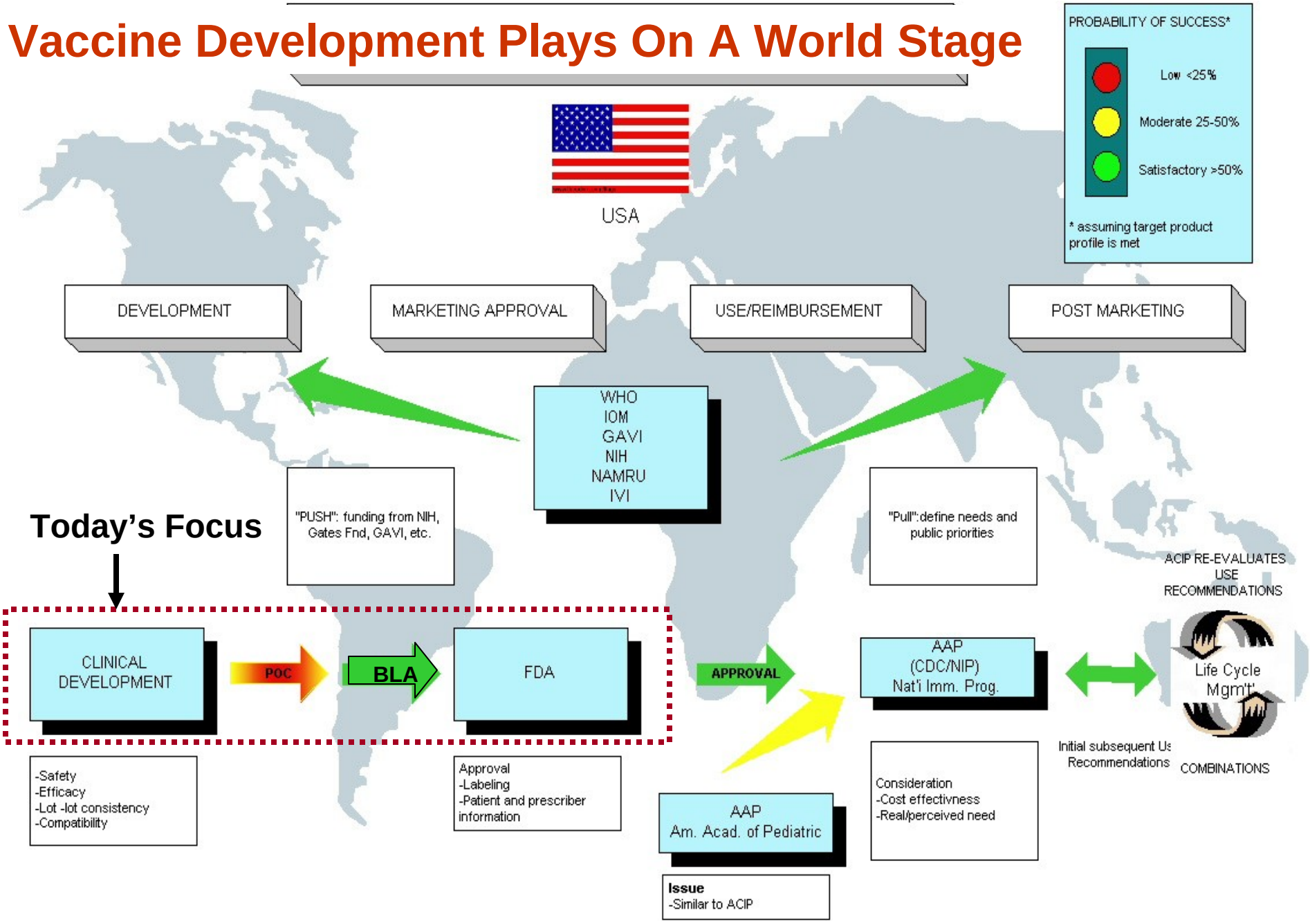
PULL

Centers for Disease Control & Prevention

Institute of Medicine

World Health Organization

Vaccine Development Plays On A World Stage



***THE PULL:* US Institute of Medicine has Prioritized National Needs Based on Cost-Effectiveness**

Priority 1 (Most Favorable: Saves money & QALYs)

- CMV under 12; group B *strep* prior to 1st pregnancy; q 5year influenza vaccine; pneumococcal vaccine for infants and over 65; vaccines for type II diabetes; MS; RA

Priority 2 (More Favorable: < $10,000 per QALY)

- Chlamydia under 12; *H. pylori* for infants; HCV for infants; HSV under 12; HPV under 12; MTB for high risk populations; *N. gonorrhea* under 12; RSV for infants and under 12 females)

Priority 3 (Favorable: > $10,000 < $100,000 per QALY)

- group A Strep for infants; group B strep for at risk adults; parainfluenza virus for infants and first pregnancy; rotavirus vaccine for infants

Priority 4 (Less Favorable > $100,000 per QALY)

- *Coccidioides immitis* for at risk infants; ETEC for infants and travelers, EPV under 12; *H. capsulatum* for at risk infants; *N meningitidis* type B for infants; *Shigella* for infants and travelers

We Will Talk About These Vaccines Today

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Vaccines vs. Therapeutics Development
What's Different?

- Establishing Safety: Higher hurdle
  - Different risk-benefit (prevention vs. treatment)

- Establishing Efficacy & Efficacy Measure
  - Validated surrogate (protective immune response)
    - Analogous to ‘sustained virological response’ for HCV or ‘hemoglobin A1C’ for diabetes
  - No surrogate (field trials or human challenge)
    - Analogous to demonstrating clinical benefit

Vaccines As A Business

Why Manufacturers Exited The Field

Long and expensive development programs

Liability

Little pricing power – vaccines are ‘a right’

Why Vaccines Are Making A Comeback

Prevnar (pneumococcal vaccine): A ‘Blockbuster’

Government intervention (e.g. shared liability)

New technology – antigen discovery & adjuvants

But – there are still only 5 major manufacturers

(Merck, Novartis, Pfizer [Wyeth], GSK, Sanofi)