



These slides are being provided in response to your request for information and not for further distribution.

Some information contained in these slides may be outside the approved Prescribing Information. This information is not intended to offer recommendations for administration of this product in a manner inconsistent with the Prescribing Information.

In order for GlaxoSmithKline to monitor safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the accompanying Prescribing Information.

FOR REACTIVE USE ONLY

Past, Present, and Future: Vaccine Innovations

Leonard Friedland, MD, FAAP

Vice President and Director, Scientific Affairs and Public Health
GSK Vaccines

Finger Lakes Area Immunization Coalition

May 15, 2019

Disclosure

Employed by GSK where I am a vaccine research physician scientist

Presentation at the invitation of Susan Sheets, RN, Maternal Child Health/Moms Program Coordinator, Wayne County Public Health

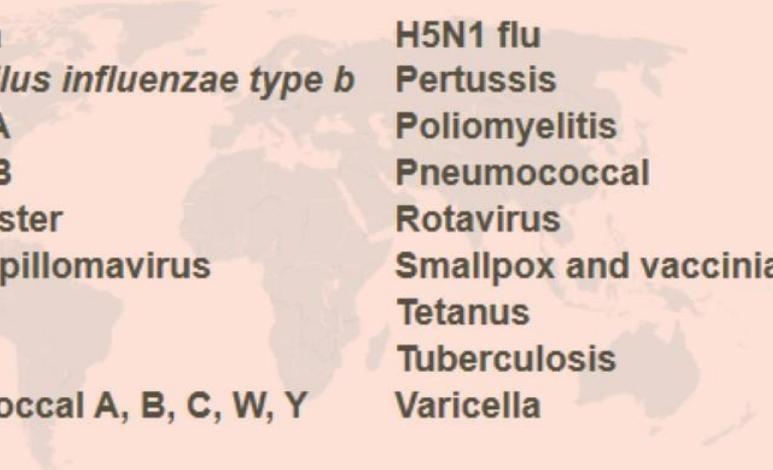
Presentation is for educational purposes only; this is not a sales, marketing or promotional presentation

Content of presentation will not include unapproved or investigational uses of products or devices

Globally, Many Diseases are Currently Preventable by Vaccination

“Vaccines are one of the greatest achievements of biomedical science and public health”³

Global public health¹



Diphtheria	H5N1 flu
<i>Haemophilus influenzae type b</i>	Pertussis
Hepatitis A	Poliomyelitis
Hepatitis B	Pneumococcal
Herpes zoster	Rotavirus
Human papillomavirus	Smallpox and vaccinia
Influenza	Tetanus
Measles	Tuberculosis
Meningococcal A, B, C, W, Y	Varicella
Mumps	

Regional focus²

Adenovirus
Anthrax
Cholera
Dengue
Japanese encephalitis
Tick-borne encephalitis
Typhoid fever
Rabies
Yellow fever

1. CDC. List of Vaccines Used in United States. <https://www.cdc.gov/vaccines/vpd/vaccines-list.html>. Accessed Jan 2017.

2. WHO. Vaccines and Diseases. <http://www.who.int/immunization/diseases/en/>. Accessed Jan 2017.

3. CDC Achievements in Public Health, 1900-1999 Impact of Vaccines Universally Recommended for Children – United States, 1990-1998. <https://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm>. Accessed Jan 2017.

Health and Human Services Healthy People 2020

Immunization and Infectious Diseases: goal

“Increase immunization rates and reduce preventable infectious diseases.”

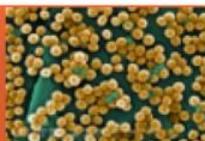
Vaccines are among the most cost-effective clinical preventive services and are a core component of any preventive services package.

Vaccine Science: Two Centuries of Continuous Research, Improvements, and Achievements



The Science of Immunology Began in the 19th Century

Microorganisms were identified as the true cause of infectious diseases



Courtesy of CDC/Janice Haney Carr/Jeff Hageman M.H.S.

Host cells that ingest and destroy invading microbes were discovered and called 'phagocytes'



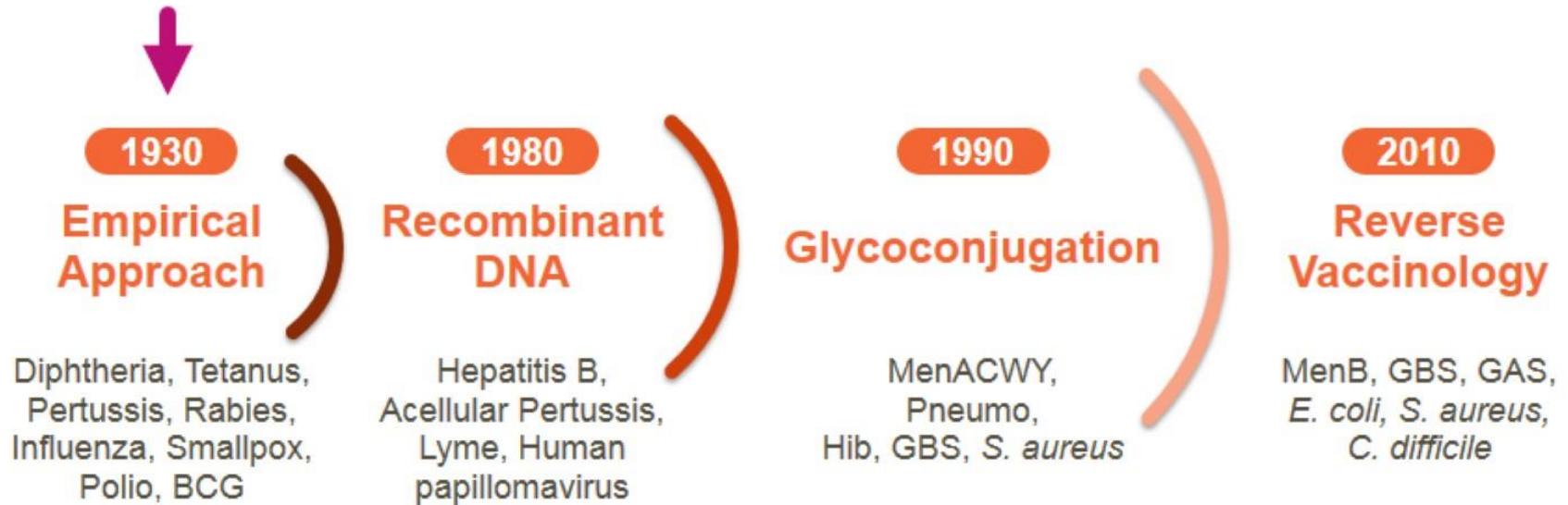
Passive immunotherapy of diphtheria with anti-diphtheria toxin antibodies discovered 'immune serum'



The antibodies theory was formulated

The concept of 'natural immunity' to infection was born

New Technologies Make Vaccines Possible That Were Previously Impossible



Growing Viruses

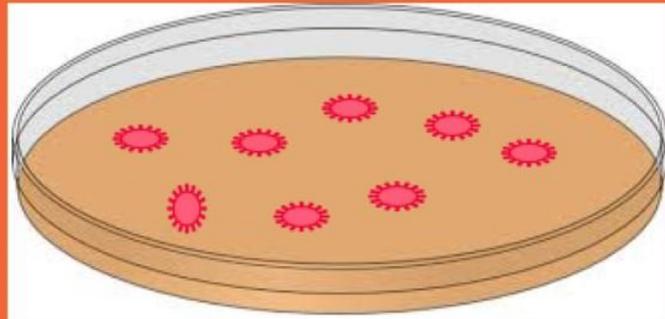
Embryonated eggs (1930s)



Courtesy of CDC

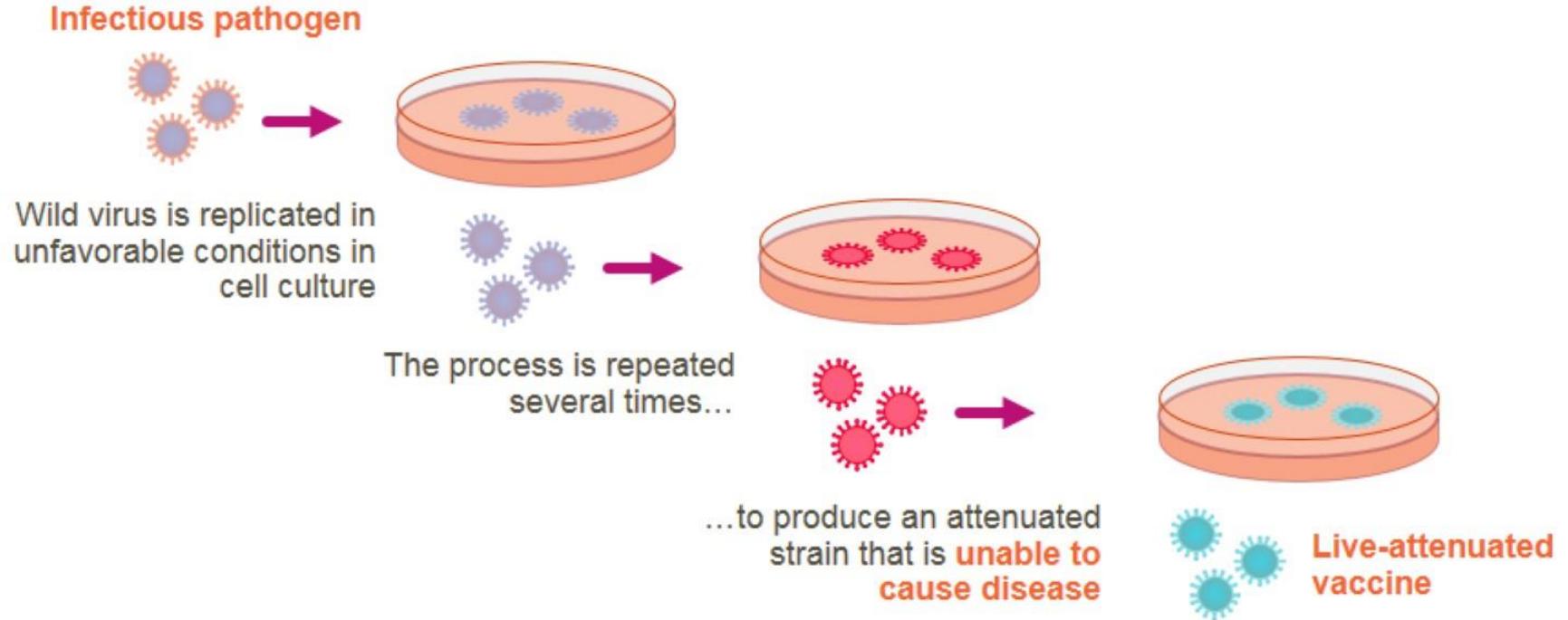
In the 1930s, Max Theiler at Rockefeller Foundation used an egg system for the development of an effective yellow fever vaccine, for which he was awarded the Nobel Prize in Medicine in 1951

Cell culture (1950s)

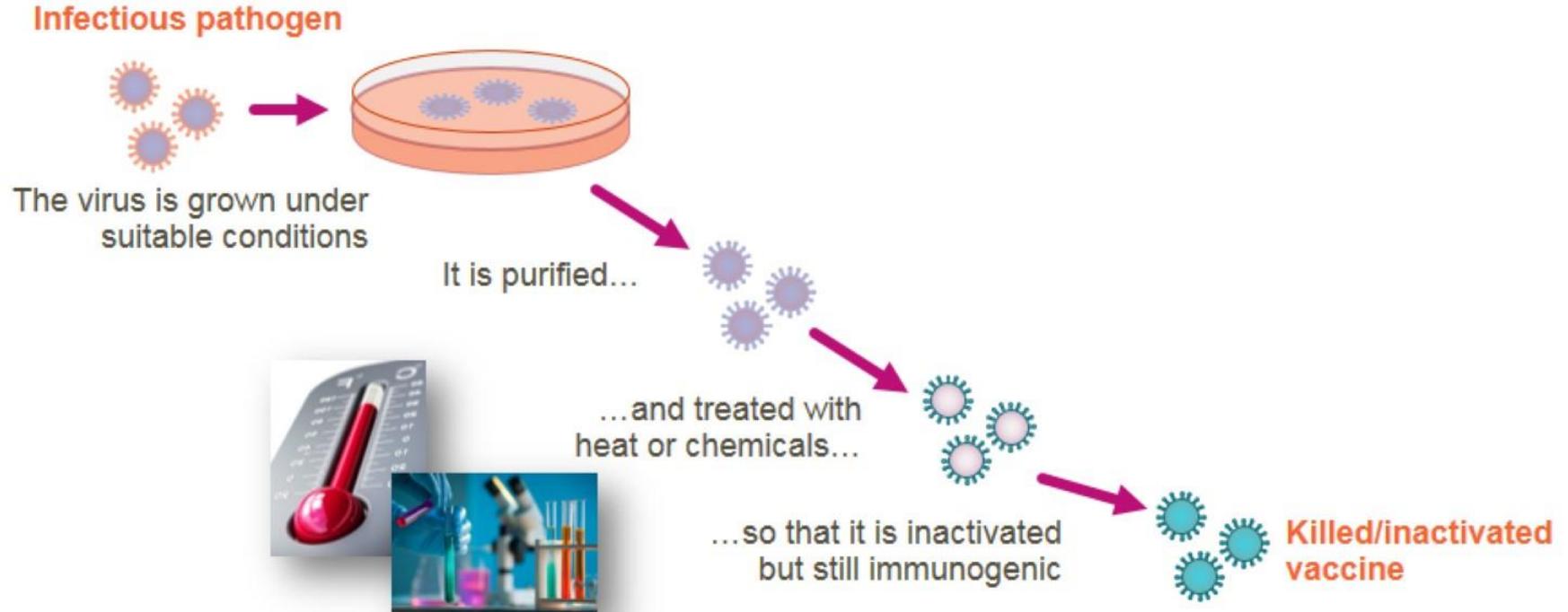


Enders, Weller and Robbins at Harvard received the Nobel Prize in Medicine in 1954 for demonstrating the ability of polio viruses to grow in cell cultures

Whole Pathogen Antigens: Live-attenuated Vaccines



Whole Pathogen Antigens: Killed/inactivated Vaccines



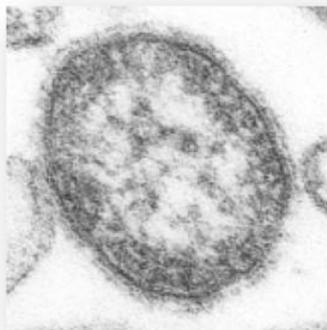
1970s

Combination Vaccines

Live-attenuated, combined MMR vaccine developed in order to minimize the total number of injections in infants

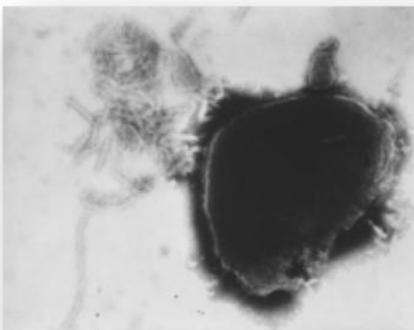
Clinical trial data demonstrate a combined antigen vaccine can be effective and can have an acceptable safety profile

Measles



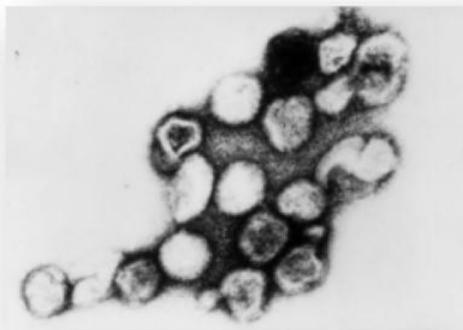
Courtesy of CDC/Cynthia S. Goldsmith, William Bellini, PhD

Mumps



Courtesy of CDC/Dr Fred Murphy

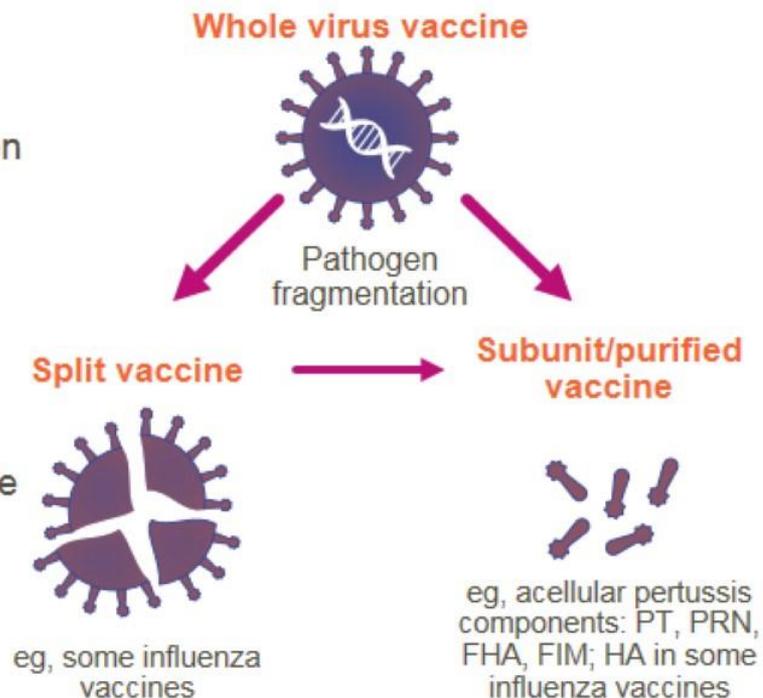
Rubella



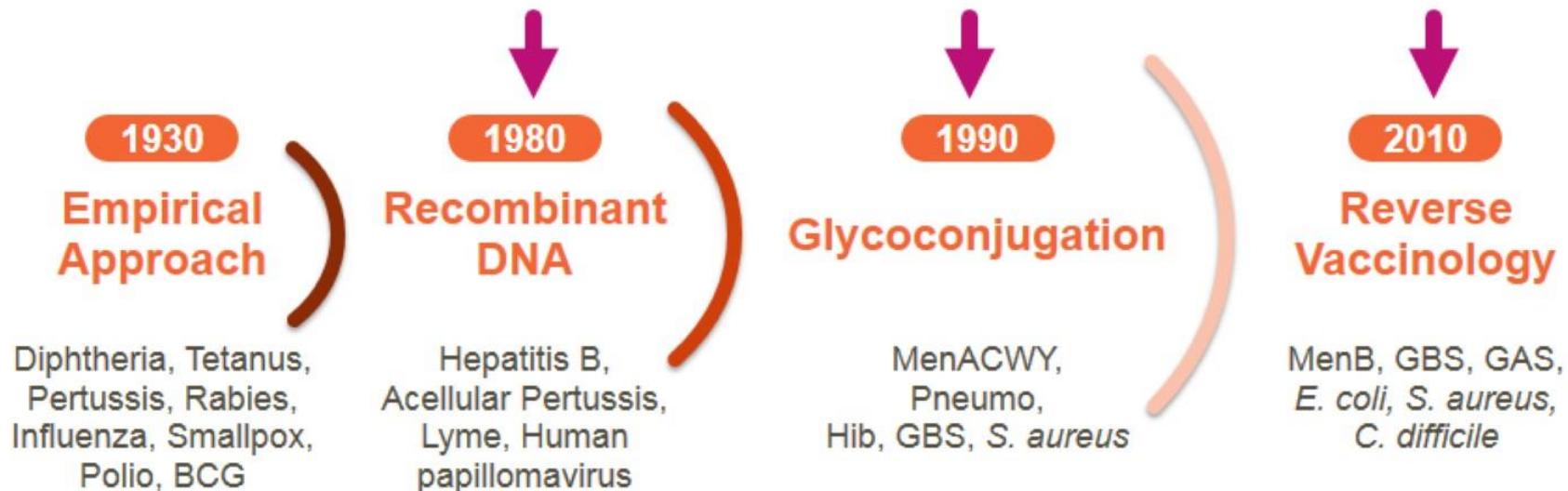
Courtesy of CDC/Dr Erskine Palmer

Split Pathogen and Subunit Vaccines

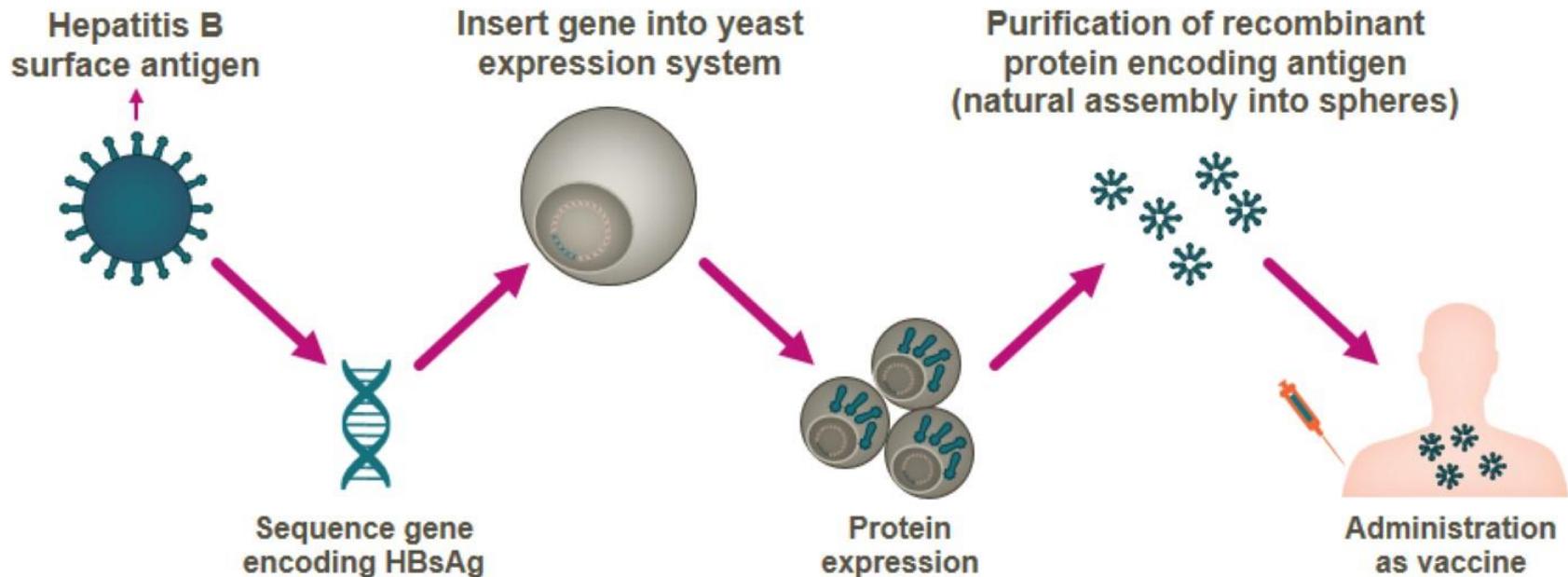
- Antigen choice: provides immune protection & technologically achievable
- Often reduced immunogenicity versus whole pathogen
- Non-infectious, low reactogenicity, acceptable tolerability
- No or limited availability of innate defensive triggers
- For subunit vaccines with lower immunogenicity, adjuvants often needed to compensate
- Facilitate supply via synthetic production versus whole pathogen



New Technologies Make Previously Impossible Vaccines a Reality

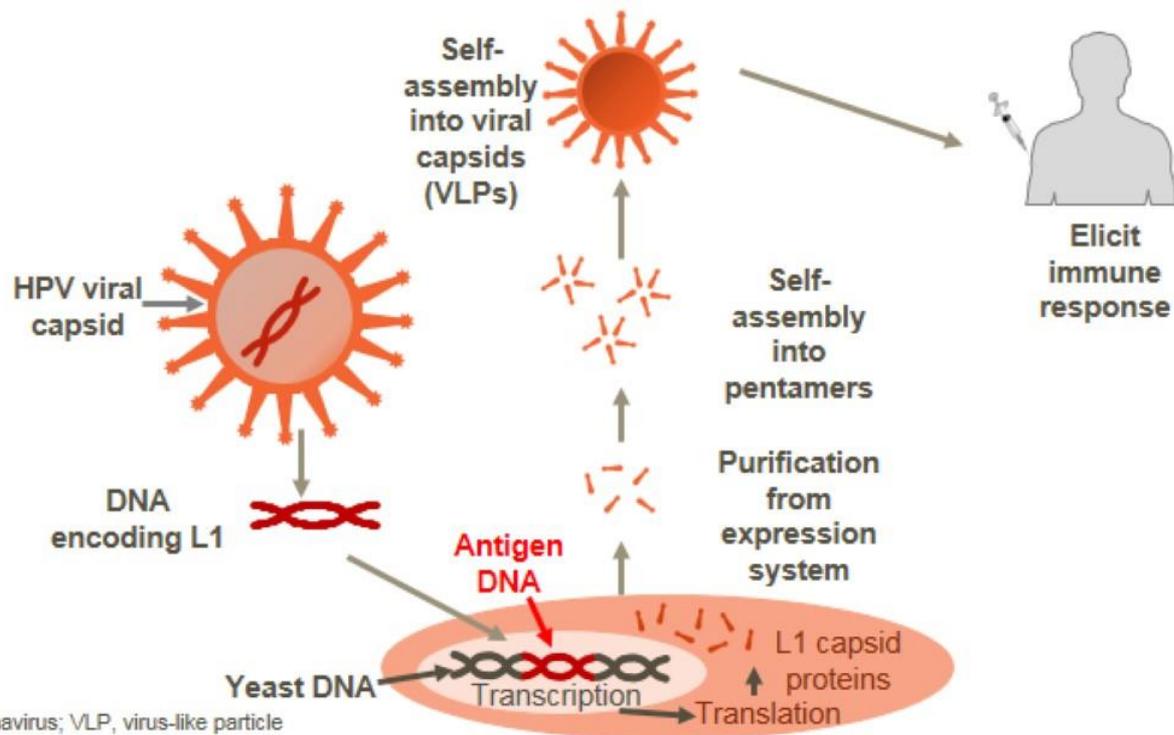


Recombinant Protein Vaccines: HBV



1990s

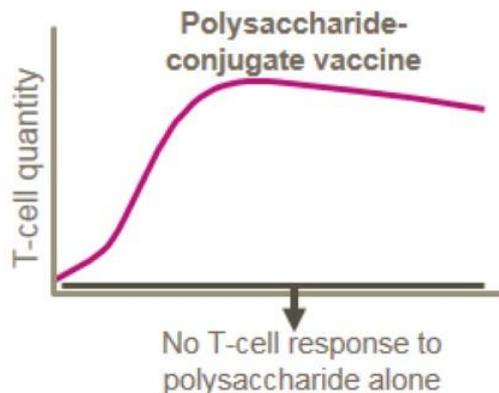
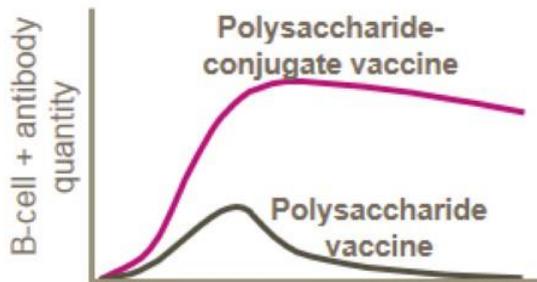
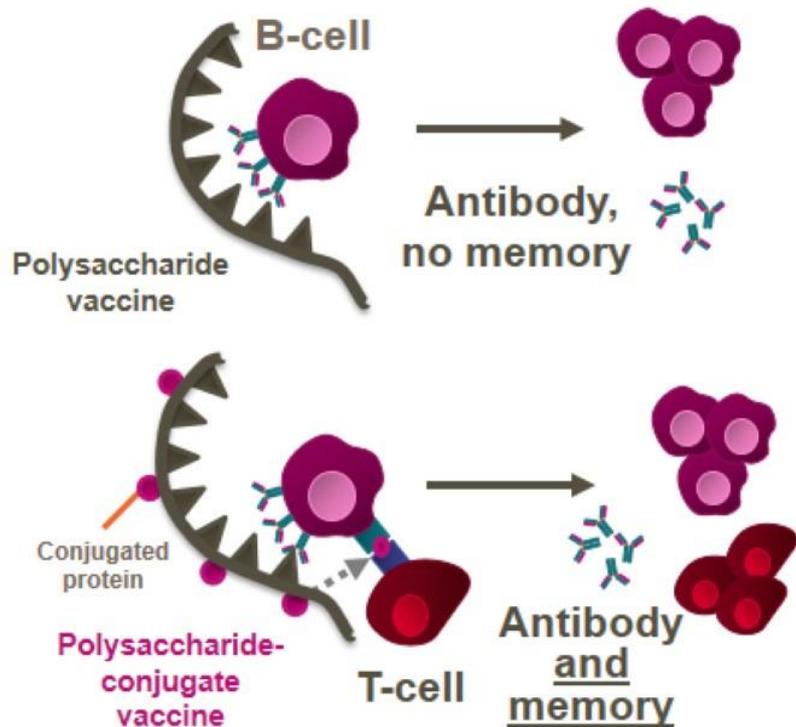
Recombinant Protein Vaccines: HPV



HPV, human papillomavirus; VLP, virus-like particle

1980s-1990s

Polysaccharide-conjugate vaccines

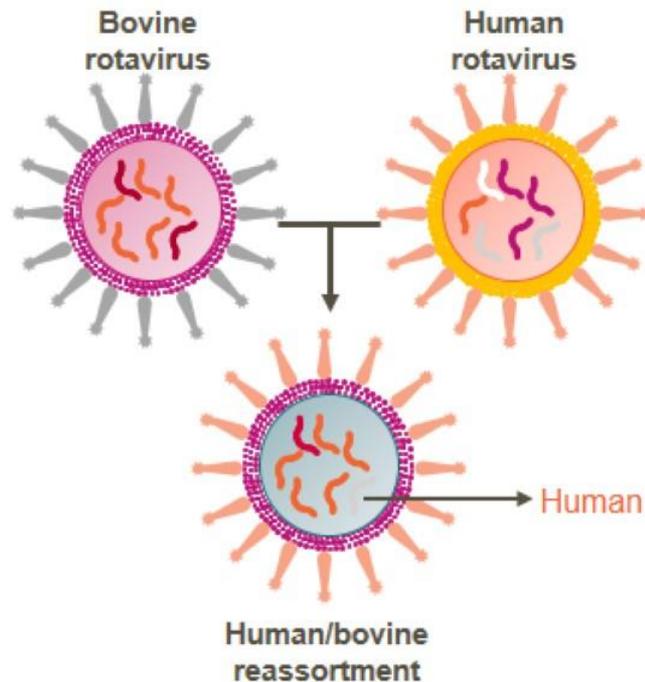


1980s-1990s

Reassortant Live-attenuated Vaccines

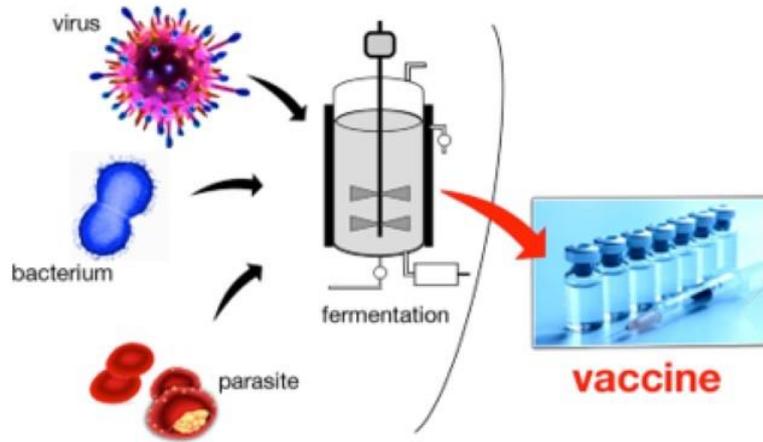
Co-infection with wild and attenuated virus strains, in cell culture, allows 'swapping' of genome segments

- eg, human/bovine reassortant rotavirus vaccine: human antigens on a bovine virus core

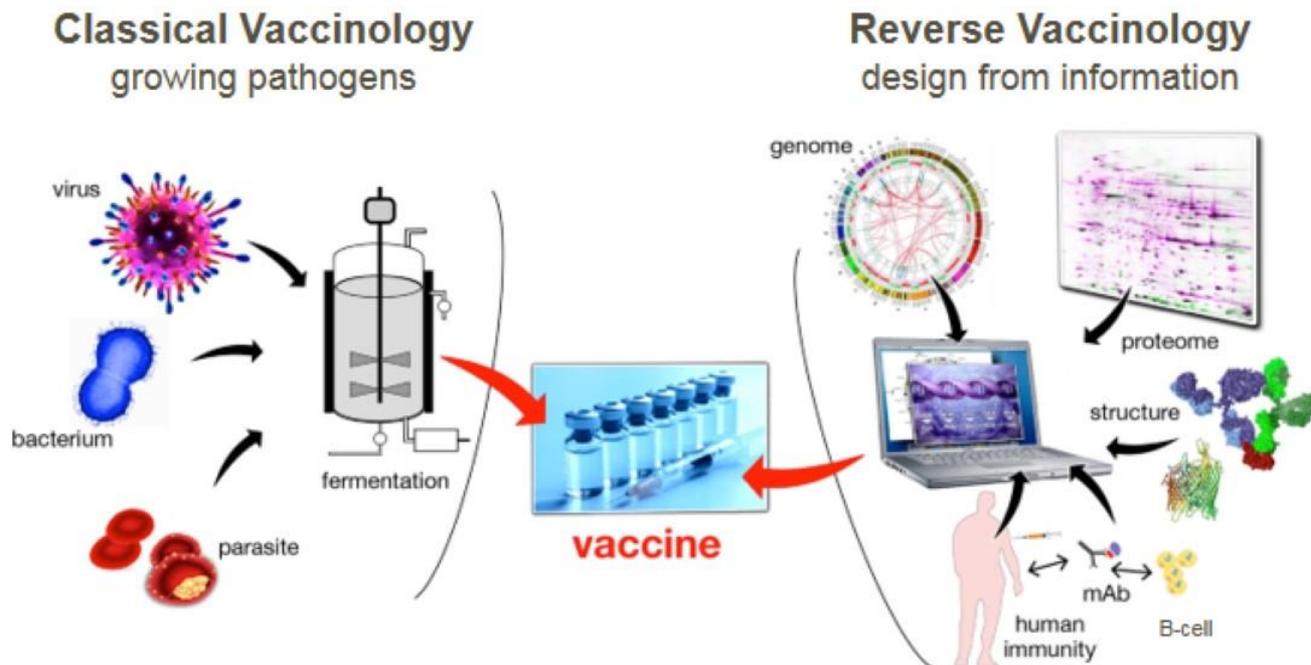


Classical Vaccinology

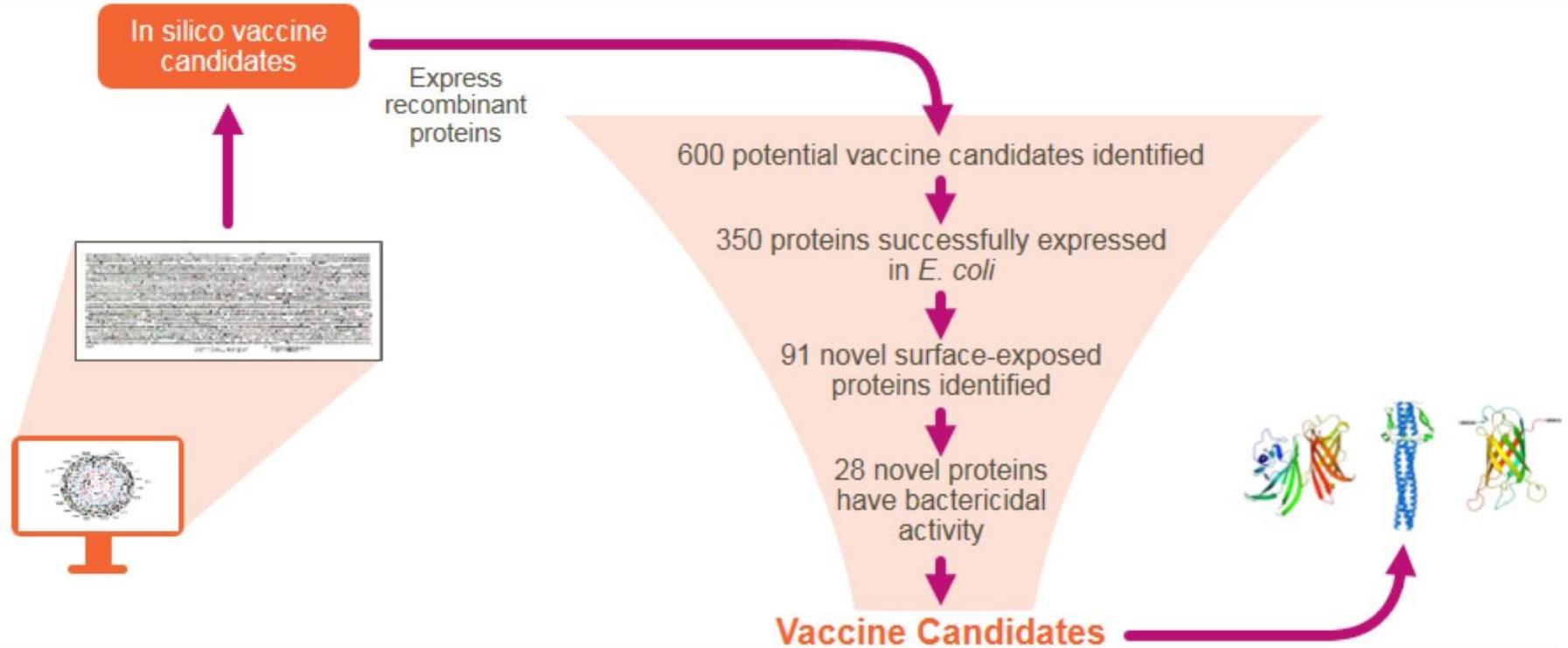
Growing Pathogens



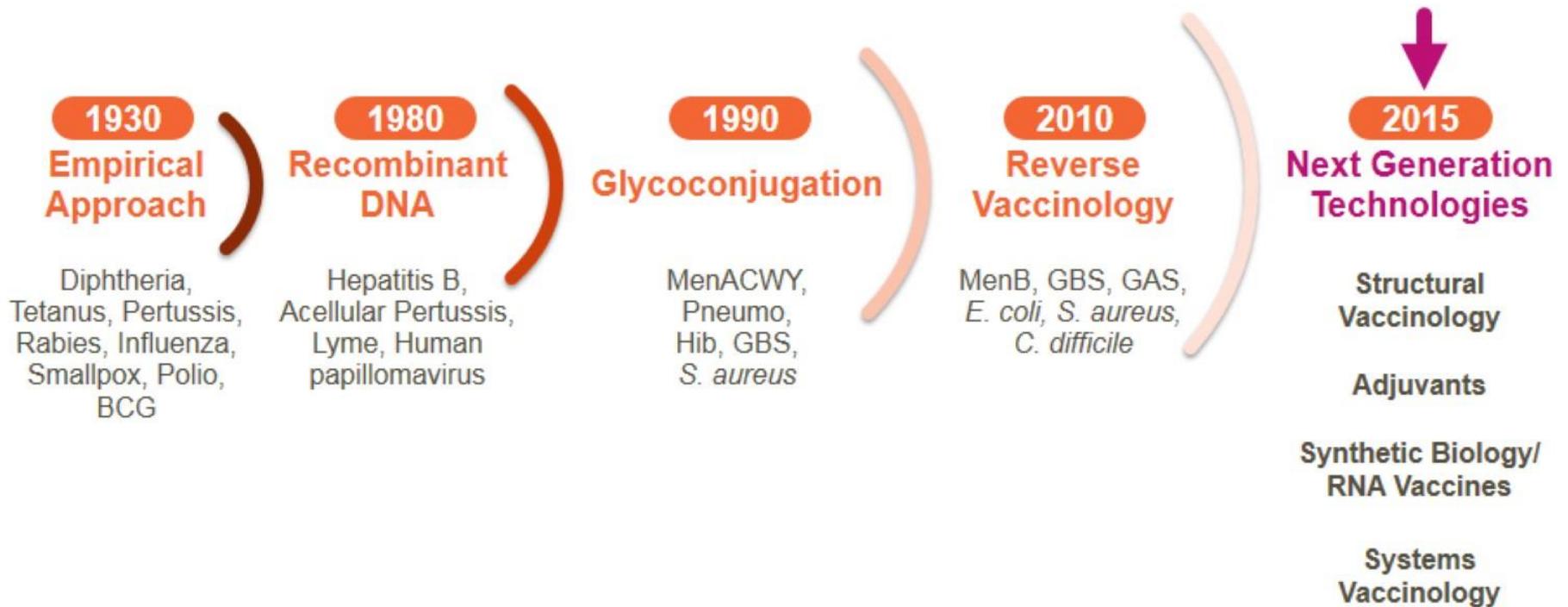
Reverse Vaccinology: Human Immunology Instructs Vaccine Antigen Design



Reverse Vaccinology: A Genomic Approach for a Meningococcus B Vaccine^{1,2}



Vaccines Today: An Explosion of New Technologies



Current Challenges for Vaccines¹

Challenging populations

due to impaired immune system (eg, elderly, children, immunocompromised)

Need for booster vaccinations

Recombinant antigens

generally less immunogenic than live or attenuated organism vaccine²

Pathogens

that require broad and complex immune response

Need for antigen sparing

potential supply problems (eg, pandemic flu)

Increase
the level of the immune response

Prolong
the duration of the immune response, improve immune memory, and protection

Overcome
a weakened immunogenicity

Induce
the generation of a high and broad immune response

Reduce
the amount of antigen needed (dose-sparing)

Examples of Novel Approaches to Vaccine Design

DNA¹

- Pathogen-derived genetic material coding for the antigens contained in a non-replicating DNA plasmid
- Antigen is expressed by the cells of the vaccine recipient

Live vectors¹

- Targeted antigens encoded by gene(s) incorporated into the vector's genetic material
- Antigens expressed by a vector (like virus or bacterium) that is non-pathogenic

Reverse vaccinology¹

- Computer analysis of the pathogen's entire genome is conducted to find genes that may be antigenic
- Vaccine candidate identified based on prediction of protein sequences similar to pathogen's genome sequences

Self-amplifying RNA²

- Synthetic virus particles include antigen proteins
- Once inside host cell cytoplasm, these self-amplify in large amounts, express antigen proteins and interact with the host immune system

Novel adjuvants and adjuvant combinations³

- Substances included in a vaccine formulation to enhance the quality and strength of the immune response induced by the vaccine antigen(s)

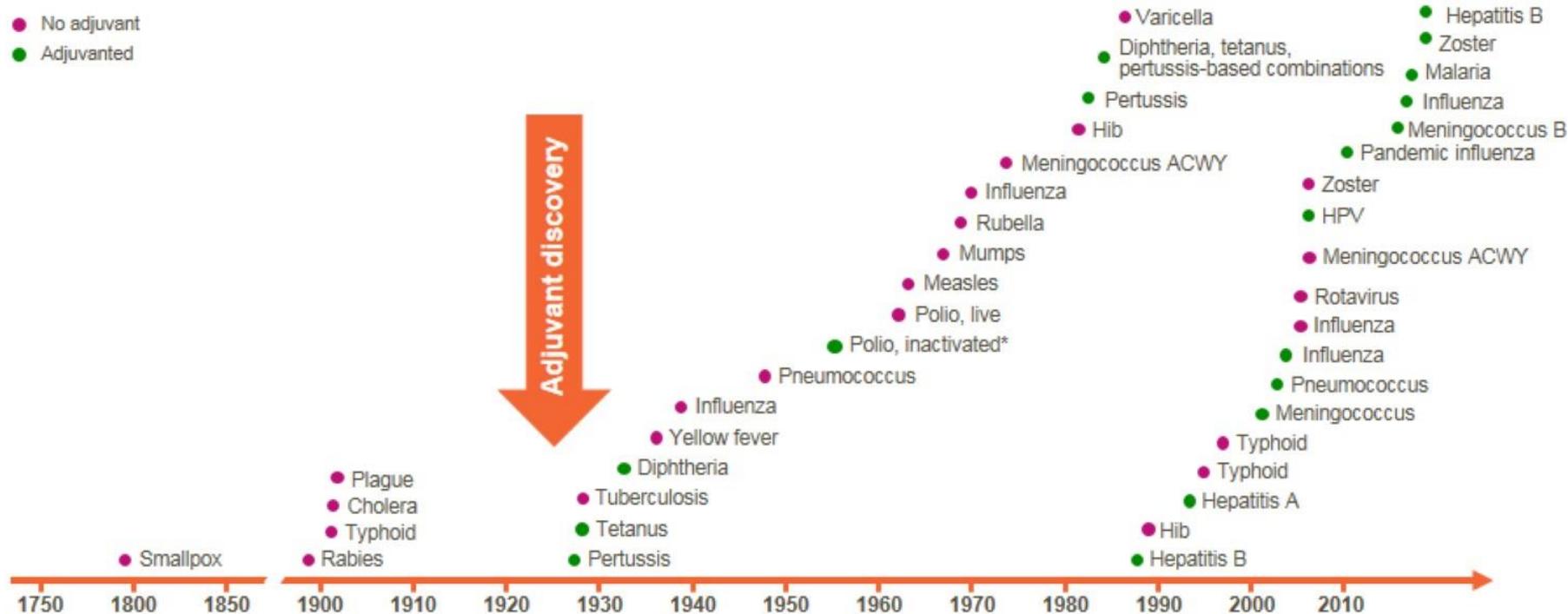
1. Stanberry L, Strugnell R. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011; Chapter 6: 155-199.
2. Geall A, et al. *Semin Immunol*. 2013;25:152-159.
3. Garçon N, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011; Chapter 3: 61-88.

Adjuvant^{1,2}

- From Latin, *adiuvare*: to aid
- Substance included in a vaccine to enhance and modulate the quality and/or strength of the immune response induced by the antigen
- Old technology, made new



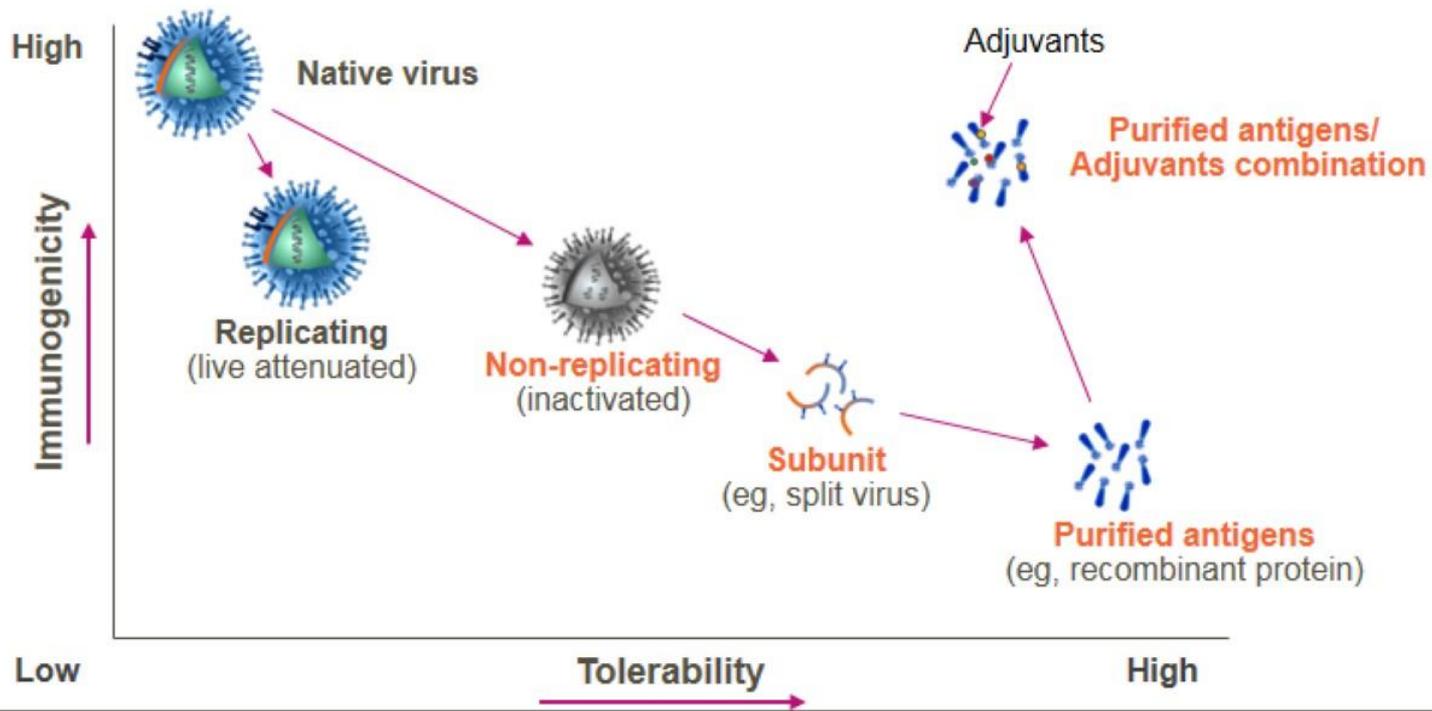
Adjuvants have a long history in the fight against infectious diseases



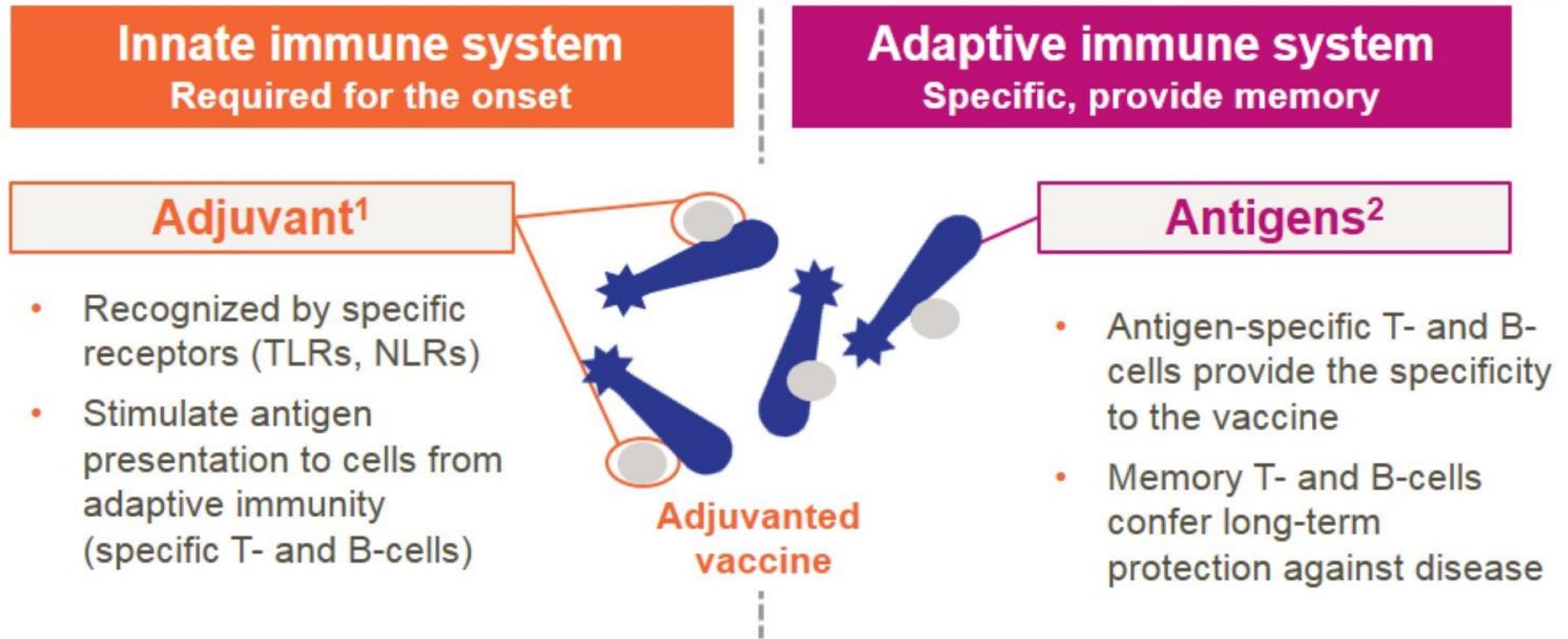
Hib=*Haemophilus influenzae* type b; HPV=human papillomavirus; IPV=inactivated polio vaccine; OPV=oral polio vaccine (live).

*IPV is adjuvanted when formulated in combination with diphtheria, tetanus, pertussis-based vaccines but is not adjuvanted when formulated as a stand-alone vaccine.

Antigens May Need Help: The Role of Adjuvants



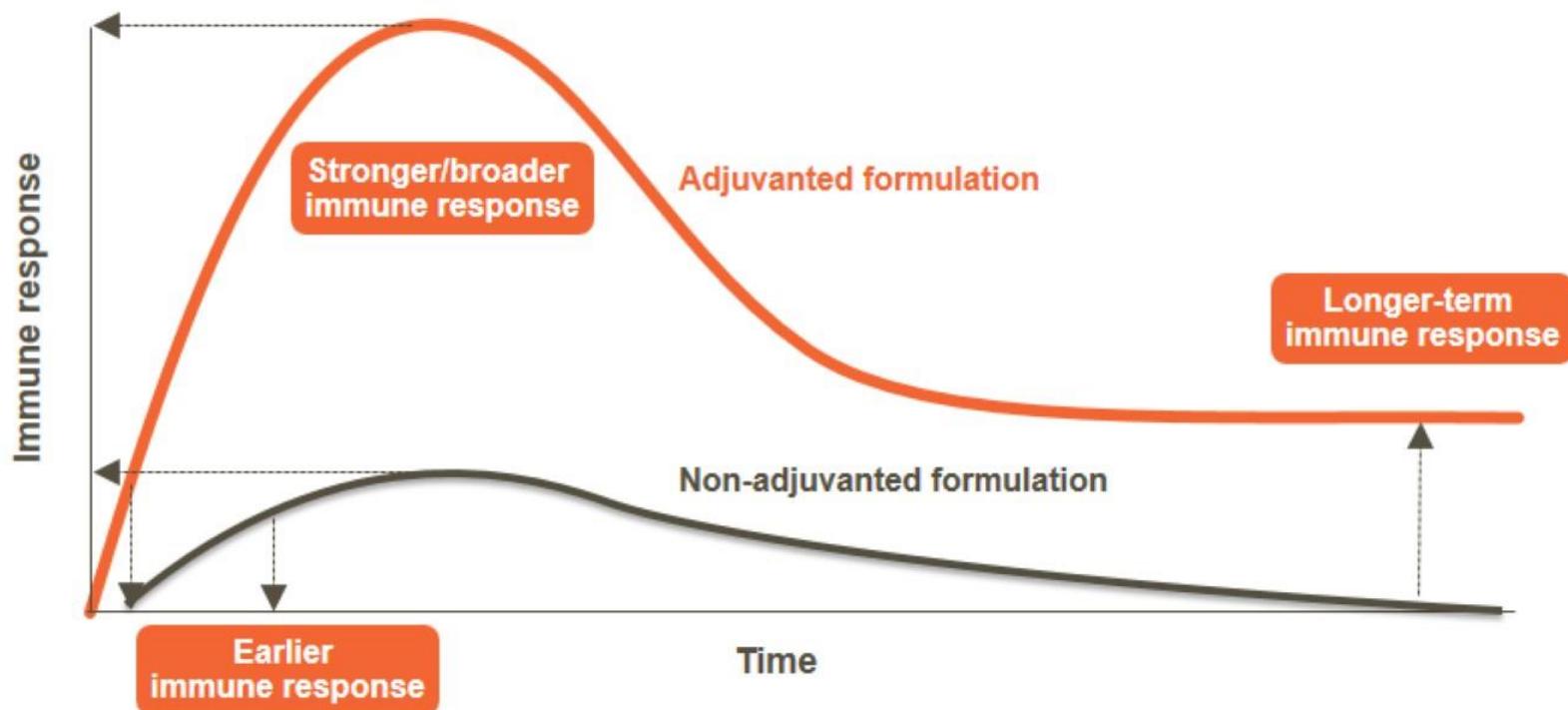
Adjuvants Work by Stimulating Innate Immunity



1. Garçon N, et al. Chapter 4 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

2. Leo O, et al. Chapter 2 in: Garçon, et al. *Understanding Modern Vaccines: Perspectives in Vaccinology*. Vol 1. Amsterdam: Elsevier; 2011.

Expected Impact of Adjuvants on Vaccine Immune Response



Adjuvants–Few Approved, Many in Development

Adjuvants in Licensed Products

Adjuvant	Mechanism or Receptor	Licensed product
Aluminum salts	Nalp3, ITAM, antigen delivery	Numerous (eg, pertussis, hepatitis, pneumococcal)
AS04	TLR4	HPV
Emulsions (MF59, AS03)	Immune cell recruitment, antigen uptake	Influenza
AS01	TLR4, inflammasome	Zoster
CpG ODN	TLR9	Hepatitis B

Adjuvants in Development

Adjuvant	Mechanism or receptor	Clinical phase
ISCOMs (Matrix-M)	Unknown	2
dsRNA analogues	TLR3	1
Flagellin	TLR5	1
C-type lectin ligands	Mincle, Nalp3	1
CD1d ligands	CD1d	1
GLA-SE	TLR4	1
IC31	TLR9	1
CAF01	Mincle, antigen delivery	1



Observed Benefits of Adjuvants in Candidate or Licensed Adjuvanted Vaccines

- Efficacy demonstrated for different antigens: Split (influenza)¹, parasite-derived (malaria)², viral glycoprotein (herpes zoster)³, viral particles (HPV)⁴
- Persistent increase in T-cell and antibody response in magnitude and quality (antibody breadth and cross-reactive T-cells)^{1,5}
- Have shown benefits across the entire age spectrum (6-month-old infants to >80-year-old-adults)^{3,6} with the possibility to adapt dosage to age (eg, use of lower dose in pediatric formulation)⁶
- Adjuvants are being used in vaccines in special populations, such as in immuno-compromised or HIV+, with acceptable safety outcomes⁷

Safety Is of Primary Importance From the Start of Development and Throughout the Entire Life of a Vaccine



- Vaccines are carefully evaluated under tight process controls and overseen by regulatory authorities
- Safety monitoring designed to rapidly identify rare and/or serious adverse events temporally linked to vaccination

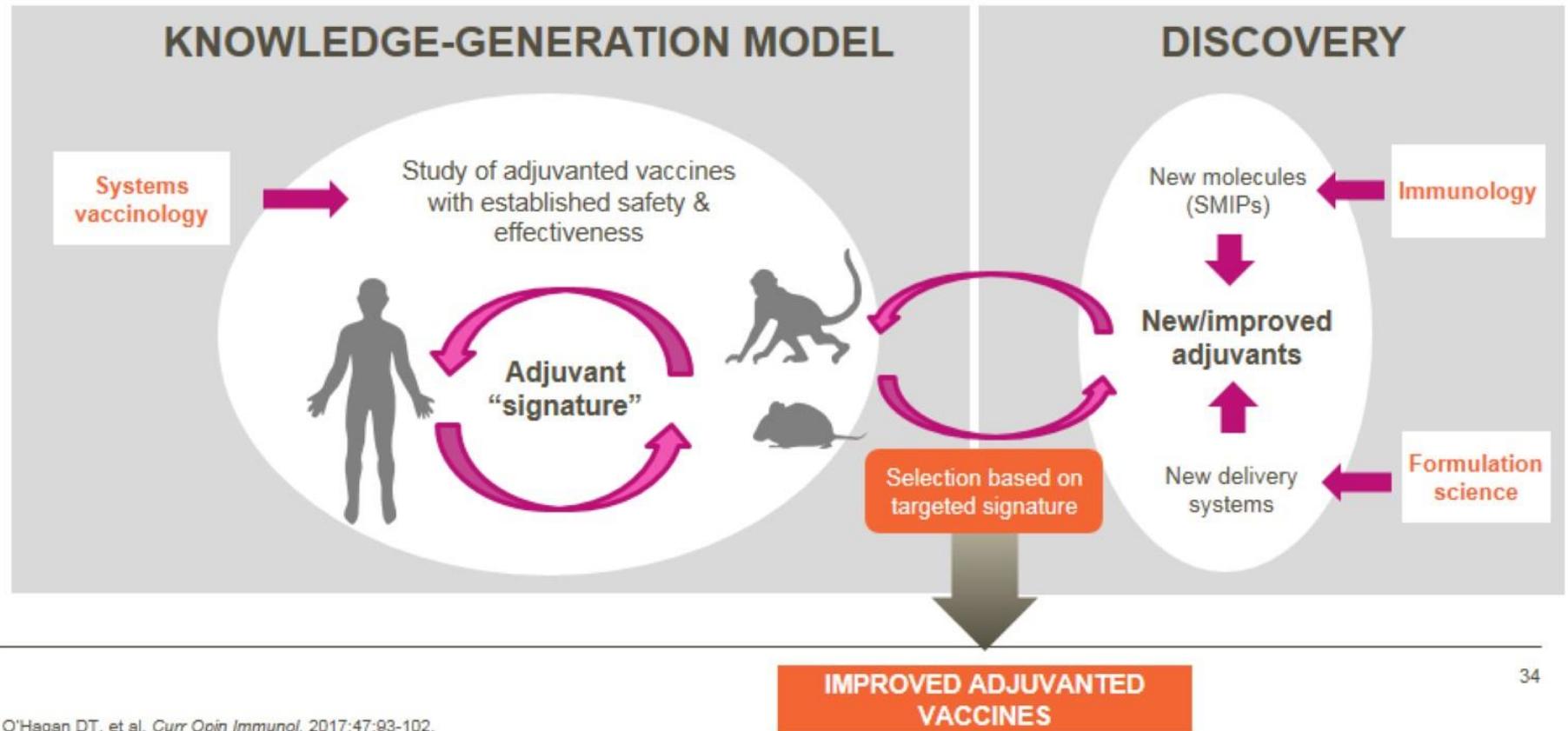
One Size Does Not Fit All

No universal adjuvant to cover all vaccine needs

Different diseases may require different immune responses to elicit protection through vaccination

Appropriate selection of adjuvant-antigen combination is key to the formulation of novel and efficacious vaccines

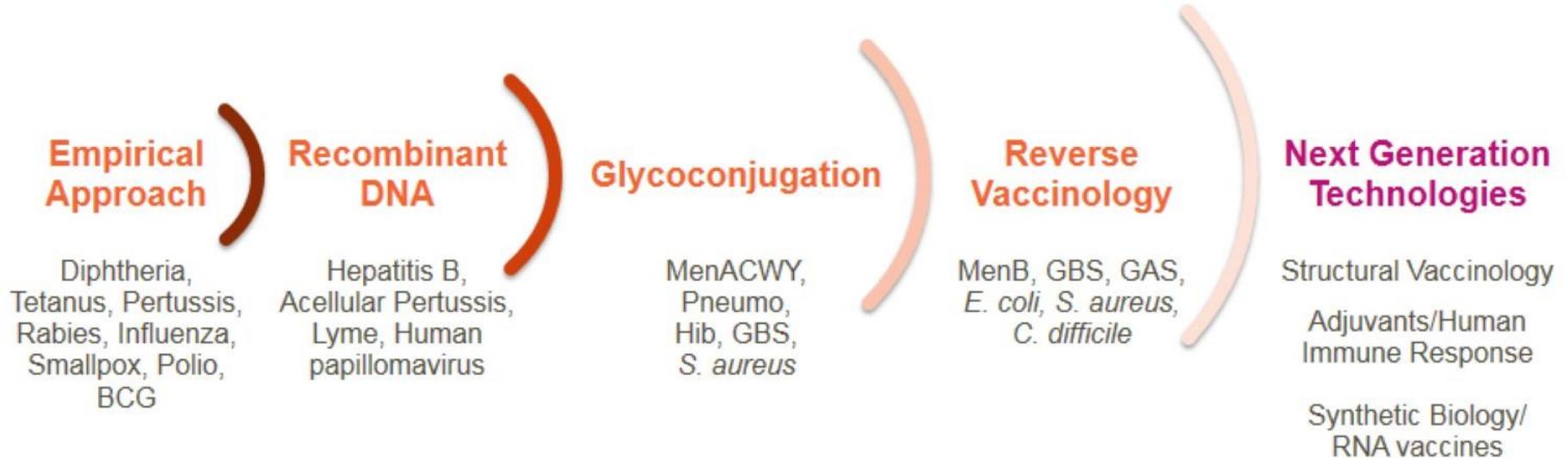
Tools to Develop the Next Generation of Adjuvants



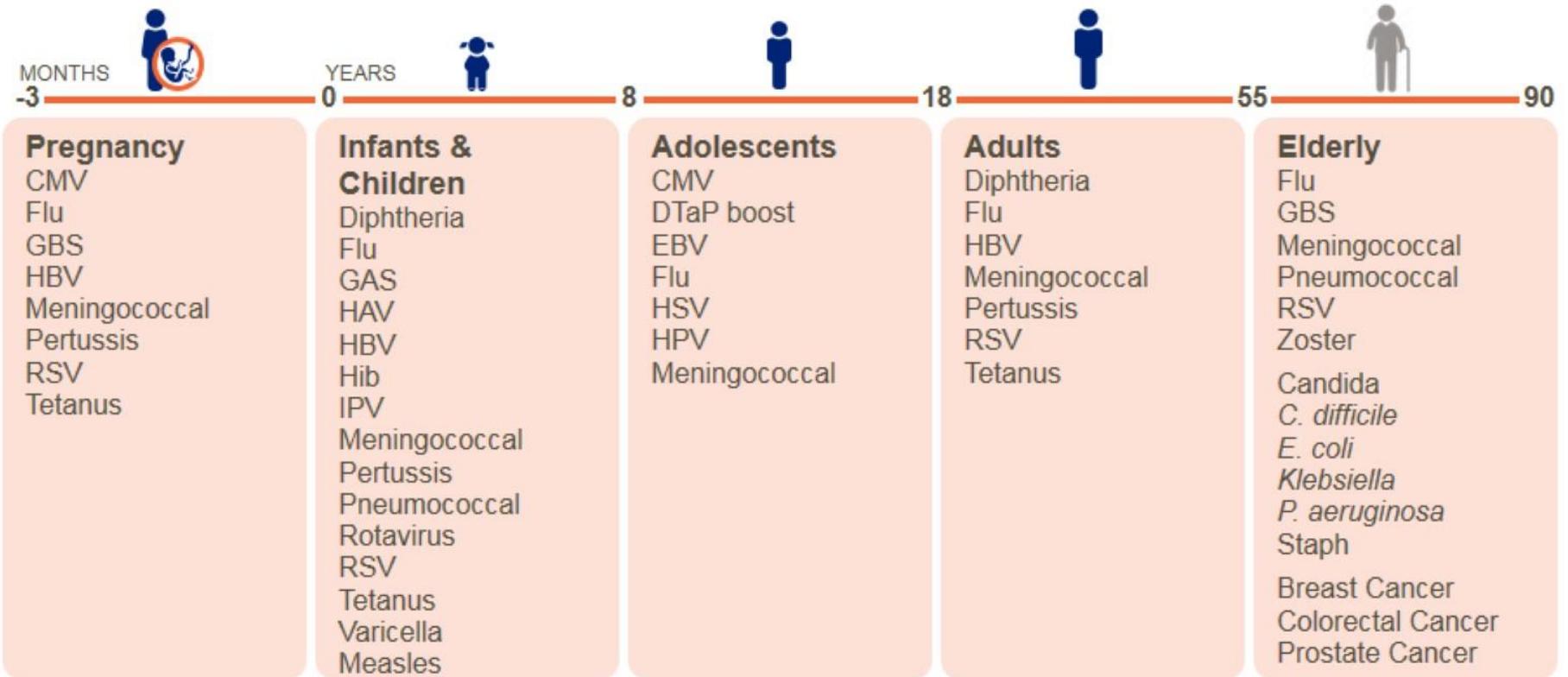


**Past, Present, and Future:
Vaccine Innovations**

How Can These Technologies Help Our Society?



Vaccines For Every Age



Vaccines For Today's Society



Poverty

Cholera
Dengue
ETEC
HAV
HBV
HEV
Flu
JEV
Malaria
MenB
Parasitic infections
Paratyphoid
Rabies
Rotavirus
Salmonella
S. enterica
S. typhimurium
Shigella
TB
Typhoid fever

Emerging Infections

AIDS
Anthrax
Avian influenza
Cholera
Diphtheria
Dengue
Ebola
EV71
Malaria
SARS
TB
Smallpox
West Nile
Yersinia

Travelers

Cholera
Dengue
ETEC
Flu
HAV
HBV
JEV
Malaria
Meningococcal
Paratyphoid
Rabies
Shigella
TB
Typhoid Fever
Yellow Fever

Patients with Chronic Diseases

CMV
Flu
Fungal infections
P. aeruginosa
Parainfluenza
RSV
Staph
TB

Immunotherapy/ Therapeutic Vaccines?

Cancer
Autoimmune diseases
Alzheimer's
Chronic infections
(HCV, HBV, HPV, HIV...)
Metabolic diseases
Allergy
Drug addiction

Discussion

Past, Present, and Future: Vaccine Innovations

Leonard Friedland, MD, FAAP

Vice President and Director, Scientific Affairs and Public Health
GSK Vaccines