ICAVT
INTERNATIONAL COLLABORATION ON ADVANCED VACCINOLOGY TRAINING

School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Update on combination vaccines and strain(s) adaptations in 2023

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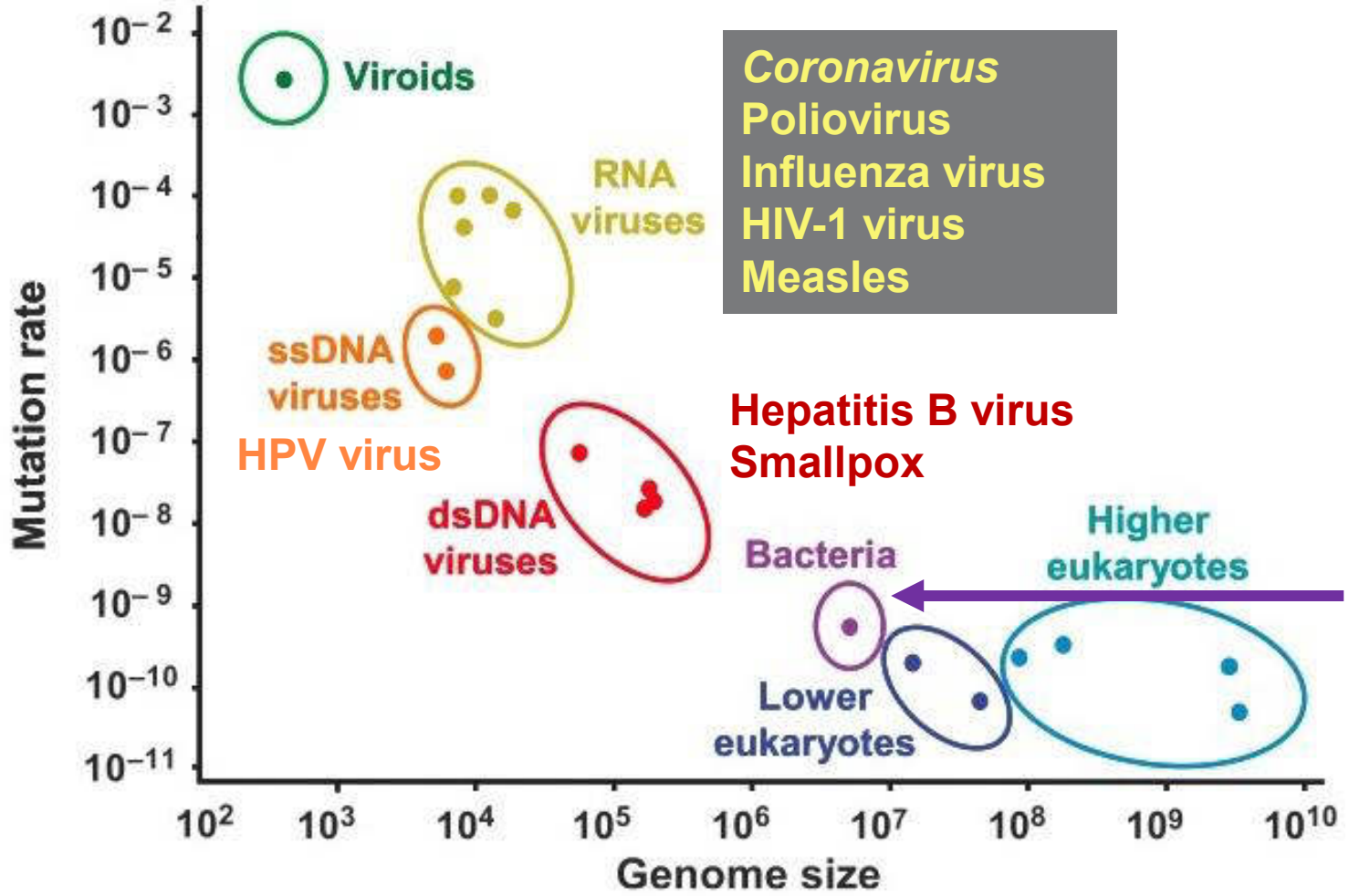
Objectives

- Biological, environmental, and population basis of variability in pathogens: mutation, adaptability, and transmission dynamics
- Understanding the population biology of pathogens (viruses or bacteria) matters including its role in selecting vaccine antigens and in assessing vaccine effectiveness.
- Basics of serotype replacement and its consequences on the vaccine strain adaptation.
- Critical elements of immunization schedule and the recent evolution of vaccines combinations
- Advantages and importance of combination vaccines

Relationship between mutation rate and genome size, with major human viral and bacterial pathogens



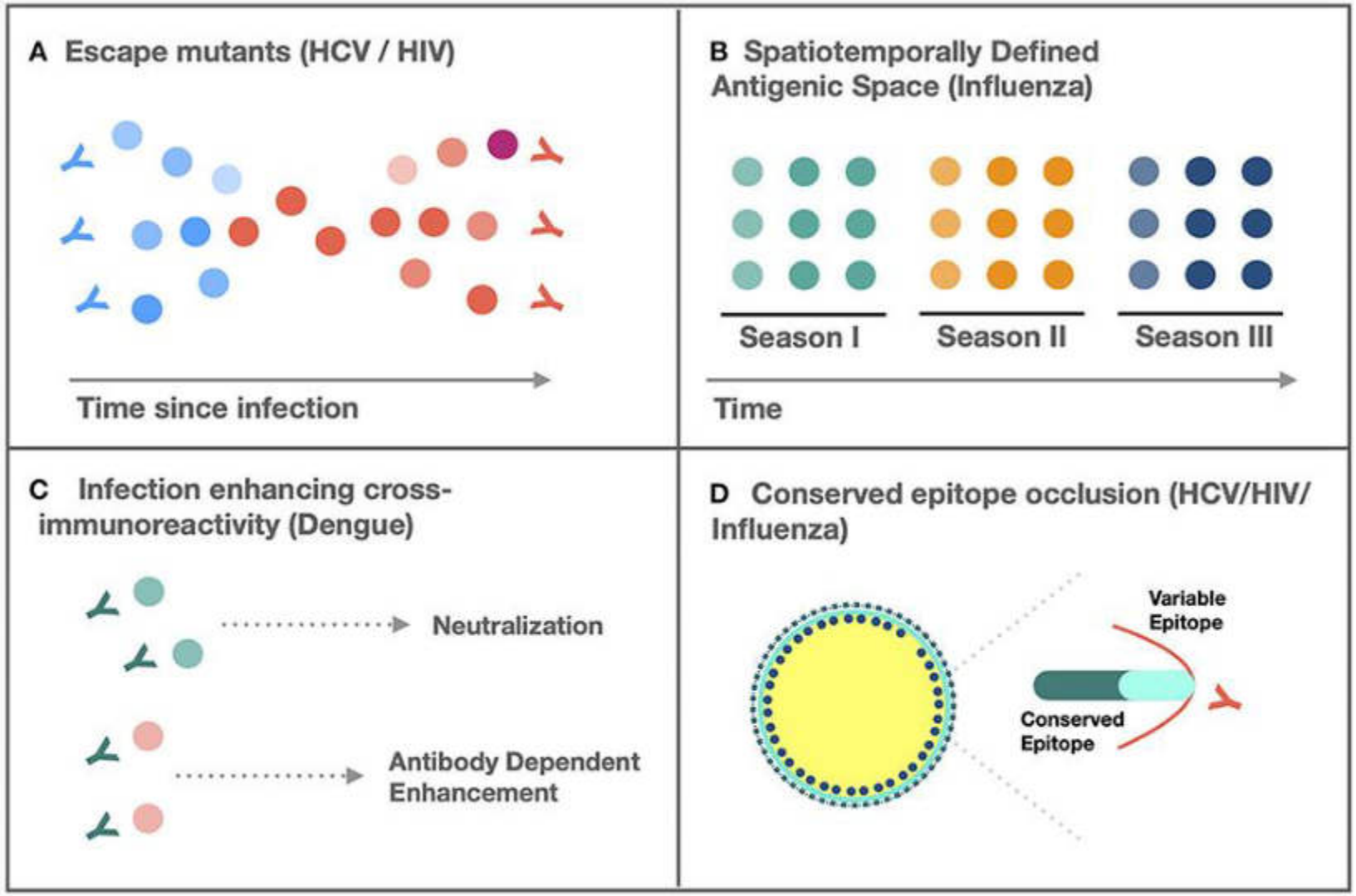
Coronavirus
Poliovirus
Influenza virus
HIV-1 virus
Measles

Hepatitis B virus
Smallpox

Corynebacterium diphtheriae
Bordetella pertussis
S. pneumoniae
Hemophilus influenzae type b

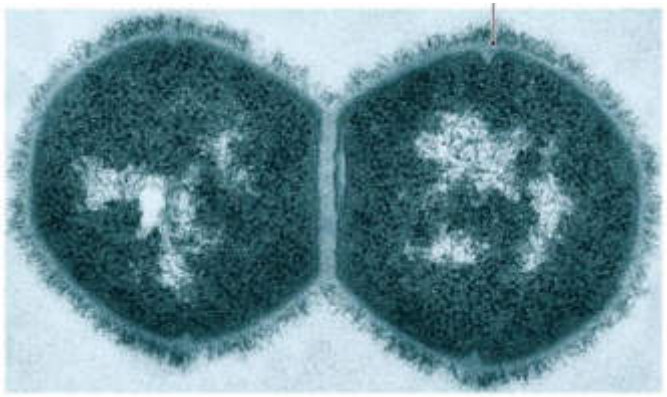
Adapted from San Juan R. et al https://doi.org/10.1128/JVI.00694-10

4 mechanisms of adaptive variation between viruses

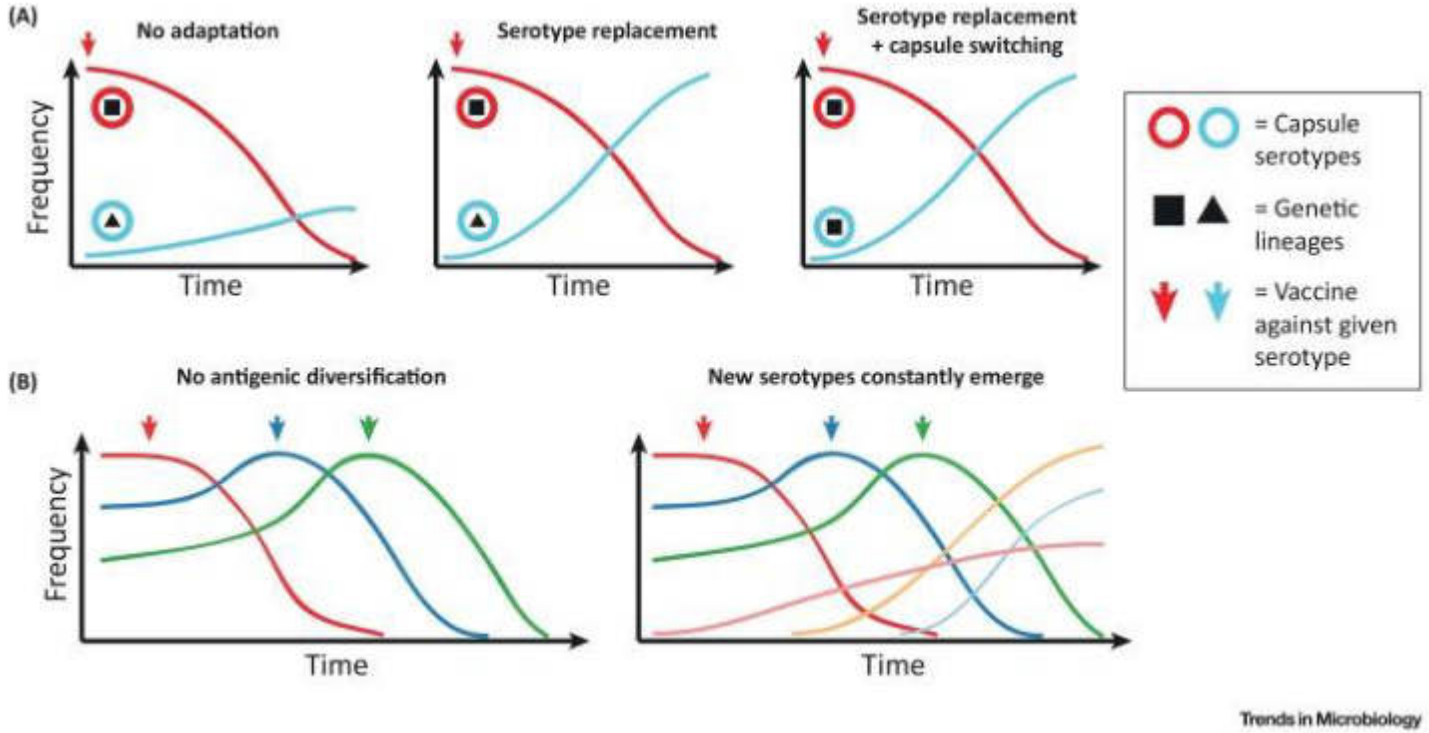


Serotype replacement (bacteria)

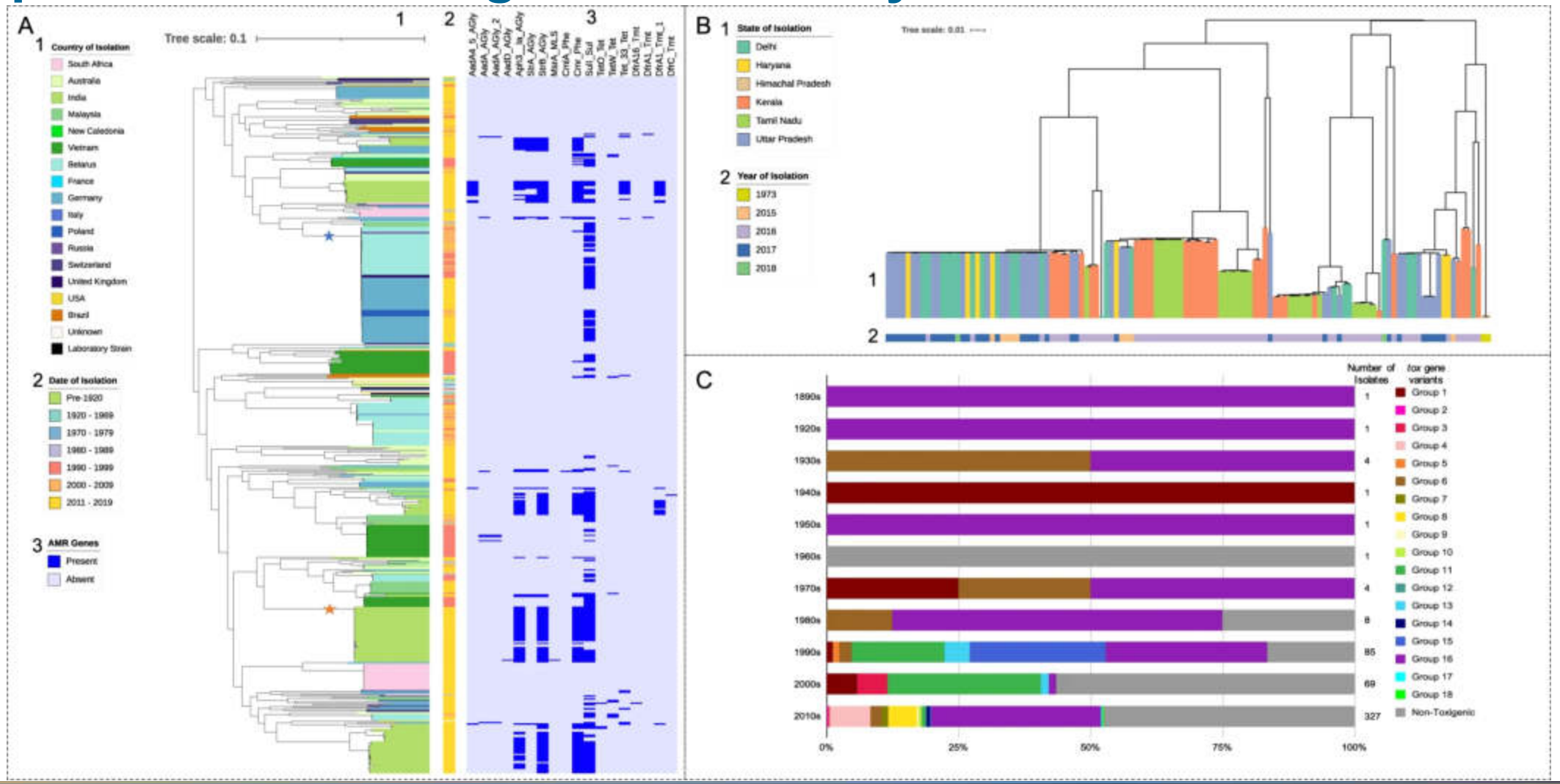
- Emergence of less common serotypes circulating between hosts, or temporally across populations, for which immunity elicited by one serotype **fails to protect against another**



Streptococcus pneumoniae



Global and Indian core gene phylogenies of Corynebacterium diphtheriae and tox gene variants by decade.



Will, R.C. *et al. Nat Commun* 12, 1500 (2021).
https://doi.org/10.1038/s41467-021-21870-5

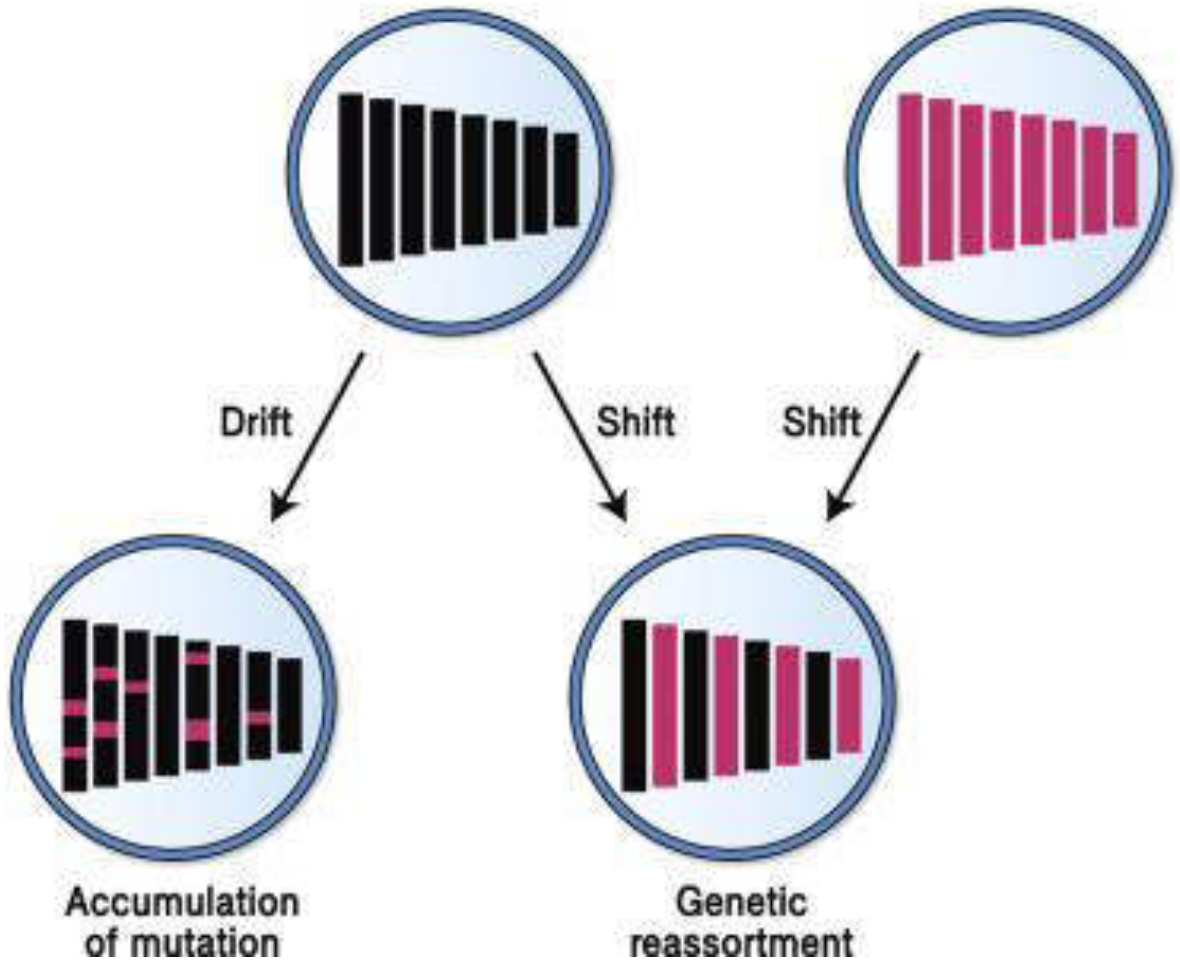
Antigenic variability (viruses)

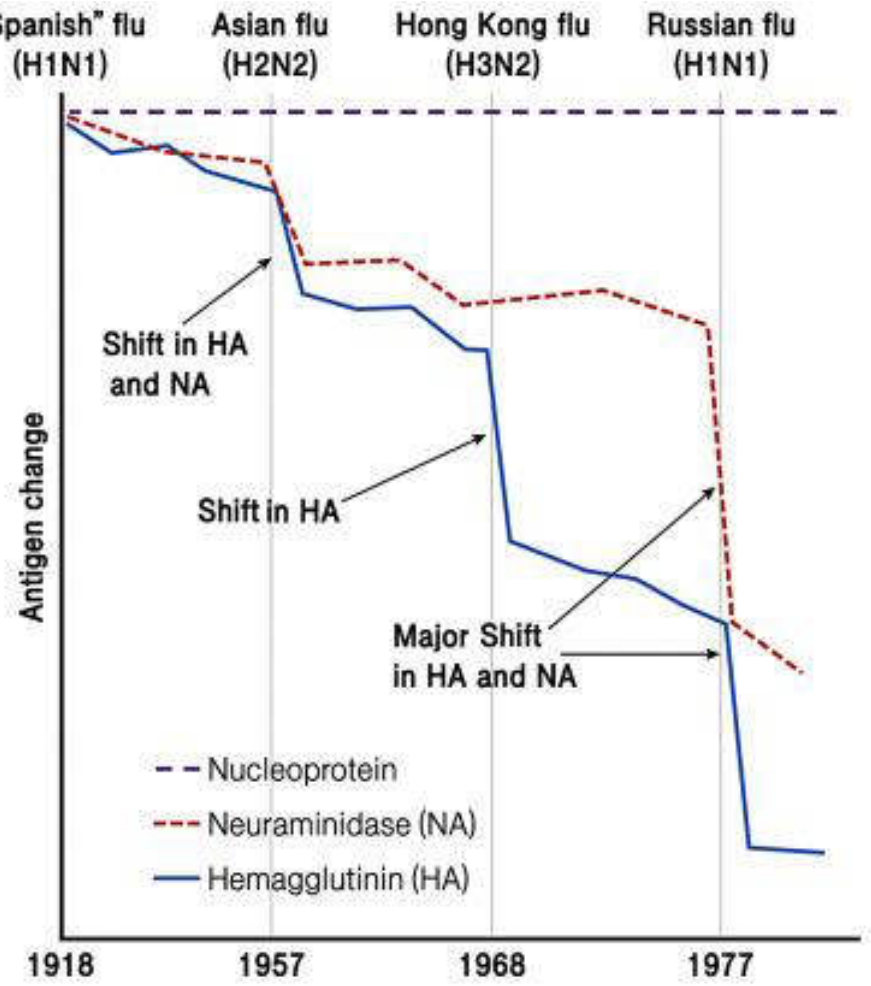
- Emergence of sequence distinct variants within a species, circulating between hosts, within hosts, or temporally across populations, for which adaptive immunity elicited by one strain **fails to protect against another**

Serotype replacement (bacteria)

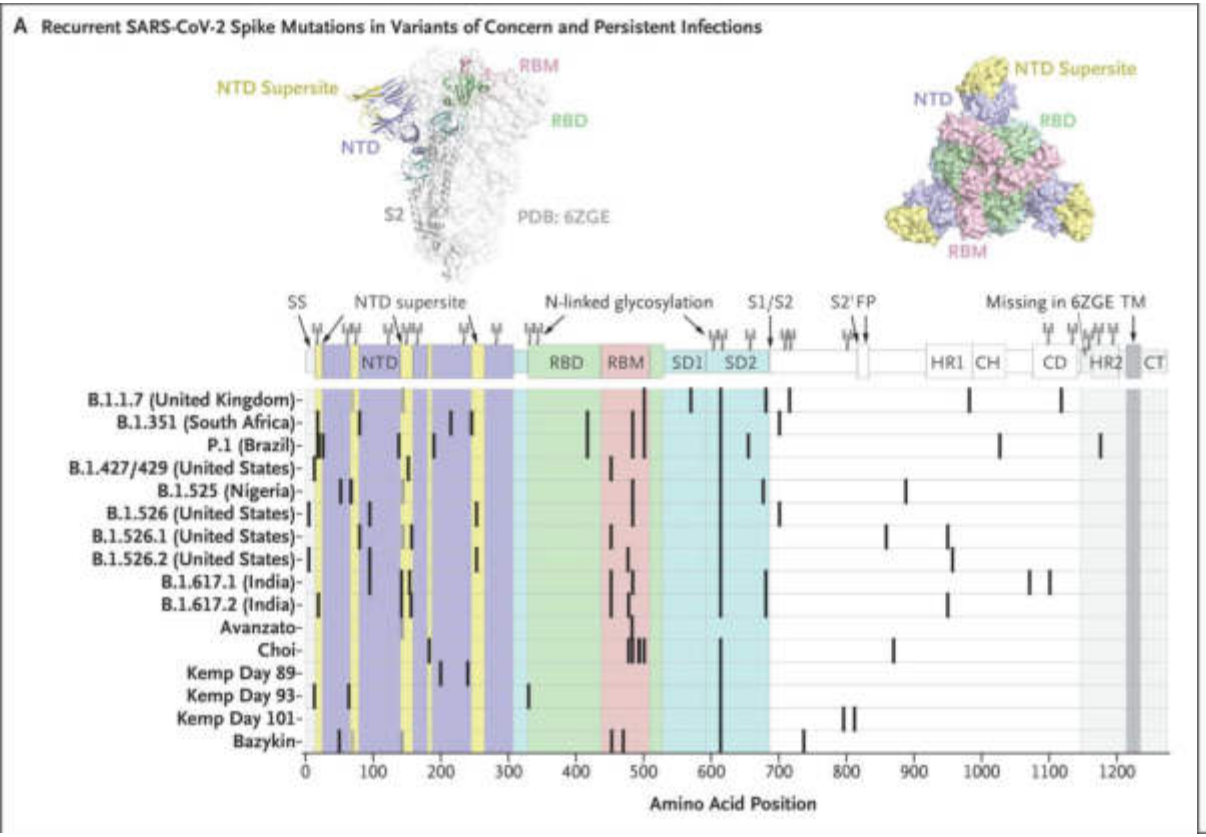
- Emergence of less common serotypes circulating between hosts, or temporally across populations, for which immunity elicited by one serotype **fails to protect against another**

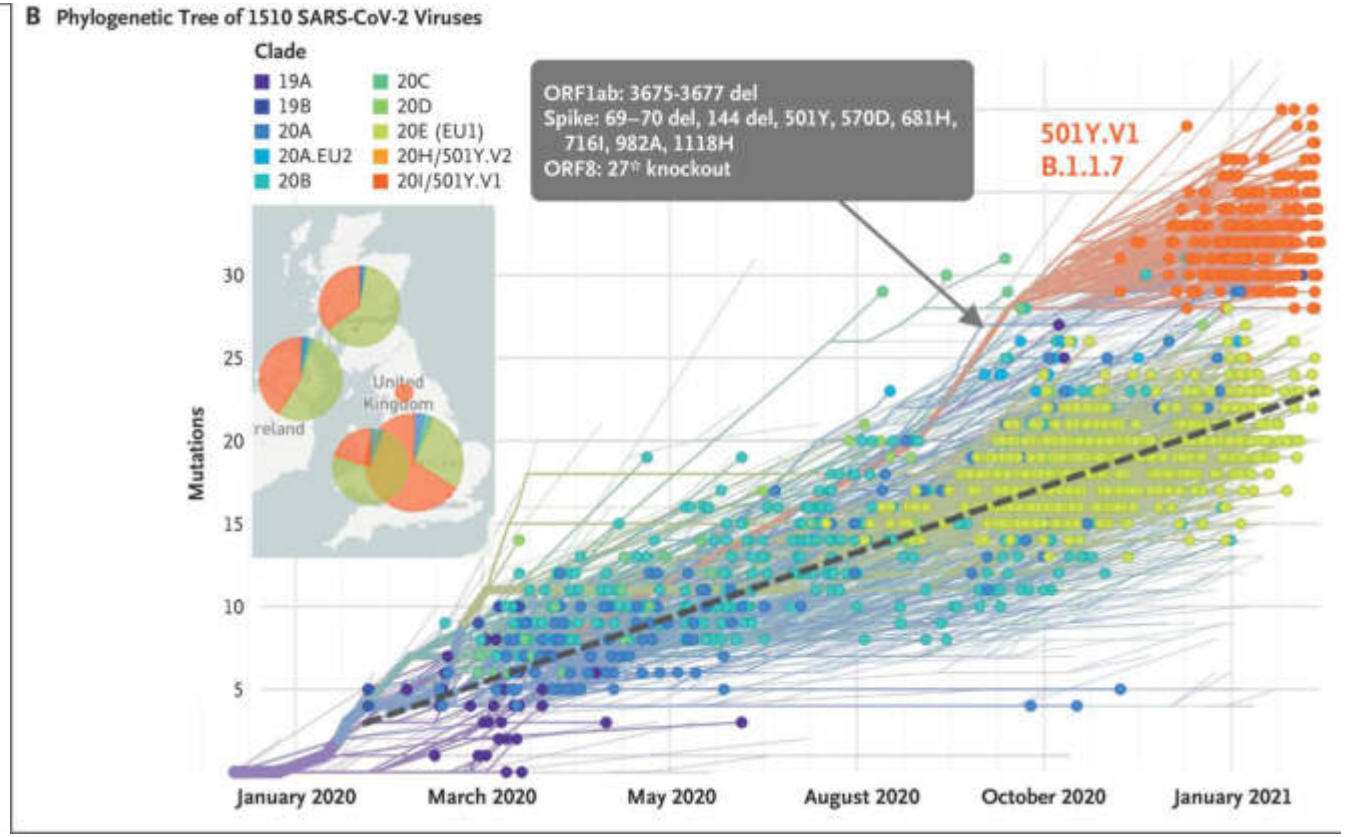
Influenza strain variation and human timeline





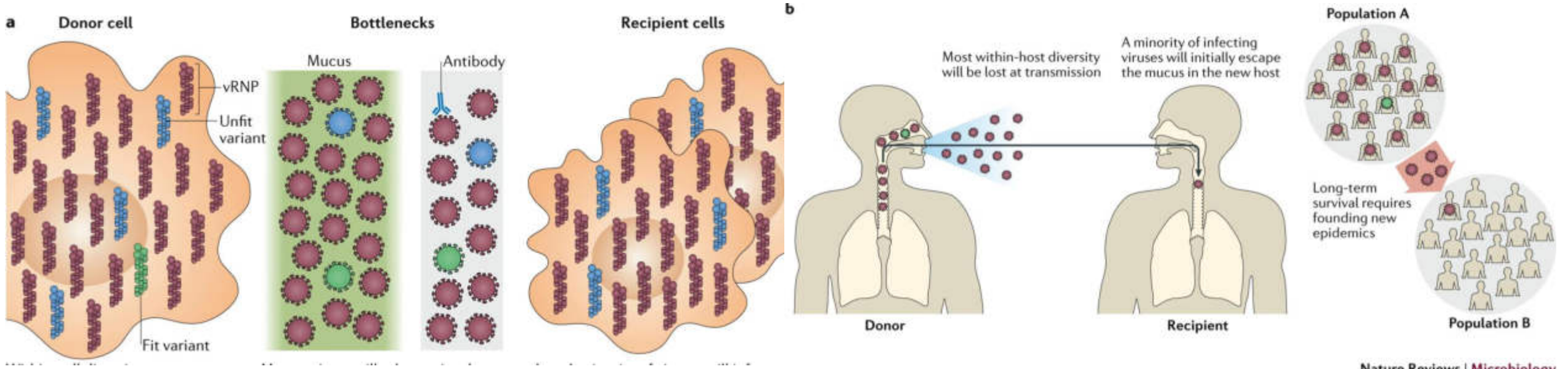
Evolution of SARS-CoV2 mutations and variants





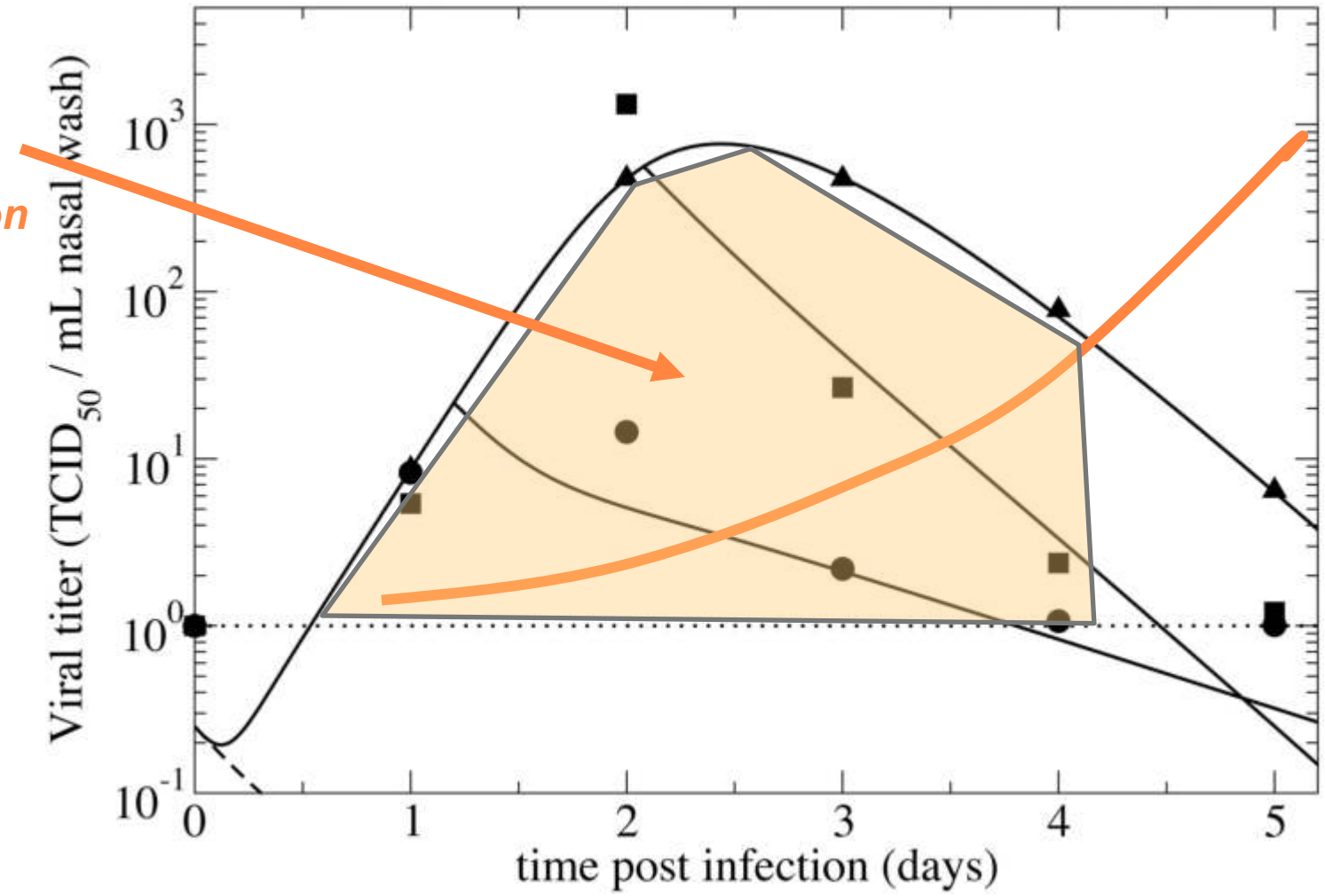
Intra-host viral mutation and selection

- Infected humans can produce **10^{12} virions**—infectious viral particles—during a respiratory virus infection
- High opportunity for mutation and selection if an infection is persistent or prolonged



Course of influenza virus infections with and without the NI zanamivir given intranasally to human volunteers

Opportunity within-host viral variation



Human controls

Early zanamavir

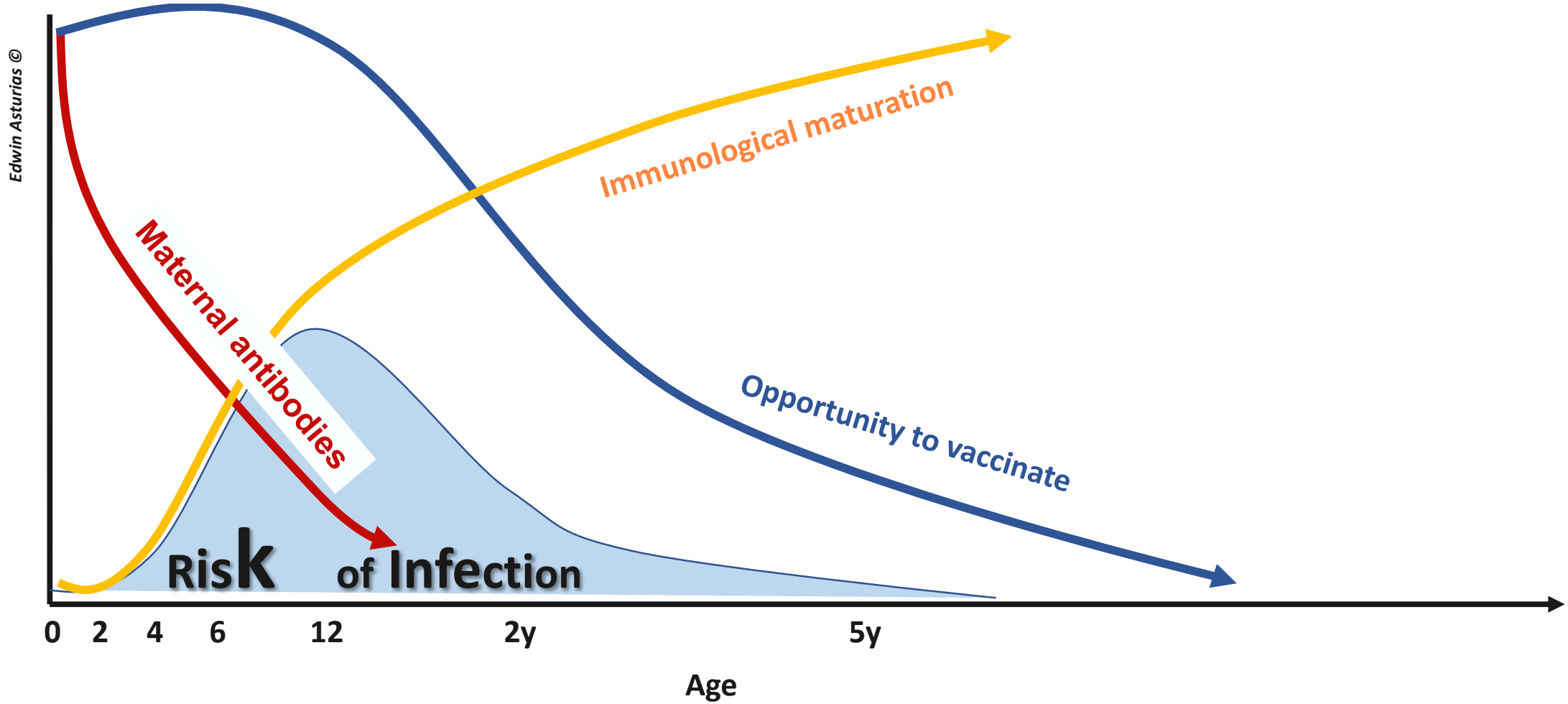
Late zanamavir

Antibody response

Adapted from **Baccam P et al. 2006** https://doi.org/10.1128/JVI.01623-05

What strain variability or serotype replacement has to do with combination vaccines?

Optimal immunization schedule provides protection at the time of greatest risk



Child Immunization schedules have evolved: USA and UK

TABLE 1. Recommended schedules for routine immunization

United States*					England and Wales†				
Age	DTP	OPV	M	SP	Age	DTP	OPV	M	SP
2–3 months	X	X			3–6 months	X	X		
3–4 months	X								
4–5 months	X	X			5–8 months	X	X		
12–18 months	X	X	X		9–14 months	X	X		
12–24 months				X	12–24 months			X	X
School entry (3–6 years)	X	X		X	School entry (3–6 years)	Td	X		X
					10–13 years				
Every 10 years	Td			X‡	School leaving	Td	X		X

DTP, Diphtheria–tetanus–pertussis vaccine; OPV, oral poliovaccine; M, measles vaccine; SP, smallpox vaccine; T diphtheria toxoid, adult type.

* Adopted from United States Public Health Service (1967): *Immunization Against Disease* 1966–67 (National Com Disease Center publication).

† Adopted from Ministry of Health (1968a,b).

‡ For high risk groups, i.e. health personnel and overseas travel—every 3 years.

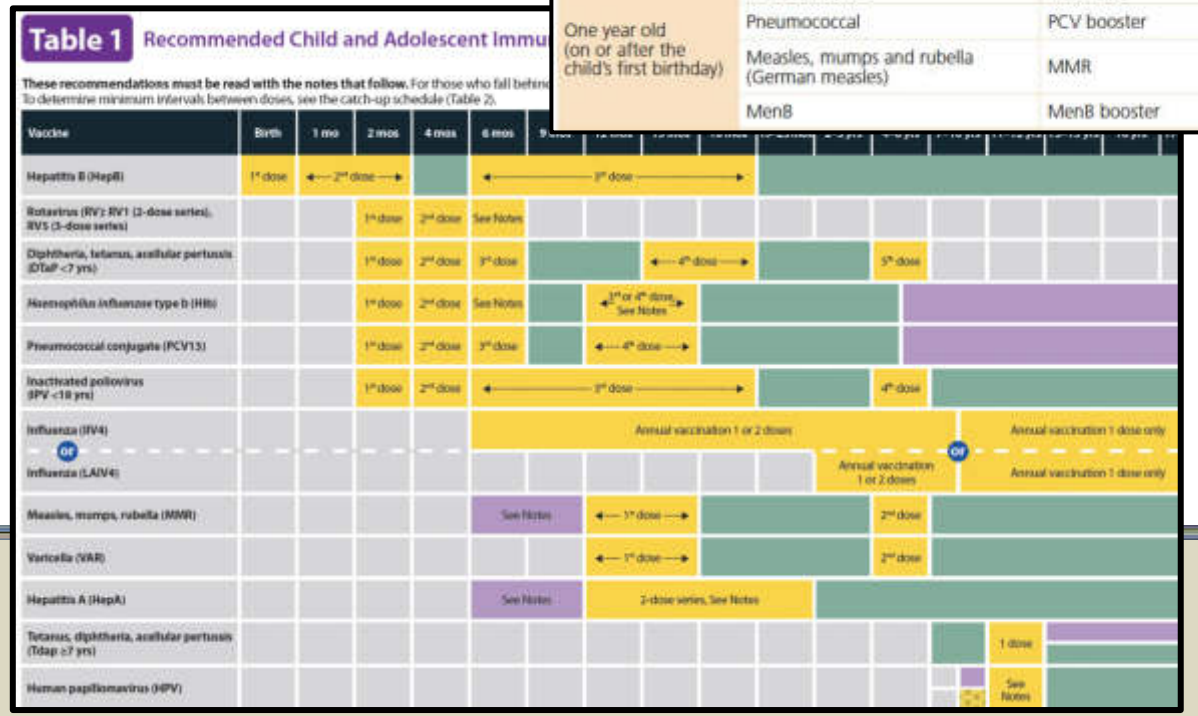
Karzon, DT. *Postgrad Med J* 45; 147: 1969

United Kingdom 2022

The routine immunisation schedule from February 2022

Age due	Diseases protected against	Vaccine given and trade name		Usual site[1]
Eight weeks old	Diphtheria, tetanus, pertussis (whooping cough), polio, *Haemophilus influenzae* type b (Hib) and hepatitis B	DTaP/IPV/Hib/HepB	Infanrix hexa or Vaxelis	Thigh
	Meningococcal group B (MenB)	MenB	Bexsero	Left thigh
	Rotavirus gastroenteritis	Rotavirus[2]	Rotarix[2]	By mouth
Twelve weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B	DTaP/IPV/Hib/HepB	Infanrix hexa or Vaxelis	Thigh
	Pneumococcal (13 serotypes)	Pneumococcal conjugate vaccine (PCV)	Prevenar 13	Thigh
	Rotavirus	Rotavirus[2]	Rotarix[2]	By mouth
Sixteen weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B	DTaP/IPV/Hib/HepB	Infanrix hexa or Vaxelis	Thigh
	MenB	MenB	Bexsero	Left thigh
One year old (on or after the child's first birthday)	Hib and MenC	Hib/MenC	Menitorix	Upper arm/thigh
	Pneumococcal	PCV booster	Prevenar 13	Upper arm/thigh
	Measles, mumps and rubella (German measles)	MMR	MMRvaxPro[3] or Priorix	Upper arm/thigh
	MenB	MenB booster	Bexsero	Left thigh

United States 2022



Vaccine Doses and Injections Required for Children Birth to 6 Years of age; United States 2023

Antigen	Doses	Antigen	Doses
Diphtheria	5	Measles	2
Tetanus	5	Mumps	2
Pertussis	5	Rubella	2
Hib	3-4	Varicella	2
Polio (IPV-3) x 4	12	Hepatitis A	2
Hepatitis B	3-4	Influenza (4) x 5	20
PCV-13 x 4	52	COVID-19	2-3
Rotavirus (5) x 3	15	**Total antigens**	**132-135**

Minimal Injections = 20

Reasons for Combining Vaccines

- Reduce injections- less trauma and pain
- Simplify immunization delivery – increase compliance
- Integrate multiple antigens from different diseases or from variants of the same pathogen
- Increase acceptance of vaccines?

What is a combination vaccine?

- Vaccine designed to protect against **two or more** diseases or against **one disease caused by different strains or serotypes**

Multiple Antigens for Distinct Pathogens	Multiple Antigens against Same Pathogen
DTP TdaP	PCV vaccines (13, 15, 20 serotypes) PPV (23 serotypes)
DTaP-HBV-Hib DTaP-HBV-Hib-IPV DTwP-HBV-Hib-IPV	Influenza (2 A + 2 B lineages)
MR MMR MMRV	COVID-19 (Wuhan + Omicron)
HepA-HepB	Dengue (4 serotypes)

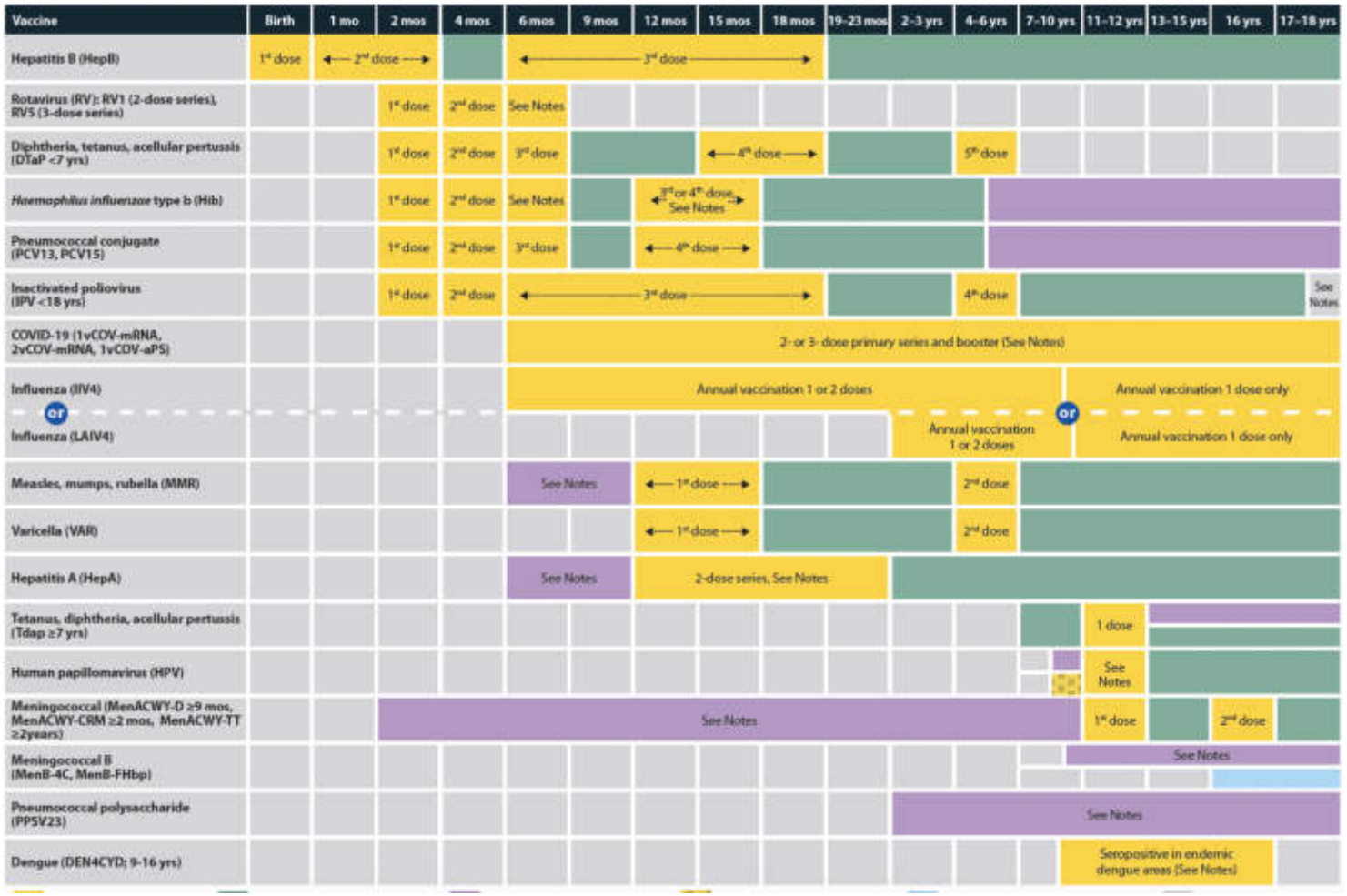
Kalies H, et al. *Pediatr Infect Dis J* 2006;25:507-12.
Marshall GS, et al. *Pediatr Infect Dis J* 2007;26:496-500.

FDA-licensed combination vaccines for different VPDs

Vaccine[b]	Trade name (year licensed)	Age range	Routinely recommended ages
HepA-HepB	Twinrix (2001)	≥18 years	3 doses on a schedule of 0, 1, and 6 months
DTaP-HepB-IPV	Pediarix (2002)	6 weeks-6 years	3-dose series at 2, 4, and 6 months of age
MMRV	ProQuad (2005)	12 months-12 years	2 doses, the first at 12-15 months, the second at 4-6 years
DTaP-IPV	Kinrix (2008)	4-6 years	5th dose of DTaP and fourth dose of IPV
DTaP-IPV/Hib	Pentacel (2008)	6 weeks-4 years	4-dose schedule at 2, 4, 6, and 15-18 months of age
Hib-MenCY	MenHibrix (2012)	6 weeks-18 months	4-dose schedule at 2, 4, 6, and 12-15 months of age[c]
DTaP-IPV	Quadracel (2015)	4-6 years	5th dose of DTaP and fourth or fifth dose of IPV
DTaP-IPV-Hib-HepB	Vaxelis (2018)	6 weeks – 4 years	3-dose series at 2, 4, and 6 months of age

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html#ref-82

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2023



Vaccine	Abbreviation(s)	Trade name(s)
COVID-19	1vCOV-mRNA	Comirnaty®/Pfizer-BioNTech COVID-19 Vaccine
		SPIKEVAX®/Moderna COVID-19 Vaccine
	2vCOV-mRNA	Pfizer-BioNTech COVID-19 Vaccine, Bivalent
		Moderna COVID-19 Vaccine, Bivalent
	1vCOV-aPS	Novavax COVID-19 Vaccine
Dengue vaccine	DEN4CYD	Dengvaxia®
Diphtheria, tetanus, and acellular pertussis vaccine	DTaP	Daptacel® Infanrix®
Diphtheria, tetanus vaccine	DT	No trade name
Haemophilus influenzae type b vaccine	Hib (PRP-T)	ActHIB® Hiberix®
	Hib (PRP-OMP)	PedvaxHIB®
Hepatitis A vaccine	HepA	Havrix® Vaqta®
Hepatitis B vaccine	HepB	Engerix-B® Recombivax HB®
Human papillomavirus vaccine	HPV	Gardasil 9®
Influenza vaccine (inactivated)	IIV4	Multiple
Influenza vaccine (live, attenuated)	LAIV4	FluMist® Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R II® Priorix®
Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D	Menactra®
	MenACWY-CRM	Menveo®
	MenACWY-TT	MenQuadfi®
Meningococcal serogroup B vaccine	MenB-4C	Bexsero®
	MenB-FHbp	Trumenba®
Pneumococcal conjugate vaccine	PCV13	Prevnar 13®
	PCV15	Vaxneuvance™
Pneumococcal polysaccharide vaccine	PPSV23	Pneumovax 23®
Poliovirus vaccine (inactivated)	IPV	IPOL®
Rotavirus vaccine	RV1	Rotarix®
	RV5	RotaTeq®
Tetanus, diphtheria, and acellular pertussis vaccine	Tdap	Adacel® Boostrix®
Tetanus and diphtheria vaccine	Td	Tenivac® Tdvax™
Varicella vaccine	VAR	Varivax®
Combination vaccines *(use combination vaccines instead of separate injections when appropriate)*		
DTaP, hepatitis B, and inactivated poliovirus vaccine	DTaP-HepB-IPV	Pediarix®
DTaP, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine	DTaP-IPV/Hib	Pentacel®
DTaP and inactivated poliovirus vaccine	DTaP-IPV	Kinrix® Quadracel®
DTaP, inactivated poliovirus, *Haemophilus influenzae* type b, and hepatitis B vaccine	DTaP-IPV-Hib-HepB	Vaxelis®
Measles, mumps, rubella, and varicella vaccine	MMRV	ProQuad®

Potential Problems With Combining Vaccines

1) Chemical interactions
2) Physical interactions
3) Competition between antigens
4) Immune alterations
5) Patent issues
6) Price (more expensive)

Combination Vaccines. in Plotkin and Orenstein. Vaccines 2023

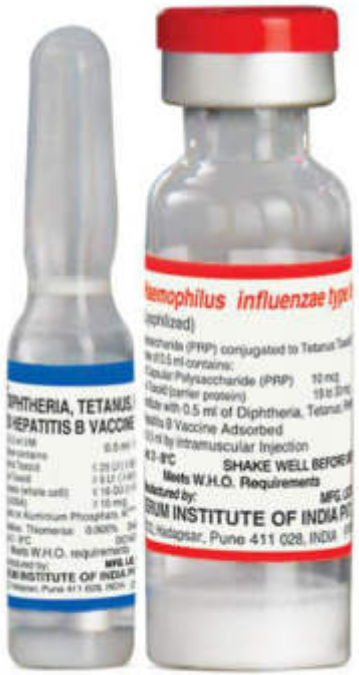
Hexavalent vaccines (DTaP vs DTwP-IPV-HepB-Hib

- DTwP interference with IPV chemistry prevented the development of a hexavalent vaccine for most of the world

DTwP-IPV-HepB liquid

+

Hib lyophilized vial



Serum Institute India Hexa vaccine

Each dose of 0.5 ml contains

Diphtheria Toxoid ≤ 25 Lf (≥ 30 IU)

Tetanus Toxoid ≥ 5 Lf (≥ 40 IU)

B. pertussis (whole cell) ≤ 16 OU (≥ 4 IU)

HBsAg (rDNA) ≥ 10 mcg

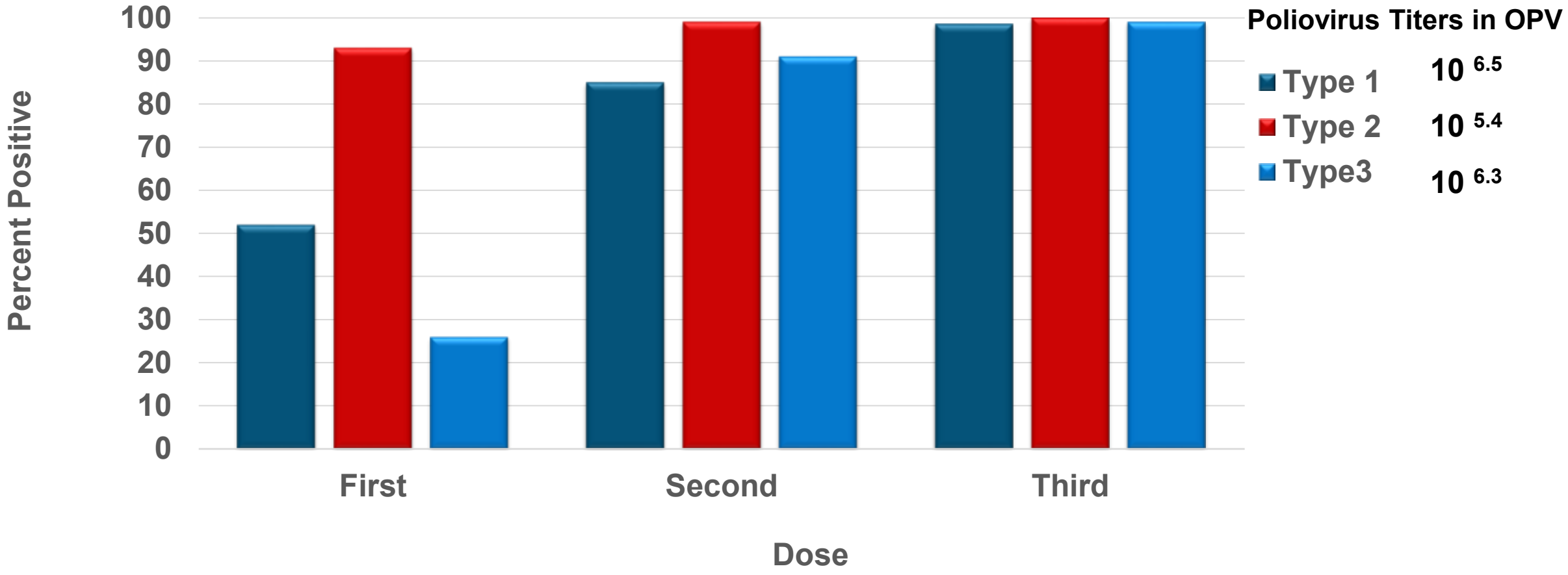
Purified Capsular Polysaccharide (PRP) 10 mcg

Tetanus Toxoid (carrier protein) 19 to 33 mcg

Adsorbed onto Aluminium Phosphate, Al+++ ≤ 1.25 mg

Preservative: Thiomersal 0.005%

Cumulative Seroresponses to Trivalent Oral Poliovirus Vaccine



Source: Cohen-Abbo. PIDJ 1995;14:103.

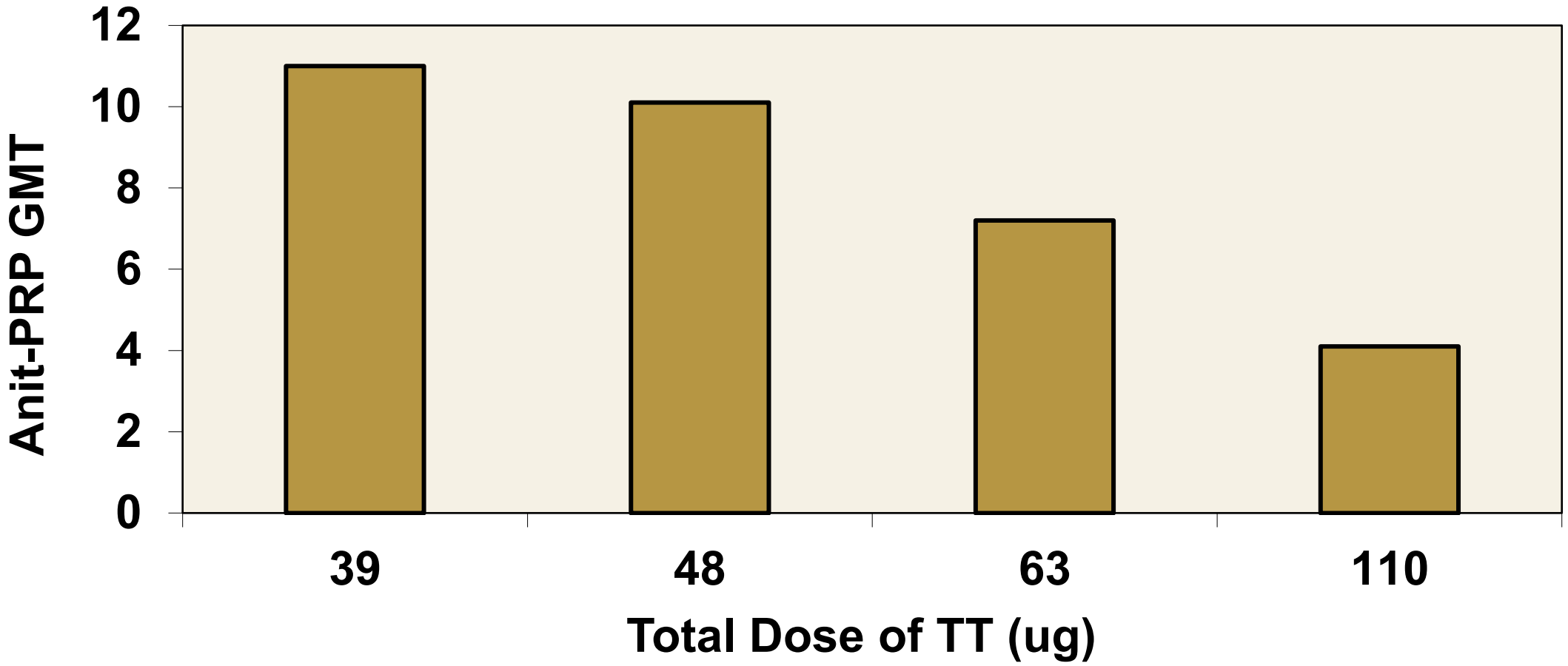
Tetanus Toxoid-containing Vaccines Administered Simultaneously to Children at 2, 4 and 6 Months of Age

Israel and Finland Studies

A:	**DTP/PRP-T (Hib)**	**Pnc-T**
B:	**DTP/PRP-T (Hib)**	**Pnc-D**

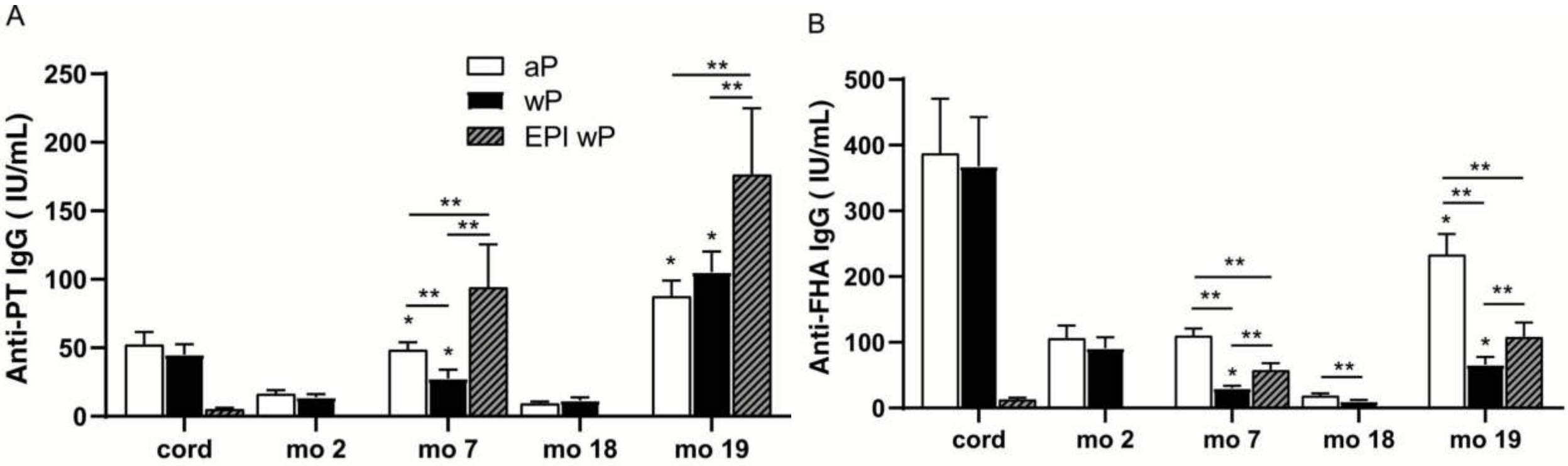
Dagan, et al. Infect Immun 1998;66:2093

Carrier Induced Suppression: Decreased Response to PRP with Increasing Total Dose of TT Administered



Dagan, et al. Infect Immun 1998;66:2093

Geometric mean concentrations of anti-PT; B), anti-FHA IgG in the acellular pertussis (aP), whole-cell pertussis (wP), and EPI wP groups at birth (cord) and months 2, 7, 18, and 19.



Maternal Tdap inhibited more pertussis-specific responses in wP vs. aP-vaccinated infants

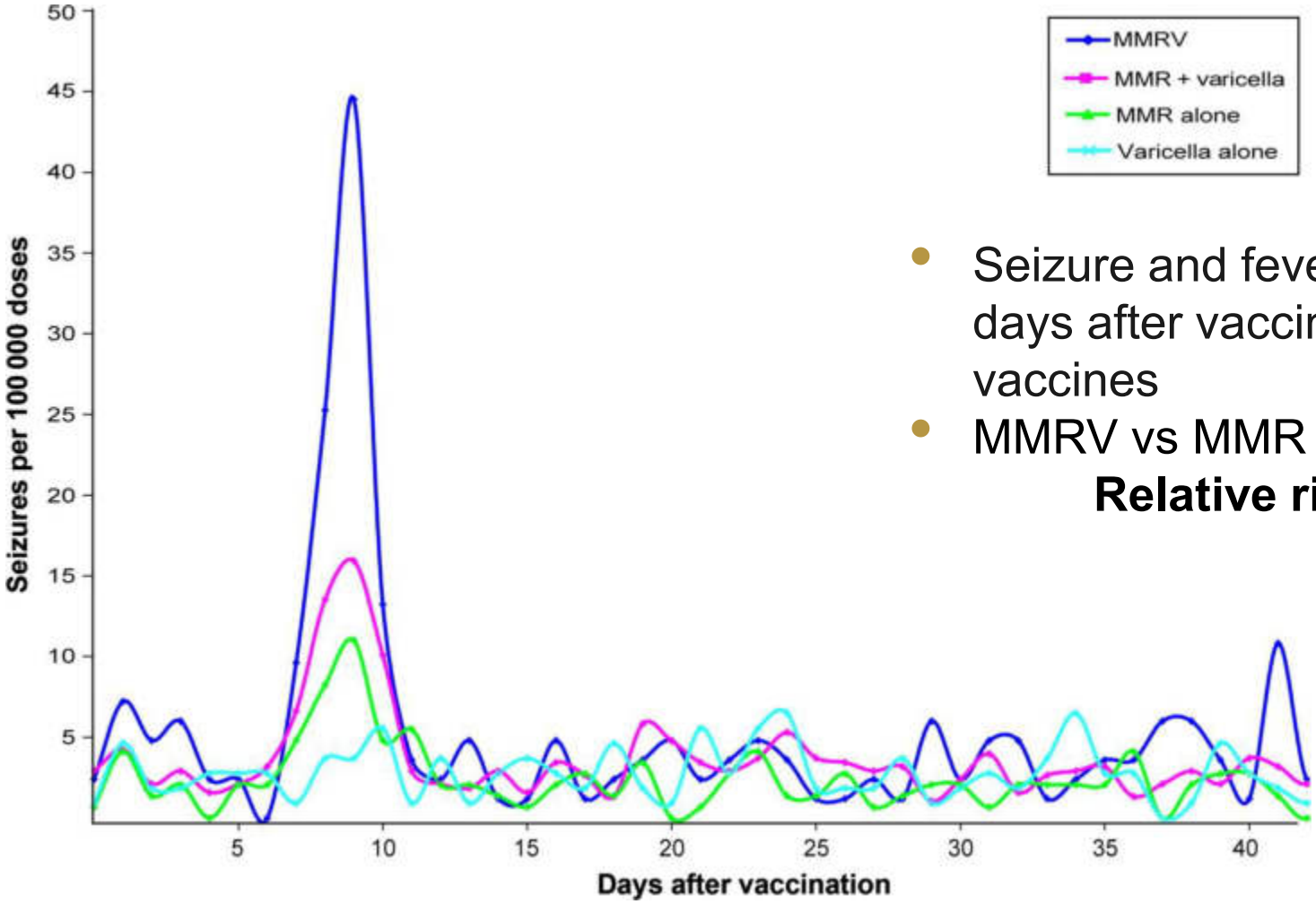
Wanlapakorn N, et al Clin Infect Dis. 2020;71(1):72-80.
doi: 10.1093/cid/ciz778.

Seroconversion after 3 doses of DTaP/IPV/Hib at 2, 3 and 4 months of age in 5-month old infants born to mothers given Boostrix-IPV, Repevax or no DTaP/IPV in pregnancy in UK

		Boostrix-IPV		Repevax		None
Poliovirus serotype	n/N	% seroconversion (95 % CI)	n/N	% seroconversion (95 % CI)	n/N	% seroconversion (95 % CI)
1	10/52	**19.2 (9.6–32.5)**	12/53	**22.6 (12.3–36.2)**	17/23	73.9 (51.6–89.8)***
2	11/54	**20.4 (10.6–33.5)**	10/56	**17.9 (8.9–30.4)**	17/24	70.8 (48.9–87.4)***
3	18/50	**36.0 (22.9–50.8)**	24/54	**44.4 (30.9–58.6)**	22/24	91.7 (73.0–99.0)***

Grassly NC, et al. Vaccine. 2023 Feb 10;41(7):1299-1302.
doi: 10.1016/j.vaccine.2023.01.035.

Postvaccination seizures among 12-23-month-olds according to vaccine received: VSD study population, USA 2000–2008

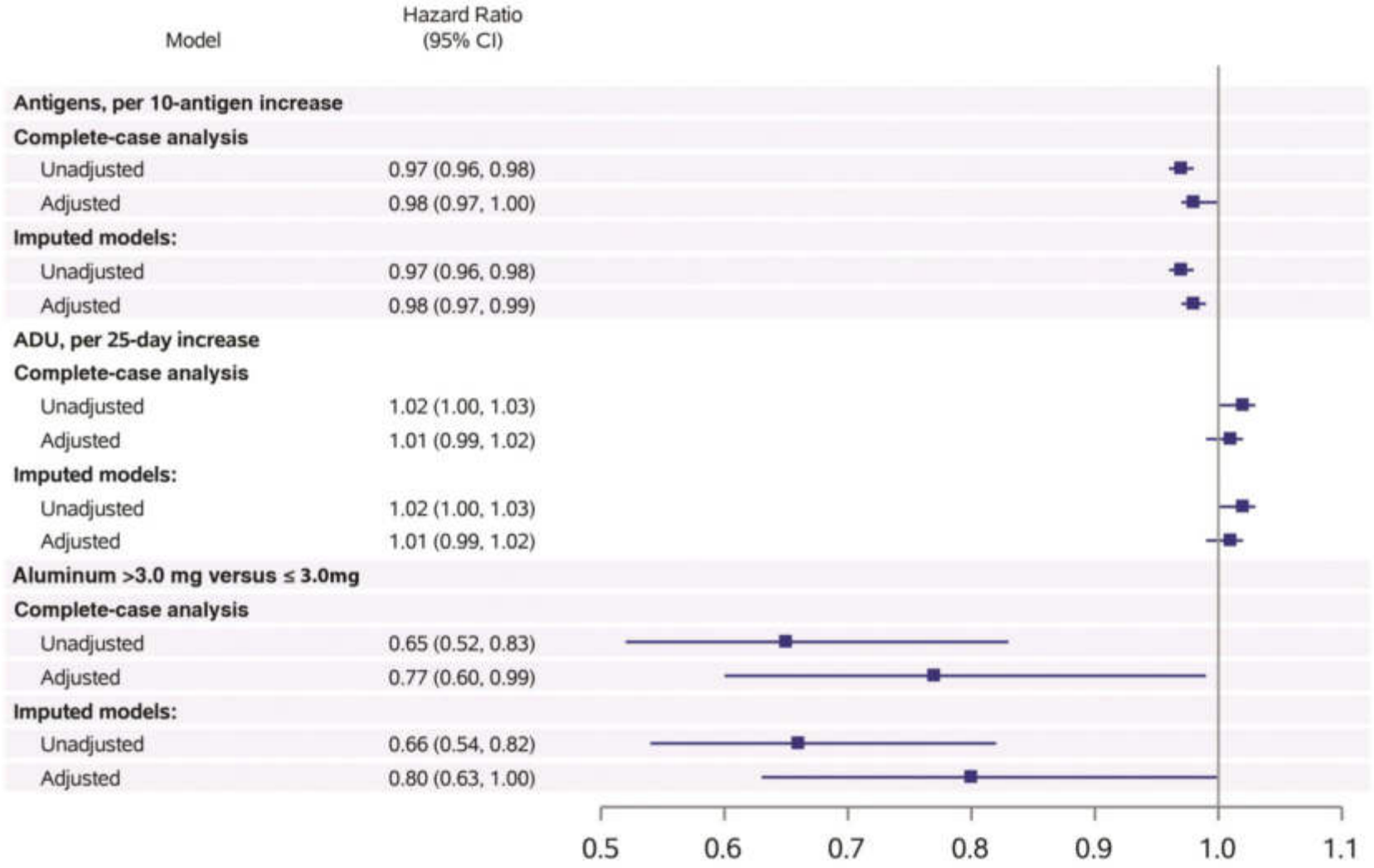


- Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines
- MMRV vs MMR + varicella vaccination
  Relative risk: 1.98 [95% CI: 1.43–2.73]

Klein NP, et al. Pediatrics. 2010;126(1):e1-8.
doi: 10.1542/peds.2010-0665.

Are multiple antigen schedules safe for children?

Risk of developing T1DM in 584,171children in the USA 2004-2014



- Avg 263 antigens
- Cumulative Ag exposure **not associated with T1DM**
- Cumulative aluminum exposure >3.00 mg was **inversely associated with T1DM**

Glanz JM, et al Pediatrics. 2021;148(6):e2021051910.
doi: 10.1542/peds.2021-051910.

Complexities of combination vaccines

- Combination products may be **more expensive** than separate vaccines
- But may be **more cost effective** if the costs of extra injections, health care provider time, and additional handling and storage are taken into consideration
- May result in **administration of extra, unneeded doses** of antigens (e.g., a booster dose of pertussis-containing vaccine may also provide extra, D and T)
- More difficult to determine which **component of a combination** vaccine is responsible for an allergic reaction or AEFI.

Summary

- **Pathogens** evolve given the opportunity at the host and population level (community and individual protection gaps)
- **Combination vaccines** can optimize delivery and compliance with immunization schedules and provide better coverage
- Combination vaccines **allow filling the gaps** of immunity against evolving variants, serotypes and multiple pathogens
- **Recognize complexity of inclusion** of combination vaccines to ensure immunity, safety and cost-effectiveness for the population