  

Vaccine administration routes

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Journées inter-DES sur la vaccination
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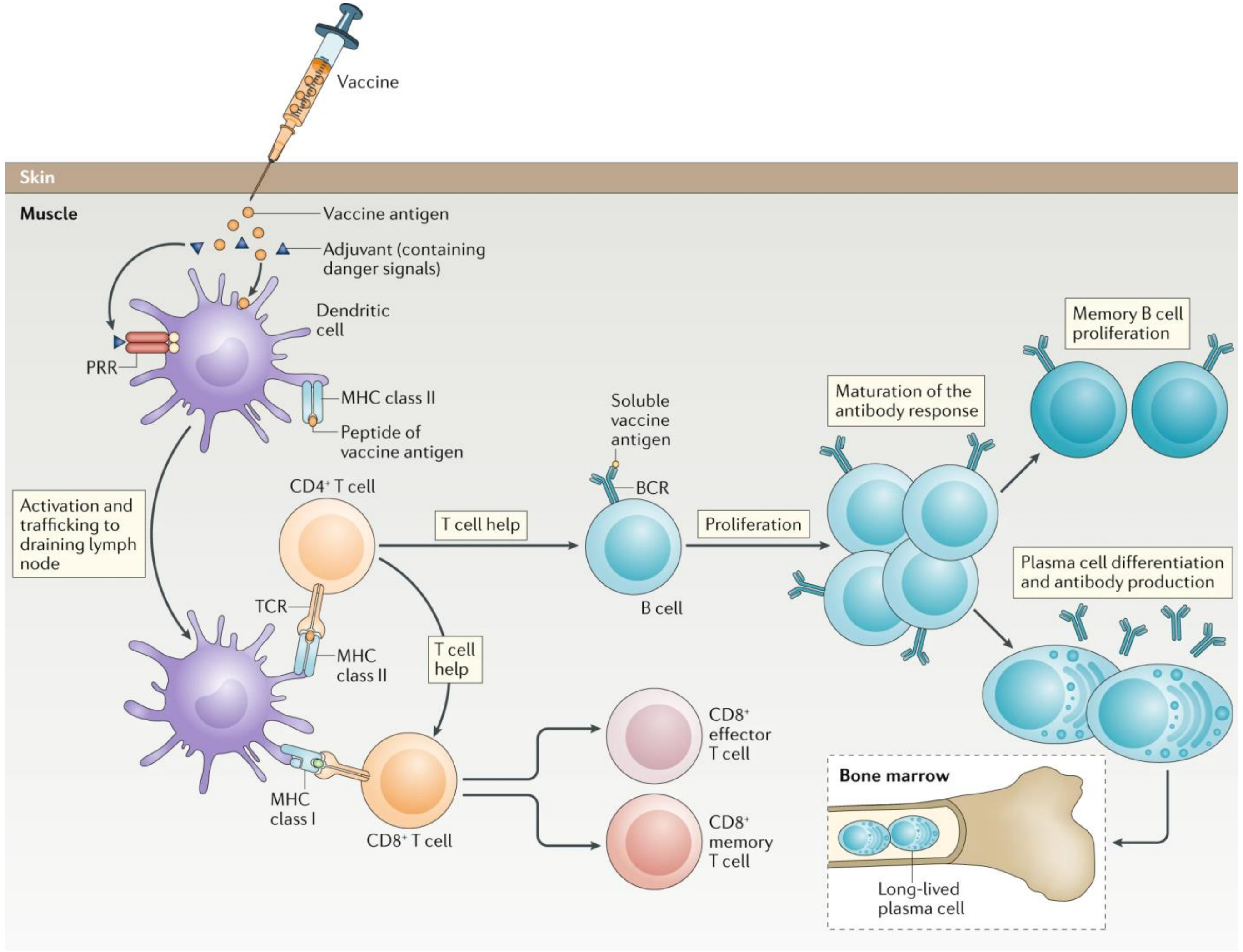
Routes of licenced vaccine administration

List of US-FDA approved live attenuated and killed vaccine.

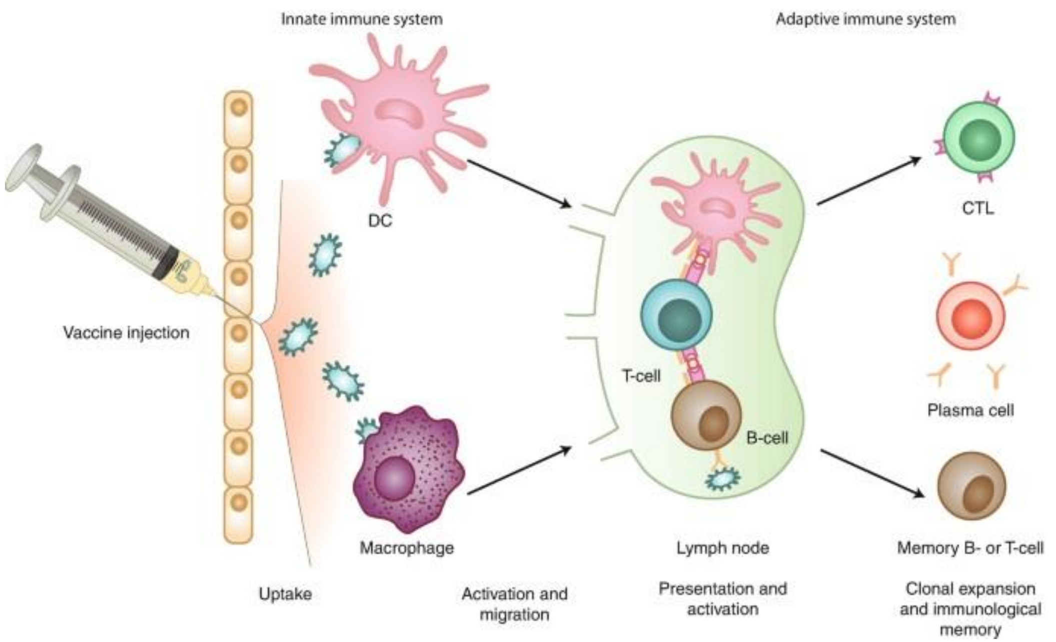
Type of vaccine	Pathogen	Vaccine name	Route	Manufacturer reference	Reference
Live- attenuated vaccine	Smallpox (Vaccinia) Vaccine	ACAM2000®	Percutaneous	Sanofi Pasteur Biologics co. Cambridge, USA	[38]
	Varicella Virus Vaccine	VARIVAX®	Subcutaneous	Merck & co., Inc. Kenilworth, USA	[39]
	Rotavirus Vaccine	Rotarix®	Oral	GlaxoSmithKline Biologicals, Brentford, UK	[40]
	Influenza Vaccine	FluMist®	Intranasal	Medimmune, LLC. Gaithersburg, MD, USA	[41]
	Ebola Zaire Vaccine	ERVEBO®	Intramuscular	Merck & Co., Inc. Kenilworth, USA	[42]
	Measles, Mumps, and Rubella Virus Vaccine	M-M-R® II	Subcutaneous	Merck & Co., Inc. Kenilworth, USA	[43]
	BCG Live	BCG Vaccine	Percutaneous	Organon Teknika Corp., LLC	[44]
	Chikungunya Vaccine, Live	IXCHIQ	Intramuscular	Valneva Austria GmbH	[45]
	Cholera Vaccine, Live, Oral	VAXCHORA	Oral	Bavarian Nordic A/S	[46]
	Dengue Tetravalent Vaccine, Live	DENGVAXIA	subcutaneous	Sanofi Pasteur, Inc.	[47]
	Influenza Vaccine, Adjuvanted	FLUAD	Intramuscular	Seqirus, Inc.	[48]
	Rabies Vaccine	RabAvert	Intramuscular	Bavarian Nordic A/S	[49]
	Tick-Borne Encephalitis Vaccine	TICOVAC	Intramuscular	Pfizer Ireland Pharmaceuticals	[50]
	Typhoid Vaccine Live Oral Ty21a	Vivotif	Oral	Bavarian Nordic (BN)	[51]
	Yellow Fever Vaccine	YF-Vax	Subcutaneous	Sanofi Pasteur, Inc	[52]
Killed vaccine	Poliovirus Vaccine	IPOL®	Intramuscularly or subcutaneously	Sanofi Pasteur, SA. Lyon, France	[43]
	Hepatitis A Vaccine	HAVRIX®	Intramuscular	GlaxoSmithKline Biologicals. Brentford, United Kingdom	[53]
	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine	INFANRIX®	Intramuscular	GlaxoSmithKline Biologicals. Brentford, United Kingdom	[54]
	Japanese Encephalitis Vaccine	IXIARO®	Intramuscular	Valneva Austria GmbH. Vienna, Austria	[55]
	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed	DAPTACEL®	Intramuscular	Sanofi Pasteur, SA. Lyon, France	[56]
Subunit vaccine	Anthrax Vaccine Adsorbed, Adjuvanted	CYFENDUS	Intramuscular	Emergent Product Development Gaithersburg Inc	[57]
	Anthrax Vaccine Adsorbed	BIOTHRAX	Intramuscular/ Subcutaneous	Emergent BioDefense Operations Lansing LLC	[58]
	Chikungunya Vaccine, Recombinant	VIMKUNYA	Intramuscular	Bavarian Nordic A/S	[59]
	Haemophilus B Conjugate Vaccine	Liquid PedvaxHIB	Intramuscular	Merck Sharp & Dohme Corp.	[60]
	Hepatitis B Vaccine (Recombinant)	RECOMBIVAX HB	Intramuscular	Merck & Co, Inc	[61]
	Human Papillomavirus 9-valent Vaccine, Recombinant	GARDASIL 9	Intramuscular	Merck & Co., Inc	[62]
	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted	AREPANRIX	Intramuscular	ID Biomedical Corporation of Quebec	[63]
	Meningococcal Group B Vaccine	BEXSERO	Intramuscular	GlaxoSmithKline Biologicals SA	[64]
	Respiratory Syncytial Virus Vaccine, Adjuvanted	AREXVY	Intramuscular	GlaxoSmithKline Biologicals SA	[65]
	Tetanus and Diphtheria Toxoids Adsorbed	TENIVAC	Intramuscular	Sanofi Pasteur Limited	[66]
	Zoster Vaccine Recombinant, Adjuvanted	SHINGRIX	Intramuscular	GlaxoSmithKline Biologicals	[67]
Nucleic acid based vaccine	COVID-19 Vaccine, mRNA	COMIRNATY	intramuscular	BioNTech Manufacturing GmbH	[68]
	COVID-19 Vaccine, mRNA	SPIKEVAX	intramuscular	Moderna Tx, Inc	[69]

Sughandi et al 2025, J Drug Deliv Science and Tech

Vaccination via skin injection

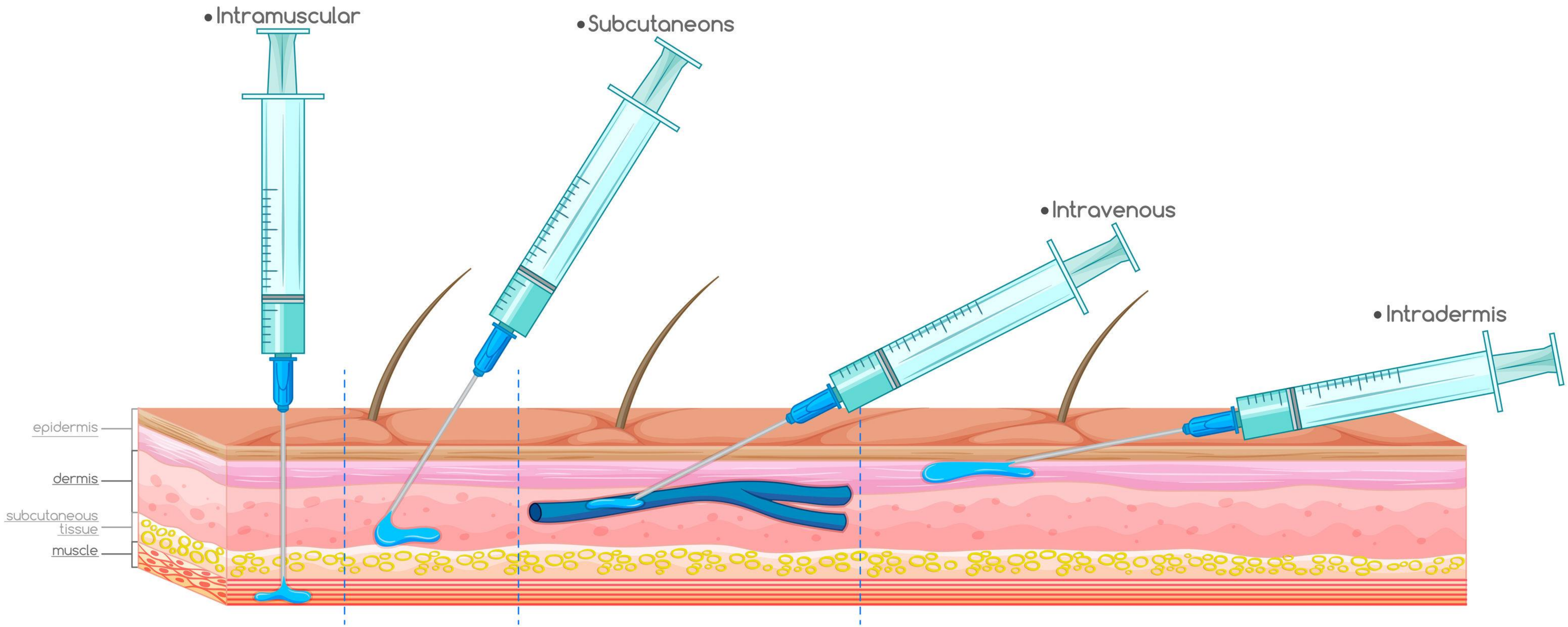


https://www.nature.com/articles/s41577-020-00479-7



https://link.springer.com/chapter/10.1007/978-3-030-00710-2_14

Different types of skin injections



https://www.technoflex.net/en/news/flexmag/flexmag-14/4-injection-methods-4-levels-of-action/

IM vs ID: dose sparing using ID

Vaccine	Vaccine type	Subject	Immunogenicity: ID vs IM vaccination	Reference
Hepatitis B vaccine	Plasma-derived hepatitis B subunit vaccine	Healthy adults	ID group had higher serum conversion when using the same dose as IM groups; similar seroconversion rates and antibody titers as ID group with 10% of dose used in IM group.	[158, 159]
Hepatitis B vaccine	Recombinant HBsAg vaccine	Hemodialysis patients	Higher seroprotection rates in the ID groups compared to IM groups	[20, 160]
Hepatitis B vaccine	Recombinant HBsAg vaccine	Healthy adults	ID group had higher serum conversion when using the same dose as IM groups; similar seroconversion rates as ID group with 20% of dose used in IM group	[161, 162]
Influenza vaccine	Trivalent inactivated split influenza vaccine	Healthy adults	Similar seroconversion rates as ID group with 20-60% of dose used in IM group	[163, 164]
Influenza vaccine	Trivalent inactivated split influenza vaccine	Infants	Similar seroconversion rates as ID group with 40% of dose used in IM group	[165]
Influenza vaccine	Trivalent inactivated split influenza vaccine	HIV-1 infected adult patients	Similar seroprotection and HAI titers as ID group with 60% of dose used in IM group	[166]
Influenza vaccine	Virosomal adjuvanted trivalent influenza vaccine	Healthy adults	Similar seroconversion rates as ID group with≤40% of dose used in IM group	[167]
Human papillomavirus (HPV) vaccine	HPV16 and HPV18 Recombinant proteins	Healthy adults	Similar seroprotection as ID group with 20% of dose used in IM group	[168]
Hepatitis A vaccine	Virosomal HAV vaccine	Healthy adults	Similar seroprotection rate as ID group with 20% of dose used in IM group	[88]
Rabies vaccine	Inactivated Rabies vaccine	Healthy Adults	Similar immune response as ID group with 10% of dose used in IM group	[169]
Rabies vaccine	Live attenuated Rabies vaccine	Healthy adults	Similar immune response as ID group with 25% of dose used in IM group	[170]

Zhang et al 2015, Expert Rev Vaccines

IM vs SC: similar responses but sometimes lower by SC route

Vaccine	Vaccine type	Subject	Immunogenicity: SC vs IM vaccination	Reference
Hepatitis B vaccine	Recombinant HBsAg protein	Healthy adults	Lower level of antibody responses in SC group compared to IM group	[99]
Influenza vaccine	Inactivated split trivalent influenza vaccines	Female elderly	Lower level of antibody responses in SC group compared to IM group	[171]
Influenza vaccine	Inactivated whole-virion influenza A vaccine with alum adjuvant	Adult men	Lower level of antibody responses in SC group compared to IM group	[93]
Influenza vaccine	Inactivated split trivalent influenza vaccines	Children with neuromuscular disease	Similar antibody titers in both SC and IM groups	[172]
Hepatitis A vaccine	Virosomal HAV vaccine	Healthy adults	Similar seroprotection rates in both SC and IM groups	[88]
Hepatitis A Vaccine	Inactivated HAV Vaccine	Healthy Adults	Similar antibody titers in both SC and IM groups	[133]
Measles-mumps-rubella-varicella (MMRV) vaccine	Live attenuated MMRV vaccine	Healthy children	Similar seroconversion rates in both SC and IM groups	[95]
Measles, mumps and rubella (MMR) vaccine	Live attenuated MMR vaccine	Healthy children	Similar antibody and T cell responses in both SC and IM groups	[173]
Diphtheria, tetanus (DT) vaccine	Toxoid	Children	Similar antibody responses in both SC and IM groups	[94]
Meningococcal vaccine	Quadrivalent polysaccharide vaccine	Adults	Similar antibody responses in both SC and IM groups	[174]
HIV vaccine	DNA vaccine prime - Ad5 viral boost	Healthy adults	Similar antibody and T cell responses in both SC and IM groups	[92]

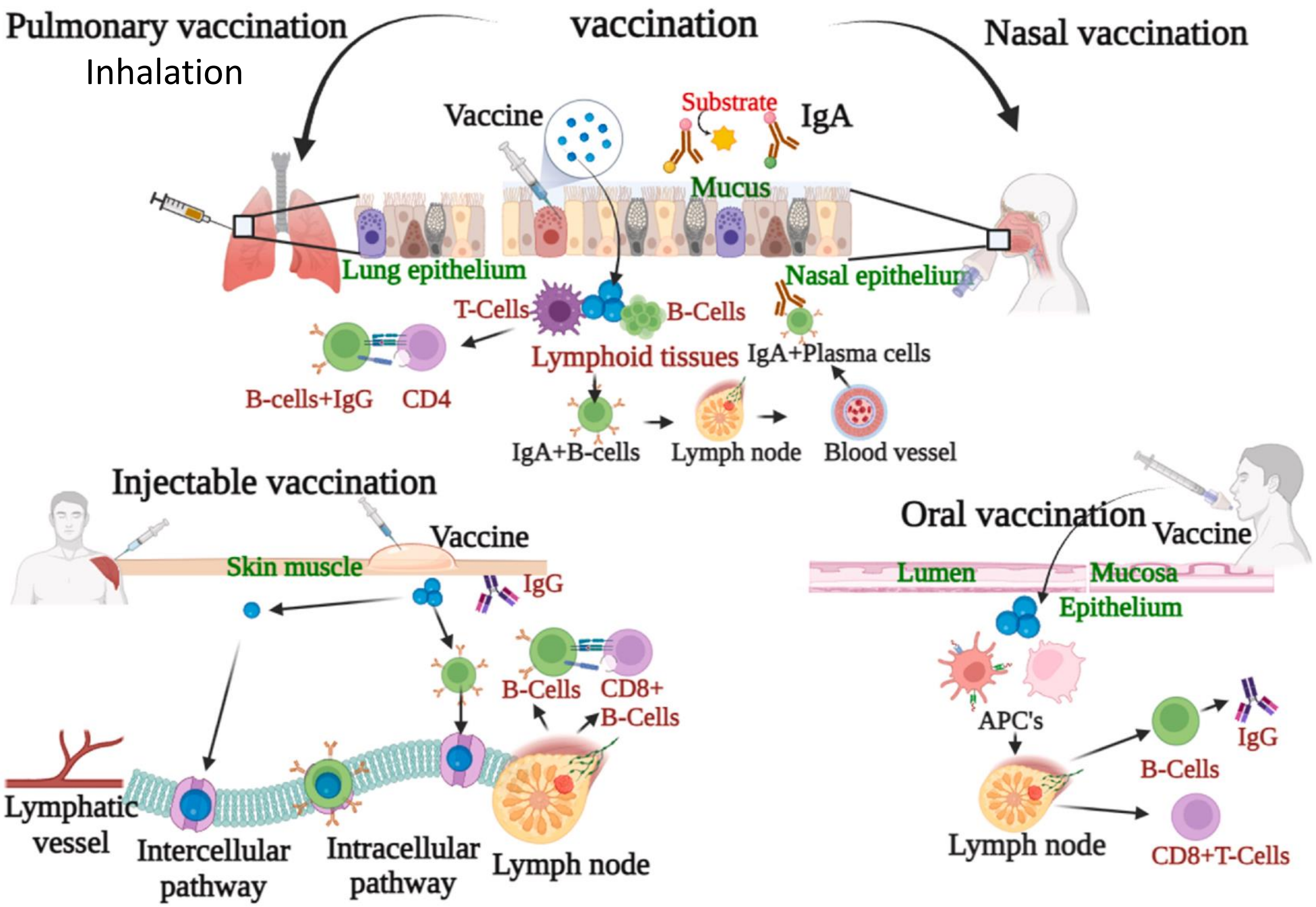
Zhang et al 2015, Expert Rev Vaccines

Impact of site of injection & needle length on immunogenicity

Vaccine type	Subjects	Injection site and needle length	Immunogenicity	Reference
Plasma-derived hepatitis B subunit vaccine	Healthy adults	Arm (1-inch), buttock (1-inch or 2-inch)	Injection at arm with 1-inch needle, at buttock using 2-inch needle or 1-inch needle achieved highest, intermediate, or lowest rate of seroconversion and titers to HBsAg, respectively	[100]
Recombinant HBsAg vaccine	Healthy infants	Quadriceps (1-inch or 5/8-inch)	1-inch needle achieved significantly higher antibody titers to HBsAg compared to 5/8-inch needle	[175]
Recombinant HBsAg vaccine	Healthy individuals aged 14-24 years	Deltoid muscle (1 -inch or 1.5-inch)	1.5-inch needle achieved significantly higher antibody titers to HBsAg compared to 1-inch needle	[176]

Zhang et al 2015, Expert Rev Vaccines

Why should several vaccine administration routes be used ?

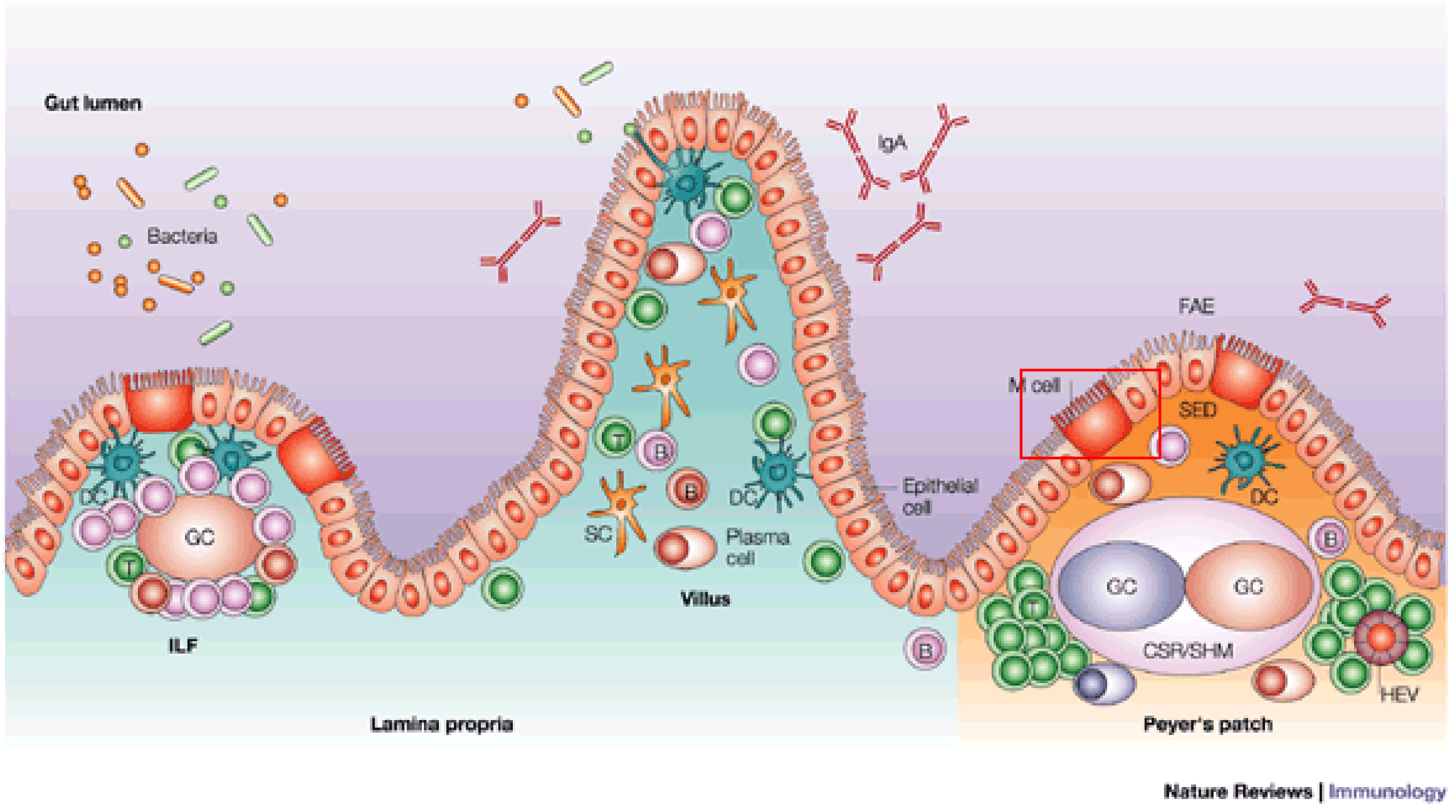


Boosting local immune responses; SIgA responses, tissue-resident memory responses

Common mucosal system

Sughandi et al 2025, J Drug Deliv Science and Tech

Mucosal-associated lymphoid tissues e.g. gut-associated lymphoid tissues



Lamina propria (Effector site)

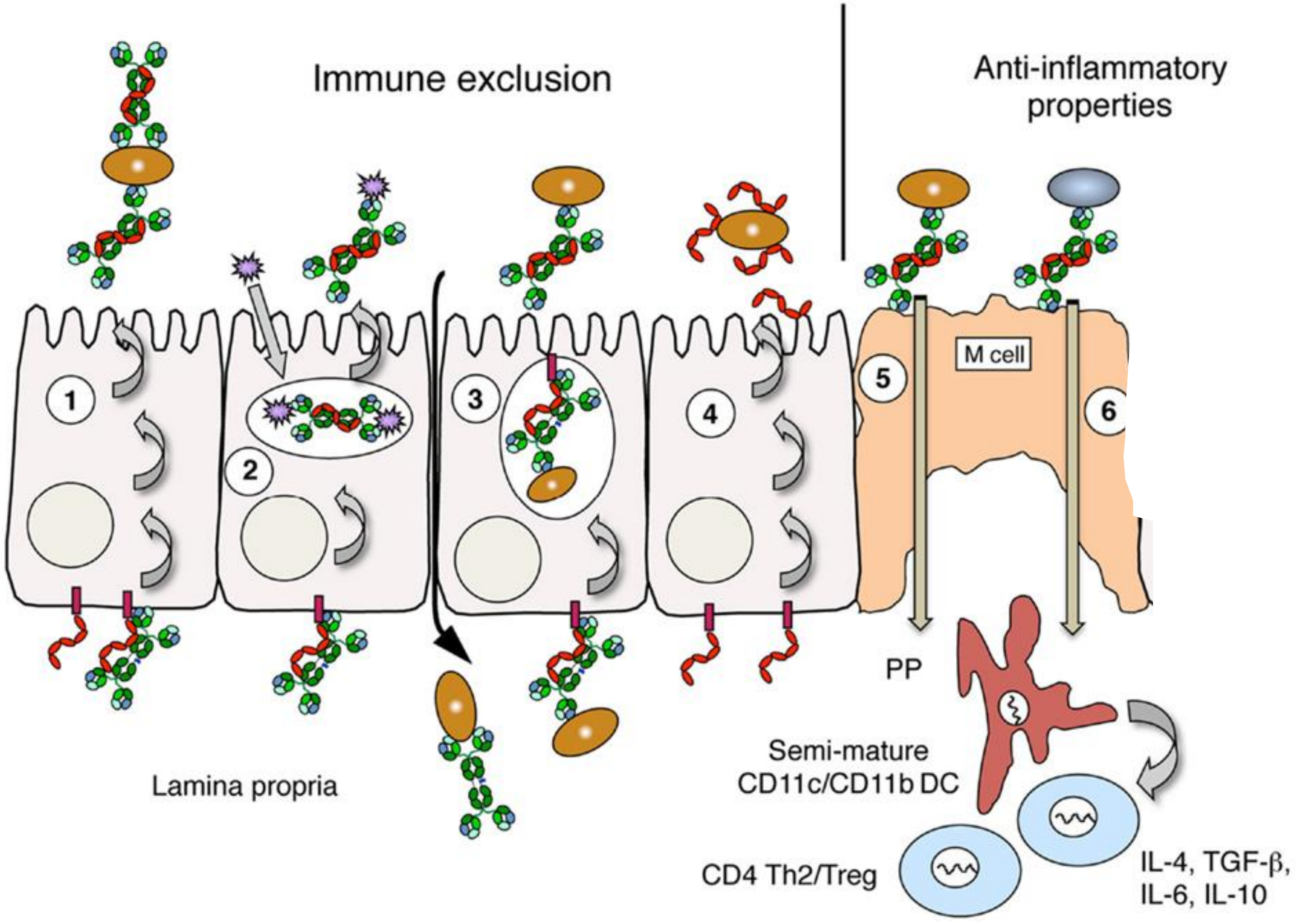
- IgA plasma cells (green)
- Intraepithelial lymphocytes
- CD4 and CD8 T cells
- Macrophages, polymorphonuclear leukocytes

Peyer's patches (Inductive site)

- Subepithelial dome with M cell (blue)
- Antigen-presenting cells (e.g. dendritic cells)
- Interfolicular regions enriched in naive T cells (red)
- Follicles enriched in naive B cells (green)

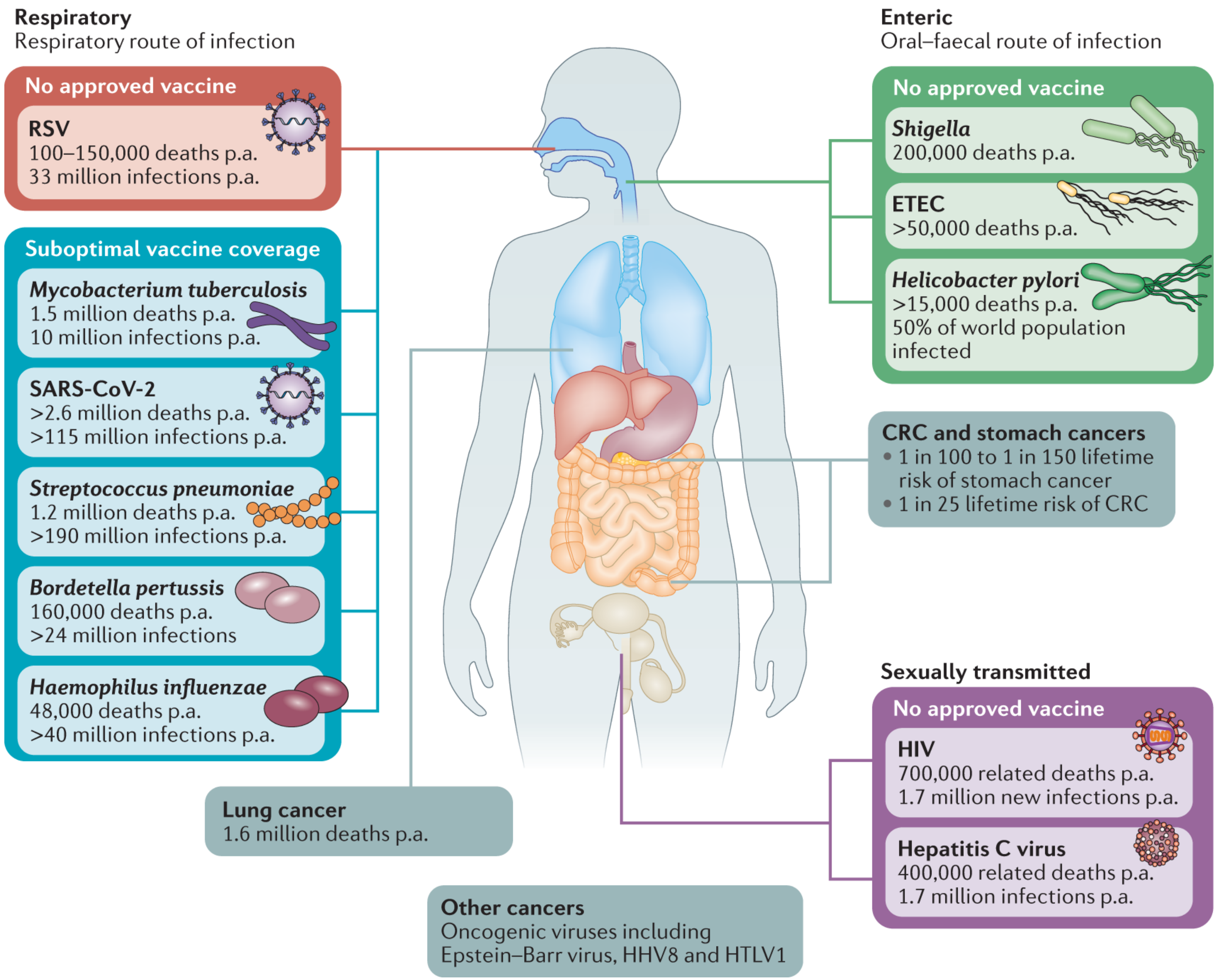
Role of SIgA at mucosal surfaces

Lumen



Lamina propria

Mucosal pathogens



Ward and Lavelle, 2021, Nat Rev Immunol

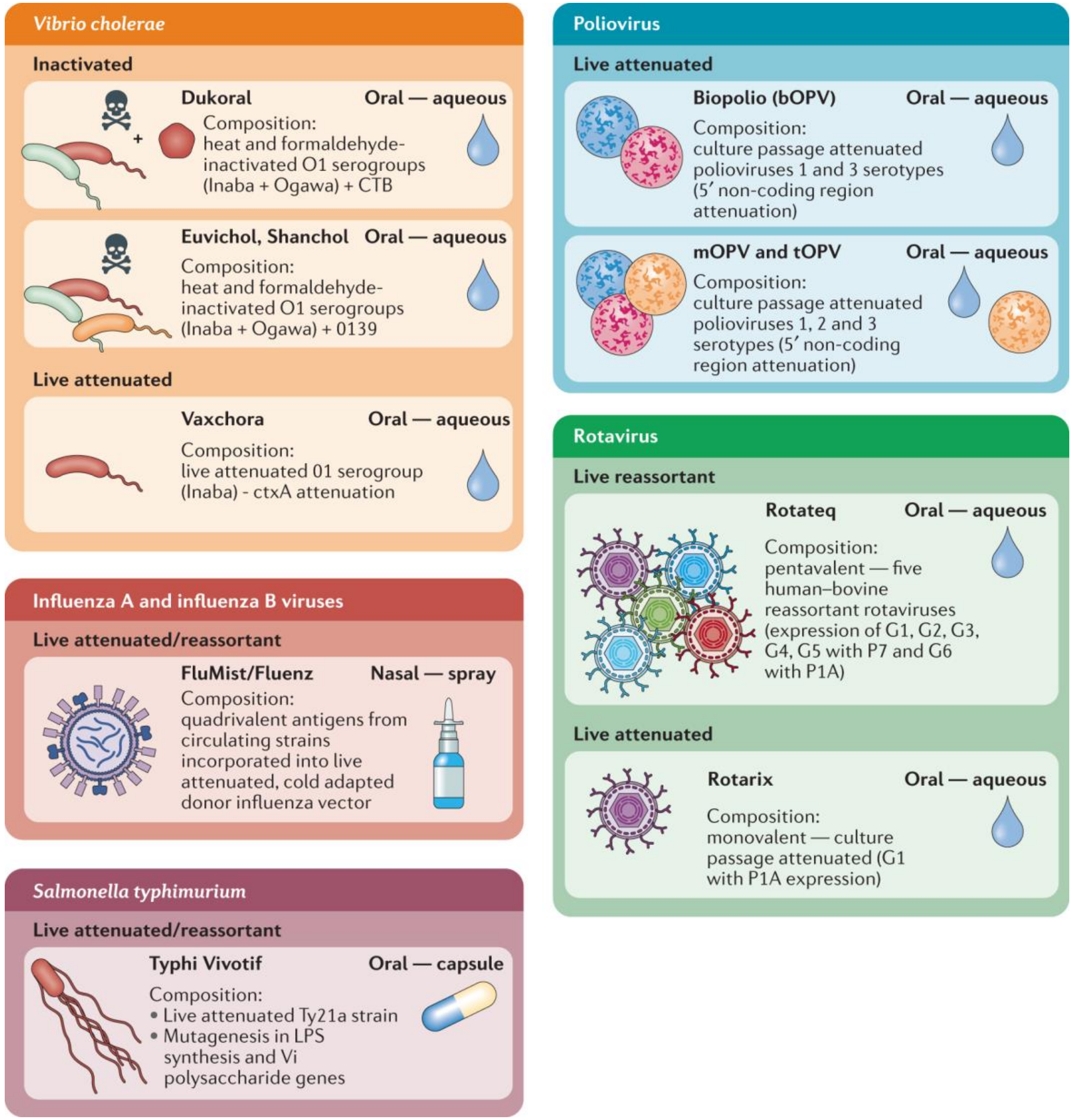
Benefits: mucosal route for vaccination

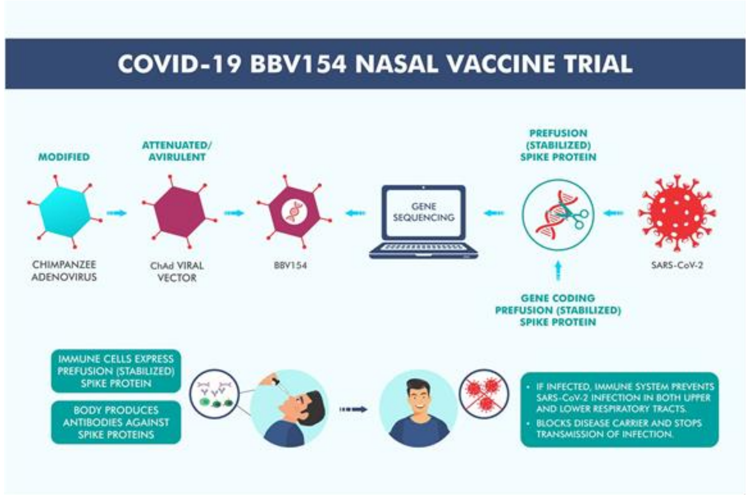
1) Needle-free strategies:

(i) Ease of administration
(ii) Non-invasiveness
(iii) High-patient compliance
(iv) Suitability for mass vaccination
(v) High safety

2) Immune responses: induction of local immune responses (mucosal sIgA, mucosal cellular responses; mucosal memory immune responses)

Only a few licensed mucosal vaccines





Bharat Biotech: Chimpanzee adenovirus-based vaccine approved in India for emergency use (2022)

CanSino: Inhaled vaccine against COVID-19 based on Adenovirus 5 approved in China (2022) + Morocco, Indonesia

dNS1-nCoV-RBD-LAIV, China

Razi Cov Pars vaccine (Iran)

Gam-COVID-Vac (Russia)

Ward and Lavelle, 2021, Nat Rev Immunol

Challenges: mucosal route for vaccination

1) Stability of vaccine formulation and vaccine uptake (delivery of antigens)

2) Local tolerance

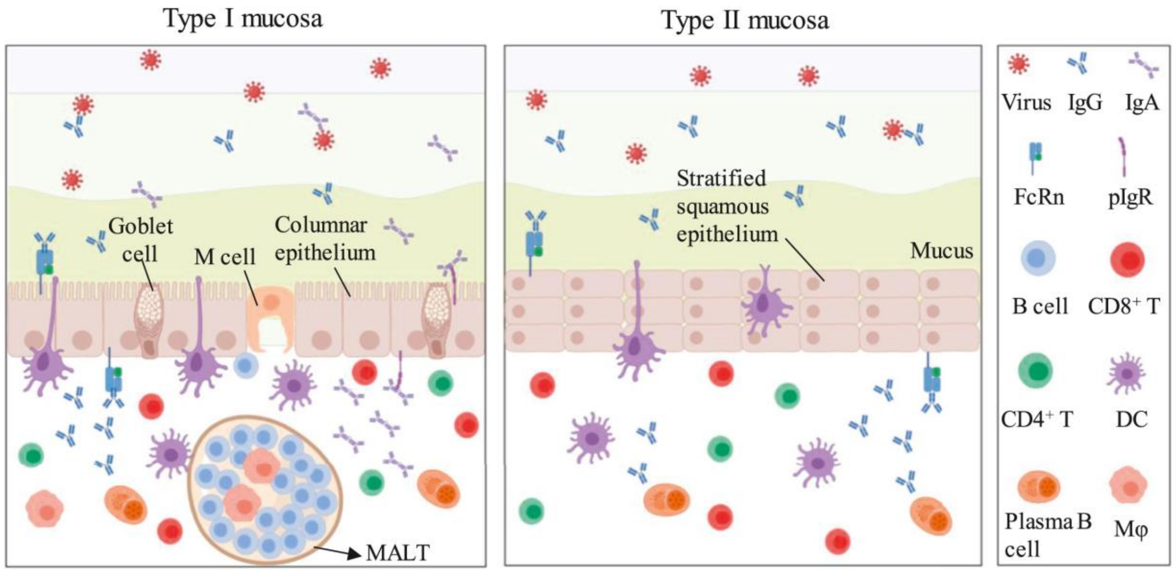
3) Induction of long-term responses

4) Criteria to approve a vaccine are currently based on systemic immune responses

Antigen delivery

Challenge: cross the epithelium barrier for inactivated vaccines, subunit vaccines or acid nucleic-based vaccines

A



B

Common barriers

❑ Structural barriers:
- Determine the route of antigen presentation
- Determine the type of antibody
- May need to migrate to nearby lymph nodes

❑ Mucus barriers:
- Size exclusion function of mucins
- Renewal frequency and flow rate
- Thickness of mucus that affects drug penetration

Special barriers

❑ Oral mucosa:
- Antigens are diluted by abundant saliva
- Immune tolerance

❑ Gastrointestinal tract mucosa:
- Gastric: pH 1.5-3.5; high concentrations of enzymes;
- Intestine mucosa: restricted penetration; GI fluid; oral tolerance

❑ Respiratory tract mucosa:
- mucociliary clearance; proteolytic enzyme

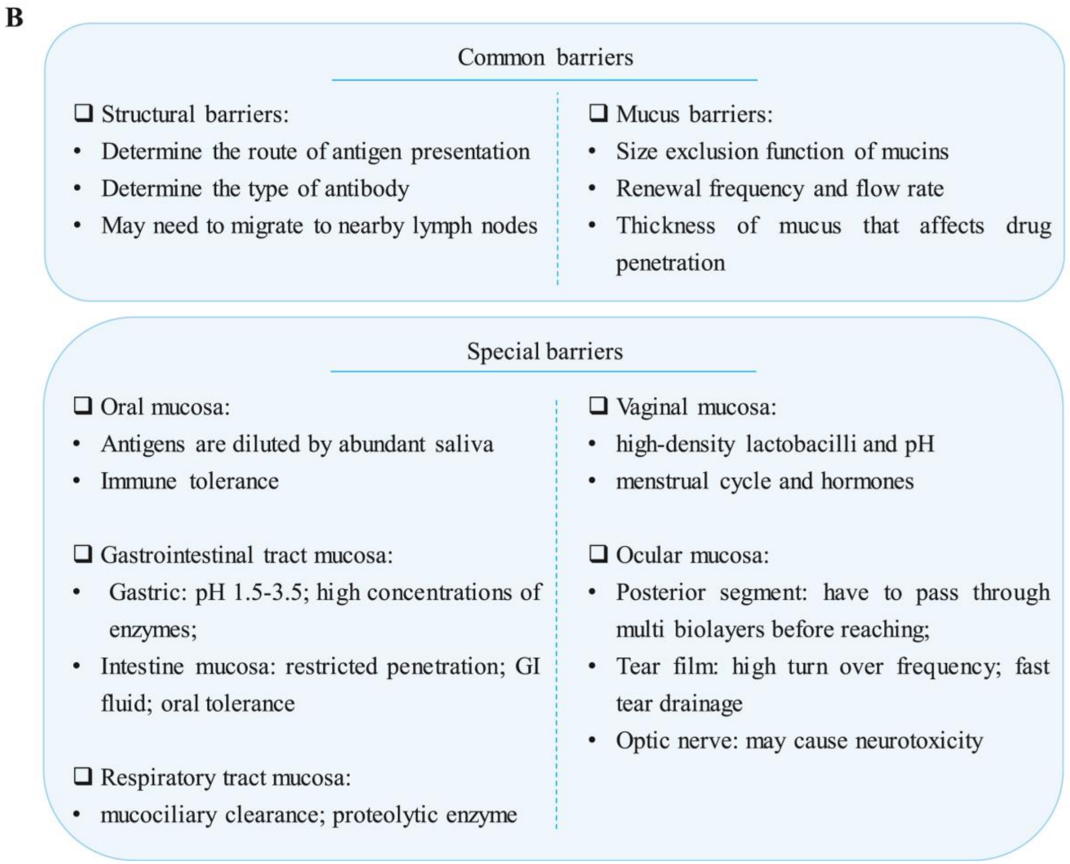
❑ Vaginal mucosa:
- high-density lactobacilli and pH
- menstrual cycle and hormones

❑ Ocular mucosa:
- Posterior segment: have to pass through multi biolayers before reaching;
- Tear film: high turn over frequency; fast tear drainage
- Optic nerve: may cause neurotoxicity

https://www.sciencedirect.com/science/article/pii/S2211383522003136#fig2

Antigen delivery

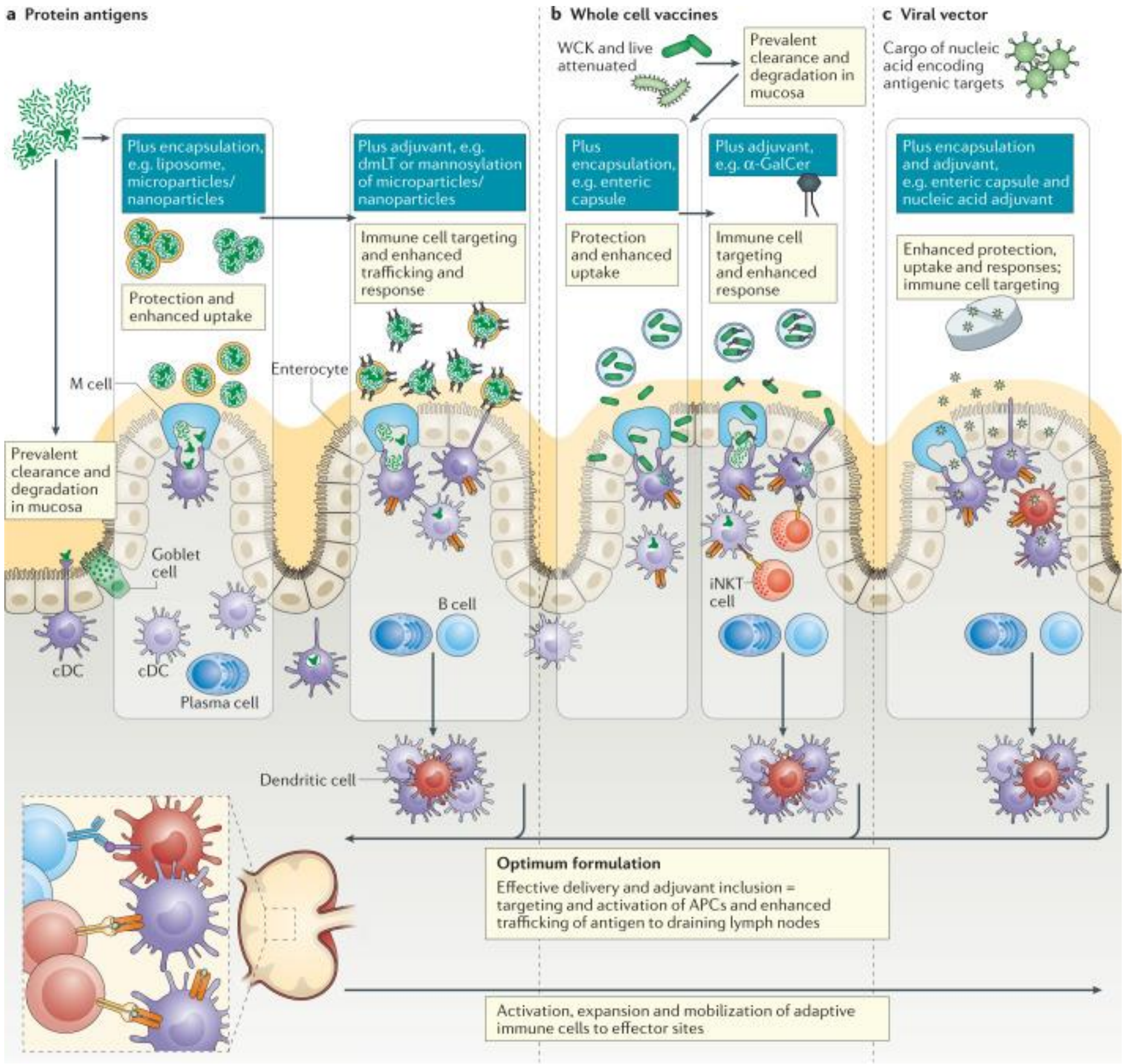
Challenge: pH, mucus, proteases at the mucosal surfaces (e.g. intestinal surfaces, pH differs based on intestinal region)



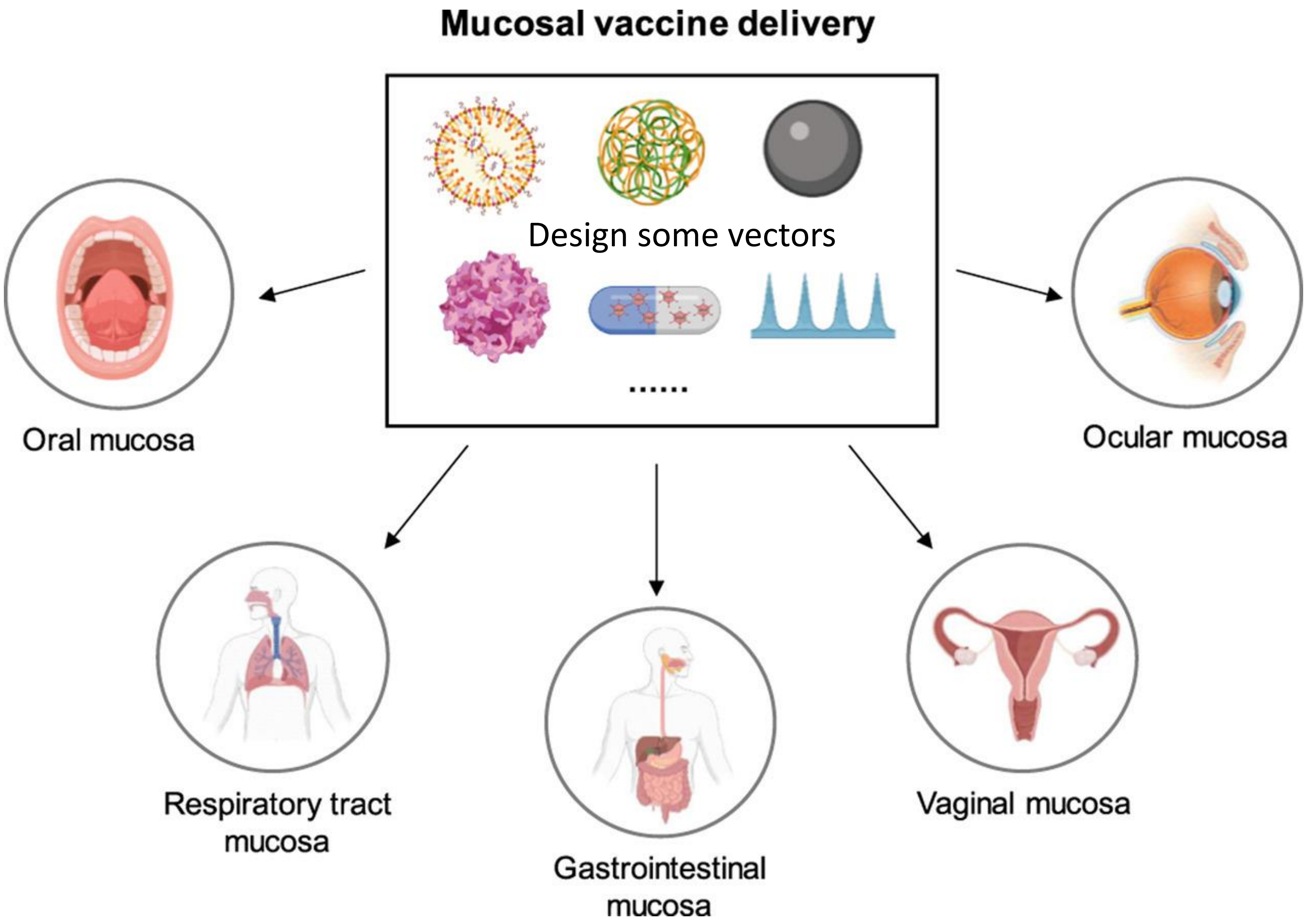
https://www.sciencedirect.com/science/article/pii/S2211383522003136#fig2

- Avoid damaging antigen
- Make sure the antigen will be delivered
- Make sure the antigen will target APCs and that there will be an activation of immune responses in lymph nodes

Challenges linked to mucosal administration



Ward and Lavelle, 2021, Nat Rev Immunol



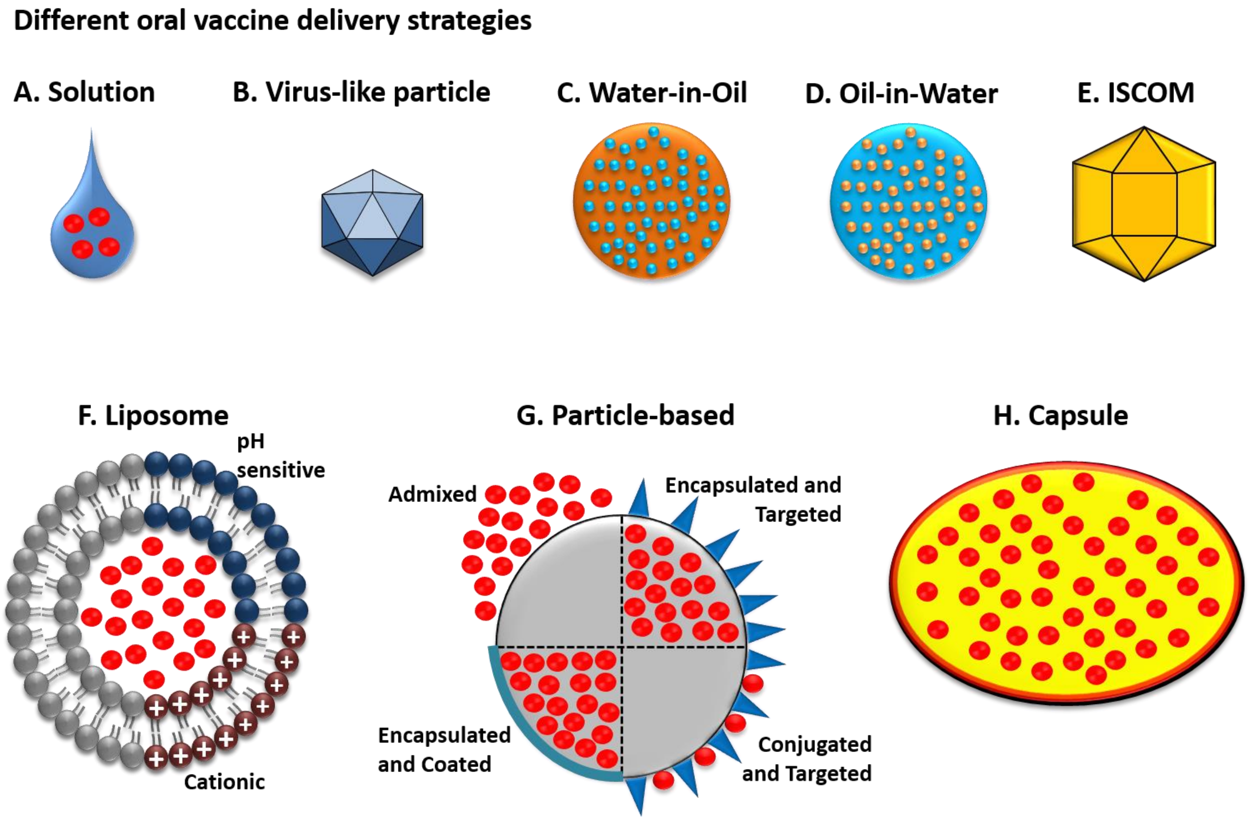
https://www.sciencedirect.com/science/article/pii/S2211383522003136#undfig1

Oral vaccination – main challenges

1. Destruction of the vaccine by stomach acids and enzymes

2. Poor oral immunogenicity of subunit antigens and but there are some whole cell killed antigens. Absence of licenced oral adjuvants

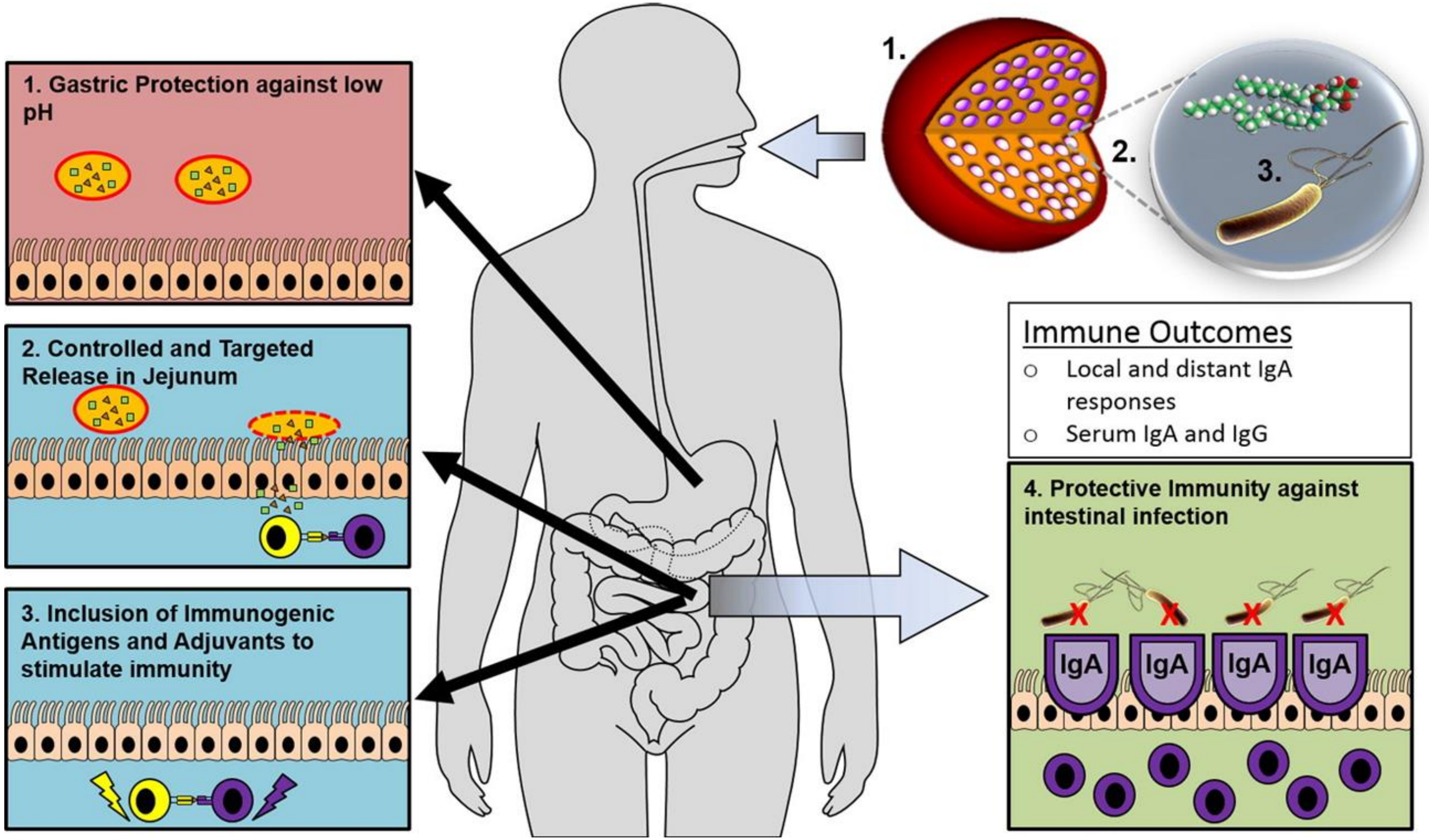
3. Lack of a comprehensive understanding of how orally active adjuvants activate gut immune responses



Davitt and Lavelle, 2015
https://doi.org/10.1016/j.addr.2015.03.007

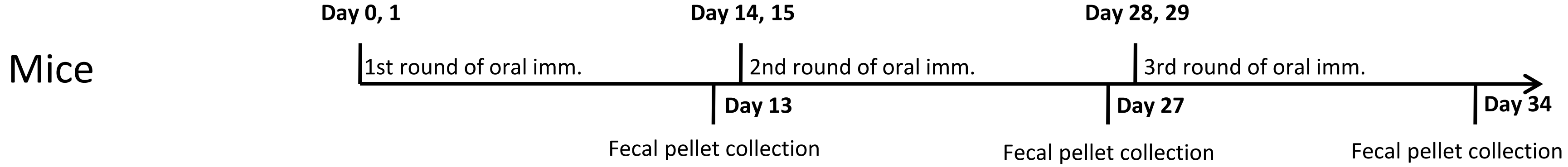
SmPill to deliver oral vaccines

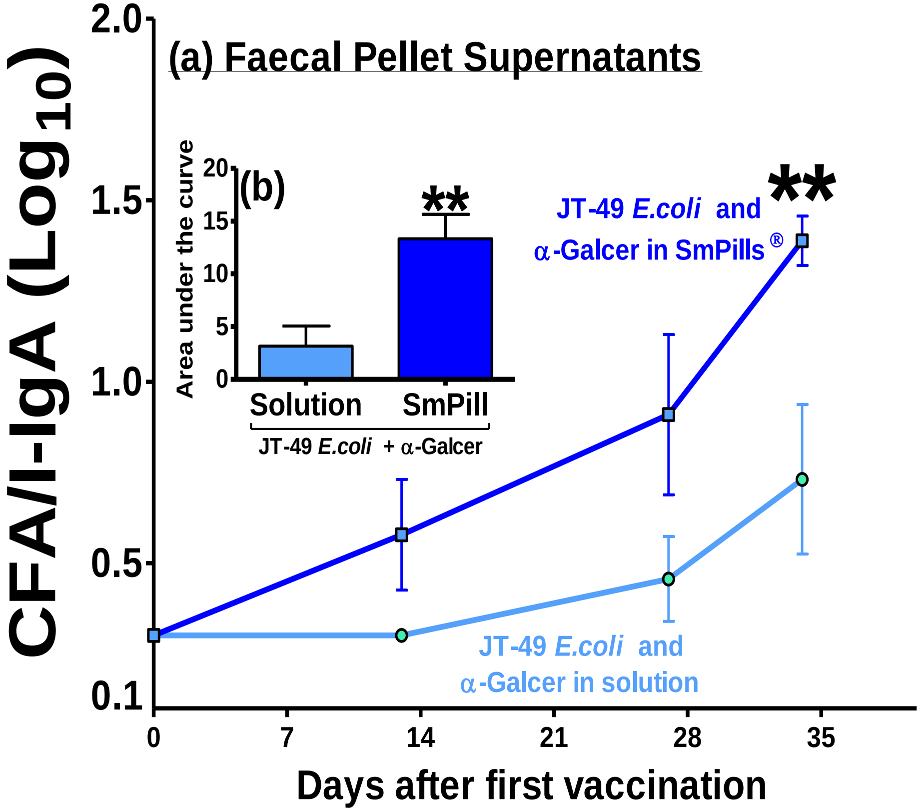
SmPill® mini-spheres
following coating



Enhancement of oral vaccine-mediated mucosal antibody responses following encapsulation of formulations in SmPill®

3 x 10^8 JT-49 *E.coli* + 10µg α-GalCer in solution or in SmPill

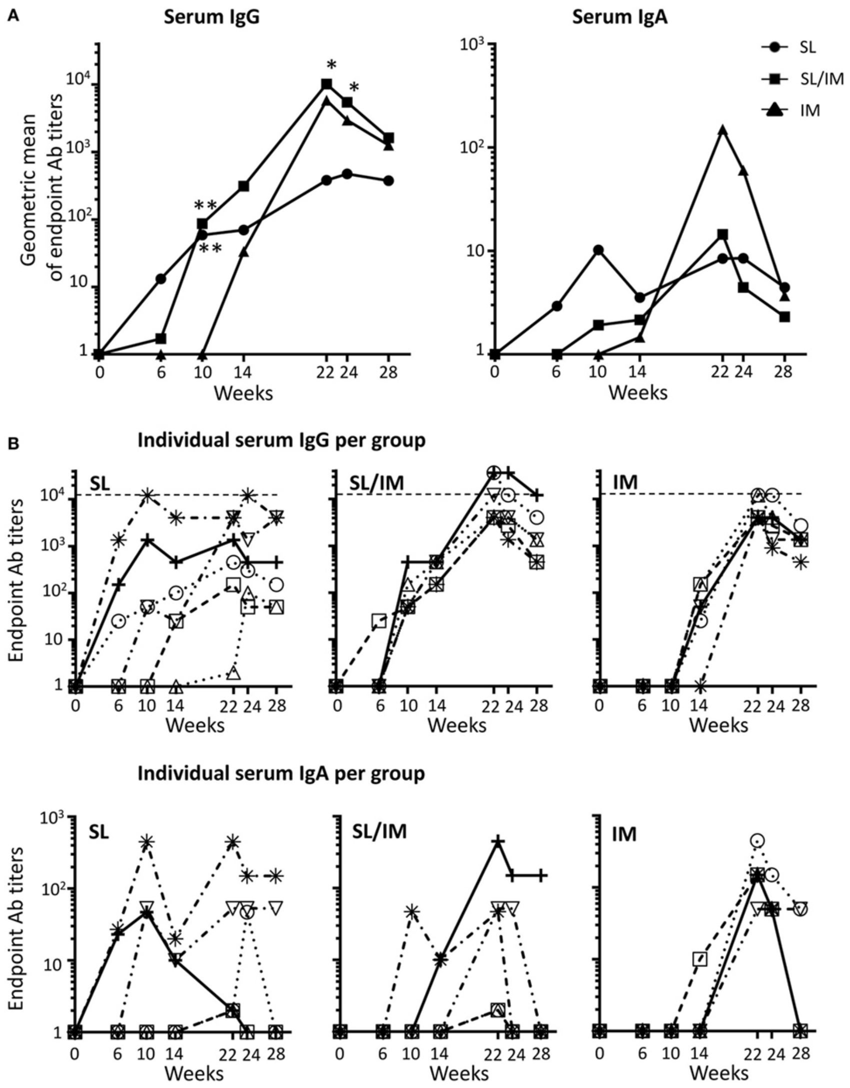




Davitt, Neela and Longet et al 2016
10.1016/j.jconrel.2016.05.001

Sublingual vaccination

Example: modified gp41 polypeptide coupled to the cholera toxin B subunit administered in liquid formulation



Heterogenous antibody responses

NHP were sedated with ketamine chlorhydrate for 1 h.

Group 1 received five SL immunizations with CTB-mgp41 (100 µg/dose of mgp41 antigen at W0, 4, and 12 and 50 µg/dose at W8 and 20) with CT (10 µg/dose). **=> Sublingual**

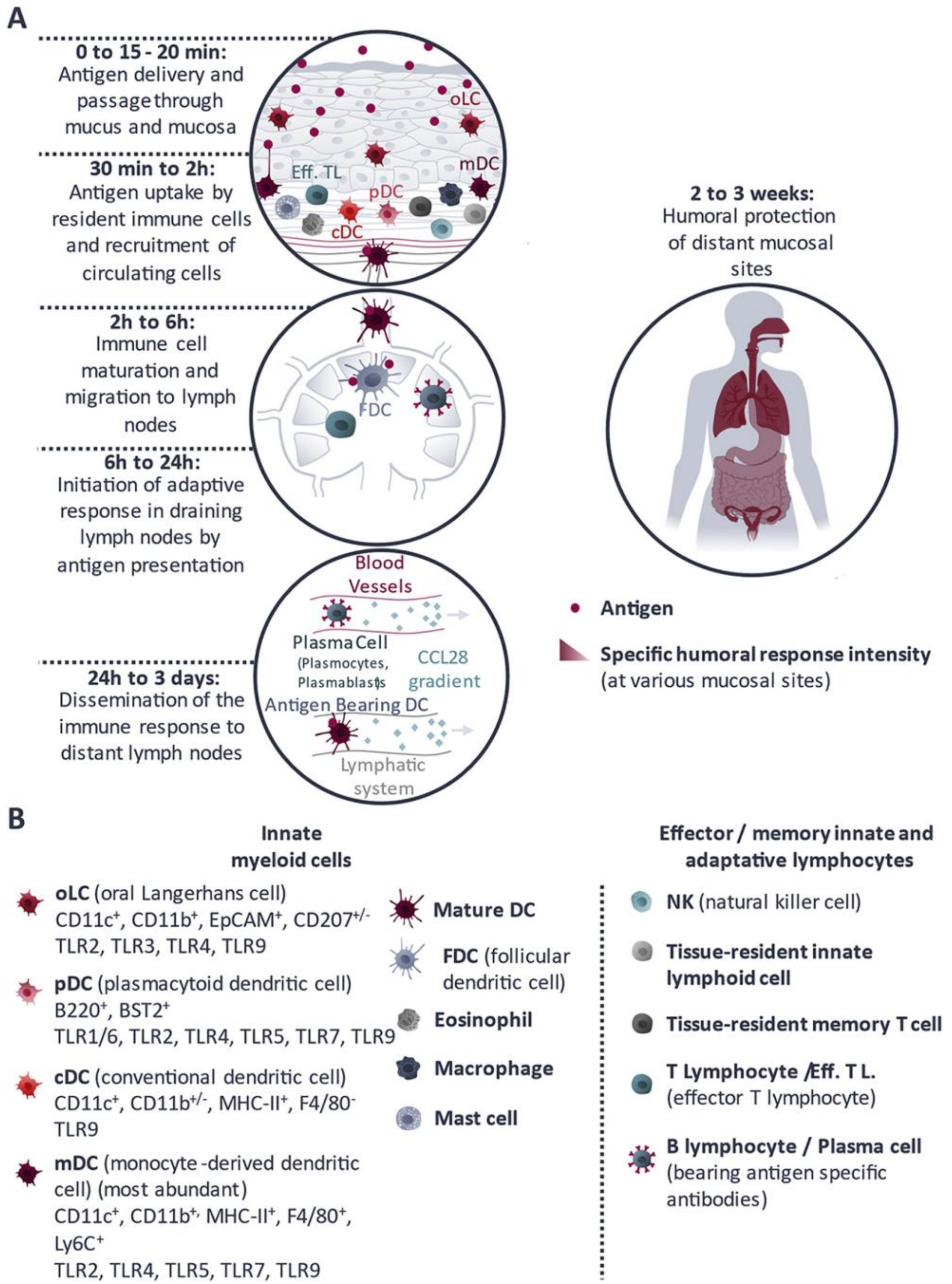
Group 2 received three SL immunizations with CTB-mgp41 and CT (SL priming) at W0, 4, and 8 similarly to group 1 followed by IM boosts with 100 µg of mgp41 in Alum (500 µg/dose) at W12 and 20. **=> Sublingual /intramuscular**

Group 3 received a SL priming with CT alone (10 µg) at W0, 4, and 8 followed by IM boosts with 100 µg of mgp41 in Alum (500 µg/dose) at W12, 20, and 28. **=> intramuscular**

The SL vaccine was administered in a 500 µL volume of PBS under the tongue of sedated animals with their head bending forward to avoid leakage of excess of vaccine and was then rinsed with PBS 15 min later in order to avoid swallowing.

Bekri et al 2017, Frontiers in Immunology

Sublingual vaccination



Antigens: Recombinant or subunit proteins	Antigens: Pathogen mimicking antigens	Formulations: No formulation	Formulations: Colloidal formulation	Formulations: Antigen linked to adjuvant	Studied disease	Refs
No delivery device						
Liquid + Easy formulation and administration - High risk of dilution in saliva						
	x	x			Influenza	[21 , 91]
	x	x			UTIs*	[92]
	x	x			TB†	[93]
	x	x			RSV‡	[50]
	x	x			HIV§	[53]
	x	x			JEV‖	[51]
	x	x			HPV¶	[23]
x		x	x	x	Influenza	[94]
x		x			PIs#	[58]
x				x	-	[19]
x				x	HIV§	[20]
x				x	ETEC**	[56]
x				x	Influenza	[57]
x			x		-	[95]
x			x	x	-	[96]
	x		x		Influenza	[97]
Transmucosal delivery device						
Needle-free injector + Enhanced antigen delivery through mucosa - Evaluation of local inflammation after delivery needed						
x		x			-	[63]
	x	x			HIV§	[31]
Microneedle array + Enhanced antigen delivery through mucosa + Versatile platform for various antigen formulations - Does not avoid partial dilution in saliva - Evaluation of local inflammation and tissue damage						
	x	x			Influenza	[65]
x			x		-	[66]
	x		x		HIV§	[67]
Mucoadhesive delivery device						
Solid or semi-solid form + Avoids dilution in saliva + Adapted fabrication process to preserve antigen and adjuvant + Enhanced thermostability + Lengthen contact time between antigens and mucosa - Has to be produced with biodegradable components						
x		x			-	[59]
	x	x			Influenza	[70 , 72]
	x	x			Poliomyelitis	[47]
	x		x		GAS††	[55]
x			x		-	[71]
	x		x	x	HIV§	[73]

Dilution rate in saliva !

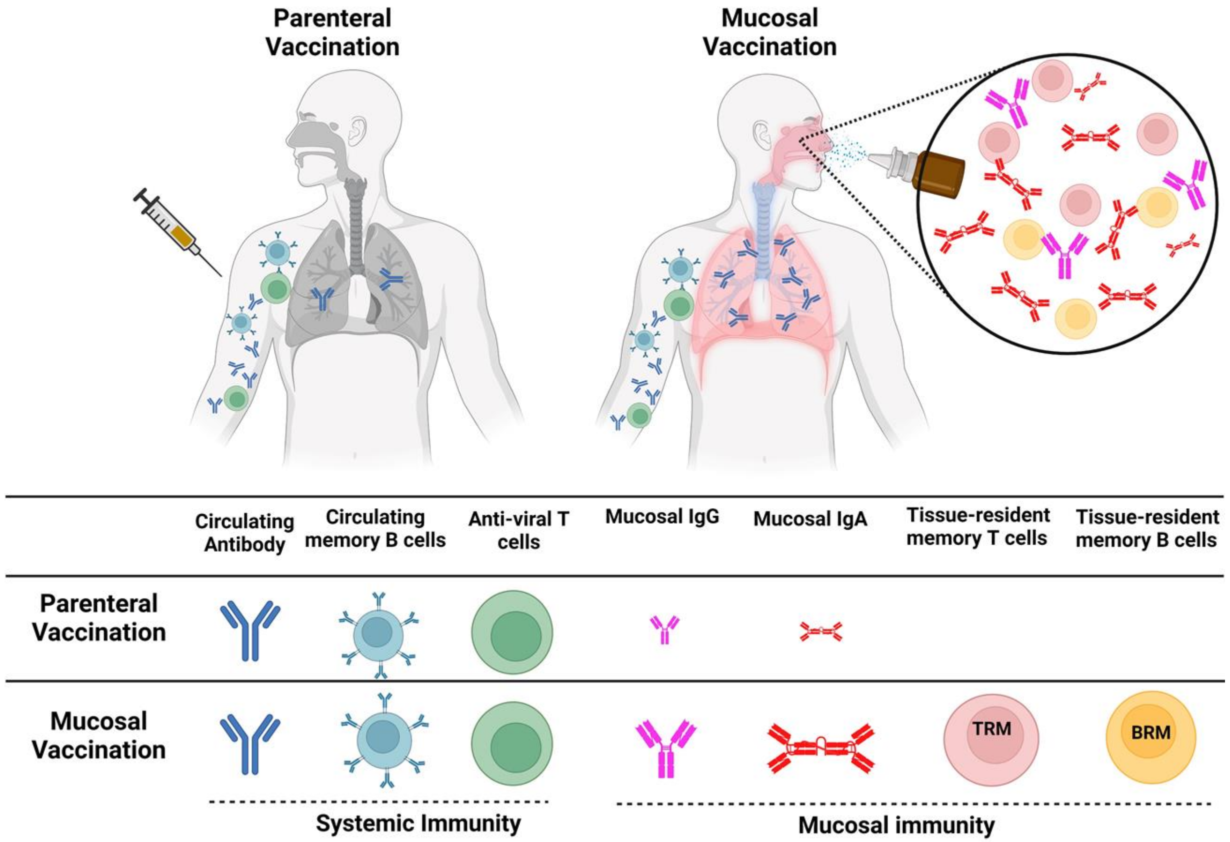
Paris et al 2021, Journal of controlled released

Intranasal vaccination – main challenges

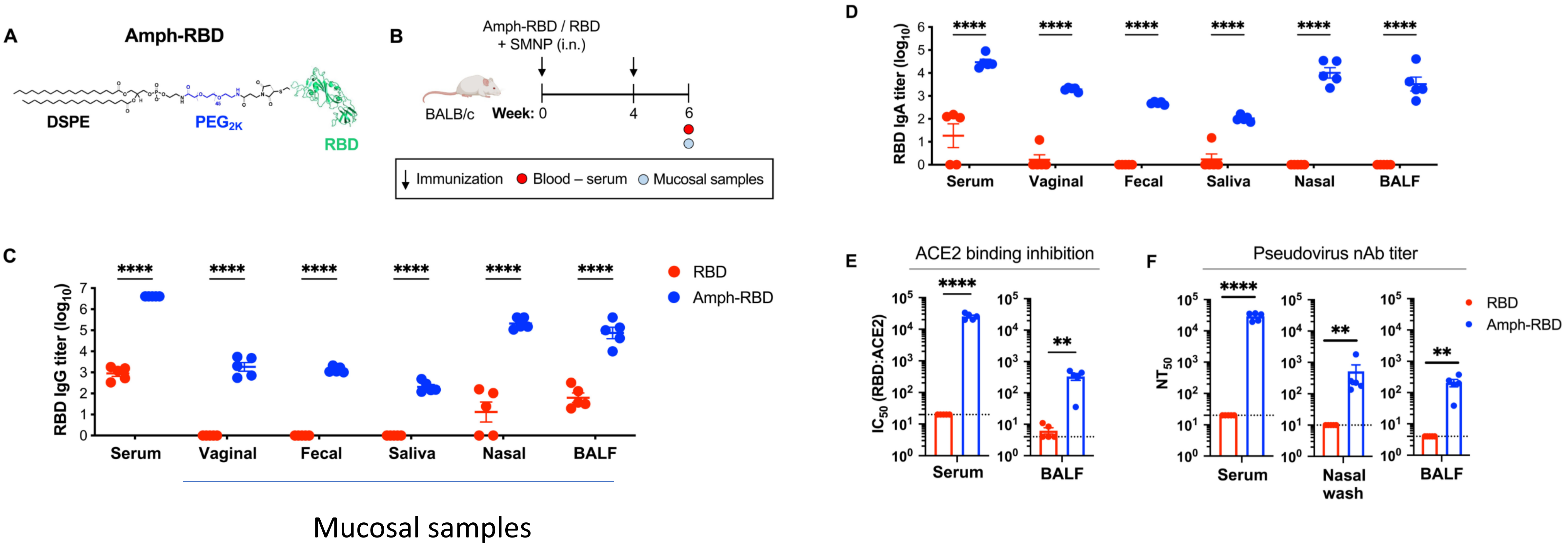
1. Destruction of the vaccine by enzymes in nasal area

2. Poor oral immunogenicity of subunit antigens. Absence of licenced nasal adjuvants

3. Lack of a comprehensive understanding of how intranasal vaccine formulation activate airway immune responses



Example: administration of SARS-CoV-2 RBD by intranasal route using an amphilic albumin which can bind to neonatal Fc receptor expressed by mucosal epithelial cells



Role of FnRn: IgG transport, IgG recycling, albumin recycling

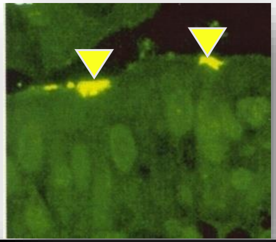
Hartwell et al 2022, Science Advances

SIgA could be used as vector

IgA Reverse Transcytosis

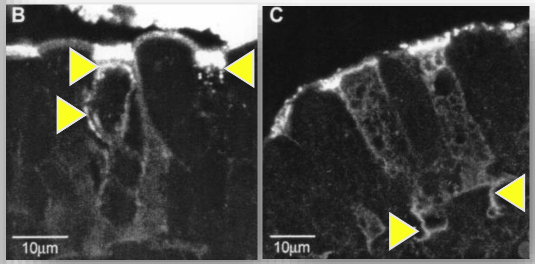
1 -SIgA binding to the surface of M cells

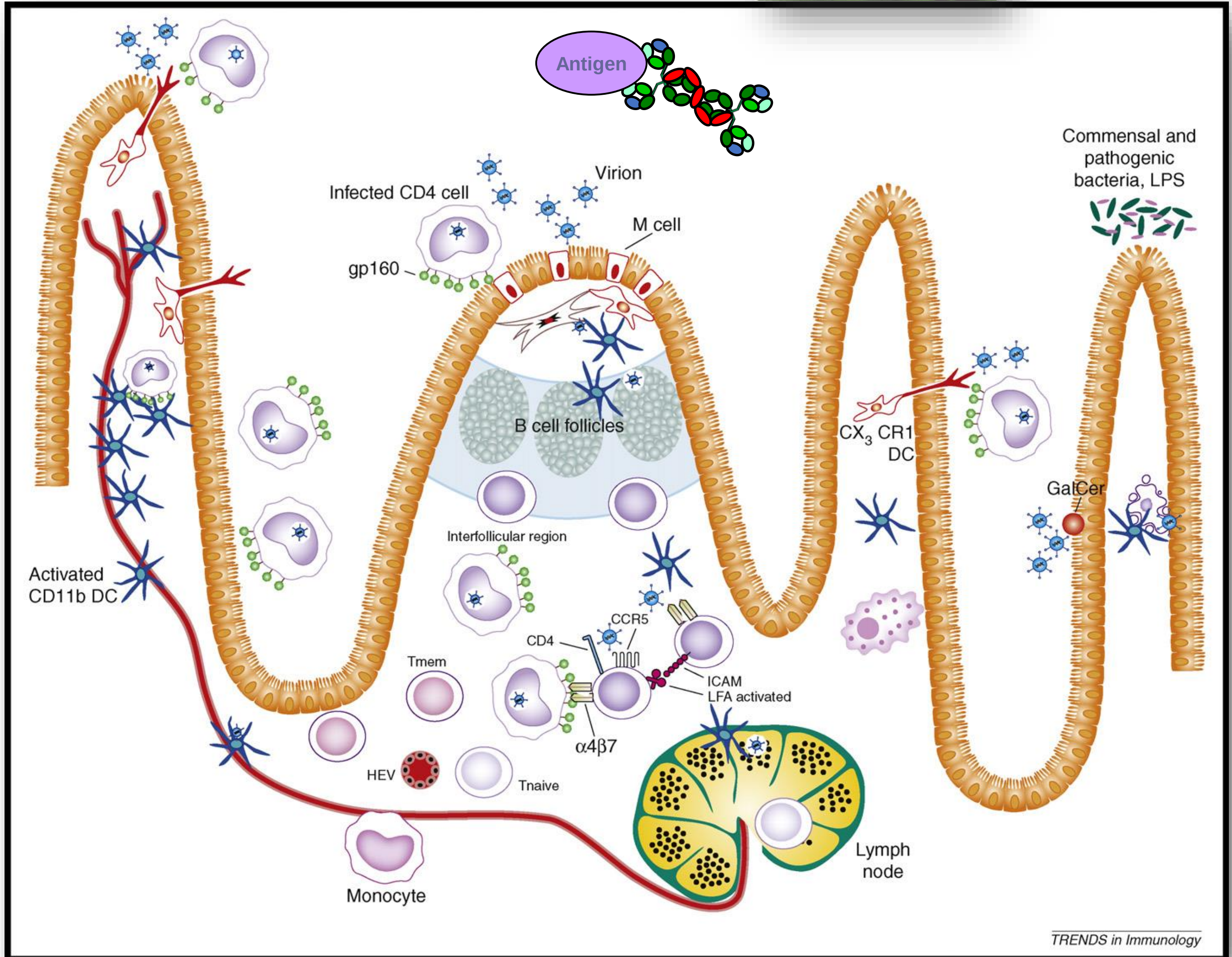
Colocalisation experience IgA - M cell in mice (Corthésy, 2007)



1 - SIgA entrance at the inner membrane of enterocytes

Coeliac: - Abnormal immune response to peptides derived from gluten (gliadin)
- Retro-transport of IgA1-gliadin complex

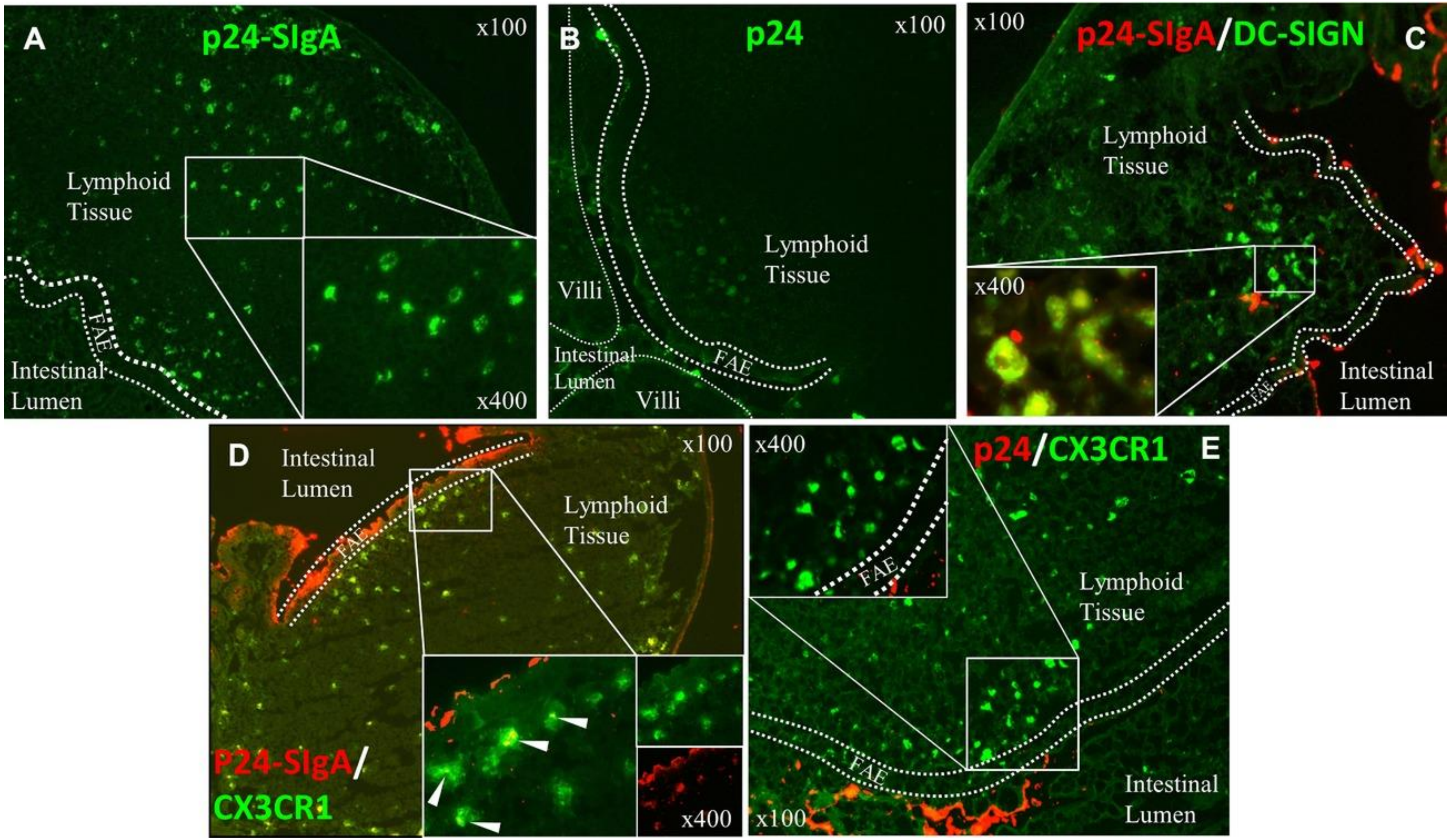




2

SIgA are associated with the PP immune cells, preferentially with CD11c^{+} DCs and CD4^{+} T cells. (Corthésy, 2007)

Specific uptake and transport of p24-SIgA across murine follicle-associated epithelium in intestine



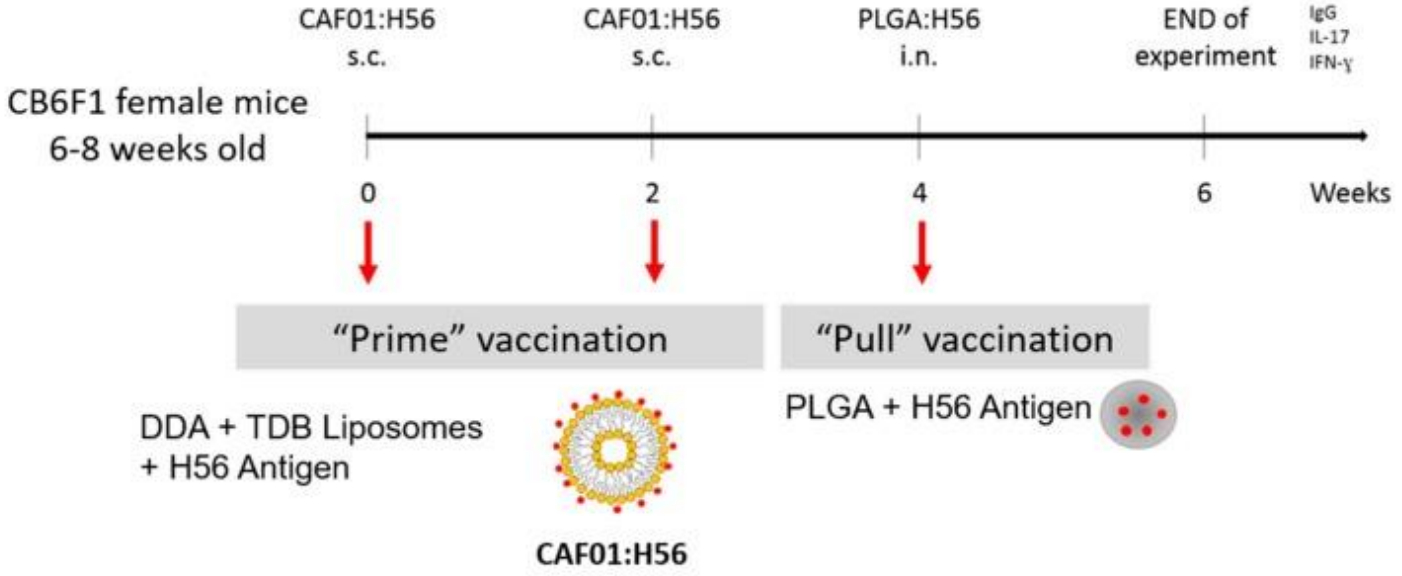
Mouse intestine

Rochereau et al 2015

Prime-pull vaccination strategy – 2x SC and 1x IN

TB vaccine candidate: H56 = antigen; CAF01 = liposome; PLGA =poly(lactic-co-glycolic acid)

Mouse model

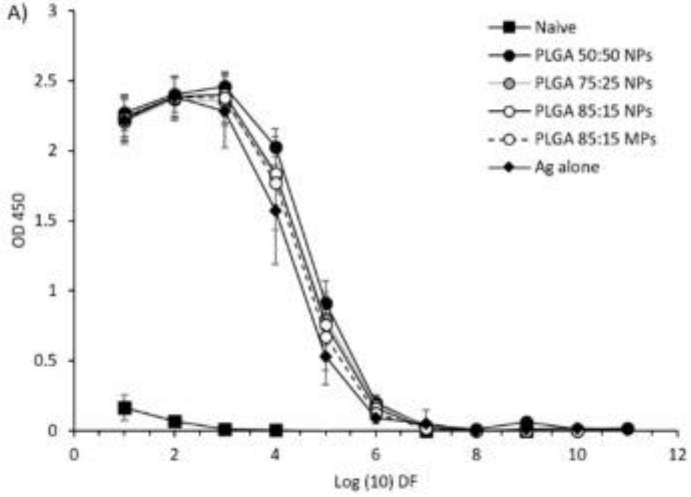


Groups	1st vaccination (s.c.)	2nd vaccination (s.c.)	3rd vaccination (i.n.)
G1: naïve or unvaccinated	N/A	N/A	N/A
G2: PLGA 50:50 NPs	CAF01:H56.	CAF01:H56	H56:PLGA 50:50 NPs
G3: PLGA 75:25 NPs	CAF01:H56	CAF01:H56	H56:PLGA 75:25 NPs
G4: PLGA 85:15 NPs	CAF01:H56	CAF01:H56	H56:PLGA 85:15 NPs
G5: PLGA 85:15 MPs	CAF01:H56	CAF01:H56	H56:PLGA 50:50 MPs
G6: Antigen alone	CAF01:H56	CAF01:H56	H56 alone

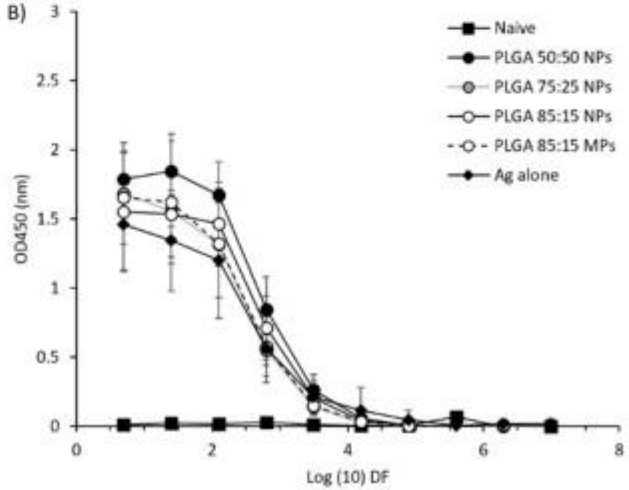
Roces et al 2019, Vaccines

IgG responses - ELISA

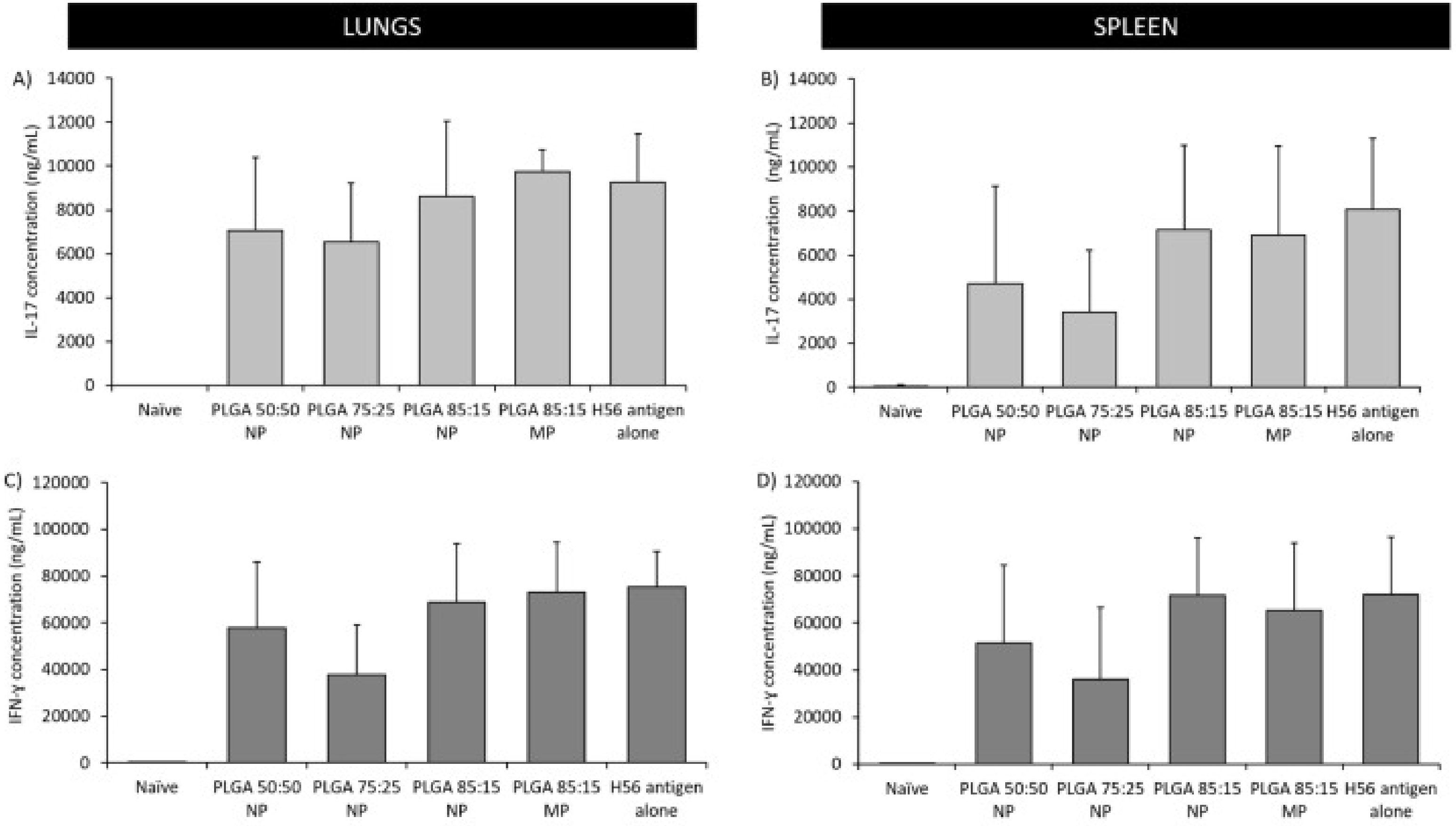
Serum



Supernatants from lung lymphocytes



Restimulation of lung cells and splenocytes with H56 for 72h hours - ELISA

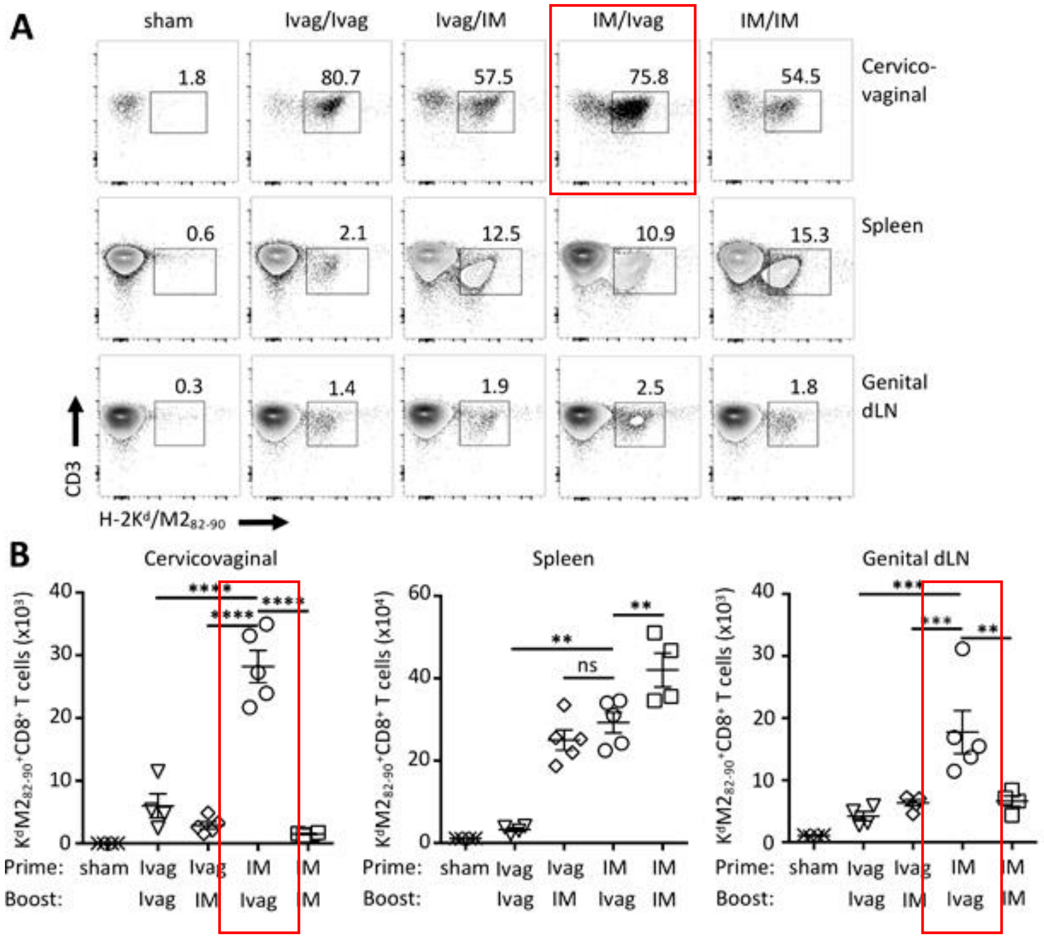


Roces et al 2019, Vaccines

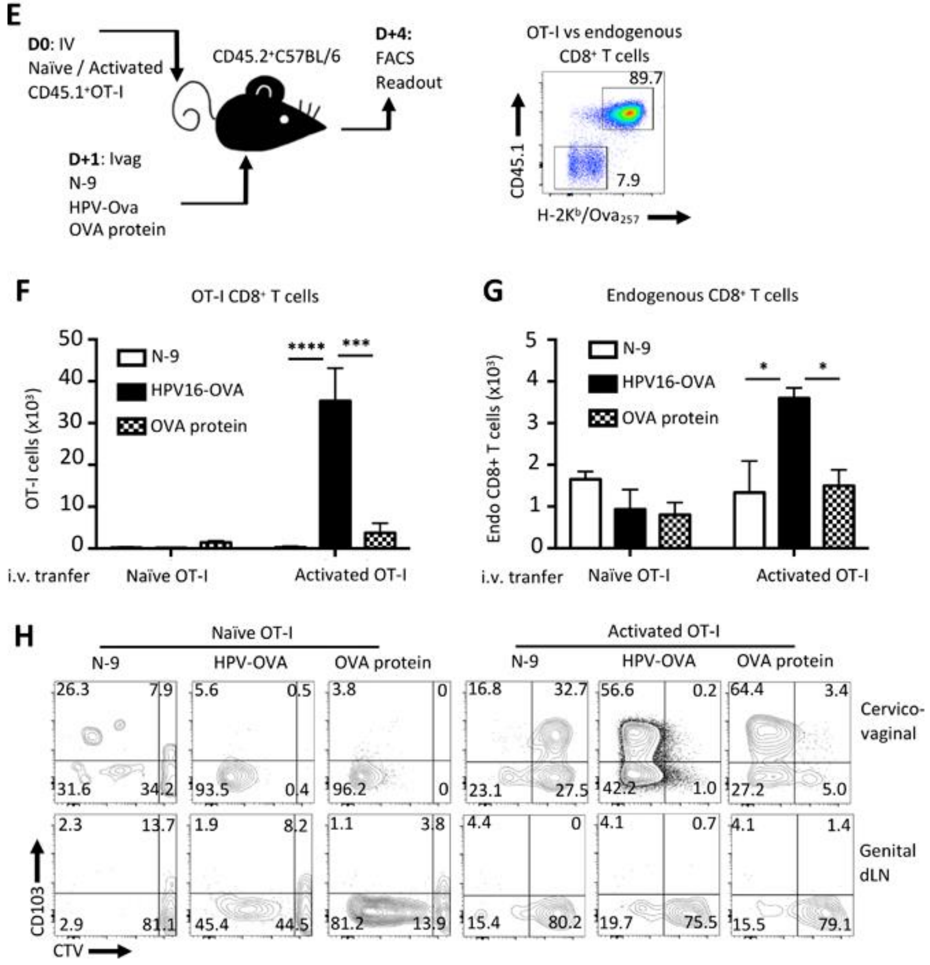
Prime-pull vaccination strategy – combinations IM and IVag

Context – HPV vaccines (IM: Ad5-based vectors and IVag: HPV Pseudovirus)

Mouse model



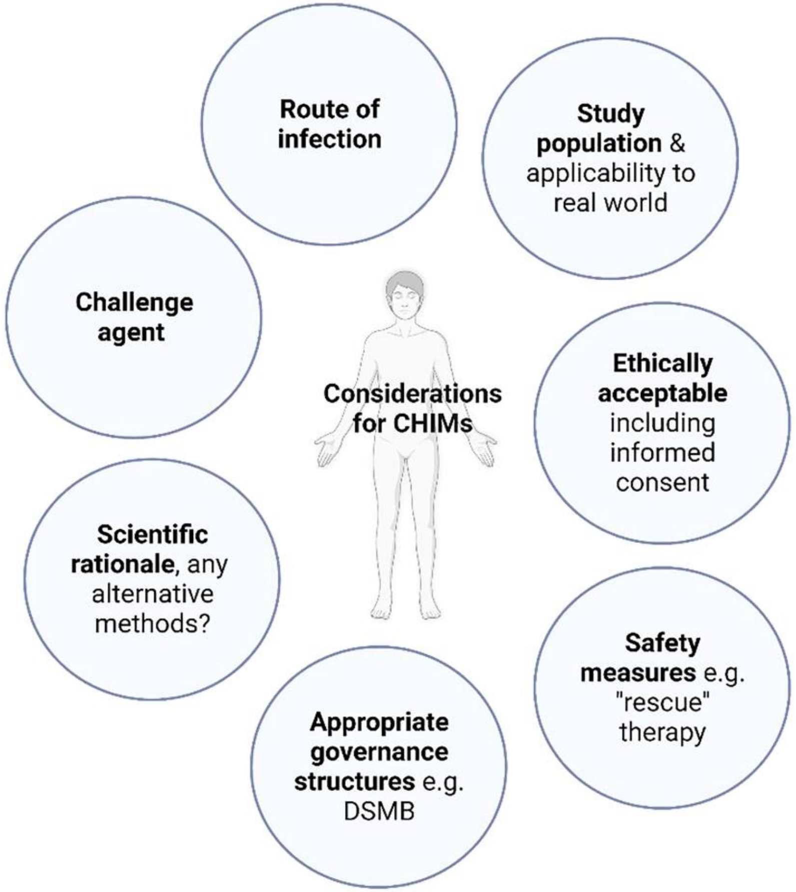
Local antigen presentation promotes in situ proliferation and upregulation of CD103 (resident marker on genital T cells)

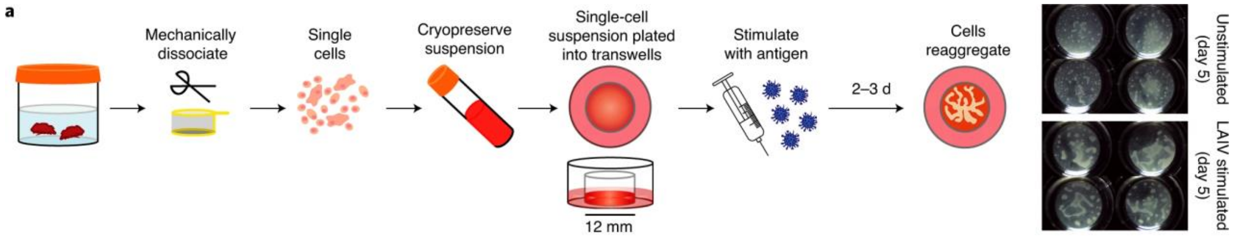


+ recruitment of activated CD8$^+$ T cells

Cuburu et al 2019, J Immunol

Human models to evaluate mucosal vaccines





Wagar et al 2024, Nat Med

https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1211388/full

Advantages & disadvantages of vaccine routes

Administration Route	Traditional			Novel	
	Oral	**Intramuscular**	**Subcutaneous**	**Microneedle**	**Inhalation**
Advantages	Painless, self-administration, induction of mucosal immunity, herd immunity	Mildly contact with immune cells to induce immune responses	Long induction period by slow and sustained adsorption	Comfortable, minimal invasive delivery, self-administration, superior and rapid immunogenicity, longer induction period by slow and sustained adsorption, less reliance on cold-chain storage, dosage sparing effect [2,3,4,5]	Induction of triple immunity, including humoral, cellular, and mucosal immunity, intercepts pathogens at the first line when they invade, dosage sparing effect, self-administration [6,7,8,9]
Disadvantages, risk or limitations	First pass effect, environmental pollution caused by feces	Pain, inflammation, anxiety, infection, contamination, professionals, and cold-chain requirement	Pain, anxiety, inflammation, infection, contamination, lower immune responses, professionals and cold-chain requirement	Skin allergy, breakage of microneedle tip, foreign substances remaining in the body, thermostability must be monitored, sterilization is challenging [2,3,4,5]	Only suitable for respiratory or gastrointestinal infectious diseases, local protection, induction of immunotolerance, inhalation rate is unstable, induced immunity is difficult to evaluate [6,7,8,9]
Approved vaccine product example	Rotavirus vaccine: live attenuated vaccines Rotarix® and RotaTeq® [10], Poliovirus vaccine: Sabin, live attenuated oral polio vaccine (OPV) [11]	MMR (Measles, mumps, rubella), a live attenuated vaccine [12] or subcutaneaous Hexyon® (Diphtheria, pertussis, tetanus, hepatitis B, poliomyelitis, and *Hemophilus influenzae* type b (Hib)), an inactivated vaccine [13] Poliovirus vaccine: Salk, an inactivated poliovirus vaccine (IPV) [14]	Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated vaccine [15,16] Intradermal Yellow fever vaccine	Influenza vaccine: Intanza® and Fluzone® [5]	Coronavirus Disease 2019 (COVID-19) vaccine: Convidecia Air®, an oral recombinant vaccine with adenovirus type 5 vector [17] iNCOVACC, an intranasal live attenuated vacc [17,18] Flumist/Fluenz

Rai et al 2024, Vaccines