

Thérapeutiques innovantes en maladies infectieuses

Vaccinologie de précision, ou comment les vaccins doivent
s'adapter aux populations et non l'inverse

Pr Stéphane PAUL (Saint-Etienne)

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : PAUL Stéphane

Titre : Vaccinologie de précision.....

- OUI NON
Consultant ou membre d'un conseil scientifique (CTV, Vaccin COVID)
- OUI NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents (Pfizer, Theradiag, MSD)
- OUI NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations (Theradiag, Takeda, MSD)
- OUI NON
Investigateur principal d'une recherche ou d'une étude clinique

Les vaccins et leurs enjeux en 2023

En 2023, les infections représentent

*30% des causes de décès

*2ème cause de décès dans le monde (après les maladies CV)

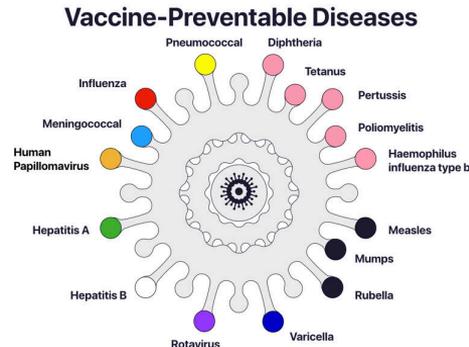
*Émergence de souches multi-résistantes aux ATB... de nouveaux virus ..

Nombreuses situations cliniques ne disposent pas de vaccins ou de vaccins insuffisamment efficaces :

- infections aux âges extrêmes de la vie (grossesse, bébés, personnes âgées)
- personnes immunodéprimés (cancers, MAI etc..)
- infections émergentes (Zika, Ebola, Sars-CoV2...)
- infections liées aux soins (*St aureus*, *C difficile*, Sars-CoV2..)

Problématique de la « vaccine hesitancy » ou hésitation vaccinale

Définition OMS (Strategic Advisory Group of Experts (SAGE): « delay in acceptance or refusal of vaccines despite availability of vaccinations services ». (Salmon DA et al. Vaccine 2015)



Maladies infectieuses ne disposant pas de vaccin efficace ou suffisamment efficace en 2023

Chlamydia

CMV

Charbon

Chikungunya

Clostridium difficile

Dengue (Takeda?)

EBV

Ebola

Helicobacter pylori

Hépatite C

Herpès

HIV

Metapneumovirus

Lyme

Malaria

MERS/SARS & co

Shigella

SRAS

Staph aureus

Strepto B

Tuberculose

VRS (GSK, Sanofi)

West Nile Virus

Virus Zika

ZVL

Coqueluche

grippe, typhoide.....

Table 1. Epidemics of the Past

Date	Epidemic
430 BC	Plague of Athens
160 AD	Plague of Antonine
542 AD	Plague of Justinian
1340 AD	The Medieval Plague
1500 AD	Plague of the Incas
1665 AD	Great Plague of London
1793 AD	Yellow fever
1832 AD	Cholera
1918 AD	Influenza
20th–21st century	Ebola, HIV, swine flu, chikungunya, Zika, COVID-19

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.

Risque pandémique+++

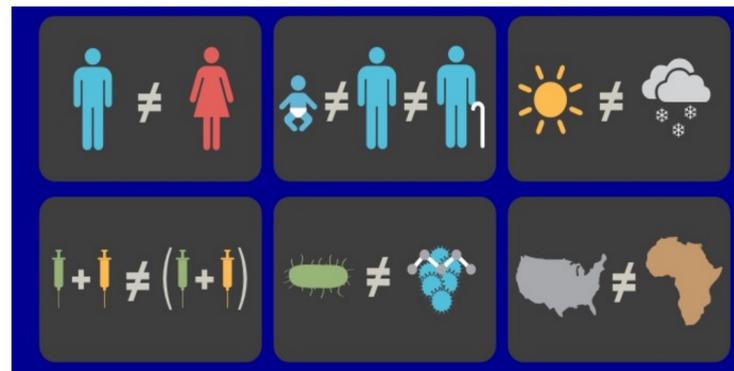
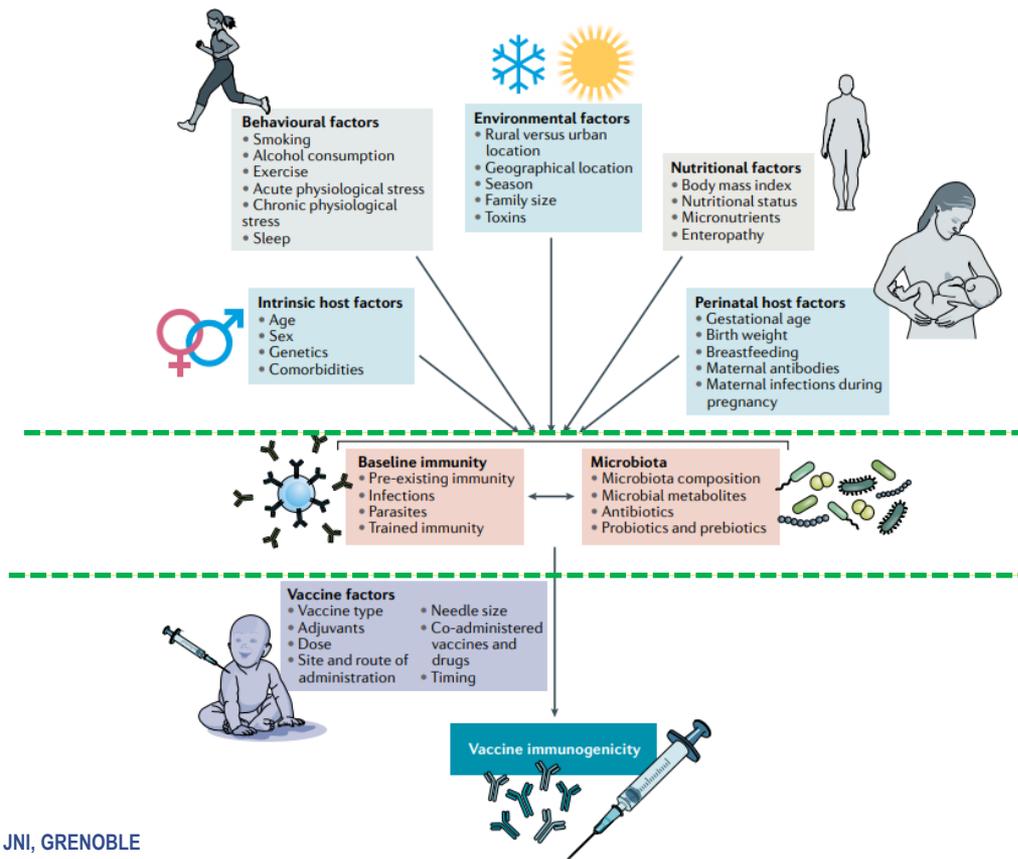
- Cancer
- Maladies neurodégénératives
- Allergies
- MAI
- Caries (Porphyromonas)
- Tabagisme/Drogues
- Vétérinaire

Et il n'y a pas que l'infectieux!!!

La Vaccination de précision?

- La médecine de précision consiste à adapter le traitement médical aux caractéristiques individuelles de chaque patient. Elle ne signifie pas littéralement la création de médicaments ...uniques pour un patient, mais plutôt la capacité de classer les individus en sous-populations qui diffèrent dans leur ...réponse à un traitement spécifique". Conseil national de la recherche
- Vaccins de précision
 - *Tiennent compte de la population cible
 - *Formulés pour activer sélectivement le système immunitaire en ciblant les sites anatomiques, les cellules et les voies moléculaires qui génèrent une réponse protectrice
 - *Si nécessaire, contiennent un adjuvant connu pour agir de manière optimale dans la population cible.

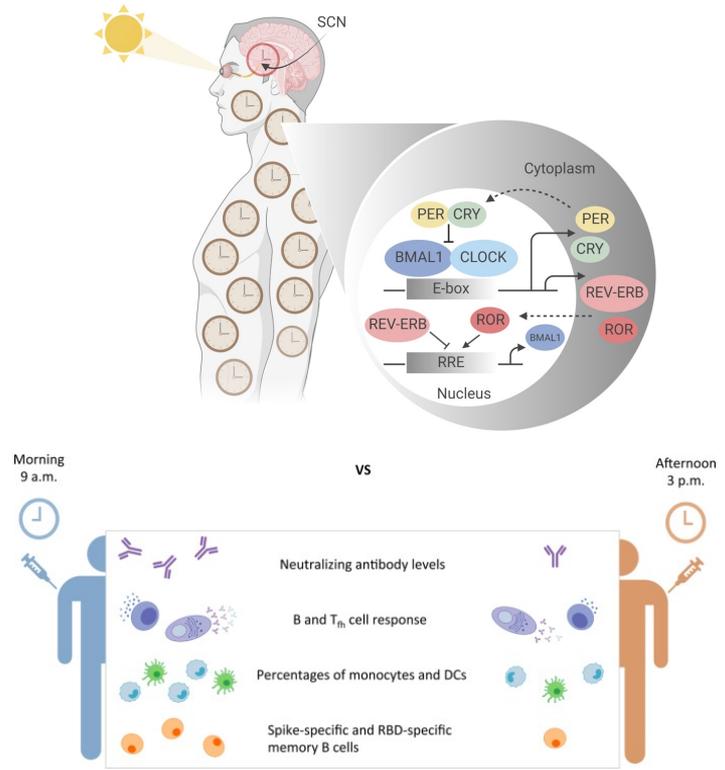
Facteurs influençant l'immunogénicité des vaccins



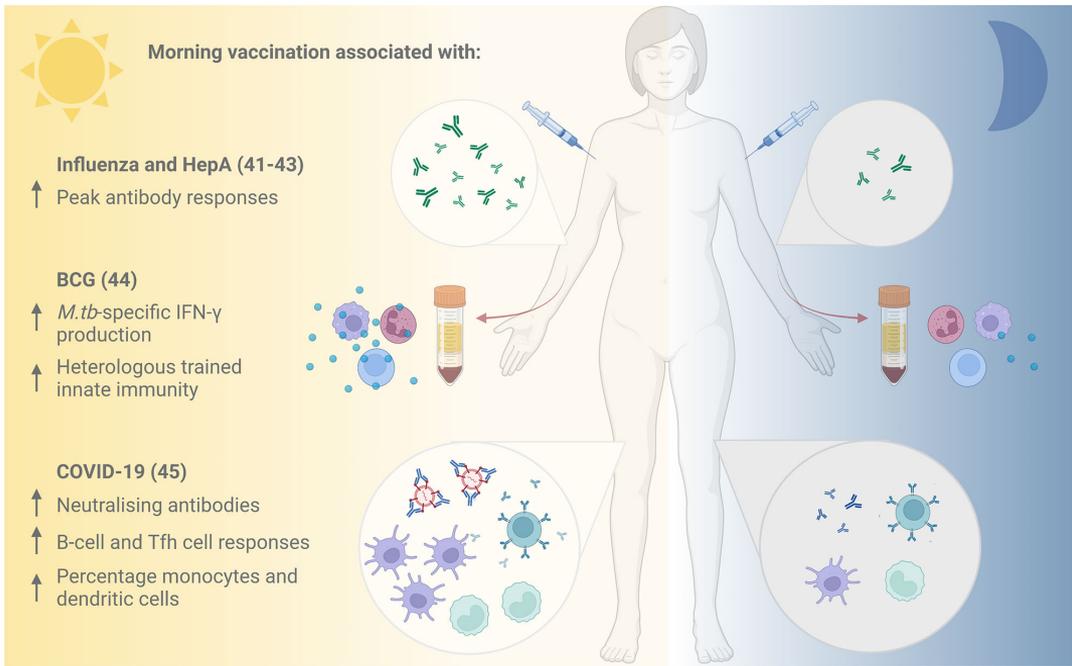
L'hétérogénéité vaccinale

La réponse vaccinale est multi-factorielle
Elle dépend bien sur de la qualité du vaccin mais pas uniquement

La Chronovaccination pour adapter les stratégies de vaccination au rythme circadien

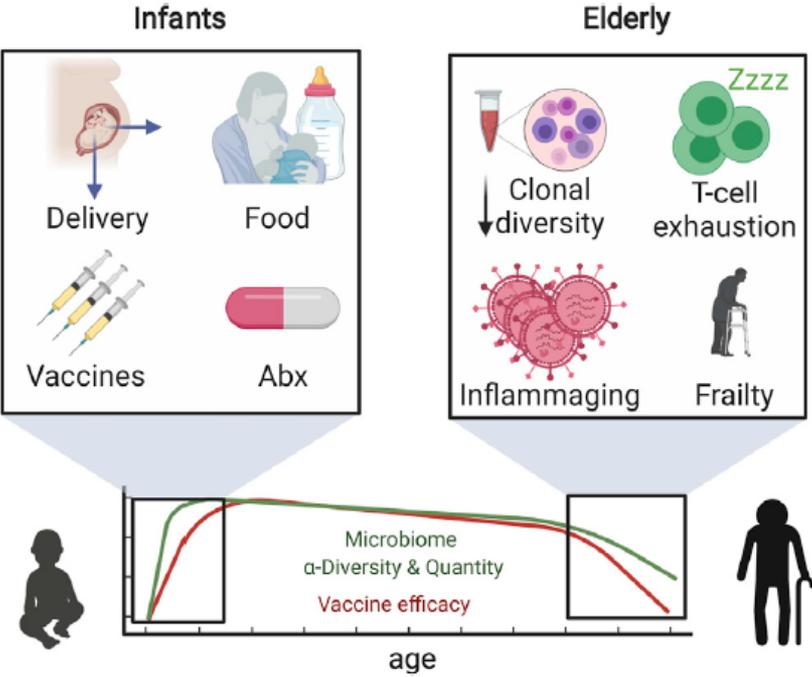
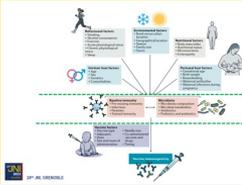


Barnoud et al., Cell Research 2021

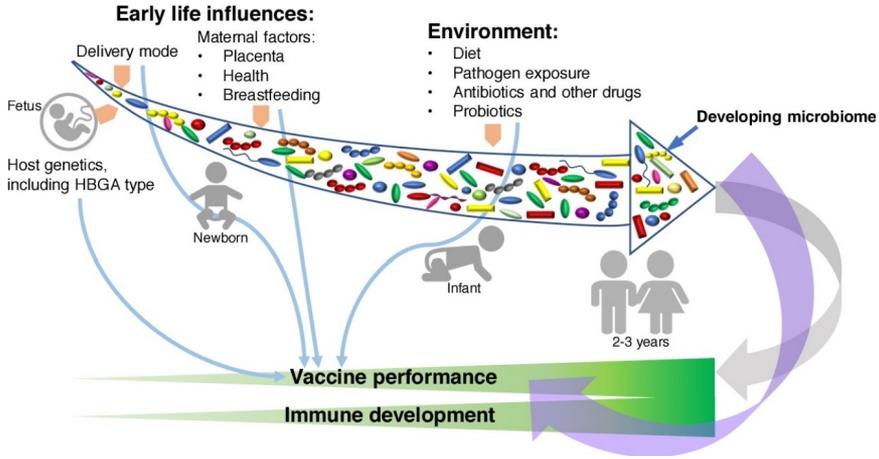


Otasowie et al., Frontier Immunol 2022

Impact du microbiote sur l'efficacité vaccinale?

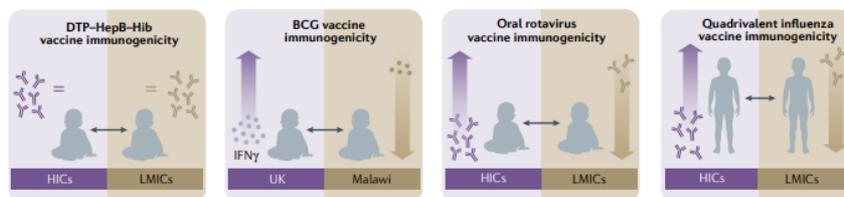
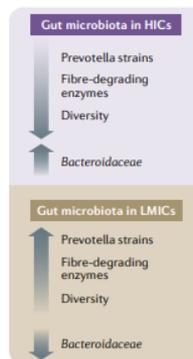
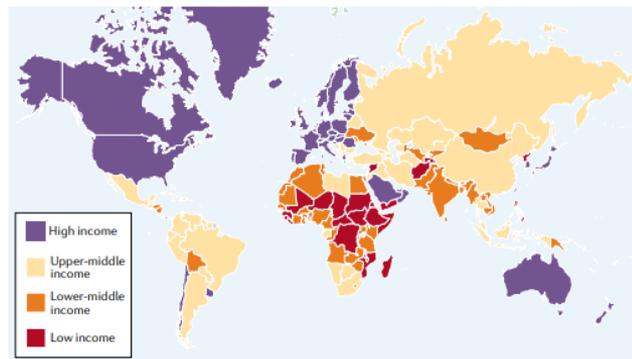
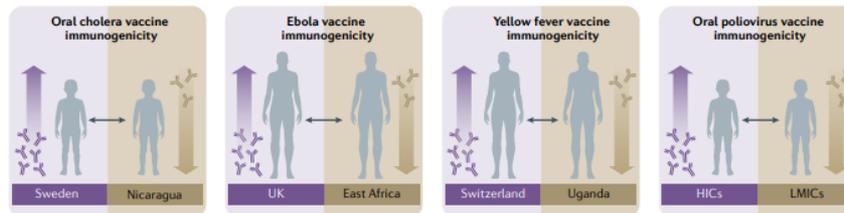
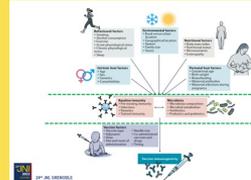


La faible diversité du microbiote des enfants et des personnes âgées corrèle avec un status immunologique altéré et une réponse vaccinale suboptimale



Unique Environmental Factors and Biological Changes in the Very Young and the Very Old that Can Be Detrimental to Vaccine Efficacy
Newborn children and elderly people undergo physiological changes and are exposed to environmental stimuli that can be detrimental to their immune system. Simultaneously, they often experience decreased microbial diversity. **These factors interplay to make them less responsive to vaccination.**

Evidence dans la littérature du rôle prédictif du microbiote dans les réponses vaccinales



Model	Vaccine	Host	Study Outcomes	Reference
Animal Studies	TIV, OPV	Mice	TLR5-mediated sensing of flagellin from gut microbiota had an adjuvant effect on TIV and OPV. No effect with adjuvanted vaccines or live-attenuated yellow fever vaccine.	(Ch et al., 2014)
	CT	Mice	The mucosal adjuvant activity of CT was mediated through the recognition of symbiotic bacteria by Nod2 in CD11c-expressing phagocytes.	(Kim et al., 2016a)
	BCG, MenB, MenC, PCV13, Hexa	Mice	Antibiotics-induced dysbiosis in infant (but not adult) mice leads to impaired antibody responses and elevated ex vivo cytokine recall responses.	(Lynn et al., 2018)
	TIV	Rhesus macaques	Subclinical CMV infection resulted in increase in butyrate-producing bacteria and lower antibody responses to influenza vaccination.	(Santos Rocha et al., 2018)
Correlative human studies	RV	Ghanaian and Dutch infants	Microbiome composition was different between RV responders and non-responders. Ghanaian responders were more similar to Dutch infants than to non-responders.	(Harris et al., 2017)
	RV	Pakistani and Dutch infants	RV response correlated with a higher relative abundance of bacteria belonging to <i>Clostridium</i> cluster XI and Proteobacteria.	(Harris et al., 2018a)
	RV, OPV	Indian infants	No differences in microbiome composition between RV responders and non-responders. Co-administered OPV reduced the response to RV.	(Parker et al., 2018)
	OPV	Indian infants	Enteric viruses have a greater impact on OPV response than the bacterial microbiota, especially for recent enterovirus infections.	(Paharaj et al., 2019)
Causation studies in humans	BCG, TT, HBV, OPV	Bangladeshi infants	High abundance of stool Actinobacteria, including <i>Bifidobacterium</i> , was associated with higher responses to oral and parenteral vaccines and with higher CD4 ⁺ T cell and antibody responses 2 years after vaccination.	(Huda et al., 2014, 2019)
	HIV	Swiss adults	The immunogenicity of HIV vaccine was correlated with microbiota clusters.	(Cram et al., 2019)
	OPV	Indian infants	Antibiotics did not improve the immunogenicity of OPV, despite the reduction of biomarkers of enteropathology and pathogenic intestinal bacteria.	(Grassly et al., 2016)
	RV, Pneumo23, TT	Dutch adults	Narrow-spectrum antibiotics resulted in higher day-7 anti-RV IgA boosting and increased RV-antigen shedding but no different absolute titers. The antibiotics did not affect pneumococcal or TT vaccination.	(Harris et al., 2018b)
	TIV	American adults	Antibiotics-induced microbiome loss impaired antibody response in subjects with low pre-existing immunity.	(Hagan et al., 2019)

TIV, trivalent inactivated influenza vaccine; OPV, oral polio vaccine; CT, cholera toxin; BCG, Bacillus Calmette-Guérin; MenB, Bexsero meningococcal serogroup B vaccine; MenC, NeisVac-C meningococcal serogroup C vaccine; PCV13, the Prevnar 13-valent pneumococcal conjugate vaccine; Hexa, the INFANRIX Hexa combination vaccine, which contains antigens from hepatitis B, diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, and inactivated poliomyelitis virus; RV, rotavirus vaccine; TT, tetanus toxoid; HBV, hepatitis B vaccine; Pneumo23, polysaccharide pneumococcal vaccine.

Rôle péroratif des antibiotiques sur la réponse vaccinale



cells in vitro. Also, 5-OP-RU was detected in the thymus after cutaneous application or oral gavage, showing that an external source can reach thymic cells.

The results indicate that thymic MAIT7 cell development depends on the in vivo production of 5-OP-RU by commensal bacteria at mucosal surfaces. This was confirmed using commensal bacterial species that do (*Enterococcus faecalis*) or do not (*Enterococcus faecalis*) produce 5-OP-RU as well as genetically engineered *Escherichia coli* strains that lack enzymes of the vitamin B₆ pathway upstream or downstream of 5-OP-RU production. However, 5-OP-RU alone was not sufficient to promote MAIT cell development in germ-free mice, which suggests that other, as yet unknown, microbial factors are also involved.

Esty Minton

ORIGINAL ARTICLE <https://doi.org/10.1038/s41586-023-03038-2>
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when analyzing LMV-treated B220⁺ tumours in mice over time, the authors found no change in their clonal composition, indicating that no such outgrowth occurs. Instead, they propose that tumours with high TMB escape tumour surveillance because particular tumour neoantigens undergo 'dilution' within the tumour, leading to weaker antitumour immunity and less immune cell infiltration.

Although the mechanisms underlying the modulation of tumour immunity by TIV require further investigation, this study shows that assessing the TMB in melanoma patients might be useful as a prognostic indicator for response to immunotherapy. Moreover, it indicates that antigen-specific immunotherapy approaches need to be targeted at antigen-presenting in a large number of clones and that agents that increase the TMB may also increase tumour heterogeneity, which should be avoided.

Alexandra Flemming

ORIGINAL ARTICLE <https://doi.org/10.1038/s41586-023-03038-2>
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RESEARCH HIGHLIGHTS



Perturbations in the gut microbiota have been shown to affect various immune components and impair the efficacy of treatments such as cancer immunotherapy. Now, work from the group of Bodo Plé and others shows that antibiotic-mediated disruption of the gut microbiota can impair the effectiveness of seasonal influenza vaccination in individuals with low levels of pre-existing immunity.

Most studies exploring how the microbiota shapes immune function have used animal models. To examine the effects of the microbiota on the human immune system, Hegen et al. vaccinated seasonal inactivated or control subjects with the seasonal trivalent inactivated influenza vaccine (TIV). They initially enrolled 22 healthy adults and subjected 11 individuals to a 5-day broad-spectrum antibiotic regimen (commencing 3 days before vaccination and ending 1 day after) and collected biological samples regularly until 1 year after vaccination. Antibiotic-treated subjects showed a marked reduction in bacterial loads and profound changes in microbial community composition, chiefly characterized by an overabundance of *Enterobacteriaceae* and reduced abundance of *Lactobacteriaceae*, *Bifidobacteriaceae*, *Blautiaceae* and *Verrucomicrobiaceae*. This restriction in bacterial diversity was apparent for at least 6 months after cessation of antibiotic administration.

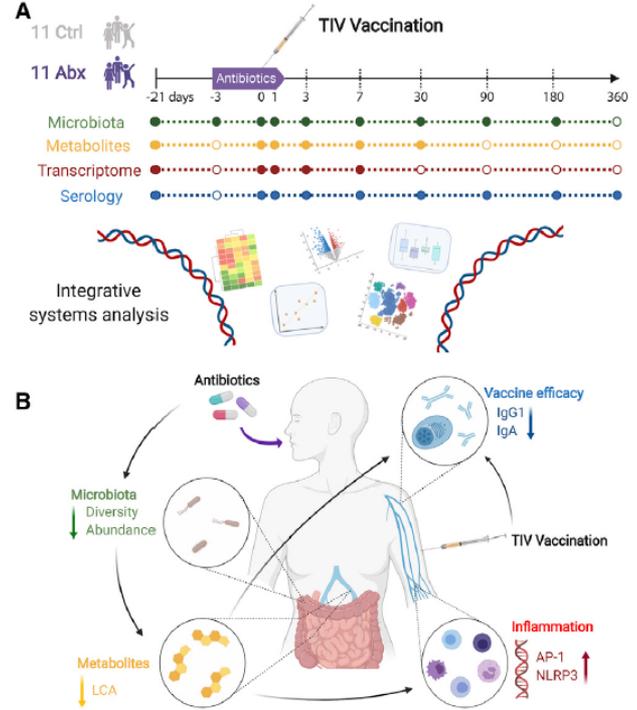
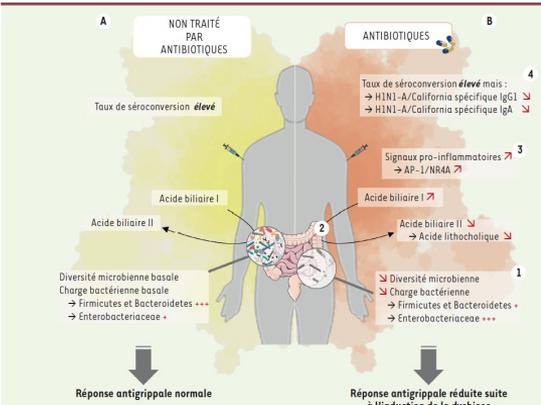
In this initial study, the authors did not use any differences between the TIV-induced antibody responses of antibiotic-treated and control individuals. However, many individuals showed high baseline antibody titres; therefore, in a subsequent study the authors enrolled additional subjects with low pre-existing titres of antibody against influenza. In this follow-up study, using individuals with limited pre-existing immunity, antibiotic treatment markedly impaired binding and neutralization antibody responses against the H1N1 A/California strain of influenza although not against the other two strains targeted by the vaccine. Inactivated antibody responses against the antibiotic-treated subjects showed markedly reduced production of IgG1 and IgA1 specific for H1N1 A/California following vaccination. The authors found that antibiotic treatment alone was associated with increased expression

of gene modules linked with pro-inflammatory signalling and dendritic cell activation, similar to what had previously been observed in elderly subjects. These changes normalized following cessation of antibiotics, suggesting they were linked with perturbations in the gut microbiota. As the gut microbiota plays an important role in dietary metabolites, the authors examined changes in the blood metabolomes of the different groups. They found that antibiotic treatment was associated with metabolic changes, including changes in bile acid and tryptophan metabolism. The gut microbiota is responsible for converting liver-derived primary bile acids into secondary bile acids; notably, treatment with antibiotics led to a dramatic reduction in levels of secondary bile acids. Accordingly, the authors found prominent differences in the metabolic response to TIV between the antibiotic-treated and control subjects.

Analyses by the authors suggested an inverse correlation between the levels of individual secondary bile acids and expression of various inflammatory modules. In particular, the secondary bile acid lithocholic acid (LCA) showed a 1,000-fold reduction in the plasma of antibiotic-treated subjects and downregulation of LCA was associated with increased expression of inflammatory signalling genes. Further gene network analyses by the authors suggested that the increased inflammatory signalling associated with secondary bile acid disturbances and the impaired IgG1 response to TIV vaccination arise as independent effects of antibiotic-mediated disturbance of the microbiota.

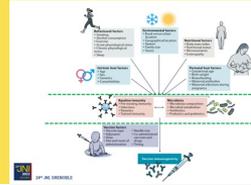
Previously, it has been previously exposed to influenza virus and this study indicates that, where pre-existing immunity exists, the immune system can maintain appropriate responses to pathogens despite significant metabolic disturbances arising from variant dysbiosis. However, in situations where immunity may be less mature (such as in adults with low pre-existing immune memory or in infants), dysbiosis may have a greater impact on the development of an appropriate immune response. Yoana Borbon

ORIGINAL ARTICLE <https://doi.org/10.1038/s41586-023-03038-2>
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Antibiotics Impair the Vaccine Response in Healthy Adults
 *11 subjects were treated with antibiotics for 5 days and vaccinated with the trivalent influenza vaccine on day 1.
 *Administration of antibiotics led to reduced microbial diversity and abundance and a consequential reduction in secondary bile acids. This in turn led to increased inflammation and a diminished vaccine response.

La sixième révolution des vaccins est en cours



1800s onwards; live attenuated smallpox, rabies, tuberculosis (BCG), yellow fever, polio (oral polio vaccine (OPV)) vaccines.

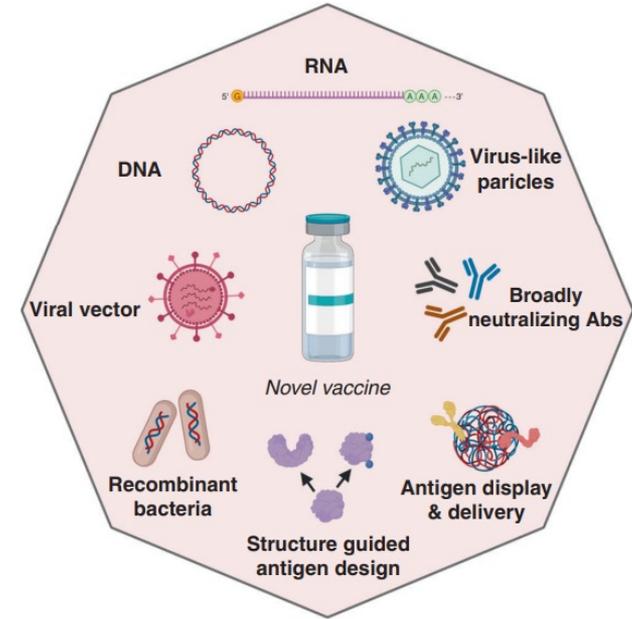
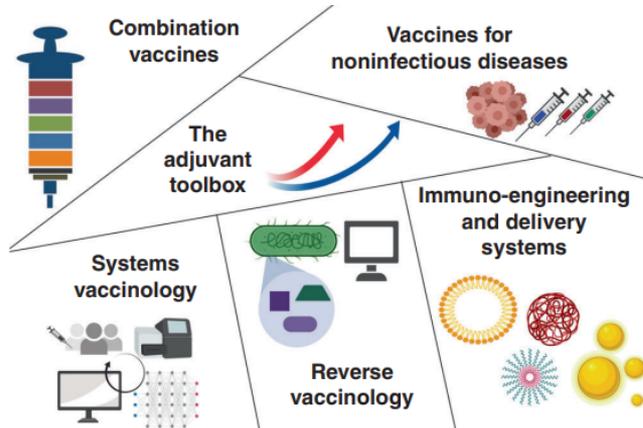
1950s; of the cornucopia of live vaccines made possible by passage in cell culture, the work by Enders, Robbins and Weller lead to the Salk and Sabin polio vaccines.

2000s; driving the immune system in the T helper 1 direction with stimuli such as vectors and adjuvants.



1880s onwards; killed vaccines for typhoid, cholera, whole cell pertussis, influenza, polio (inactivated polio vaccine (IPV)).

1980s; Hepatitis B vaccine (HBV), the 1st recombinant-antigen-based vaccine, incorporated the viral surface proteins, derived from molecular biology production.



Recent advances in vaccine design technologies enabled by novel delivery systems

Comment améliorer l'immunogénicité des vaccins?

Table 2. New Strategies for Inactivated Vaccine Discovery

Strategy

Protein-conjugated capsular polysaccharides

Reverse vaccinology

Antigen identification by transcriptomics and proteomics

Structural analysis

Development of new adjuvants (including cytokines)

DNA plasmids

mRNA and self-amplifying RNA

Abbreviation: mRNA, messenger RNA.

Table 3. New Strategies for Attenuated Vaccine Discovery

Strategy

Temperature-sensitive mutations and reassortment

Viral recombinants and deletion mutants

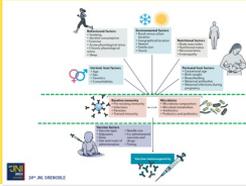
Codon de-optimization

Vectors that present genes from pathogens

Plotkin S, CID 2023

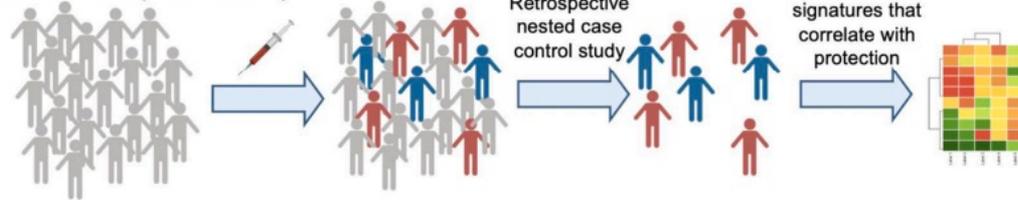
System vaccinology
Reverse vaccinology
Structural vaccinology

La system vaccinology devrait permettre d'accélérer le développement des vaccins de sixième génération



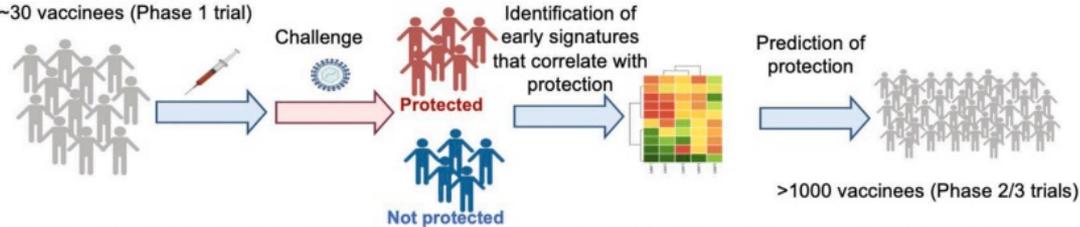
a) Vaccines with unknown correlate of protection

>1000 vaccinees (Phase 2/3 trials)



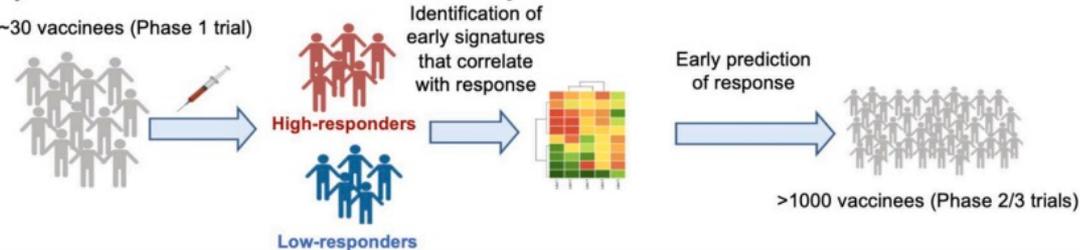
b) Vaccines with established human challenge models

~30 vaccinees (Phase 1 trial)

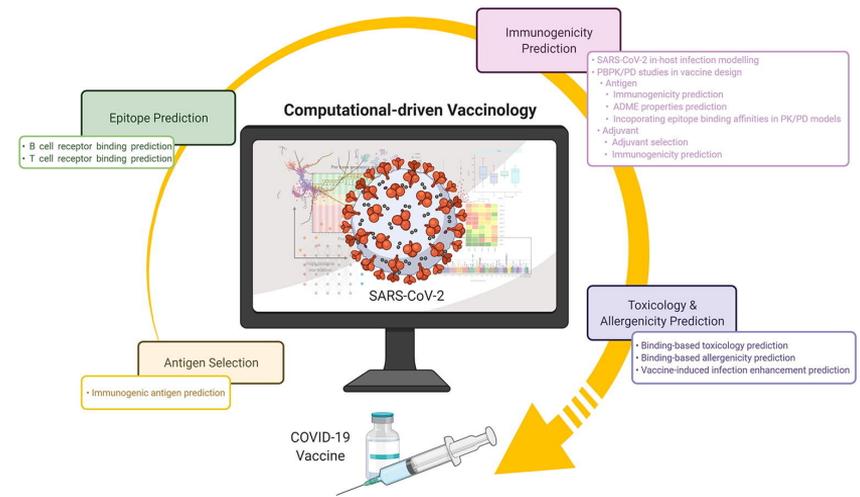
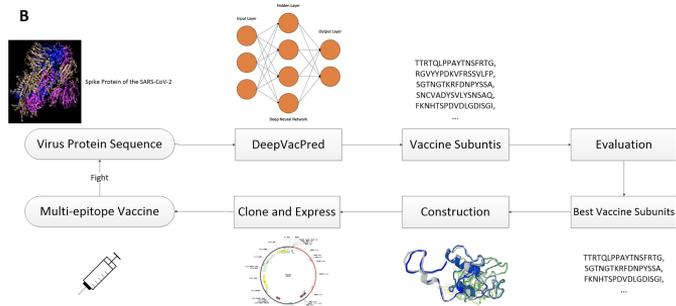
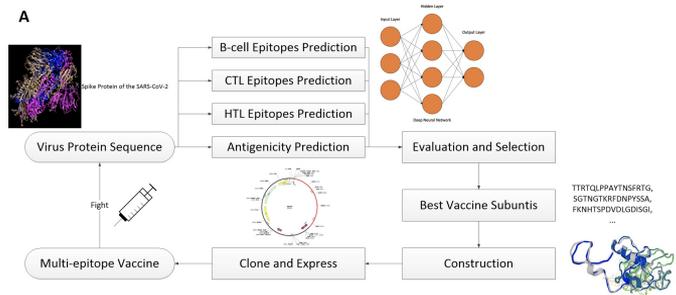
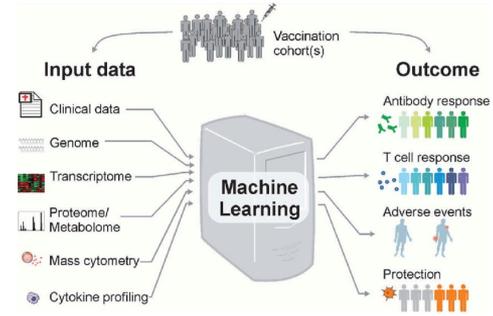
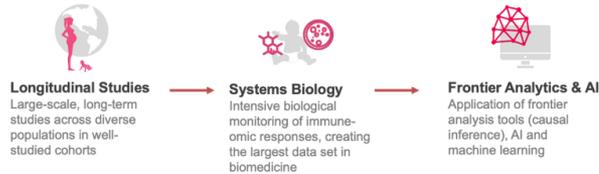
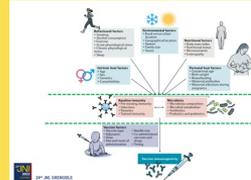


c) Vaccines with known correlate of protection

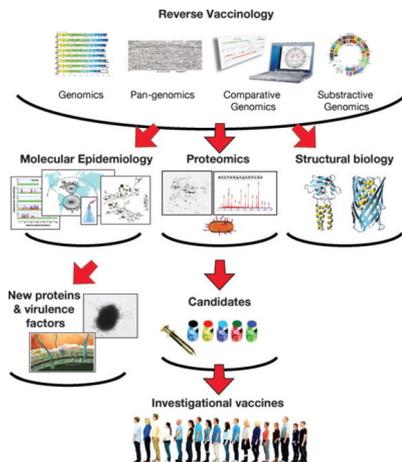
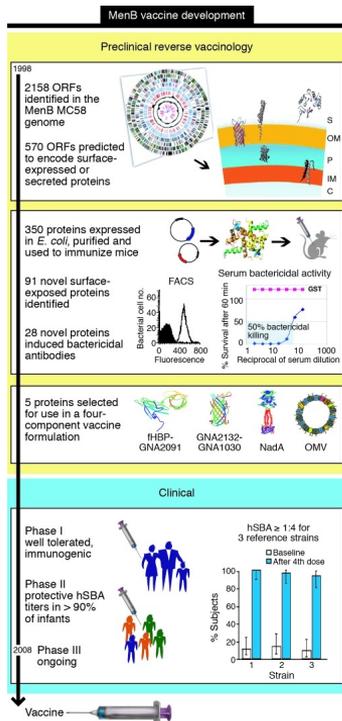
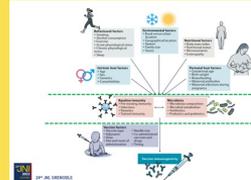
~30 vaccinees (Phase 1 trial)



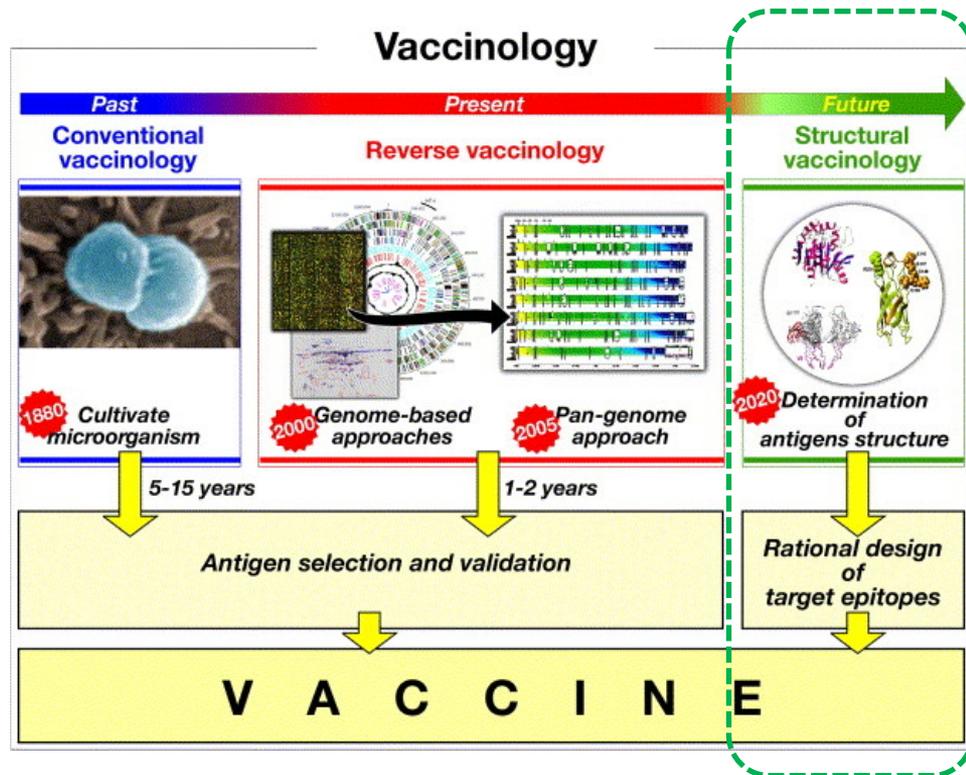
La system vaccinology devrait permettre d'accélérer le développement des vaccins de sixième génération



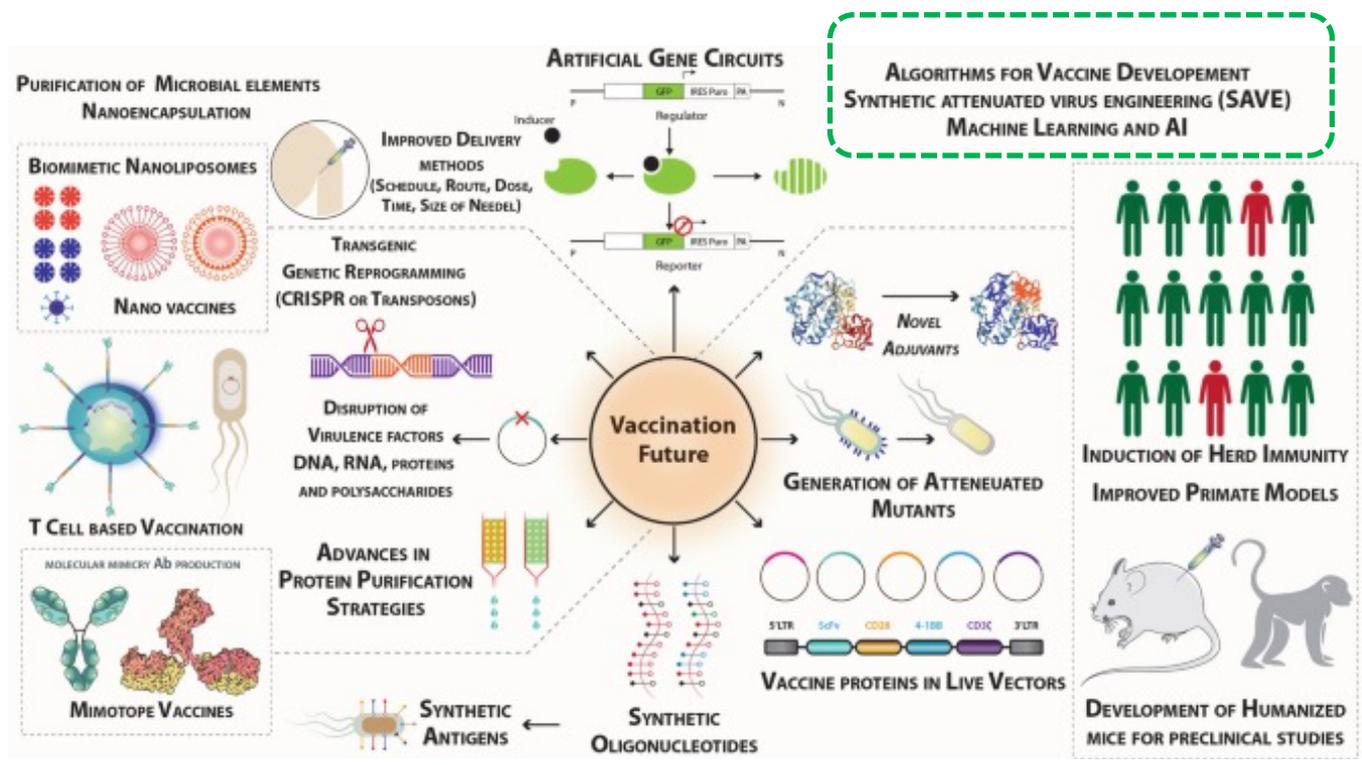
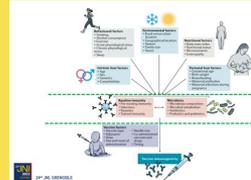
Vers le développement de la vaccinologie structurale



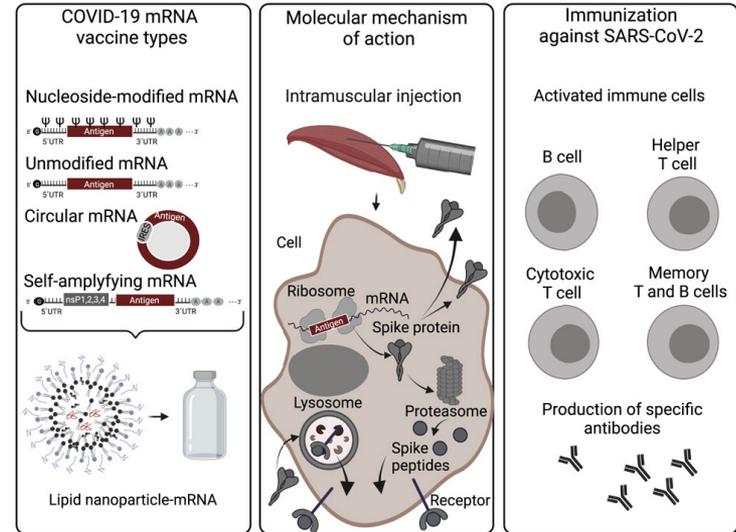
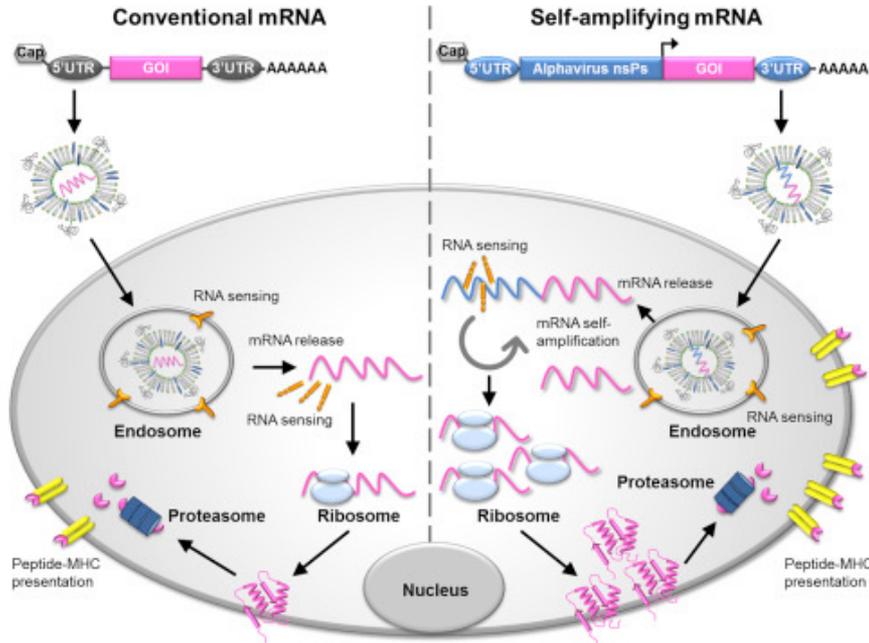
Très lourd et ne fonctionne pas toujours



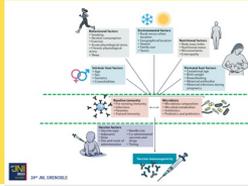
Développement d'outils pour la vaccination structurale



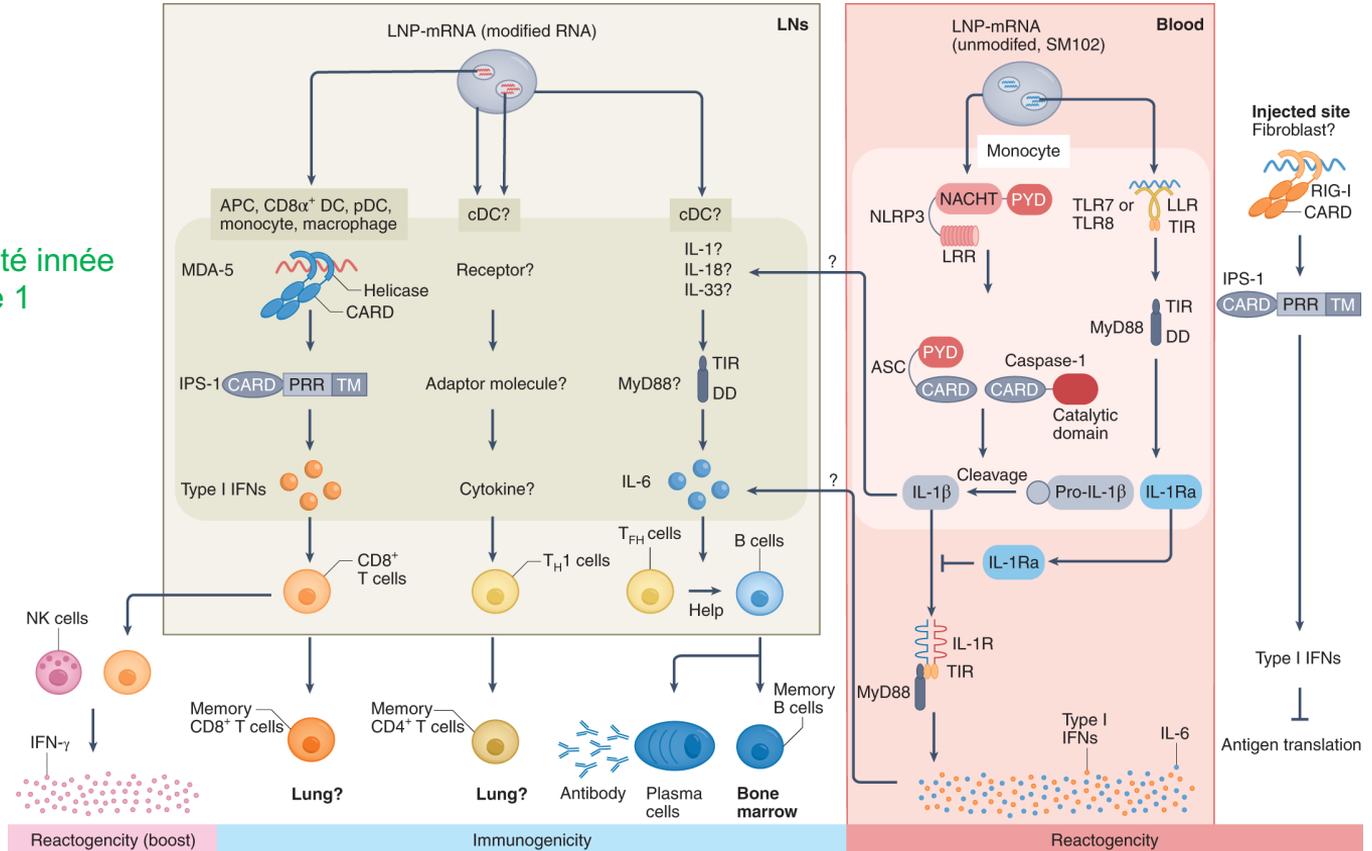
La révolution des vaccins ARNm



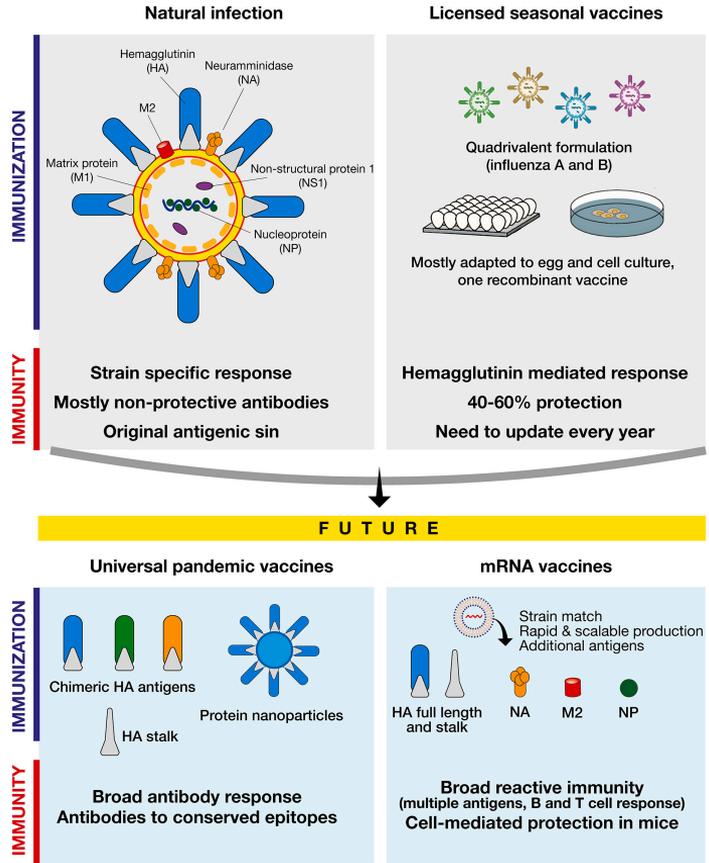
Mecanismes d'immunogénicité/réactogénicité des vaccins LNP mRNA



Forte induction de l'immunité innée
Réponse IFN de type 1



Les vaccins ARNm un vrai « game changer »?



Dans PNAS, McMahon rapporte un nouveau vaccin quadrivalent mRNA modifié HA, NA, NP, M2 efficace chez la souris

Pas pour tout....
 Qualité conformationnelle des antigènes?
 Réponse mémoire courte?
 Induction mucoale?

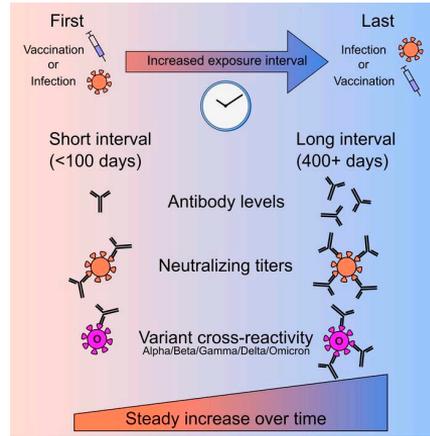
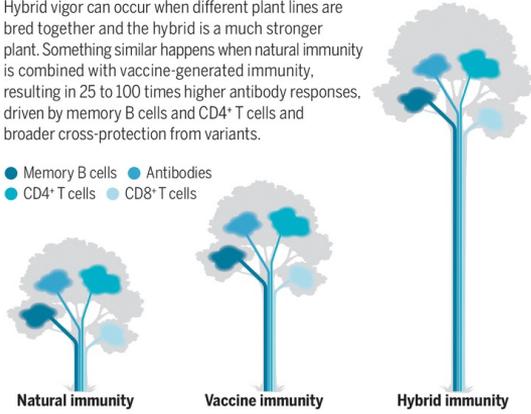
Attrait de l'immunité hybride ou des stratégies de prime-boost hétérologue



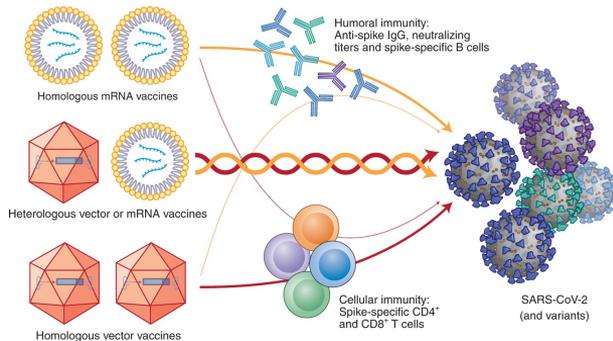
Hybrid vigor immunity with COVID-19 vaccines

Hybrid vigor can occur when different plant lines are bred together and the hybrid is a much stronger plant. Something similar happens when natural immunity is combined with vaccine-generated immunity, resulting in 25 to 100 times higher antibody responses, driven by memory B cells and CD4+ T cells and broader cross-protection from variants.

- Memory B cells
- CD4+ T cells
- Antibodies
- CD8+ T cells



Heterologous mieux que Homogeneous
Infection + vaccin mieux que vaccin + infection
Espacement des doses
Meilleure mémoire immunitaire
Meilleure immunité mucoale

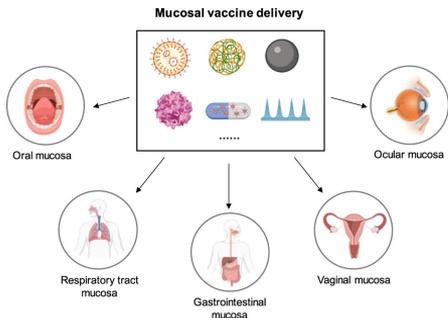
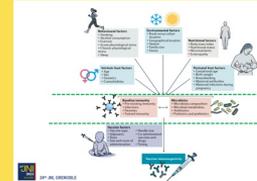


Level of immune protection against variants

	Non-Omicron		Omicron		
	Ancestral	Delta	BA.1	BA.2.12.1	BA.4, BA.5
a	High	High	Low	Low	Low
b	Medium	Medium	Low	Low	Low
c	High	High	High	Low	Low
d	High	High	High	Not known	Not known
e	High	High	Low	Low	Low



Développement de la vaccination mucosale



Différentes voies
Safety?

Vibrio cholerae

Inactivated

Dukoral Oral — aqueous
Composition: heat and formaldehyde-inactivated O1 serogroups (Inaba + Ogawa) + C7B

Live attenuated

Euvichol, Shanchol Oral — aqueous
Composition: heat and formaldehyde-inactivated O1 serogroups (Inaba + Ogawa) + 0139

Vaxchora Oral — aqueous
Composition: live attenuated O1 serogroup (Inaba) - ctaA attenuation

Influenza A and influenza B viruses

Live attenuated/reassortant

FluMist/Fluenz Nasal — spray
Composition: quadrivalent antigens from circulating strains incorporated into live attenuated, cold adapted donor influenza vector

Salmonella typhimurium

Live attenuated/reassortant

Typhi Vivotif Oral — capsule
Composition: Live attenuated Ty21a strain
• Mutagenesis in LPS synthesis and Vi polysaccharide genes

Poliovirus

Live attenuated

Biopolio (iOPV) Oral — aqueous
Composition: culture passage attenuated polioviruses 1 and 3 serotypes (5' non-coding region attenuation)

mOPV and rOPV Oral — aqueous
Composition: culture passage attenuated polioviruses 1, 2 and 3 serotypes (5' non-coding region attenuation)

Rotavirus

Live reassortant

Rotateg Oral — aqueous
Composition: pentavalent — five human-bovine reassortant rotaviruses (resorption of G1, G2, G3, G4, G5 with P1A and G6 with P1A)

Live attenuated

Rotarix Oral — aqueous
Composition: monovalent — culture passage attenuated (G1 with P1A expression)

Respiratory
Respiratory route of infection

No approved vaccine

RSV
100–150,000 deaths p.a.
33 million infections p.a.

Suboptimal vaccine coverage

Mycobacterium tuberculosis
1.5 million deaths p.a.
10 million infections p.a.

SARS-CoV-2
>2.6 million deaths p.a.
>115 million infections p.a.

Streptococcus pneumoniae
1.2 million deaths p.a.
>190 million infections p.a.

Bordetella pertussis
160,000 deaths p.a.
>24 million infections

Haemophilus influenzae
48,000 deaths p.a.
>40 million infections p.a.

Lung cancer
1.6 million deaths p.a.

Other cancers
Oncogenic viruses including Epstein-Barr virus, HHV8 and HTLV1

Enteric
Oral-faecal route of infection

No approved vaccine

Shigella
200,000 deaths p.a.

ETEC
>50,000 deaths p.a.

Helicobacter pylori
>15,000 deaths p.a.
50% of world population infected

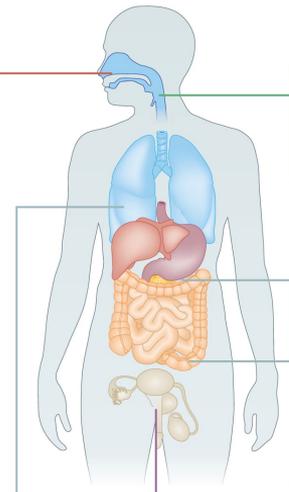
CRC and stomach cancers
• 1 in 100 to 1 in 150 lifetime risk of stomach cancer
• 1 in 25 lifetime risk of CRC

Sexually transmitted

No approved vaccine

HIV
700,000 related deaths p.a.
1.7 million new infections p.a.

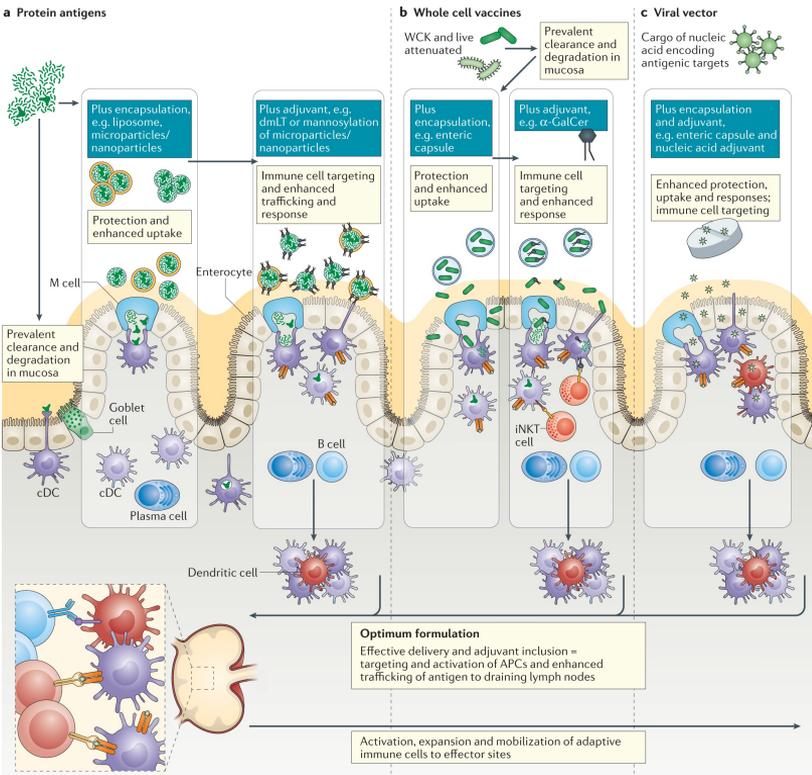
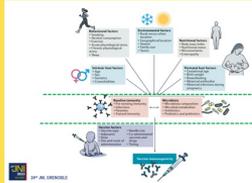
Hepatitis C virus
400,000 related deaths p.a.
1.7 million infections p.a.



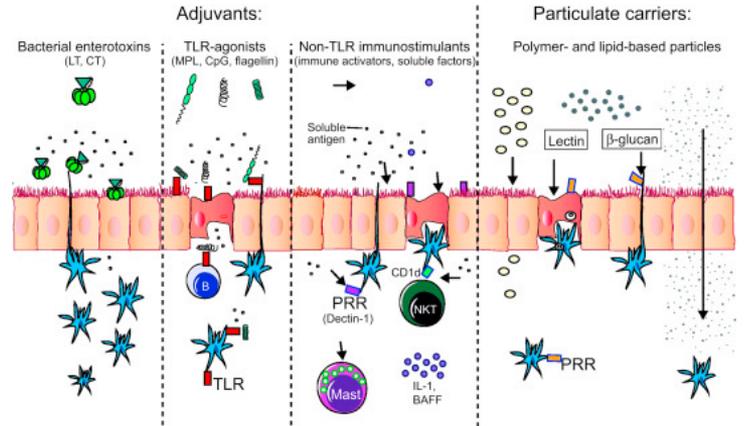
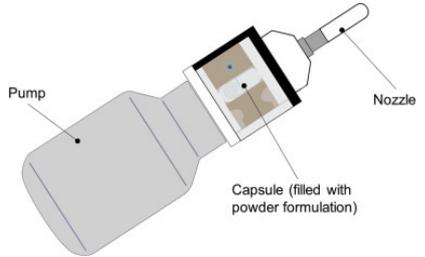
Très peu d'AMM

La grande majorité des pathogènes traversent efficacement les muqueuses

Développement de la vaccination mucosale

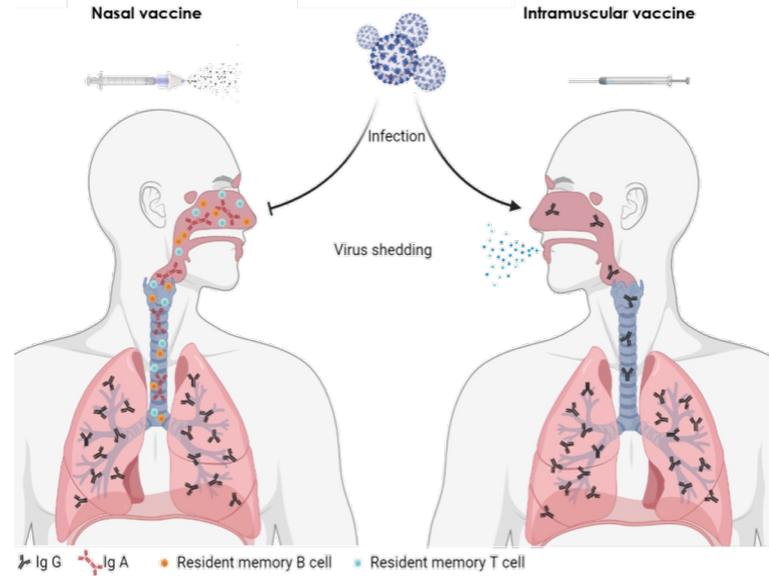
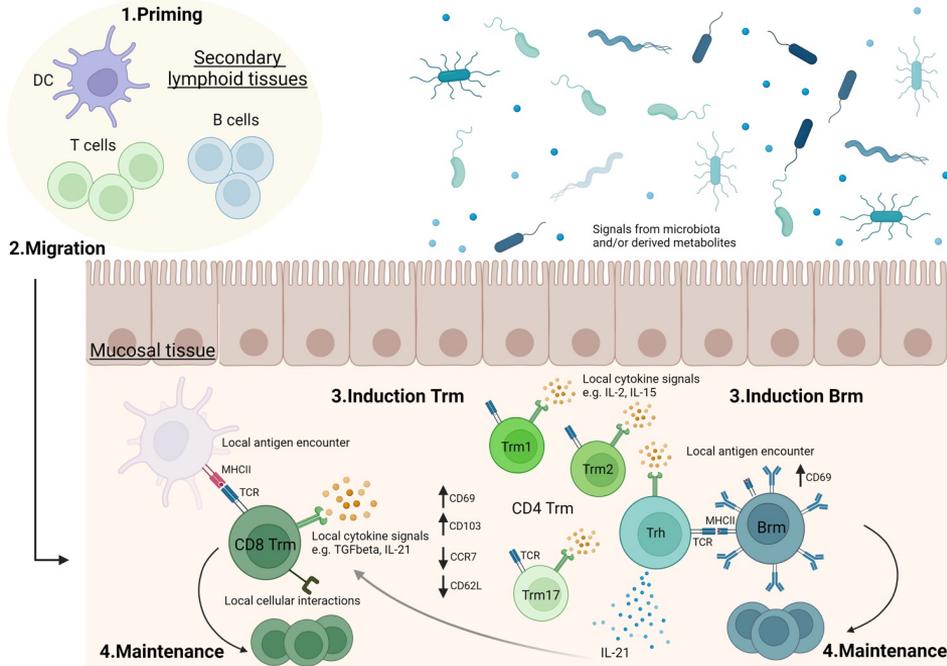
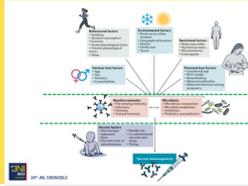


LoValTech, Tours, France



Besoin de « devices » efficaces
Besoin de meilleurs adjuvants

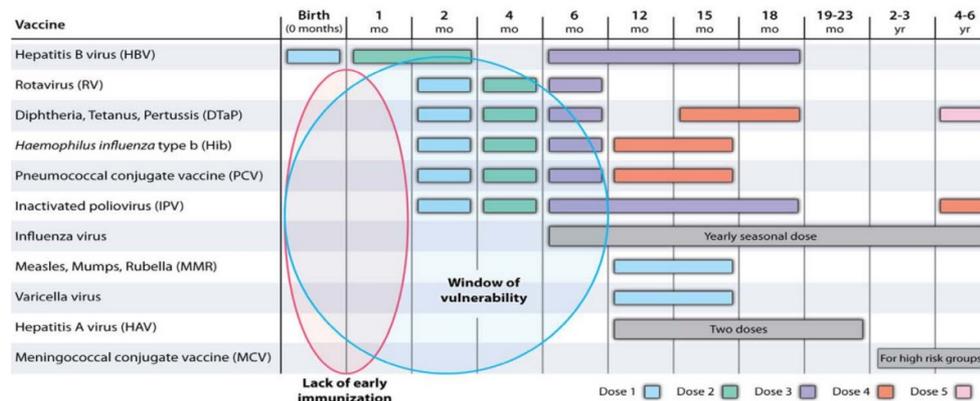
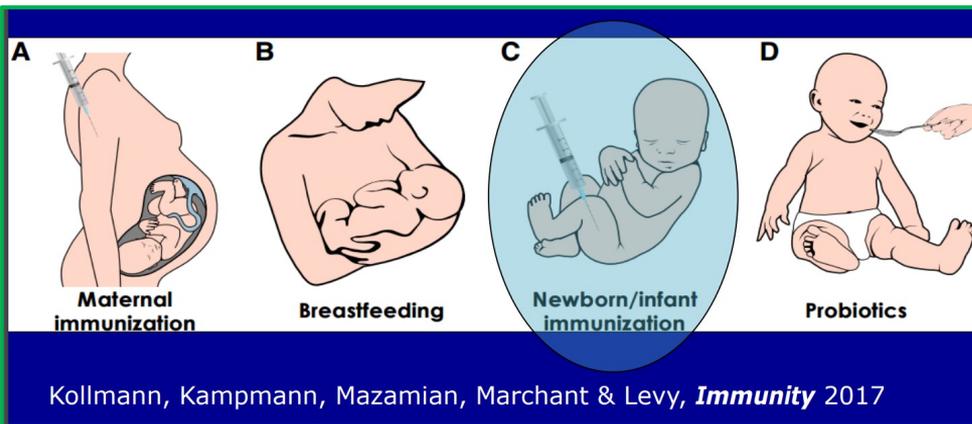
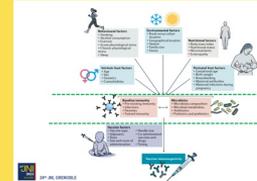
Cibler les cellules résidentes mémoires au niveau des muqueuses



LoValTech

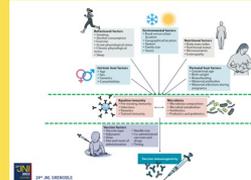
Adjuvants
Vaccins vivants
Voie muqueuse

Les challenges de la vaccination pédiatrique (immunisation précoce & multi-dose)



Sanchez-Schmitz G, Levy O *Sci Transl Med* 2011

Intérêt de l'immunisation maternelle



Comment

Group B streptococcal maternal vaccination, the goal is near

Infections are the foremost cause of neonatal mortality worldwide, and group B streptococcus (GBS) remains a leading cause of neonatal sepsis and meningitis.^{1,2} In *The Lancet Infectious Diseases*, Shahr Madhi and colleagues³ report the first phase 3/2 randomized trial on a trivalent GBS vaccine in 60 non-pregnant and 320 pregnant (in the third trimester) healthy black-African women.³

In many high-income countries, neonatal meningitis, maternal protective immunity, resulting in a specific transplacental IgG passage, IgG transfer would protect neonates from birth through the first weeks post-partum, when late-onset disease occurs. Madhi and colleagues present results from their large and challenging randomised trial on a new capsular polysaccharide trivalent vaccine, based on CRM₁, as the conjugate protein. The capsular polysaccharide represented serotypes Ia, Ib, and II which are associated



Articles

Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial

Shaha A Madhi, Clara L Galand, Linlin Jiao, Anthony Koon, Nando Goemaere, Frederik Willem*, Monayefeh Ouhgben, Ayke Schlegel van Meulen*, Sheryl Baker, Peter M Du-P*, Vito Naranjo*, Karen Skidow*



Streptocoque B

Vaccin polysidique conjuguésérotypes Ia, Ib, et III

VRS nanoparticule dirigée contre la protéine de fusion du VRS

Women of Childbearing Age and RSV F Vaccine • JID 2016:213 (1 February)

The Journal of Infectious Diseases
MAJOR ARTICLE



A Randomized, Blinded, Controlled, Dose-Ranging Study of a Respiratory Syncytial Virus Recombinant Fusion (F) Nanoparticle Vaccine in Healthy Women of Childbearing Age

Gregory M. Shaw,¹ Louis F. Price,¹ D. Nigel Thomas,¹ Gale Smith,¹ Dale Kasperowicz,¹ Heavie Lu,¹ David Pflanz,¹ David Jiao,¹ Susana P. Robinson,¹ and Frank A. Tenover¹

¹Division of Infectious Diseases and Department of Molecular Virology and Microbiology and Pathology, Baylor College of Medicine, Houston, Texas

Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial

Milagritos D Tapia, Samba O Sow, Bouba Tamboura, Ibrahim Tégreté, Marcelo F Pasetti, Mamoudou Kodjo, Uma Omwuchelwa, Sharon M Tennant, William C Blackwelder, Flanon Coulibdy, Awa Traoré, Adama Mamby Keita, Fadima Cheikh Haidara, Fatoumata Diallo, Moussa Daoumba, Doh Sanog, Ellen DeMatt, Nicholas H Schusterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

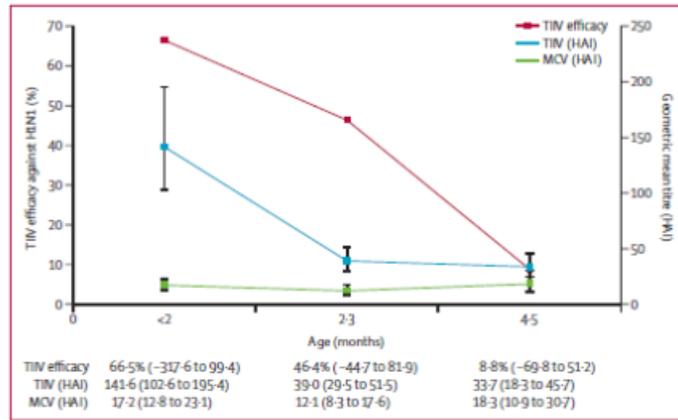
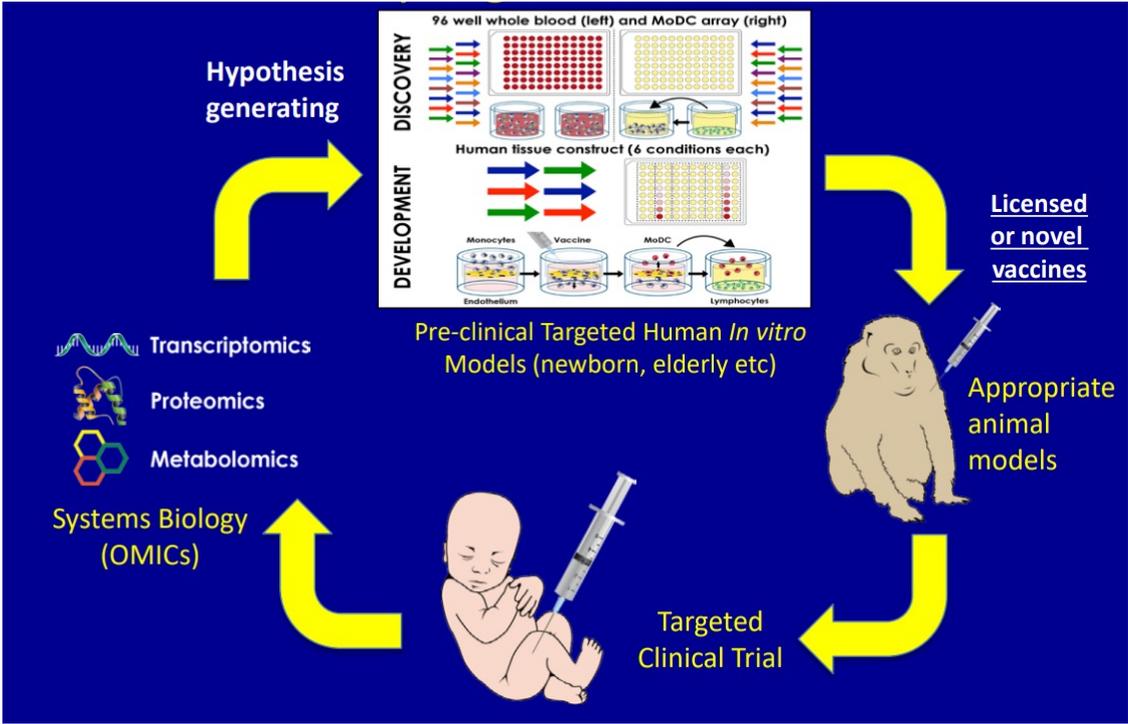


Figure 2: Vaccine efficacy and HAI antibody geometric mean titres in infants, by age and maternal vaccine group. Error bars and data in parentheses show 95% CIs. TIV - trivalent inactivated influenza vaccine. MCV - quadrivalent meningococcal conjugate vaccine. HAI - hemagglutination inhibition antibodies.

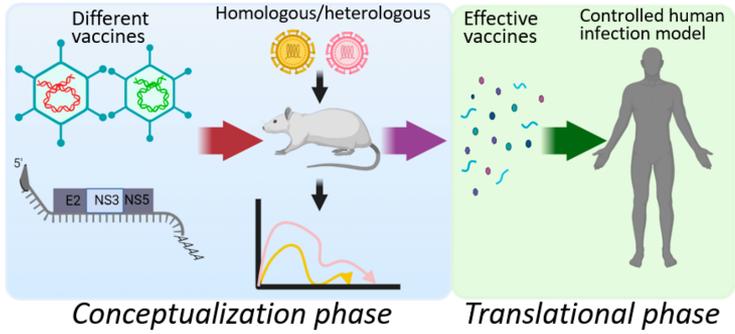
Développement d'outils pour la vaccination de précision



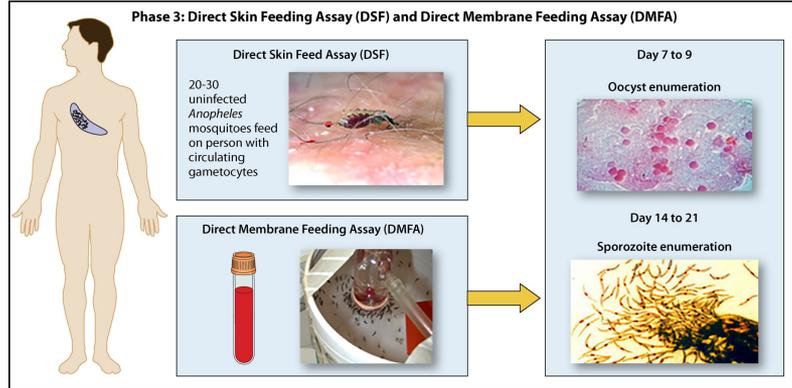
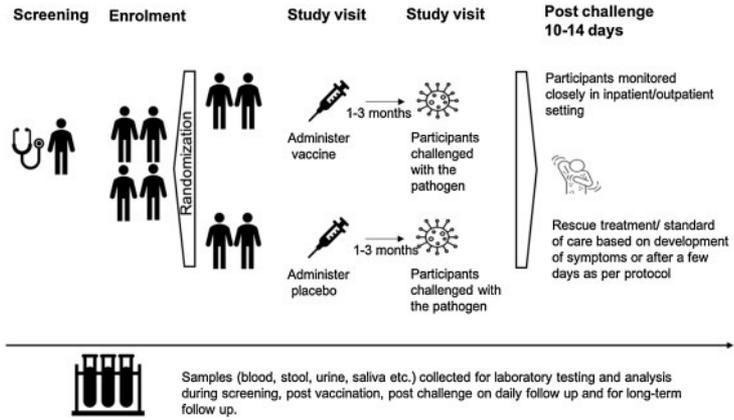
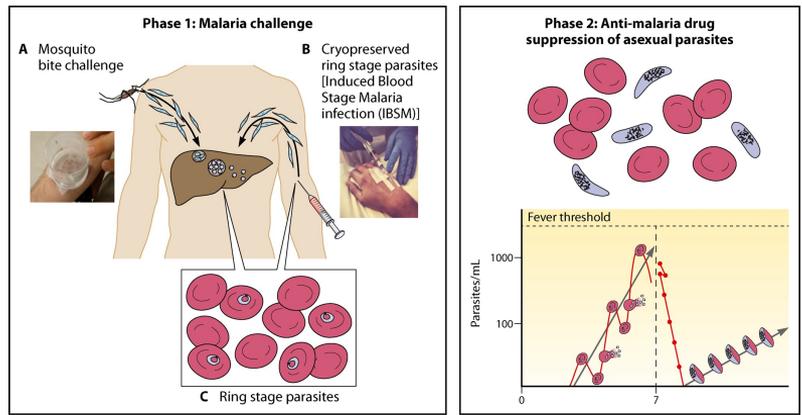
- *Modèles *in vitro* / *ex vivo* adaptés
- *Modèles *in vivo* adaptés
- *Challenges?



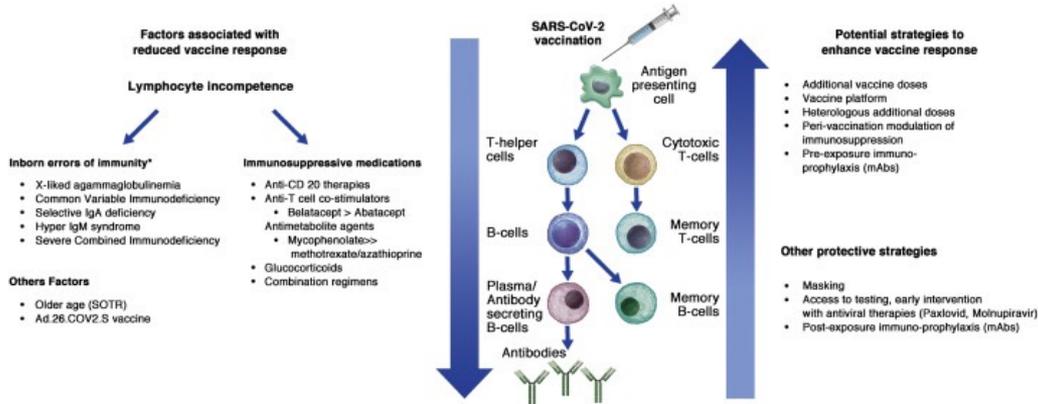
Le Challenge Humain pour accélérer le développement des vaccins?



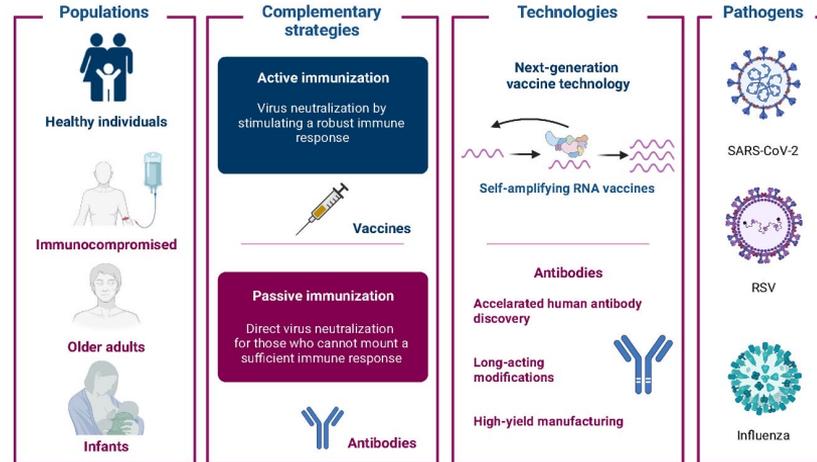
Challenge malaria



Améliorer l'efficacité vaccinale dans les populations à risques, oui mais comment?



High dose (Flu)
 Vacins vivants/autres
 Immunisation maternelle
 Adjuvants
 Voie muqueuse



Bloquer l'inflammation
 FMT
 Sérothérapie
 Planifier la vaccination

Futur de la Vaccination?

*Epidémiologie des pathogènes émergents et des zoonoses

*Vaccination personnalisée/précision (HLA, sex etc..)

*Structurale et reverse vaccinology

*Nouvelles plateformes vaccinales (mRNA)

*Nécessité d'avoir de nouveaux adjuvants (approuvés)

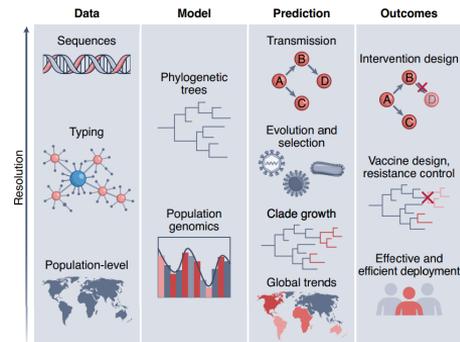
*Nouvelles stratégies pour induire une meilleure mémoire

*Réduire la réactogénicité

*Développement des stratégies muqueuses (device)

*Comment mieux vacciner les populations cibles

*Améliorer l'évaluation (CHIM model)



Problem	Solution
Immune memory	More stimulus of Tfh cells Role of IL-7?
	Stronger induction of innate immunity by TLR agonists
Multiplicity of virulence antigens in complex pathogens	Antigenomics—analysis of natural immune responses
Multiple HLA types	Polyepitope vaccines
Conserved epitopes	Structural biology
Finding correlates of protection	Systems biology ^a
Immaturity and postmaturity of the immune system	Add cytokines or neutralize cytokines?
Mucosal immunization with nonreplicating antigens	Use nanoemulsions?
Adjuvants capable of selectively expanding cell types: dendritic, B, Th1, Th2, Th17, CD4 ⁺ , CD8 ⁺ , or Tregs	Use single or combined TLR ligands?
The difficulty to generate T-cell immunity without replicating vaccines	Adjuvants?

Abbreviations: HLA, human leukocyte antigen; IL-7, interleukin 7; Tfh, T follicular helper; TLR, Toll-like receptor; Tregs, regulatory T cells.

^aAnalysis of humoral and cellular immune responses.