JNI 24es Journées Nationales d'Infectiologie
Grenoble
et la région Auvergne-Rhône-Alpes
ALPEXPO
du mercredi 7 au vendredi 9 juin 2023

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……

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

Membre de la CTV à l'HAS

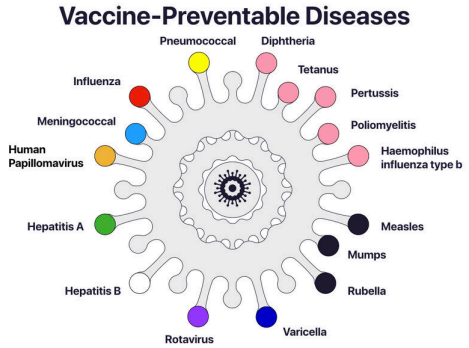
Les vaccins et leurs enjeux en 2023

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)

Utilisation d'ATB+++, dysbiose, inflammation chronique

Comment améliorer l'efficacité de la vaccination dans les populations à risques?

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

Chlamydia	Lyme
CMV	**Malaria**
Charbon	MERS/SARS & co
Chikungunya	Shigella
Clostridium difficile	SRAS
Dengue (Takeda?)	*Staph aureus*
EBV	*Strepto B*
Ebola	**Tuberculose**
Helicobacter pylori	VRS (GSK, Sanofi)
Hépatite C	West Nile Virus
Herpès	Virus Zika
HIV	ZVL
Metapneumovirus	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

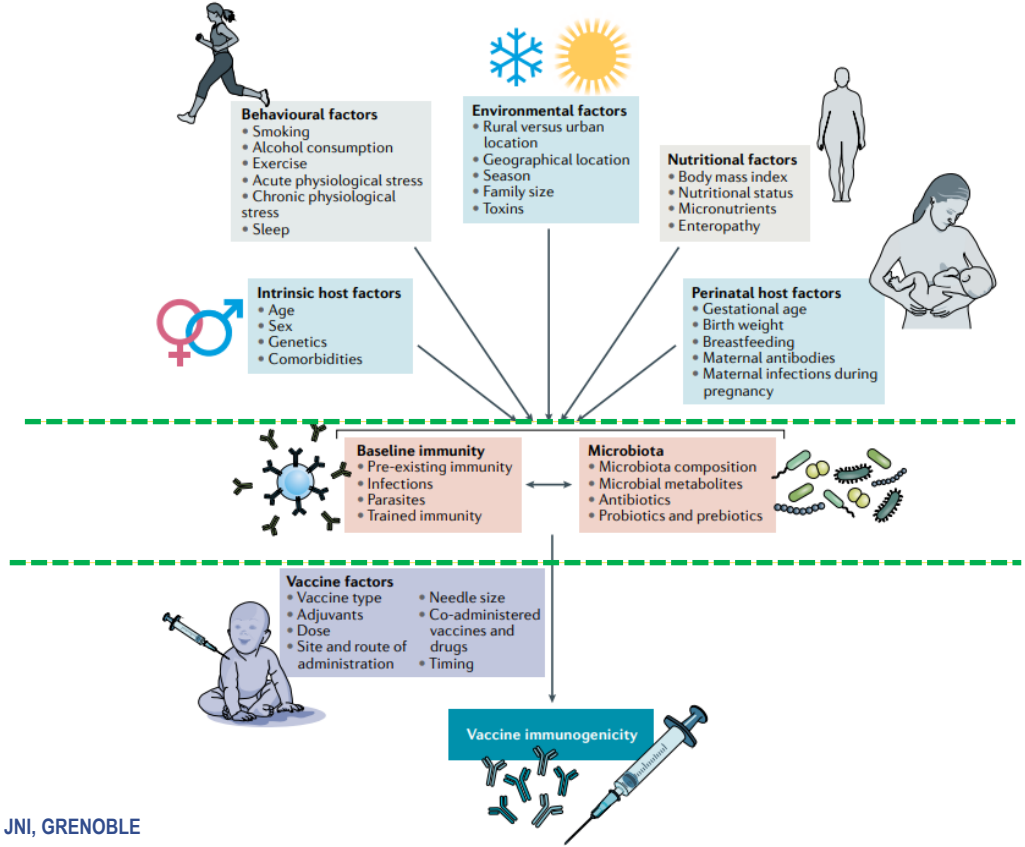
Et il n'y a pas que l'infectieux!!!

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.

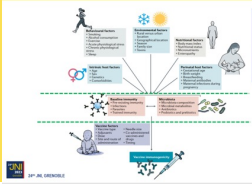
Facteurs influençant l'immunogénicité des vaccins

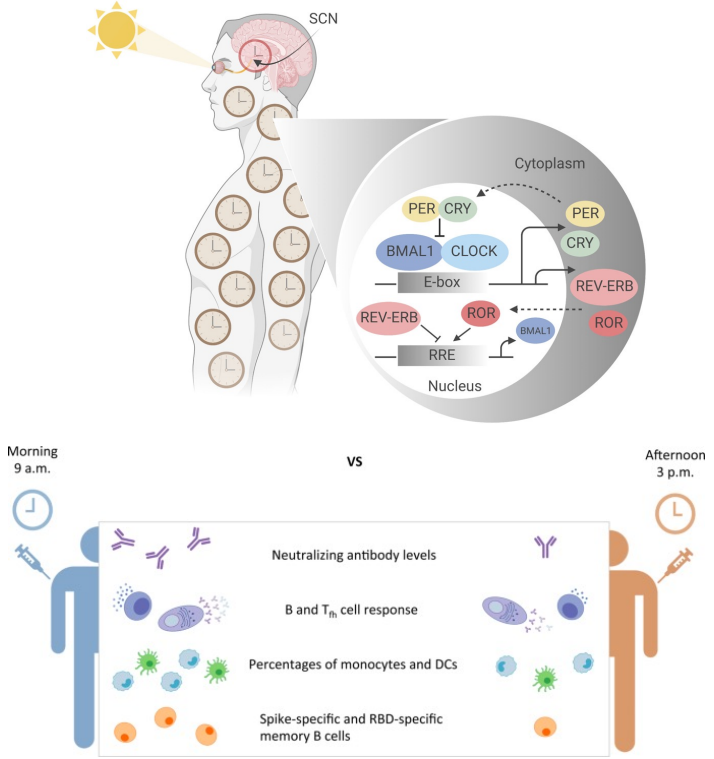


L'hétérogénéité vaccinale

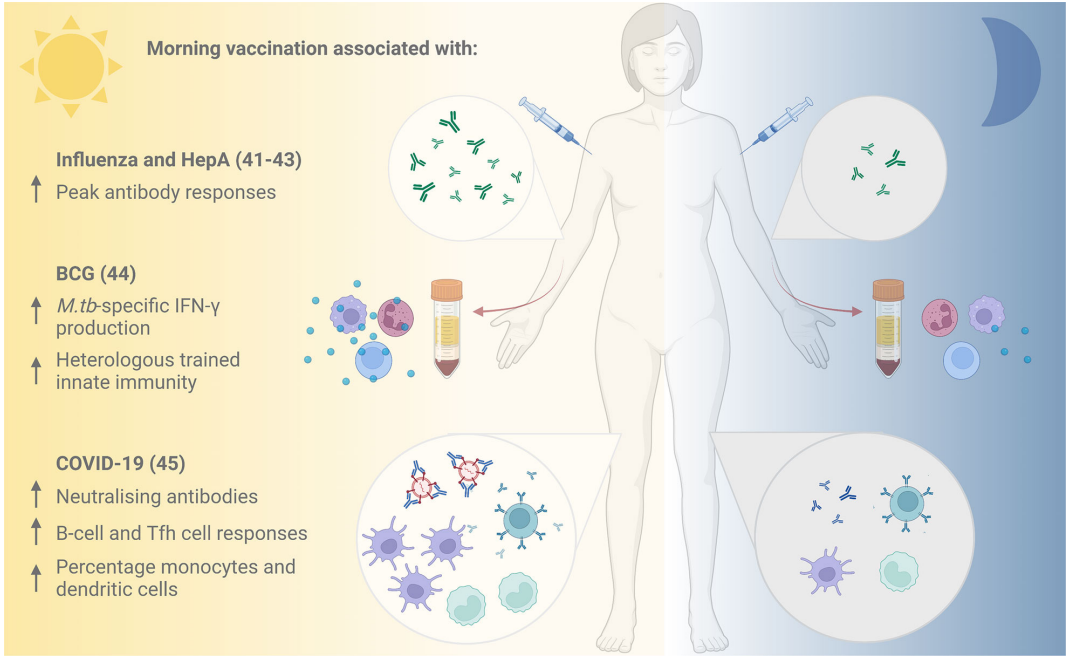
La réponse vaccinale est multi-factorielle
Elle dépend bien sur de la qualité du vaccin mais pas uniquement

La Chronovaccination pour adapter les stratégies de vaccination au rythme circadien



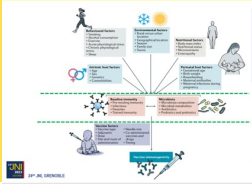


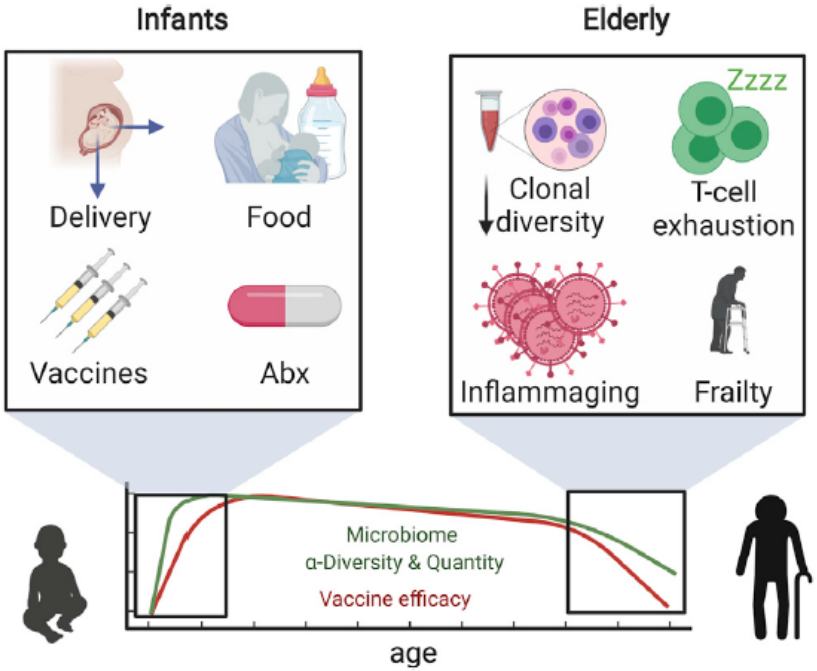
Barnoud et al., Cell Research 2021



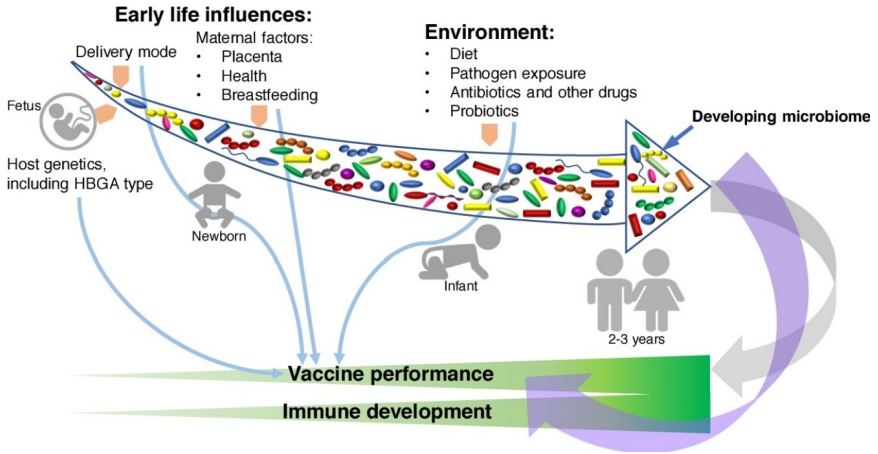
Otasowie et al., Frontier Immunol 2022

Impact du microbiote sur l'efficacité vaccinale?





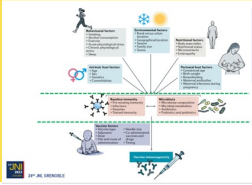
La faible diversité du microbiote des enfants et des personnes âgées corrèle avec un status immunologique altéré et une réponse vaccinale suboptimale

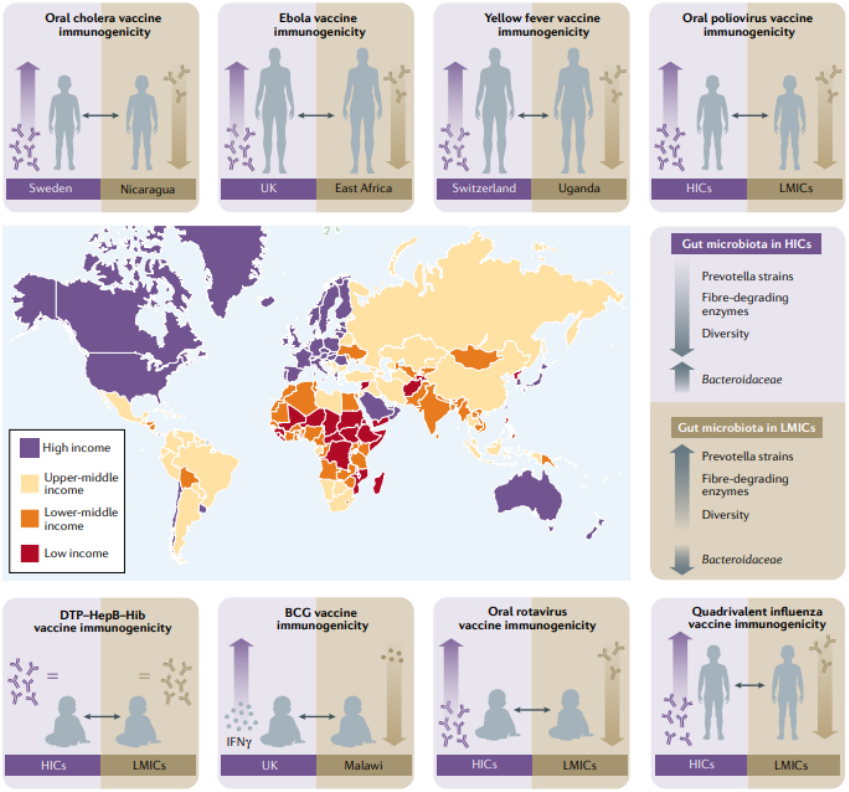


Unique Environmental Factors and Biological Changes in the Very Young and the Very Old that Can Be Detrimental to Vaccine Efficacy

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 role prédictif du microbiote dans les réponses vaccinales

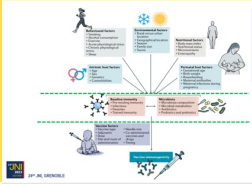




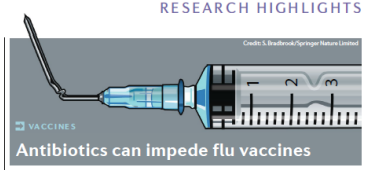
Model	Vaccine	Host	Study Outcomes	Reference
Animal Studies	TIV, OPV	Mice	TLR5-mediated sensing of flagellin from gut microbiota had an adjuvant effect on TIV and OPV. No effect with adjuvanted vaccines or live-attenuated yellow fever vaccine.	(Oh et al., 2014)
	CT	Mice	The mucosal adjuvant activity of 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 *Clostridium* 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.	(Praharaj et al., 2019)
	BCG, TT, HBV, OPV	Bangladeshi infants	High abundance of stool Actinobacteria, including *Bifidobacterium*, 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)
Causation studies in humans	OPV	Indian infants	Antibiotics did not improve the immunogenicity of OPV, despite the reduction of biomarkers of enteropathy 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 toxoid; BCG, Bacillus Calmette-Guérin; MenB, Bexsero meningococcal serogroup B vaccine; MenC, NeisVac-C meningococcal serogroup C vaccine; PCV13, the Prevenar 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 péjoratif des antibiotiques sur la réponse vaccinale



RESEARCH HIGHLIGHTS



VACCINES

Antibiotics can impede flu vaccines

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 Bali Pulendran 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, Hagan et al. vaccinated antibiotic-treated 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 over-abundance of Enterobacteriaceae and reduced proportions of Lachnospiraceae, Ruminococcaceae, Bacteroidaceae and Veillonellaceae. This restric-tion in bacterial diversity was apparent for at least 6 months after cessation of antibiotics administration.

In this initial study, the authors did not see 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) following TIV vaccination. Specifically, the antibiotic-treated subjects showed markedly impaired 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, similarly 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 microbiote. As the gut microbiota plays an important role in dietary metabolism, the authors examined changes in the blood metabolomes of the different groups. They found that antibiotic treatment was associated with metabolite 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.

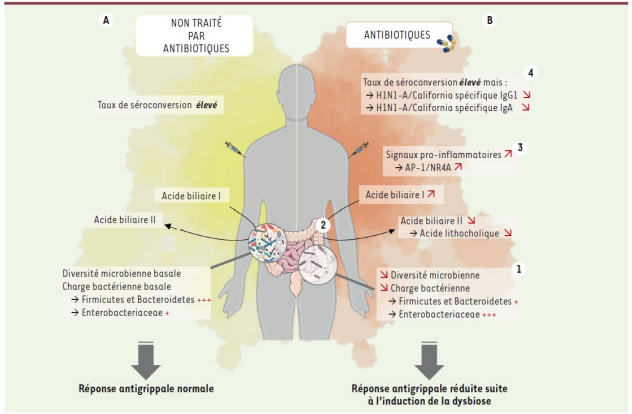
Analyses by the authors suggested an inverse correlation between the levels of individual secondary bile acids and expression of various inflammatory modules. In particular, the second-ary bile acid lithocholic acid (LCA) showed a 1,000-fold reduction in the plasma of antibiotic-treated subjects and downregulation of LCA was associated with increased expression of inflam-masome 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.

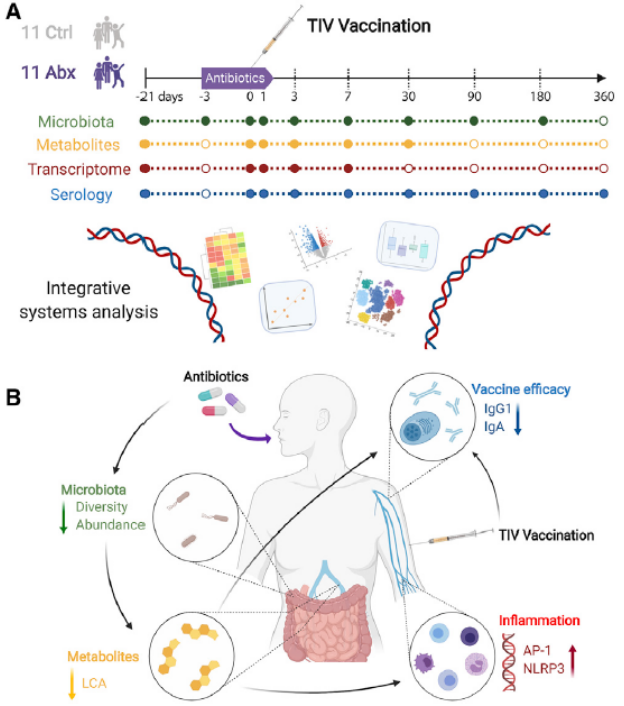
Virtually all humans have been previously exposed to influenza virus and this study indicates that, where pre-existing immunity exists, the immune system can maintain appropriate responses to pathogens despite significant metabolic disturbances arising from transient dysbiosis. However, in situations 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.

Yvonne Bordon

ORIGINAL ARTICLE Hagan, T. et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. Cell 178, 1313–1328 (2019)

NATURE REVIEWS | IMMUNOLOGY VOLUME 19 | NOVEMBER 2019 | 683



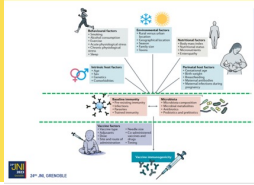


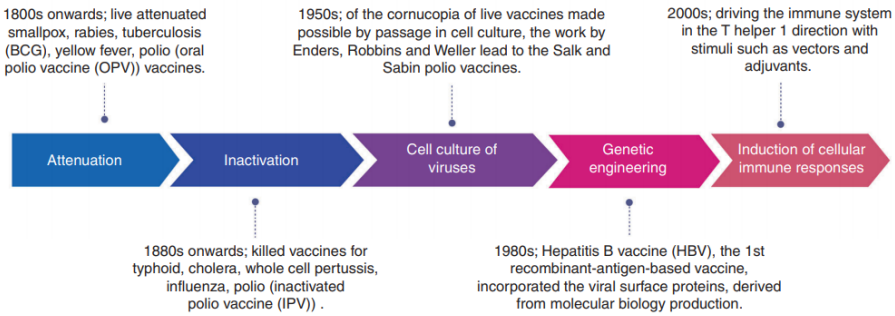
Antibiotics Impair the Vaccine Response in Healthy Adults

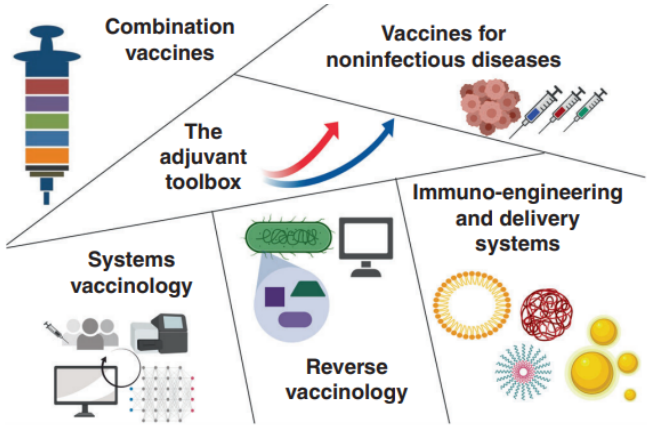
*11 subjects were treated with antibiotics for 5 days and vaccinated with the trivalent influenza vaccine on d4

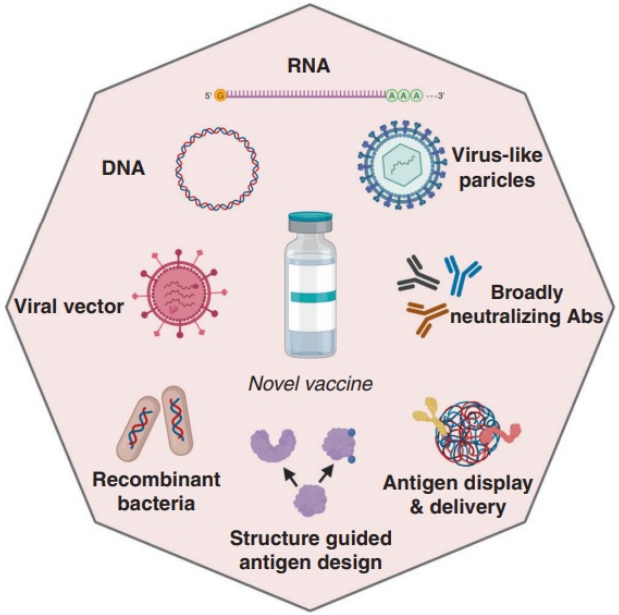
*Administration of antibiotics led to reduced microbial diversity and abundance and a consequential reduction in secondary bile acids. This in turn led to increased inflammation and a diminished vaccine response.

La sixième révolution des vaccins est en cours









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.

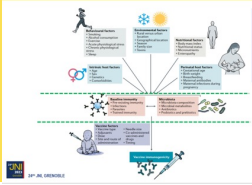
Table 3. New Strategies for Attenuated Vaccine Discovery

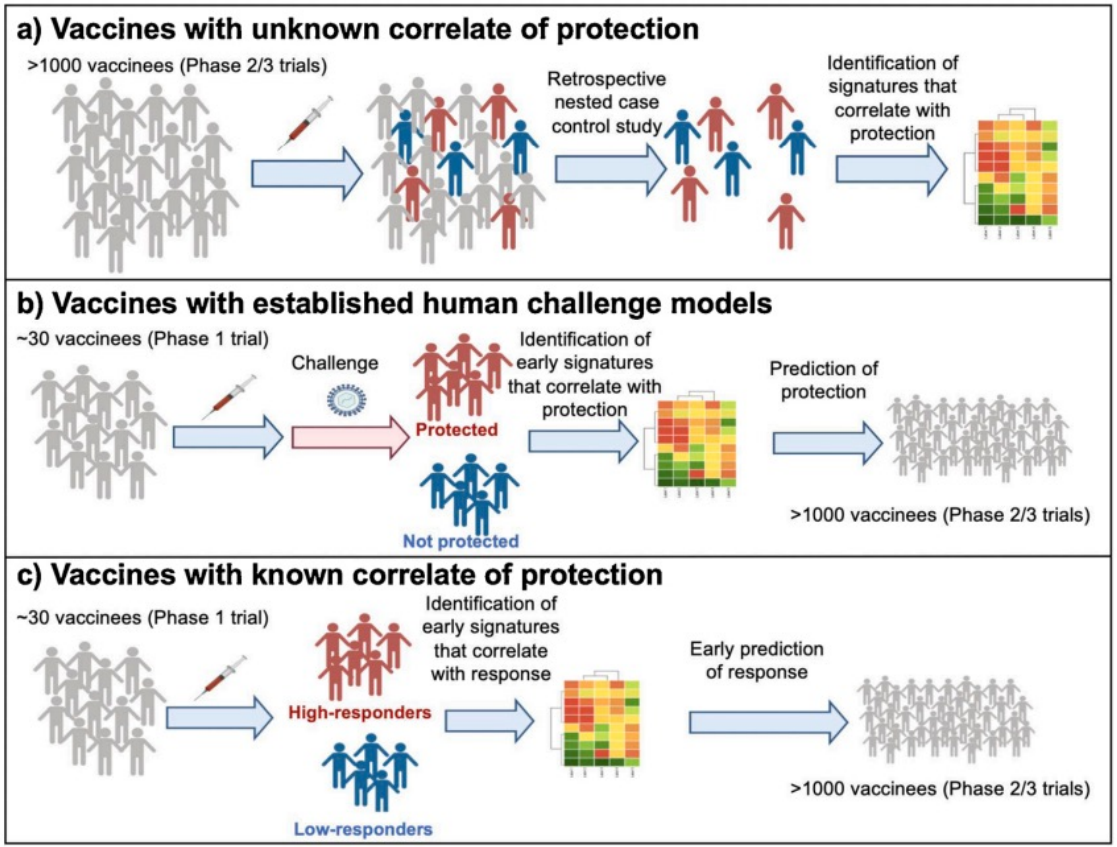
Strategy
Temperature-sensitive mutations and reassortment
Viral recombinants and deletion mutants
Codon de-optimization
Vectors that present genes from pathogens

Plotkin S, CID 2023

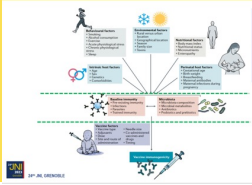
System vaccinology
Reverse vaccinology
Structural vaccinology

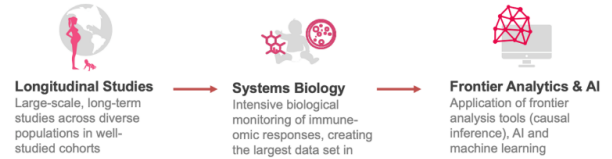
La system vaccinology devrait permettre d'accélérer le développement des vaccins de sixième génération

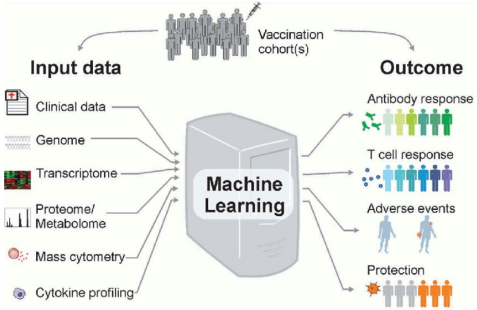


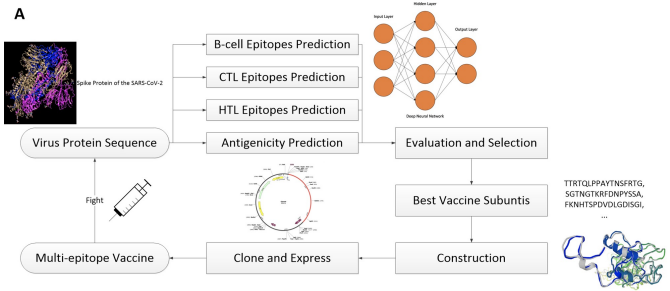


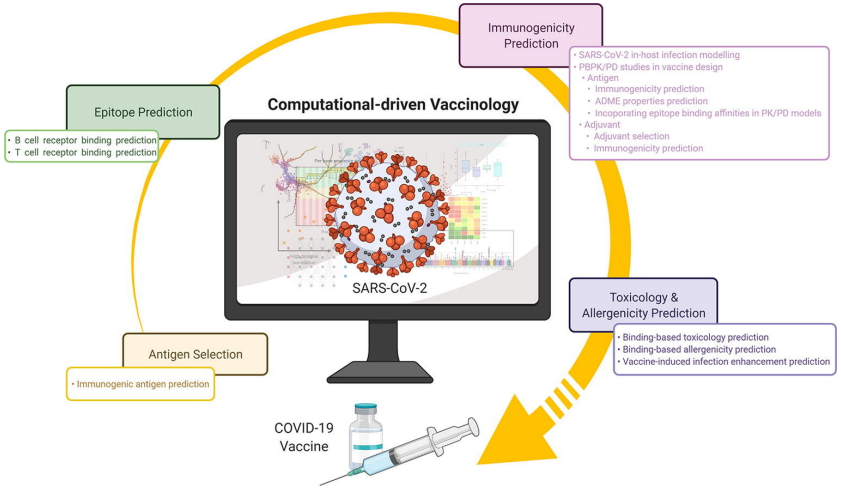
La system vaccinology devrait permettre d'accélérer le développement des vaccins de sixième génération



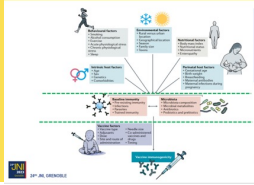


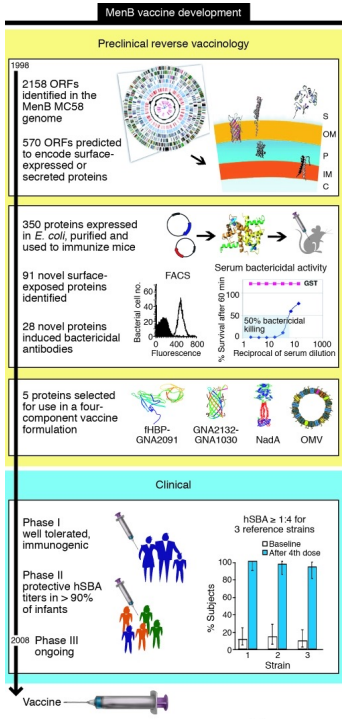


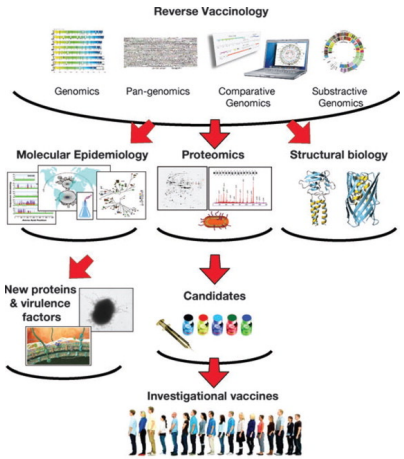




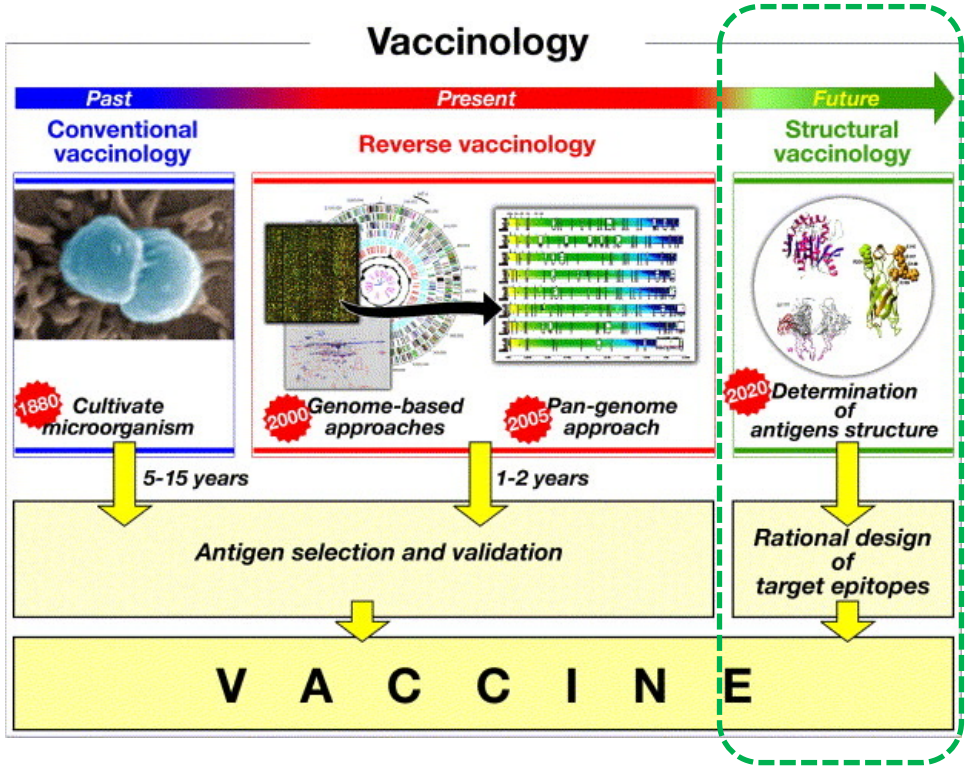
Vers le développement de la vaccinologie structurale



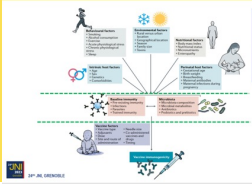


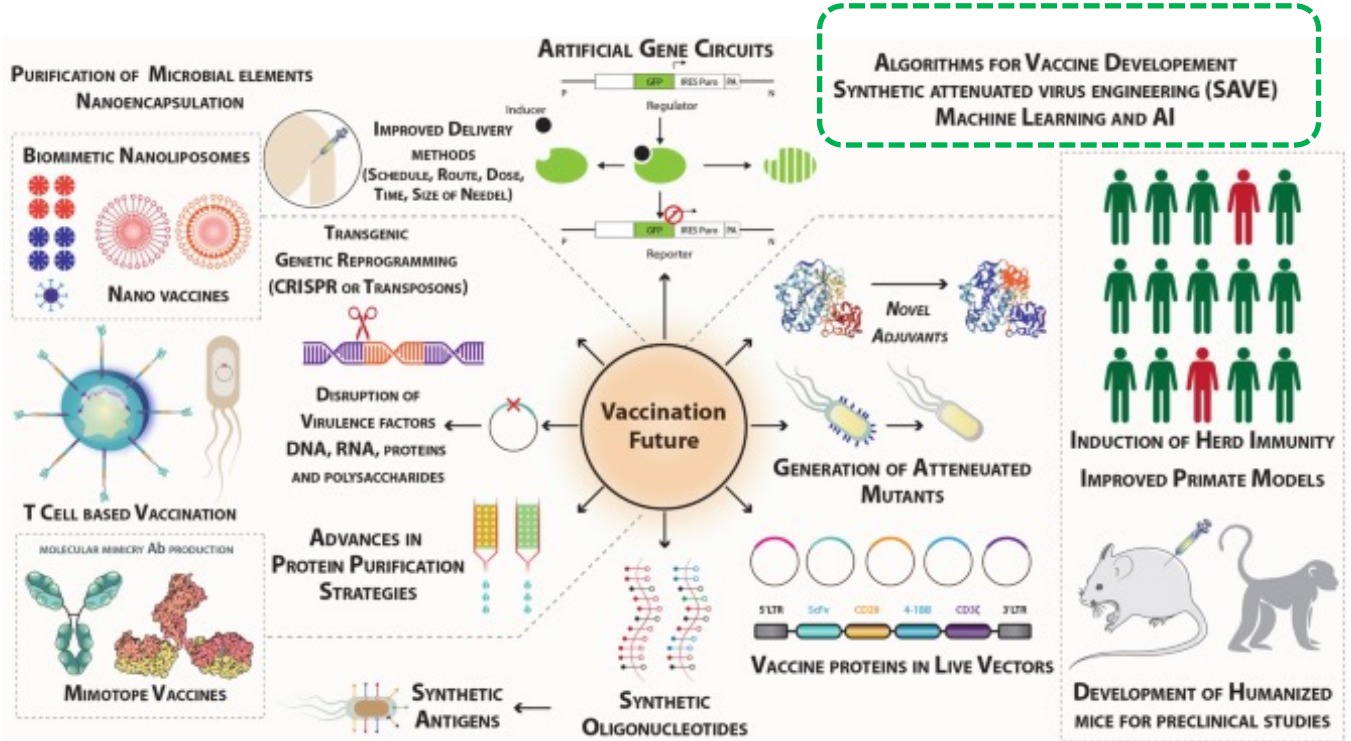


Très lourd et ne fonctionne pas toujours



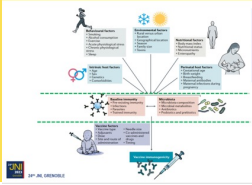
Développement d'outils pour la vaccination structurale

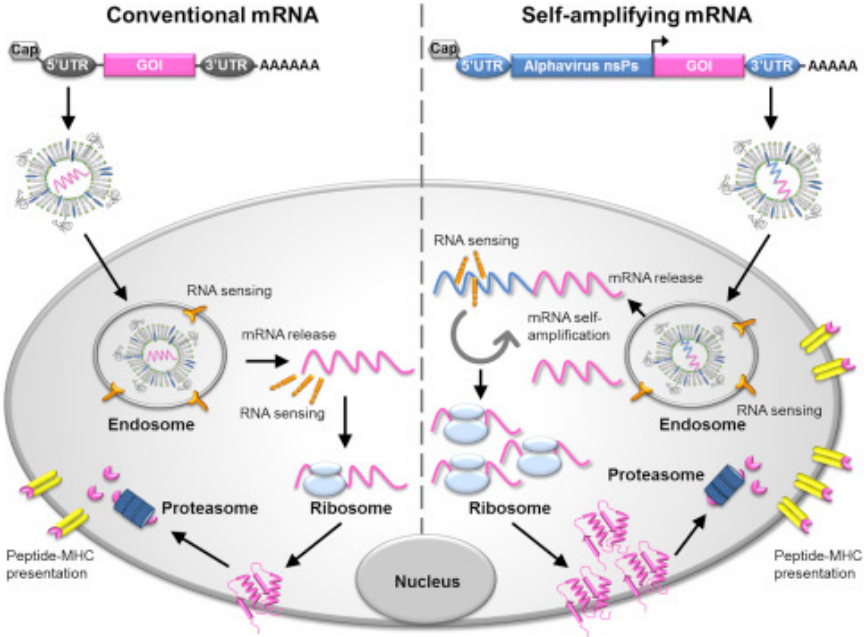


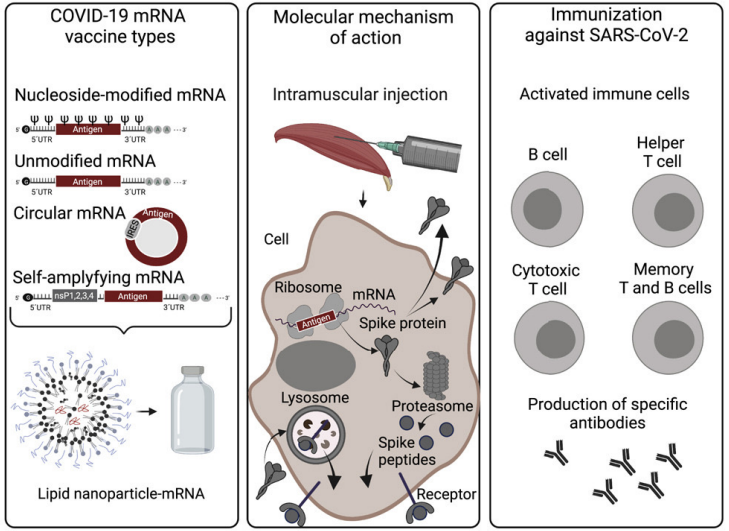


BIOCLUSTER

La révolution des vaccins ARNm

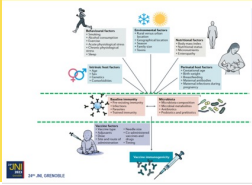




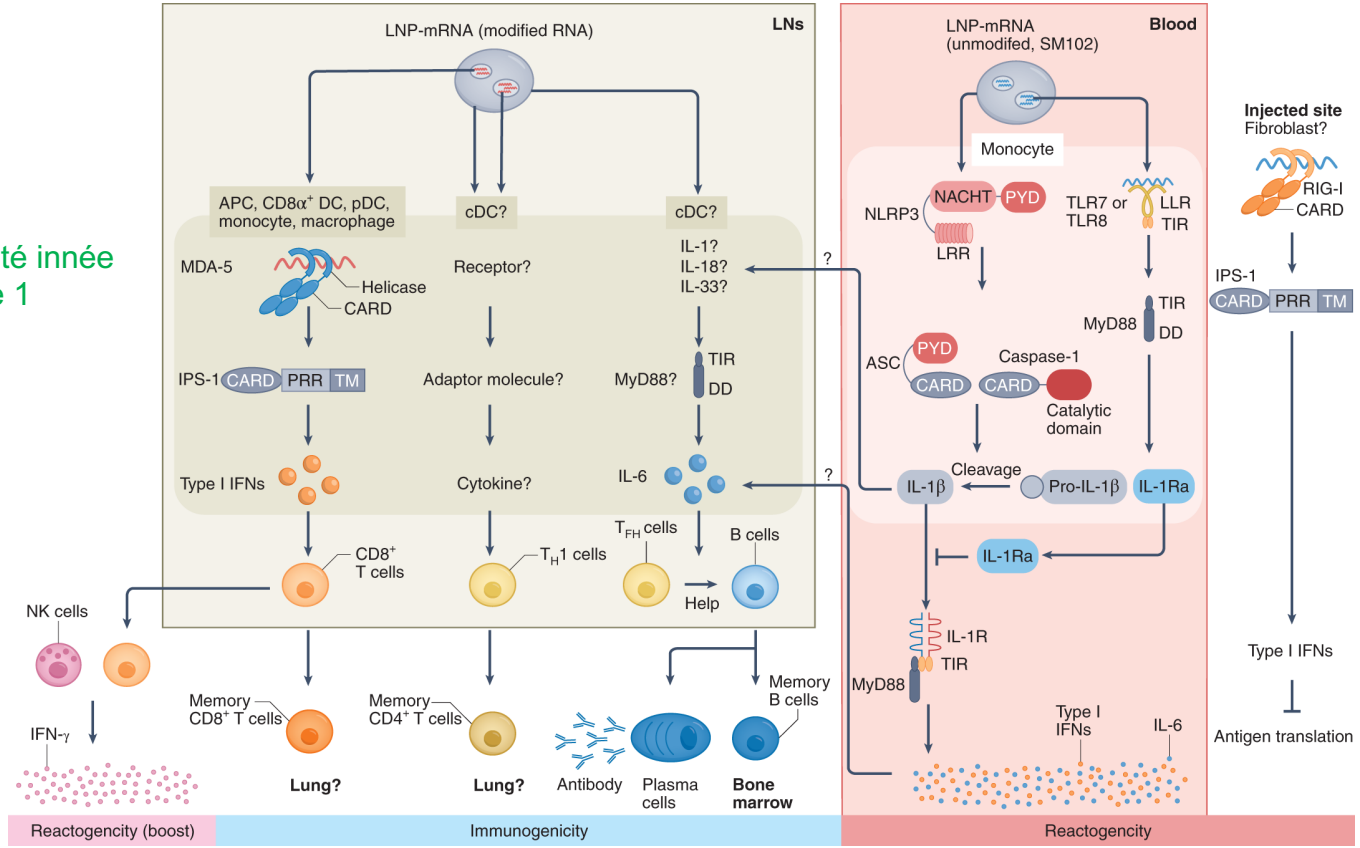


Conventionnel ou auto-réplicatif? Antigénicité? Réactogénicité?

Mecanismes d'immunogénicité/réactogénicité des vaccins LNP mRNA

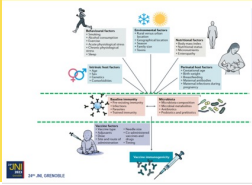


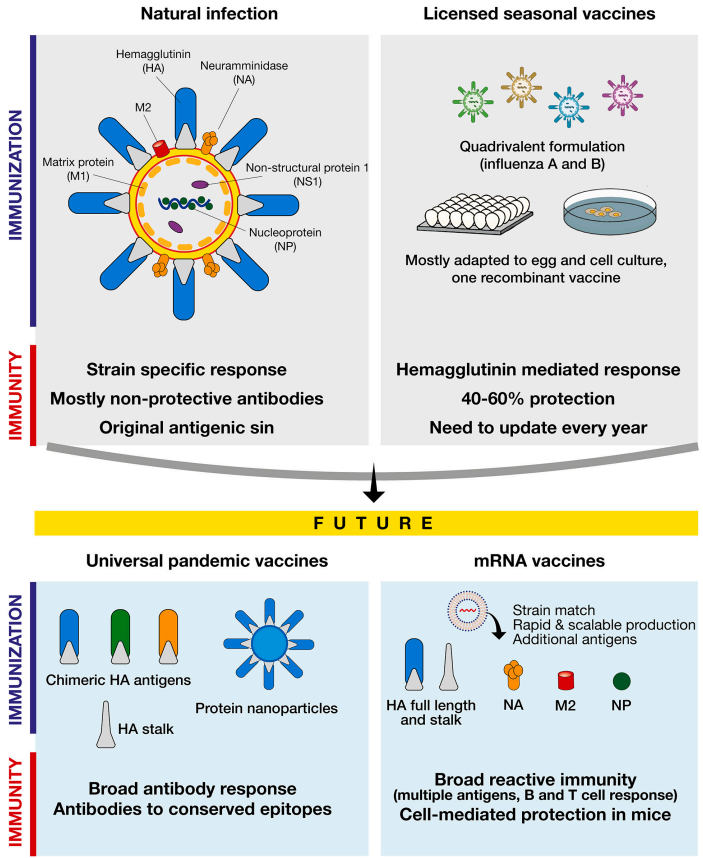
Forte induction de l'immunité innée
Réponse IFN de type 1



Kobiyama et al., Nature Immunol. 2022

Les vaccins ARNm un vrai « game changer »?



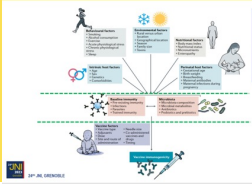


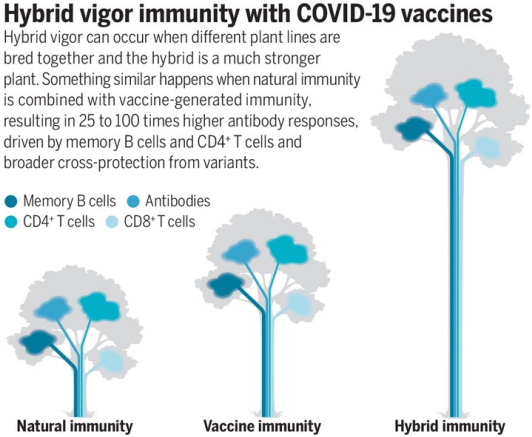
Dans PNAS, McMahon rapporte un nouveau vaccin quadrivalent mRNA modifié HA, NA, NP, M2 efficace chez la souris

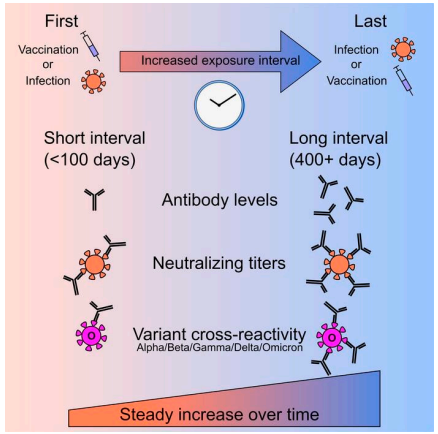
Pas pour tout….
Qualité confoirmationnelle des antigènes?
Réponse mémoire courte?
Induction mucosale?

Pecetta et al., PNAS. 2022

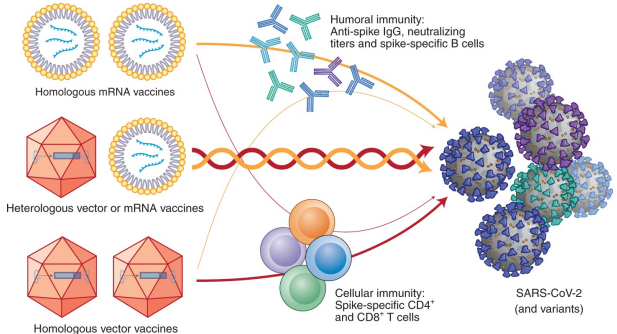
Attrait de l'immunité hybride ou des stratégies de prime-boost hétérologue







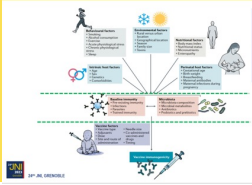
Heterologous mieux que Homogeneous
Infection + vaccin mieux que vaccin + infection
Espacement des doses
Meilleure mémoire immunitaire
Meilleure immunité mucosale

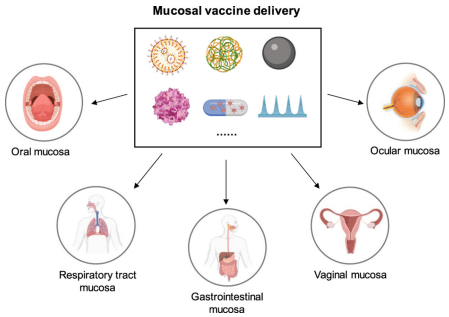


	Level of immune protection against variants				
	Non-Omicron		Omicron		
	Ancestral	Delta	BA.1	BA2.12.1	BA.4, BA.5
a	High	High	Low	Low	Low
b	Medium	Medium	Low	Low	Low
c	High	High	High	Low	Low
d	High	High	High	Not known	Not known
e	High	High	Low	Low	Low

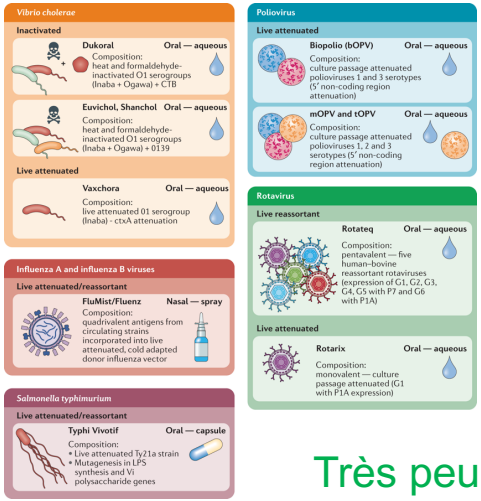
Ancestral or Alpha infection
Delta infection
Omicron infection
Vaccination

Développement de la vaccination mucosale

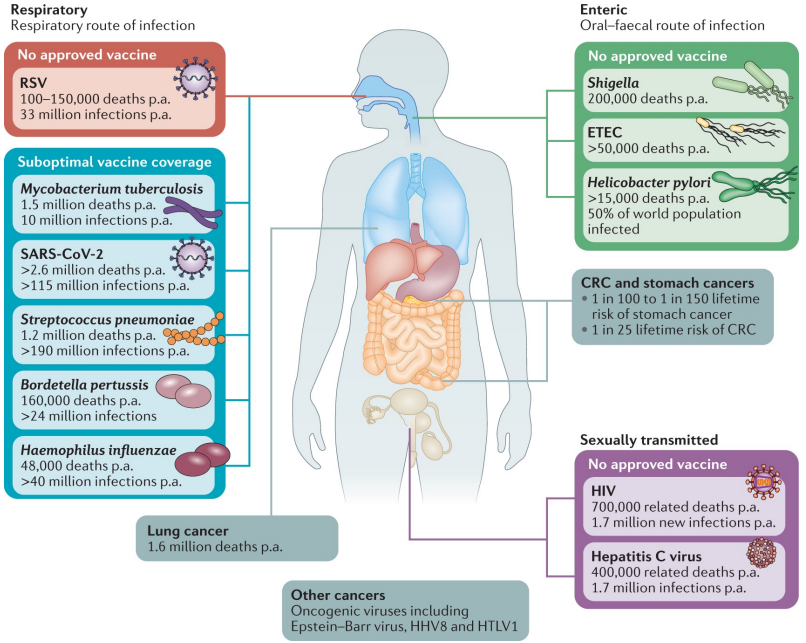




Différentes voies
Safety?

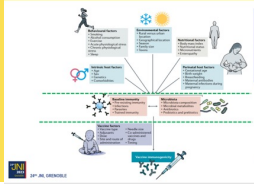


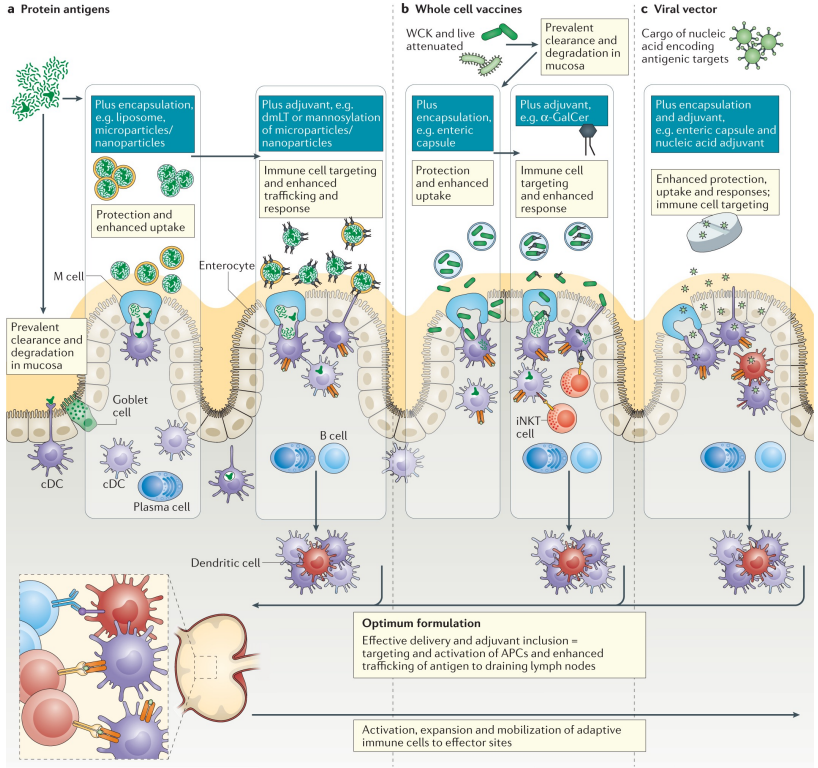
Très peu d'AMM



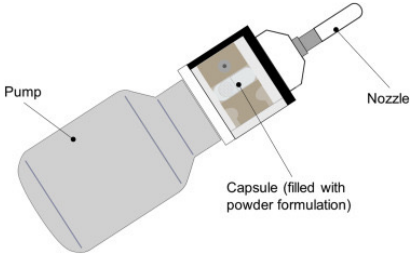
La grande majorité des pathogènes traversent efficacement les muqueuses

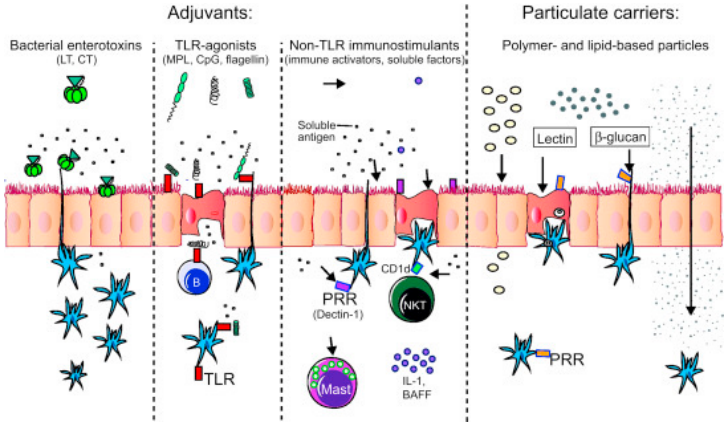
Développement de la vaccination mucosale





LoValTech, Tours, France

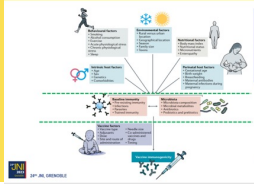


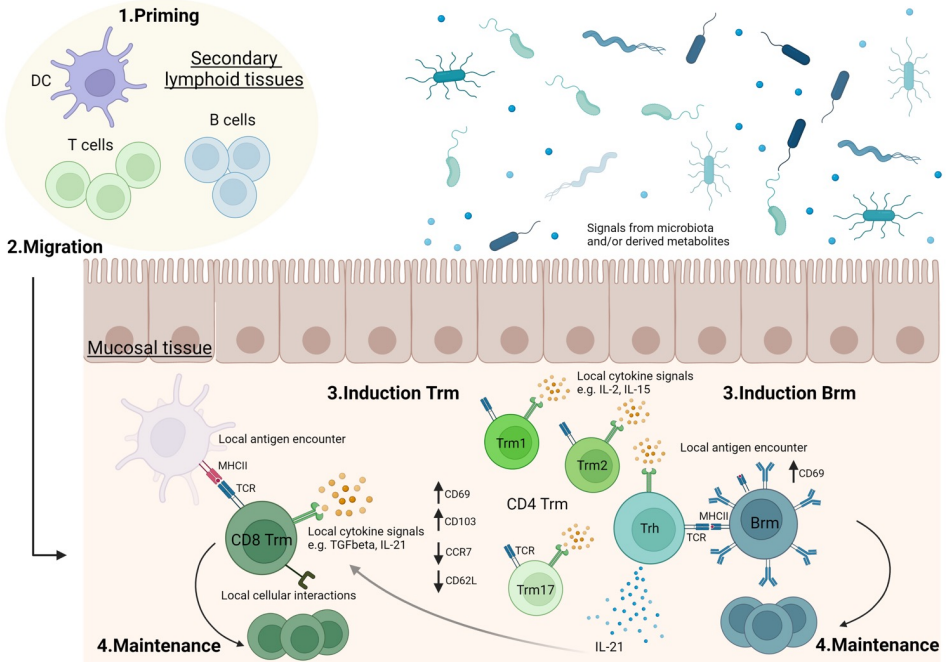


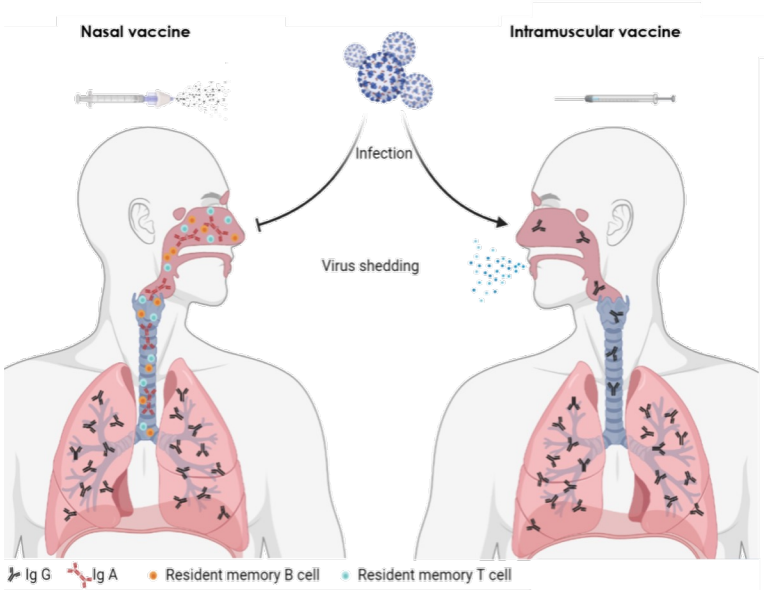
Besoin de « devices » efficaces

Besoin de meilleurs adjuvants

Cibler les cellules résidentes mémoires au niveau des muqueuses



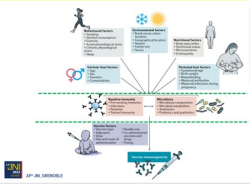


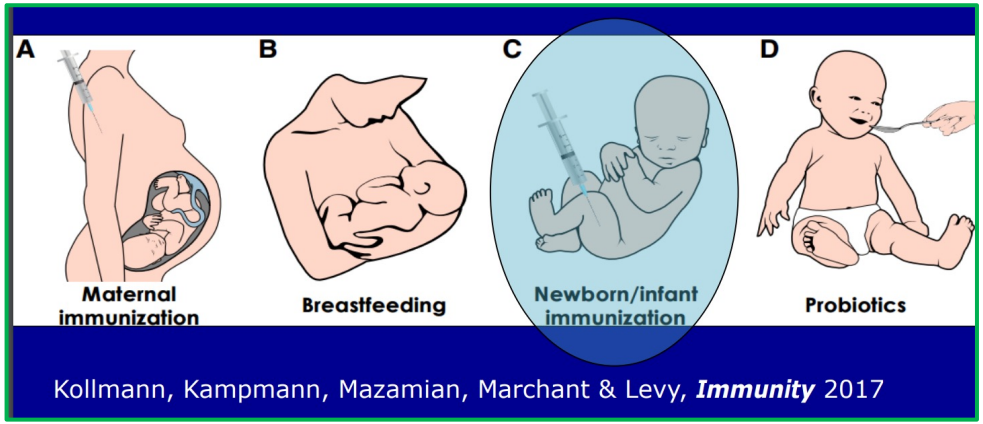


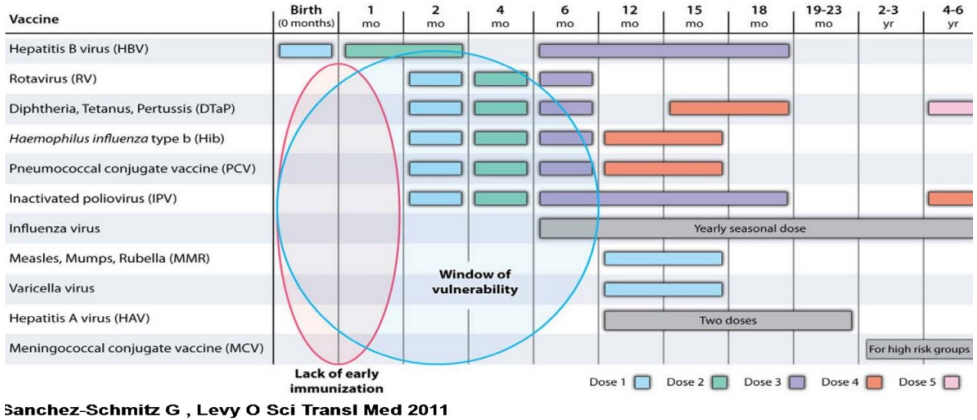
LoValTech

Adjuvants
Vaccins vivants
Voie muqueuse

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

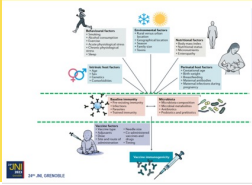






Sanchez-Schmitz G , Levy O Sci Transl Med 2011

Intérêt de l'immunisation maternelle



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Maternal Immunization

Saad B. Omer, M.B., B.S., M.P.H., Ph.D.

N ENGL J MED 376;13 NEJM.ORG MARCH 30, 2017

Comment

Group B streptococcal maternal vaccination, the goal is near

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

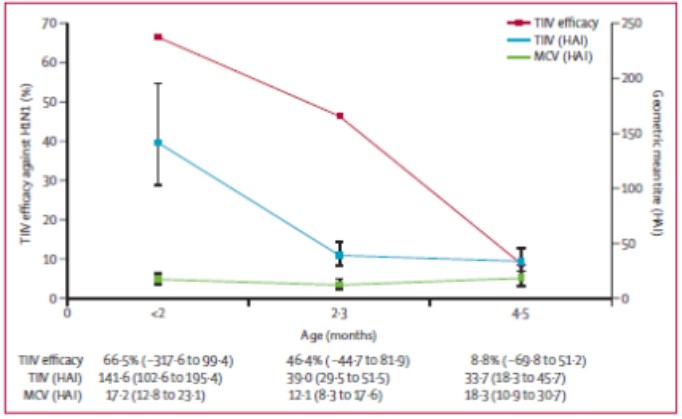
Shabir A Madhi, Clare L Cutland, Lisa Jose, Anthonet Koen, Nineska Govender, Frederick Wittke*, Maroanfolo Olugbosi, Ajoke Sobanjo-ter Meulen*, Sherryl Baker, Peter M Dull*, Vas Narasimhan*, Karen Slobod*

Streptocoque B

Vaccin polyosidique conjuguésérotypes Ia, Ib, et III

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, Boubou Tamboura, Ibrahima Téguété, Marcela F Pasetti, Mamoudou Kodio, Uma Onwuchekwa, Sharon M Tennant, William C Blackwelder, Flanon Coulibaly, Awa Traoré, Adama Mamby Keita, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine



	<2	2-3	4-5
TIV efficacy	66·5% (−317·6 to 99·4)	46·4% (−44·7 to 81·9)	8·8% (−69·8 to 51·2)
TIV (HAI)	141·6 (102·6 to 195·4)	39·0 (29·5 to 51·5)	33·7 (18·3 to 45·7)
MCV (HAI)	17·2 (12·8 to 23·1)	12·1 (8·3 to 17·6)	18·3 (10·9 to 30·7)

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.

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

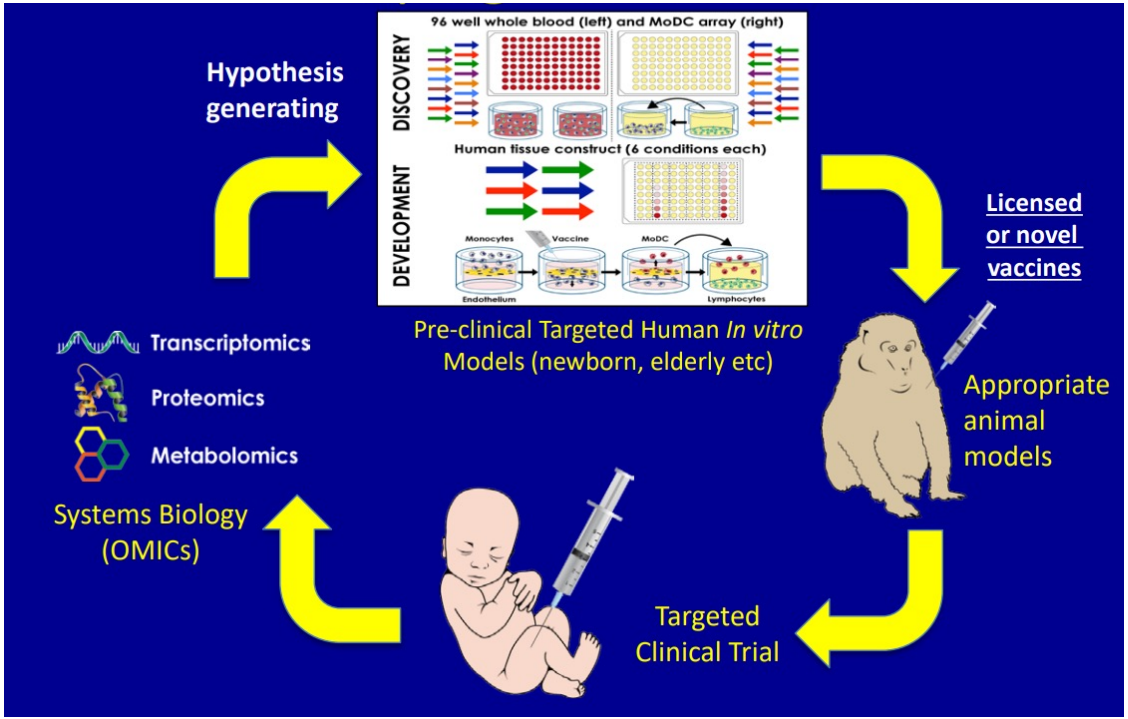
MAJOR ARTICLE

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. Glenn,[1] Louis F. Fries,[1] D. Nigel Thomas,[1] Gale Smith,[1] Etai Kpamegan,[1] Hanxin Lu,[1] David Flyer,[1] Dawud Jani,[1] Sonia P. Hickman,[1] and Pedro A. Prado[1]

[1]Novavax, Inc, Gaithersburg, Maryland; and [2]Department of Molecular Virology and Microbiology, and Pediatrics, Baylor College of Medicine, Houston, Texas

Développement d'outils pour la vaccination de précision

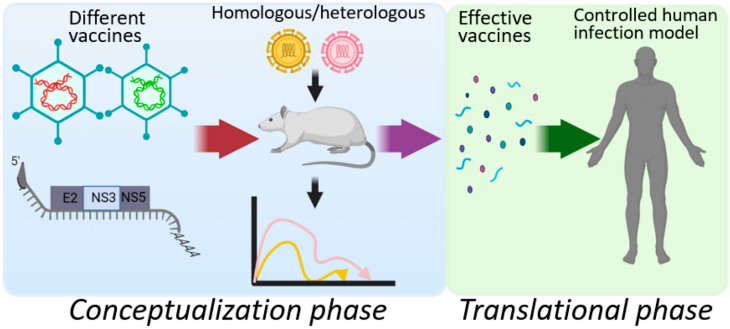


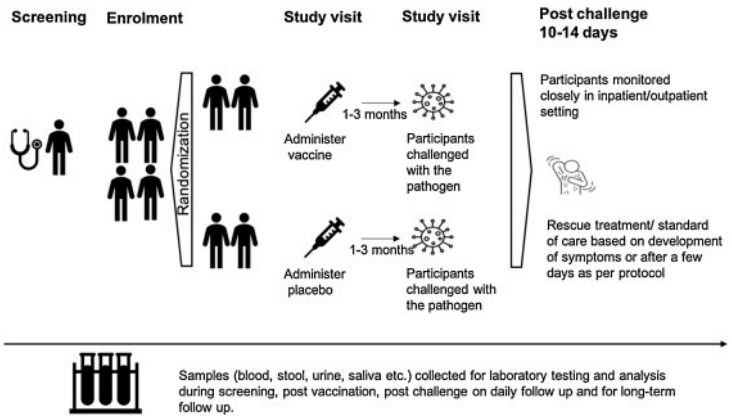
*Modèles *in vitro* / *ex vivo* adaptés

*Modèles *in vivo* adaptés

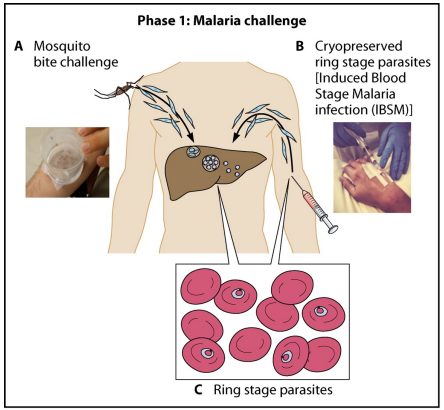
*Challenges?

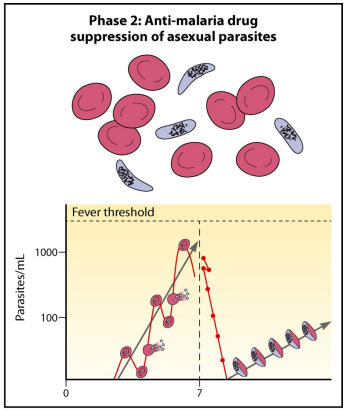
Le Challenge Humain pour accélérer le développement des vaccins?

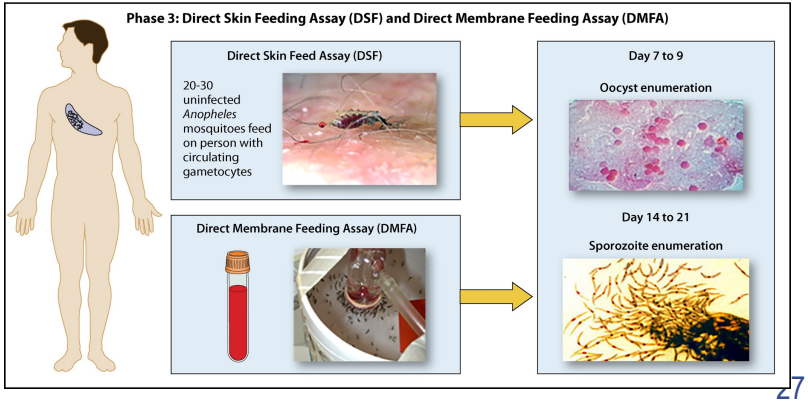




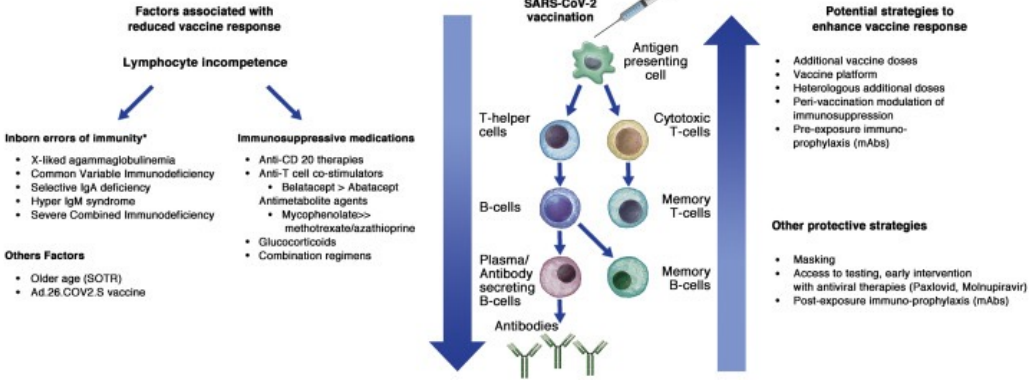
Challenge malaria

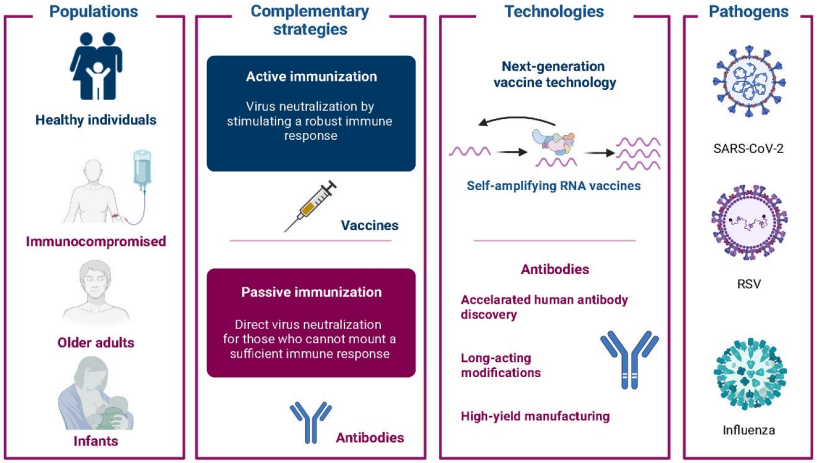






Améliorer l'efficacité vaccinale dans les populations à risques, oui mais comment?





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

Bloquer l'inflammation
FMT
Sérothérapie
Planifier la vaccination

Futur de la Vaccination?

*Epidemiologie 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)

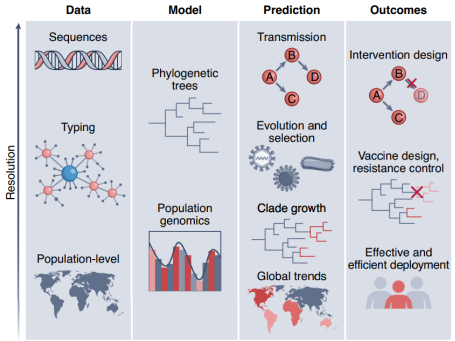
*Nouvelle stratégies pour induire une meilleure mémoire

*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.

[a]Analysis of humoral and cellular immune responses.