Université Paris Cité

Vaccins en phase 3

Odile Launay

Journée du groupe vaccination prévention de la Spilf
Paris, 12 mai 2023

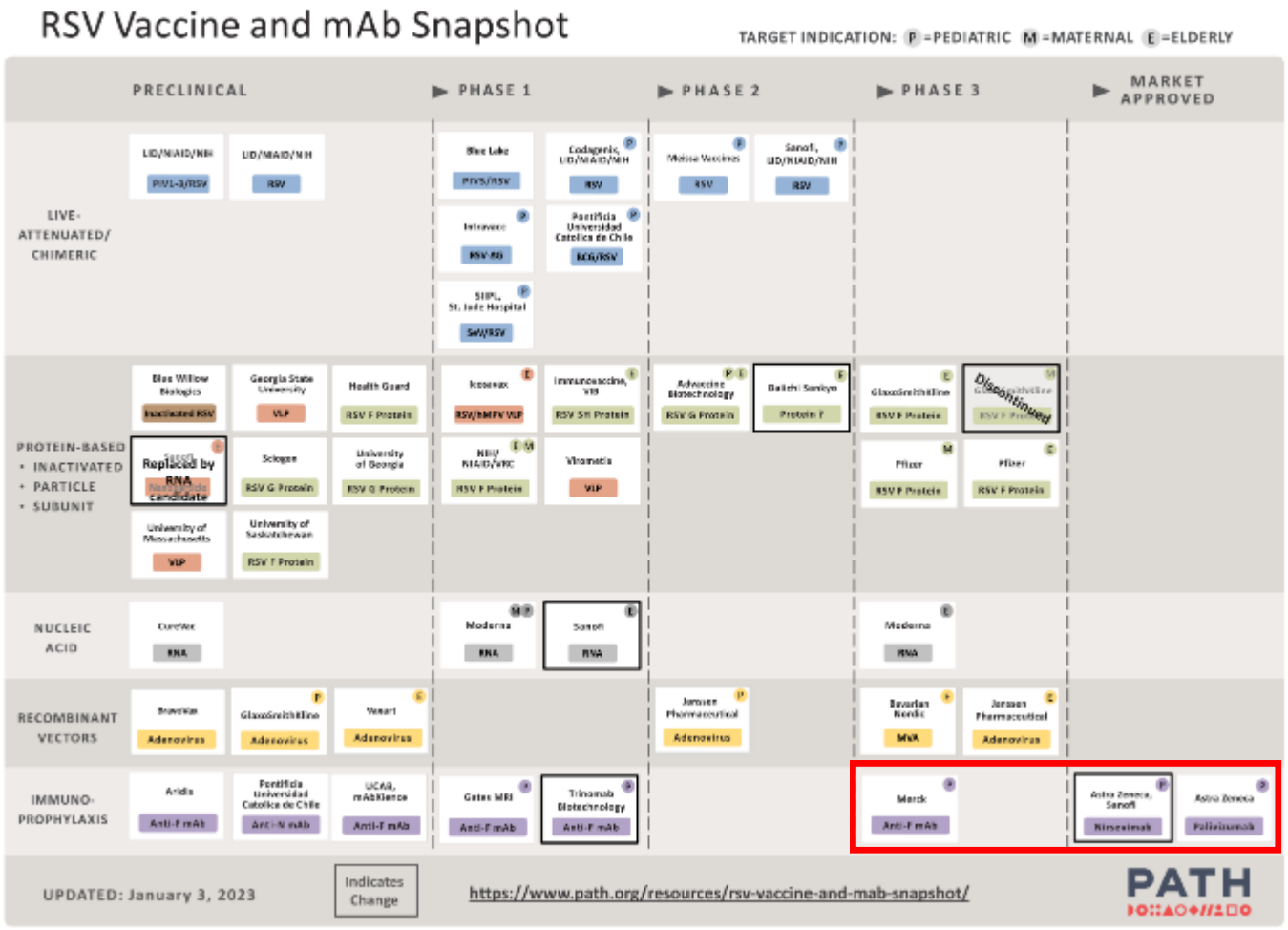
Déclaration d’intérêts : 2019-2023

- Intérêts financiers : aucun
- Liens durables ou permanents : aucun
- Intervention ponctuelles :
  - Recherches/essais cliniques : MSD, GSK bio, Sanofi Pasteur, Janssen, Pfizer, AstraZénéca, Moderna
  - Aides pour des recherches : MSD, GSK bio, Sanofi Pasteur, Janssen, Pfizer
  - Advisory Boards/DSMB : Sanofi Pasteur, Janssen, Pfizer
  - Cours, formations : Pfizer, MSD, Sanofi Pasteur, AstraZénéca
- Intérêts indirects : aucun

Plan

- Vaccins VRS et grippe
- Vaccins pneumo
- Vaccins CMV
- Vaccins Dengue
- Autres

VRS



Palivizumab (Synagis)

AMM 2004, indications restreintes

Nirsevimab (Beyfortus)

AMM 31/10/2022

prévention des infections des voies respiratoires inférieures causées par le VRS chez le nouveau-né et le nourrisson, pendant la première saison de circulation du virus à laquelle ils sont confrontés

Nirsevimab : 2 essais randomisés

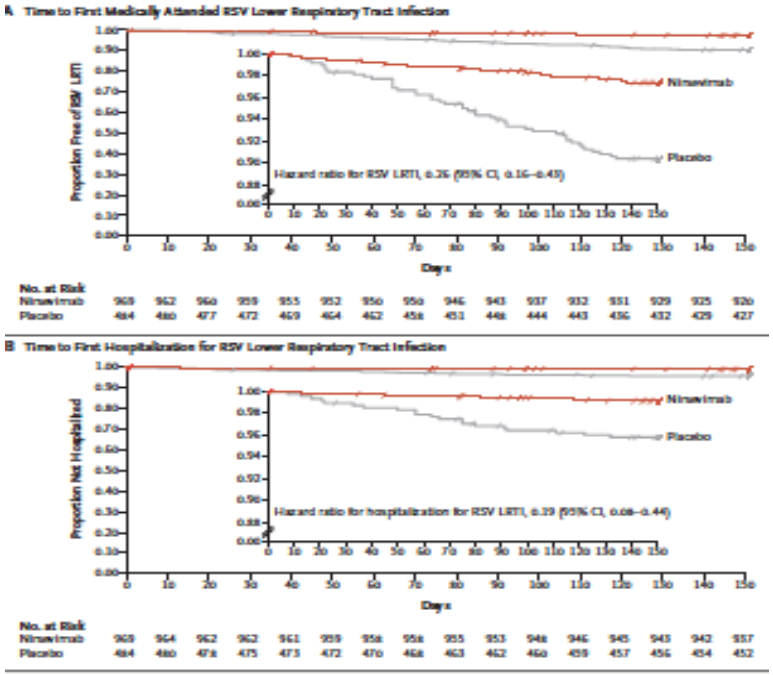
The NEW ENGLAND JOURNAL of MEDICINE

JULY 30, 2020

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Theresa Takas, B.S., Joseph B. Domachowske, M.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simões, M.D., Mark T. Esser, Ph.D., Ann A. Shen, Ph.D., Filip Dubovsky, M.D., Tonya Villafana, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group*

- Nirsevimab (SP/AZ)
- IgG1 kappa monoclonale, dirigée contre un épitope conservé présent sur la protéine de fusion du VRS
- ½ vie prolongée permettant une injection couvrant la période de circulation du VRS (5 mois)
- **Nourrissons nés prématurés (29-35 SA)**
- Randomisation 2:1 vs placebo (969:484)
- Efficacité:
  - réduction de 70% des infections respiratoires basses (2,6% vs 9,5%)
  - 78% des infections respiratoires basses hospitalisées



Nirsevimab : 2 essais randomisés

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D.,

N Engl J Med 2022;386:837-46.
DOI: 10.1056/NEJMoa2110275

- **Nourrissons nés après 35 SA**
- Randomisation 2:1 vs placebo (994:496)
- Efficacité:
  - réduction de 74,5% des infections respiratoires basses (1;2% vs 5%)
  - Hospitalisations: 6 (0,6) dans le groupe nirsevimab vs 8 dans le groupe placebo (1,6%)

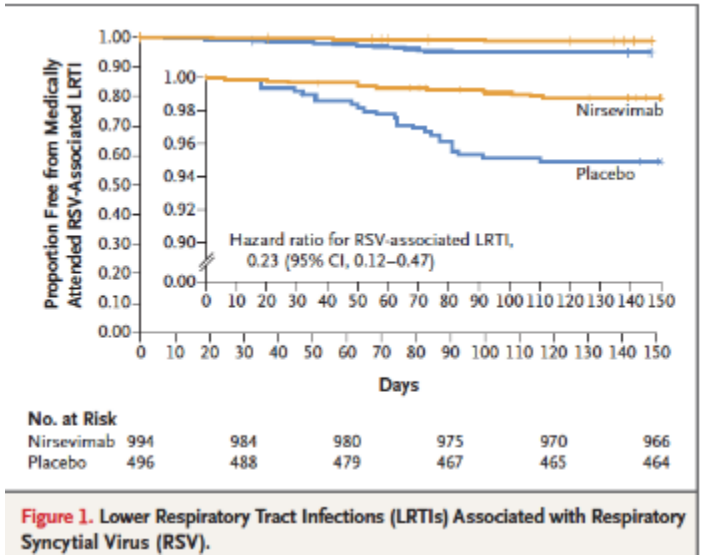


Figure 1. Lower Respiratory Tract Infections (LRTIs) Associated with Respiratory Syncytial Virus (RSV).

Nirsevimab

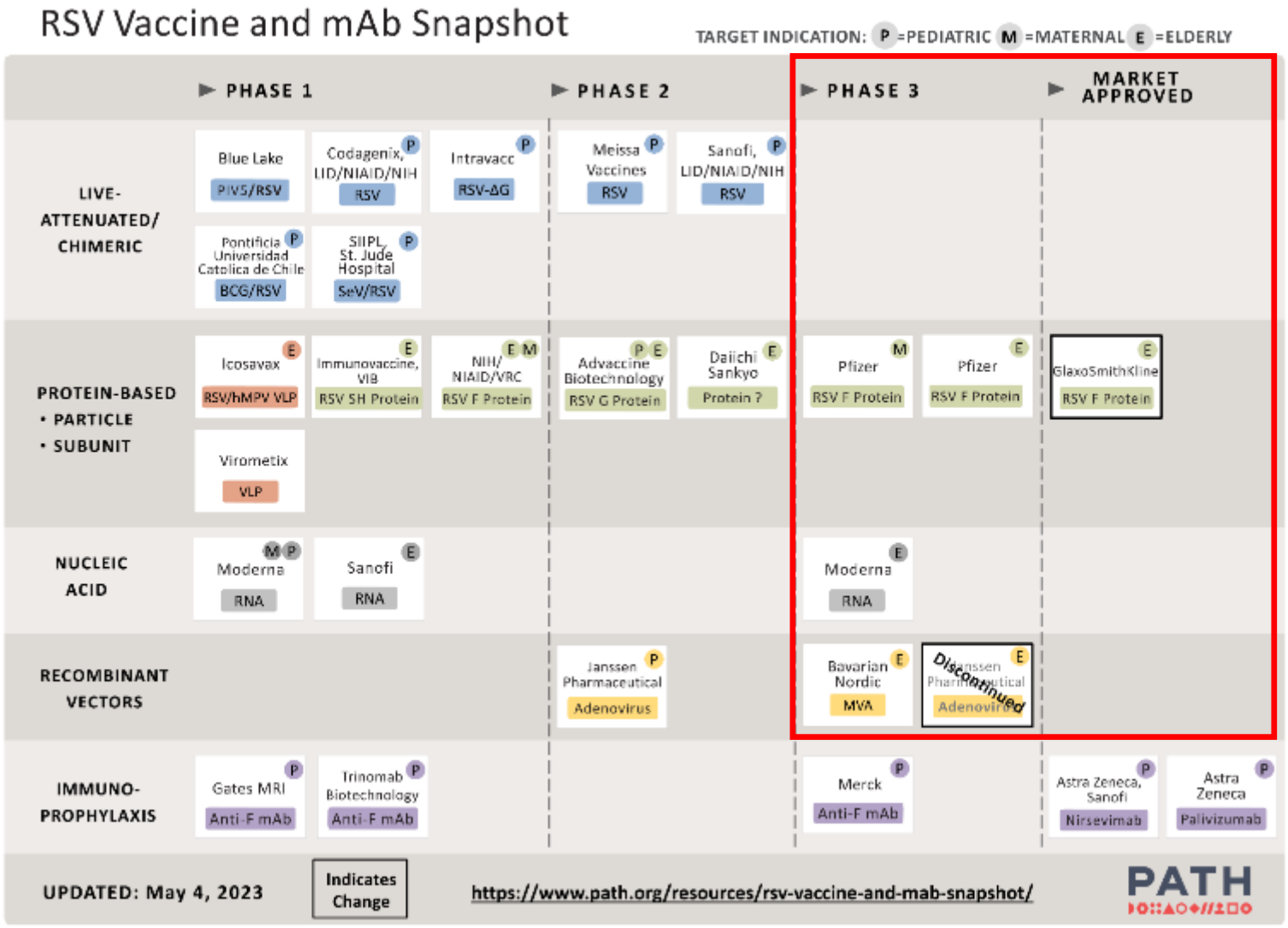
16/09/2022

Le CHMP recommande l'approbation de Beyfortus® (nirsevimab) pour la prévention des infections par le VRS chez le nourrisson

Beyfortus should be given before the RSV season (when there is a risk of RSV infection in the community) or as soon as possible after birth for infants born during the RSV season.

AMM 31 octobre 2022

Vaccin VRS


RSV Vaccine and mAb Snapshot
TARGET INDICATION: P =PEDIATRIC M =MATERNAL E =ELDERLY
PHASE 1
PHASE 2
PHASE 3
MARKET APPROVED
LIVE-ATTENUATED/ CHIMERIC
Blue Lake
PIV5/RSV
Codagenix, LID/NIAID/NIH
RSV
Intravacc
RSV-ΔG
Meissa Vaccines
RSV
Sanofi, LID/NIAID/NIH
RSV
Pontificia Universidad Catolica de Chile
BCG/RSV
SIIPL, St. Jude Hospital
SeV/RSV
PROTEIN-BASED • PARTICLE • SUBUNIT
Icosavax
RSV/hMPV VLP
Immunovaccine, VIB
RSV SH Protein
NIH/ NIAID/VRC
RSV F Protein
Advaccine Biotechnology
RSV G Protein
Daiichi Sankyo
Protein ?
Pfizer
RSV F Protein
Pfizer
RSV F Protein
GlaxoSmithKline
RSV F Protein
Virometix
VLP
NUCLEIC ACID
Moderna
RNA
Sanofi
RNA
Moderna
RNA
RECOMBINANT VECTORS
Janssen Pharmaceutical
Adenovirus
Bavarian Nordic
MVA
Janssen Pharmaceutical
Adenovirus
Discontinued
IMMUNO-PROPHYLAXIS
Gates MRI
Anti-F mAb
Trinomab Biotechnology
Anti-F mAb
Merck
Anti-F mAb
Astra Zeneca, Sanofi
Nirsevimab
Astra Zeneca
Palivizumab
UPDATED: May 4, 2023
Indicates Change
https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/
PATH

Vaccin VRS chez la femme enceinte

Pfizer Announces Positive Top-Line Data of Phase 3 Global Maternal Immunization Trial for its Bivalent Respiratory Syncytial Virus (RSV) Vaccine Candidate

Tuesday, November 01, 2022 - 06:30am

The observed efficacy for severe medically attended lower respiratory tract illness (severe MA-LRTI) was 81.8% (CI: 40.6%, 96.3%) through the first 90 days of life. Substantial efficacy of 69.4% (CI: 44.3%, 84.1%) was demonstrated for infants over the six-month follow-up period.

Vaccin VRS chez la femme enceinte

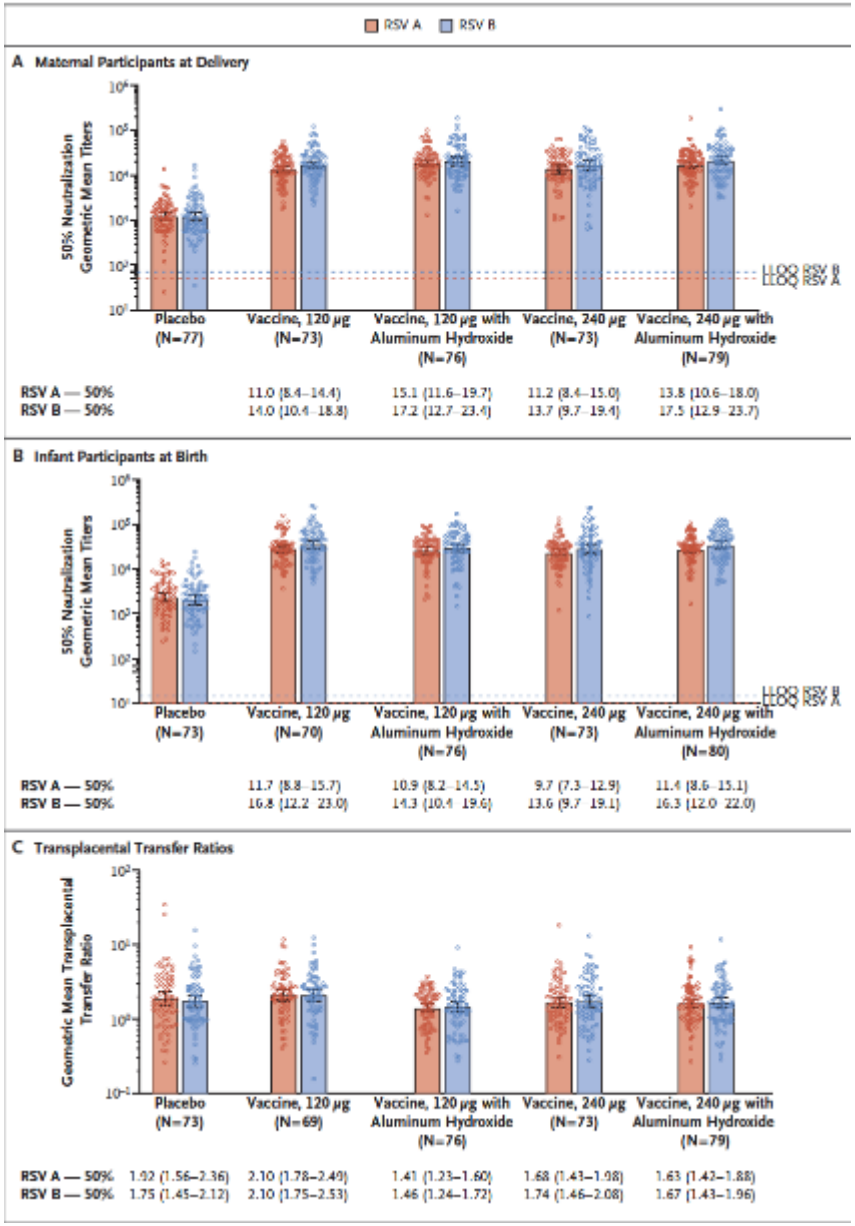
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

Eric A.F. Simões, M.D., Kimberly J. Center, M.D., Alan T.N. Tita, M.D., Ph.D.,

N ENGL J MED 386;17 NEJM.ORG APRIL 28, 2022



- Essai phase 2B
- Vaccin bivalent (RSV A et B) protéine F (forme préfusion) recombinante +/- Alum
- Vaccination entre24 -36 SA
- 1 dose de vaccin
- dose de 120 microgrammes sans alum pour la phase 3

(Maternal Immunization Study for Safety and Efficacy; ClinicalTrials.gov number, NCT04424316).

Vaccin VRS chez la femme enceinte

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

Eric A.F. Simões, M.D., Kimberly J. Center, M.D., Alan T.N. Tita, M.D., Ph.D.

N ENGL J MED 386;17 NEJM.ORG APRIL 28, 2022

Table 2. Efficacy of Maternal Vaccination against RSV-Associated Lower Respiratory Tract Illness in the U.S. Cohort of 508 Infants.

Efficacy End Point	RSVpreF Vaccine (N=405)	Placebo (N=103)	Estimated Vaccine Efficacy (95% CI)
	number of infants with event		*percent*
Any medically attended RSV-associated lower respiratory tract illness*	3	5	84.7 (21.6 to 97.6)
Medically attended severe RSV-associated lower respiratory tract illness†	1	3‡	91.5 (–5.6 to 99.8)

Phase 3 en cours

A Trial to Evaluate the Efficacy and Safety of RSVpreF in Infants Born to Women Vaccinated During Pregnancy.

(Maternal Immunization Study for Safety and Efficacy; ClinicalTrials.gov number, NCT04424316).

Vaccin VRS

- **Protéine recombinante** (Prefusion RSV F glycoprotéine) **Arexvy**
- Adjuvanté par **AS01**
- Essai de phase 3, randomisé, vs placebo,
- 25 000 participants de 60 ans et plus
- une dose de vaccin
- Analyse intermédiaire
- Autorisation EMA: 28/04/2023

PRESS RELEASE

GSK

For media and investors only

Issued: 10 June 2022, London UK – LSE Announcement

GSK announces positive pivotal phase III data for its respiratory syncytial virus (RSV) vaccine candidate for older adults

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel,

N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023

Vaccin VRS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel,

N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023

- efficacité vaccinale sur les IRA avec atteinte des VRI : **82,6 % (IC à 96,95 % :**

- efficacité vaccinale constante sur l'ens clinique de la mala

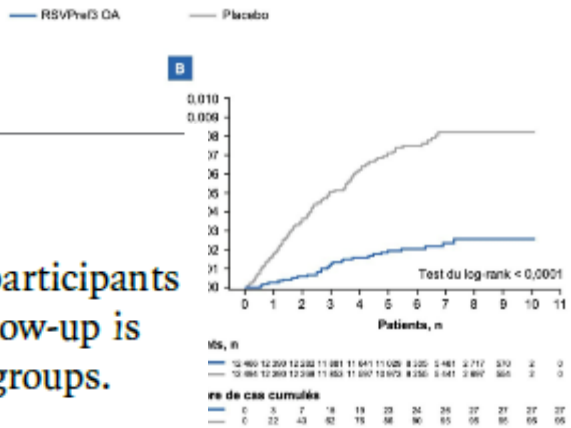
IRA : 71,7 % [IC 95 % :

formes sévères d'IRA

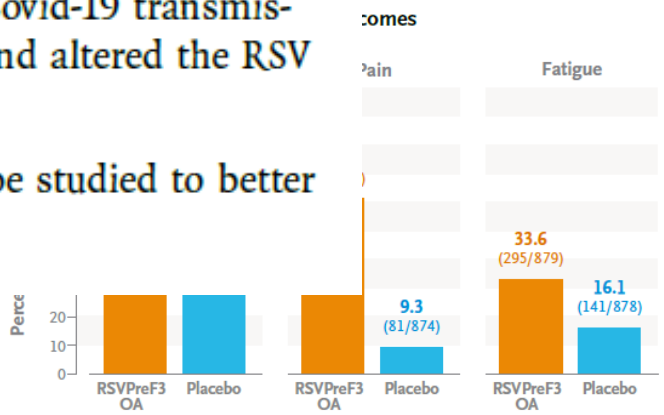
VRI :94,1 % [IC 95

LIMITATIONS AND REMAINING QUESTIONS

- A small number of frail participants and participants ≥80 years of age were included; longer follow-up is needed to determine efficacy in these subgroups.
- The trial had limited ability to detect rare side effects.
- Public health measures to limit Covid-19 transmission reduced the spread of RSV and altered the RSV season.
- Additional RSV seasons need to be studied to better understand vaccine efficacy.



à VRS avec atteinte des voies
A (B) - incidence cumulée



Vaccin VRS

moderna

NEWS RELEASE

Moderna Announces mRNA-1345, an Investigational Respiratory Syncytial Virus (RSV) Vaccine, Has Met Primary Efficacy Endpoints in Phase 3 Trial in Older Adults

Essai de phase 2/3, Randomisé, Observer-Blind, Placebo-Controlled Study
37 000 adultes ≥60 ans

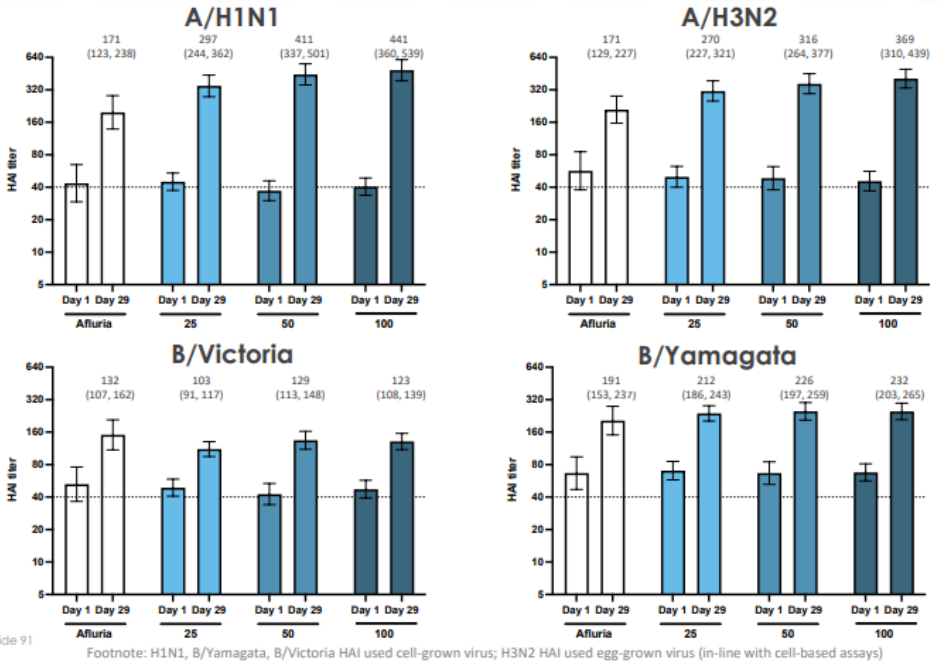
syncytial virus (RSV) in older adults. Following review by an independent Data and Safety Monitoring Board (DSMB), the primary efficacy endpoints have been met, including vaccine efficacy (VE) of 83.7% (95.88% CI: 66.1%, 92.2%; p<0.0001) against RSV-associated lower respiratory tract disease (RSV-LRTD) as defined by two or more symptoms. Based on these results, Moderna intends to submit for regulatory approval in the first half of 2023.

group. The other primary efficacy endpoint against RSV-LRTD defined by three or more symptoms was also met, with a VE of 82.4% (96.36% CI: 34.8%, 95.3%; p=0.0078). The trial is ongoing, and additional efficacy analyses are planned as cases accrue, including for severe RSV.

no safety concerns identified. Safety and tolerability will continue to be followed in this ongoing study. To date most solicited adverse reactions were mild or moderate and the most commonly reported solicited adverse reactions in the mRNA-1345 group were injection site pain, fatigue, headache, myalgia, and arthralgia. The overall rate of severe (Grade 3 or greater) solicited systemic adverse reactions was 4.0% for mRNA-1345 and 2.8% for placebo. The overall

Vaccin grippe ARNm

Geometric mean titers (GMTs) across all ages



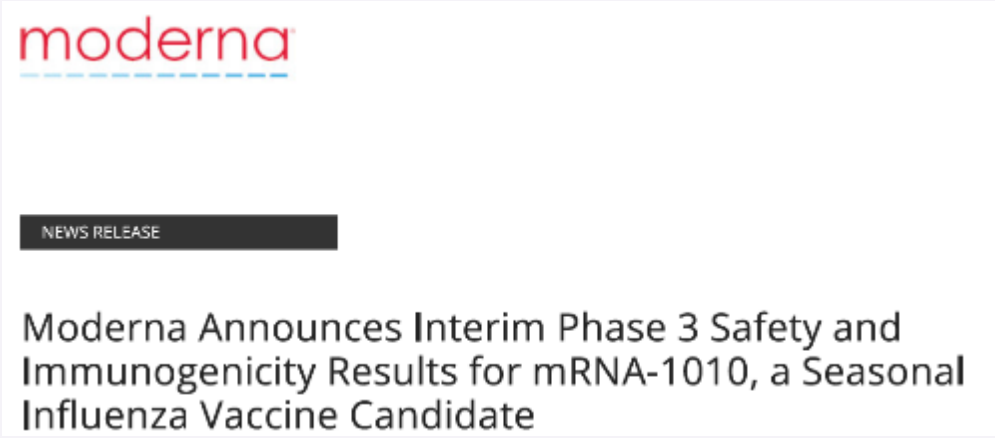
- mRNA-1010 elicits high HAI antibody titers, substantially exceeding 1:40 threshold associated with a 50% reduction in risk of infection
- Day 29 antibody levels are comparable to Afluria for influenza B and higher than Afluria for influenza A strains

Slide 91

Footnote: H1N1, B/Yamagata, B/Victoria HAI used cell-grown virus; H3N2 HAI used egg-grown virus (in-line with cell-based assays)

moderna

Vaccin grippe ARNm



This Phase 3 randomized, observer-blind study was designed to evaluate the safety and immunological non-inferiority of mRNA-1010 to a licensed seasonal influenza vaccine in adults 18 years and older. The trial enrolled 6,102 adults across Argentina, Australia, Colombia, Panama, and the Philippines during the Southern Hemisphere influenza season. Participants were randomly assigned to receive either a single dose of mRNA-1010 or a single dose of a licensed seasonal influenza vaccine as a comparator. mRNA-1010 encodes for hemagglutinin (HA), a major influenza surface glycoprotein considered an important target to generate protection against influenza and is the primary target of currently available influenza vaccines.

Vaccin grippe ARNm

moderna

mRNA-1010 demonstrated superiority on seroconversion rates for A/H3N2 and A/H1N1, superiority on geometric mean titer ratios for A/H3N2, and non-inferiority on geometric mean titer ratios for A/H1N1

Non-inferiority was not met for seroconversion rates and geometric mean titer ratios for the influenza B/Victoria- and B/Yamagata-lineage strains

mRNA-1010 showed an acceptable safety and tolerability profile

mRNA-1010 was found to be generally well-tolerated. 70% of mRNA-1010 recipients reported solicited adverse reactions (SARs) compared to 48% of participants in the active comparator group. A lower rate of SARs was observed in older age groups compared to the younger adult groups. The majority of SARs were grade 1. Pain and axillary swelling were the most common local SARs, and headache, myalgia, and fatigue were the most common systemic SARs reported. No significant differences in unsolicited adverse events, serious adverse events, or adverse events of special interest were observed between the mRNA-1010 and comparator groups.

Vaccins pneumocoque

couverture sérotypique des vaccins actuels

Sérotypes	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	8	10A	11A	12F	15B	22F	33F	2	9N	17F	20
Vaccin polysaccharidique																								
PPSV23 (Merck)	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vaccins conjugués																								
PCV13 (Pfizer)	●	●	●	●	●	●	●	●	●	●	●	●	●											
PCV15 (Merck)	●	●	●	●	●	●	●	●	●	●	●	●	●						●	●				
PCV20 (Pfizer)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●				

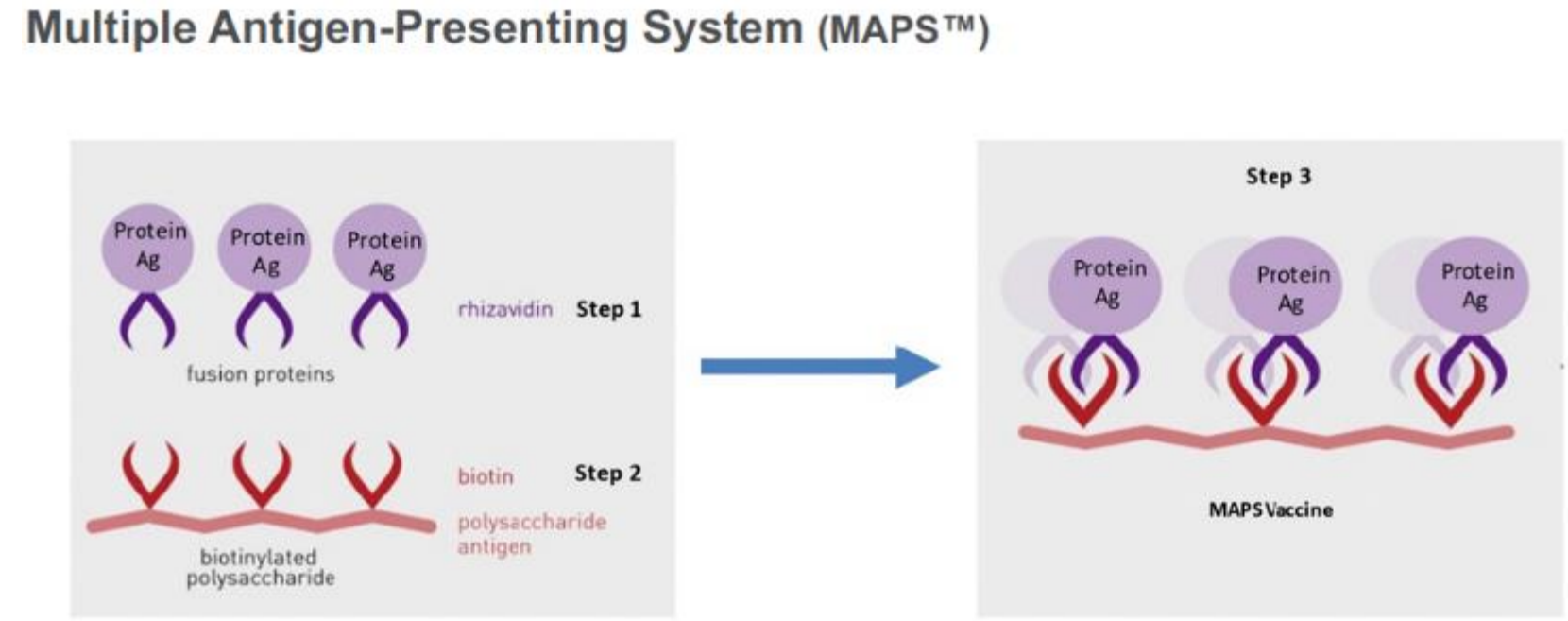
- Les sérotypes additionnels choisis pour leur contribution aux infections invasives de par le monde.[1-5]
- Certains associés à un fort taux de mortalité : 8, 10A, 11A, 15BC, 22F, 33F
- 4 ont une sensibilité diminuée aux antibiotiques : 11A,15B/C, 22F, 33F
- et/ou à des méningites : 10A, 15B/C, 22F, 33F

PCV13=13-valent pneumococcal conjugate vaccine; PCV15=15-valent pneumococcal conjugate vaccine PCV20=20-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine.

Vaccins pneumocoque

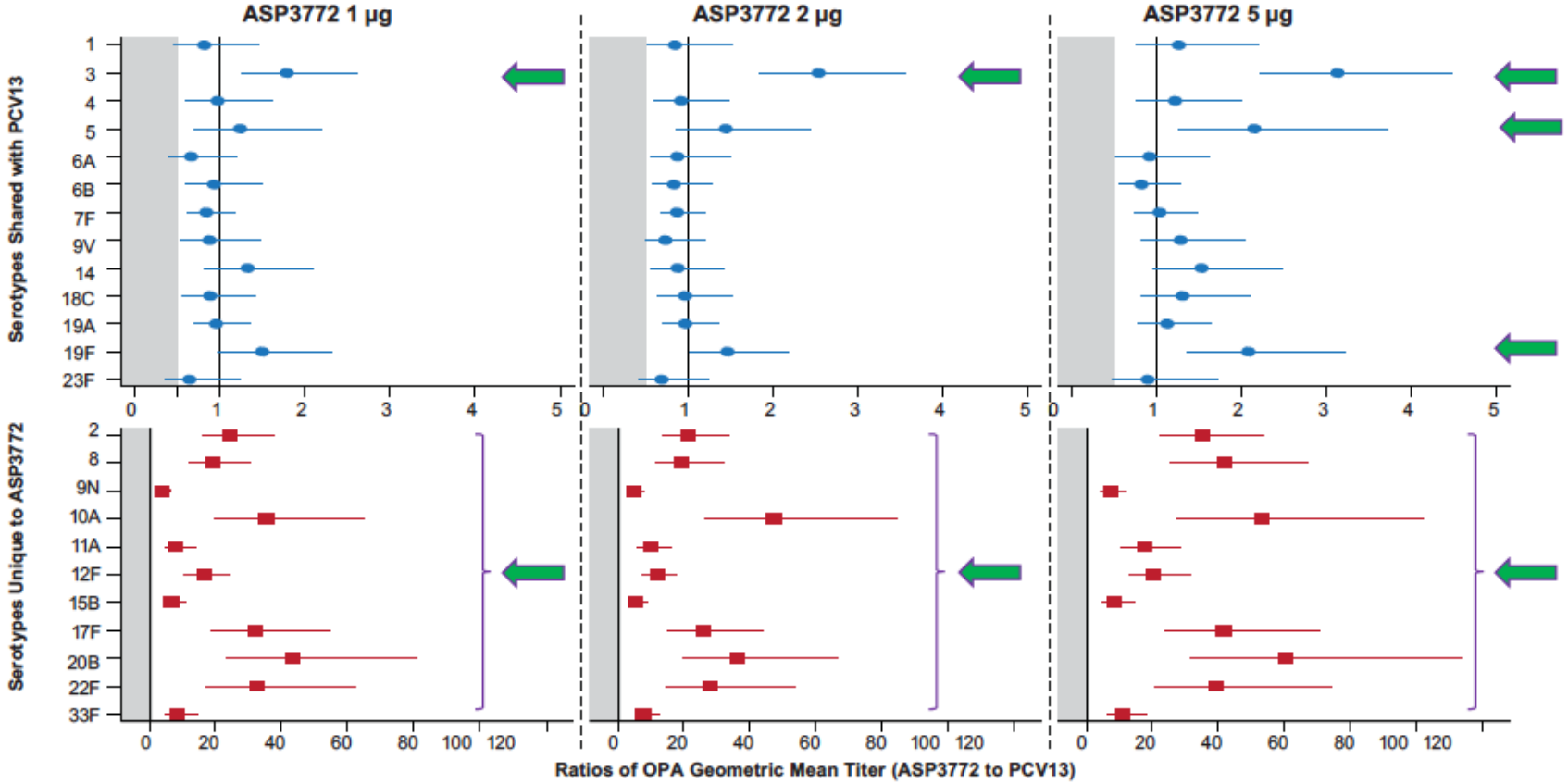
- **Vaccin 21 valent**: V116, phases 3 en cours dans différentes populations

- **Vaccin ASP3772** : 24 valent : 13 du CPV13+ 11 sérotypes additionnels utilise la technologie MAPS (*Multiple Antigen Presenting System)* protéine porteuse constituée de 2 protéines du pneumocoque conservées sp1500 et sp085 : protéine de virulence et induisant une immunité protectrice



Vaccins pneumocoque: ASP3772

Immunogenicity of ASP3772 Was Better Than PCV13 for ST 3 at All Doses, STs 5 and 19F at ASP3772 5 µg, and All Unique STs: Similar to PCV13 for Remaining Shared STs

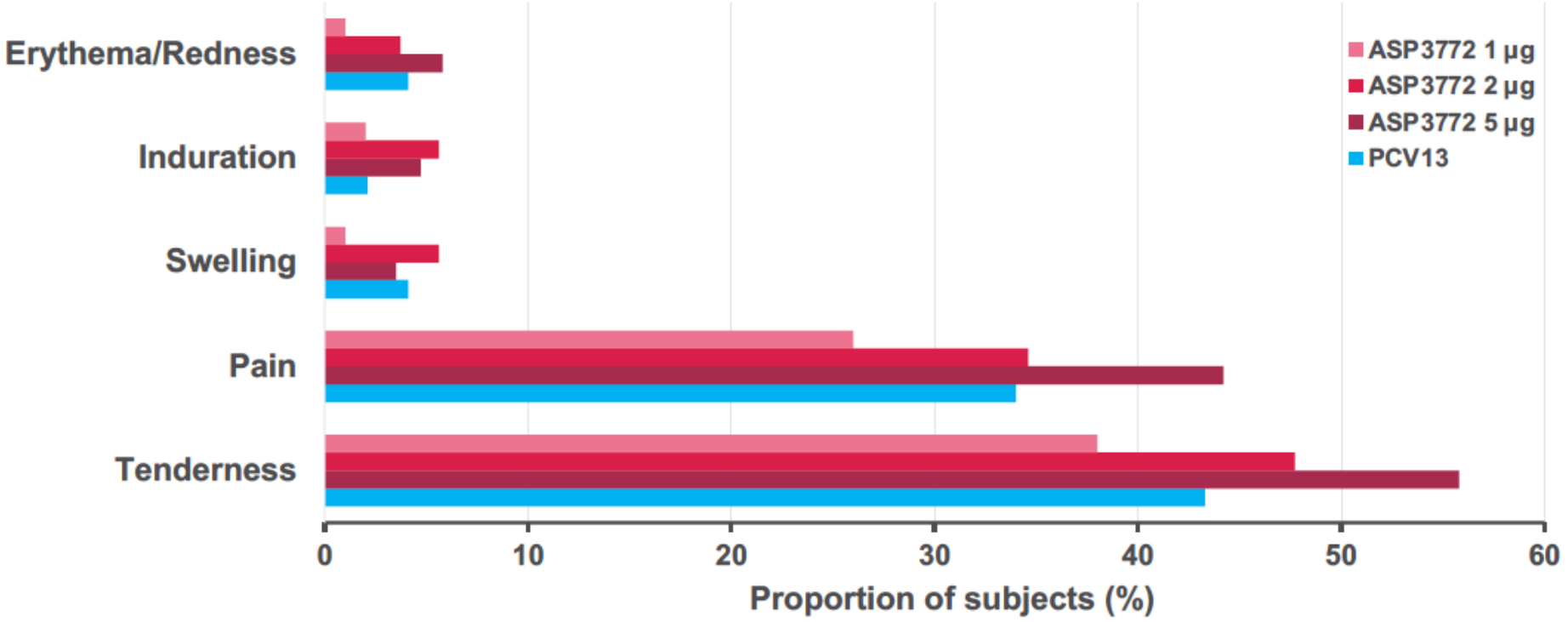


The point estimate is the ratio of the geometric means. Whiskers extend to the 95% confidence interval of the ratio. Gray area indicates ratio of 0.5 or below. Note different scales on ordinate axis.
Abbreviations: OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine.

Green arrows point to significantly higher ratio

Vaccins pneumocoque: ASP3772

Frequently Reported Local Reactions Were Tenderness and Pain With No Clear Difference Across ASP3772 and PCV13 Cohorts



Vaccin CMV

Table 3
CMV vaccines in development.

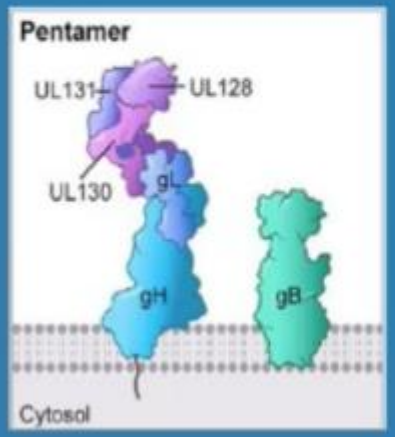
Type of vaccine	Developer	Ref. #
Attenuated strain (Towne)	Wistar Inst./Med Coll VA	[41]
Recombinants with wild virus (Towne-Toledo)	Medimmune	[44]
Replication-defective virus	Merck	[51]
Vectored:		
Canary Pox	Sanofi	[52]
MVA	City of Hope	[57]
Adeno	Queensland Inst.	[58]
LCMV	Hookipa	[55]
VSV	Yale	[59]
Recombinant gB glycoprotein with adjuvant	Sanofi Pasteur, GSK	[45–47]
Soluble Pentamers	Redbiotech, GSK, Humabs	[49]
DNA plasmids	Astellas, Inovio	[61,63]
Self-replicating RNA	Moderna	[54,62]
Peptides	City of Hope	[64]
Dense bodies	Vaccine Project Management (Germany) and Serum Inst. India	[61]
Virus-like particles	Variations Bio	[56]

Modified mRNA Vaccine

Composition: modified mRNA vaccine encoding CMV pentamer complex and glycoprotein antigens (gB)[a,b]

- **Phase 2**, randomized, observer-blind, placebo-controlled, dose-finding trial
- 3 doses in 180 healthy CMV-seronegative and 72 CMV-seropositive males and females, 18 to 40 years old
- Placebo vs mRNA (50 µg, 100 µg, 150 µg)

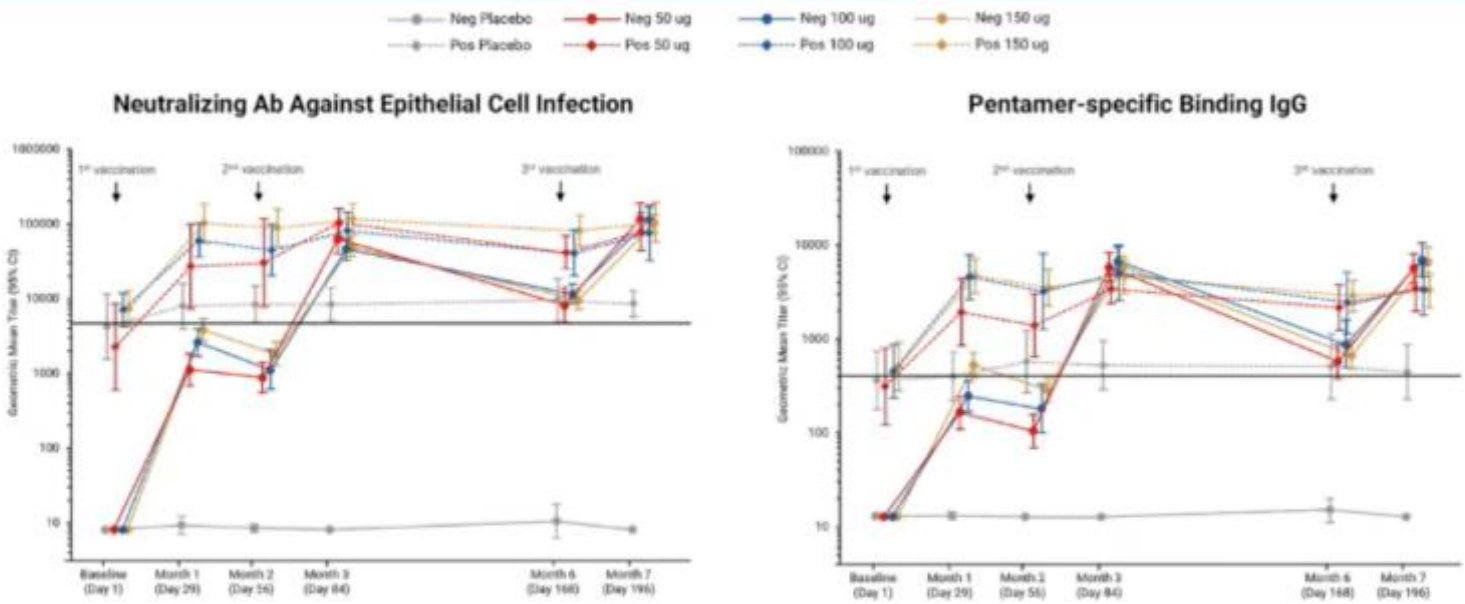
CMV vaccine (mRNA 1647)[a]



GMT, antibody geometric mean titre; LNP, lipid nanoparticle; nAb, neutralizing antibody.

a. Panther L. Presented at: Annual Conference on Vaccinology Research; April 20, 2021; Bethesda, Maryland; b. ClinicalTrials.gov. Accessed April 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04232280.

Modified mRNA Vaccine: Immunogenicity



Immunogenicity: antibody response against pentamer

Seronegative: after 3rd dose, nAB GMT against epithelial cell infection × 20 baseline GMT in seropositives

Seropositive: after 3rd dose, nAB GMT against epithelial cell infection increased × 6.8-fold over baseline

Panther L. Presented at: Annual Conference on Vaccinology Research; April 20, 2021; Bethesda, Maryland.

Phase 3 en cours chez des femmes en âge d’avoir des enfants et exposées

Vaccins Chikungunya

Safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted chikungunya virus-like particle vaccine: a randomised, double-blind, parallel-group, phase 2 trial

Sean R Bennett, James M McCarty, Roshan Kamath Pan, Jason Mendy, Jason S Richardson, Jonathan Smith, Jeff Alexander, John L Ludgerwood, Paul Andrè de Lorme, Sarah Royalty Travis, Kelly L Warfield, Lisa Beck

Lancet Infect Dis 2022; published online June 13. https://doi.org/10.1016/S1473-3099(22)00226-2.

Novel chikungunya vaccine shows promise for durable protection

JCI insight

Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera

Pierre Roques, … , Urban Lundberg, Andreas Meinke

JCI Insight. 2022;7(14):e160173. https://doi.org/10.1172/jci.insight.160173.

Deux vaccins en phase 3

1. Vaccin VLP adjuvanté avec l'Alum
2. Vaccin vivant atténué par délétion génique: evaluation en 'fast track' par la FDA

Flickr/ASCOM Prefeitura de Votuporanga

Vaccin Dengue

APJAI Asian Pacific Journal of Allergy and Immunology

REVIEW ARTICLE

Dengue vaccine: Global development update

Eakachai Prompetchara,[1,2,3] Chutitorn Ketloy,[3,4] Stephen J. Thomas,[5] Kiat Ruxrungtham[6,6]

Table 1. Dengue vaccine candidates currently evaluate in clinical trials

Vaccine type	Vaccine name/Strategy	Developer	Clinical Trial Phase
Attenuated chimera	**CYD, Denvaxia®:** Yellow fever 17D vaccine virus backbone chimerized with prM and E proteins from DENV-1-4	Sanofi-Pasteur	Licensed, Post licensed evaluation is on-going
	TV003/TV005: Attenuated by deletion of 30 nucleotides from 3' UTR of DENV-1, DENV-3 DENV-4, and a chimeric DENV-2/DENV-4	US NIH	Phase III
	DENVax: Use attenuated DENV-2 PDK-53 as the backbone and replace with prM and E of other serotypes (DENV-2/-1, -2/-3, and -2/-4 chimeras)	US CDC/Inviragen/ Takeda	Phase III
Inactivated virus	**Purified formalin-inactivated virus (PIV)** formulated with adjuvants	WRAIR/GSK	Phase I
DNA vaccine	**Monovalent DENV-1** prME delivered by needle-free biojector **Tetravalent prM/E** formulated with Vaxfectin	US NMRC	Phase I
Subunit vaccine	**V180:** 80% of N-terminal E protein produced in insect cell formulated with ISOCOMATRIX and alhydrogel	Hawaii Biotech Inc. and Merck	Phase I
Heterologous prime/boost	**TLAV-prime/PIV-boost and *vice versa***	US Army Medical Research and Materiel Command	Phase I

Vaccins et antibiorésistance

Table 2 Vaccine candidates in clinical development with the potential to prevent diseases caused by pathogens highlighted in this review

Vaccine	Composition	Latest trials
C. difficile		
PF-06425090 (Pfizer)[58]	Genetically/chemically inactivated *C. difficile* toxins A and B ClinicalTrials.gov identifier NCT03090191	Phase 3
ACAM-CDIFF (Sanofi)[86]	Formalin-inactivated wild-type toxoid (A and B) ClinicalTrials.gov identifier NCT01887912	Phase 3
VLA84 (Valneva)[87]	Recombinant fusion protein consisting of truncated toxin A and B ClinicalTrials.gov identifier NCT02316470	Phase 2
S. aureus		
SA4Ag (Pfizer)[88]	CP5/CP8-CRM_{197}, P-Y variant ClfA, MntC ClinicalTrials.gov identifier NCT02388165	Phase 2b
4C-Staph (GSK)[89]	Csa1A (Sur2), FhuD2, EsxA/EsxB, HIAH35L ClinicalTrials.gov identifier NCT01160172	Phase 1
Group B *Streptococcus*		
Trivalent GBS vaccine (GSK)[90]	Capsular epitopes of GBS serotypes Ia, Ib and III conjugated to CRM197 ClinicalTrials.gov identifier NCT02270944	Phase 2
Bivalent GBS protein vaccine (Minervax)[91]	N-terminal domains of the Rib and alpha C surface proteins	Phase 1
E. coli		
EcoXyn-4V (GlycoVaxyn)[92]	*E. coli* bioconjugate vaccine ClinicalTrials.gov identifier NCT02289794	Phase 1
FimH adhesin vax[93] (Sequoia)	Protein-based vaccine	Phase 1
JNJ63871860 (Janssen)[94]	*E. coli* bioconjugate vaccine	Phase 2

Merci pour votre attention