



Vaccins et Vaccination anti-Covid19

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Liens d'intérêt: Janssen: vaccin VIH (Consultations)

Vaccins et Vaccination anti-Covid19

- **Développement accéléré des vaccins anti-Covid19**
 - Composition
 - Essais cliniques d'efficacité
- **Vaccinations anti-Covid19**
 - Corrélat de protection
 - Efficacité en vie réelle
 - Tolérance
 - Efficacité contre les variants
 - Décroissance de l'efficacité vaccinale et Rappels
- **Le Futur des Vaccins et des Vaccinations anti-Covid19**

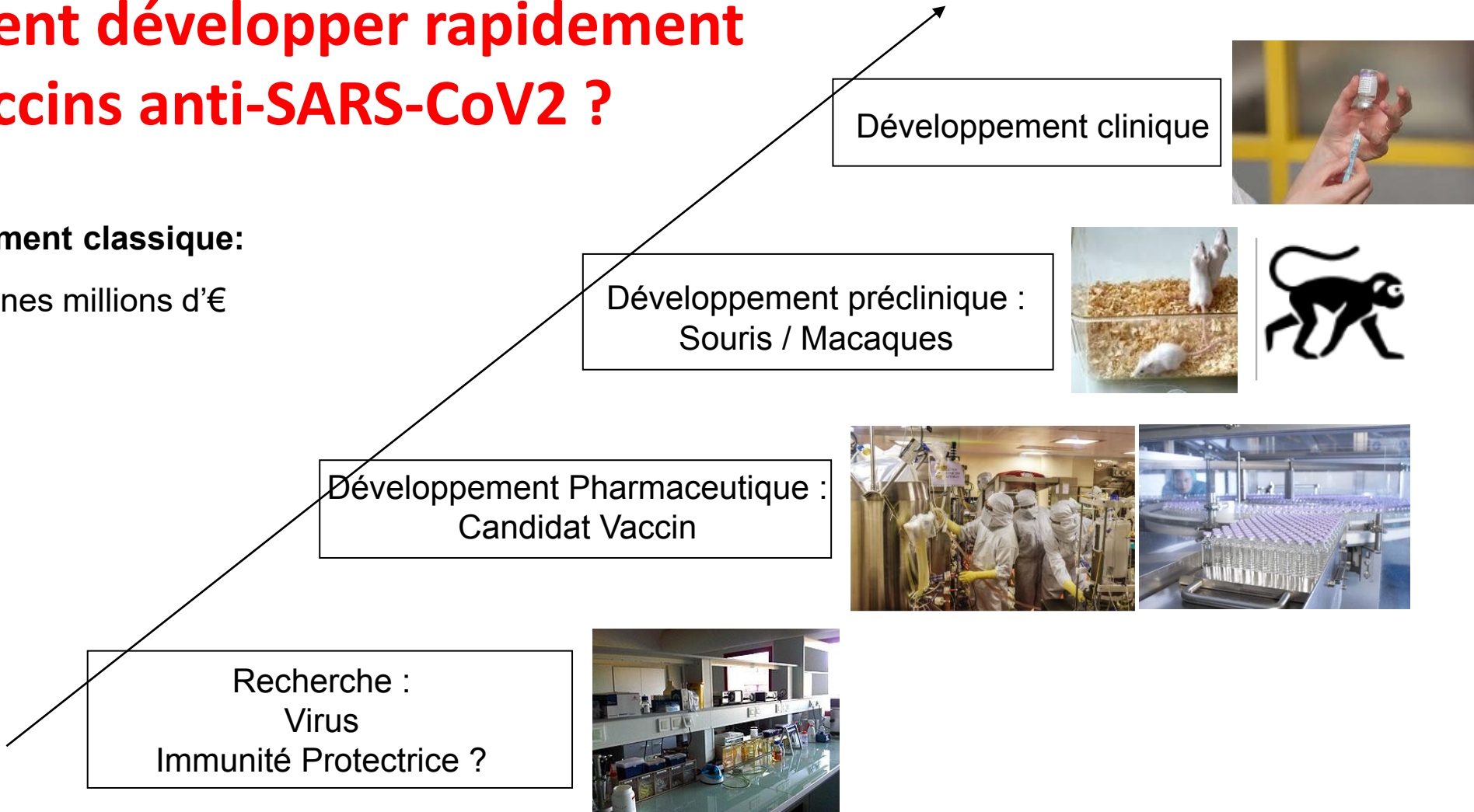


Comment développer rapidement des Vaccins anti-SARS-CoV2 ?

Développement classique:

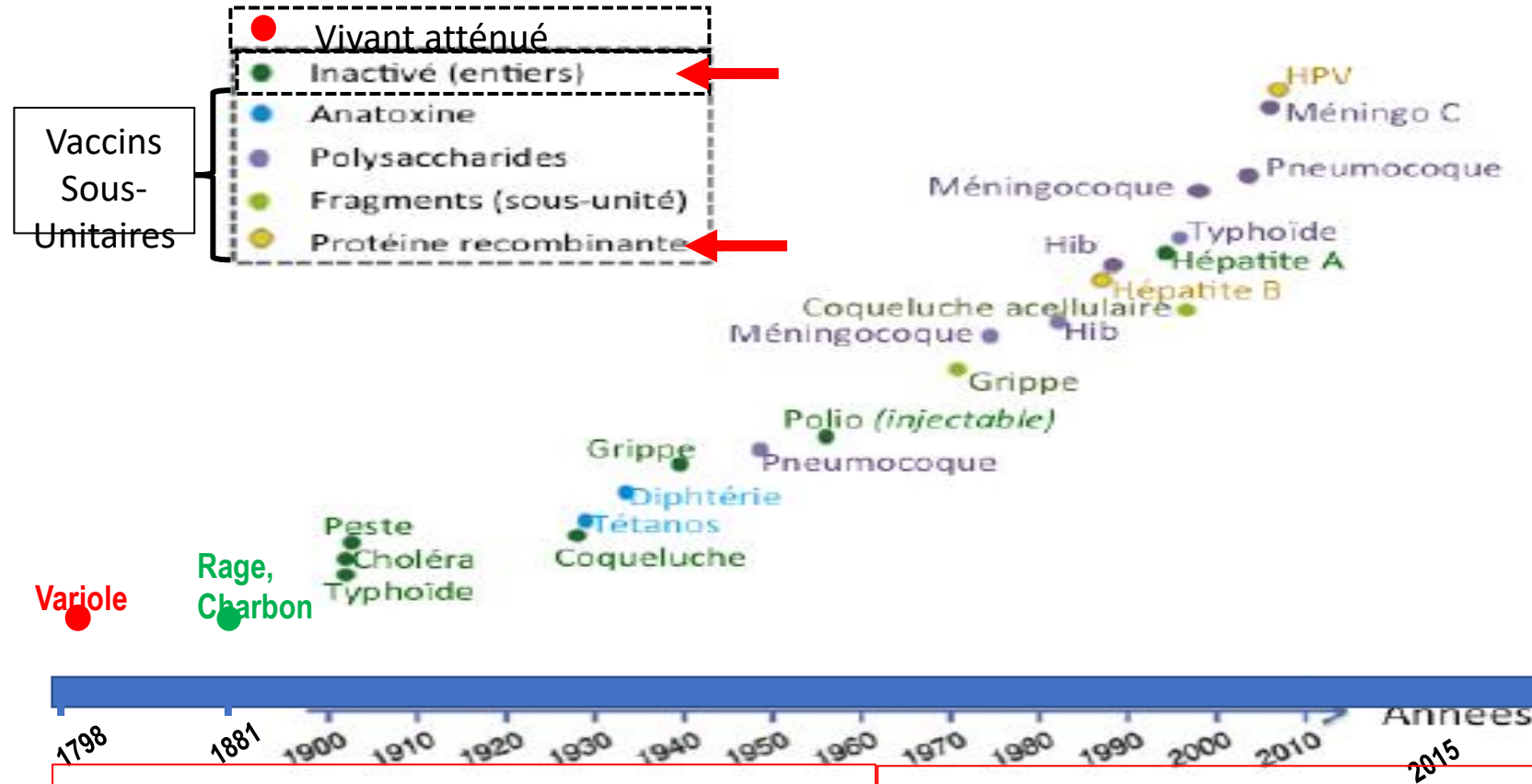
Plusieurs 10nes millions d'€

> 10 ans



Développement rapide de Vaccins anti-SARS-Cov2

Les Vaccins classiques du 20^e siècle peuvent-ils être utiles ?



- **Vaccins Vivants ou Inactivés:**
 - Avantages :
 - Pas de design**
 - Limitations:
 - Sécurité
 - Production , Adaptation / variants

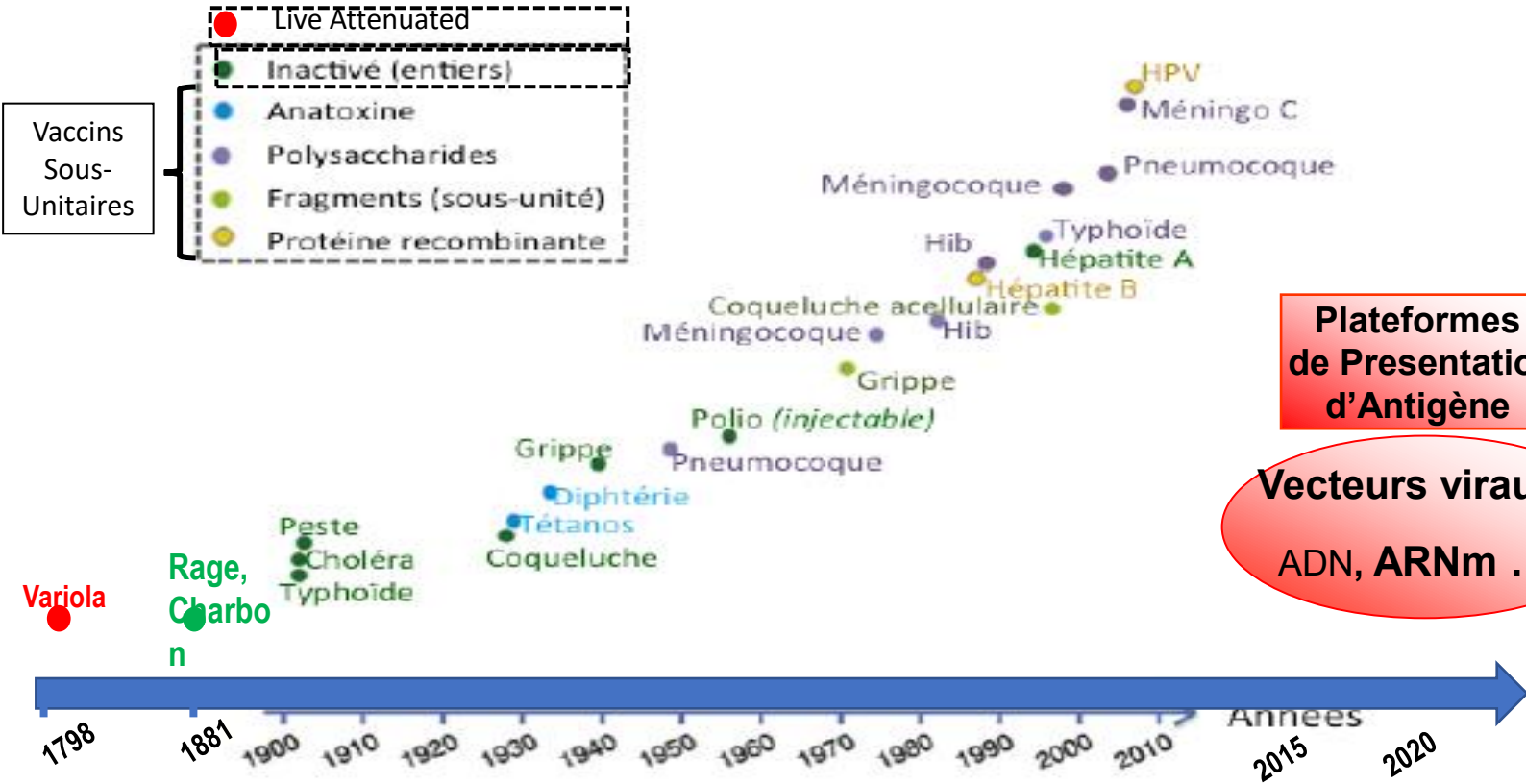
- **Protéines Recombinantes:**
 - Avantages:
 - Forte Immunogenicité si Adjuvant**
 - Sécurité**
 - Limitations:
 - Design de l'Antigène; Production; Adaptation / variant

Développement rapide de Vaccins anti-SARS-Cov2

Approches Classiques ?

ou

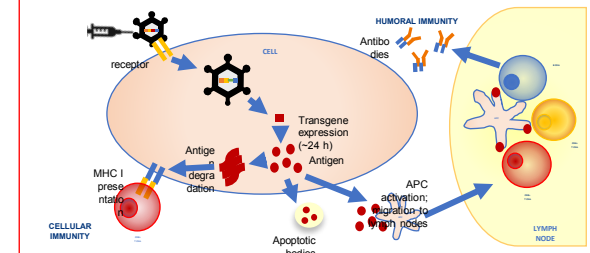
Innovantes ?



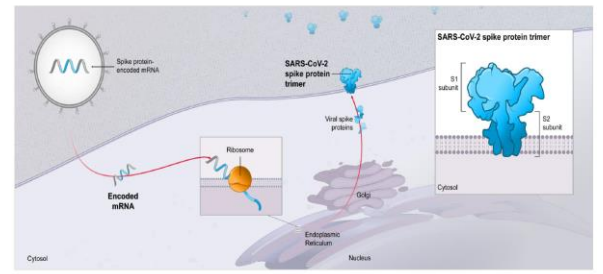
Plateformes de Présentation d'Antigène

Vecteurs viraux
 ADN, ARNm ...

Vecteurs Viraux Recombinants



ARNm



- Vecteurs Recombinants ou ARNm
 - Avantages :
 - Design de l'Ag Rapide et flexible
 - Immunogénicité sans adjuvant
 - Limitations:
 - Immunité anti-Vecteur

Développement rapide de Vaccins anti-Covid19

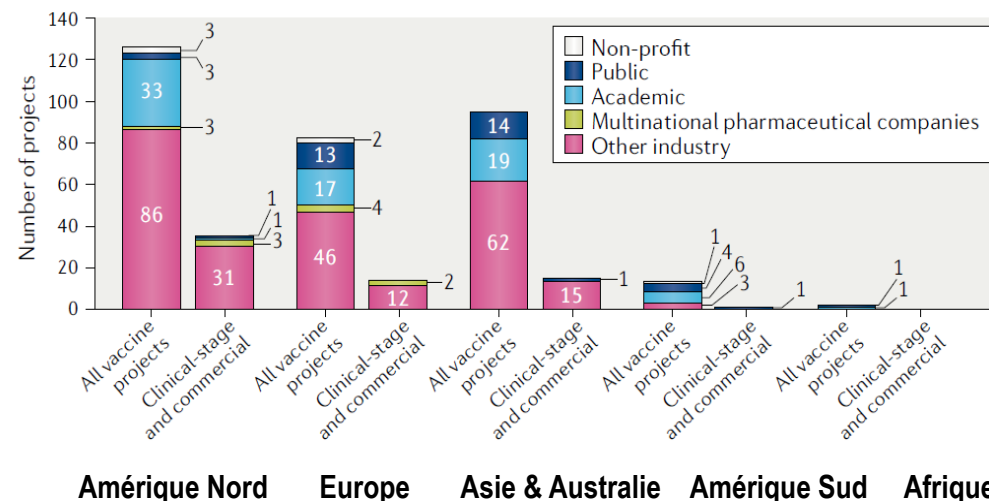
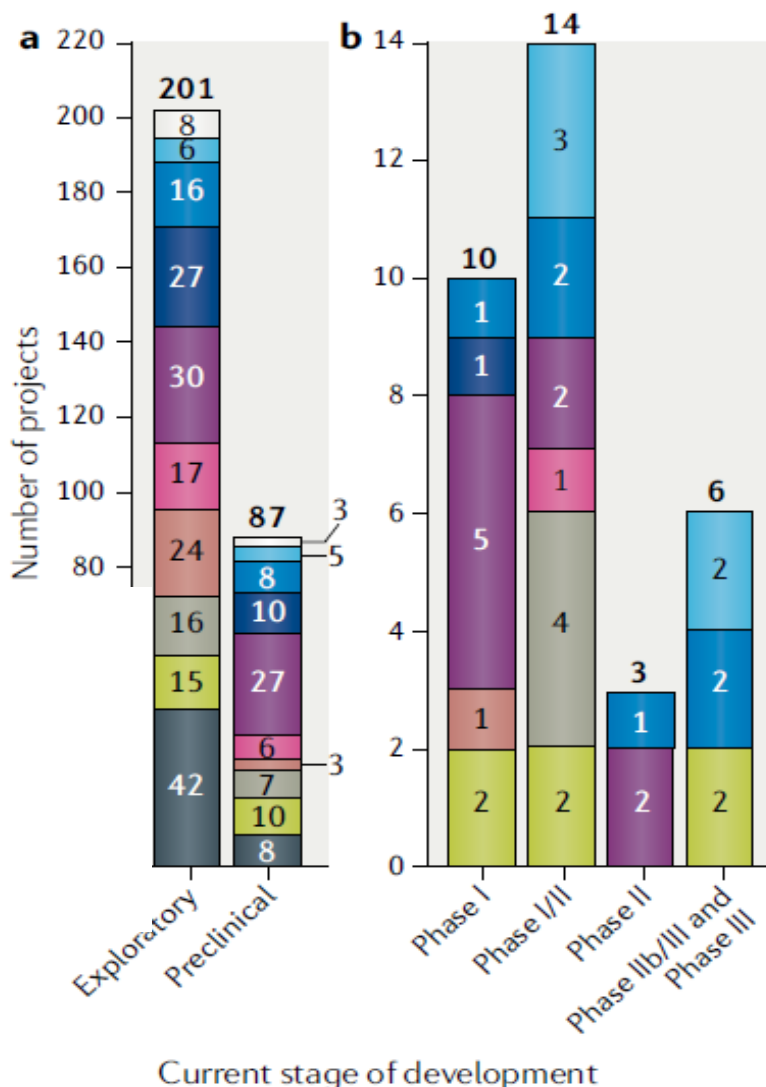
Le « Paysage » des Vaccins anti-Covid19 en Octobre 2020

T T Le Nature Rev. Drug Discov. Oct20

- Tous types de vaccins
- **290** en stade pré-clinique
- **33** en phases cliniques

Type, Nombre et Stade de développement

- Virus Inactivé
- Vecteur Non répliatif
- Vecteur Répliatif
- Protéine recombinante
- Peptides
- (Vlp)
- ADN
- ARN
- Autres



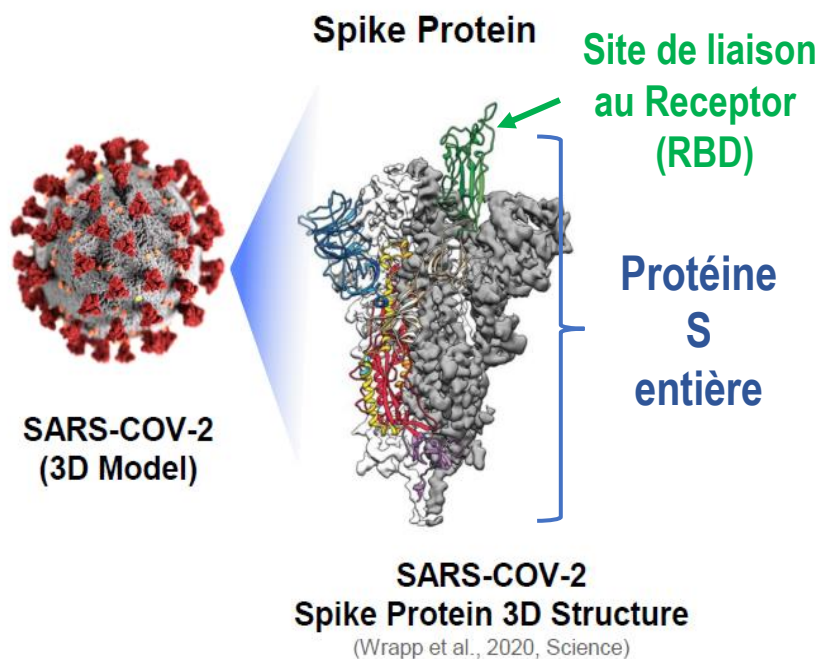
Profil des Développeurs de vaccins Covid19

- Tous continents
- Origine industrielle >50% cas

Quelle Immunité protectrice anti-SARS-CoV2 ? Etat des connaissances Hiver 2020

➤ SARS-CoV2 et Spicule S

(Zhou P et al. Nature 2020; Wrapp et al. Science 20)

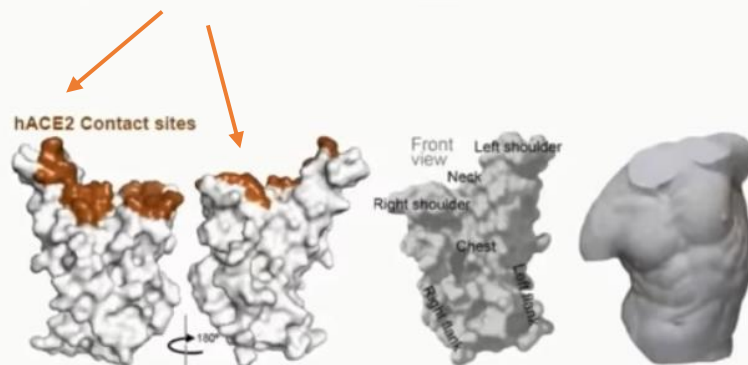


➤ Anticorps:

- chez >95% sujets infectés
- taux << chez A-symptomatiques

➤ Anticorps Neutralisants = Anti-Spike (RBD)

- chez les convalescents, **persistent > 8 mois**
- ne croisent pas avec autres CoronaVirus
- **dirigés contre le site de liaison RBD**



Source: <https://ssrn.com/abstract=3725763> & Dejnirattisai W. The antigenic anatomy of SARS-CoV-2 receptor binding domain, 2020 (Pre-print)

**Réponses
Protectrices?**
d'après autres
infections à CoronaV

Jiang HW et al. doi: <https://doi.org/10.1101/2020.03.20.20039495> medRxiv;

Jiang S et al. Trends in Immunology, May 2020;

Kai-Wang To K et al. www.thelancet.com/infection 2020

Long QX et al. Nat.Med. 2020.; Peng Y., bioRxiv. 2020.; Wajnberg A et al., Science 2020).

Sun B et al. Emerg Microbes Infect. 2020; Ni L et al Immunity. 2020

Grifoni A et al. Cell. 2020; Vabret N et al. Immunity 2020, 52, 910.

Développement clinique des Vaccins anti-Covid19

➤ 1ere vague:

- Vaccins vivants atténués;
- **vaccins Inactivés** (Sinovac, SinoPharm)

➤ Vaccins ARNm

- **BNT 162b2** (BioNTec/Pfizer); **m1273** (Moderna/NIH)

➤ Vecteurs Viraux recombinants non réplicatifs :

- **ChAdOx-CoV2** (AZ); **Ad26-CoV2** (J&J);
- Ad5-CoV+Ad26CoV2 (Sputnik)

➤ 2^e vague :

- **Nanoparticule recombinante** (Novavax), + **adjuvant**
ou **Protéine recombinante + adjuvant** (Sanofi/GSK)

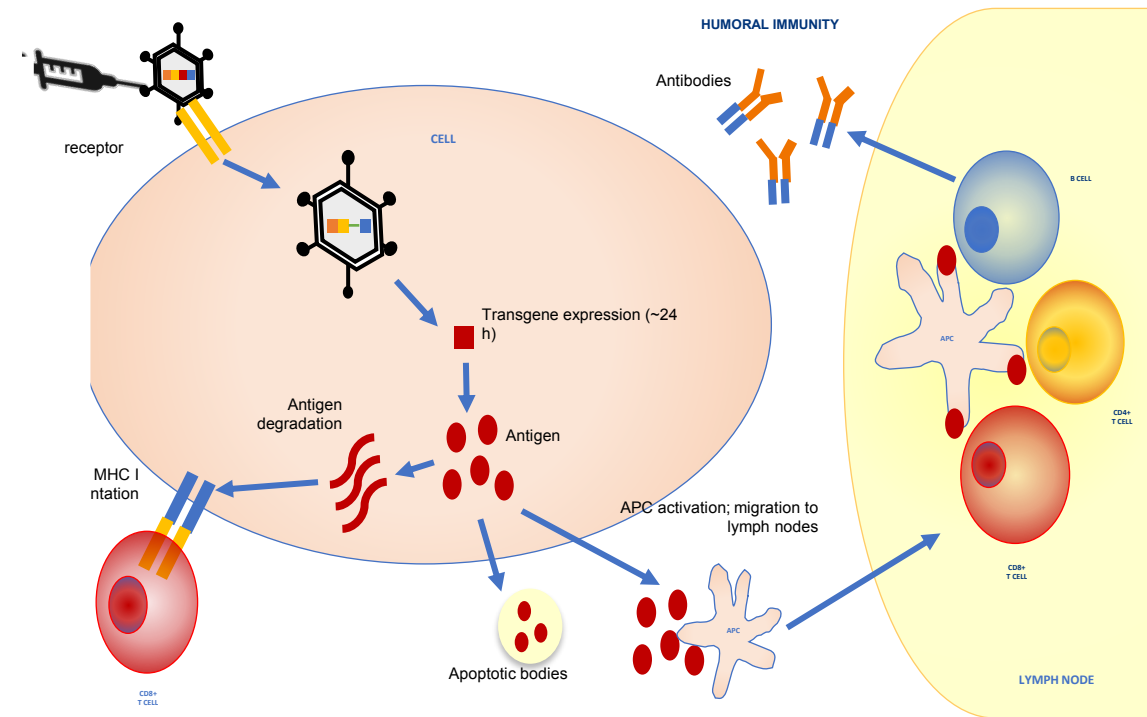
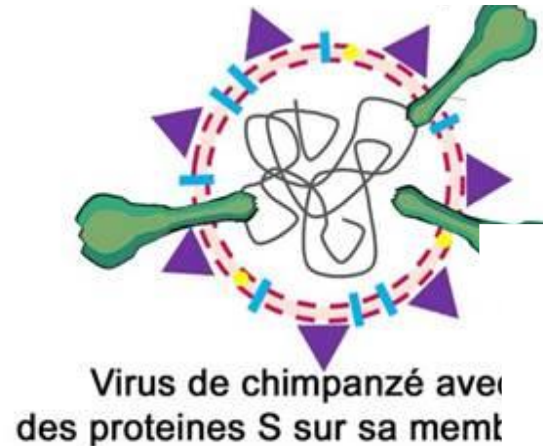
■ **Dirigés contre l'antigène **Spike****

■ **Objectifs :**

➤ **Ac Neutralisants**
(+ réponse Th1)

➤ **Prévention de la maladie l'infection**

Vaccins à Vecteurs viraux Recombinants



- ✓ Initialement développé contre le VIH
- ✓ vecteurs (PoxV, AdénoV, VSV...) atténué ou non répliatif
- ✓ recombiné pour genes du virus ciblé (Ebola, SARS-CoV2...)
- ✓ => réponses immunes spécifiques du virus ciblé

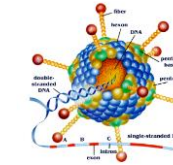
➤ **Succès du vaccin anti-Ebola: Efficacité de 99% en Phase 3 du vaccin VSV recombinant / enveloppe d'Ebola** (Lancet 2016, 2017)
Approbation 2019 / EMA & FDA :

Vecteurs viraux Recombinants

ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques

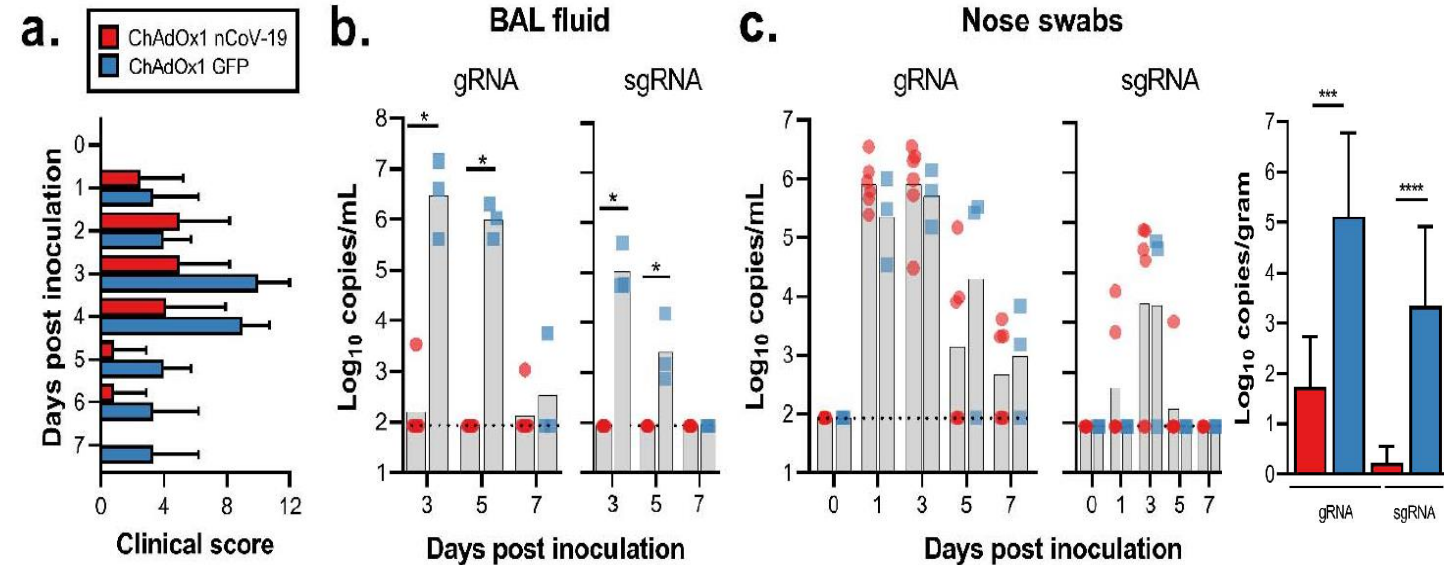
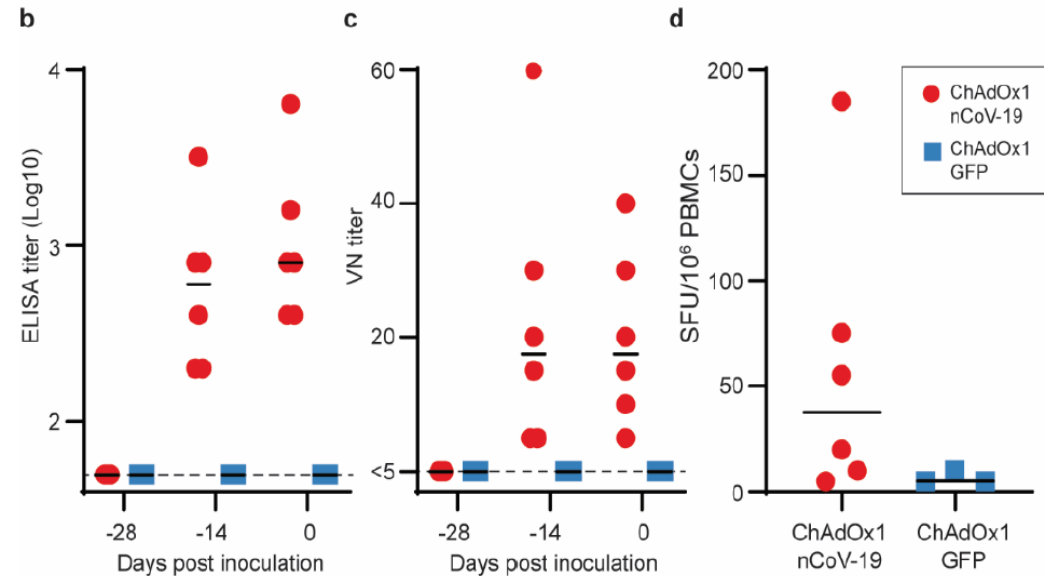
N van Doremalen et al. *bioRxiv. May. 2020* doi: 10.1101/2020.05.13.093195

- **Vaccin : ChimpAdenoV recombinaé pour la Spike de SARS-CoV2**
- Etude chez le Macaque: 1 seule injection



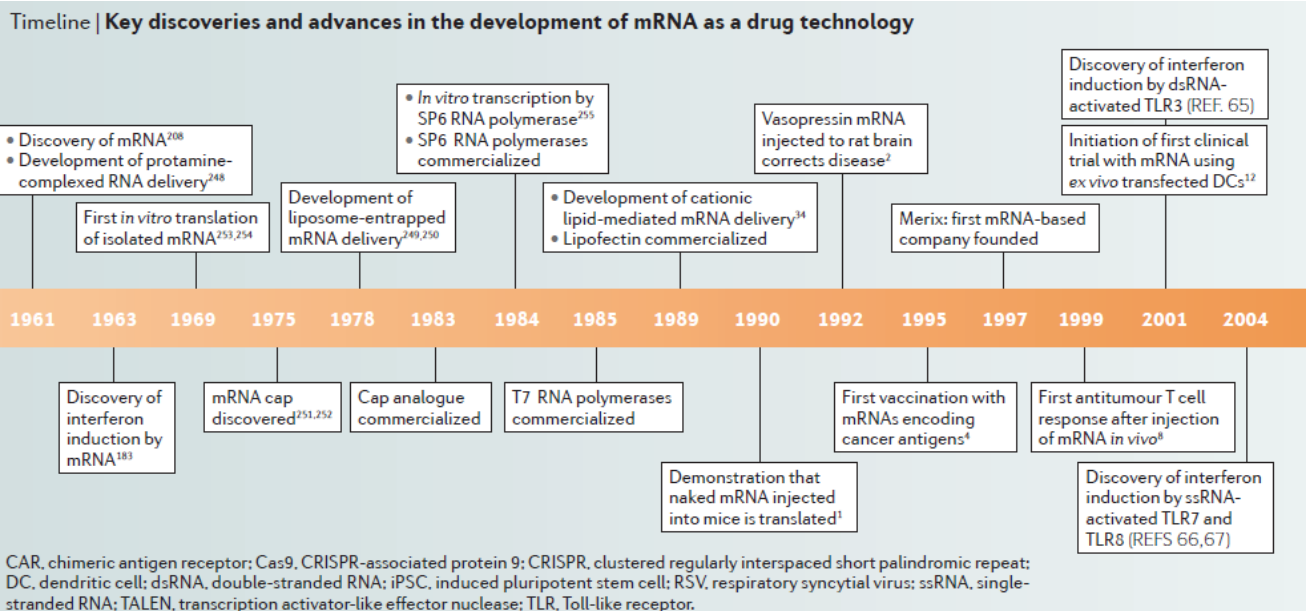
- Induction de réponses
 - Anticorps avec **Ac Neutralisants**
 - Réponses Cellulaires T

- **Réduction de Charge virale dans :**
 - Lavage alvéolaire
 - Muqueuse Nasale (moindre)



mRNA-based therapeutics — developing a new class of drugs

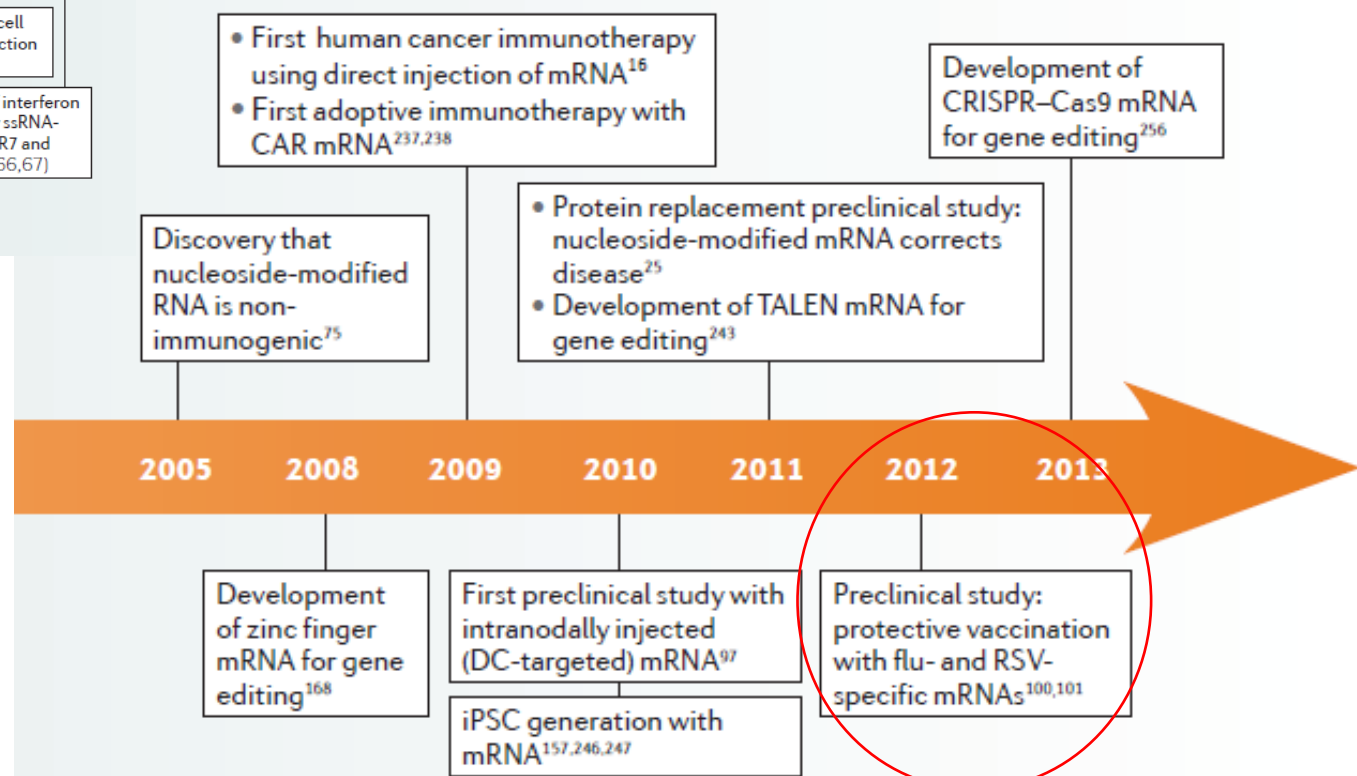
Ugur Sahin^{1,2}, Katalin Karikó^{2,3} and Özlem Türeci¹



CAR, chimeric antigen receptor; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeat; DC, dendritic cell; dsRNA, double-stranded RNA; iPSC, induced pluripotent stem cell; RSV, respiratory syncytial virus; ssRNA, single-stranded RNA; TALEN, transcription activator-like effector nuclease; TLR, Toll-like receptor.

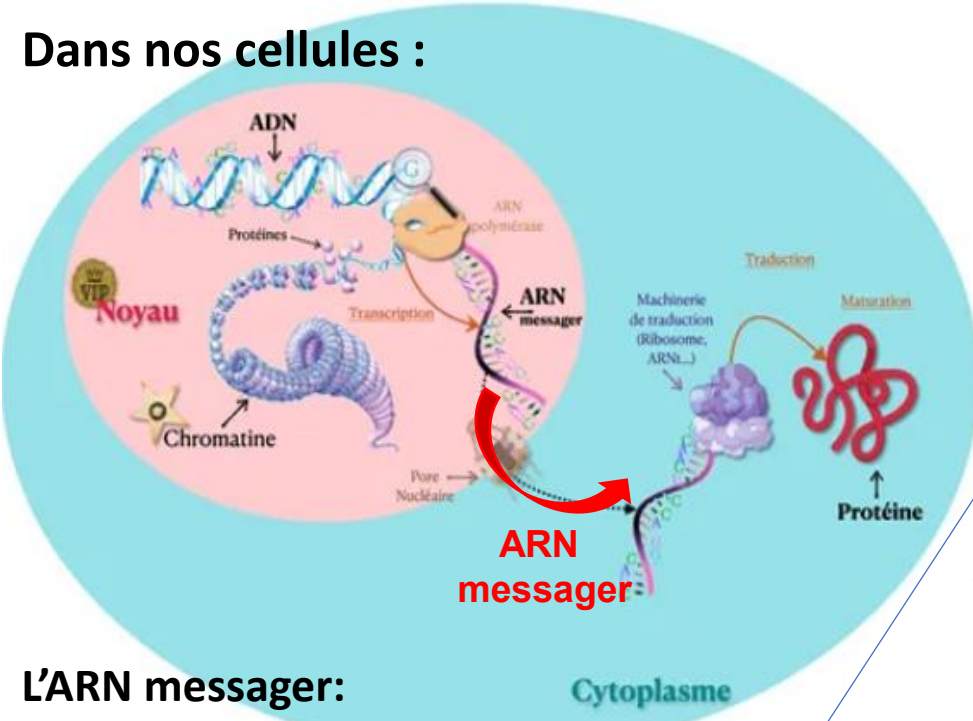
• vaccins ARNm anti-infectieux en développement Clinique:

- Phase 1 & 2 :
 - Grippe,
 - Zika,
 - VZV
 - RSV.....



Vaccination par ARN-messenger

Dans nos cellules :



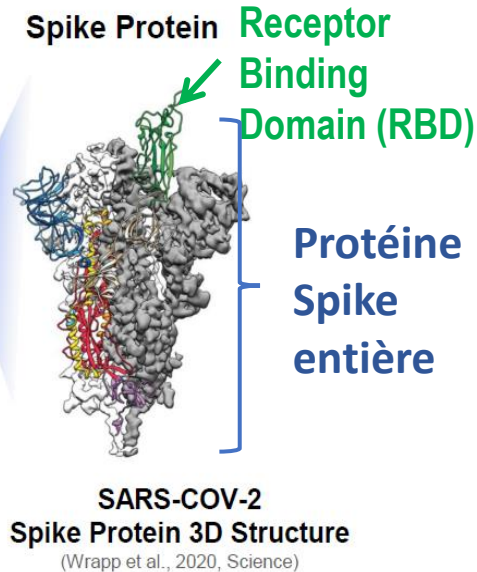
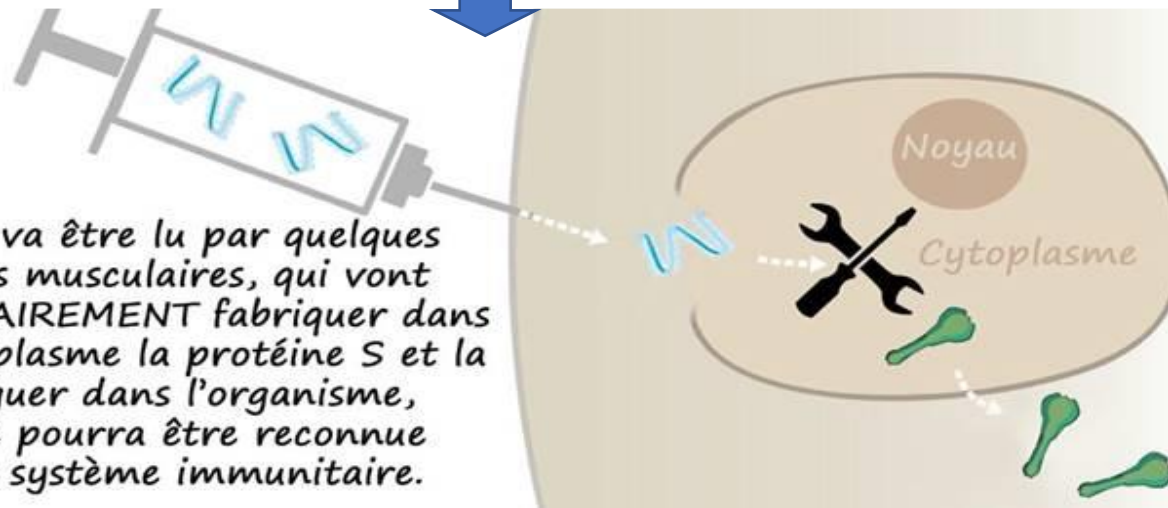
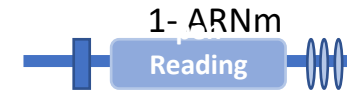
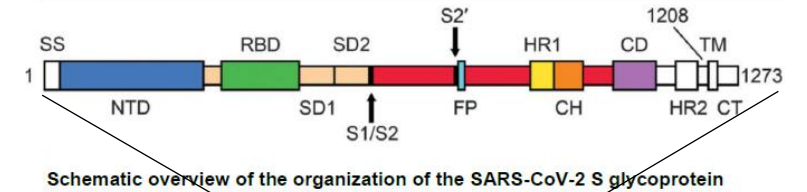
L'ARN messenger:
= immédiatement dégradée
= ne retourne PAS au noyau

Mécanisme vaccinal

enrobée dans une capsule biodégradable

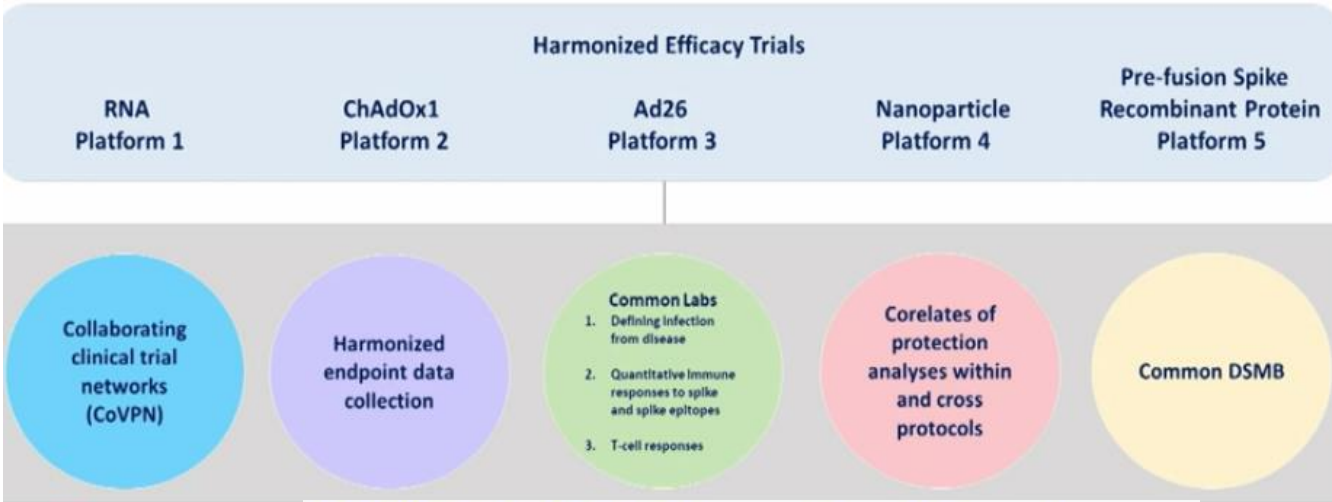
L'ARN va être lu par quelques cellules musculaires, qui vont **TEMPORAIREMENT** fabriquer dans leur cytoplasme la protéine S et la relarguer dans l'organisme, où elle pourra être reconnue par le système immunitaire.

Copie de l'ARNm du SARS-CoV2



Harmonisation des Essais cliniques de vaccins anti-Covid19: USA : Opération WARP

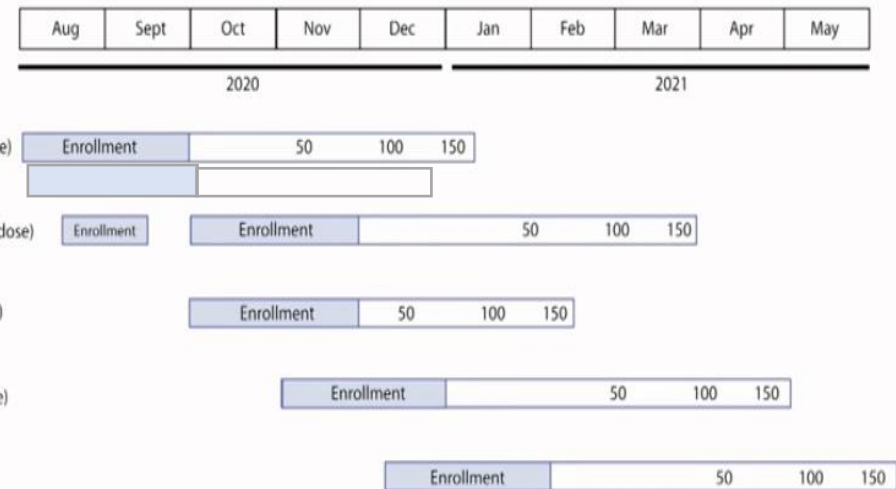
Organizational Structure of OWS Clinical Trials Program



Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid	moderna	Enrolled	Ongoing
	BIONTECH Pfizer	Enrolled	Ongoing
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Ongoing
	janssen Johnson & Johnson	Enrolled	Ongoing
Protein subunit	MERCK	Ongoing	--
	NOVAVAX Creating Tomorrow's Vaccines Today	Ongoing	Ongoing

The Estimated Course of the Clinical Trials in OWS



NIAID COVID-19 Prevention Network



Vaccins ARNm anti-Covid-19: Tolérance et Immunogénicité

RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study

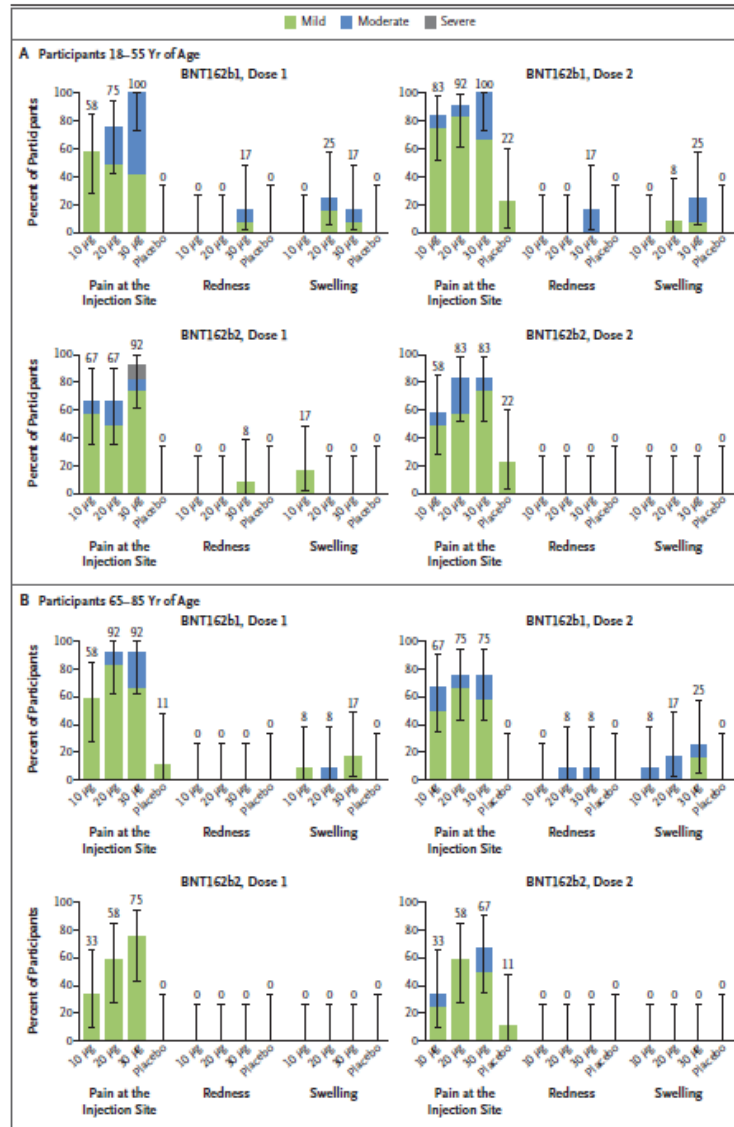
RE Walsh, R Frenck et al.

2020, at NEJM.org.

DOI: 10.1056/NEJMoa2027906

➤ Tolérance

➤ Pas d'EIG

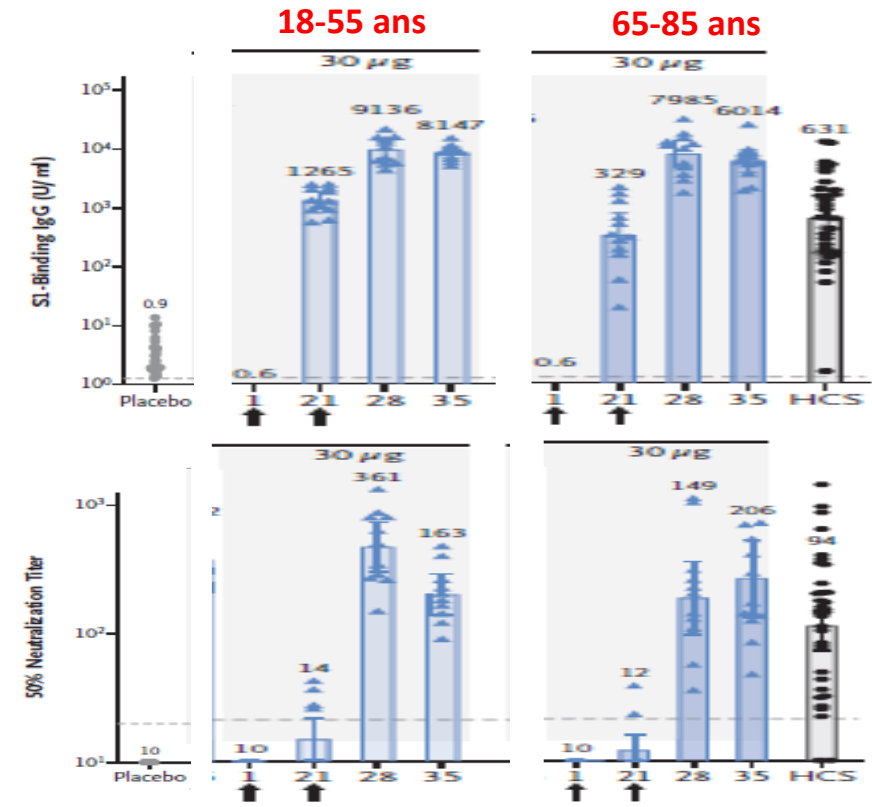


➤ **Vaccin Pfizer : ARNm modifié de Spicule en Liponanoparticules**
 X Doses vs Placebo en 2 injections à J0, J21, 2 populations (N=12/bras)

➤ Immunogénicité

➤ Anticorps anti-S

➤ Ac Neutralisants



➤ **Anticorps Neutralisants :**
 < chez >65 ans mais équivalents aux convalescents
 + Réponses cellulaires T

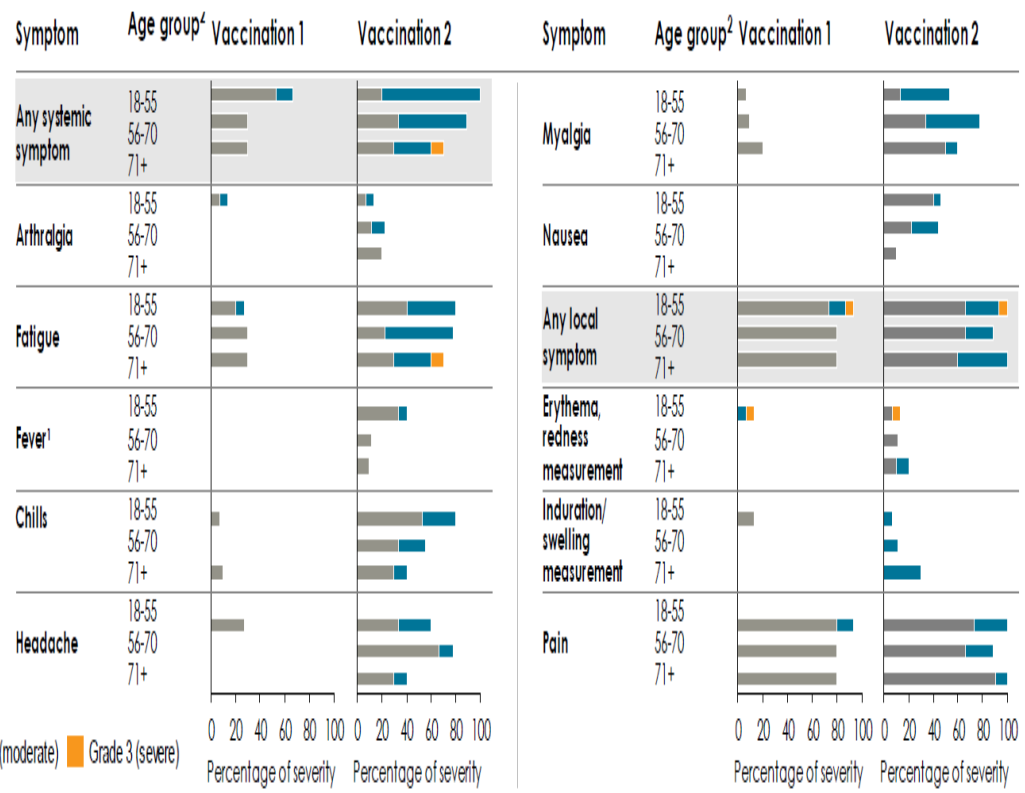
Vaccins ARNm anti-Covid-19: Tolérance et Immunogénicité



An m-RNA vaccine against SARS-CoV2 : Ph 2

Jackson L, Anderson EJ, Roupael NG, et al. N Engl J Med. 14 Jul 2020; DOI: 10.1056/NEJMoa2022483
 Adrian B. McDermott, N. Engl. J. Med Dec 2020

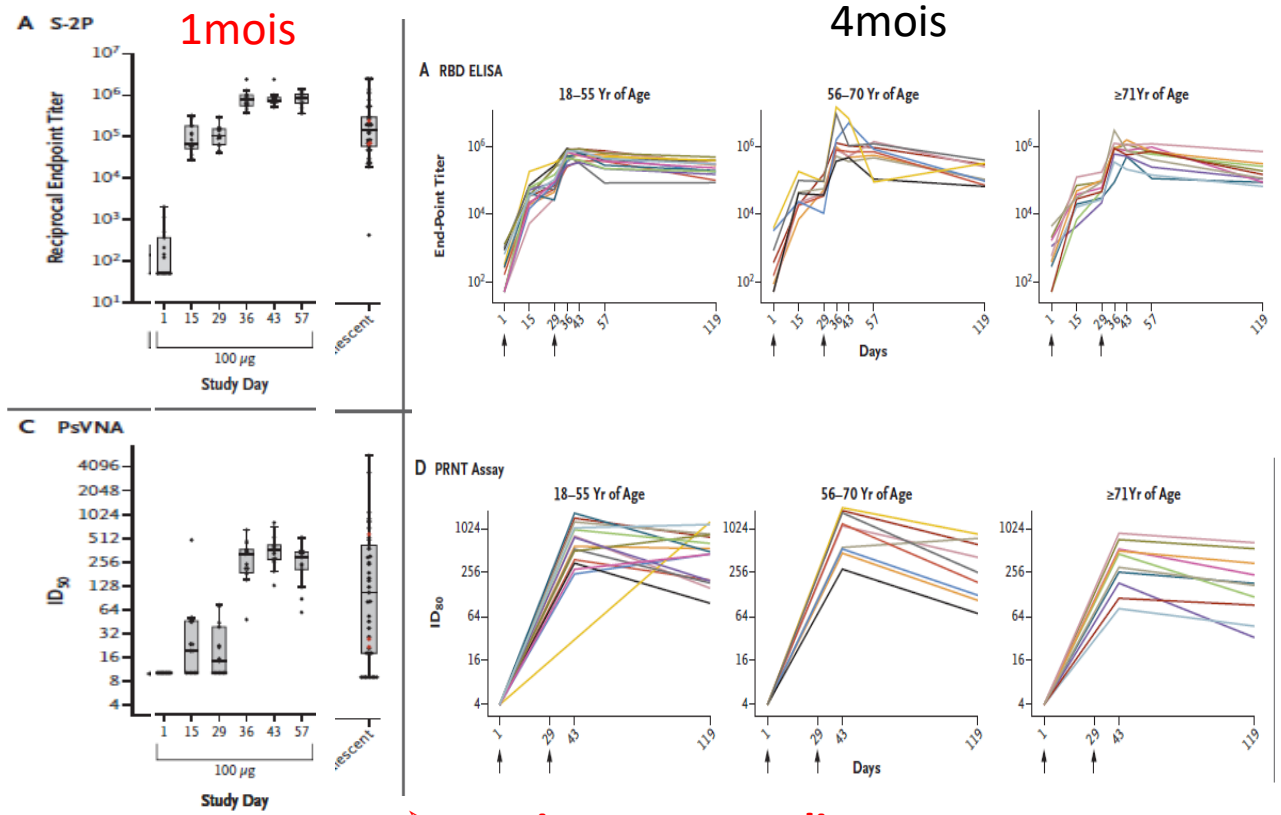
➤ Tolérance



➤ Pas d'EIG

➤ Vaccin Moderna: ARNm modifié de Spicule en LNP :
 100µg, 2 injections: J0-J29; 3 gp d'Adultes sains 18-55 / 56-70 / >71 ans

➤ Immunogénicité



➤ Anticorps Neutralisants :
 ➤ Durabilité : sur 4-8 mois
 + Réponses cellulaires T

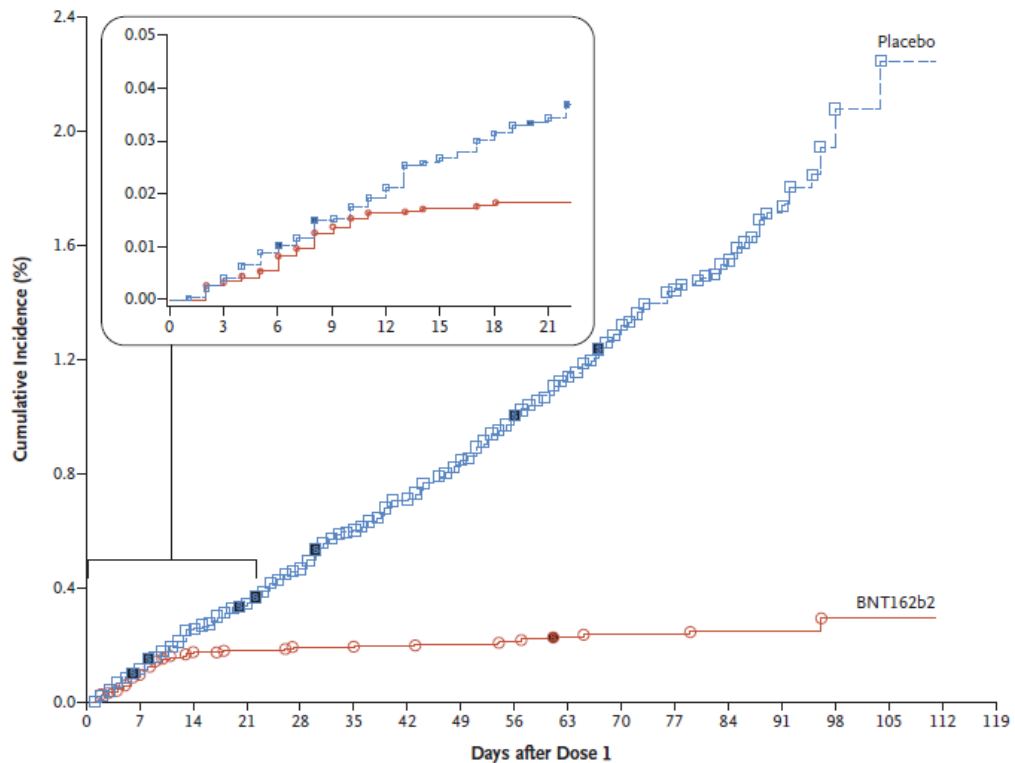
ORIGINAL ARTICLE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

FP Polack et al.

This article was published on December 10, 2020, at NEJM.org

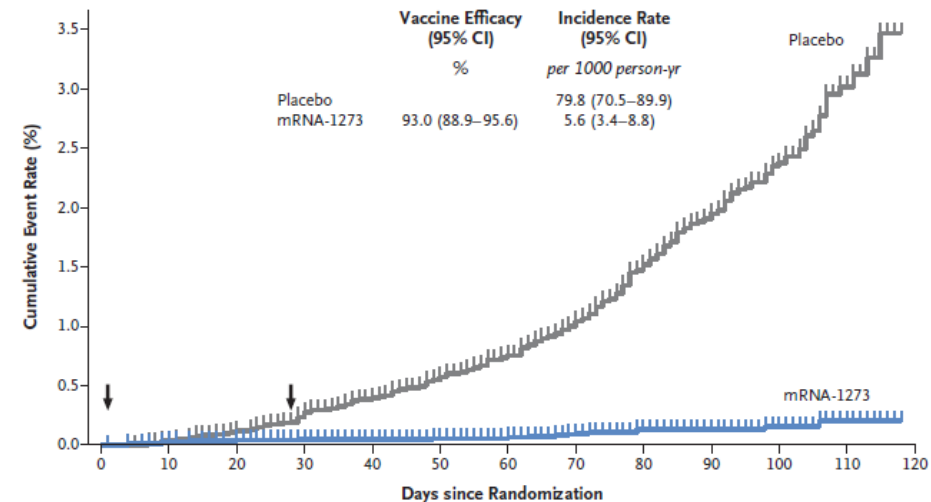


Efficacy End-Point Subgroup	BNT162b2, 30 µg (N=21,669)		Placebo (N=21,686)		VE (95% CI) percent
	No. of participants	Surveillance time person-yr (no. at risk)	No. of participants	Surveillance time person-yr (no. at risk)	
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert,

Modified Intention-to-Treat Analysis



Subgroup	Placebo (N=14,073) no. of events/total no.	mRNA-1273 (N=14,134) no. of events/total no.	Vaccine Efficacy (95% CI)	
			VE (%)	95% CI
All patients	185/14,073	11/14,134	94.1	(89.3–96.8)
Age				
≥18 to <65 yr	156/10,521	7/10,551	95.6	(90.6–97.9)
≥65 yr	29/3552	4/3583	86.4	(61.4–95.2)
Age, risk for severe Covid-19				
18 to <65 yr, not at risk	121/8403	5/8396	95.9	(90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4	(76.9–98.7)
≥65 yr	29/3552	4/3583	86.4	(61.4–95.2)
Sex				
Male	87/7462	4/7366	95.4	(87.4–98.3)
Female	98/6611	7/6768	93.1	(85.2–96.8)
At risk for severe Covid-19				
Yes	43/3167	4/3206	90.9	(74.7–96.7)
No	142/10,906	7/10,928	95.1	(89.6–97.7)
Race and ethnic group				
White	144/8916	10/9023	93.2	(87.1–96.4)
Communities of color	41/5132	1/5088	97.5	(82.2–99.7)

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

www.thelancet.com Published online December 8, 2020

Merryn Voysey*, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Wee*, Pedro M Folegatti*, Parvinder Kaur*

Développement clinique

1er essai de Ph3 : en fait 2 avec **design peu clair** :

2 doses différentes (LD vs HD)

2 populations d'âge différent

fD: <55 ans,

FD: 18->70 ans et 79%<55

2 efficacités : fD: 90% vs FD: 62%

2^e essai Ph3: Af Sud: Pb des variants

3^e essai Ph3 : US

Résultats :

76% VE/ f. Symptom.

100% VE/Décès

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0.5%)	44.1 (248 299)	101/5829 (1.7%)	149.2 (247 228)	70.4% (54.8 to 80.6)†
COV002 (UK)	86	18/3744 (0.5%)	38.6 (170 369)	68/3804 (1.8%)	145.7 (170 448)	73.5% (55.5 to 84.2)
LD/SD recipients	33	3/1367 (0.2%)	14.9 (73 313)	30/1374 (2.2%)	150.2 (72 949)	90.0% (67.4 to 97.0)‡§
SD/SD recipients	53	15/2377 (0.6%)	56.4 (97 056)	38/2430 (1.6%)	142.4 (97 499)	60.3% (28.0 to 78.2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0.6%)	56.2 (77 930)	33/2025 (1.6%)	157.0 (76 780)	64.2% (30.7 to 81.5)‡
All SD/SD recipients	98	27/4440 (0.6%)	56.4 (174 986)	71/4455 (1.6%)	148.8 (174 279)	62.1% (41.0 to 75.7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0.1%)	10.3 (248 299)	11/5829 (0.2%)	16.3 (247 228)	36.4% (-63.8 to 75.3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0.6%)	54.4 (248 299)	112/5829 (1.9%)	165.5 (247 228)	67.1% (52.3 to 77.3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0.9%)	69.8 (151 673)	40/3350 (1.2%)	96.0 (152 138)	27.3% (-17.2 to 54.9)
LD/SD recipients	24	7/1120 (0.6%)	41.4 (61 782)	17/1127 (1.5%)	100.6 (61 730)	58.9% (1.0 to 82.9)‡
SD/SD recipients	45	22/2168 (1.0%)	89.4 (89 891)	23/2223 (1.0%)	92.9 (90 408)	3.8% (-72.4 to 46.3)
Any NAAT-positive swab	221	68/5807 (1.2%)	100.0 (248 299)	153/5829 (2.6%)	226.0 (247 228)	55.7% (41.1 to 66.7)

Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia

Denis Y Logunov*, Inna V Dolzhikova*, Dmitry V Shcheblyakov, Amir I Tukhvatulin, Olga V Zubkova, Alina S Dzharullaeva, Anna V Kovyrshina, Lancet [https://doi.org/10.1016/S0140-6736\(21\)00234-8](https://doi.org/10.1016/S0140-6736(21)00234-8)

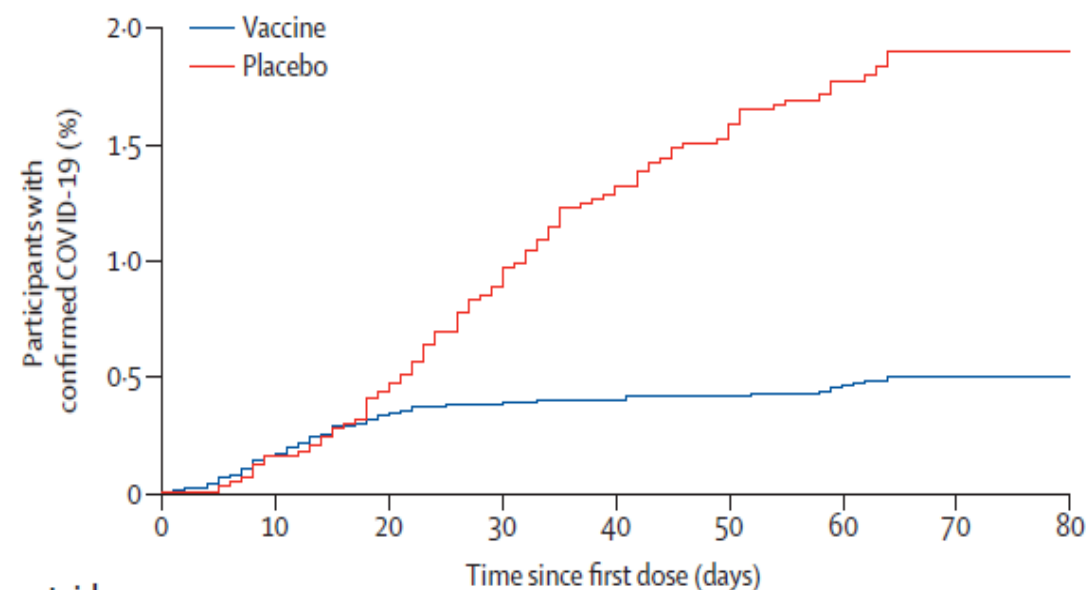


➤ SPUTNIK: 2 vecteurs AdénoV: Ad26-S puis Ad5-S: 2 injections at 21d

	Vaccine (n=14 964)	Placebo (n=4902)
Sex		
Female	5821 (38.9%)	1887 (38.5%)
Male	9143 (61.1%)	3015 (61.5%)
Race		
White	14741 (98.5%)	4830 (98.5%)
Age group, years		
18-30	1596 (10.7%)	521 (10.6%)
31-40	3848 (25.7%)	1259 (25.7%)
41-50	4399 (29.4%)	1443 (29.4%)
51-60	3510 (23.5%)	1146 (23.4%)
>60	1611 (10.8%)	533 (10.9%)
Age, years	45.3 (12.0)	45.3 (11.9)

Concomitant diseases (diabetes, hypertension, ischaemic heart disease, obesity)†	3687/14 944 (24.7%)	1235/4892 (25.2%)
Risk of infection in volunteers‡		
High	65/14 567 (0.4%)	23/4778 (0.5%)
Medium	3853/14 567 (26.5%)	1280/4778 (26.8%)
General	10649/14 567 (73.1%)	3475/4778 (72.7%)

➤ Vaccine Efficacy : 91,6%



	0	10	20	30	40	50	60	70	80
Number at risk (number of COVID-19 cases)									
Vaccine	16 427 (0)	15 338 (35)	15 717 (61)	14 683 (66)	10 970 (70)	6 686 (71)	3 314 (77)	398 (79)	
Placebo	5 435 (0)	5 121 (10)	5 046 (30)	4 895 (54)	3 662 (71)	2 223 (87)	1 106 (92)	133 (96)	

Vaccins Inactivés anti-Covid19

JAMA | Original Investigation

Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults

X Jiang et al. JAMA 2021

A Randomized Clinical Trial

Characteristic	No. (%)		
	WIV04 vaccine group (n = 12 743)	HB02 vaccine group (n = 12 726)	Alum-only group (n = 12 737)
Age, mean (SD), y	36.2 (9.2)	36.1 (9.3)	36.1 (9.3)
Age groups			
<60 y	12 530 (98.3)	12 525 (98.4)	12 539 (98.4)
≥60 y	213 (1.7)	201 (1.6)	198 (1.6)
Sex ^b			
Male	10 706 (84.0)	10 750 (84.5)	10 805 (84.8)
Female	2037 (16.0)	1976 (15.5)	1932 (15.2)

Vaccin Inactivé SINOVAC : CoronaVac:

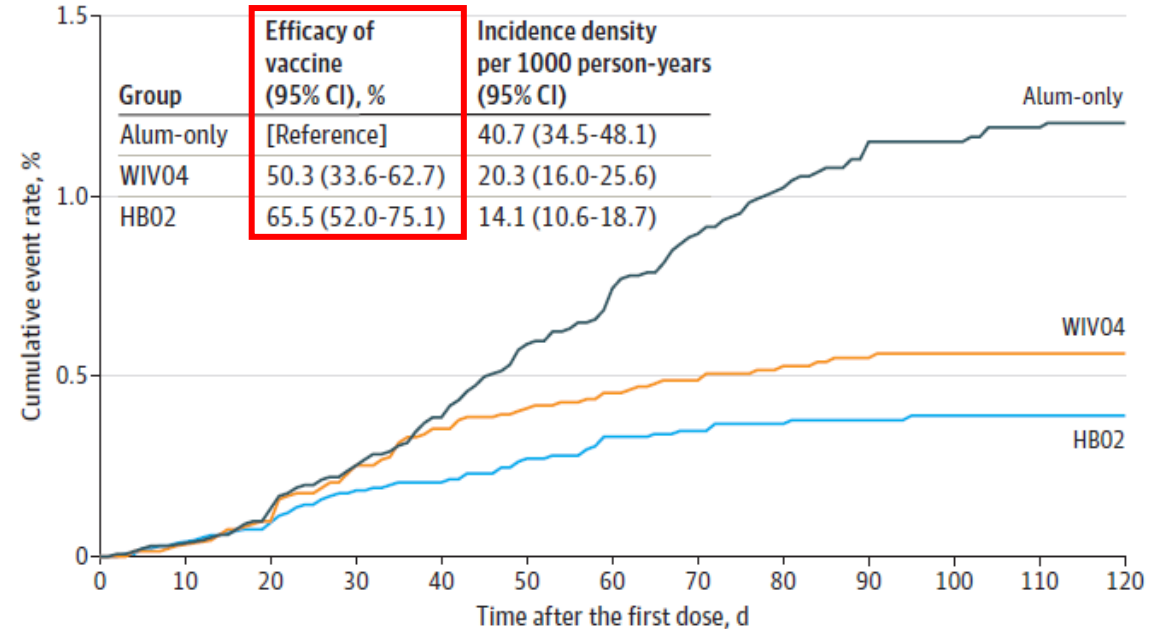
2 injections à 3 semaines:

Efficacité / infection symptomatique : 50-65 % (72-78% en Mod. Int. Treat analysis)

A Modified full analysis population-1

Group	Efficacy of vaccine (95% CI), %	Incidence density per 1000 person-years (95% CI)
Alum-only	[Reference]	44.7 (36.6-54.6)
WIV04	72.8 (58.1-82.4)	12.1 (8.3-17.8)
HB02	78.1 (64.8-86.3)	9.8 (6.4-15.0)

B Full analysis population-1



No. of participants at risk

Alum-only	13425	13273	12981	12749	12594	11857	11501	10900	9672	8041	7728	7430	665
WIV04	13428	13294	12979	12771	12622	11984	11614	11012	9780	8074	7772	7502	665
HB02	13436	13300	12993	12781	12624	11953	11618	11008	9783	8134	7844	7573	653

Principaux Vaccins anti-Covid19 disponibles (Novembre 2021)

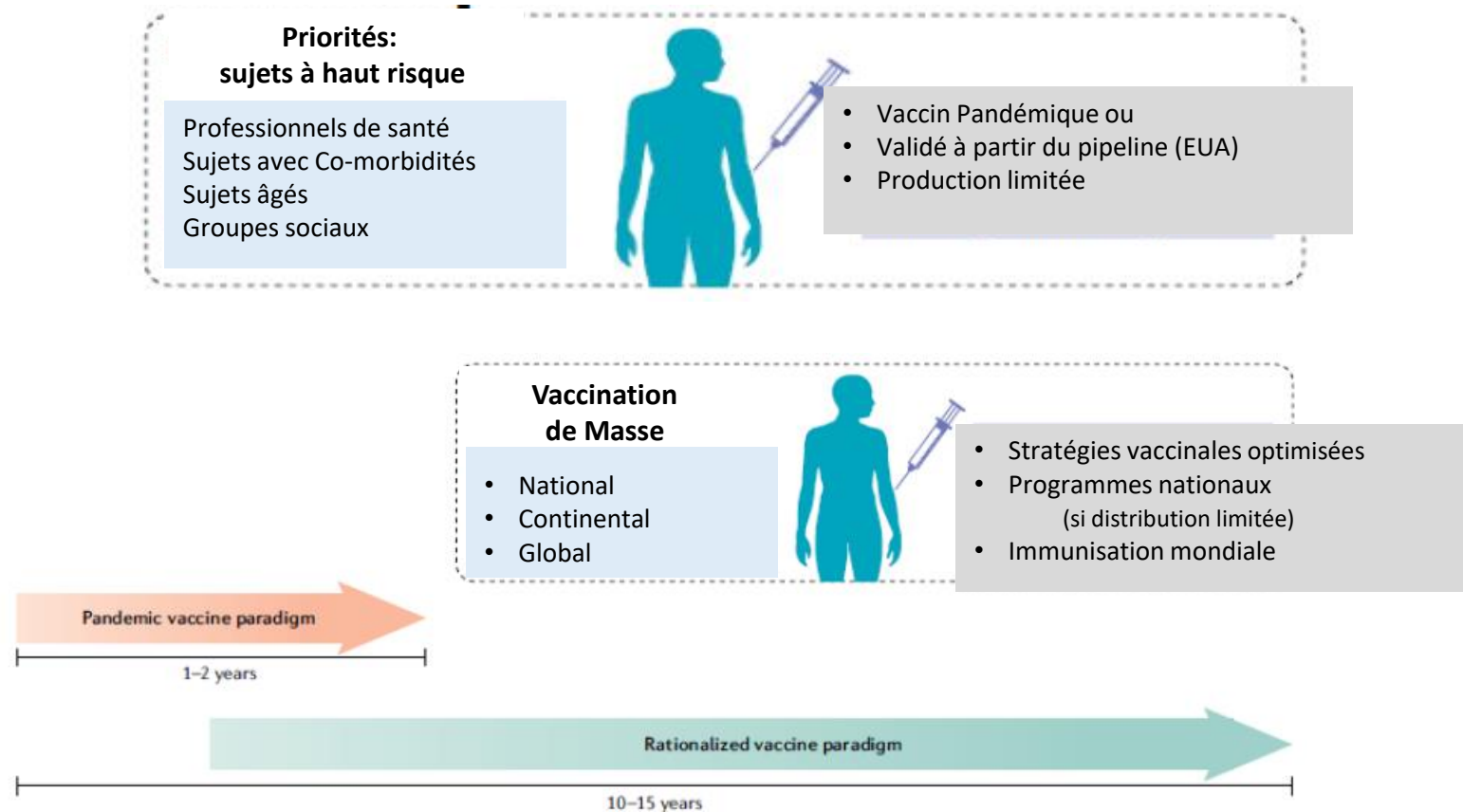


Vaccins	Origine	Cible	Vecteurs	Efficacité	Vaccins Variants	pays Autorisants
ARNm						
Cominarty	Pfizer/BioNTc	All/US	Spicule	95%	B1.351 en dev. Ph1/2	US+UK+EU + 55
Moderna Covid19	Moderna	US	Spicule	94%	B1.351 en dev. Ph2	US+UK+EU + 21
CVnCoV	Curevac/GSK	All/US			B1.351 en dev.	Ph3
Vecteurs viraux recombinants						
Vaxzevria / Covishield	AZ	UK	Spicule	ChAd3	82%	UK+EU + 99
					B1.351 en dev.	
Sputnik	I Gamaleya	R	Spicule	Ad26+Ad5	91%	R + 58 (EU, OMS: Re-Evaluation.)
JNJ	Johnson & Johnson	NL/US	Spicule	Ad26	72%	en dev. US+EU + 20
Vaccins Inactivés						
Coronovac	Sinovac	C	Virus entier	79%	?	C+WHO+ 27
BBIBP	Beijing I /SinoPharm	C	Virus entier	51%	?	44
<i>Nanoparticules/Proteine recombinante</i>						
NVX-CoV2373	Novavax	US	Spicule	82%	en dev.	En évaluation

Qui et comment vacciner contre Covid19 ou SARS-CoV2 ?

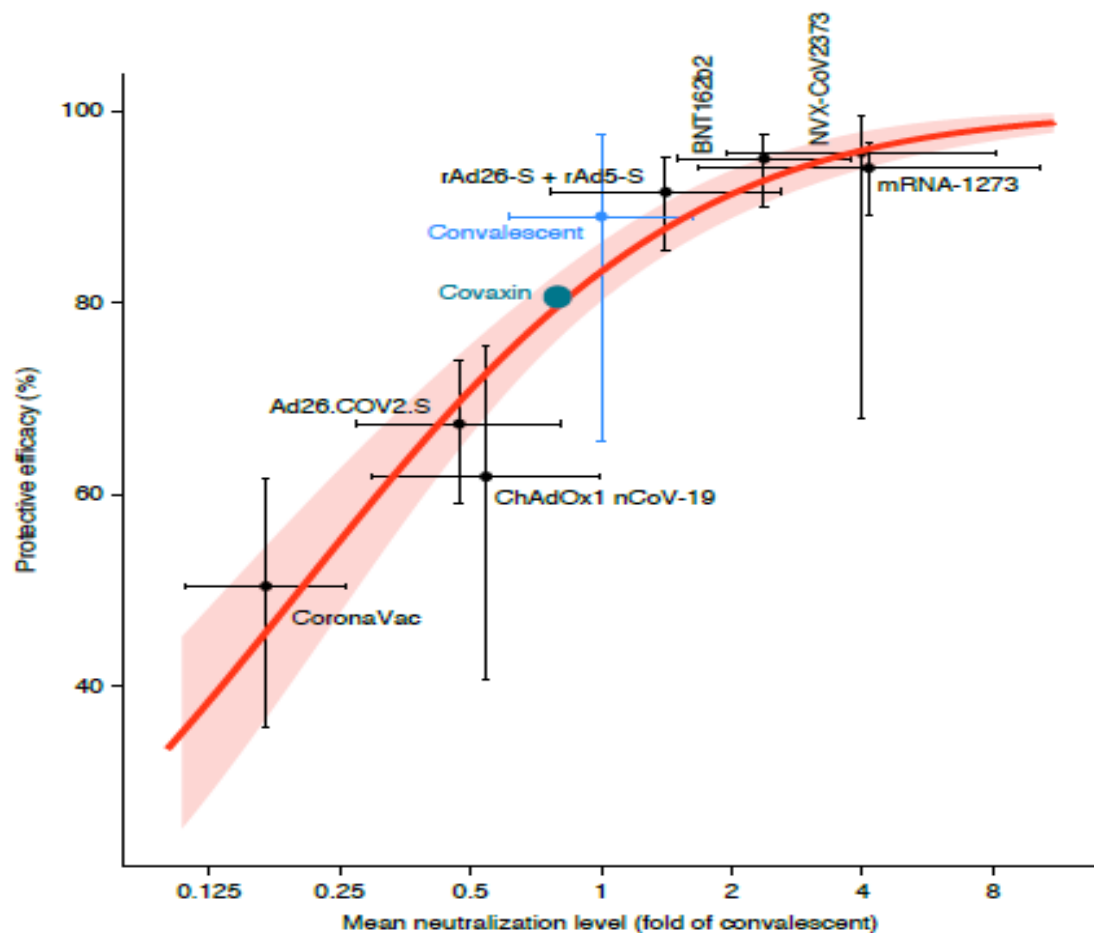
Scénarios possibles de vaccination anti-Covid19

From M Jeyanathan et al. Nature Rev. Immunol. Oct.2020



Correlats Immuns d' Efficacité Vaccinale

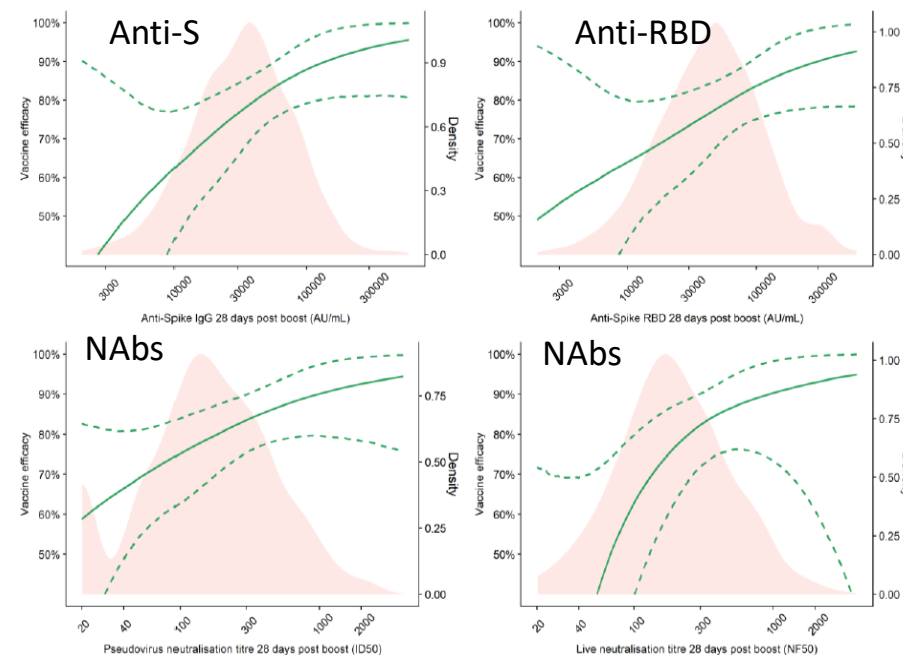
- **Ac Neutralisants corrélat à sévérité et prédisent protection** (Khoury S, Nat.Med. 21)



- **1st corrélat de protection**
 (post-AZ study / Alpha (Feng S, Nat Med 2021)

➤ **VE = 80% / symptômes = anti-S IgG = 264 BAU/mL**

(95% CI 108, 806), WHO international standard (NIBSC code 20/136).

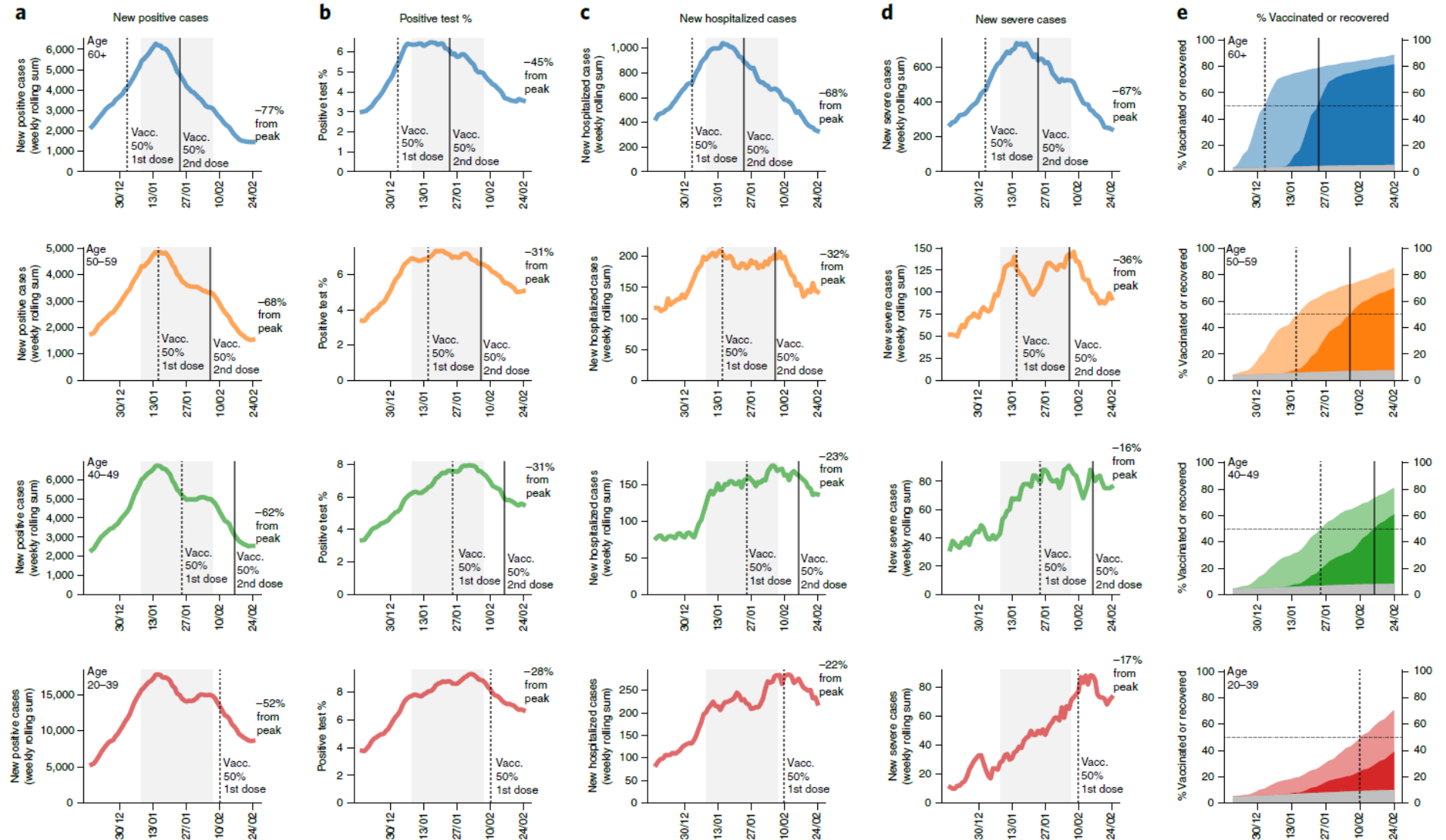


- **Contre Variants ???**

Efficacité vaccinale en vie réelle des vaccins ARNm anti-Covid-19: Expérience Israélienne

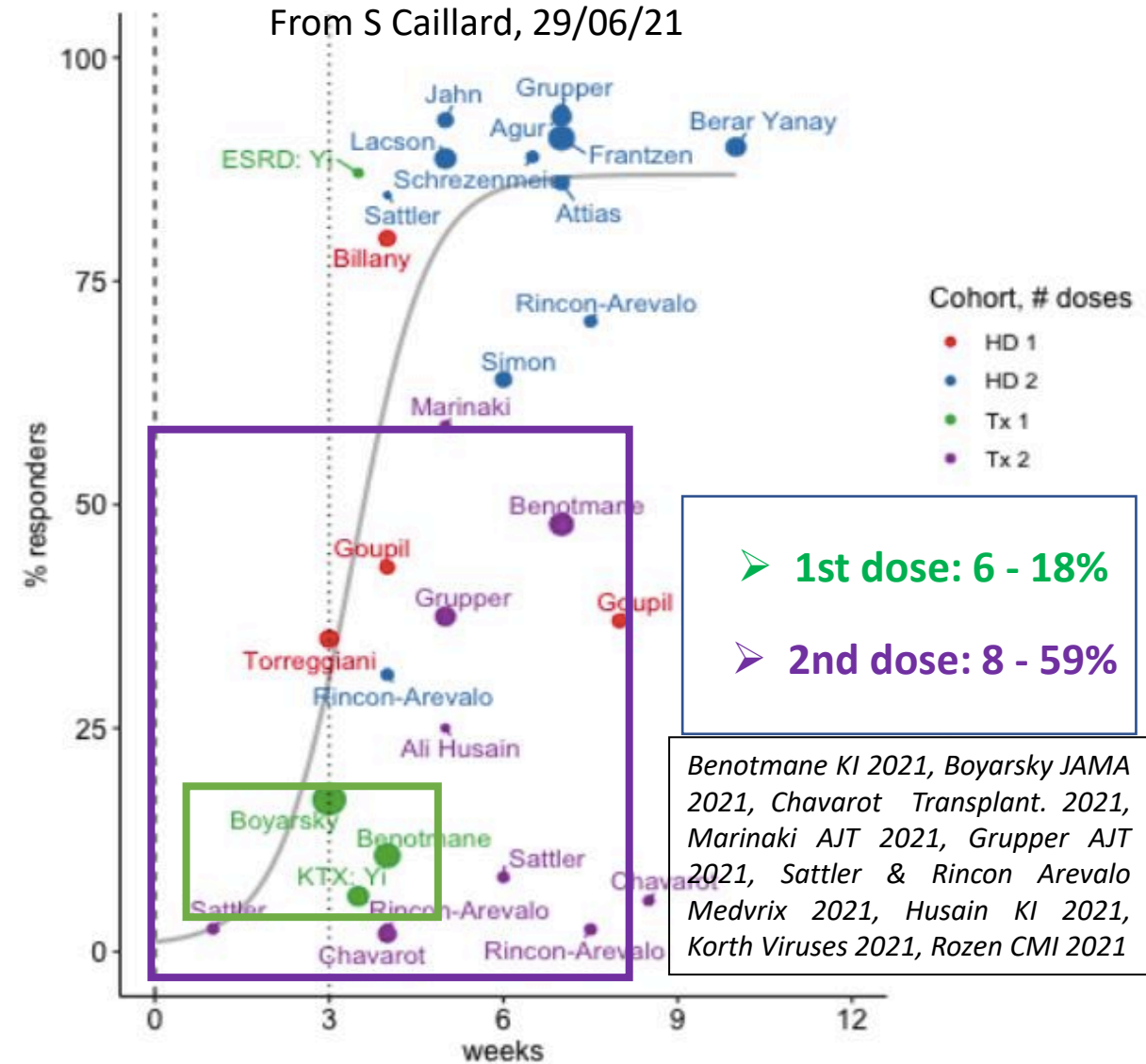
NATURE MEDICINE <https://doi.org/10.1038/s41591-021-01337-2> **ARTICLES**

H Rossman et al.



Kidney Transplants

From S Caillard, 29/06/21



ATU: 3/8/2021 :

- **casirivimab/imdevimab** : cocktail de 2 Ac Monoclonaux neutralisants : réduisent de 75% le risque d'infection:
 - Symptomatique chez contacts PCR-
 - Severe chez patients infectés
- **Prophylaxie Severely Immunosuppressed patients** :
 - Transplantés
 - Traitements immunosuppresseurs lymphopéniants, LNH, LLC...
 - Ins. Rénaux sévères
 - DIP
 - Autre cause d'immunodépression avec faible Réponse vaccinale: VIH non contrôlé...
- **PEP: Non ou Faibles Répondeurs** à vaccination
- **PreEP: Non Répondeurs**



Sécurité et Tolérance des Vaccins anti-Covid19

EMA : Status as of 28/10/2021 in the EU/EEA

➤ ARNm:

Comirnaty 428,000,000 Doses
in the EU/EEA
412,571* Reports of **suspected
side effects = 0,09%**
(see www.adrreports.eu)

Spikevax 61,600,000 Doses
in the EU/EEA
94,636* Reports of **suspected
side effects = 0,15%**
(see www.adrreports.eu)

➤ Vecteurs recombinants

Vaxzevria 68,800,000 Doses
in the EU/EEA
214,528* Reports of **suspected
side effects = 0,3%**
(see www.adrreports.eu)

Janssen 16,300,000 Doses
in the EU/EEA
28,244* Reports of **suspected
Side effects = 0,17%**
(see www.adrreports.eu)

* medical events observed after vaccination, but not necessarily related to or caused by the vaccine.

Sécurité en vie réelle des vaccins anti-SARS-CoV2: accidents thrombo-emboliques liés aux Vecteurs AdénoV recombinants



➤ **4 / 4 / 2021:** sur 34 millions de vaccins par ChAd3-CoV2 (VAXZEVRIA (AZ))

169 cas de thrombose du sinus caverneux (CVST) + 53 cas thrombose veines splanchniques (SVT) chez sujets < 60 ans, majoritairement des femmes, après 1e injection



Mécanisme ? Réponse immune Ac anti-plaquettes (anti-Pf4) ? Proche des thrombopathies à l'héparine?

Thrombotic Thrombocytopenia
after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D.,
Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

NEJM, 2021, DOI: [10.1056/NEJMoa2104840](https://doi.org/10.1056/NEJMoa2104840)

Thrombosis and Thrombocytopenia
after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D.,
Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D.,
Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D.,
Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D.,
Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D.,
and Pål A. Holme, M.D., Ph.D.

NEJM, 2021, DOI: [10.1056/NEJMoa2104882](https://doi.org/10.1056/NEJMoa2104882)

➤ **20 / 4 / 2021 : Vaccin COVID-19 Janssen: lien possible**

**Effet de classe ? Mais risques <<< bénéfiques des vaccins
Indication maintenue chez > 55 / 60 ans**

Tolérance du Vaccin Moderna anti-COVID-19



➤ Myocardites et pericardites

PRAC: Mai 2021 : 16 cas de myocardite et 18 cas de pericardite dans EU/EEA to EudraVigilance



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

sur 19 million doses = **2 cas / millions**

chez 16 – 30 ans (garçons)

formes modérées à sévères, pas de décès)

Juillet 2021 : liste les 2 complications comme **effets secondaires dans le RCP**

+ avertissement aux personnels de santé et personnes recevant le vaccin

Novembre : **Ne remet pas en cause le Rapport BENEFICE / RISQUE**

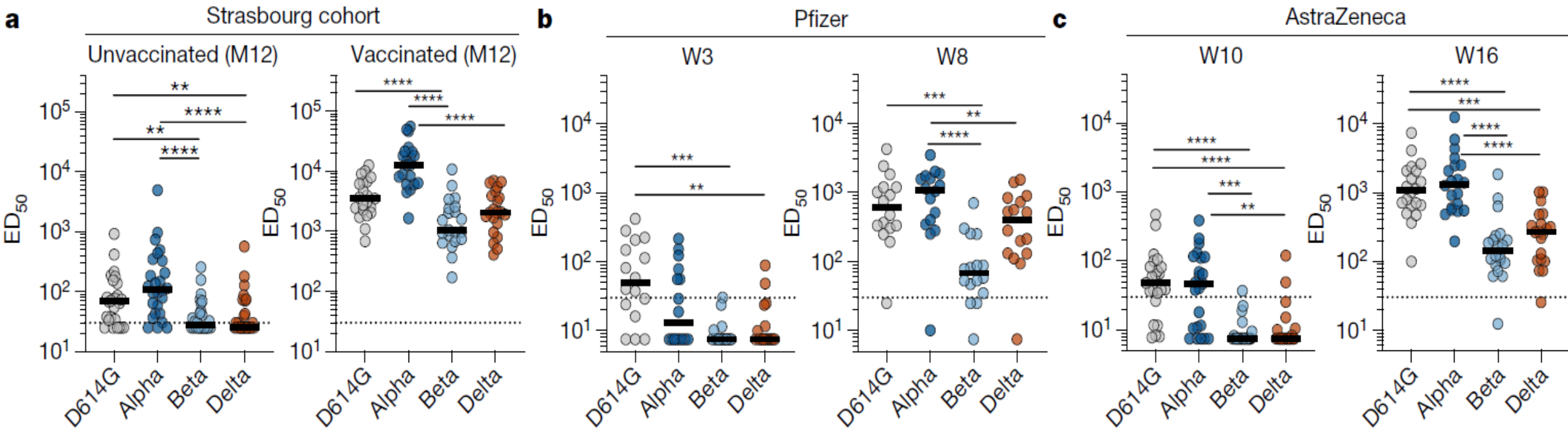
du VACCIN MODERNA

- Gargano JW, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morbidity and mortality weekly report*. 2021;70(27):977-982.
- Surveillance of myocarditis (inflammation of the heart muscle) cases between December 2020 and May 2021. News release. Israeli Ministry of Health; June 2, 2021. <https://www.gov.il/en/departments/news/01062021-03>. Accessed July 13, 2021.
- Montgomery J et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. *JAMA Cardiol*. 2021.
- Bozkurt B et al.. Myocarditis with COVID-19 mRNA Vaccines. *Circulation*. 2021.

➤ **Syndrome de fuite capillaire** : PRAC = **safety signal** : 6 cas dans EudraVigilance database. association causale avec vaccination ???? En revue.

Efficacité Vaccinale face aux Variants d'échappement

D Planas et al. Nature 2021



- **Activité Neutralisante des sérums de vaccinés (Pfizer et AZ):**
 - Conservée / Alpha ,
 - Intermediaire / Delta,
 - 1 log Diminuée / Beta

Impact de la vaccination en France : **≥ 75 ans et contre sévérité** 11/10/21, K

Surveillance pharmaco-épidémiologique de la vaccination contre la COVID-19

Type de réduction du risque	Fenêtre de temps	Suivi (mois)	N total	Type de vaccin	Réduction des risques
Période > Alpha]2-3] mois	105294	Moderna	- 96% (90% ; 98%)
			890008	Pfizer	- 93% (91% ; 94%)
]3-4] mois	51144	Moderna	- 99% (96% ; 100%)
			397316	Pfizer	- 95% (94% ; 96%)
]4-5] mois	19222	Moderna	- 98% (94% ; 99%)
			347972	Pfizer	- 97% (96% ; 97%)
	>5 mois	15282	Pfizer	- 94% (84% ; 98%)	

Autorisations
Pfizer: 21/12/20
Moderna: 8/1/21
AZ : 29/1/21
Janssen: 11/3/21

Type de réduction du risque	Fenêtre de temps	N total	Type de vaccin	Réduction des risques
Tous vaccins	Entre 20/6 et 20/7: Delta passé de 36 à 85%,		Tous	-
	Suivi du 14ème jour après la 2ème dose	1965202		

- **Efficacité en vie réelle des vaccins ARNm / Hospitalisations après 2 doses** (AZ: pb intervalle entre doses) chez **3,6 millions vaccinés** / 3,2 non vaccinés
 - >2 mois et 5 mois = **96 - 98%**
= Période **Alpha**
 - = **absence de déclin à 6 mois de EV / Hospit.** chez **≥ 75 ans**
 - entre 20/6 et 20/7 = **84%**
= Période **Delta**

Impact de la vaccination en France : **50-74 ans et contre sévérité**

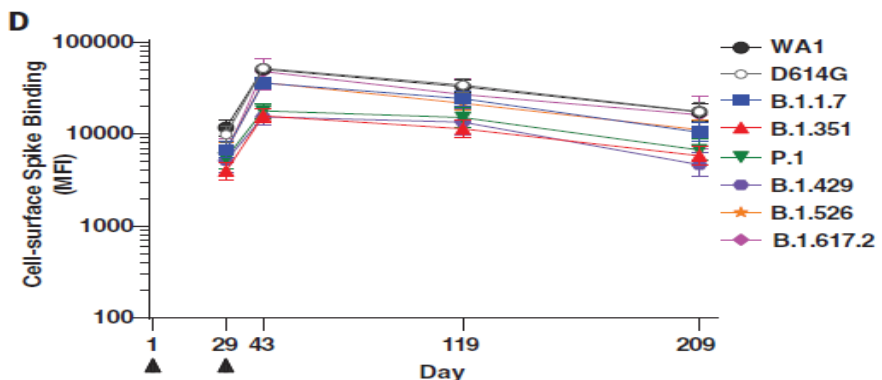
11/10/21, *MJ Jabagi et al.*

Fenêtre de temps	N total	Spécialité de vaccin	Réduction des risques
Suivi du 7ème jour après la 2ème dose	595704	MODERNA	93% (88% ; 96%)
	1945136	ASTRAZENECA	92% (86% ; 95%)
	4536056	PFIZER	91% (90% ; 92%)

- **EV en vie réelle** chez **7,7 millions** de **vaccinés 50-74 ans** vs 7,7 non vaccinés
 - **96% et 97%** après **3-4 mois et 4-5 mois**.
 - **92%** entre 20/6 et 20/7/2021 = Période **Delta**.

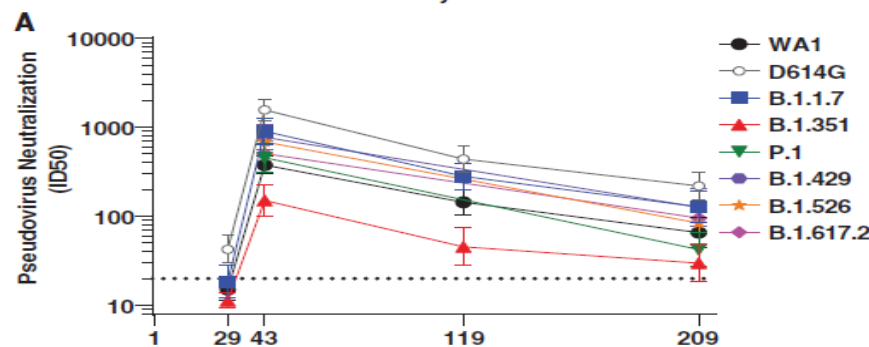
Décroissance post-vaccinale de l'immunité contre les variants

Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants *A Pegu et al. Science 2021*



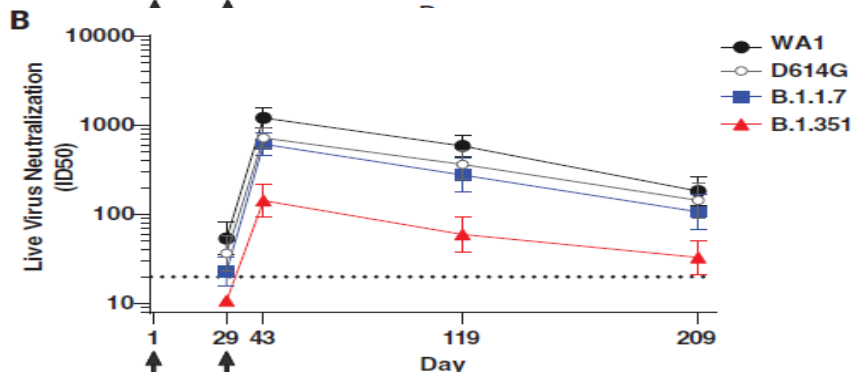
➤ 2e dose = nécessaire à Neutralisation large

➤ Décroissance Ac parallèle/ variants



➤ Durabilité Ac Neutralisants:

> 6 months



➤ Mais efficacité / Variants ???

mRNA Vaccination Induces Durable Immune Memory to SARS-CoV-2 with Continued Evolution to Variants of Concern

Goel, Painter, Apostolidis, and Mathew et al. 2021 doi: <https://doi.org/10.1101/2021.08.23.457229>

▪ **Décroissance des titres**

d'Ac : 1/2-life : 2 mois,

= Dynamique typique

d'une réponse immune

Normale

▪ **Augmentation Progressive de**

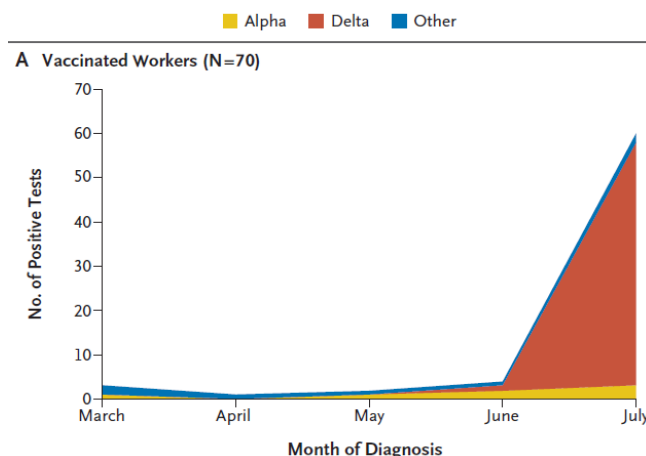
la **Memoire**

Décroissance de l'efficacité vaccinale ou Effet confondant du Delta ?

Institute	Référence	Study/Population	Results	Limits
Pfizer ; University of New-York	Polack et al. NEJM. 383(27), 2603-2615.	<ul style="list-style-type: none"> ● Pfizer placebo-controlled, observer-blinded, pivotal efficacy trial (130 sites USA ; 1 Argentina; 2 Brasil ; 4 S-Africa; 6 : Germany; 9 :Turkey) ● n > 40 000 ● VE + safety > 6-months post- vaccination ● Criteria: > 12y, No prior Covid-19 	<ul style="list-style-type: none"> ● VE / symptomatic infection = 91.3% over 6 mo ● 2 - 4 mo post dose 2: 90.1%, ● 4 - 6 mo: 83,7% 	<ul style="list-style-type: none"> ● No data on asymptomatic infection
Public Health England, NIHR LSH	Andrew, N. et al. 2021. Cold Spring Harbor Laboratory.	<ul style="list-style-type: none"> ● Test-negative case-control design ● n > 3 million (39%=AZ, 32%= Pfizer, 2.4% =Moderna) ● Alpha + Delta ● Hospitalisation <14 d post + PCR ● Death<28d post + PCR ● Match / age, comorbidity 	<ul style="list-style-type: none"> ● VE / symptomatic Delta >dose2: ● 1 wk : VXZ=63%, BNT =92.4%, mRNA1273=-95.2 ● 10-14 wks : VXZ=59.3% ; BNT=-80.3% ; mRNA1273 = 90.3% ● VE/ hospitalization/Delta : ● > 1wk: VXZ=-94%, BNT= 99.7%, mRNA1273 =-97.5%] ● 2-9 wks : VXZ=-95%, BNT=98.4% , mRNA1273 =100% 	<ul style="list-style-type: none"> ● No control of data monitoring ● Bias? ● No mRNA1273a data > 14 wks or death ● Prior infection excluded only if PCR

Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce *J Keehner et al. NEJM, 2021*

- **VE chez les PFS vaccinés**
Avril = 90%
Juillet = 65%
- **Mais survenue du variant Delta**



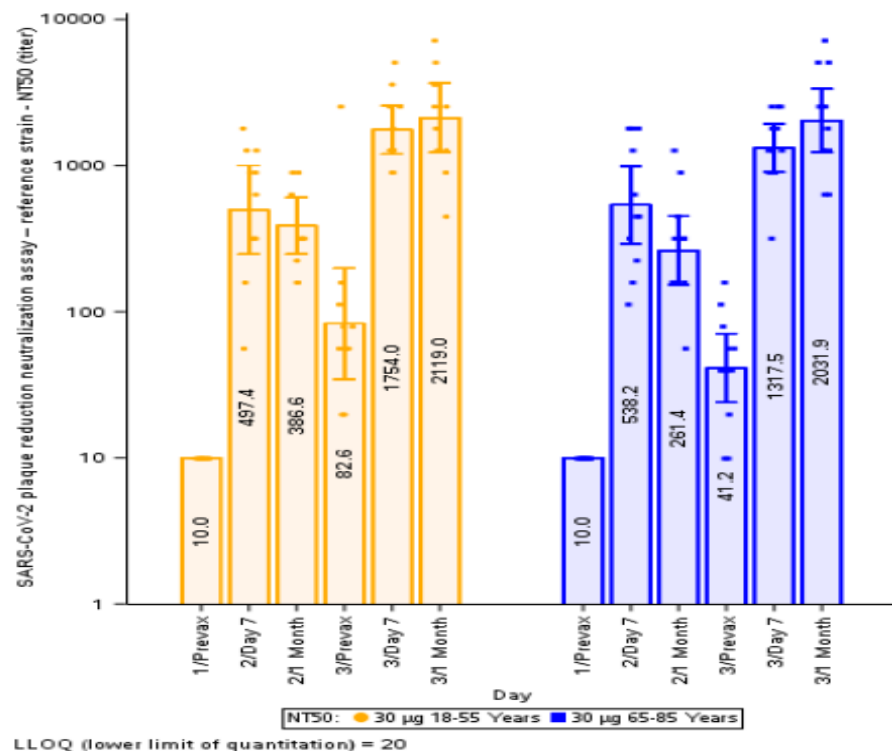
EV contre :

- **l'infection: décroît de 80-90% post-D2 à 50% à 6 mois**
- **les formes sévères: Stable mais légère décroissance : 80-92%**

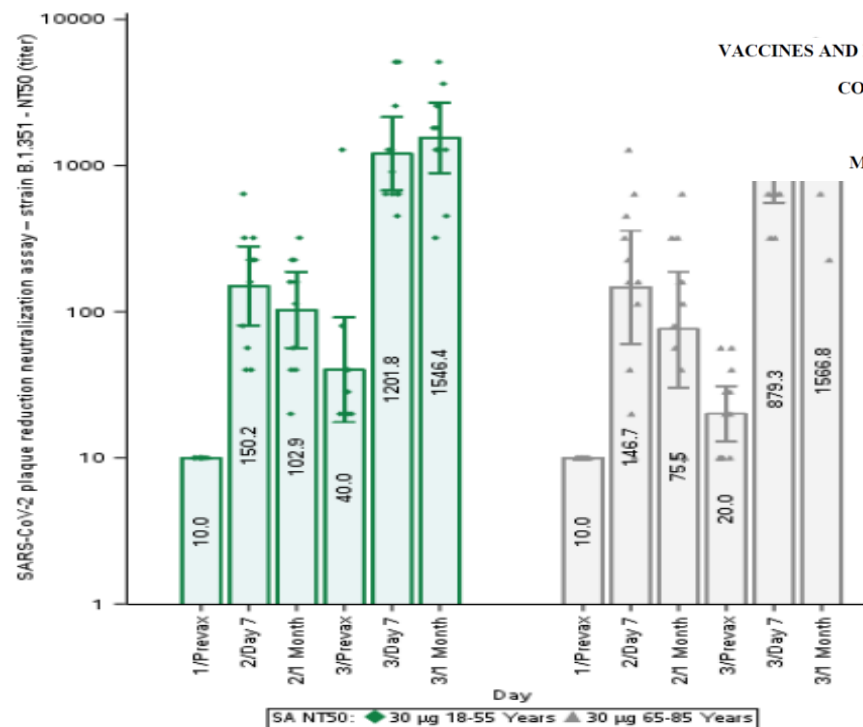
-Goldberg et al (2021) Waning immunity after the BNT162b2 vaccine in Israël, NJEM 2021 ; -Cohn, B.A. et al (2021), Science.; -Rosenberg et al (2021), Cold Spring Harbor Laboratory.; -Chemaitelly et al (Octobre 2021), NEJM; -Nordström et al (Octobre 2021), The Lancet Regional Health – Europe (p.100249)

Effet des **Rappels** de vaccination

BNT162b2 Boost 6 mois post Primovaccination :



Wild-type (Reference Strain)



Beta variant (B.1.351)

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY
 COMMITTEE BRIEFING DOCUMENT
ocoa@tda.nhs.gov
 MEETING DATE: 17 September 2021

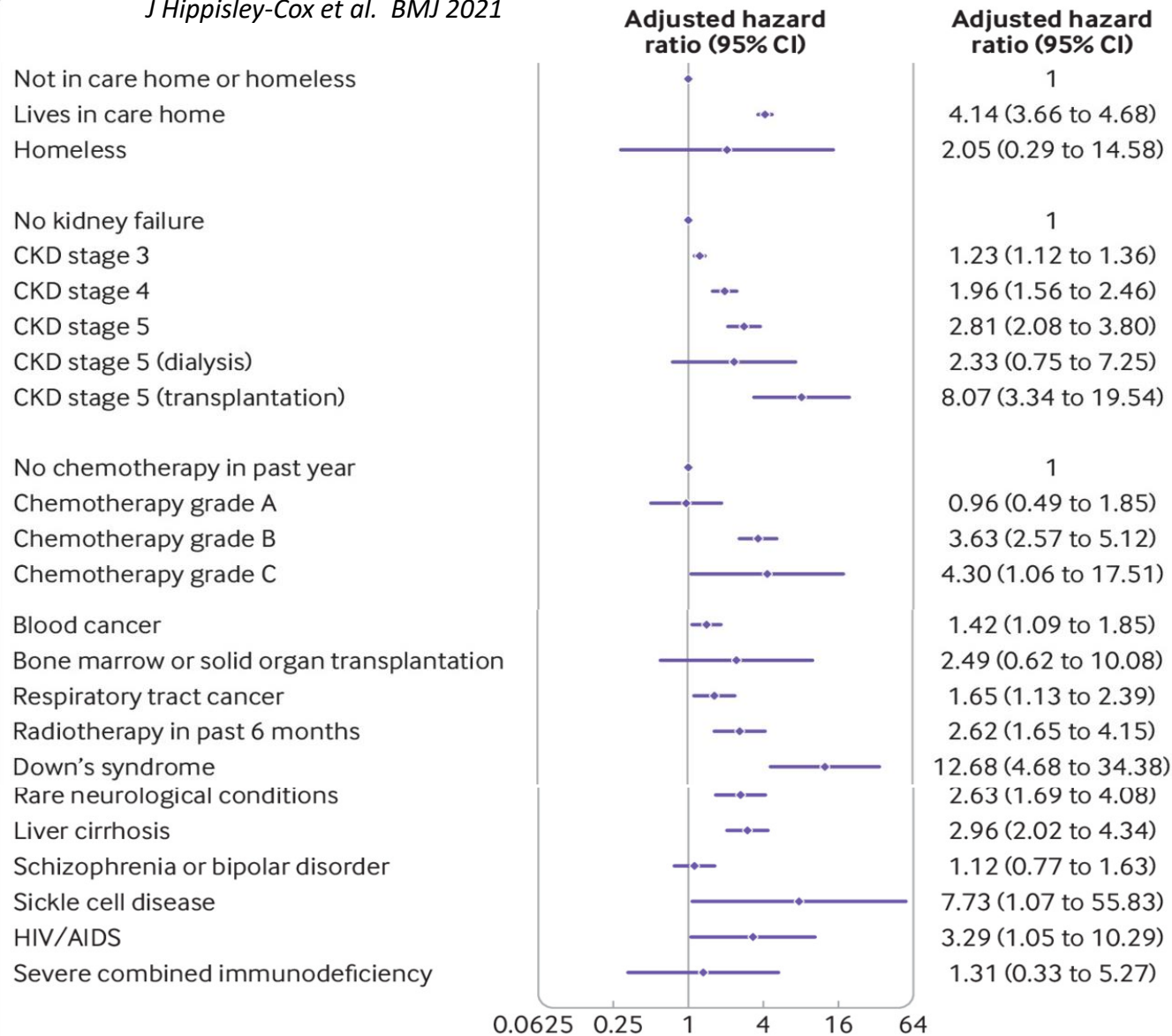
- Augmentation de 10-fois increase activité Neutralisante : chez:
 - Jeunes et
 - Agés

- Augmentation du Spectre
- Tolérance
- VE démontrée en Israel (*Bar-On et al. 2021*)

Chez Qui faire des Rappels ?

Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study

J Hippisley-Cox et al. BMJ 2021



➤ Recommandations actuelles









➤ Sujets âgés > 65 years old

Facteurs de risque et Immunodéprimés

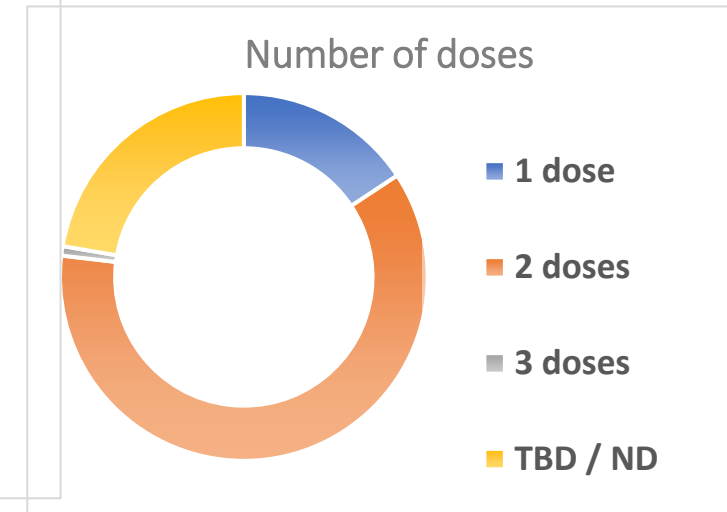
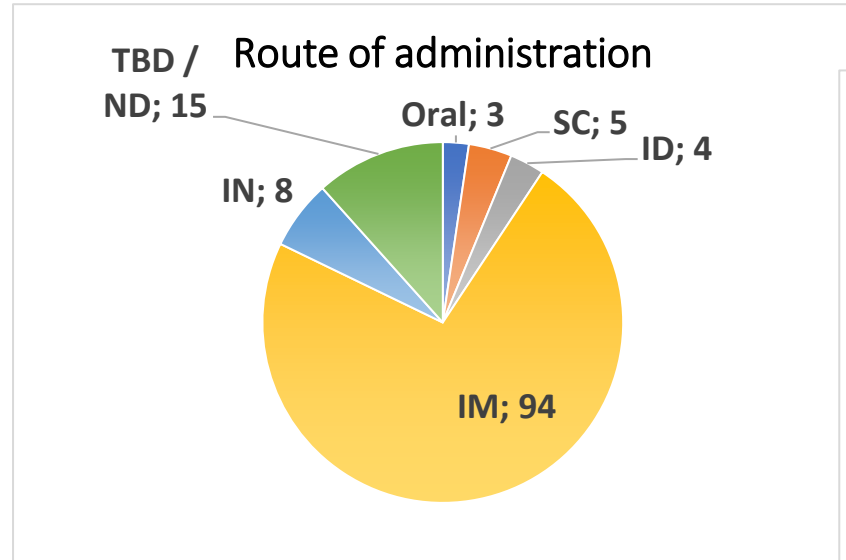
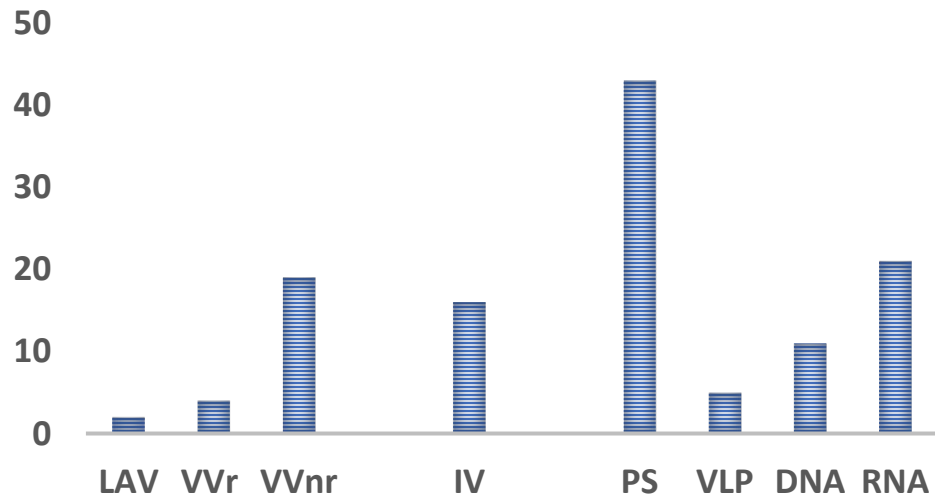
➤ 6 mois après PrimoVacc (3 pour ImmunoDep)

➤ 15/12 : Plus de 50 ans

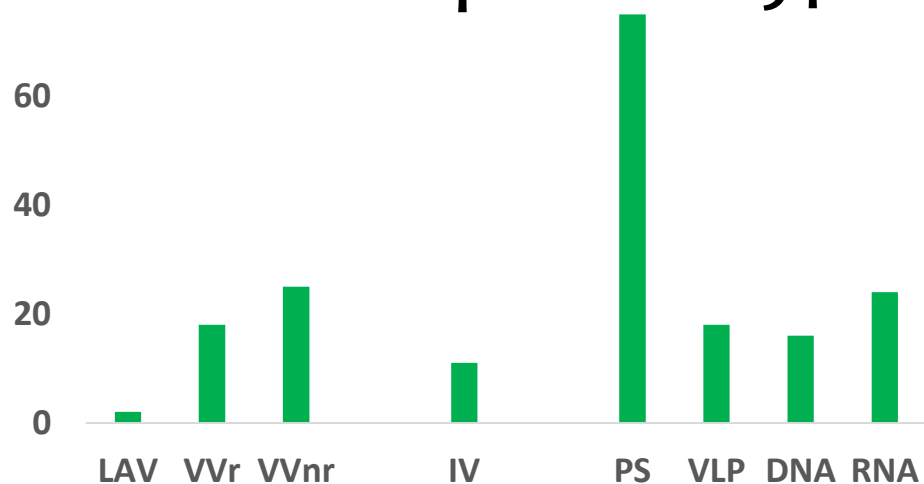
Vaccins en cours d'évaluation par l'OMS (11 / 11/ 2021)

Manufacturer / WHO EUL holder	Name of Vaccine	NRA of Record	Platform	EOI accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Decision date***
 Sinopharm / BIBP ¹ Beijing Institute of Biological Products Co., Ltd. (BIBP)	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	NMPA	Inactivated	✓	✓	✓	Finalized 2 and 5 dose presentation (new manufacturing site)	07 May 2021 TBC after ongoing inspection
 Sinovac Sinovac Life Sciences Co., Ltd. Sinovac Life Sciences Co., Ltd.	COVID-19 Vaccine (Vero Cell), Inactivated/ Coronavac™	NMPA	Inactivated, produced in Vero cells Inactivated	✓	✓		Finalized 2 dose presentation	01 June 2021 30 September 2021
 THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	Sputnik V	Russian NRA	Human Adenovirus Vector-based Covid-19 vaccine Rec Adenovirus Vector	Additional information submitted	Several meetings have been and continue to be held.	"Rolling" submission incomplete.	Process restarted, awaiting completion of rolling submission and CAPAs to last inspection-	Anticipated date will be set once all data is submitted and follow-up of inspection observations completed.
 BHARAT BIOTECH Bharat Biotech, India	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)/ COVAXIN	DCGI	Whole-Virion Inactivated Vero Cell Inactivated	✓	✓	✓	Finalized	03 November 2021
 Sinopharm / WIBP ²	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	NMPA	Inactivated	✓	✓	Rolling data started 23 July 2021	Ongoing	To be confirmed
 康希诺生物 CanSinoBio	Ad5-nCoV	NMPA	Rec Adenovirus Vector	✓	✓	Rolling data started 09 August 2021	Ongoing; inspection ongoing	TBC
 NOVAVAX	NVX-CoV2373/Covovax	EMA	Rec. Spike Nanopartic.	✓	✓	Rolling data started 19 August 2021	Ongoing	TBC
 SANOFI	CoV2 preS dTM-AS03 vaccine	EMA	Rec. Spike Protein	✓		Rolling data started 30 July 2021	Ongoing	TBC

➤ Clinical phase : N=121



➤ Pre-Clinical phase : N=194



- Vaccine Type : Proteine >> ARNm = VVnr
- Vaccine Route : IM >> IN > SC, ID, Or
- Vaccine Dose: 2 doses >> 1 dose



Futurs Vaccins anti-Covid19

➤ Pour **ACCES GLOBAL** à Immunisation Primaire

➤ Pour un contrôle global de la maladie et réduction du **risque d'émergence de variants**

➤ **COVAX** : collaborer pour un accès mondial et équitable aux vaccins anti-COVID-19

BILL & MELINDA
GATES foundation

CEPI

FIND
Because diagnosis matters

Gavi
The Vaccine Alliance

The Global Fund

Unitaid
Innovation in Global Health

W
wellcome

World Health
Organization

WORLD BANK GROUP

➤ Pour Rappels

➤ Pour une adaptation éventuelle aux variants

➤ Pour Vaccination des enfants de 5-12 ans ??

Comité Scientifique Vaccins Covid19

President : MP Kieny

- B Autran
- C Bardin
- X de Lamballerie
- B Fanget
- A Fischer
- B Fritzell
- A Fischer
- O Launay
- S Paul
- CA Siegrist
- M De wilde

Comité d'Orientation de la Stratégie Vaccinale

President : A Fischer

- B Autran
- C Bardin
- N Brun
- Y Caillie
- A Fontanet
- J Gaillat
- F Jusot
- X de Lamballerie
- D Heard
- M Heard
- H Monnier
- H Partouche
- P Peretti-Watel

MabTher Reacting group:

Coordonnation : Brigitte Autran,

- Xavier de Lamballerie:
- Jeremie Guedj
- Nathan Pfeiffer-Smadja
- Florence Ader
- Bruno Hoen
- Alexandre Duvignaud
- Laurence Weiss
- Guillaume Martin-Blondel,
- Jacques-Eric Gottenberg,
- Olivier Saint-Lary,
- Odile Launay,