



Evaluer la balance bénéfique/risque des médicaments. Les leçons de la pandémie

Pr Jean-Luc Cracowski,
Centre Régional de Pharmacovigilance de Grenoble

Liens d'intérêt

Déclaration publique d'intérêts consultable sur <https://dpi.sante.gouv.fr/>



Didier Raoult ✓
@raoult_didier



Nos deux articles publiés ce soir permettent de continuer à démontrer :

1. L'efficacité de notre protocole, sur 80 patients.
2. La pertinence de l'association de l'hydroxychloroquine et de l'azithromycine, grâce à des recherches réalisées dans notre laboratoire de confinement P3.



Didier Raoult ✓ @raoult_didier

Nouveaux résultats de l'IHU Méditerranée Infection : 80 patients traités par une association hydroxychloroquine/azithromycine.
mediterranee-infection.com/wp-content/upl...

10:30 PM · 27 mars 2020



♥ 13,9 k 💬 1 k 🔗 Copier le lien du Tweet

Evaluation descriptive, non quantitative par la FDA

<i>Benefit-Risk Integrated Assessment</i>		
<i>Benefit-Risk Dimensions</i>		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

<https://www.fda.gov/files/about%20fda/published/Benefit-Risk-Assessment-in-Drug-Regulatory-Decision-Making.pdf>
Last accessed Sept. 2021

Un vaccin efficace à 90% : quatre questions sur l'annonce fracassante de Pfizer

Le 9 novembre 2020 à 17h10, modifié le 10 novembre 2020 à 07h16

Les résultats brandis conjointement par le laboratoire et BioNTech sont prometteurs. D'autres étapes sont toutefois nécessaires avant d'envisager une commercialisation.



Contre le variant indien, le vaccin Pfizer efficace à 88 %, celui d'AstraZeneca à 60 %

Publié le 23 mai 2021 à 05h16 - Mis à jour le 28 mai 2021 à 17h11 · 🕒 Lecture 2 min. *Le Monde*

Covid : le vaccin de Moderna efficace à 100 % chez les adolescents

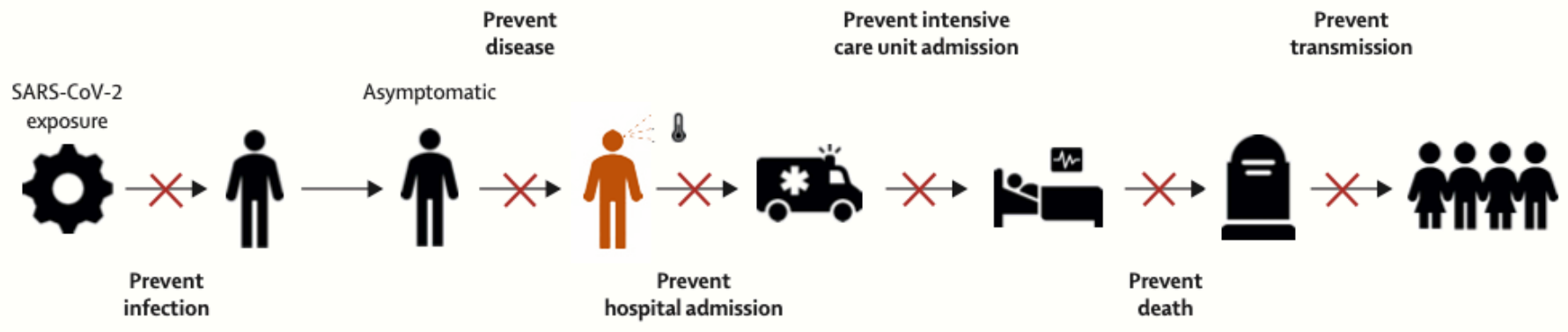
Les Echos Publié le 25 mai 2021 à 15:38

Vrai ou Fake : les vaccins sont-ils efficaces contre le variant Delta ?

Publié le 02/07/2021 17:50 Mis à jour le 02/07/2021 17:50

franceinfo:

Efficacité des vaccins de la COVID



Efficacité des vaccins de la COVID

Quel nombre de sujets dans les essais ?

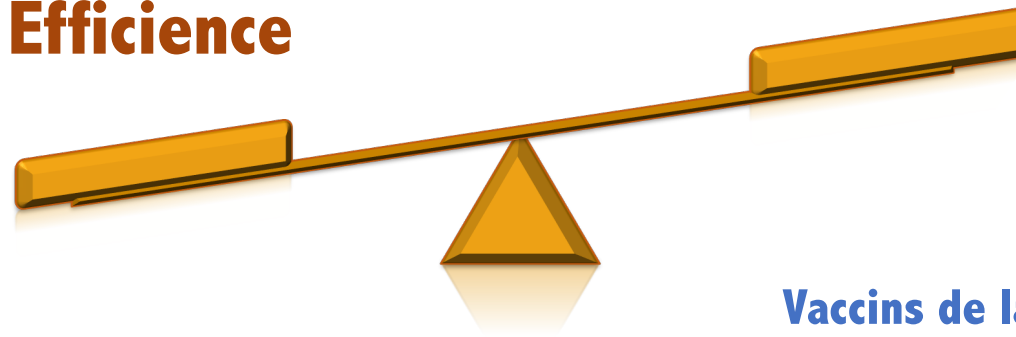
	Infection	Symptomatic infection	Hospital admission	Death
0.12 infections per 1000 people per day over 6 months*				
20–29 years	1880	3154	183 930	619 130
>80 years	1880	3154	10 364	24 494
0.013 infections per 1000 people per day over 6 months†				
20–29 years	17 876	29 816	1 722 106	5 796 166
>80 years	17 876	29 816	97 304	229 584

Bénéfice(s)

Risque(s)

**Efficacité
Effectivité
Efficience**

iatrogénie



Vaccins de la Covid

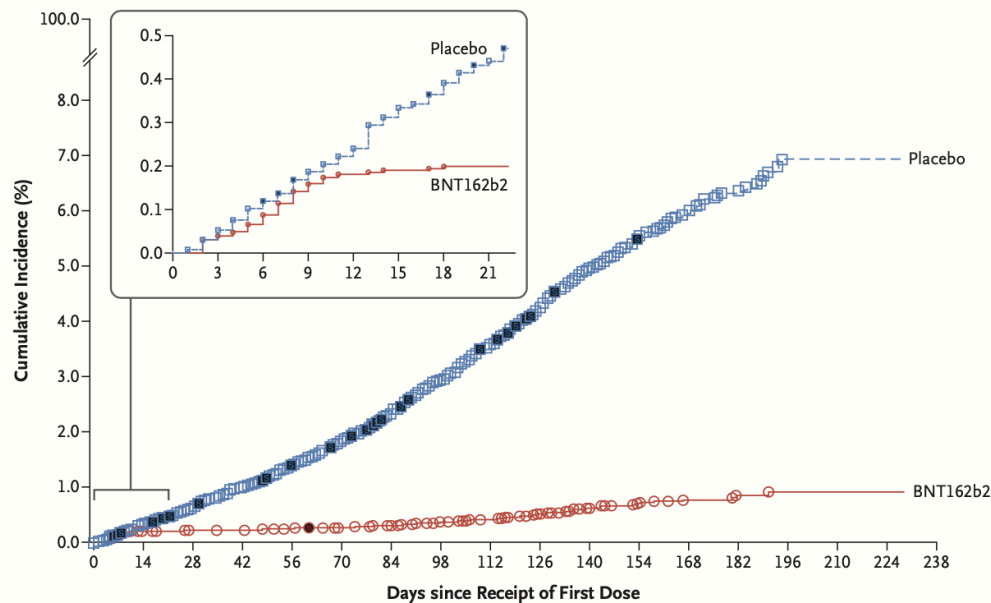
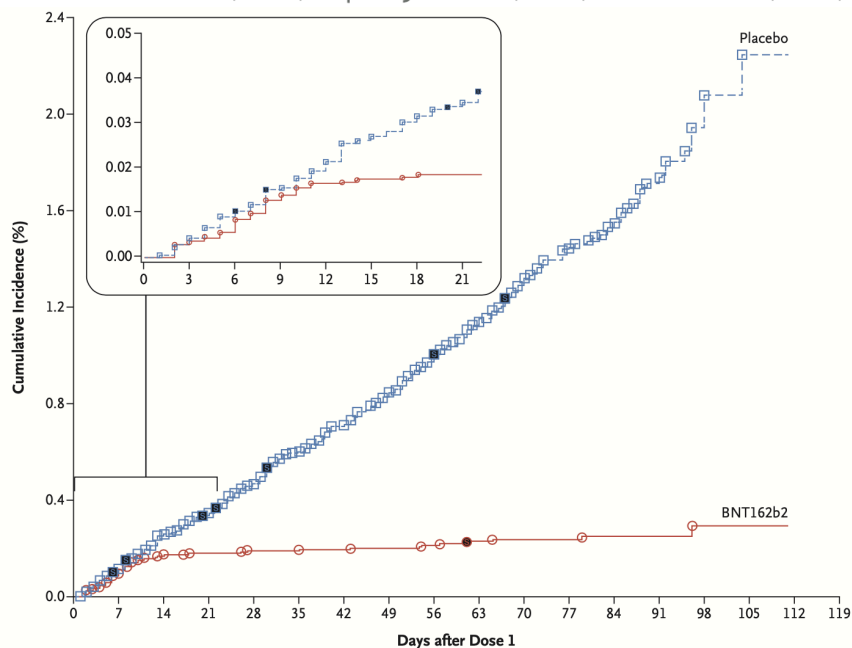
ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months

S.J. Thomas, E.D. Moreira, Jr., N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart,

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D.,



Efficacy End-Point Subgroup	BNT162b2, 30 µg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time person-yr (no. at risk)	No. of participants	Surveillance time person-yr (no. at risk)	percent
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)

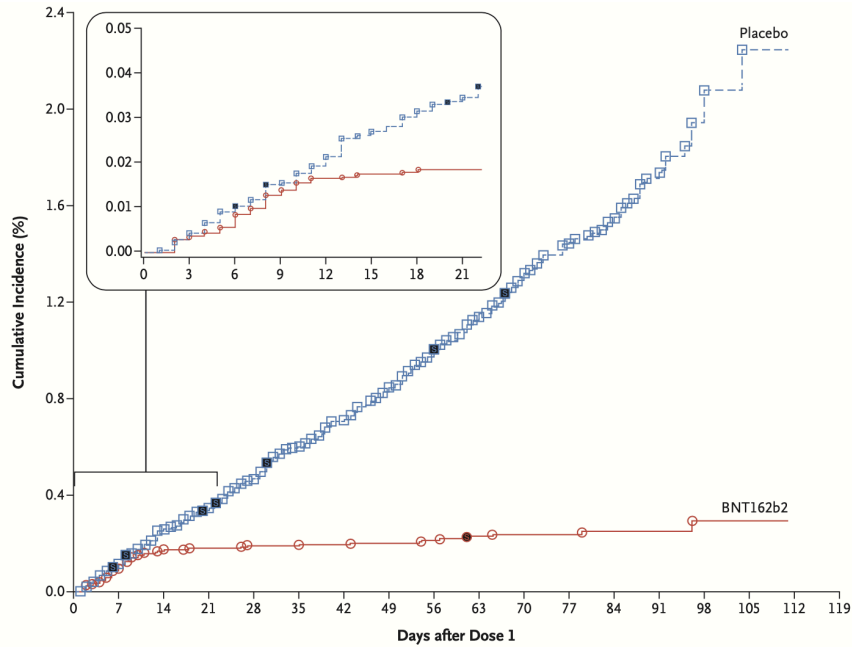
Efficacy End Point

Efficacy End Point	BNT162b2 (N=23,040)			Placebo (N=23,037)			Vaccine Efficacy % (95% CI)
	No. of cases	Surveillance time 1000 person-yr	No. at risk	No. of cases	Surveillance time 1000 person-yr	No. at risk	
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.2 (88.9 to 93.0)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

ORIGINAL ARTICLE

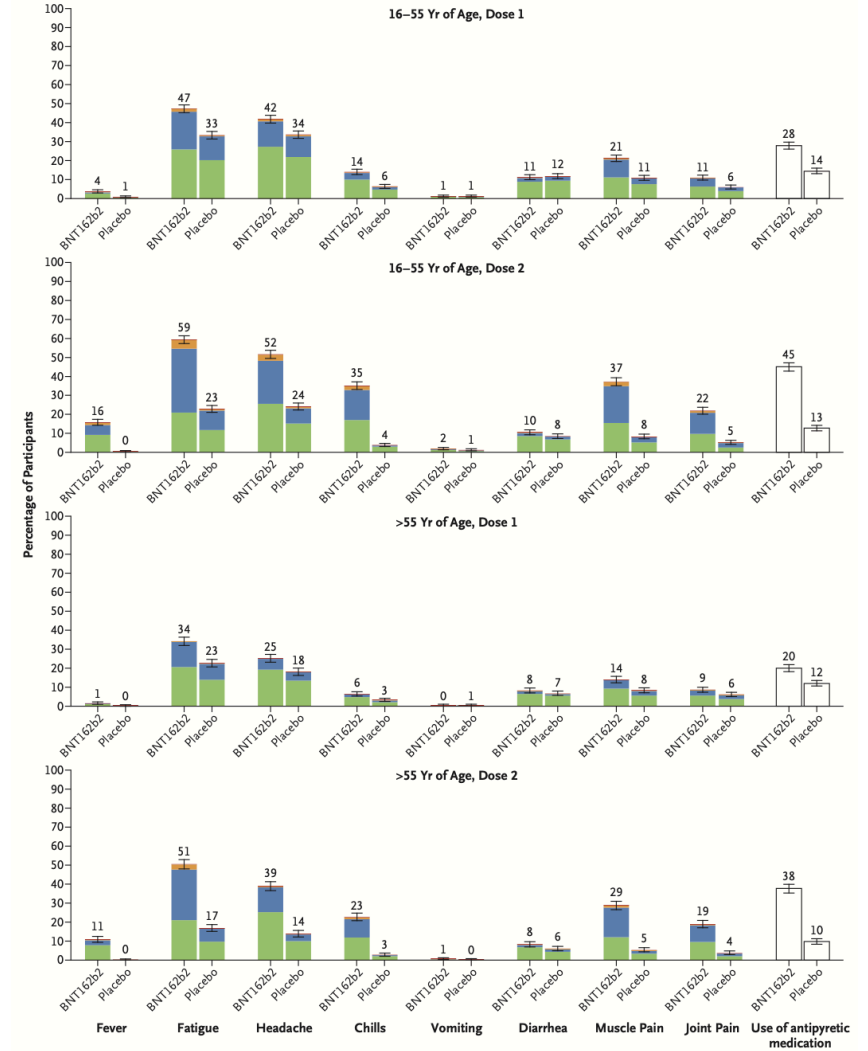
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B Systemic Events and Use of Medication

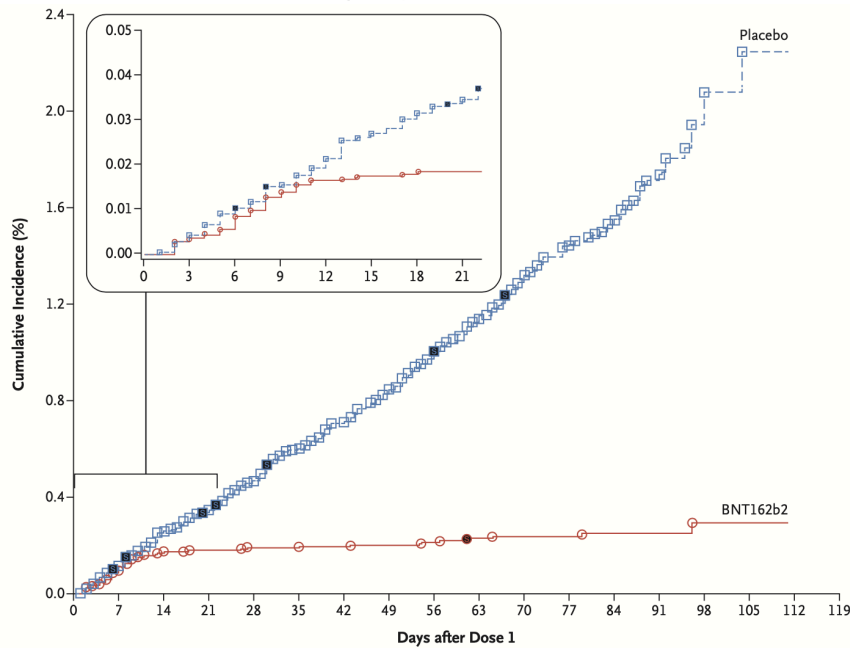


ORIGINAL ARTICLE



Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, **none reported an immediate adverse event** (occurring within 30 minutes after dosing) **that was indicative of an allergic reaction to vaccine.**

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population)

Aucune notion de myocardite/péricardite

Impossibilité de détecter des effets indésirables de fréquence rare dans les essais cliniques

Chiffre souvent retrouvé : au cours des essais cliniques, un EI dont la fréquence est de 1/n, sera détecté avec 95% de chance si la population de l'essai est de 3n :
-> Myocardites 3/100 000 chez les hommes de moins de 30 ans...

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Bénéfice(s)

Risque(s)

Essais cliniques

Pharmacoépidémiologie

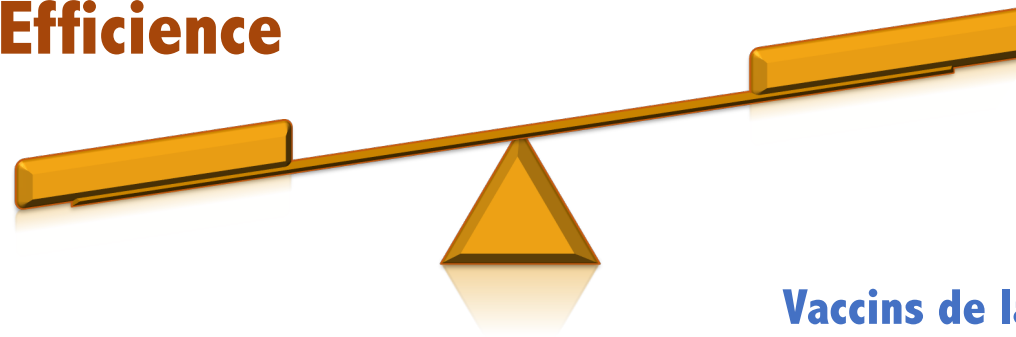
Essais cliniques

Pharmacovigilance

Pharmacoépidémiologie

Efficacité
Effectivité
Effizienz

iatrogénie



Vaccins de la Covid

Calcul de l'efficacité des vaccins de la COVID

Table 2. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S (N=19,514)		Placebo (N=19,544)		Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,306)		Placebo (N=19,178)		Vaccine Efficacy (95% CI)
	no. of cases	person-yr	no. of cases	person-yr		%	no. of cases	person-yr	no. of cases	
Moderate to severe–critical Covid-19	116	3116.6	348	3096.1	66.9 (59.0–73.4)	66	3102.0	193	3070.7	66.1 (55.0–74.8)

JANSSEN	Vaccinated group	Placebo or control
Moderate to severe-critical COVID nb cases	116	348
No Covid nb subject (person.year)	3000,6	2748,1
Event rate	0,037	0,112

Sadoff et al NEJM 2021.DOI:
10.1056/NEJMoa2101544

Efficacy= Relative risk reduction = 1-RR = 66,9 %

Number needed to vaccinate = 1/absolute risk reduction = 1/(CER-VER) = 13,3

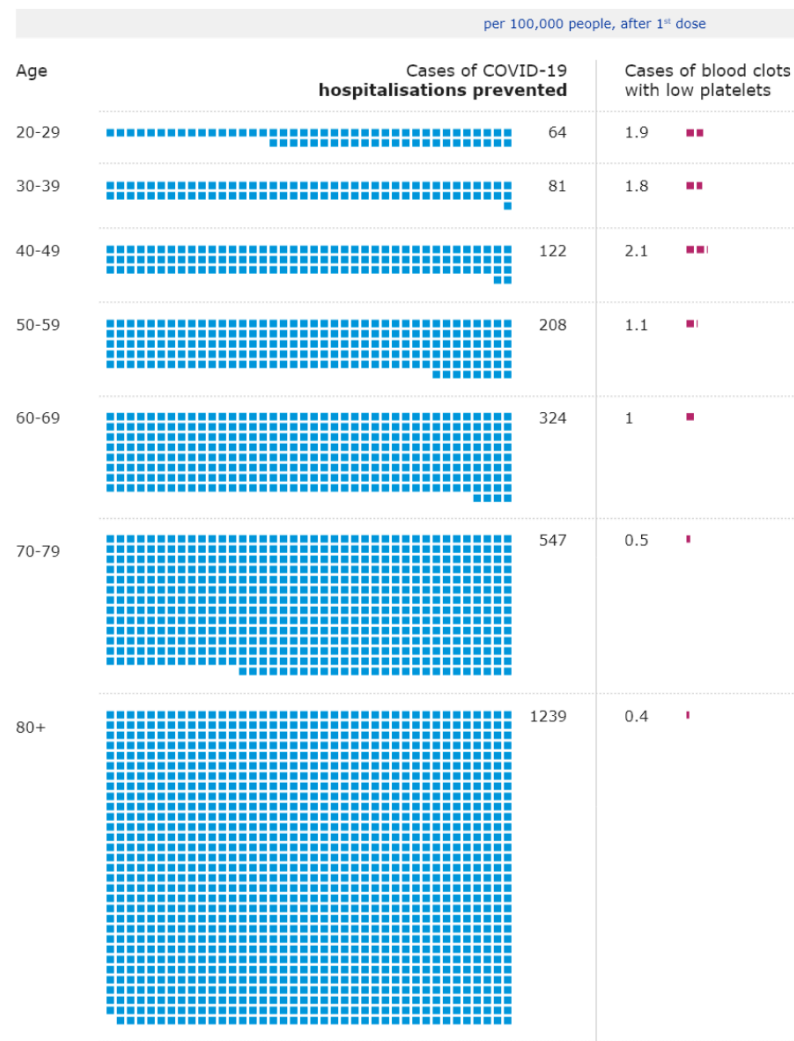
Situation **hypothétique** de doublement de l'incidence des cas

JANSSEN	Vaccinated group	Placebo or control
Moderate to severe-critical COVID nb cases	116 x 2 =232	348 x 2 =696
No Covid nb subject (person.year)	2884	2400
Event rate	0,074	0,224

Efficacy= Relative risk reduction = $1-RR = 66,9 \%$

Number needed to vaccinate = $1/\text{absolute risk reduction} = 1/(\text{CER-VER}) = 6,66$

High infection rate*



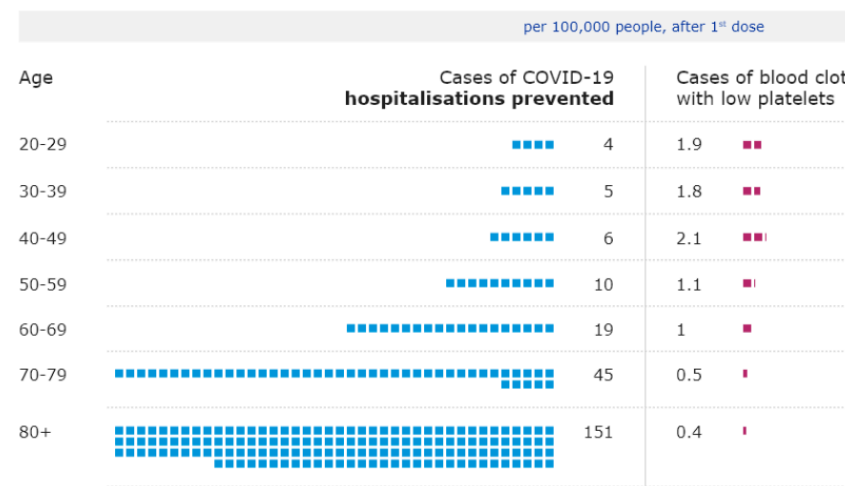
* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Annex to Vaxzevria Art.5.3 - Visual risk contextualisation

Low infection rate*

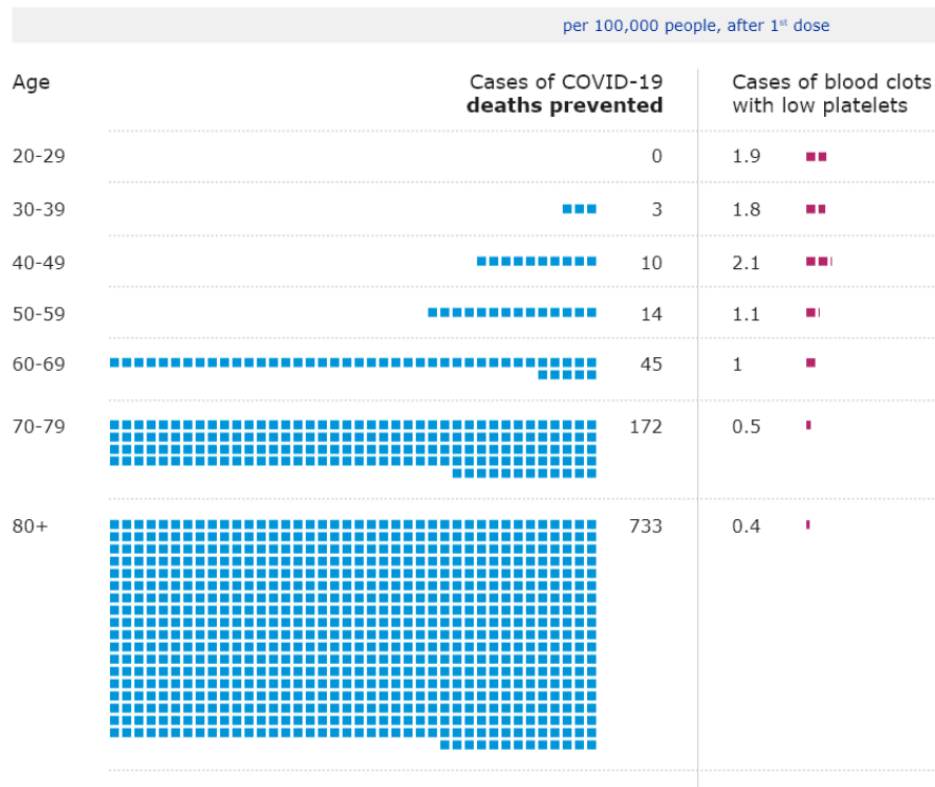


* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

23 April 2021 EMA/234525/2021
European Medicines Agency

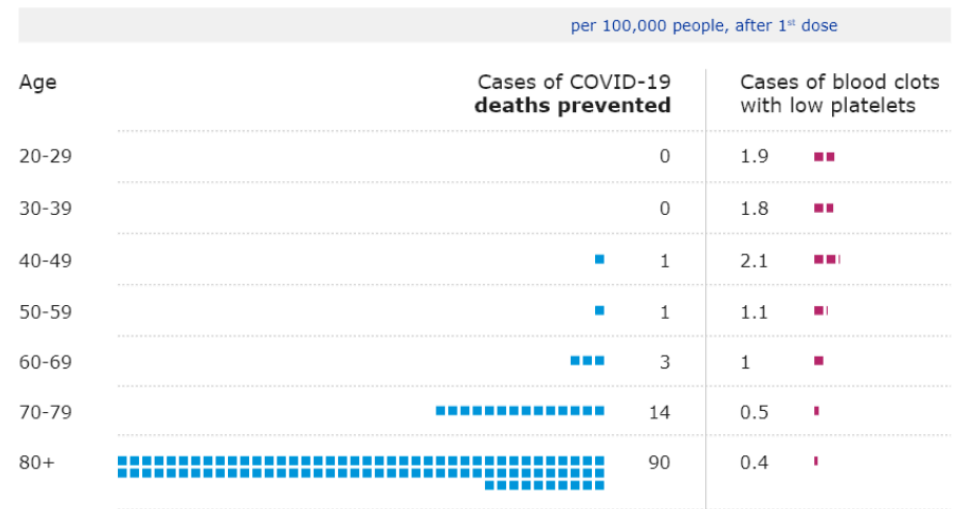
Bénéfice(s)

High infection rate*

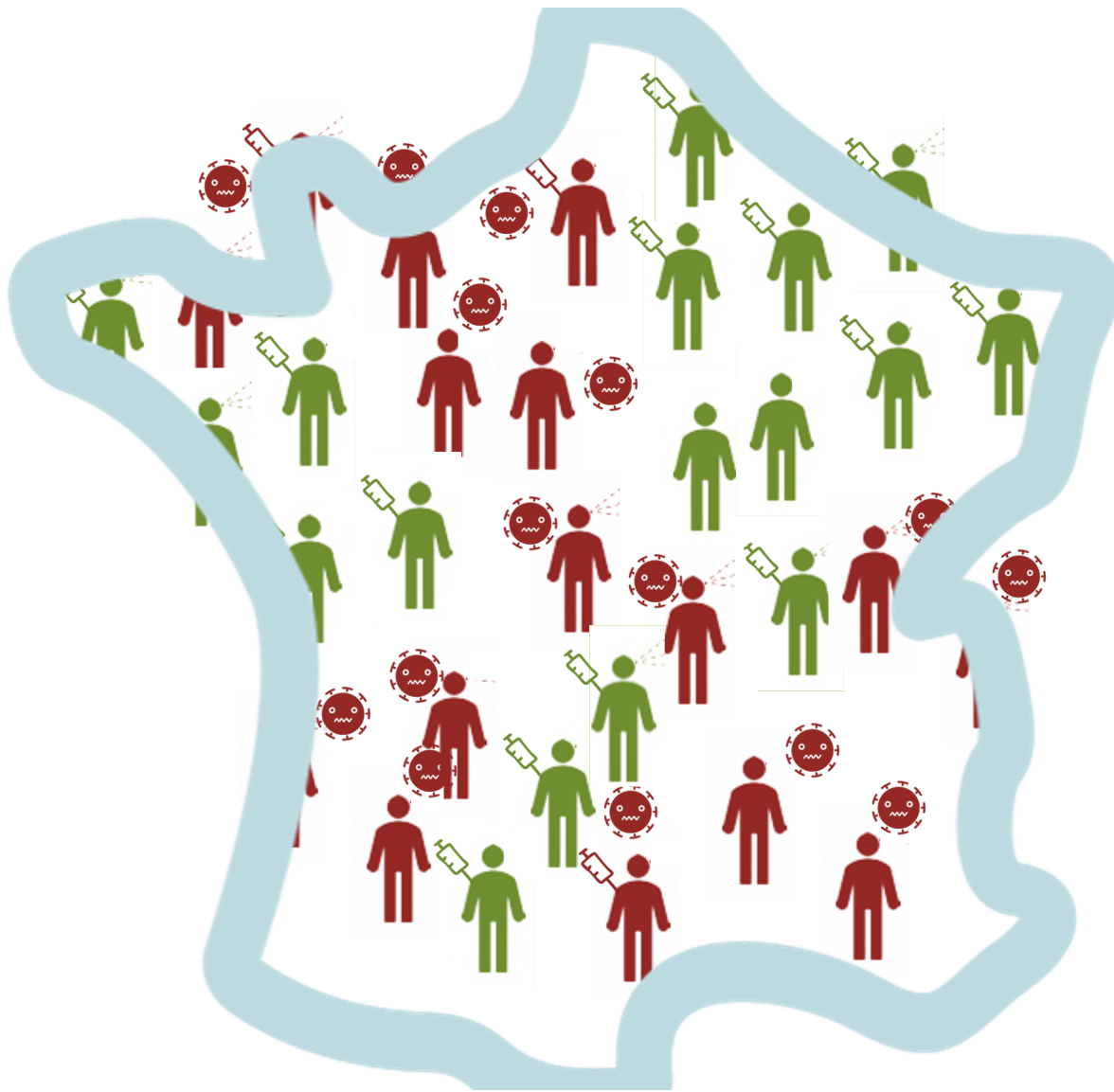


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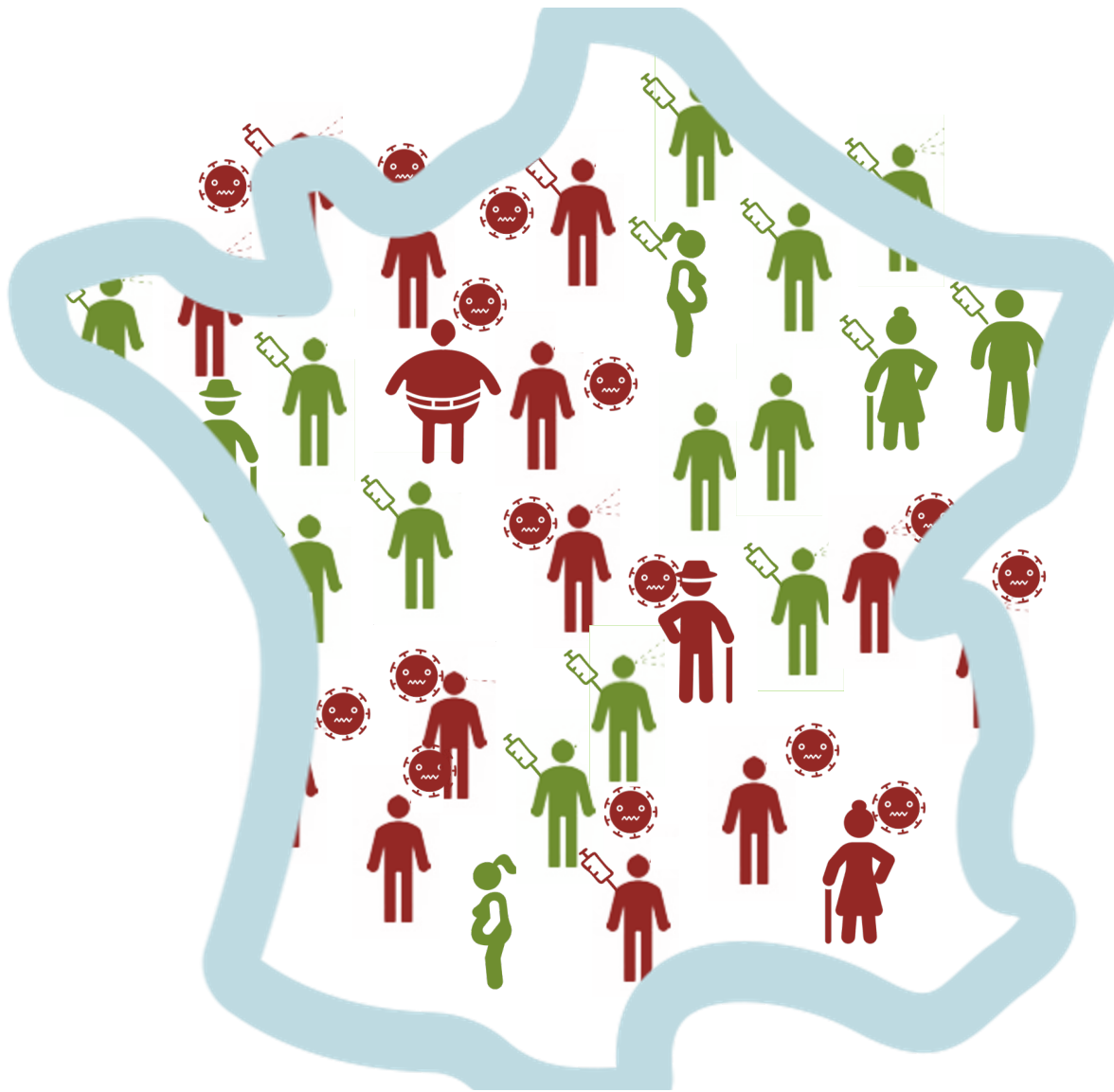
Low infection rate*



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**Calcul de l'effectivité
des vaccins de la COVID**
Cohort designs

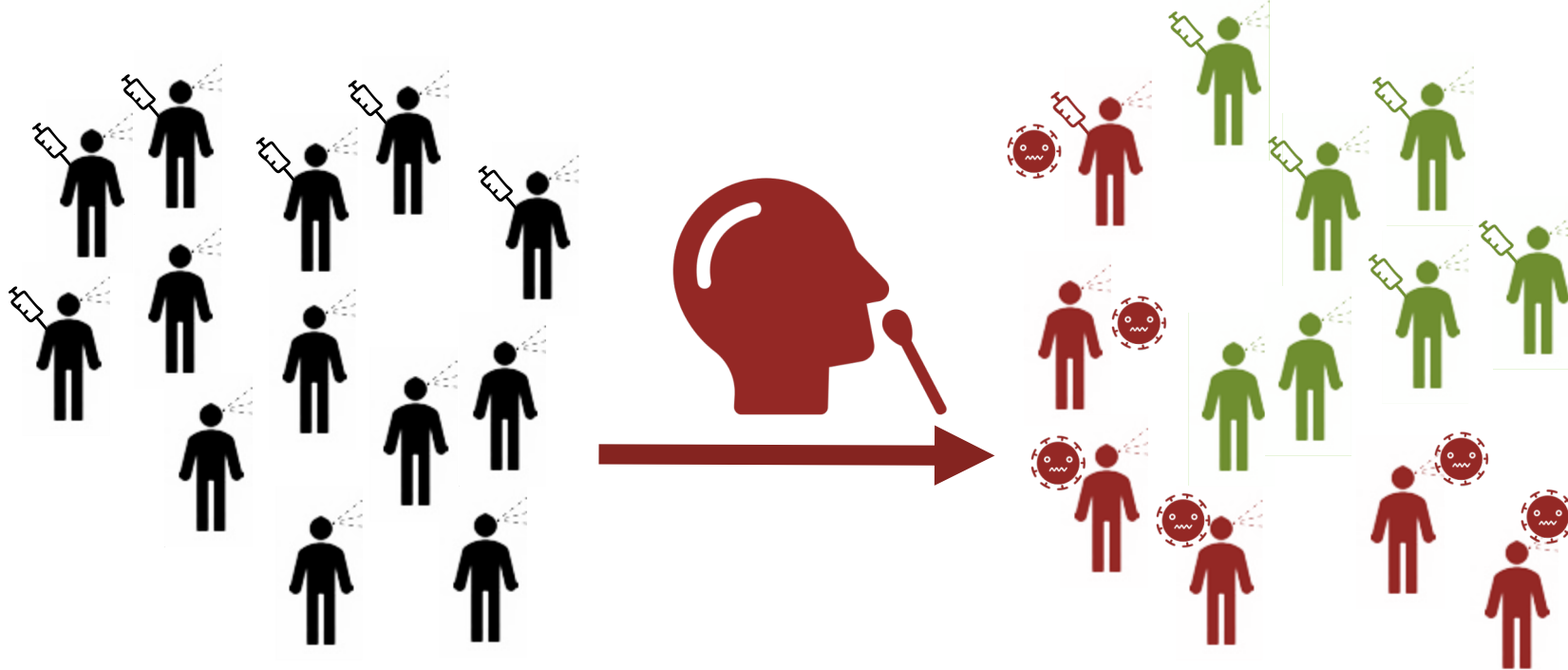


Calcul de l'effectivité des vaccins de la COVID

Cohort designs

Calcul de l'effectivité des vaccins de la COVID

test negative designs



Bénéfice(s)

Risque(s)

Essais cliniques

Pharmacoépidémiologie

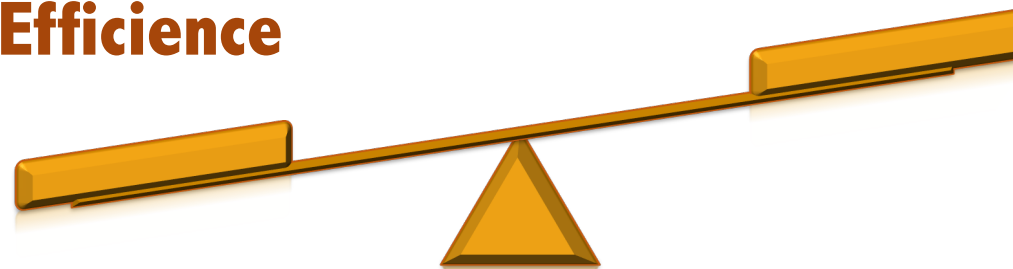
Essais cliniques

Pharmacovigilance

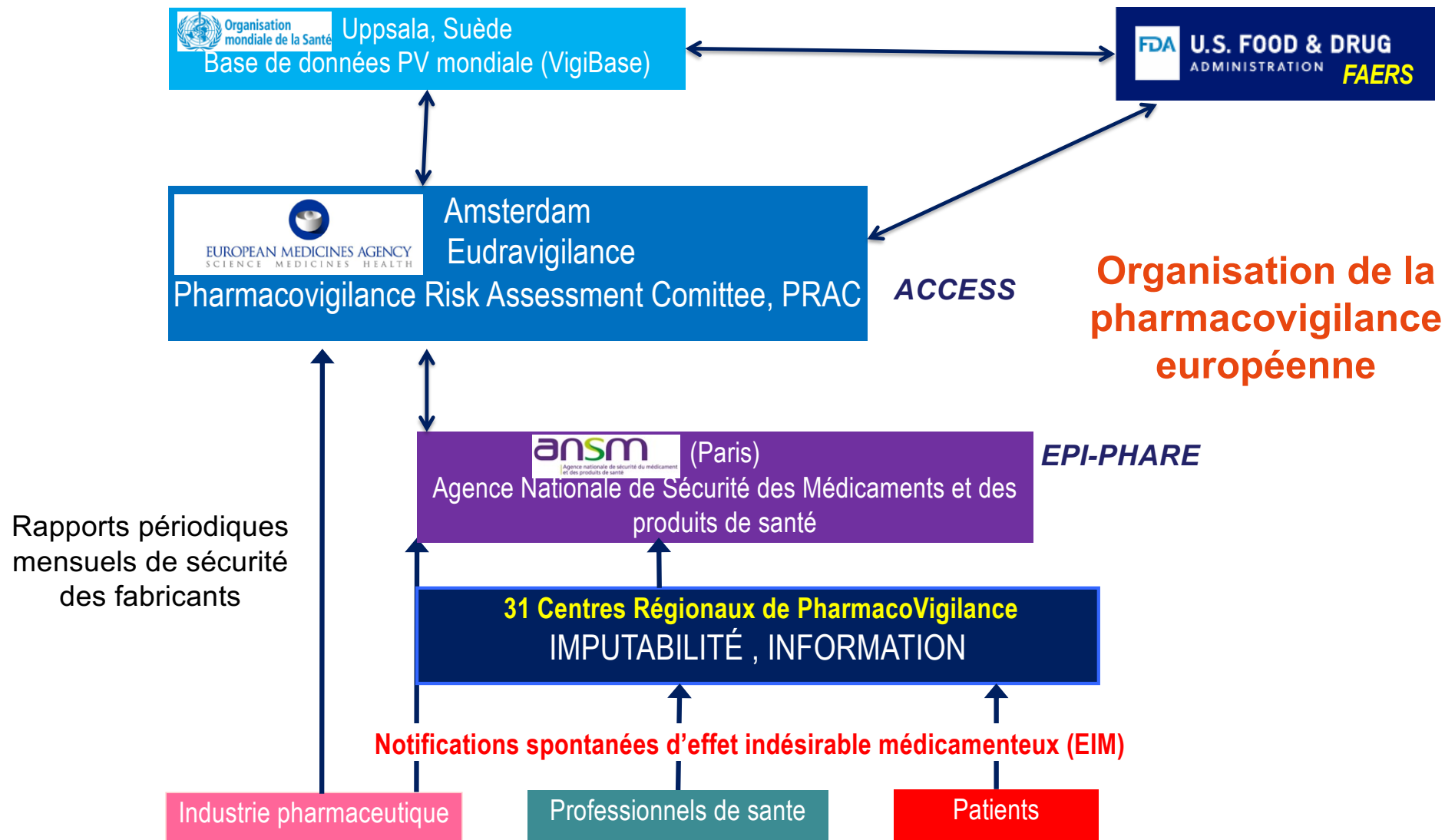
Pharmacoépidémiologie

Efficacité
Effectivité
Effcience

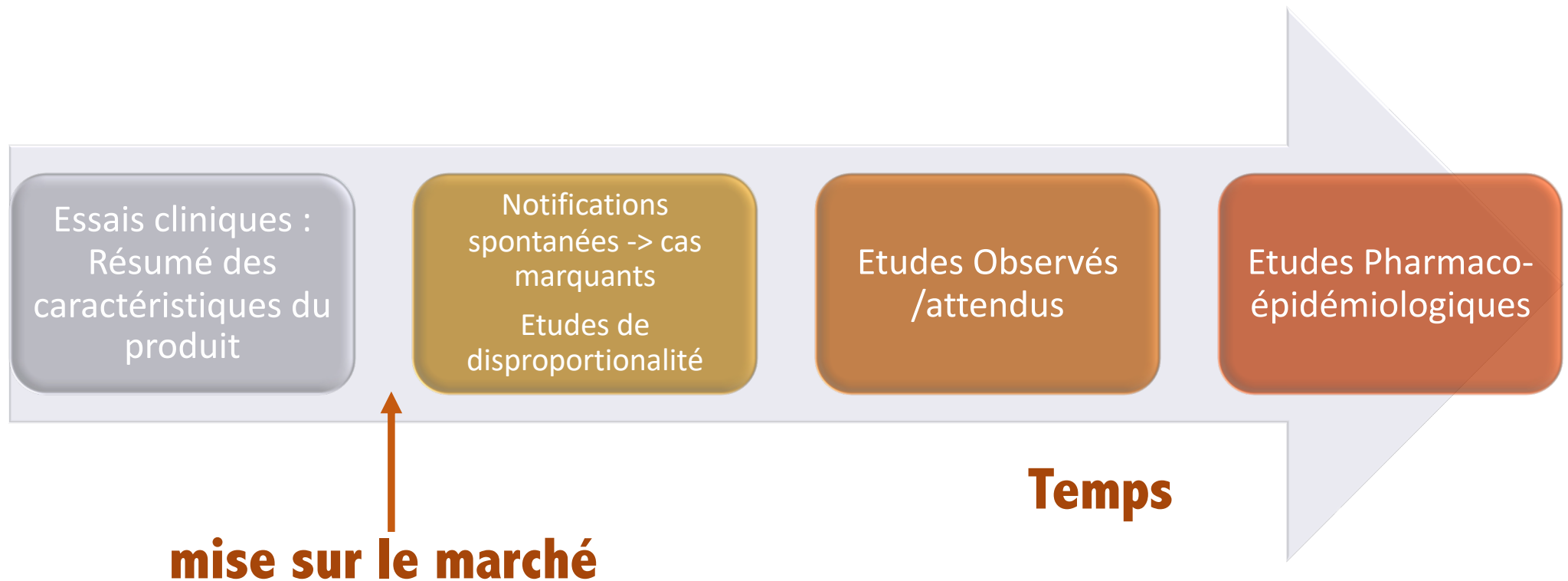
iatrogénie



Vaccins de la Covid

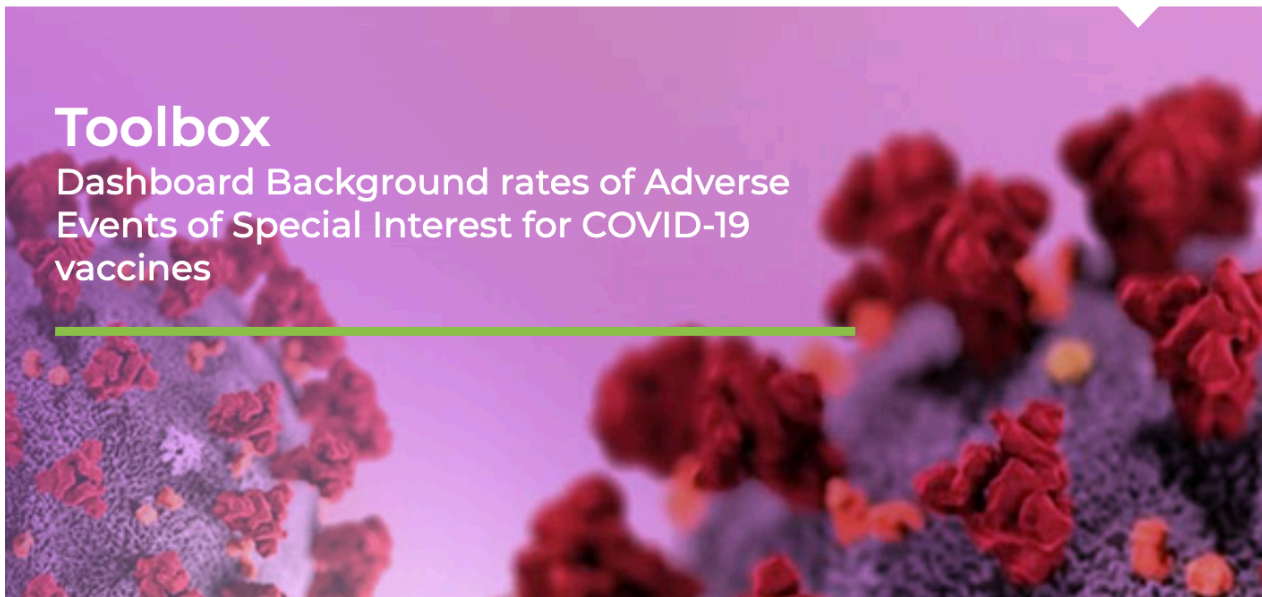


Evaluer l'iatrogénie des vaccins de la Covid-19



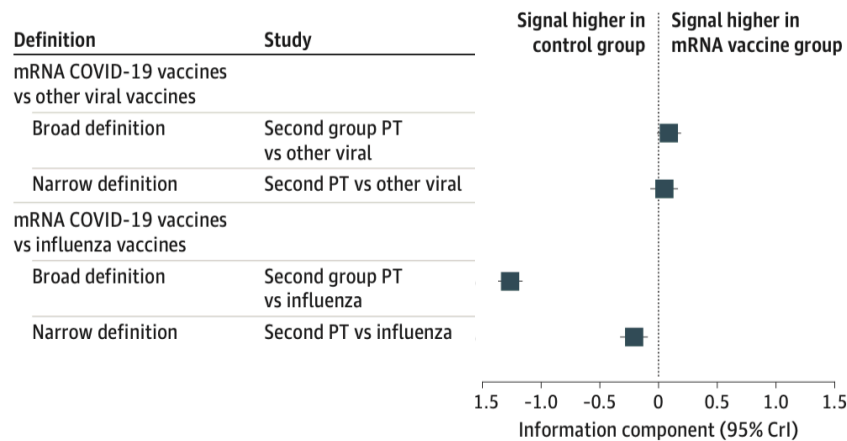
Toolbox

Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines



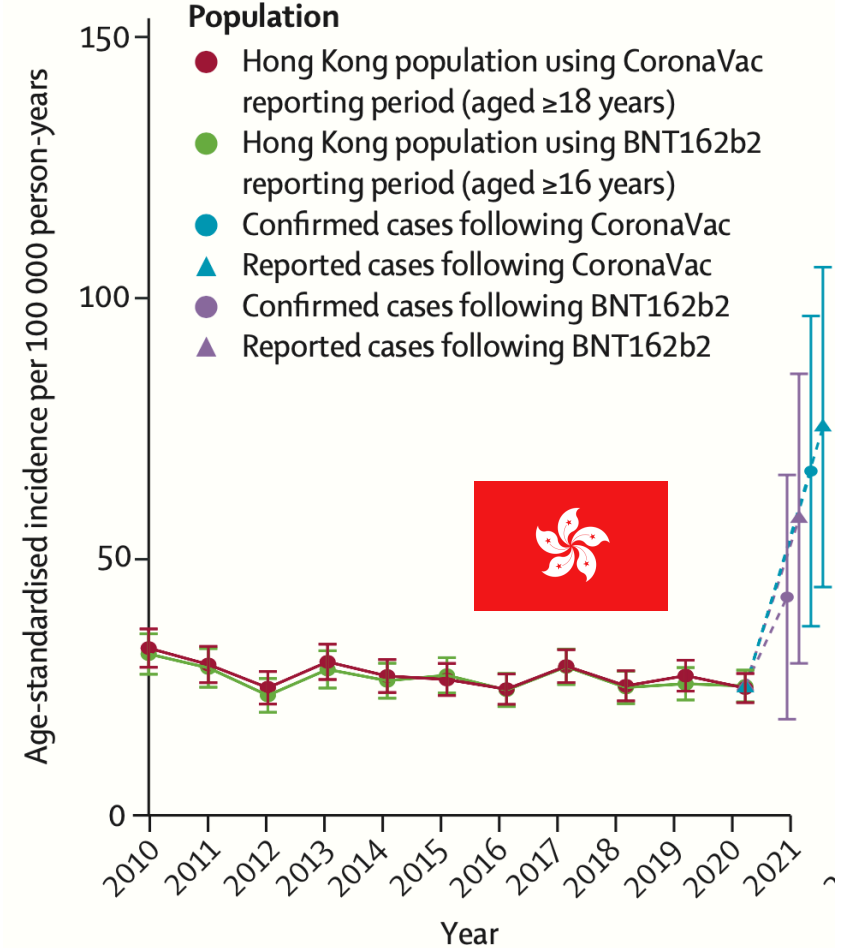
Exemple des paralysies faciales

Etudes de disproportionnalité



Renoud et al, *JAMA Int Med* 2021, 2021

Total Etudes observés/attendus

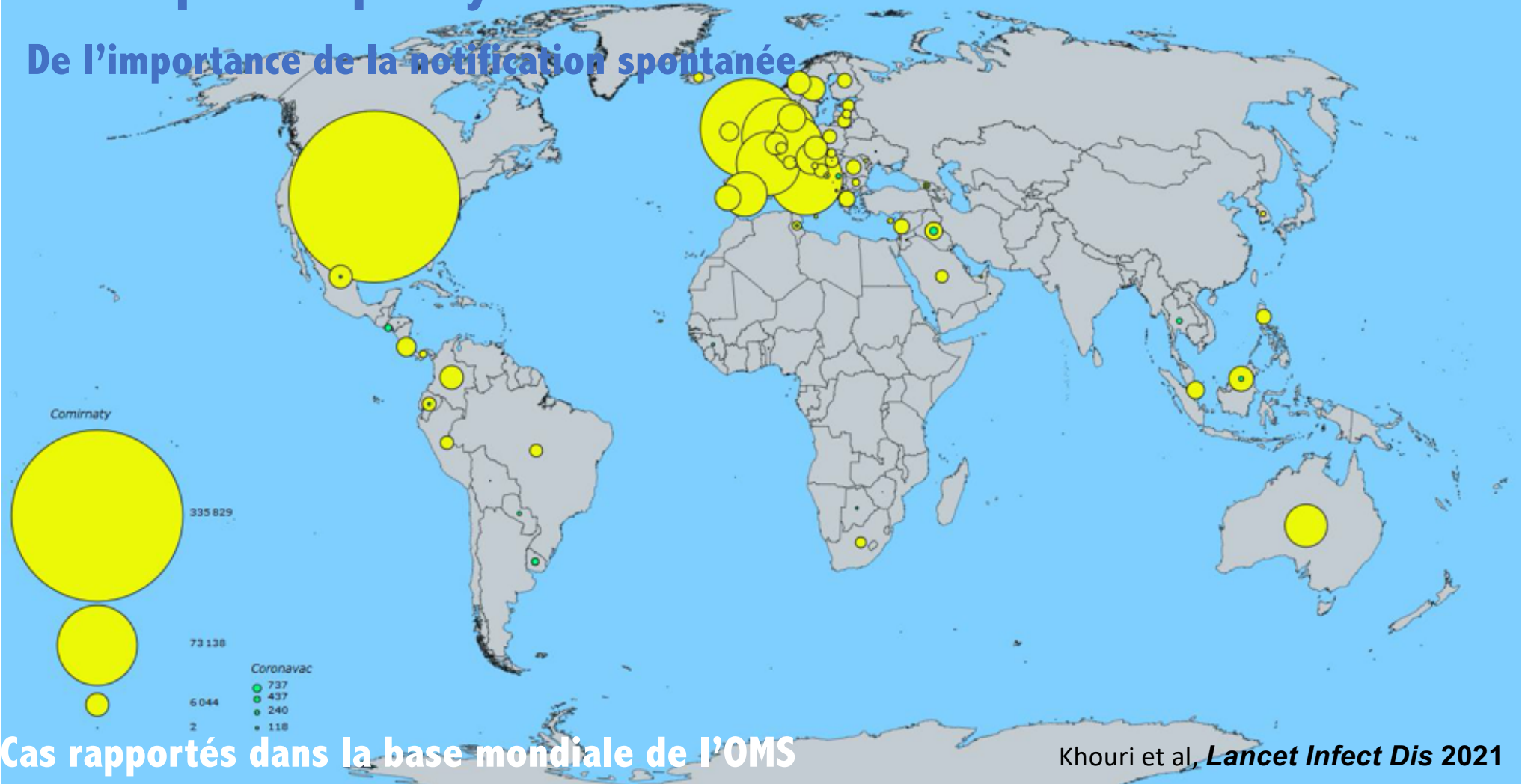


Wan et al, *Lancet Infect Dis* 2021

August 16, 2021 [https://doi.org/10.1016/S1473-3099\(21\)00451-5](https://doi.org/10.1016/S1473-3099(21)00451-5)

Exemple des paralysies faciales

De l'importance de la notification spontanée



Cas rapportés dans la base mondiale de l'OMS

Khouri et al, *Lancet Infect Dis* 2021

	Number of case patients (n=298)	Number of controls (n=1181)	Crude odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Total						
Not vaccinated	256 (86%)	1097 (93%)	1 (ref)	..	1 (ref)	..
CoronaVac	28 (9%)	53 (4%)	2.451 (1.477-4.067)	0.0005	2.385 (1.415-4.022)	0.0011
BNT162b2	14 (5%)	31 (3%)	2.062 (1.061-4.009)	0.033	1.755 (0.886-3.477)	0.11



Table 3: Risk of Bell's palsy among participants in the nested case-control study

Etude cas –contrôle nichée

Wan et al, *Lancet Infect Dis* 2021

August 16, 2021 [https://doi.org/10.1016/S1473-3099\(21\)00451-5](https://doi.org/10.1016/S1473-3099(21)00451-5)

Exemple des paralysies faciales

Etude de cohorte

Table 2. Adverse Events Associated with SARS-CoV-2 Vaccination.*

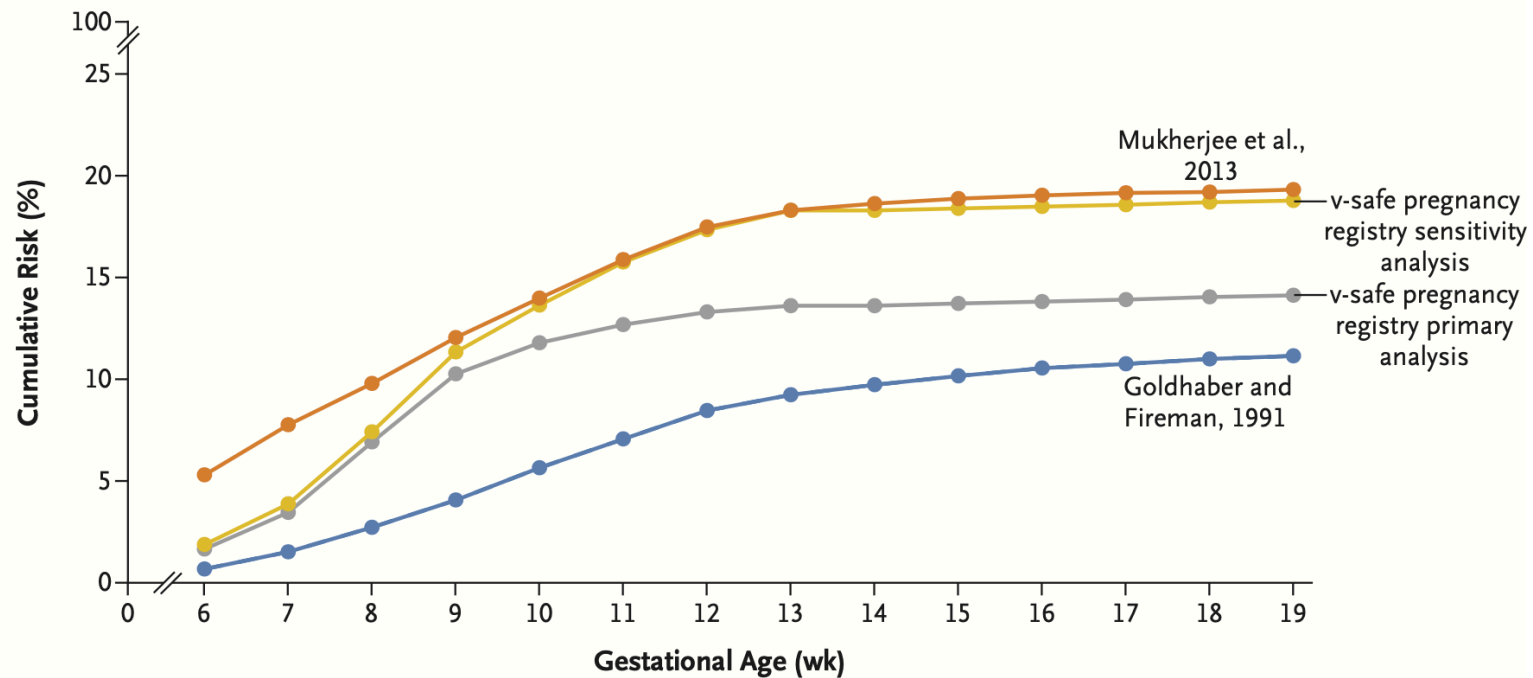
Event	Adverse-Event Cohort in Each Group	Vaccinated Group	Control Group	Risk Ratio (95% CI)	Risk Difference (95% CI)
	no. of persons	no. of events			
Bell's palsy	923,692	81	59	1.32 (0.92 to 1.86)	3.5 (-1.1 to 7.8)



Barda et al, *NEJM* 2021

DOI: 10.1056/NEJMoa2110475

Etude observés-attendus Exemple des fausses couches



Zauche et al, *NEJMed* 2021
Sept, 2021 DOI: 10.1056/NEJMc2113891

Etudes observés/attendus. Exemple des fausses couches



Iatrogénie des vaccins de la COVID : cohort studies

Barda et al, NEJM 2021
DOI: 10.1056/NEJMoa2110475

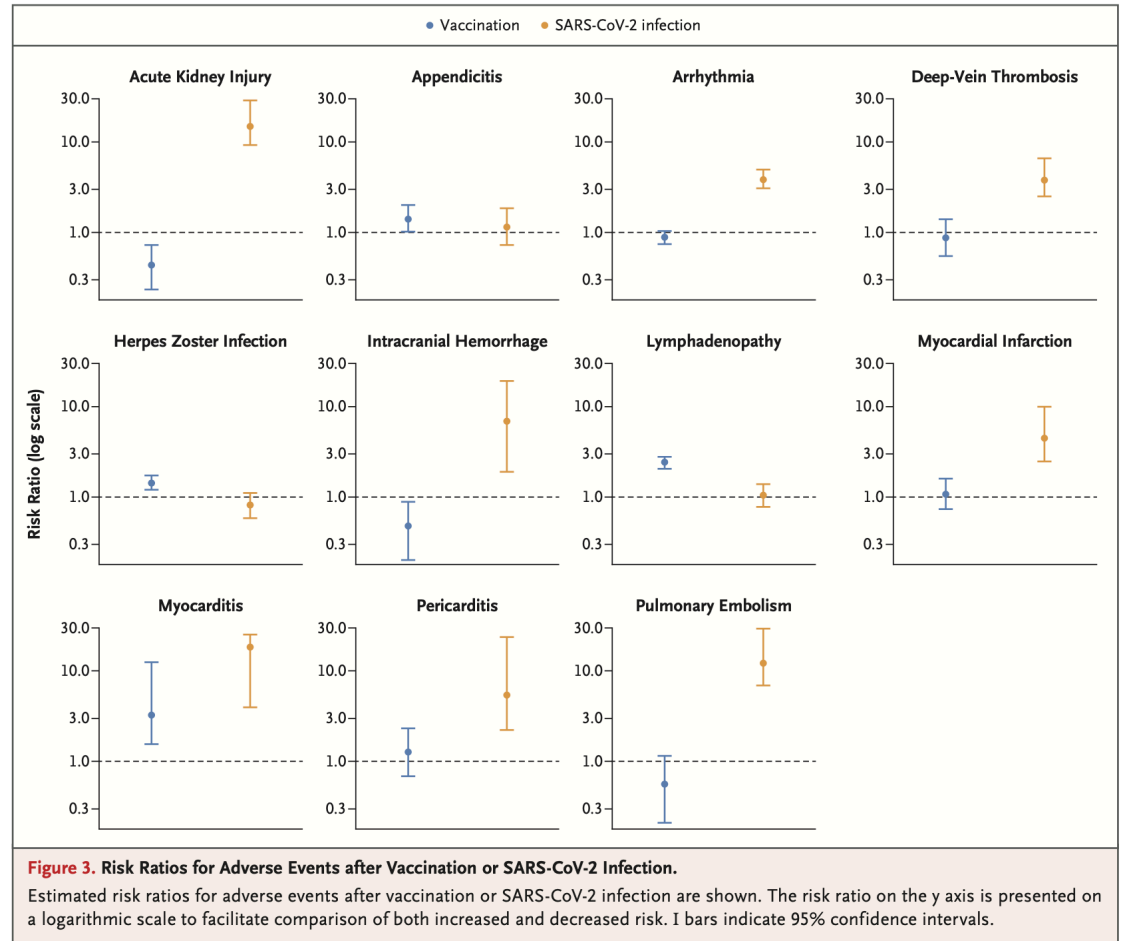
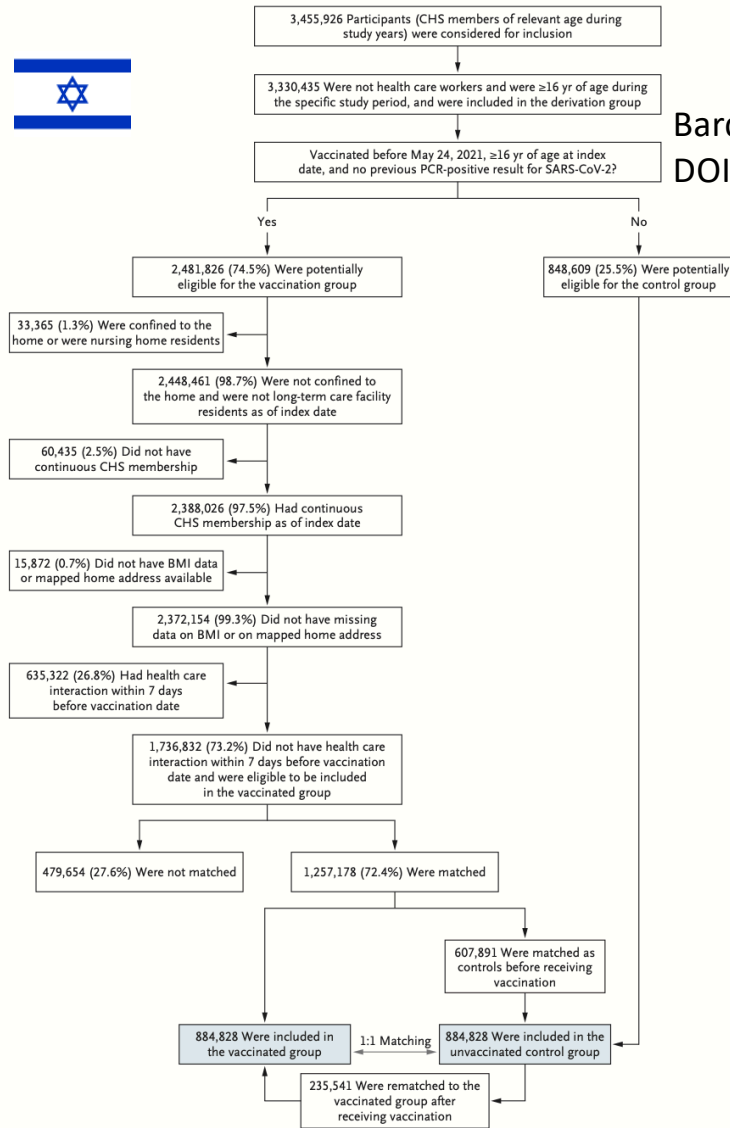
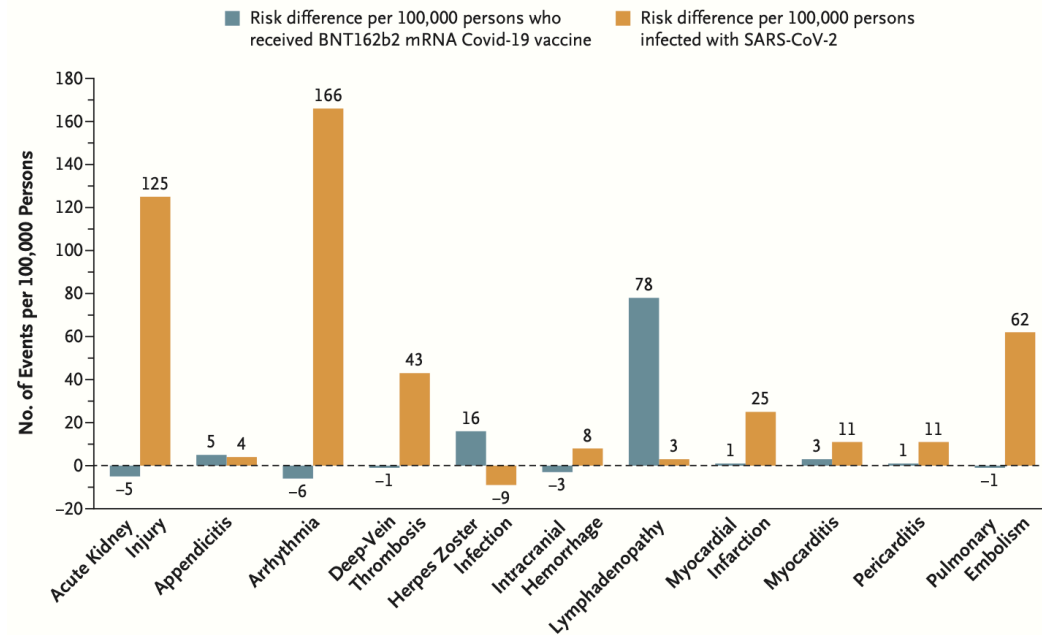


Table 2. Adverse Events Associated with SARS-CoV-2 Vaccination.*

Event	Risk Ratio (95% CI)	Risk Difference (95% CI)
		<i>no. of events/100,000 persons</i>
Acute kidney injury	0.44 (0.23 to 0.73)	-4.6 (-7.8 to -1.8)
Anemia	0.79 (0.67 to 0.93)	-18.7 (-32.1 to -6.1)
Appendicitis	1.40 (1.02 to 2.01)	5.0 (0.3 to 9.9)
Arrhythmia	0.89 (0.74 to 1.04)	-6.1 (-14.7 to 1.8)
Arthritis or arthropathy	0.95 (0.65 to 1.34)	-0.8 (-6.3 to 4.2)
Bell's palsy	1.32 (0.92 to 1.86)	3.5 (-1.1 to 7.8)
Cerebrovascular accident	0.84 (0.54 to 1.27)	-1.6 (-5.3 to 2.0)
Deep-vein thrombosis	0.87 (0.55 to 1.40)	-1.1 (-4.5 to 2.7)
Herpes simplex infection	1.13 (0.95 to 1.38)	4.8 (-1.9 to 12.4)
Herpes zoster infection	1.43 (1.20 to 1.73)	15.8 (8.2 to 24.2)
Intracranial hemorrhage	0.48 (0.20 to 0.89)	-2.9 (-5.6 to -0.5)
Lymphadenopathy	2.43 (2.05 to 2.78)	78.4 (64.1 to 89.3)
Lymphopenia	0.26 (0.00 to 1.03)	-0.9 (-2.0 to <0.1)
Myocardial infarction	1.07 (0.74 to 1.60)	0.8 (-3.3 to 5.2)
Myocarditis	3.24 (1.55 to 12.44)	2.7 (1.0 to 4.6)
Neutropenia	0.87 (0.46 to 1.66)	-0.5 (-2.8 to 1.8)
Other thrombosis†	0.46 (0.19 to 0.91)	-2.2 (-4.6 to -0.3)
Paresthesia	1.12 (0.98 to 1.24)	10.8 (-1.8 to 21.4)
Pericarditis	1.27 (0.68 to 2.31)	1.0 (-1.6 to 3.4)
Pulmonary embolism	0.56 (0.21 to 1.15)	-1.5 (-3.6 to 0.4)
Seizure	0.99 (0.62 to 1.64)	-0.4 (-3.0 to 3.1)
Syncope	1.12 (0.94 to 1.34)	6.2 (-3.2 to 15.4)
Thrombocytopenia	0.94 (0.63 to 1.27)	-0.6 (-4.6 to 2.3)
Uveitis	1.27 (0.68 to 2.67)	1.0 (-1.5 to 3.8)
Vertigo	1.12 (0.97 to 1.28)	9.3 (-2.5 to 20.0)

Iatrogénie des vaccins de la COVID : cohort studies



Barda et al, NEJM 2021
 DOI: 10.1056/NEJMoa2110475

<https://sfpt-fr.org/>

Réponses d'experts à vos questions

sur les médicaments et le COVID-19



Société Française de
Pharmacologie et de Thérapeutique

Pour signaler un effet indésirable lié à la vaccination anti-
COVID-19

Centre régional de pharmacovigilance

<https://signalement.social-sante.gouv.fr/>