Vaccins contre les infections émergentes (Covid-19, Ebola, Dengue, Chikungunya…)

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Prevention Vaccinale des Infections Emergentes

1. **Quelles familles de vaccins pour les infections émergentes** ?
    - **Classiques** : vaccins **vivants atténués** (Ex: mPox, Chikungunya…), Vaccins **inactivés** (Ex: Covid-19), Vaccins **protéiques** et à pseudo-particules (Ex: covid 19, Chikungunya)
    - **Issus du génie génétique** : **Vecteurs viraux recombinants** (Ex: Ebola**), Vaccins à ARN messager** (Ex : Covid-19)

2. **Développement, indications Vaccins contre les infections émergentes,** efficacité vaccinale et limites :
    - contre la Pandémie émergente**: Covid-19**
    - contre les **infections émergentes** :
        - **Ebola**
        - **Dengue**
        - **Chikungunya**

3. **Vers une production / Répartition équitable des vaccins** (Ex: CEPI)

PATHOGENS PRIORITIZATION

A SCIENTIFIC FRAMEWORK FOR EPIDEMIC AND PANDEMIC RESEARCH PREPAREDNESS

HEALTH EMERGENCIES programme

JUNE 2024

World Health Organization

R&DBlueprint
Powering research to prevent epidemics

Table 1. Families and Pathogens that were prioritized in the 2024 update, as compared with the 2017 and 2018 prioritization processes[4].

	2017	2018	2024		
Family	**Priority Pathogens**	**Priority Pathogens**	**PHEIC risk**	**Priority Pathogens**	**Prototype Pathogens**
Adenoviridae			Low-Medium		Recombinant Mastadenovirus
Adenoviridae			Low-Medium		Mastadenovirus blackbeardi
Anelloviridae			Low		
Arenaviridae	Arenaviral hemorrhagic fevers including Lassa Fever	Lassa Fever virus	High	Mammarenavirus lassaense	Mammarenavirus lassaense
Arenaviridae			High		Mammarenavirus juninense
Arenaviridae			High		Mammarenavirus lujoense
Astroviridae			Low		Mamastrovirus virginiaense
Bacteria			High	Vibrio cholerae serogroup 0139	
Bacteria			High	Yersinia Pestis	
Bacteria			High	Shigella dysenteriae serotype 1	
Bacteria			High	Salmonella enterica non typhoidal serovars	
Bacteria			High	Klebsiella pneumoniae	
Bornaviridae			Low		Orthobornavirus bornaense
Coronaviridae	Middle East Respiratory Syndrome Coronavirus	Middle East Respiratory Syndrome Coronavirus	High	Subgenus Merbecovirus	Subgenus Merbecovirus
Coronaviridae	Other highly pathogenic coronaviral diseases such as Severe Acute Respiratory Syndrome	Severe Acute Respiratory Syndrome	High	Subgenus Sarbecovirus	Subgenus Sarbecovirus
Filoviridae	Filoviral diseases Ebola	Ebola virus disease	High	Orthoebolavirus zairense	Orthoebolavirus zairense
Filoviridae	Filoviral diseases Marburg	Marburg virus disease	High	Orthomarburgvirus marburgense	
Filoviridae			High	Orthoebolavirus sudanense	
Flaviviridae	Zika virus	Zika virus	High	Orthoflavivirus zikaense	Orthoflavivirus zikaense
Flaviviridae			High	Orthoflavivirus denguei	Orthoflavivirus denguei
Flaviviridae			High	Orthoflavivirus flavi	
Flaviviridae			High		Orthoflavivirus encephalitidis
Flaviviridae			High		Orthoflavivirus nilense
Hantaviridae			High	Orthohantavirus sinnombreense	Orthohantavirus sinnombreense
Hantaviridae			High	Orthohantavirus hantanense	
Hepadnaviridae			Low		Orthohepadnavirus hominoidei genotype C
Hepeviridae			Low		Paslahepevirus balayani genotype 3
Herpesviridae			Low		
Nairoviridae	Crimean Congo Haemorrhagic Fever	Crimean Congo Haemorrhagic Fever	High	Orthonairovirus haemorrhagiae	Orthonairovirus haemorrhagiae
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H1	Alphainfluenzavirus Influenzae H1
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H2	
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H3	
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H5	Alphainfluenzavirus Influenzae H5
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H6	
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H7	
Orthomyxoviridae			High	Alphainfluenzavirus Influenzae H10	
Papillomaviridae			Low		
Paramyxoviridae	Nipah and related henipaviral diseases	Nipah and henipaviral diseases	High	Henipavirus nipahense	Henipavirus nipahense
Parvoviridae			Low		Protoparvovirus carnivoran
Peribunyaviridae			Low		Orthobunyavirus oropoucheense
Phenuiviridae	Severe Fever with Thrombocytopenia Syndrome		High	Bandavirus dabieense	Bandavirus dabieense
Phenuiviridae	Rift Valley Fever	Rift Valley Fever	High		Phlebovirus riftense
Picobirnaviridae			Low		Orthopicobirnavirus hominis
Picornaviridae			Medium	Enterovirus coxsackiepol	
Picornaviridae			Medium		Enterovirus alphacoxsackie 71
Picornaviridae			Medium		Enterovirus deconjucti 68
Pneumoviridae			Low-Medium		Metapneumovirus hominis
Polyomaviridae			Low		
Poxviridae			High	Orthopoxvirus variola	
Poxviridae			High		Orthopoxvirus vaccinia
Poxviridae			High	Orthopoxvirus monkeypox	Orthopoxvirus monkeypox
Retroviridae			Medium	Lentivirus humimdef1	Lentivirus humimdef1
Rhabdoviridae			Low		Genus Vesiculovirus
Sedoreoviridae			Low		Genus Rotavirus
Spinareoviridae			Low		Orthoreovirus mammalis
Togaviridae			High	Alphavirus chikungunya	Alphavirus chikungunya
Togaviridae			High	Alphavirus venezuelan	Alphavirus venezuelan
Pathogen X	Pathogen X	Pathogen X		Pathogen X	

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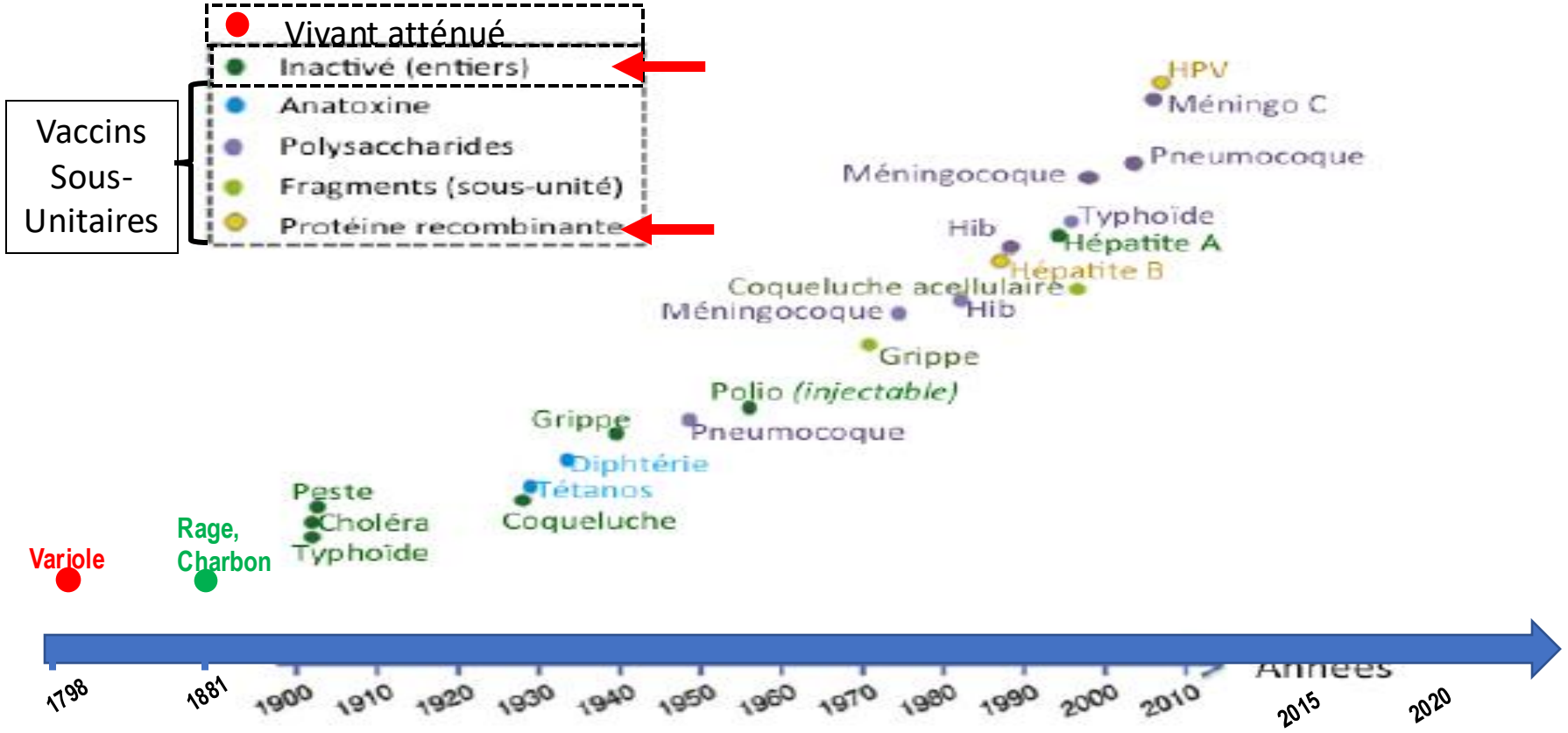
Infections émergentes et développements vaccinaux : Vaccins classiques



- **Vaccins Vivants ou Inactivés:**
  - Avantages : **Pas de design**
  - Limitations: Sécurité

- **Protéines Recombinantes:**
  - Avantages: Forte **Immunogenicité si Adjuvant Sécurité**
  - Limitations: Adjuvantation

➢ Inf. Emergentes: **mPox**, *Chikungunya* Covid-19, **Chikungunya**

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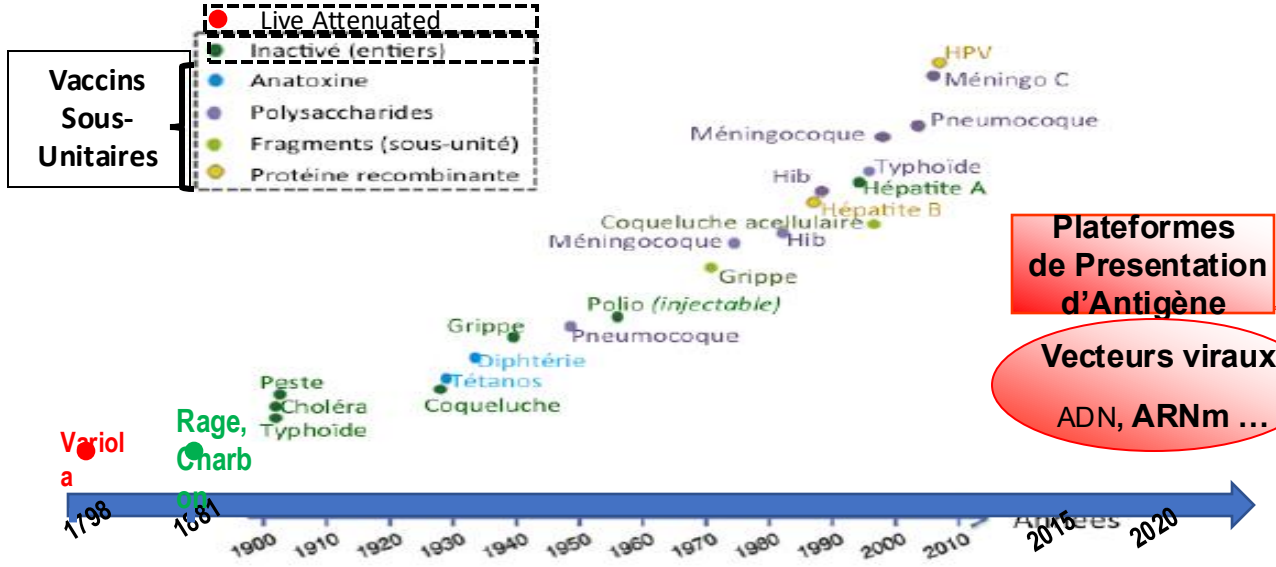
Infections émergentes et développements vaccinaux : Nouveaux Vaccins : Vecteurs viraux recombinants et ARNm

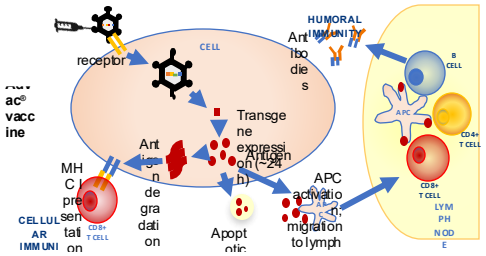


Plateformes de Presentation d'Antigène

Vecteurs viraux

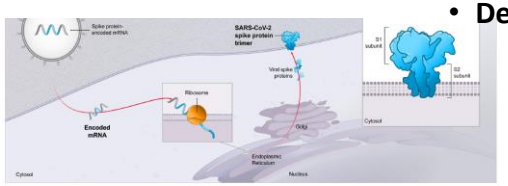
ADN, **ARNm …**

➢ Vecteurs Viraux Recombinants



- **AMM: Ebola**
- **Developpement clinique:**
  - **HIV**
  - **Zika**
  - **RSV**
  - **…**

➢ ARNm



- **Developpement clinique :**
  - **Influenza**
  - **Zika**
  - **RSV**
  - **CMV…**

- ADN, Vecteurs Recombinants ou ARNm
  - Avantages :
    - **Design de l'Ag Rapide et flexible**
    - **Vecteurs viraux et ARNm « nu »: Forte Immunogenicité sans adjuvant**
  - Limitations:
    - ADN nu: tres faible immunogénicité: quasi-abandonné
    - Vecteurs viraux: Immunité anti-Vecteur

➢ Inf. Emergentes: **Ebola, Covid-19, Dengue**

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Impact vaccine formulation on immunogenicity and tolerance : Balance benefits / risks

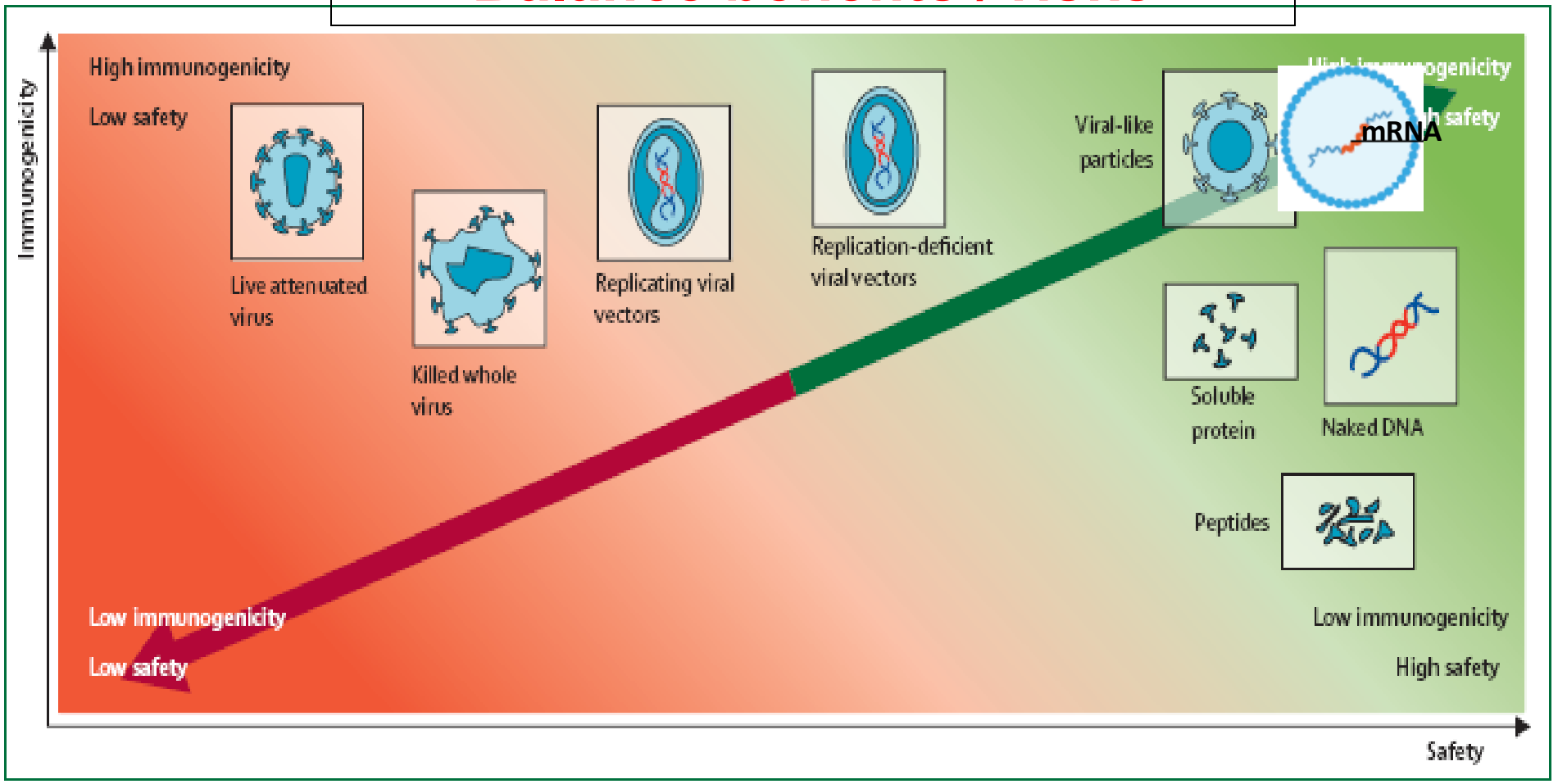

Figure 1: Different HIV-1 vaccine strategies—immunogenicity versus safety issues
HIV-1 strategies have been distributed according to their immunogenicity and safety. The representation on the two axes are based on an arbitrary comparative scale.

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Vaccins à base de vecteurs viraux Recombinants

➢ **1ers Succès: vaccin anti-Ebola, anti-SARS-COV2**

▪ Vecteurs viraux :

✓ **Atténués, Non réplicatifs :**

- ✓ **Issus de virus faiblement pathogènes** (Ex: **VSV**: virus de la stomatite vésiculeuse (Vaccin **Ebola**) ou virus vaccinaux
- ✓ **Par modifications Génétiques:**
  - **adénovirus** humains ou simiens
  - **poxvirus:** MVA, NYVAC (dérivé de vaccine)

✓ **peu ou pas prévalents chez l'homme**: faible immunité pré-existante / vecteur

✓ **Transgène recombinant: ADN codant pour l'antigene d'intéret du pathogène ciblé** (Ex: Env V.Ebola, Spike SARS-CoV2…)

▪ Immunisation / Vecteur viral recombinant :

✓**Injecté dans cellules :**

✓PAS d'integration,

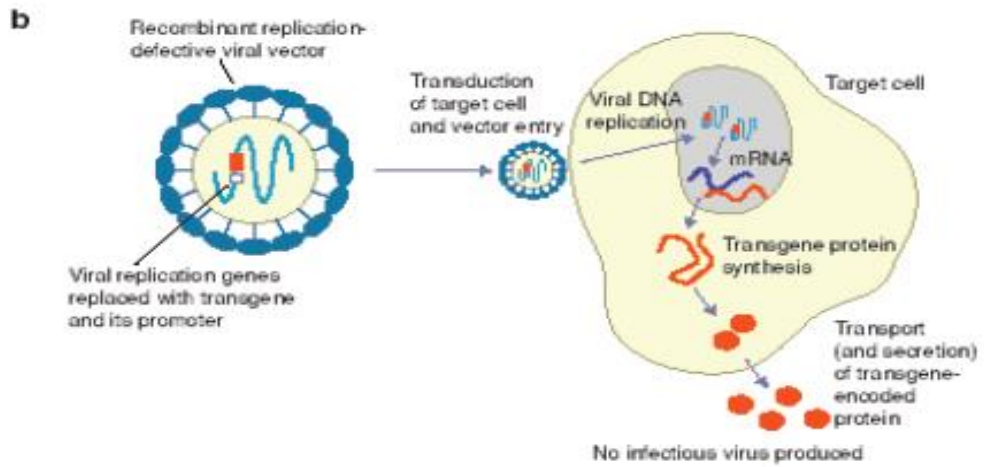
✓production de protéine par cellule transduite

✓**Induction de réponses immunes:**

=> Anticorps + Cellules T

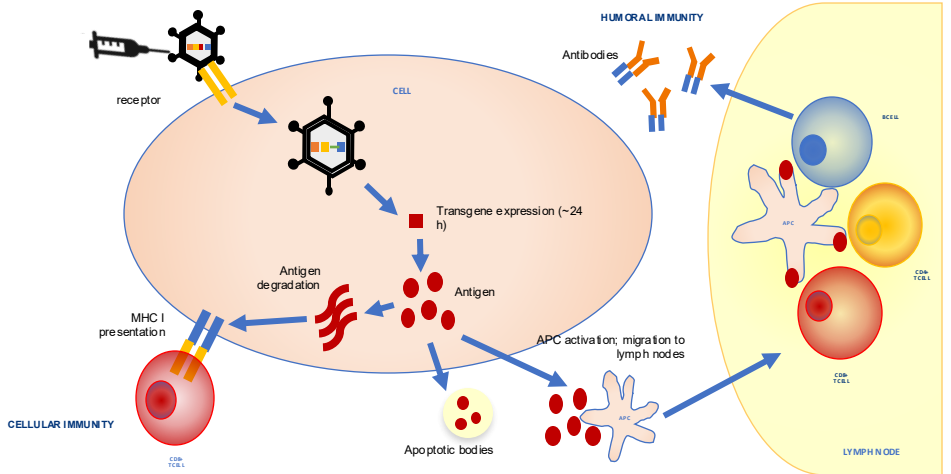
✓**Pas de contre-indication chez l'Immuno-Déprimé**

(vaccin Non réplicatif)



Construction of a typical replication-defective recombinant virus

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press



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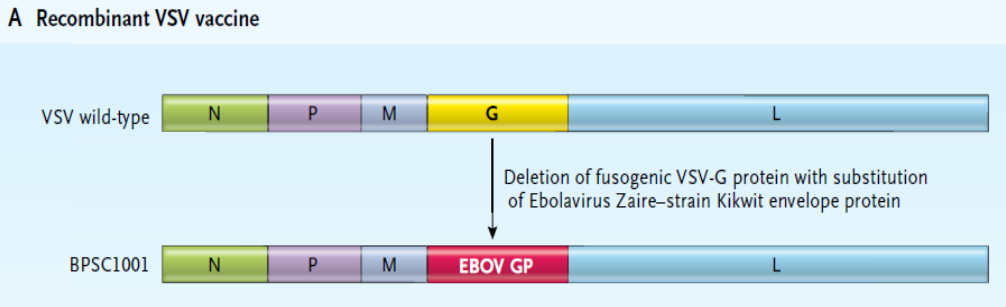
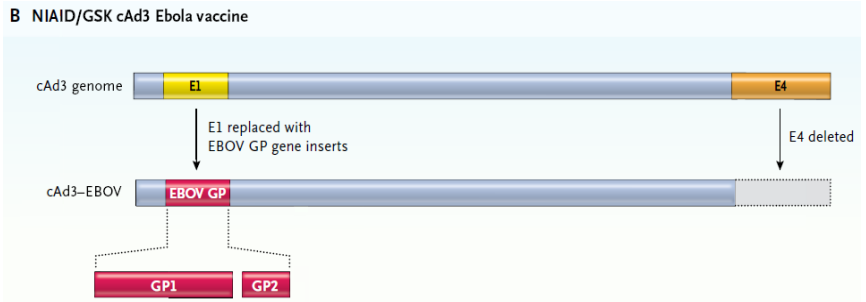
Vaccins à vecteur viral recombinant anti-Ebola

- **Vecteur: virus de Stomatite Vésiculaire (VSV) doublement modifié / génétique:**
  - développement académique + firme Biotech (Canada) : **2000-2003:**
    - Délétion du gène G (fusogénique) => Réplication virale Déficiente
    - Substitution pour exprimer le gène d'enveloppe du virus Ebola-Zaire:



  - Essais cliniques de Phase 1 : 2010-15

- **Vecteurs Adénovirus:**
  - **Vaccin Chimp-Adenovirus : ChAd3-EBO-Z** = Adenovirus Type 3 du Chimpanzé doublement modifié / génétique: **Univ. Oxford**
    - Délétion de gènes => Réplication Déficiente
    - Recombiné / gène d'enveloppe EBO-Z



  - **Vaccin Adeno-26-EBO-Z :**
    - Atténué et Peu prévalent chez l'homme
    - construction proche Ad26-EBO-Z

Efficacité clinique des Vaccins à vecteur viral recombinant anti-Ebola: 2015/2016/17

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, Ira M Longini, Matthias Egger, Natalie E Dean, W John Edmunds, Anton Camacho, Miles W Carroll, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Stefanie Hossmann, Mandy Kader Kondé, Souleymane Kone, Eeva Kuisma, Myron M Levine, Sema Mandal, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, Conall H Watson, Sakoba Kéïta, Marie Paule Kieny*, John-Arne Rottingen*

Lancet 2015; 386: 857–66

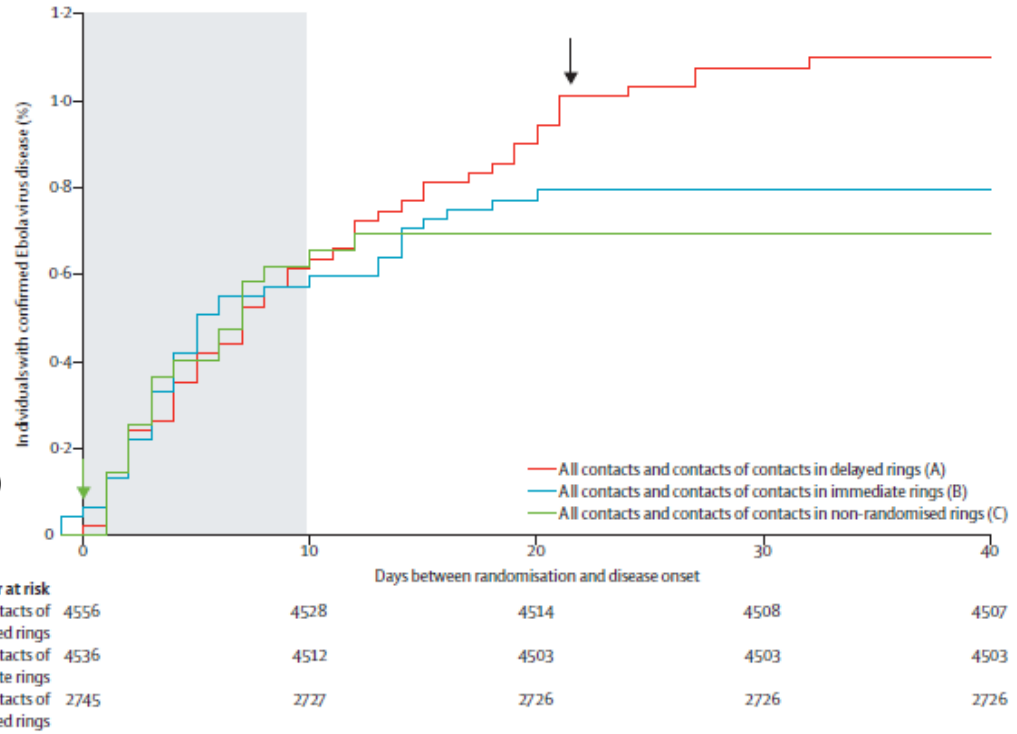
Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

AM Henao-Restrepo, Lancet 2017

- **Essai Clinique de Phase 2b:** en Guinée: 2015-16
- Design : en **Anneau autour des cas** :

⇒ **100% efficacité vaccinale**

(Aucun cas à partir de 10j post-vaccin)



Number at risk					
All contacts and contacts of contacts in delayed rings	4556	4528	4514	4508	4507
All contacts and contacts of contacts in immediate rings	4536	4512	4503	4503	4503
All contacts and contacts of contacts in non-randomised rings	2745	2727	2726	2726	2726

⇒ **Mais effets secondaires fréquents**

	0–30 min	31 min to 3 days	4–14 days
Children aged between 6–<18 years (n=194)			
Arthralgia	0	3 (3·5%)	1 (9·1%)
Diarrhoea	0	0	1 (9·1%)
Fatigue	0	10 (11·6%)	1 (9·1%)
Fever	0	1 (1·2%)	1 (9·1%)
Headache	0	47 (54·7%)	4 (36·4%)
Induration	0	0	0
Injection pain	0	9 (10·5%)	0
Muscle pain	0	4 (4·7%)	1 (9·1%)
Myalgia	0	4 (4·7%)	1 (9·1%)
Vomiting	0	1 (1·2%)	0
Other adverse events	0	7 (8·1%)	1 (9·1%)
Total	0	86 (100·0%)	11 (100·0%)
Adults aged 18 years and older (n=5643)			
Arthralgia	3 (2%)	851 (13·5%)	79 (12·3%)
Diarrhoea	0	53 (0·8%)	15 (2·3%)
Fatigue	5 (3·3%)	1233 (19·5%)	112 (17·4%)
Fever	2 (1·3%)	8 (0·1%)	2 (0·3%)
Headache	41 (27·3%)	1563 (24·7%)	177 (27·5%)
Induration	0	1 (<1%)	0
Injection pain	70 (46·7%)	362 (5·7%)	8 (1·2%)
Muscle pain	7 (4·7%)	875 (13·8%)	55 (8·5%)
Myalgia	6 (4·0%)	816 (12·9%)	47 (7·3%)
Vomiting	0	21 (0·3%)	4 (0·6%)
Other adverse events	16 (10·7%)	537 (8·5%)	145 (22·5%)
Total	150 (100·0%)	6320 (100·0%)	644 (100·0%)

Data are n (%); individuals might have had more than one adverse event.

Table 5: Frequency of solicited adverse events by time since vaccination in children and adults

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Vaccins Ebola

⇒Vaccin rVSV-ZEbovGP

- 2003 : Brevet
- 2015-16 : Essai clinique => Efficacité
- **2019** :
  - pre-qualification / OMS

  => Autorisation (AMM) / EMA (Nov. 19)

  autorisation FDA (Dec. 19)
  - Distribué en RDC en 2019 à:
    - >250 000 contacts (GAVI)
    - 60 000 personnels de santé

FIRST VACCINE AGAINST DEADLY EBOLA VIRUS WINS APPROVAL

The shot has already been given to hundreds of thousands of people in ongoing Africa outbreak.

An Ebola vaccine has been approved by the European Medicines Agency.

Nature | Vol 575 | 21 November 2019 |

➢ ***'Make Ebola a thing of the past'***

⇒ **Autres vaccins autorisés : ChAd3-ZEBOV, Ad26/MVA-ZEBOV**

⇒ **Indications : Prevention de l'infection** Ebola (EVD, *Zaire ebolavirus):*

- ⇒ **adultes** ≥18 ans
- ⇒ **Epidémies**: **Sujets contacts** , Population :
- ⇒ **Professionnels** exposés à haut risque d'infection : santé, laboratoire, transp. (EMA; ACIP; OMS)

⇒ **Applications : Epidémies Ebola Virus RDC** 2018-19, 2022, 2025

- **Questions en suspens:**

1. **Durabilité des réponses immunes?**
   - **Etude en RDC en 2018: 608 vaccines: 1 injection, moy:** 35 ans, PfSanté: 40%; Contact antérieur avec cas Ebola: 32%

   ➢ Répondeurs:

   ➢ **87.2% 21 j** post-vaccin :

   ➢ **95,6%6 mo** post-vaccin

   ➢ **Persistance des taux d'Ac après 1 seule injection**

   ➢ **=> contrôle des pics épidémiques**

   ➢ **Persistance à + Long terme?**

2. **Réactivité croisée avec autres FlaviV ???**

   ➢ **EVD à Virus Soudan : Réactivité croisée insuffisante: => Nécessité d'adaptervaccin**

   ➢ **Autres FlaviV: pas de réactivité croisée**

2022 SVD outbreak in Uganda: summary

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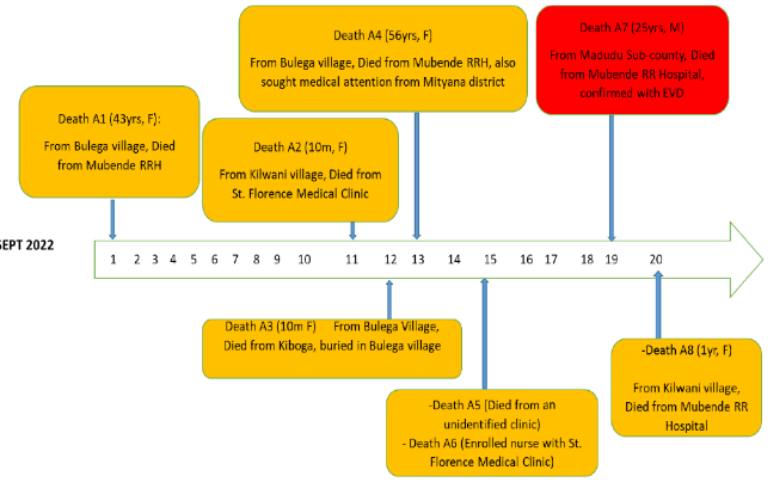

20th Sept 2022: MOH declared an outbreak of Ebola SUDV in Mubende.

Cumulatively:

- **Total of 9 Districts were affected.**

Cases:

- **164 cases (142-confirmed, 22-probable).**

Deaths:

- **55 - cumulative confirmed deaths (49 - ETU, 5 - HF non-ETU, 1 - Community).**
- **22 probable deaths.**
- **CFR:**
  - **39.0% among the confirmed,**
  - **47.0% among all cases (confirmed and probable).**

Health workers infections and deaths:

- **Total # of HCWs infe**
- **Total # of HCWs dea**

Recoveries:

- **Total number of rec**

Total # of contacts followed up

Souche EbolaV Sudan diffère de la souche ZEBOV

Solidarity against ebola

Development and implementation of a protocol to evaluate the safety immunogenicity and efficacy of SUDV candidate vaccines during the 2022 SUDV outbreak-SOLIDARITY TRIAL -- Solidarity against Ebola / 'Tokemeza Ebola

World Health Organization

- **Necessité de developper et évaluer un vaccin adapté à SUDV**
- **2025 : Essai clinique en cours**

Working together to find a vaccine against Ebola in Uganda

Bruce J Kirenga MBchB, Mmed, PhD, FRCP; On behalf of the trial team

Makerere University Lung Institute
MAKERERE UNIVERSITY COLLEGE OF HEALTH SCIENCES
Science for Healthy Lungs

World Health Organization

R&DBlueprint
Powering research to prevent epidemics

anti-Covid19 Vaccines

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SARS-CoV2 Covid19 : Mars-Avril 2020

Coronavirus disease 2019 (COVID-19) Situation Report – 71

World Health Organization

Data as reported by national authorities by 10:00 CET 31 March 2020

SITUATION IN NUMBERS
total (new) cases in last 24 hours

Globally
750 890 confirmed (57 610)
36 405 deaths (3301)

Western Pacific Region
104 868 confirmed (1093)
3671 deaths (22)

European Region
423 946 confirmed (31 131)
26 694 deaths (2733)

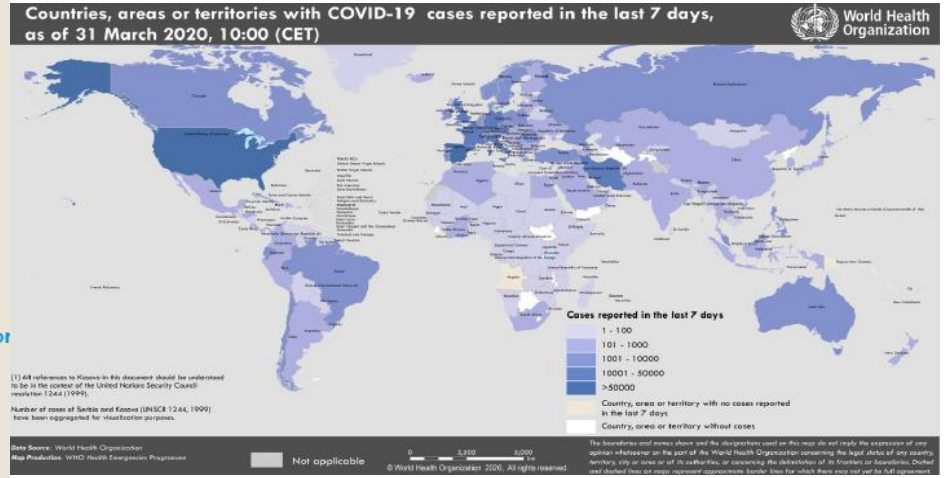
South-East Asia Region
4215 confirmed (131)
166 deaths (8)

Eastern Mediterranean Regior
50 349 confirmed (4020)
2954 deaths (142)

Region of the Americas
163 014 confirmed (20 935)
2836 deaths (379)

African Region
3786 confirmed (300)
77 deaths (17)

WHO RISK ASSESSMENT
Global Level Very High



Coronavirus disease 2019 (COVID-19) Situation Report – 85

World Health Organization

Data as received by WHO from national authorities by 10:00 CET, 14 April 2020

total (new cases in last 24 hours)

Globally
1 844 863 confirmed (71 779)
117 021 deaths (5369)

European Region
943 272 confirmed (29 923)
80 712 deaths (3293)

Region of the Americas
644 986 confirmed (34 244)
25 551 deaths (1792)

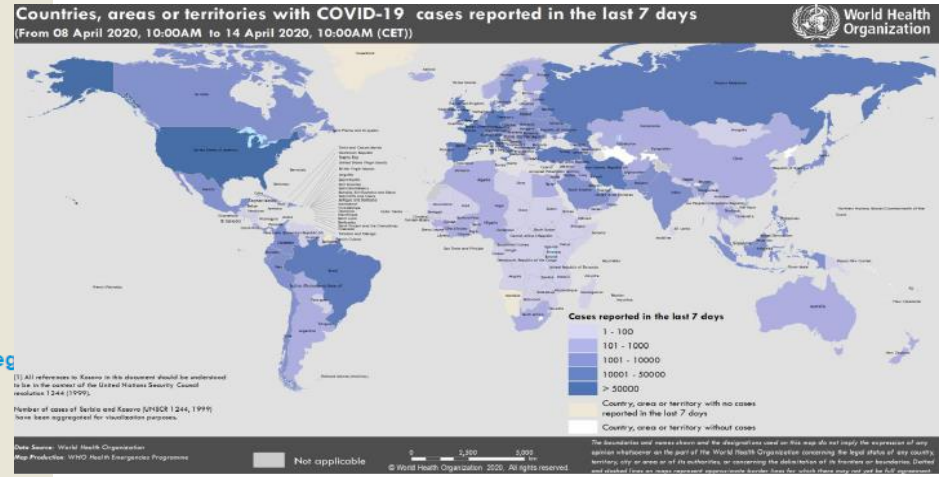
Western Pacific Region
122 805 confirmed (1379)
4161 deaths (36)

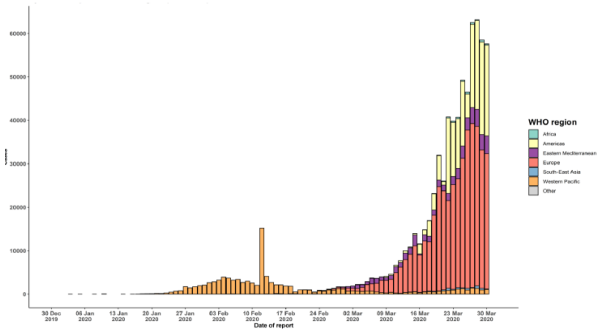
Eastern Mediterranean Reg
103 638 confirmed (3925)
5255 deaths (148)

South-East Asia Region
18 663 confirmed (1780)
829 deaths (63)

African Region
10 787 confirmed (528)
501 deaths (37)

WHO RISK ASSESSMENT
Global Level Very High

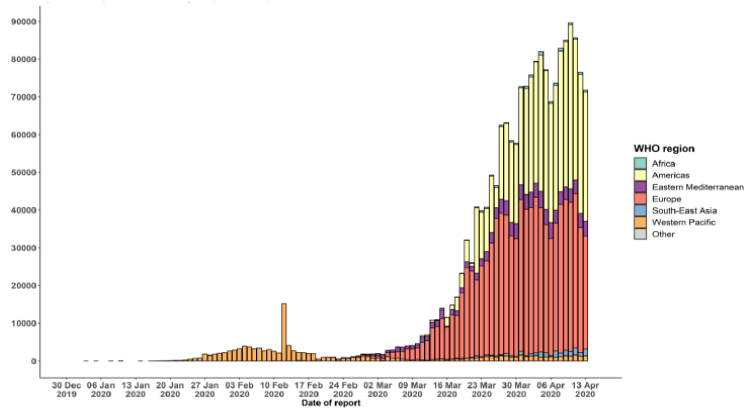




STRATEGIC OBJECTIVES

WHO's strategic objectives for this response are to:

- Interrupt human-to-human transmission including reducing secondary infections among close contacts and health care workers, preventing transmission amplification events, and preventing further international spread*;
- Identify, isolate and care for patients early, including providing optimized care for infected patients;
- Identify and reduce transmission from the animal source;
- Address crucial unknowns regarding clinical severity, extent of transmission and infection, treatment options, and accelerate the development of diagnostics, therapeutics and vaccines;
- Communicate critical risk and event information to all communities and counter misinformation;
- Minimize social and economic impact through multisectoral partnerships.



anti-Covid19 Vaccines

SARS-CoV2 Covid19 : Mars-Avril 2020

Organisation mondiale de la Santé

- **WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020**

In the past two weeks, the number of cases of COVID-19 outside China has increased 13-fold, and the number of affected countries has tripled

….

- We have therefore made the assessment that COVID-19 can be characterized as a pandemic

…..

- **Let me summarize it in four key areas:**

  - **First, prepare and be ready.**
  - **Second, detect, protect and treat.**
  - **Third, reduce transmission.**
  - **Fourth, innovate and learn.**

Vaccin anti-Covid-19 à **vecteur viral recombinant** (Chad-Ad3: AZD1222)

23 November 2020 07:00 GMT

Analyse Interimaire de l'AZD1222 à 2 doses différentes (**UK, Brazil) *sur un*** total de 131 COVID-19 cas :

- **Primary endpoint :** **COVID-19 cas 14 jours ou + après 2 doses**
  - **1/2 dose suivie d'1 dose pleine** : n=2,741: **VE = 90%** (p<=0.0001; borne inf.???).
  - **2 doses pleines à 1 mois d'écart (ou +)** : n=8,895 : **VE = 62%.** (p<=0.0001).
  - Analyse Combinée (n=11,636): **average VE = 70%.**
    - ***Pas d'hospitalisations ou formes severes***
- DSMB : pas d'EIG liés au vaccin

➢ ***Resultats "demontrent l'efficacité vaccinale "***

➢ **Mais:** **design peu clair :** 2 bras mal définis (erreurs de doses), délai entre doses pas clair

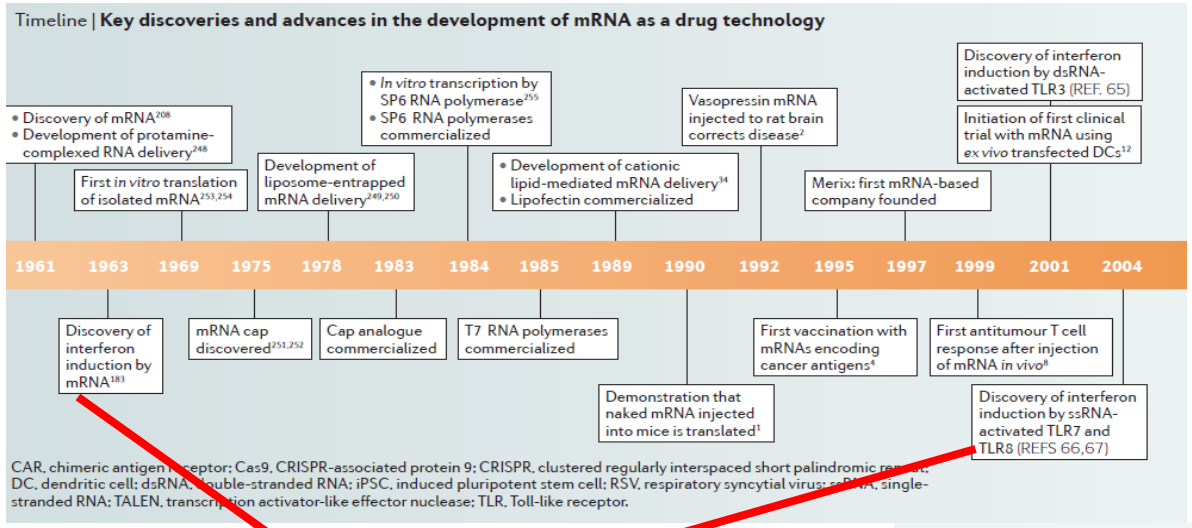
effectifs très limités

durabilité de la protection inconnue

protection / transmission (???)

B Autran

Vaccin anti-Covid-19 à **ARN messager**



mRNA-based therapeutics — developing a new class of drugs

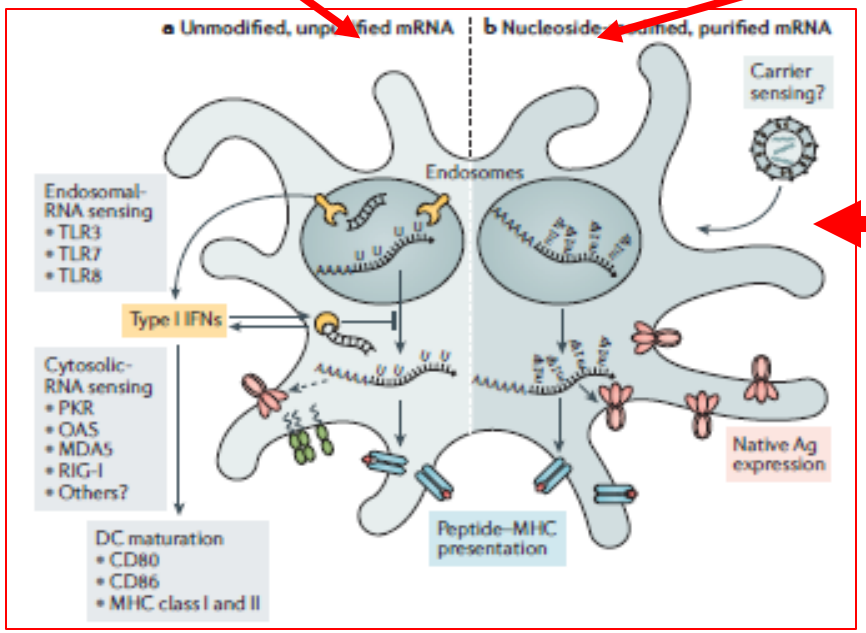
Ugur Sahin[1,2], Katalin Karikó[2,3] and Özlem Türeci[1]

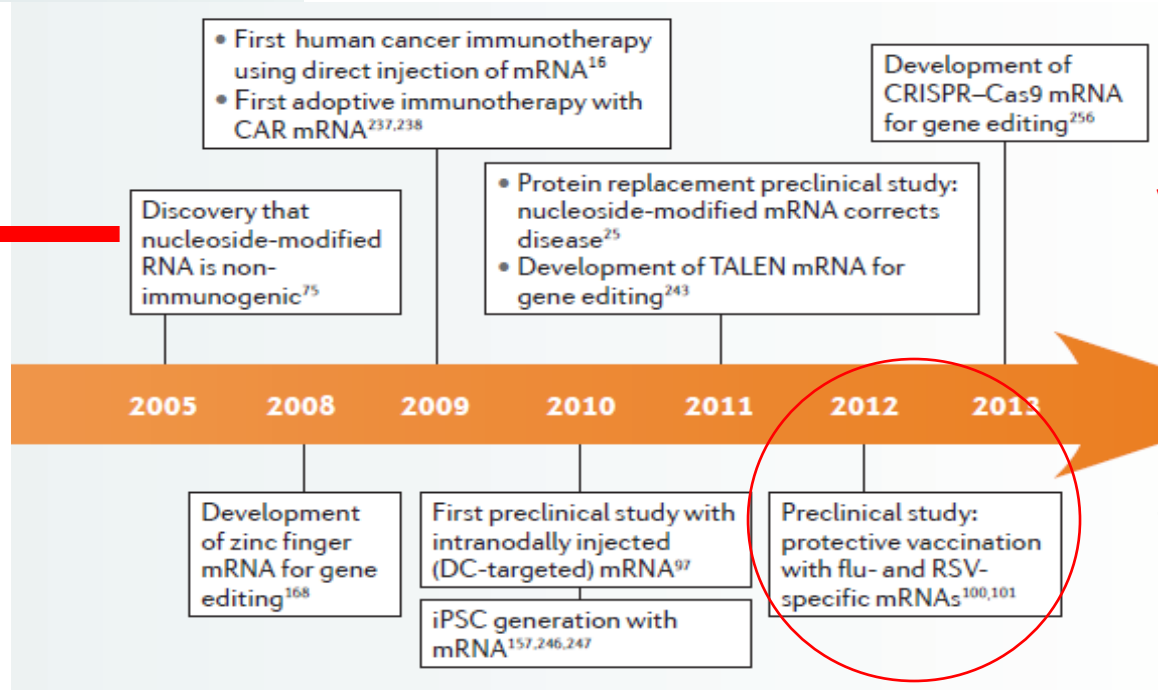
NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | OCTOBER 2014 | 759

mRNA vaccines — a new era in vaccinology

Norbert Pardi[1], Michael J. Hogan[1], Frederick W. Porter[2] and Drew Weissman[1]

NATURE REVIEWS | DRUG DISCOVERY VOLUME 17 | APRIL 2018 | 265





Vaccins ARNm / infections

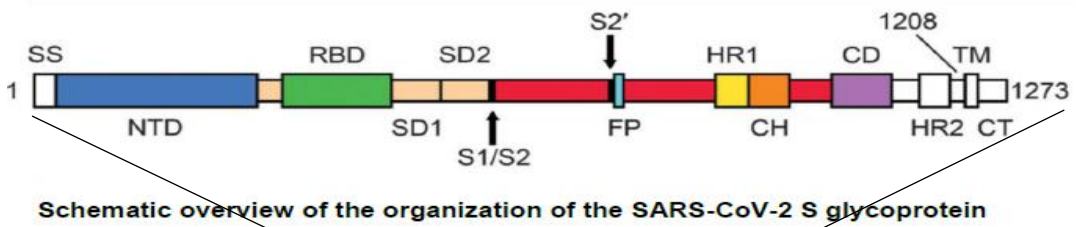
Phase 1 & 2 avant Covid-19:

- Flu
- Zika,
- Zona
- Bronchiolitis……
  ……

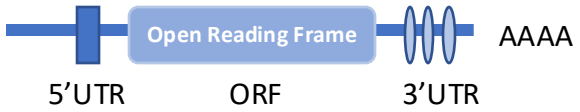
- / **cancers:** 19 essais

B Autran

mRNA Vaccines



Schematic overview of the organization of the SARS-CoV-2 S glycoprotein



1- mRNA Modifications : Pseudo-uridin remplace Uridin

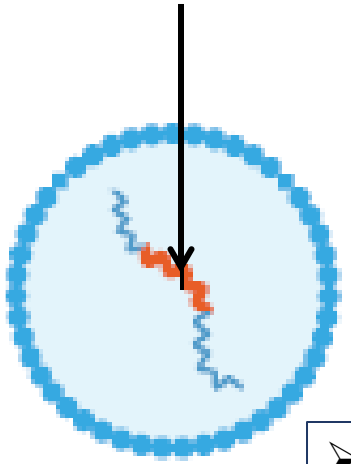
⇒diminution des réponses intra-cell anti-mRNA

⇒stabilisation des messagers et

⇒Augmentation de traduction

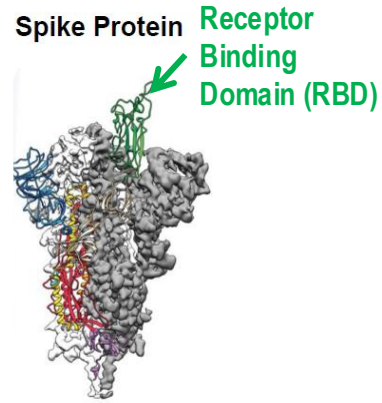
2- Insertion des ARNm dsn LipoNanoParticules:

- Protègent mRNA
- Augmentent
  - Endocytose par cellules Dendritiques
  - Immunogenicity



IIM

3- *Spike protein in-vivo* Synthesis



SARS-COV-2
Spike Protein 3D Structure
(Wrapp et al., 2020, Science)

- ARNm RESTE ds CYTOSOL
  - **NON Intégré dans l'ADN**
- **Production intra-cellulaire de Protéine** codée par ARNm
- ELIMINATION rapide (8-10j)

mRNA vaccine Efficacy in Phase 3 Trials

The NEW ENGLAND JOURNAL of MEDICINE

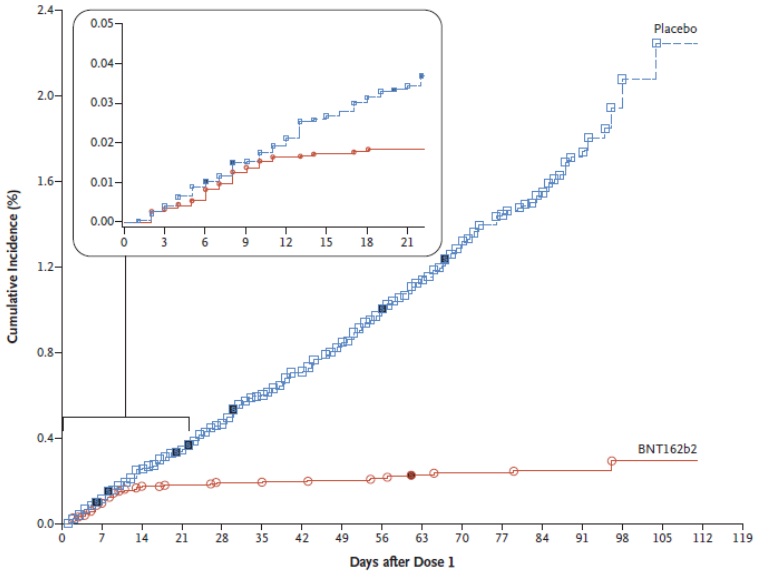
ORIGINAL ARTICLE

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

DOI: 10.1056/NEJMoa2034577

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

FP Polack et al.



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)

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on December 30, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2035389

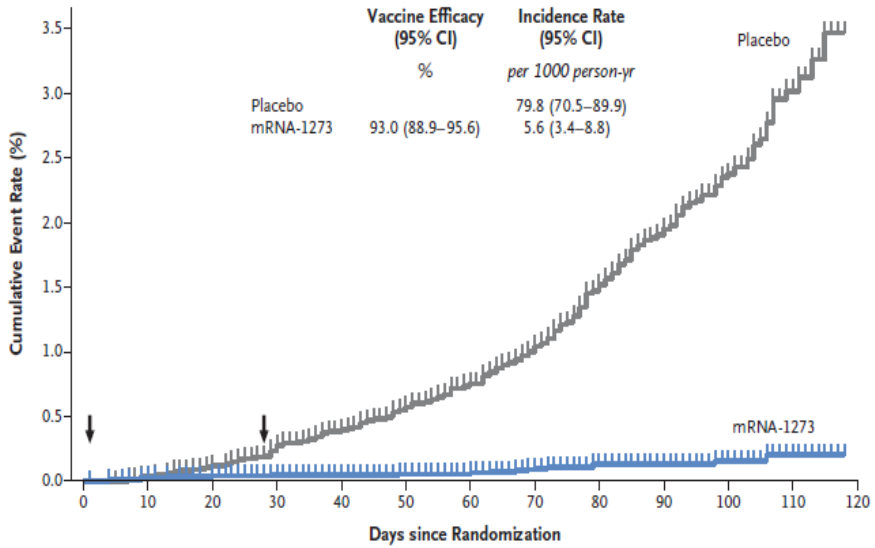
ORIGINAL ARTICLE

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, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

Modified Intention-to-Treat Analysis

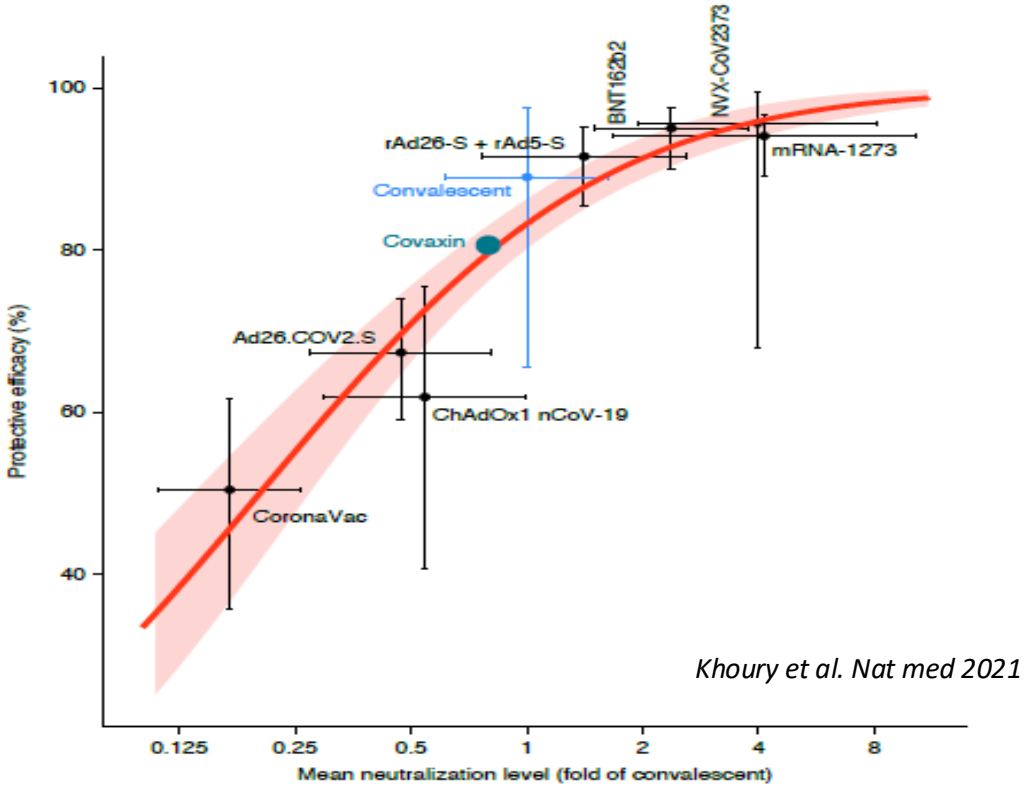
	Vaccine Efficacy (95% CI)	Incidence Rate (95% CI)
	%	*per 1000 person-yr*
Placebo		79.8 (70.5–89.9)
mRNA-1273	93.0 (88.9–95.6)	5.6 (3.4–8.8)



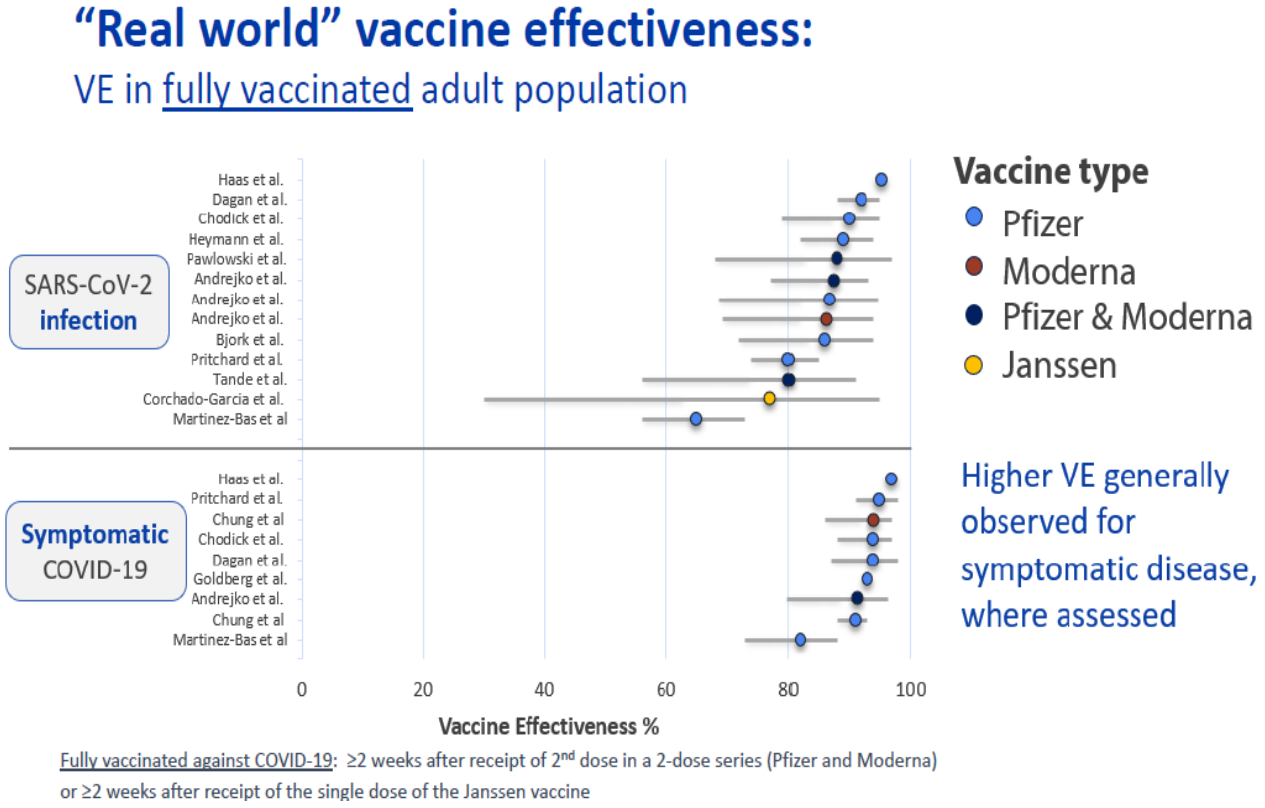
Vaccins anti-Covid-19 : Analyse comparative des Corrélats immuns de protection et de l'Efficacité vaccinale en vie réelle (Effectiveness)

Modelisation de l'EV des vaccins Covid-19 :

➢ **correlation aux Ac Neutralisants**



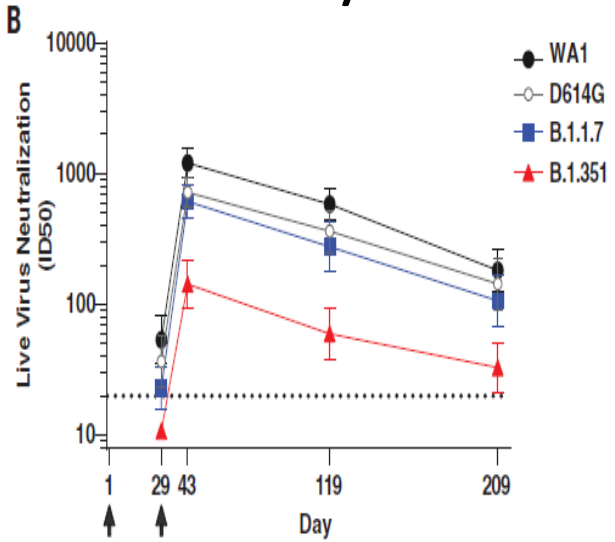
Khoury et al. Nat med 2021



B Autran

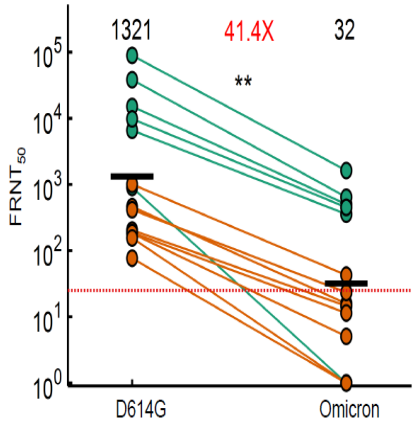
Décroissance rapide des taux d'anticorps apres Primo-vaccination
Bénéfice du rappel

➢ Décroissance des Anticorps 6 mois apres vaccination et / variants

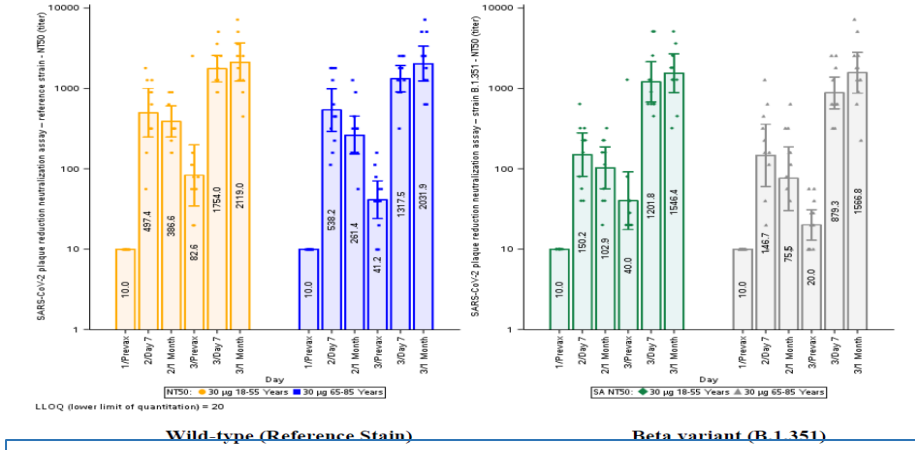


A Pegu et al. Science 2021

SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 *S Cele et al.*



➢ Effets bénéfiques du Rappel / virus d'origine

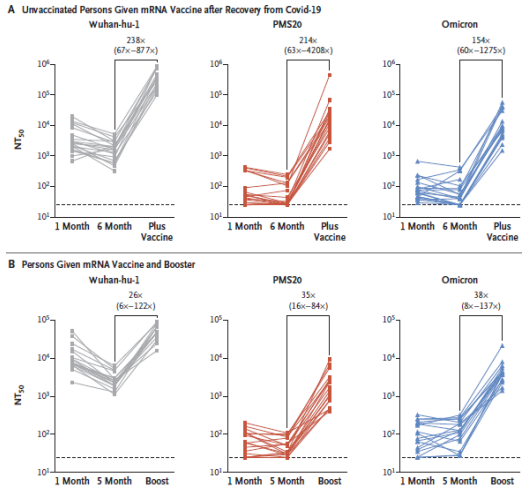


VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE BRIEFING DOCUMENT
MEETING DATE: 17 September 2021

➢ **Augmentation rapide x 10-100 fois Anticorps Neutralisants :**
- ➢ Chez Jeunes et Agés
- ➢ Contre les variants, incluant Omicron

Plasma Neutralization of the SARS-CoV-2 Omicron Variant

F Schmidt et al. NEJM 2021



Adaptation annuelle des vaccins anti-Covid-19 aux variants majoritaires circulants

➢ *2023 : WHO Statement on the antigen composition of COVID-19 vaccines*

https://www.who.int/news/item/18-05-2023-statement-on-the-antigen-composition-of-covid-19-vaccines

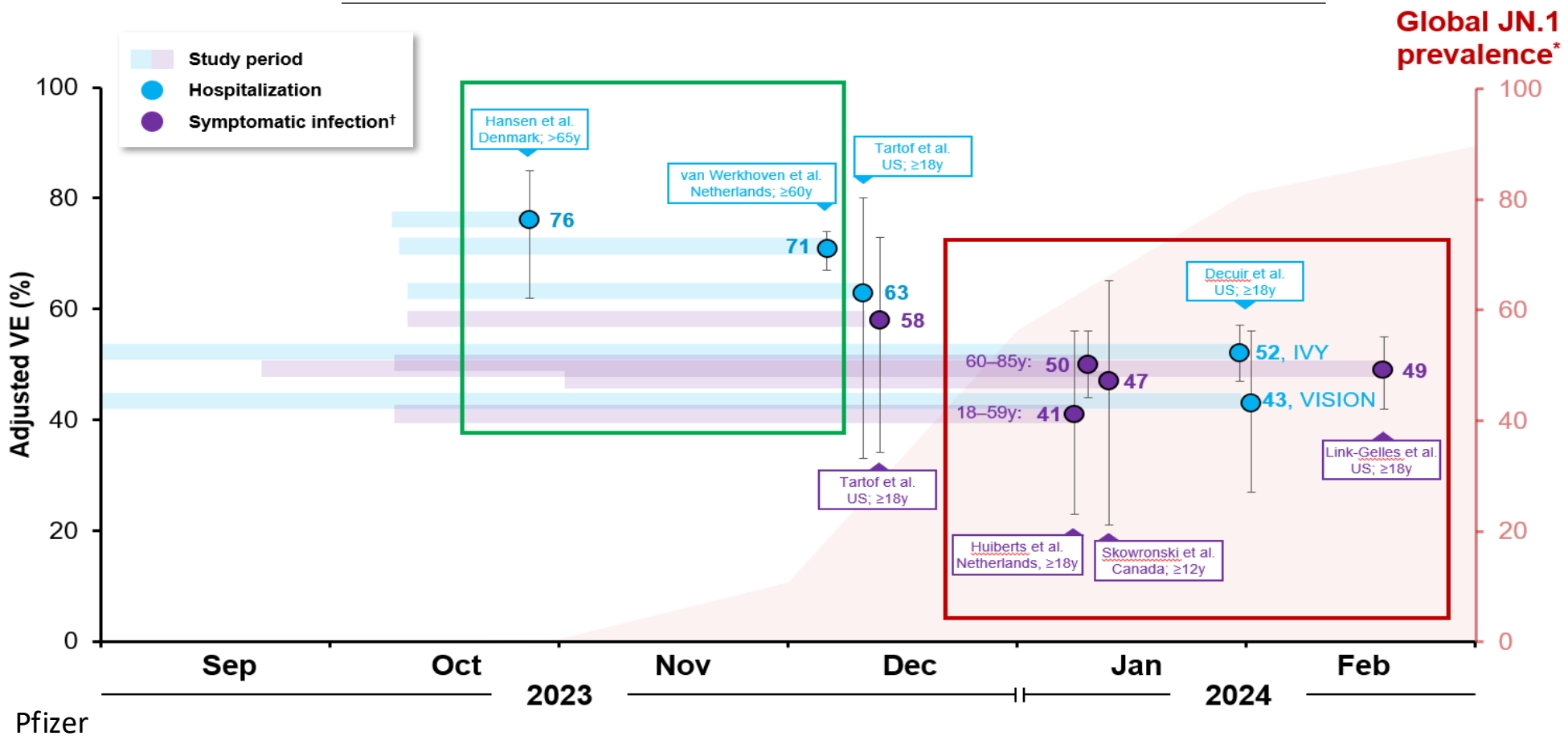
- TAG-CO-VAC**Recommande**
  - **d'adapter la composition des vaccins COVID-19 pour accroitre la réponse immune / SARS-CoV-2 variants, circulants :**
    - ➢ **lignage XBB.1 predomine globalement :**
      - ➢ vaccin COVID-19 doit induire Ac Neutralisants/ XBB pour améliorer la **protection / maladie symptomatique**
  - **Ne plus inclure le virus ancestral dans les futurs vaccins Covid-19**
  - Par un vaccin **monovalent Omicron-XBB.1 descendent lineage (XBB.1.5)**

➢ *2024, 2025 WHO Statements on the antigen composition of COVID-19 vaccines :*

Recommande vaccin monovalent Omicron-XBB.1 descendent lineage: JN1.

- ➢ **Populations** ciblées : **Personnes à haut risque de formes graves:** **âgées (>60 ou 65 ans) ou avec comorbidités**
- ➢ **Périodicité : annuelle** (automne, avec grippe) ou **bi-annuelle** (automne + printemps)

Efficacité vaccinale en vie réelle : Vaccin 2023 (XBB.1.5)



- **Protection Initiale Robuste / f. sévères**
- **Decroit au cours de la saison 2023/2024**
- **Mais conserve haut niveau de protection / formes sévères**

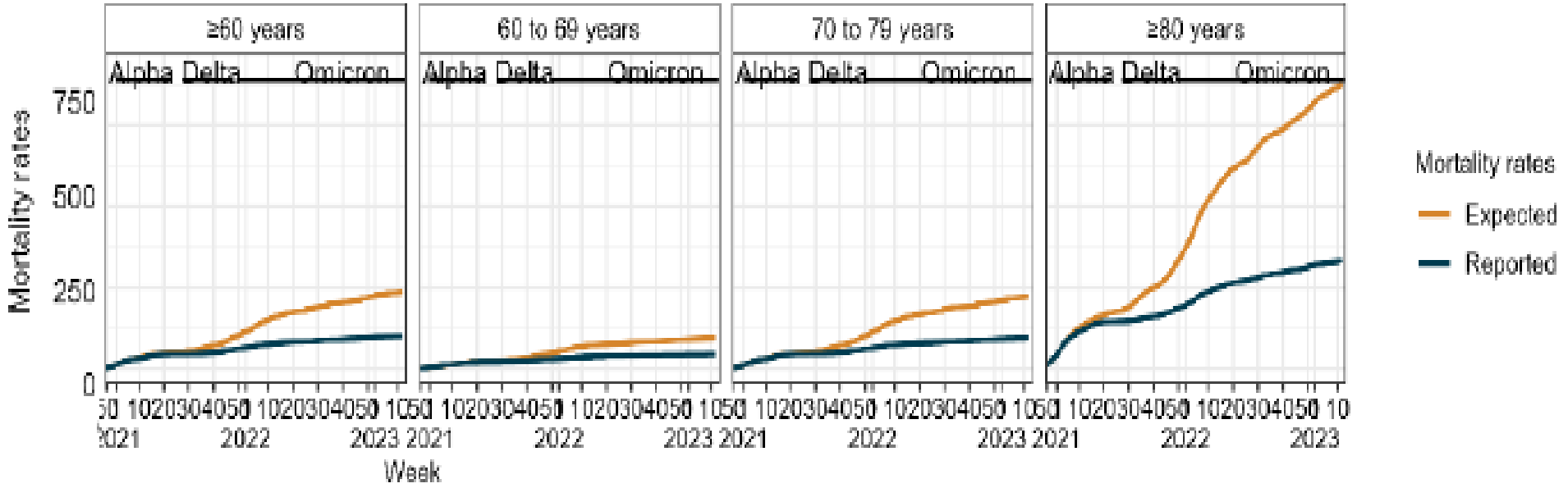
VE, vaccine effectiveness
*Historical data from: https://cov-spectrum.org. Accessed 2024 March 14. † Includes outcomes such as symptomatic infections, outpatient visits, and infections that were almost all symptomatic.
Hansen CH et al. Lancet Infect Dis 2024;24:e73-4; van Werkhoven CH et al. Euro Surveill 2024;29:pii=2300703; Tartof SY et al. medRxiv 2024; DeCuir J et al. MMWR 2024;73:180–188; Huiberts AJ et al. Euro Surveill 2024;29:pii=2400109; Skowronski DM et al. Euro Surveill 2024;29:pii=2400076; Link-Gelles R et al. MMWR 2024;73:77-83 and updated at ACIP

B Autran

Covid-19 : 2020-2023 vaccine Effectiveness in Europe

Pre-print : **Estimated number of lives directly saved by COVID-19 vaccination programs in the WHO European Region, December 2020 to March 2023** :
The WHO European Respiratory Surveillance Network https://doi.org/10.1101/2024.01.12.24301206

➢ **34 pays/regions : N vies sauvées / age avec vaccins (surtout ARNm) / variant**



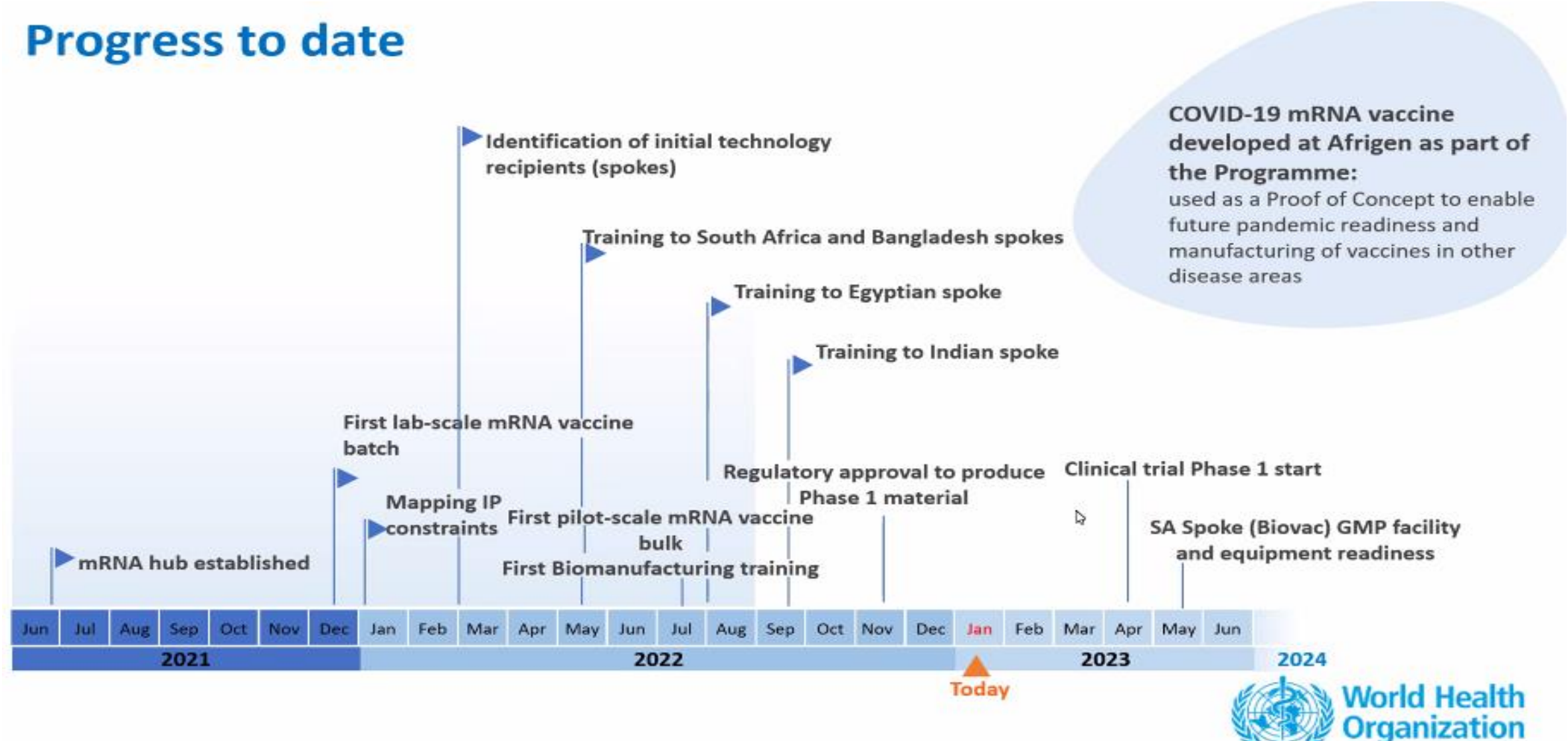
Vaccins => 57% reduction de mortalité (15%-75%) = **1.1 ~1.4 million vies sauvées ≥ 25 ans** (0.7 - 2.6 million):

96% = ≥60 ans; 52% = ≥80 ans;

67% = pdt vague Omicron.

To Improve access to mRNA vaccination in LMICs:

WHO « technology transfer hub » de l'OMS



Vaccins contre **Dengue, Chikungunya**

- **Pays avec transmission de dengue/zika/chikununya**

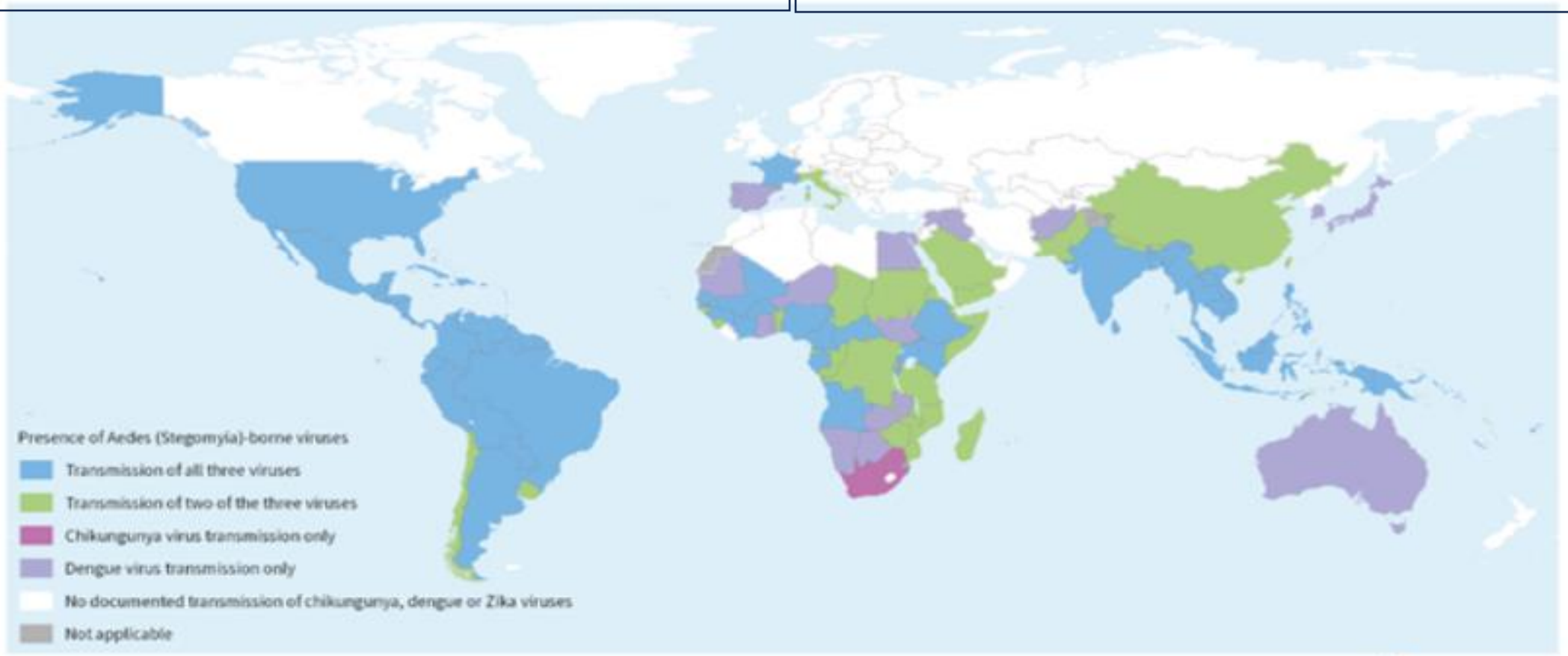
April 2024

➢ **5.6 milliards personnes à risque** / arbovirus

- **Transmission: Aedes Aegypti et A. Albopictus** (moustique tigre

⇒ mêmes facteurs d'augmentation d'incidence :

= Changement Climatique + Fragilité systems soins



✓ **Absence d'ARV => Nécessité de Vaccins**

World Health Organization

DENGUE

✓ **DENV: Flavivirus (comme YFV, ZIKAV…), 4 sérotypes : DEN-1, DENV-2, DENV-3, DENV-4**

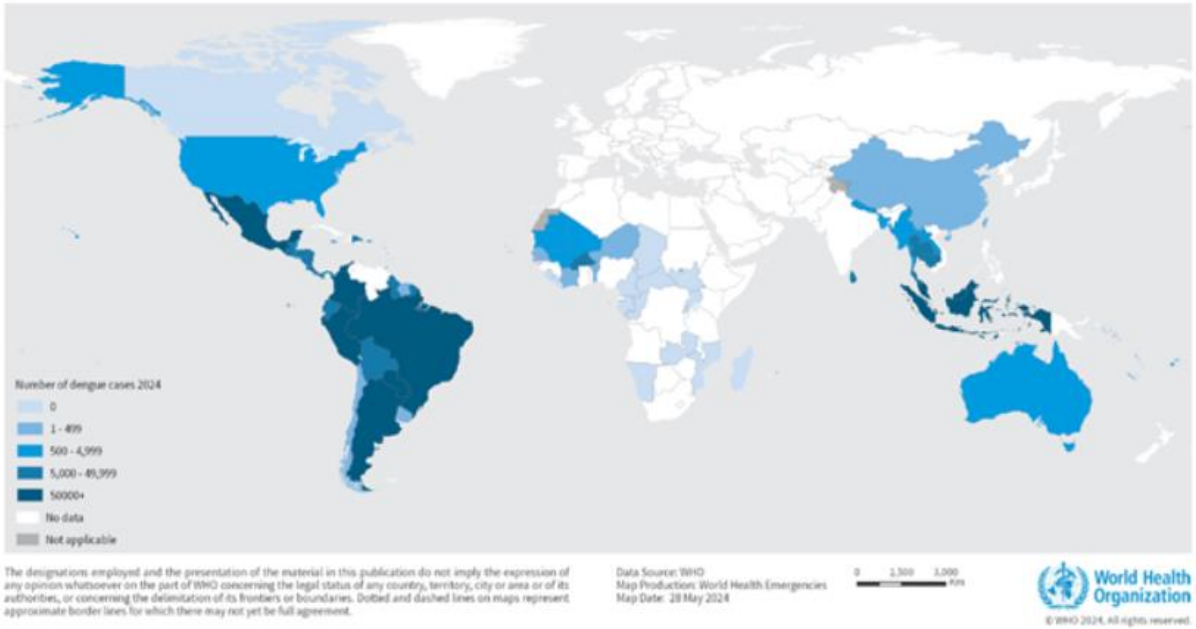
➢ **Fardeau global** : **Augmentation** +++ incidence: (OMS) : de 505 430 en 2000 **à 14.6 million en 2024**

mais 3/4 sous-rapportés (a- ou pauci-symptomatiques).

➢ **Dengue endémique ds >100 pays** sur tous les continents :

- **> Ameriques** : >13 million cas en 2024, et **territoires français ultra-marins *(Antilles – Guyane)***
- **Nouvelles aires**: Europe & Mediterranée orientale : 2024: **308 cas autochtones en France, Italie, Espagne en 2024**

Figure 2: Geographical distribution of dengue cases as reported to WHO from January to April 2024*



Vaccins anti-Dengue : Problemes de développement

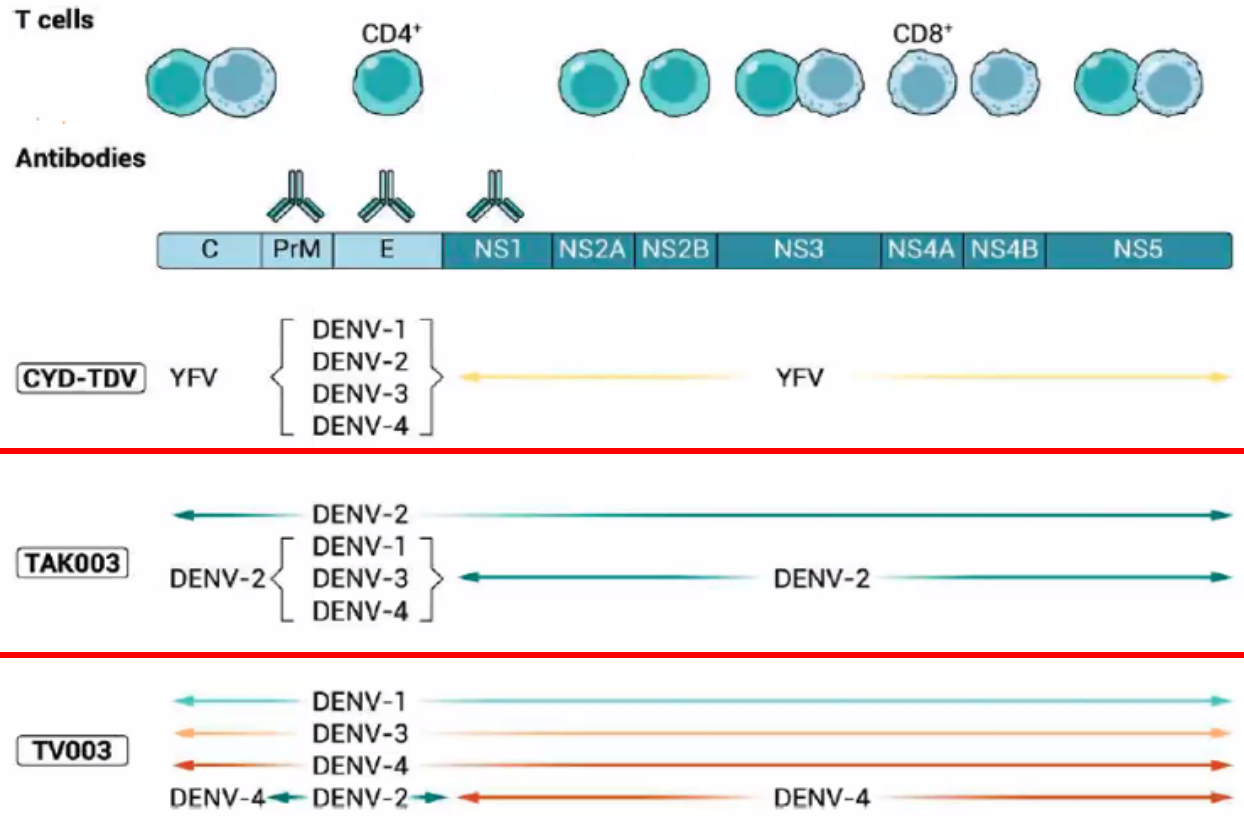
- **4 sérotypes : DEN-1, DENV-2, DENV-3, DENV-4**
- Interférence de la réponse immunitaire :
  - **Facilitation / Ac faiblement Neutralisants**

    (réactivité croisée entre 4 sérotypes)
- **Absence de bons corrélats de protection**
  - Faible spécificité Ac anti-dengue (autres FlaviV.)

Problemes liés au vaccin sanofi:

- Vecteur recombinant : vaccin YFV
- Faible immunité induite / Denv-2
- Faible protection / infection
- Risque accru d'hospitalisation des jeunes enfants vaccinés
- Risque accru chez sujets séronégatifs avant vaccin
- Approuvé chez sujets séropositifs seuls…
- 2024: Dengvaxia (sanofi) = **RETIRE** (bénéfice risque insuffisant)

Dengue tetravalent chimeric vaccines in clinical – all live attenuated vaccines



CYD-TDV/Dengvaxia
Sanofi Pasteur
Yellow fever vaccine backbone
Approved with restrictions

TV003/LATV
NIAID, Butantan, Merck
C-terminal deletion of 30 AA
Phase III

DENVax/Qdenga
Takeda
Cell culture attenuated
Approved in EU, Indonesia, Brazil, Thailand
UK, Argentina
Withdrew from FDA approval, could not provide data requested by FDA

Ooi, Scie Transl Med 2023
Wilder-Smith, Curr Opin Infect Dis, 2022
Paz-Baily, The Lancet, 2024

Three-year efficacy and safety of Takeda's dengue vaccine candidate

		Placebo (N = 6317)	TAK-003 (N = 12 704)	Efficacy % (95% CI)
VCD				
Overall		179/6201 (3.1)	208/12 435 (1.7)	44.7 (32.5–54.7)
SP		128/4502 (3.1)	139/8968 (1.6)	48.3 (34.2–59.3)
SN		51/1698 (3.2)	69/3465 (2.1)	35.5 (7.3–55.1)
SP	DENV-1	69/4502 (1.7)	77/8968 (0.9)	45.4 (24.5–60.6)
	DENV-2	34/4502 (0.8)	20/8968 (0.2)	72.1 (51.6–84.0)
	DENV-3	20/4502 (0.5)	37/8968 (0.4)	15.2 (−46.1 to 50.8)
	DENV-4	6/4502 (0.1)	5/8968 (<0.1)	61.9 (−24.9 to 88.4)
SN	DENV-1	28/1698 (1.8)	49/3465 (1.5)	17.2 (−31.8 to 47.9)
	DENV-2	16/1698 (1.0)	5/3465 (0.1)	84.9 (58.7–94.5)
	DENV-3	6/1698 (0.4)	11/3465 (0.3)	9.5 (−144.7 to 66.5)
	DENV-4	1/1698 (<0.1)	4/3465 (0.1)	−99.0 (−1680.3 to 77.8)
SP	4–5 y	16/457 (3.9)	34/941 (3.8)	2.5 (−76.6 to 46.2)
	6–11 y	75/2401 (3.4)	75/4743 (1.6)	51.9 (33.8–65.1)
	12–16 y	37/1644 (2.4)	30/3284 (0.9)	61.1 (37.1–76.0)
SN	4–5 y	16/331 (5.2)	17/652(2.8)	47.4 (−4.3 to 73.4)
	6–11 y	27/1051 (2.8)	40/2165 (1.9)	30.0 (−14.0 to 57.1)
	12–16 y	8/316 (2.7)	12/648 (1.9)	29.0 (−73.6 to 71.0)
Hospitalized VCD				
Overall		34/6201 (0.6)	21/12 435 (0.2)	70.8 (49.6–83.0)
SP		26/4502 (0.6)	12/8968 (0.1)	78.4 (57.1–89.1)
SN		8/1698 (0.5)	9/3465 (0.3)	45.0 (−42.6 to 78.8)
SP	DENV-1	10/4502 (0.2)	6/8968 (<0.1)	71.6 (21.7–89.7)
	DENV-2	9/4502 (0.2)	2/8968 (<0.1)	89.4 (51.1–97.7)
	DENV-3	6/4502 (0.1)	4/8968 (<0.1)	69.6 (−7.9 to 91.4)
	DENV-4	1/4502 (<0.1)	0/8968(0)	100.0 (NE–NE)
SN	DENV-1	5/1698 (0.3)	2/3465 (<0.1)	80.6 (−0.1 to 96.2)
	DENV-2	2/1698 (0.1)	0/3465 (0)	100.0 (NE–NE)
	DENV-3	1/1698 (<0.1)	7/3465 (0.2)	−246.6 (−2716.1 to 57.3)
	DENV-4	0/1698 (0)	0/3465 (0)	NE
SP	4–5 y	1/457 (0.2)	4/941 (0.4)	−80.7 (−1517.3 to 79.8)
	6–11 y	18/2401 (0.8)	5/4743 (0.1)	87.0 (65.0–95.2)
	12–16 y	7/1644 (0.5)	3/3284 (<0.1)	79.9 (22.1–94.8)
SN	4–5 y	2/331 (0.6)	1/652 (0.2)	73.0 (−197.4 to 97.6)
	6–11 y	5/1051 (0.5)	7/2165 (0.3)	28.7 (−124.9 to 77.4)
	12–16 y	1/316 (0.3)	1/648 (0.2)	52.3 (−669.7 to 97.0)

Data under the placebo and TAK-003 groups are presented as number of VCD or hospitalized VCD/number of evaluable participants (number of VCD cases per 100 person years at risk). Only the first instance of VCD was included in efficacy evaluation. For serotype-specific efficacy calculations, only the first instance of VCD from the individual serotype in question was included, regardless of previous instances of VCD from other serotypes. Participants were classified as seronegative when testing seronegative for all dengue serotypes at baseline. Participants were classified as seropositive when demonstrating a reciprocal neutralizing antibody titer ≥ 10 against at least one dengue serotype at baseline.

Abbreviations: CI, confidence interval; NE, not estimable; SN, seronegative at baseline; SP, seropositive at baseline; VCD, virologically confirmed dengue.

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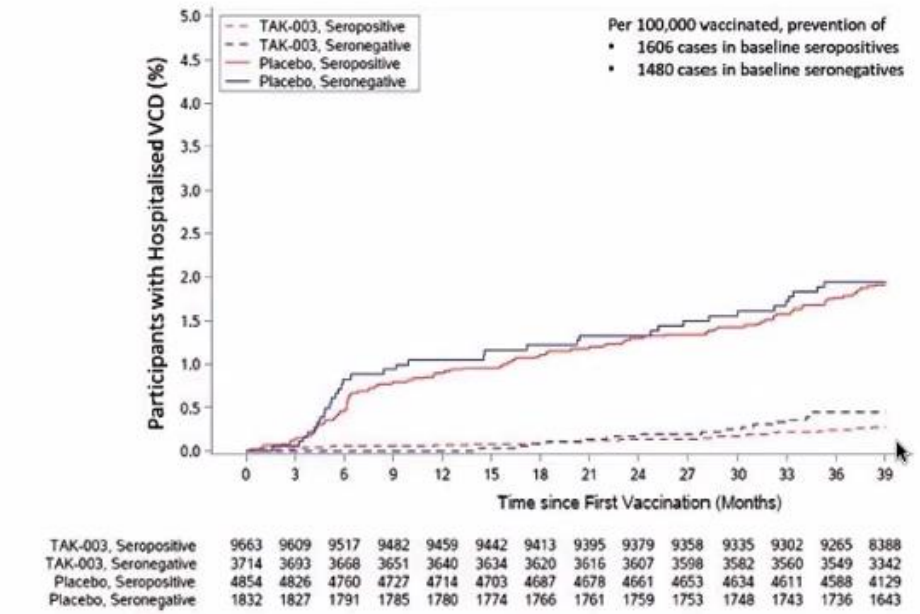


TAK-003, Seropositive	9663	9609	9517	9482	9459	9442	9413	9395	9379	9358	9335	9302	9265	8388
TAK-003, Seronegative	3714	3693	3668	3651	3640	3634	3620	3616	3607	3598	3582	3560	3549	3342
Placebo, Seropositive	4854	4826	4760	4727	4714	4703	4687	4678	4661	4653	4634	4611	4588	4129
Placebo, Seronegative	1832	1827	1791	1785	1780	1774	1766	1761	1759	1753	1748	1743	1736	1643

- **Efficacité vaccinale contre Hospitalisations: = 71%**
- **chez Séropositifs** (=45% chez séronégatifs)

Rivera, CID, 2023

VACCINS **DENGUE**

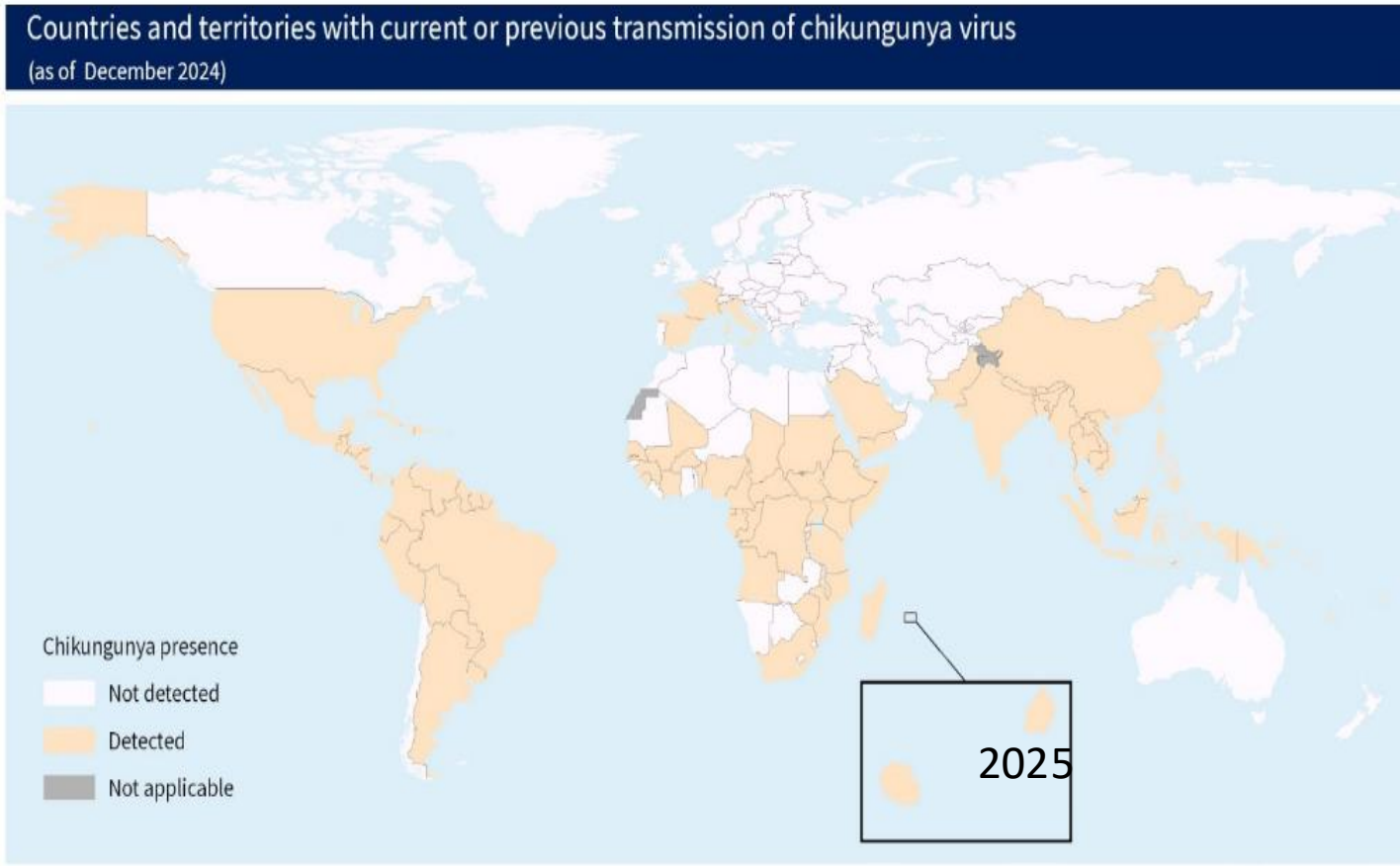
Organisation mondiale de la Santé

- **Qdenga®** (TAK-003) : **vaccin vivant atténué** = sérotypes 1, 2, 3 et 4 recombinés à partir de la souche DENV2.
  - schéma à **2 doses, espacées de 3 mois**
  - OMS : **pour sujets SEROPOSITIFS**
    - **Recommandé** : enfants de **6 à 16 ans** **dans les zones à forte intensité de transmission** (> 60 % de personnes séropositives avant 9 ans ou 16 ans parmi les patients hospitalisés au moment du pic)
    - **Proposé** : personnes avec **comorbidités** (dont **Drépanocytose**) **en zone d'endémie, jusqu'à 60 ans**,
      - Ex: France: Antilles/Guyane , Réunion-Mayotte (Recos HAS)
    - **Envisager** l'introduction dans les programmes de vaccination systématique si l'intensité de la dengue = problème de santé publique (mais transmission souvent géographiquement hétérogène => introduction ciblée à l'échelle infranationale: ex: Argentine Nord).
    - **Voyageurs** vers pays de haute endémie : **si séropositifs**
  - **Contre-indications (= celles des vaccins vivants atténués) : grossesse , allaitement, immunodépression, VIH symptomatique à CD4 bas**;
  - **=> Nécessité d'évaluation approfondie du profil efficacité-risque** pour **DENV3 et DENV4** chez les **séronégatifs**.
- Autres vaccins en cours d'évaluation.

> **Vaccination anti-Dengue = Un des éléments d'une stratégie intégrant :**
>
> **Lutte anti-vectorielle + prise en charge adéquate des cas + éducation et mobilisation des communautés**

CHIKUNGUNYA

(Homme cassé en swahili)



- CHIKV = Togavirus (different de Dengue = Flavivirus);
- Epidémiologie: Origine: Afrique (environ 500 ans)

  => Extension géographique :

  - 1952:1e Tanzanie => 1958: 1er foyer urbain : Thailande
  - 1970s: Inde
  - 2004: Ocean Indian => importants foyers (Reunion : 2006); 2013: Amerique/Caraibes .
  - **2024: 119 pays** (Brésil: 235 000 cas et 140 décès) **+ transmission autochthone ds 6 regions OMS**

    => 2025 = 270 000 cas mondiaux **(120 cas autochtones F. métrop.)**

  - Taux d'attaque élevé, mais immunité de groupe stoppe foyers (1 an)

- Clinique: **Fièvre +** **<u>Arthralgies sévères</u>**, <u>souvent handicapantes et durables</u> +/- arthrites, myalgies, céphalées éruptions cutanées

  ➢ **Rares cas sévères ou mortels : encéphalopathie fœtale et Nné**, et **f. sévères chez sujets âgés ou avec co-morbidités**

Vaccins CHIKUNGUNYA

➢ **2 vaccins** homologués dans plusieurs pays et/ou recommandés pour les populations à risque:

✓ **Xchiq** : **vaccin vivant atténué:** AMM /FDA et EMA 2024:

- **Essais Ph1-2 seuls : 99% répondeurs (Ac. Neutralisants)**
  - ➢ **MAIS PAS de Phase 3 = EFFICACITE NON EVALUEE en phase EPIDEMIQUE**
- **Indications: adultes** en situation épidémique**; + vaccin voyageur**
  - ➢ **Contre-indications des vaccins vivants atténués : Immunodépression**
- **1e Utilisation en phase épidémique : La Réunion Av. 2025:** Priorisation : Sujets à risque de f. graves ;
  - **Complications :** début de campagne: **2 décès post-vaccins chez sujets âgés / F. grave Chik post-vaccinal** par réplication incontrôlée du vaccin vivant atténué dans un contexte d'immunosénescence
    - ➢ **Restriction d'utilisation chez sujets <65 ans**
      - ➢ **Nécessité de ré-évaluer Balance bénéfices / Risques**

✓ **VIMKUNIA : vaccins à pseudo-particules protéiques** (Env1 & 2+capside): **AMM/FDA, EMA, OMS: 2025**

- **Essais Ph1-2 seuls : 87-98% répondeurs (Ac. Neutralisants) =>** **MAIS PAS de Phase 3 = EFFICACITE NON EVALUEE en phase EPIDEMIQUE**
- **Indications: adultes** en situation épidémique**; + vaccin voyageur**
  - ➢ **PAS de Contre-indications** / Immunodépression, Immunosenescence

ONU / OMS : Coalition des Innovations pour la Preparation aux Epidemies (CEPI)

CEPI: Driving Progress Towards Epidemic Preparedness And Response.
Gouglas D[1], Christodoulou M[1], Plotkin SA[2], Hatchett R Epidemiol Rev. ***2019 Nov 1.***

- **2017 after the Ebola epidemics (2014-15):**
  - To sustain vaccine development and global preparadness against epidemics.
  -
- **> 750 millions US$ for** :
  - vaccines :**Lassa Virus,**
    Middle East Respiratory Syndrome coronavirus (MersCo),
    Nipah Virus,
  - **Quick response vaccine platforms**
- Major role of PPie
- **priorités :**
  - diversification of vaccines in development **: Rift Valley Fever, Chikungunya;**
  - **Technical and regulatory processes specific for these vaccines and EID**
  - **Sustainable industrial solutions to ensure safety and immunogénicity**;
  - **Stocks of** candidate vaccines for Emergency trials and usages

5: Further development across multiple platforms is needed to optimise for speed and effectiveness, but not all are likely to enable achievement of the 100-day goal

Timeline suitable for 100 day goal | Potential to reach 100 days (with targeted preparation)

Platform	Description	Minimal time until first batch[1]	Ability to pre-optimise processes prior to outbreak	CD independent of immunogen knowledge	Key limitations	Example vaccines
RNA	Delivery of RNA of antigen using lipid nanoparticles (LNPs)	3+ weeks	✓ Similar process (assuming use of same LNP)		Plasmid DNA can be rate-limiting raw material	COVID-19
Viral vector	Delivery of DNA or RNA of antigen using viral vectors	10-12 weeks	✓ Unique viral banks required	✗	Long release assays required (e.g., replication competent virus)	COVID-19, Ebola, Zika, influenza, HIV
Recombinant protein	Protein vaccine based on viral antigens	Similar to viral vector	✗ Optimise cell growth, protein folding & formulation w/ adjuvant	Viral antigen needs to be known & targetable	Protein folding and formulation difficult to standardise	COVID-19, hepatitis B, shingles HPV
Virus-like Particles	Virus-resembling molecules with multiple surface antigens	Longer than recombinant proteins	✗ Optimise cell growth, protein folding, complex assembly and formulation		Protein folding and formulation difficult to standardise; complex molecules due to need for self-assembly	Hepatitis B, HPV
Inactivated vaccine	Inactivated or altered replication-deficient virus	Speed determined by ability to use high BSL facilities, cell line availability & scalability and viral doubling time	✓ Relatively simple to manufacture but growth may be virus-specific	✓ Whole virus vaccines requires limited knowledge of specific antigens	Weaker immune response / multiple doses; release test to ensure full inactivation	COVID-19, influenza (shot), hepatitis A, polio (shot), rabies
Live attenuated vaccine	Genetically modified virus which does not cause disease		✗ Genetic manipulation unique to virus		Not suitable for people with compromised immune system	MMR, rotavirus, smallpox, shingles, yellow fever

Cell growth required

Timelines until first batch vary between platforms but so does their immune response & side effect profile and need for immunogen identification

1. Excluding release testing

Note: PD = process development; CD = candidate development

Source: External stakeholder interviews, literature research