EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Evaluation and authorization of adult vaccines

AIB, 6 December 2023

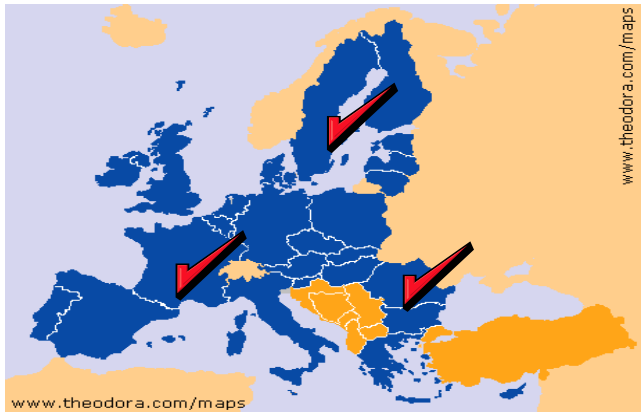
- Dr. Marco Cavaleri
- Head of Health Threats and Vaccines Strategy
- Chair of EMA Emergency Task Force

The EU procedures for marketing authorisation

Centralised Procedure (via EMA)

Mutual Recognition procedure

Decentralised Procedure



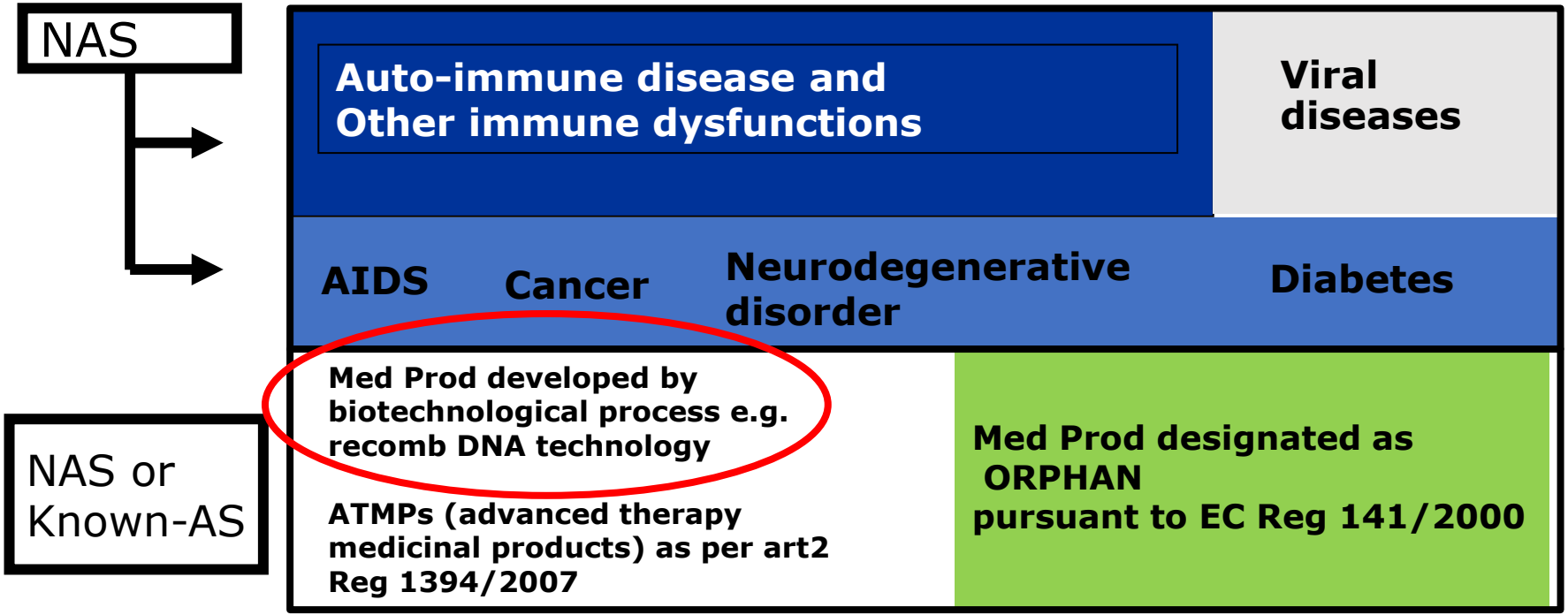
Better Resource Utilisation
Harmonised Scientific Opinions
Harmonised Information to Doctors / Patients

The centralised procedure CP

- **1 Marketing Authorisation** valid in EU: centrally authorised product (CAP)
- **1 Invented name** (Tradename)
- **1 Common Labelling** (23 languages+ IS/NO)
  - Summary of Product Characteristics (SmPC)
  - User Package Leaflet & Package Labelling
- **Maximum time limit for evaluation**
  - 210 days from validation to Opinion

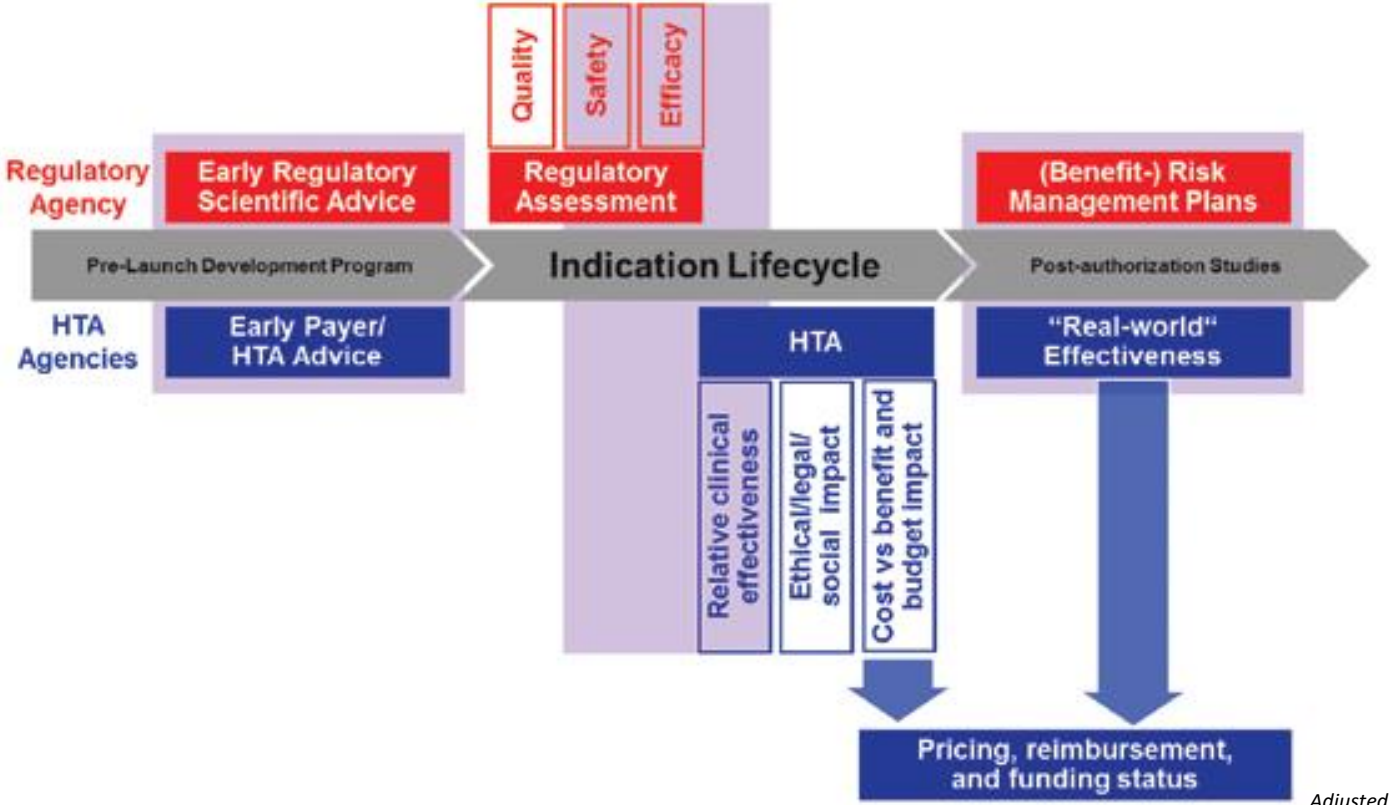
Access to Medicines: Mandatory Scope

Art 3(1) Reg. 726/2004, Annex



NAS: new active substance -- AS: active substance

Two decision making processes



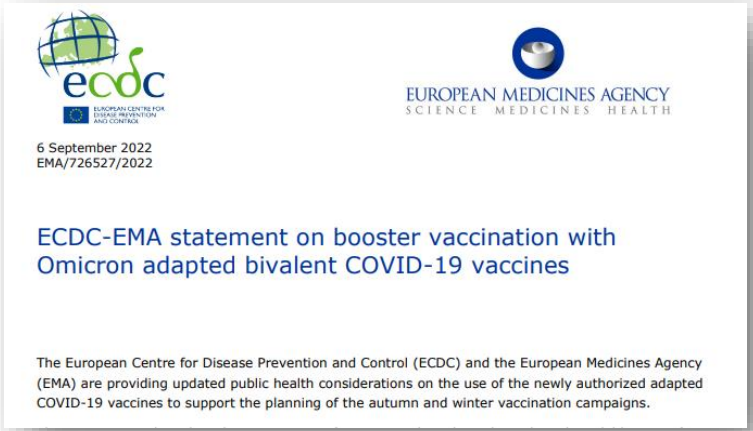
Adjusted from Bramley et al., 2017

<u>Vaccines:</u>

Besides HTAs, NITAGs play a major role in defining national recommendations

Engagement and collaboration

- Engaging with **patients and healthcare professionals** in EMA's pandemic task force, regular meetings, user testing information materials
- **Working together** with European Commission (DG SANTE & HERA), ECDC, national medicines regulators
- Cooperation with **DG HERA** on horizon scanning & intelligence gathering and development of medical countermeasures
- Provision of **joint EMA-ECDC guidance** to support national vaccination campaigns



ecdc

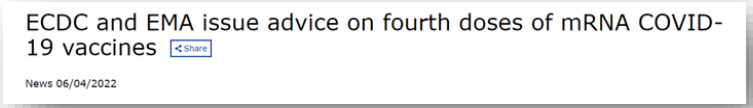
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 September 2022
EMA/726527/2022

ECDC-EMA statement on booster vaccination with Omicron adapted bivalent COVID-19 vaccines

The European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) are providing updated public health considerations on the use of the newly authorized adapted COVID-19 vaccines to support the planning of the autumn and winter vaccination campaigns.



ECDC and EMA issue advice on fourth doses of mRNA COVID-19 vaccines

Share

News 06/04/2022

Requirement for approval - efficacy studies

- Absolute protective efficacy of vaccines by comparing the reduction in the incidence of the infectious disease in question vs. the incidence in a group that receives placebo in a prospective individually randomised and double-blind trial

- If there is an EU authorised vaccine, the trial may be designed to estimate the relative efficacy of the candidate vs the licensed vaccine with a non-inferiority (or superiority) design

- Case definitions to be used for the primary analysis and any alternative case definitions for secondary analyses usually comprise clinical signs and/or symptoms typical of the infectious disease together with laboratory confirmation of the aetiology

- If a candidate vaccine contains antigens derived from several but not all known subtypes of a pathogen it may be acceptable that the primary endpoint is based on cases of disease due to any subtype included in the vaccine.

Vaccine name	Manufacturer	Vaccine type	Adjuvant	Administration/posology/strength	indication
Abrysvo	Pfizer	recombinant RSVPreF bivalent subgroups A and B produced in CHO cells by recombinant DNA technology	none	IM, 1 dose (120ug) to both pregnant women (WoG 24-36) and adults	LRTD in infants & >60 years

Table 4 Vaccine efficacy of Abrysvo against RSV disease - active immunisation of individuals 60 years of age and older – Study 2

Efficacy endpoint	Abrysvo Number of cases N=18 058	Placebo Number of cases N=18 076	VE (%) (95% CI)
First episode of RSV-associated lower respiratory tract illness with ≥2 symptoms[a]	15	43	65.1 (35.9, 82.0)
First episode of RSV-associated lower respiratory tract illness with ≥3 symptoms[b]	2	18	88.9 (53.6, 98.7)

CI – confidence interval; RSV – respiratory syncytial virus; VE – vaccine efficacy

[a] In an exploratory analysis in RSV subgroup A (Abrysvo n=3, placebo n=16 VE was 81.3% (CI 34.5, 96.5); and in RSV subgroup B (Abrysvo n=12, placebo n=26) VE was 53.8% (CI 5.2, 78.8).

[b] In an exploratory analysis in RSV subgroup A (Abrysvo n=1, placebo n=5) VE was 80.0% (CI -78.7, 99.6); and in RSV subgroup B (Abrysvo n=1, placebo n=12) VE was 91.7% (CI 43.7, 99.8).

AREXVY Produces Durable Vaccine Efficacy Against RSV-LRTD Over 2 Full Seasons

	Median Follow-Up (months)	AREXVY Number of events	Placebo Number of events	VE (95% CI) *W/o season as covariate#*	VE (95% CI) *W/ season as covariate¶*
Single Dose					
Season 1* VE 1	**6.7**	**7** / 12,466	**40** / 12,494	**82.6%** (57.9, 94.1)	82.6% (57.9, 94.1)
Mid Season 2 Post dose 1	**14**	**15** / 12,469	**85** / 12,498	**80.9%#** (66.7, 89.8)	77.3%¶ (60.2, 87.9)
Season 2 Only Post dose 2	**6.4**	**20** / 4,991	**91** / 10,031	**56.1%** (28.2, 74.4)	56.1% (28.2, 74.4)
Season 1 + 2**	**18**	**30** / 12,469	**139** / 12,498	**74.5%#** (60.0, 84.5)	67.2%¶ (48.2, 80.0)
Annual (2 doses, ~12 months apart)					
Season 2 Only Post dose 2	**6.4**	**20** / 4,966	**91** / 10,031	**55.9%** (27.9, 74.3)	55.9% (27.9, 74.3)
Seasons 1 + 2**	**18**	**30** / 12,469	**139** / 12,498	**74.5%#** (60.0, 84.4)	67.1%¶ (48.1, 80.0)

Modified exposed set
***96.95% CI for VE 1; ****97.5% CI for Season 1 + 2**

Options for use of biomarkers as surrogate endpoints for licensure

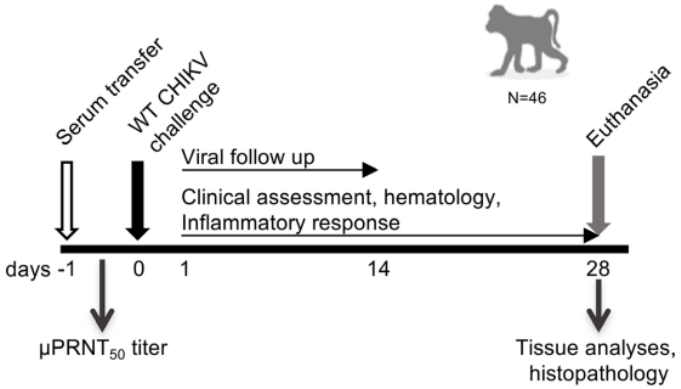
- An immune correlate of protection is available

- An immune marker that is suitable to infer protection is available and applicable, and field efficacy trials are not feasible

- None of the above and field efficacy trials not feasible…..need to be creative

Correlate of protection is available

- **Immune correlate of protection**: an immune parameter that has been demonstrated to correlate with protection at defined values
- Established correlates of protection exist for some infectious agents, e.g. tetanus, diphtheria, polio, hib, HBV
- ICP may derive from pivotal Phase III studies conducted with first-in class vaccine
- Effectiveness studies or natural infection sero-epidemiological studies could provide evidence on correlates of protection
- In some cases, human challenge studies or animal models of infection could help in indicating potential correlates of protection



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

Pierre Roques,[1] Andrea Fritzer,[2] Nathalie Dereuddre-Bosquet,[1] Nina Wressnigg,[2] Romana Hochreiter,[2] Laetitia Bossevot,[1] Quentin Pascal,[1] Fabienne Guehenneux,[3] Annegret Bitzer,[2] Irena Corbic Ramljak,[2] Roger Le Grand,[1] Urban Lundberg,[2] and Andreas Meinke[2]

[1]Université Paris-Saclay, INSERM, CEA, Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Fontenay-aux-Roses, France. [2]Valneva Austria GmbH, Campus Vienna Biocenter 3, Vienna, Austria. [3]Valneva SE, Saint Herblain, France.

Table 2. Peak viremia for animals with different µPRNT$_{50}$ titer thresholds.

		µPRNT$_{50}$ ≥ 50 (*n* = 13)	µPRNT$_{50}$ ≥ 100 (*n*=4)	µPRNT$_{50}$ ≥ 150 (*n* = 2)
Peak viremia (copies/mL) Day 2–6	Geometric mean	941.1	16.3	10
	[95% CI]	[100, 8846]	[4, 77]	[10, 10]
Number of NHPs with detected CHIKV RNA	Not detected	4 (30.8%)	3 (75.0%)	2 (100%)
	Detected	9 (69.2%)	1 (25.0%)	0 (0.0%)

The geometric mean for the peak viremia (copies/mL) is shown for each group of animals assigned to the 3 µPRNT$_{50}$ thresholds. Numbers of animals with or without detectable CHIKV RNA were calculated for the 3 µPRNT$_{50}$ thresholds. Therefore, animals with an µPRNT ≥ 150 are included in the µPRNT$_{50}$ ≥ 100 and µPRNT$_{50}$ ≥ 50 columns, and animals with an µPRNT ≥ 100 are included in the µPRNT$_{50}$ ≥ 50 column. Peak copies/mL values reported as 0 were set to 10 for this summary.

jciinsight-7-160173.pdf (nih.gov)

An immune marker suitable to infer protection is available

- ICPs not fully established, but data points towards the definition of a threshold value for a specific immune marker that appears to correlate with protection, e.g. IgG elicited by conjugated pneumococcal vaccine for specific serotypes

- If no ICP or threshold for benchmarking immunogenicity of vaccines is available, it could still be possible to use an immune marker that best represent response to a vaccine that showed efficacy, e.g. aP and COVID-19 vaccines

- For traditional influenza vaccines based on HA, HI titres above 1:40 have been used for comparing immunogenicity BUT do not represent an established correlate of protection

Vidprevtyn beta - COVID-19 vaccine - immunobridging to Comirnaty

Vidprevtyn Beta induces superior BA.1 titers vs BNT162b2 prototype in fully validated PsVN assay

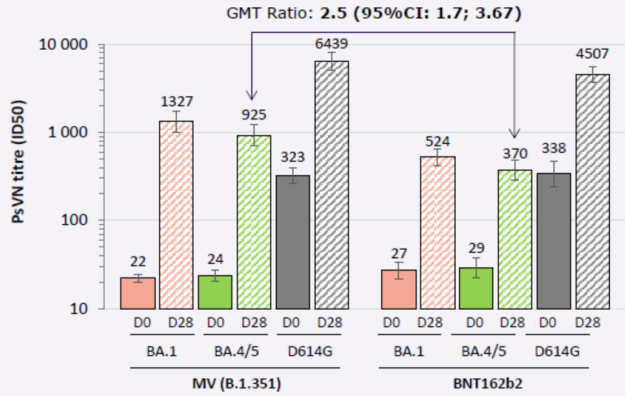
Primary objective: Superiority of D28 GMT against Omicron BA.1

Strain	M	Sanofi B.1.351 (N=54) GMT (95% CI)	M	BNT162b2 (N=60) GMT (95% CI)	Sanofi B.1.351 / BNT162b2 GMT ratio (95% CI)	Superiority
Omicron BA.1	54	**1327.5** (1005.0, 1753.4)	58	**524.0** (423.3, 648.6)	2.53 (1.80, 3.57)	**Yes**

Superiority is concluded if the lower limit of the 2-sided 95% CI of the GMT ratio > 1.2

Vidprevtyn Beta induces higher cross-neutralizing BA.4/5 antibodies vs BNT162b2 prototype in fully validated PsVN assay

Results consistent with responses to Omicron BA.1 and D614G



sanofi

VIDPREVTYN BETA - EMA/RAPPORTEURS/ETF CORE TEAM MEETING - 06 OCTOBER - CONFIDENTIAL

Second generation vaccines with additional subtypes – 20valent PnC Vaccine

Table 3. OPA GMTs 1 Month After Vaccination in Participants 60 Years of Age and Older Given Apexxnar Compared to Prevenar 13 for the 13 Matched Serotypes and to PPSV23 for the 7 Additional Serotypes (Study 1007)[a,b,c,d]

	Apexxnar (N = 1157–1430)	Prevenar 13 (N = 1390–1419)	PPSV23 (N = 1201–1319)	Vaccine Comparison	
	GMT[e]	GMT[e]	GMT[e]	GMT Ratio[e]	95% CI[e]
Serotype					
1	123	154		0.80	0.71, 0.90
3	41	48		0.85	0.78, 0.93
4	509	627		0.81	0.71, 0.93
5	92	110		0.83	0.74, 0.94
6A	889	1165		0.76	0.66, 0.88
6B	1115	1341		0.83	0.73, 0.95
7F	969	1129		0.86	0.77, 0.96
9V	1456	1568		0.93	0.82, 1.05
14	747	747		1.00	0.89, 1.13
18C	1253	1482		0.85	0.74, 0.97
19A	518	645		0.80	0.71, 0.90
19F	266	333		0.80	0.70, 0.91
23F	277	335		0.83	0.70, 0.97
Additional Serotypes					
8	466		848	0.55	0.49, 0.62
10A	2008		1080	1.86	1.63, 2.12
11A	4427		2535	1.75	1.52, 2.01
12F	2539		1717	1.48	1.27, 1.72
15B	2398		769	3.12	2.62, 3.71
22F	3666		1846	1.99	1.70, 2.32
33F	5126		3721	1.38	1.21, 1.57

Apexxnar – SmPC

Controlled human infection models – Approval of Vaxchora for prevention of cholera

Table 1: Protective Efficacy in the Prevention of Moderate to Severe Diarrhoea Following Challenge with *V. cholerae* O1 El Tor Inaba at 10 Days and 3 Months Post-Vaccination (Intent-to-Treat Population)

Parameter	Vaxchora 10 Day Challenge N=35	Vaxchora 3 Month Challenge N=33	Combined Placebo 10 Day or 3 Month Challenge N=66
Number of Subjects with Moderate or Severe Diarrhoea (Attack Rate)	2 (5.7%)	4 (12.1%)	39 (59.1%)
Protective Efficacy % [95% CI]	90.3% [62.7%, 100.0%]	79.5% [49.9%, 100.0%]	-

Safety database case by case, but sufficient to estimate the frequency of uncommon adverse events occurring in 1/1000 vaccinated persons

Comirnaty safety at time of initial approval – safety database > 21,000 subjects

Unfavourable Effects								
Lymphadenopathy		% (denominator)	0.3% (n=21720)		0% (N=21728)		Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants
Facial paralysis		Number of cases	4		1			
Hypersensitivity/immunisation reaction		Number of cases	13		6			
			Post dose 1	**Post dose 2**	**Post dose 1**	**Post dose 2**	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
Pain at injection site	16-55 years	%	83%	79%	14%	12%		
	>55 years		71%	66%	9%	8%		
Headache	16-55 years		42%	52%	34%	24%		
	>55 years		25%	39%	18%	14%		
Fatigue	16-55 years		25%	39%	25%	39%		
	>55 years		34%	51%	23%	17%		

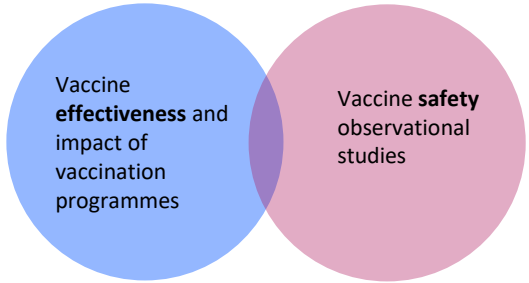
https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

Vaccine Monitoring Platform (VMP)

- EMA and ECDC **extended mandates** require to study vaccine use, effectiveness and safety
- **EMA-ECDC Co-leadership and co-delivery:**
- Main platform where post-authorisation vaccine research in EU is coordinated
- Independent studies (run separately or jointly by the two agencies)
- Synergies and exchange of scientific evidence
- Facilitate dissemination of evidence to decision makers

EU Immunisation and Vaccine Monitoring Board (IVMAB) provides scientific input and advice to the VMP on:

- key research questions
- **Study methodologies**, infrastructures and networks
- **Interpretation and use of study results**
- **Dissemination** of evidence generated to decision-makers



Conclusions

- Most vaccine are approved in the EU by EMA via the centralised procedure
- Price/reimbursement and recommendations for use are defined and tailored at national level
- Safety assessment in clinical trials should cover a population of at least 3000 individuals to be followed up for 6 months or more (2 months minimum)
- If an ICP is available, clinical immunogenicity data will suffice for licensure, otherwise clinical efficacy data are needed
- In case no ICP, and field efficacy trials problematic, but an immune marker applicable, comparison of immune response to a vaccine that showed efficacy/effectiveness (or bridged to one that showed efficacy) is acceptable, e.g. COVID vaccines
- In case no ICP or possibility to bridge immune response, agencies open to discuss use of alternative strategies
- Plans for effectiveness measurement post-approval to be discussed early with regulators to gain good understanding of what can be achieved post-approval