Workshop with the Developing Countries Vaccine Manufacturers Network (DCVMN) on Collaborative Registration Procedure (CRP) for vaccines

World Health Organization

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WHO PQ assessment

Prequalification (PQ) 1987

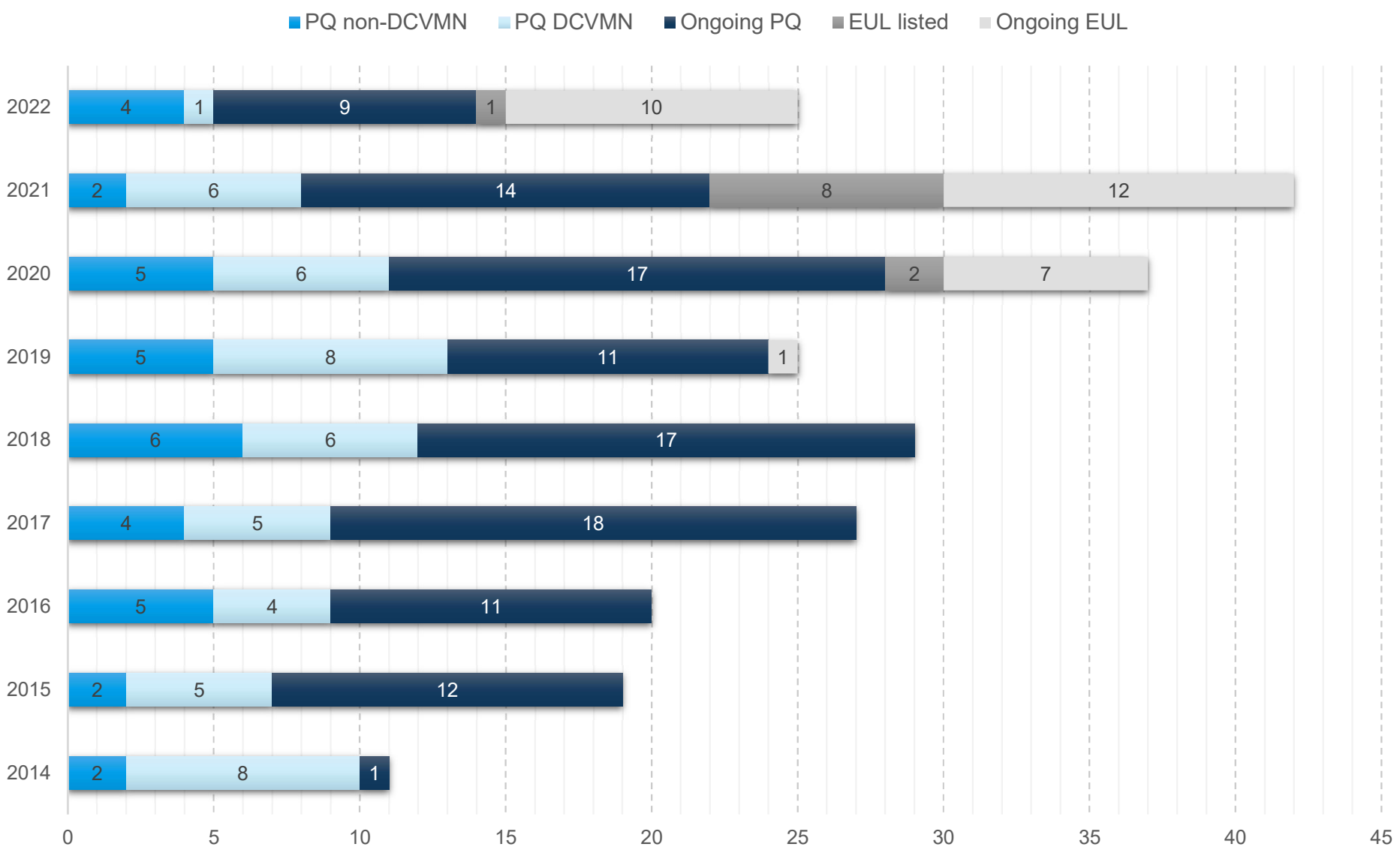
- Review of extensive quality, safety and efficacy and PSPQ for international supply*
- Assessment performed by WHO independent experts
- Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings
- Post-PQ monitoring
- Reassessment/requalification

Emergency Use Listing (EUL) 2015

- **Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs**
- **Rolling review of data**
- Assessment performed by WHO independent experts in collaboration with National Regulatory Authorities (WLA)
- Reliance on WLA - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings
- **Post- deployment monitoring**
- **Time limited recommendation**
- **Development should continue for MA/PQ**

*Dossier review, testing and inspection

Number of vaccines PQed and EUL from 2014 to 2022



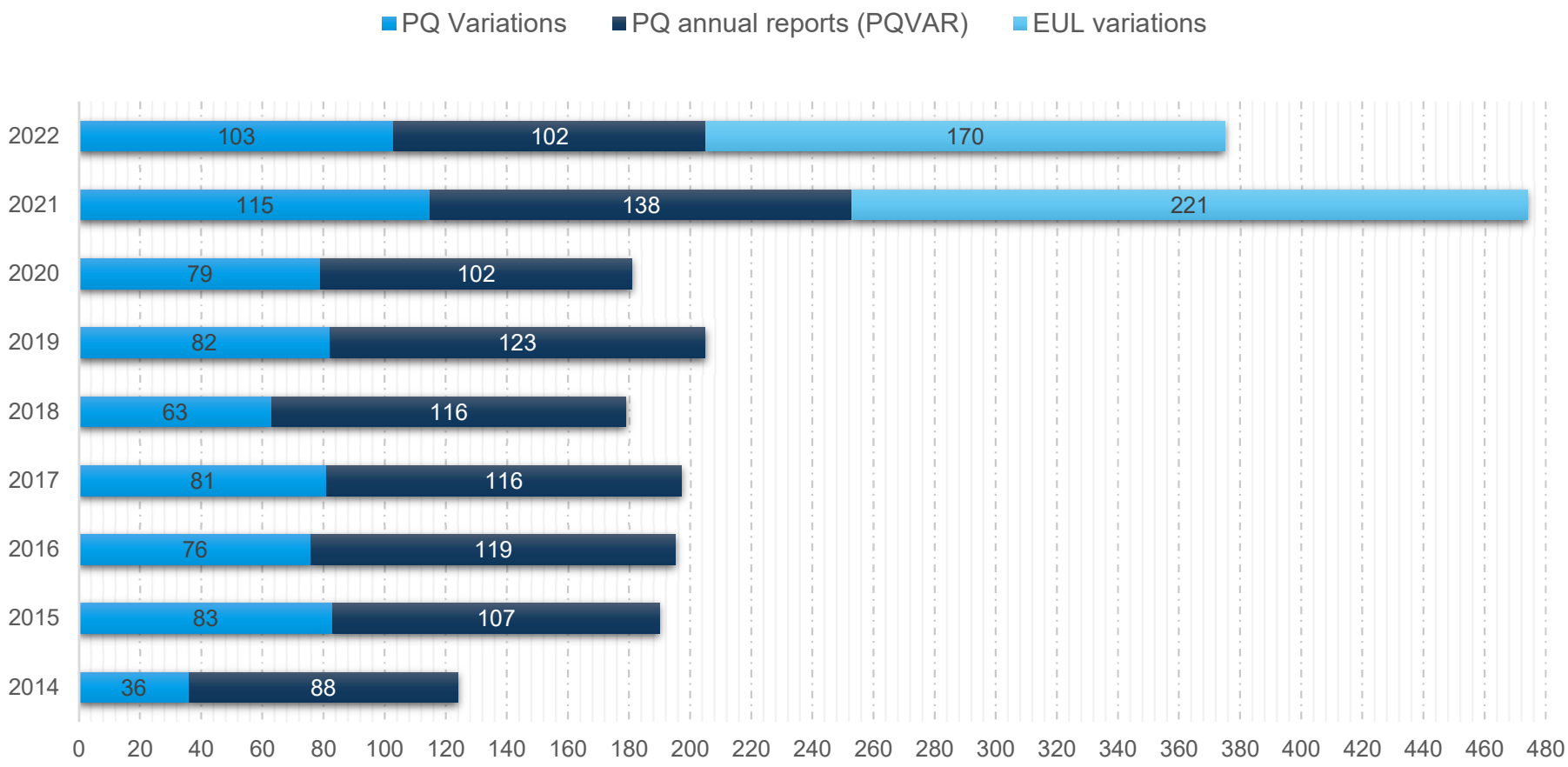
Vaccines Post monitoring activities

- Continuous monitoring of the quality, safety, efficacy and programmatic of vaccines under PQ and EUL
- Variations
- Annual Report evaluation
- Reassessment
- Targeted testing program
- Monitoring/Investigation of vaccine quality and cold chain complaints
- Monitoring/investigation of Adverse Events following immunization (AEFI)

Other activities.

- Collaborative National Registration
- Technical Review of tenders for UNICEF
- Technical support to member states

Post-PQ and Post EUL activities



Achievements (2020-2022) - Vaccines

PQ

- 21 vaccines PQed
- Support UN agencies
- Support member states briefings on malaria and Ebola.
- Support suitability of vaccine applications during tender process.
- Assessment of 246 variations

EUL

- 11 vaccines (19) Covid 19 vaccines
- 1 nOPV2 vaccine
- Support member states through reliance
- Briefing workshops
- One on one support (meetings, emails)
- Assessment of changes, 454 Post EUL submissions

Other

- Snake antivenoms risk benefit
- Monkeypox, 2 vaccines
- Release of polio vaccines into WHO stockpiles,
- 169 lots of mOPV vaccines 462 MD
- 201 lots of tOPV vaccines, 315 MD
- 181 lots of nOPV2, 749 MD

History of the CRP for Vaccines

- 2004/2005 : WHO/SEARO requested the support from PQ vaccine to facilitate the registration of vaccines. It consisted to share summary protocol and sample testing results. **Called expedited license procedure**
- 2011/2012 : Principles of the CRP (sharing reports of the assessment process) firstly used for registration of MenAfriVac in 26 countries of the African belt.
- 2015 : CRP Procedure (under revision) used as a pilot to facilitate registration of IPV vaccine. Joint review option
- 2016 : CRP for vaccines endorsed by ECBS
- 2016 to 2018 : CRP procedure used on ad hoc basis to facilitate registration of other vaccines.

Implementation of Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (WHO/IVB/07.08)

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Firstly used for registration of MenAfriVac in 26 countries of the belt

Experiences of the CRP for Vaccines

2016 : an intensive collaboration with **Ukraine** took place in the context of the collaborative procedure.

- 2 BCG vaccines (India and Bulgaria)
- DT (Bulgaria)
- 2 DTwP (India)
- DTwP-HepB-Hib (India)
- Hib (India)

➢ Documents shared :

- ✓ GMP inspection
- ✓ Assessment reports (clinical and quality)
- ✓ PQ approval letter.
- ✓ Distribution data
- ✓ PSURs.

Experiences of the CRP for Vaccines

2017 :

- NRA of the Republic of **Zimbabwe** to use the collaborative procedure for the registration of the BCG vaccine manufactured in India.
- the **DRC** applied to use the procedure for the registration of the absorbed pentavalent vaccine DTwP-HepB-Hib manufactured by a Korean company.
  - ➢ Information provided is usually summarized in a tabular format:
    - ✓ GMP site inspections
    - ✓ Assessment reports (quality and clinical)
    - ✓ Information on WHO independent testing.
    - ✓ PQ approval letter.
    - ✓ Decision on post PQ actions (e.g.: variations).

Experiences of the CRP for Vaccines

2018 :

- NRA of **Thailand** to use the collaborative procedure for the registration of Tetanus vaccine (adsorbed), DTP (whole cell) vaccine (adsorbed), DTwP-HepB-Hib, TCV manufactured in India.
- Documentation shared with **Ukraine** on tetanus vaccine (adsorbed) manufactured in Indonesia and **Belarus** on a pentavalent vaccine manufactured in Korea.

➢ Information provided is usually summarized in a tabular format:

- ✓ GMP inspections
- ✓ Assessment reports (quality and clinical)
- ✓ PQ approval letter
- ✓ Decision on post PQ actions (e.g.: variations).

Challenges

- Procedure applied on an ad-hoc basis, however lack of feedback on the registration process.

- WHO reports have been for internal use. Gap analysis ongoing.

- WHO reports of vaccines PQed some years ago are outdated and does not consider the latest changes recently implemented. Some vaccines have been replaced by combined vaccines and monovalent components are monitored as part of the combos.

- Some actions need to be taken to ensure satisfactory implementation of the procedure on timely fashion.

- Limited resources in the vaccines PQ and competing priorities.

- Product Life cycle management.

Way forward

- Fulfil PQ core activities

- Continue mapping of the current regulatory pathways in countries critical to ensure efficient use of resources. REG

- Identification of constraints for implementation of the procedure in countries. i.e local agent available in countries, inspection and testing requirements, market size (interest from manufacturers to submit an application). REG

- Definition of priority vaccines representing public health benefits, ie vaccines to contain an outbreak, vaccines under shortages.

Way forward

- Implementation of actions to ensure preparedness for sharing reports, once resources are available.
- PQ to identify reports of PQed vaccines that can be shared (2017)
- Questions from countries to be addressed by manufacturers. (similar to PQ abbreviated approach)
- Reliance mechanism for product life cycle management.
- Apply lessons learned from the facilitation of covid 19 vaccines – for public health emergencies, ie polio, Ebola, malaria

WHO regulatory preparedness for COVID-19 vaccines

WHO released “Considerations for the assessment of COVID-19 vaccines” (Nov2020) and addendum March 2021


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CONSIDERATIONS FOR EVALUATION OF COVID19 VACCINES

Points to consider for manufacturers of COVID19 vaccines

Version 24 September 2020

Vaccine and Immunization Devices Assessment Team (VAX)
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WHO issued a call for Expressions of Interest for Emergency Use Listing of COVID-19 Vaccines (2020)


First Invitation to manufacturers of vaccines against Covid-19 to submit an Expression of Interest (EOI) for evaluation by the WHO (Prequalification and/or EUL)

1. **Introduction:**

The World Health Organization (WHO), through its Department of Regulation and Prequalification (RPQ), provides advice to the United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies. The purpose of the WHO prequalification assessment is to provide assurance that candidate vaccines: (a) meet the WHO recommendations on quality, safety and efficacy, including compliance with WHO recommended Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards; and (b) meet the operational specifications for packaging and presentation of the relevant UN agency. This is to ensure that vaccines provided through the UN for use in national immunization services in different countries are safe and effective, and are suitable for the target populations, at the recommended immunization schedules, and with appropriate concomitant products.

Several conditions apply for PQ evaluation (a) the vaccine is considered a priority for UN supply; (b) complies with mandatory characteristic for programmatic suitability http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en /index.html, (c) the National regulatory authority (NRA) responsible for the regulatory oversight of the product has been assessed by WHO as "functional", and (d) a marketing authorization (MA) or emergency use authorization (or equivalent) has been granted by the relevant NRA.

The PQ process takes into account needs from WHO programmes (e.g. Immunization, Vaccines and Biologicals) and the International Health Regulations to comply with eradication, elimination or control initiatives as well as recommendations of WHO's Strategic Advisory Group of Experts (SAGE) on immunization.

WHO RPQ has also developed the Emergency Use Listing (EUL) process to expedite the availability of unlicensed medical products needed in public health emergency situations. The process assists interested UN procurement agencies and Member States in determining the acceptability of using specific products in the context of a public health emergency (PHE), based on an essential set of quality, safety, and efficacy/immunogenicity data.

The EUL procedure defines (a) the steps that WHO will follow to establish eligibility of unlicensed products for assessment under this procedure, (b) the essential information required, and (c) the process to be used in conducting the assessment to determine whether an unlicensed product can be listed on a time limited basis, while further data are being gathered and evaluated. In addition, draft points to consider for the assessment of Covid-19 vaccines have been developed and published.

Call for EOI Covid-19_ V8-FINAL_ 01/10/2020

... Revised guidelines 30 March 2022 and 2nd call for EOI in 2022

Source: https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf?ua=1

In-country expedited approval for use & post-listing monitoring: the WHO regulatory alignment roadmap*

1. Preliminary activities	2. Launching of EOIs	3. Submissions & assessment	4. Recommendation for listing	5. Post-listing monitoring
• **Global regulatory cooperation** • Establishment of **strategies for expedited approval** in participants & post-listing monitoring	• **Manufacturers EOIs** (Phase IIb/III & approval by NRA/SRA in charge of oversight within 6 months & compliance with criteria for assessment) • Discussions on **rolling submission** procedure	• Establishment of **assessment pathway** according to NRA/SRA in charge of oversight • Establishment of **Review Committee** (NRA/SRA in charge of oversight & regulators /reviewers from potential user participants)	• **Approval** granted by NRA/SRA in charge of oversight • **Technical Advisory Group** convened (post-listing commitment) • **WHO EUL recommendation** with conditions	• Implementation of **strategies for safety, quality & effectiveness monitoring** • **Validity of listing** based on new data generated • Possible **conversion of EUL to PQ**

COVAX | EUL | NRA reliance on EUL

Facilitated access to countries

- **Sharing of assessment/ inspection reports / lot release** with regional-designated country reps
- WHO-facilitated **national approval process**

* *Roadmap for WHO Assessment of* vaccine x *during the COVID-19 Public Health Emergency*

Countries with access

COUNTRY	Tozinameran	AZD 1222	COVISHIELD SII	Janssen	Moderna	BIBP	Sinovac	Bharat	Novavax	Covovax SII	CanSino	total dossiers
101	63	81	58	67	53	61	47	20	22	11	14	497

Countries with access

COUNTRY	Pfizer	AZD1222	COVISHIELD SII	Janssen	Moderna	BIBP	Sinovac	Bharat	Novavax	Covovax SII	CanSino
101	63	81	58	67	53	61	47	20	22	11	14
Afghanistan		√	√								
Algeria	√	√	√	√							√
Angola	√	√	√	√	√						
Argentina	√	√		√	√	√	√				
Armenia	√	√	√	√	√	√	√				√
Azerbeijan	√	√	√								
Bangladesh	√	√		√	√	√	√		√		√
Barbados				√		√					
Belize		√									
Benin	√	√	√	√	√	√	√	√	√	√	
Bolivia						√					
Bosnia (BIH)	√	√									
Botswana	√	√	√	√				√		√	
Brazil						√			√		√
Brunei	√	√		√		√					
Burkina Faso	√	√	√			√					
Burundi	√	√	√	√	√						
Cabo Verde	√		√	√	√	√	√	√	√	√	
Cameroon		√		√		√					
Caricom	√	√	√	√	√	√	√	√	√	√	√
Chile	√	√		√	√	√		√	√		
Comoros		√		√		√	√				
Costa Rica		√	√	√		√	√				
Cote d'Ivoire	√	√	√	√	√	√					√
Dominican Republic	√	√	√	√	√	√	√		√		
DRC			√					√			
Ecuador	√	√	√	√	√	√	√	√	√		√
Egypt	√	√		√	√	√	√				
El Salvador	√	√	√			√					
Eswatini					√						
Ethiopia		√	√	√	√	√	√				
Fiji			√	√		√					
Gabon		√	√	√	√	√	√				
Gambia (The)	√	√	√	√	√	√	√				
Georgia	√	√	√	√		√	√				
Ghana					√		√				
Guatemala	√	√	√	√	√						
Guinee	√	√			√	√					
Guyana		√									
Grenada	√		√								
Haiiti		√	√	√	√					√	
Honduras	√	√	√	√		√					
Indonesia	√	√		√	√						
Iraq	√	√		√		√	√				
Iran	√	√	√	√	√	√					
Jamaica	√		√	√	√	√	√				
Jordan		√		√	√		√	√	√	√	
Kazakhstan	√										
Kenya	√		√	√	√	√	√				
Lao PDR	√		√	√	√	√	√				
Liberia	√						√	√	√	√	√
Libya		√									
Madagascar	√	√	√	√		√	√	√	√	√	
Malaysia		√		√		√		√	√		
Malawi	√	√	√		√	√	√	√			
Maldives	√	√		√		√	√	√			
Mauritania	√	√	√	√	√	√	√				
Mexico		√		√	√						
Moldova	√	√	√	√	√	√	√	√		√	
Montenegro		√									
Morocco		√	√								
Mozambique	√	√	√	√		√	√	√	√	√	√
Namibia	√	√	√	√	√	√	√				
Nepal			√		√	√	√				
Nicaragua	√	√	√	√	√						
Niger	√	√	√	√	√	√					
Nigeria	√	√	√	√	√	√	√	√	√		√
Pakistan	√				√						
Panama	√	√		√						√	
Paraguay	√			√			√		√		
Peru	√	√	√	√	√	√	√		√		√
Philippines		√		√	√	√	√				
PNG	√	√	√	√	√	√					
Qatar		√									
Republic of Serbia		√				√					
Rwanda	√	√	√	√	√	√					√
Saudi Arabia		√				√	√		√		
Saint Lucía		√									
Senegal	√	√	√		√	√	√		√	√	
Seychelles							√				
Sierra Leone	√	√	√	√		√					
Somalia		√									
South Africa		√	√	√		√	√				
South Sudan		√	√	√	√						√
Sri Lanka	√	√	√	√	√	√	√	√			
Sudan	√	√	√	√	√	√					
Syria	√	√	√	√			√				
Tanzania	√	√	√	√	√	√	√		√		
Tajikistan	√	√	√	√	√	√	√				
Tchad	√			√		√					
Thailand								√		√	
Togo	√	√	√		√						
Tonga		√									
Tunisia	√	√	√	√	√	√	√	√	√		√
Trinidad and Tobago		√	√								
Uganda	√	√		√	√		√				
Ukraine		√		√	√	√		√			
Uruguay	√	√					√				
Vietnam		√									
Yemen		√	√	√			√				
Zambia	√	√	√	√	√	√	√				
Zimbabwe				√	√	√					

BACK UP

Vaccines PQ in 2020

PQ vaccines 2020 11 vaccines (13 presentations)				
PQ date	Vaccine	No. Doses	Manufacturer	Country
21/01/2020	Hepatitis B (paediatric)	1	Lg Chem Ltd	Republic of Korea
28/01/2020	Rotavirus (live attenuated)	1 & 2	Serum Institute of India Pvt. Ltd.	India
07/02/2020	Influenza seasonal (Trivalent)	10	Seqirus Limited	Australia
09/03/2020	Diphteria-Tetanus (reduced antigen content)	20	Biological E. Limited	India
25/03/2020	Dengue	5	Sanofi Pasteur	France
21/04/2020	Polio Vaccine - Inactivated (IPV)	5	AJ Vaccines A/S	Denmark
31/08/2020	Polio Vaccine - Oral (OPV) Trivalent	20	PT Bio Farma (Persero)	India
15/10/2020	Influenza, seasonal (Quadrivalent)	10	Sanofi Pasteur	France
04/12/2020	Typhoid (conjugate)	1 & 5	Biological E. Limited	India
18/12/2020	Influenza Pandemic H5N1	1	AstraZeneca Pharmaceuticals LP.	UK
21/12/2020	Polio Vaccine - Inactivated Sabin (sIPV)	5	LG Chem Ltd	Republic of Korea

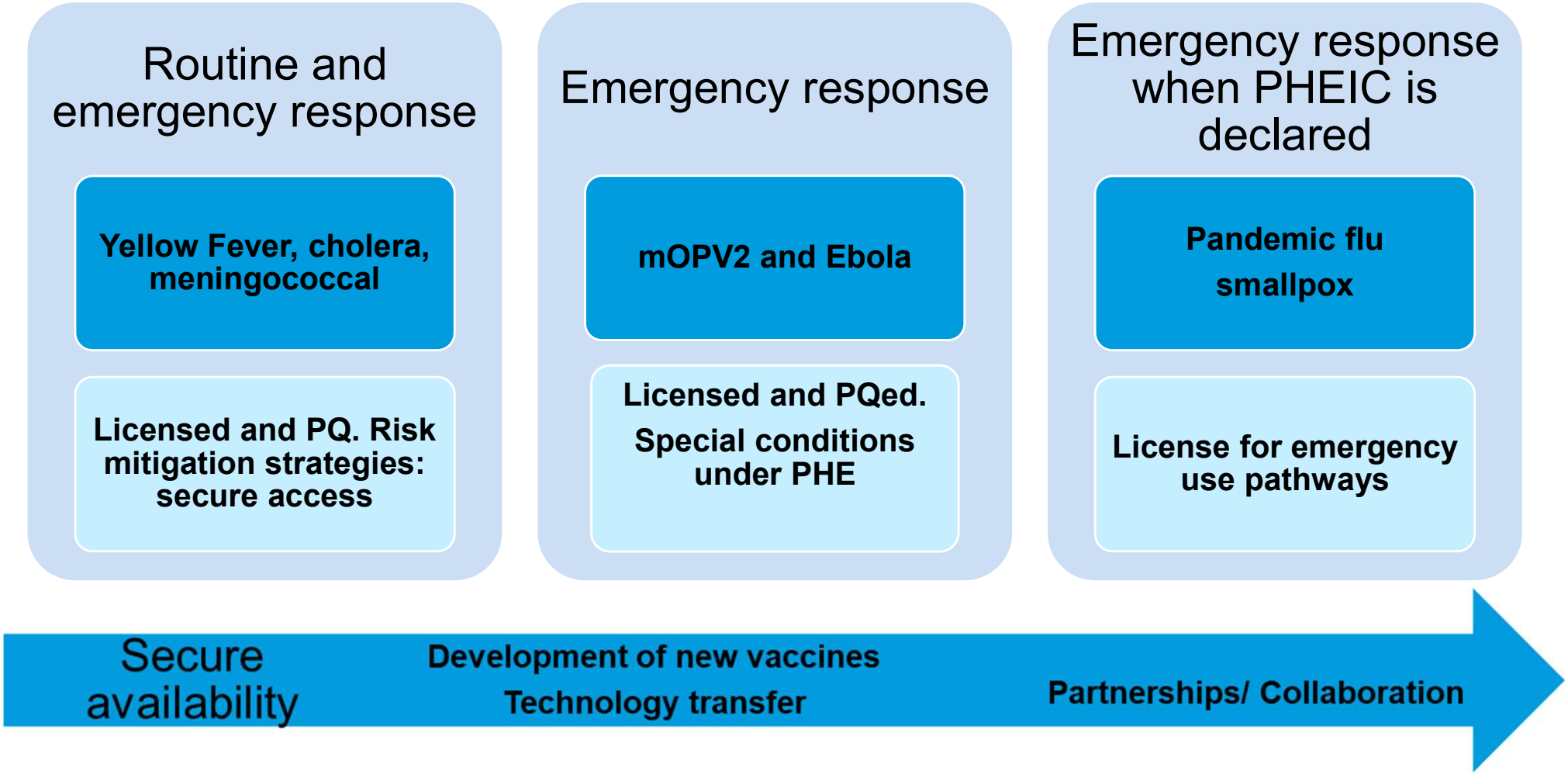
https://extranet.who.int/pqweb/vaccines/prequalified-vaccines

Vaccines PQ in 2021

PQ vaccines 2021 6 vaccines (7 presentations)				
PQ date	Vaccine	No. Doses	Manufacturer	Country
18/02/2021	Rotavirus (live, attenuated)	1	Serum Institute of India Pvt. Ltd	India
26/04/2021	Influenza, seasonal (Trivalent)	10	Instituto Butantan	Brazil
27/04/2021	Ebola vaccine (MVA-BN-Filo [recombinant]) Ebola vaccine (Ad26.ZEBOV-GP [recombinant])	1	Janssen Vaccines, Branch of Cilag GmbH International	Switzerland
18/06/2021	Rotavirus (live attenuated)	1 & 5	Bharat Biotech International Limited	India
01/06/2021	Polio Vaccine - Inactivated Sabin (sIPV)	1	LG Chem Ltd	Republic of Korea
14/10/2021	Human Papillomavirus (Bivalent)	1	Xiamen Innovax Biotech Co. Ltd.	People's Republic of China

https://extranet.who.int/pqweb/vaccines/prequalified-vaccines

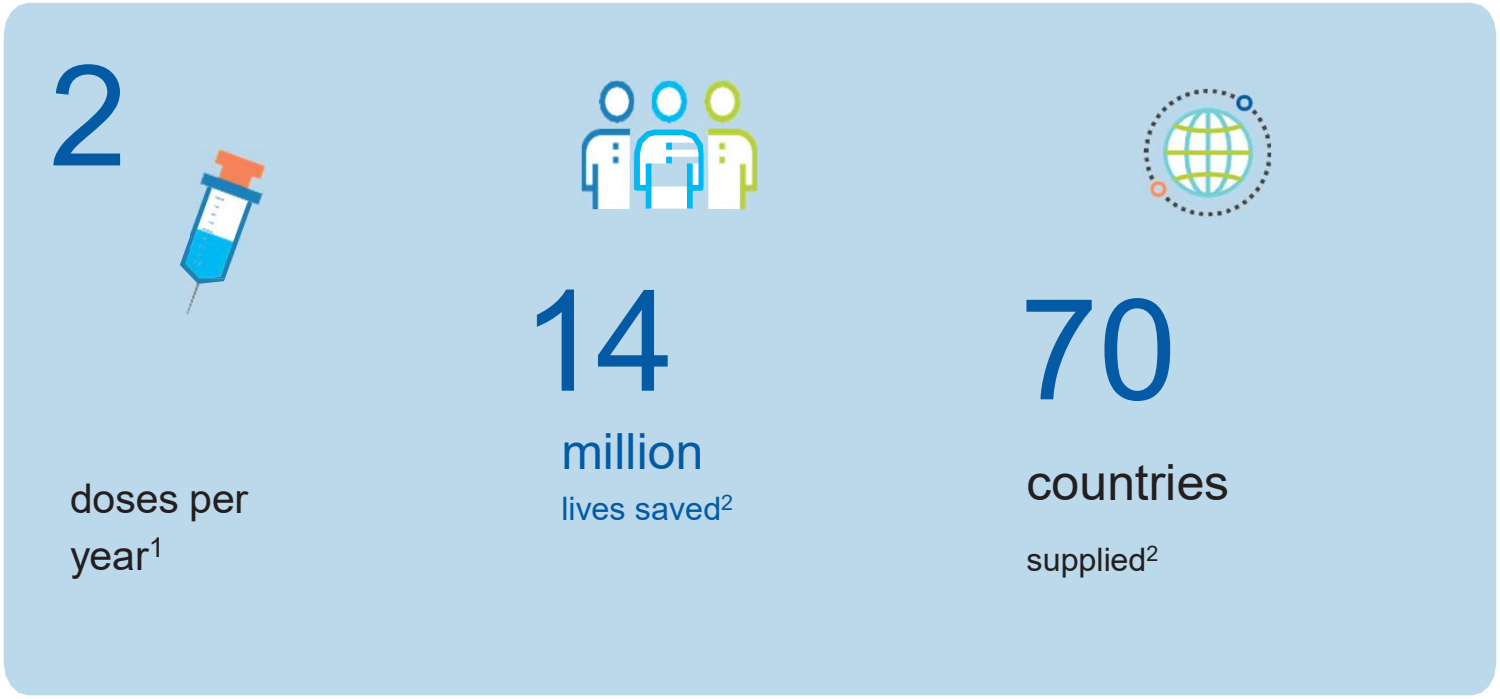
Vaccines for emergency response: WHO stockpiles



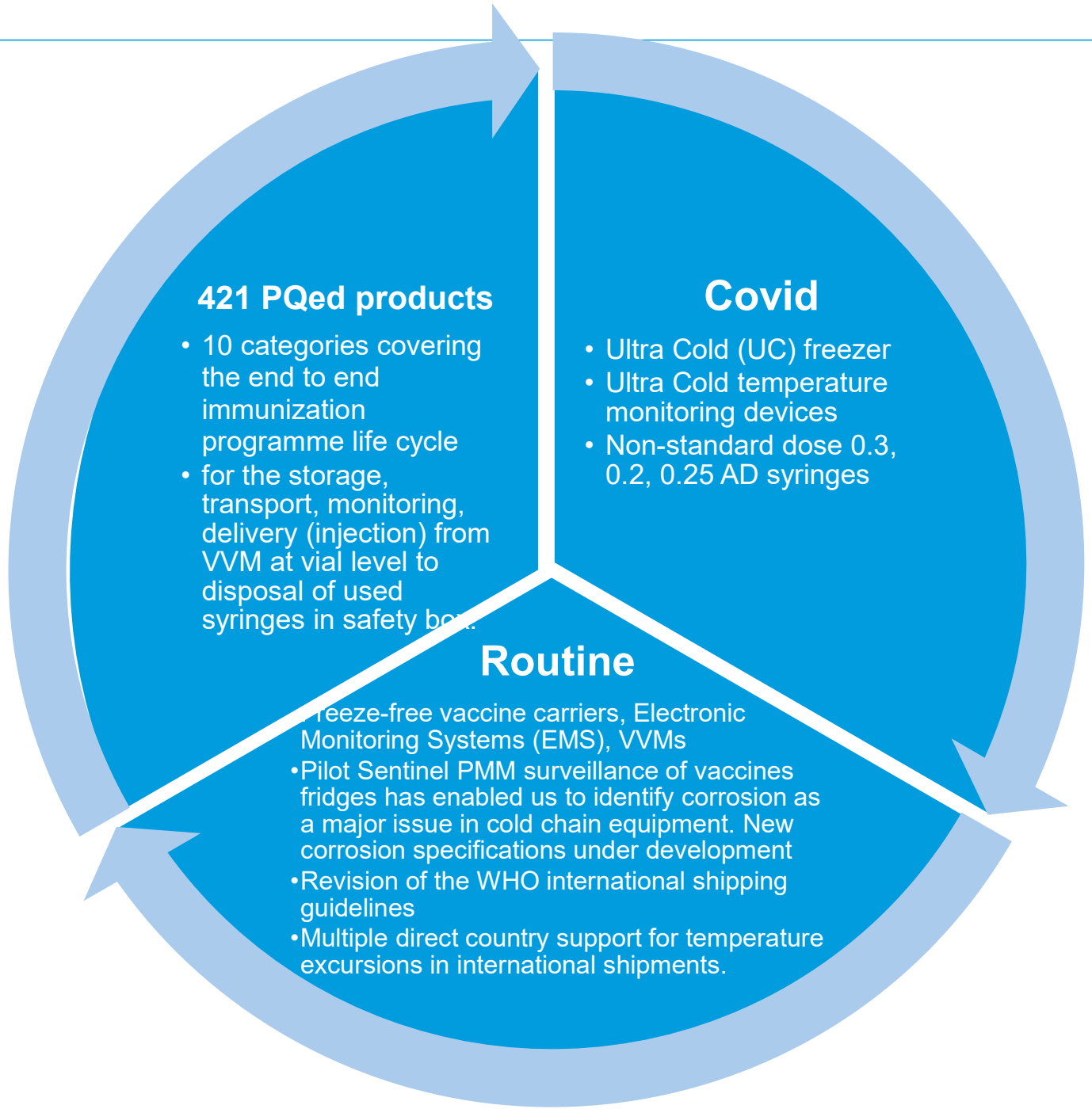
Prequalification of vaccines and Immunization equipment

Each year, UNICEF supplies over two billion doses of vaccines, to reach approximately 45 per cent of the world's children under five years of age. This annual investment, totaling $1.656 billion in 2019, supports routine immunization programmes, preventive campaigns and outbreak response around the world. GAVI claims 14 million deaths averted.

UN agencies only procures WHO specified, verified and prequalified immunization equipment and devices.



Achievements - Immunization equipment



Risk-benefit assessment of snake antivenoms

- Expanded programme supported by $3 million in funding from Wellcome Trust
- Global burden of snakebite affects 4.5-5.5 million people/yr and claims 80,000-140,000 lives annually
- Focus on assessing products from Africa, Middle East and Asia aims to reduce the mortality and morbidity in the worst-affected regions of the world by up to 50%.
- Goal is identify products that can be recommended for procurement on the basis of comprehensive dossier review, laboratory evaluation and GMP compliance.
- 7 sub-Saharan African products already evaluated. 1 reapplication received and a second one pending submission.
- 8 product applications under assessment that are marketed in South Asia and 9 more for products marketed in North Africa & the Middle East.

Risk-benefit assessment of snake antivenoms

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Benefits

- Procedure has already resulted in substantial new investment by manufacturers aimed at attaining GMP compliance, improving the design and efficacy of antivenoms, and introducing new production technologies.
- Provides procurement agencies with greater confidence in products that NRAs may not have the capacity to adequately assess themselves.
- Supports decision-making on product registration by regulatory agencies
- Stimulated interest in development of new products by manufacturers who see the procedure as a precursor to possible future prequalification of antivenoms.
- Recommended products are likely to be taken up for use in regional antivenom stockpiles to increase access to safe and effective products.

Figure 1 summarises the progression of the PQS applications since 2008.

Figure 1: Number of products reviewed since 2008