World Health Organization
National Control Laboratory Network for Biologicals

Vaccines' testing by WHO and the WHO-National Control Laboratory Network for Biologicals (WHO-NNB)

Dr Ute Rosskopf

Organigram

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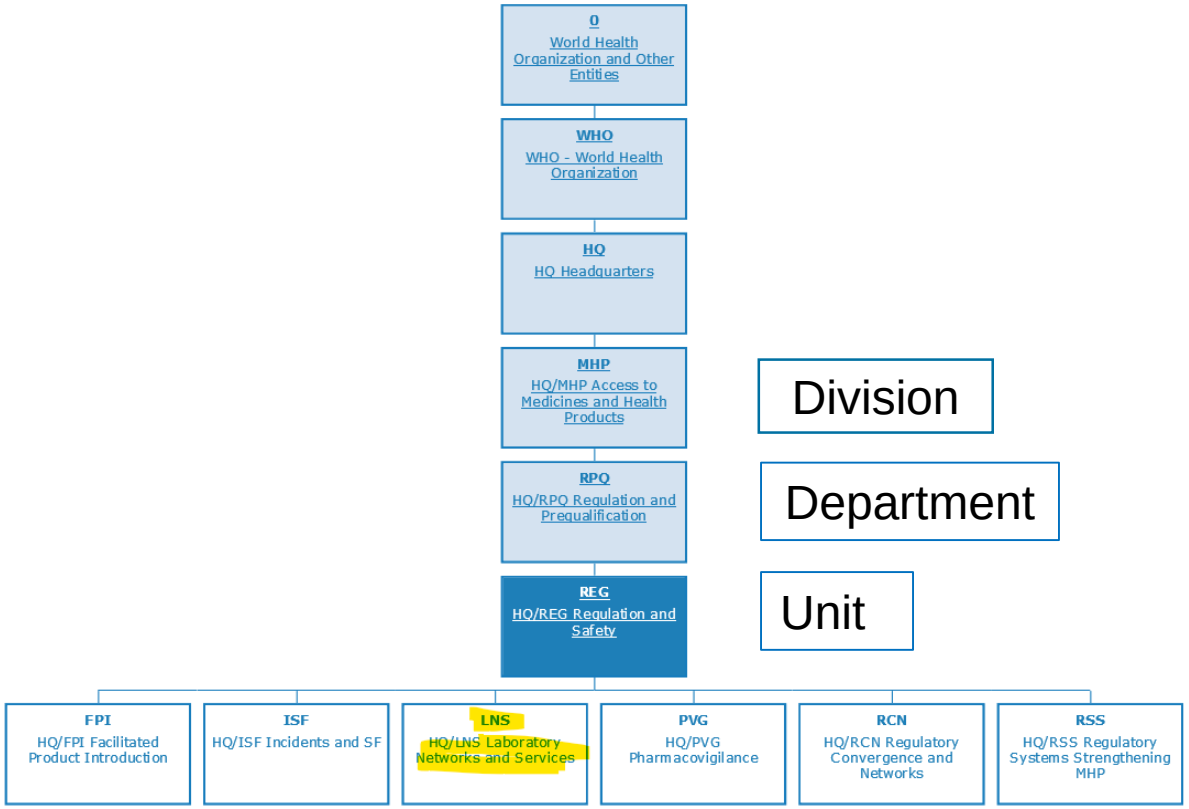

Presentation outline

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1 WHO prequalification

2 WHO vaccines' testing

3 Challenges

4 WHO-National Control Laboratory Network for Biologicals

WHO Prequalification

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Assurance of the quality of the key products:

Diagnostics (incl. medical devices),Medicines , Vaccines & Vector control

- to increase the capacity to manufacture and regulate quality-assured products
- to harmonize quality assurance standards
- to provide assurance that products meet consistent quality standards
- to create global competition for quality-assured products and
- to detect and address quality failures.

Prequalification - Vaccines

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"Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies"

- Created in 1987
- Underwent revision in 2010 (effective from January 2012, WHO Technical Report Series 978, Annex 6)
- Service provided to purchasing and procuring UN agencies/ international procurement

Prequalification – Vaccines cont.

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Prequalification of vaccines - Provisions

- Vaccine on the priority list for prequalification
- Functionality of the national regulatory agency (NRA): Producing country must meet WHO vaccine regulation indicators
- Three pillars of vaccine evaluation:

WHO reviews the vaccine dossier (quality & clinical data)

WHO inspects the manufacturing site

WHO tests the final product

Prequalification – finalization

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Prequalification of vaccines - Listing

- Issuance of acceptability letter
- Vaccine published on the WHO website:
  https://extranet.who.int/gavi/PQ_Web/
- Listed vaccines (more than 100) not only purchased by UN agencies, but also directly by countries & non governmental organizations

22 producing countries
>100 receiving countries

Laboratory testing by WHO

Pre- and post prequalification (PQ) testing

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Initial evaluation of a new product – Pre PQ

(WHO TRS no. 978, Annex 6, chapter 3.4)

- Three final lots tested for consistency of final product characteristics
- Testing by two laboratories (plus NCL)

➔ WHO test report shared with the manufacturer

Annually performed targeted testing – Post PQ

(WHO TRS no. 978, Annex 6, chapter 10)

- Lots selected by WHO – risk based approach
- Two to three lots close to expiry dates
- Testing by one laboratory

➔ WHO testing outocme reported to donors

Testing through contracted laboratories

- Based on a forecast – in total 15 contracts have been issued to cover > 350 tests for the current biennium 2020-2021

➔Paid service - Identical fees for each test parameter

The independent testing of vaccines is part of the procedure for evaluation of the acceptability, in principle, of vaccines for purchase by United Nations agencies (Technical report series 978).

WHO contract laboratories

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1) Biologics and Genetic Therapies Directorate (BGTD), Health Canada
2) Bulgarian Drug Agency, Bulgaria
3) Institute of Biological Products (Ministry of Public Health), Thailand
4) Institute of Biological Products Control (IBPC), National Institutes for Food and Drug Control (NIFDC), China
5) National Center for the Control and Evaluation of Medicines (CNCF), Istituto Superiore di Sanità (ISS), Italy
6) National Drug and Health Products Safety Agency (ANSM), France
7) National Institute for Biological Standards & Control (NIBSC), bacterial division, UK
8) National Institute for Biological Standards & Control (NIBSC), viral division, UK
9) National Institute of Food & Drug Safety Evaluation (NIFDS), Republic of Korea
10) National Institute of Public Health & Environment Protection (RIVM), The Netherlands
11) Paul-Ehrlich-Institut (PEI), Germany
12) Sciensano, Belgium
13) South African National Control Laboratory for Biological Products, South Africa
14) Swiss Agency for Therapeutic Products (Swissmedic), Switzerland
15) National Quality Control Laboratory of Drug and Food (NQCLDF), Indonesia

WHO contract laboratories

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- Service run by the WHO Laboratory Networks & Services (LNS) Team
- Control laboratories are qualified by WHO
- Audits are performed at regular intervals
- Laboratory contracts are time-limited
- Identical fees are paid

Initial evaluation for PQ

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- Three to five final lots are tested for consistency of final product characteristics
- Lots need to be formulated from consecutive bulk lots
- Additional information e.g. validation documents may be requested
- Usually potency is tested. On occasions other relevant tests can be performed
- Reference reagents are requested if applicable (HepB vaccine, Influenza vaccine)
- Lots are tested in parallel by two WHO laboratories
- (in case of inconsistent results: results of the national control laboratory are requested)

→ WHO test report shared with the manufacturer

Post pre-qualification monitoring

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Targeted testing of prequalified vaccines

- Annually performed
- At the beginning of each year WHO approaches manufacturers to provide an overview of vaccine lots supplied to countries through UN agencies, but also direct purchases
- Lots for testing are selected by WHO
- Usually two to three lots close to their expiry dates are chosen
- Selection on a risk based approach
- Testing by one contract laboratory

→ WHO testing outcome reported to donors

Post pre-qualification monitoring

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Reporting of lot release data

Annual review of national lot release reports by WHO provided by responsible national authorities

By > 10 laboratories based on currently 19 agreements

- WHO request to report in the beginning of the year
- Templates provided
- Reports evaluated by WHO
- Data anonymized for WHO report to donors
- Reporting of lot release data is a contract parameter - paid service by WHO

Information-sharing Agreements from manufacturers

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Total formerly signed agreements: **19**

1. Laboratory	Country	Manufacturer
IPH	Belgium	GSK Belgium, Pfizer, Sanofi Pasteur
BDA	Bulgaria	BB-NCIPD
ANSM	France	Pfizer, Sanofi Pasteur
PEI	Germany	Merck & Co
NQCLDF	Indonesia	PT BioFarma
CNCF (ISS)	Italy	GSK Italy
NIFDS	Republic of Korea	Eubiologics, GreenCross, Janssen (formerly Berna Biotech), LG Chem
IBP	Thailand	GPO-MBP
RIVM	The Netherlands	Bilthoven Biologicals, Merck & Co
NIBSC bacterial	UK	GSK Italy, Valneva,
NIBSC viral	UK	Merck & Co

WHO report on vaccine testing-related activities to donors

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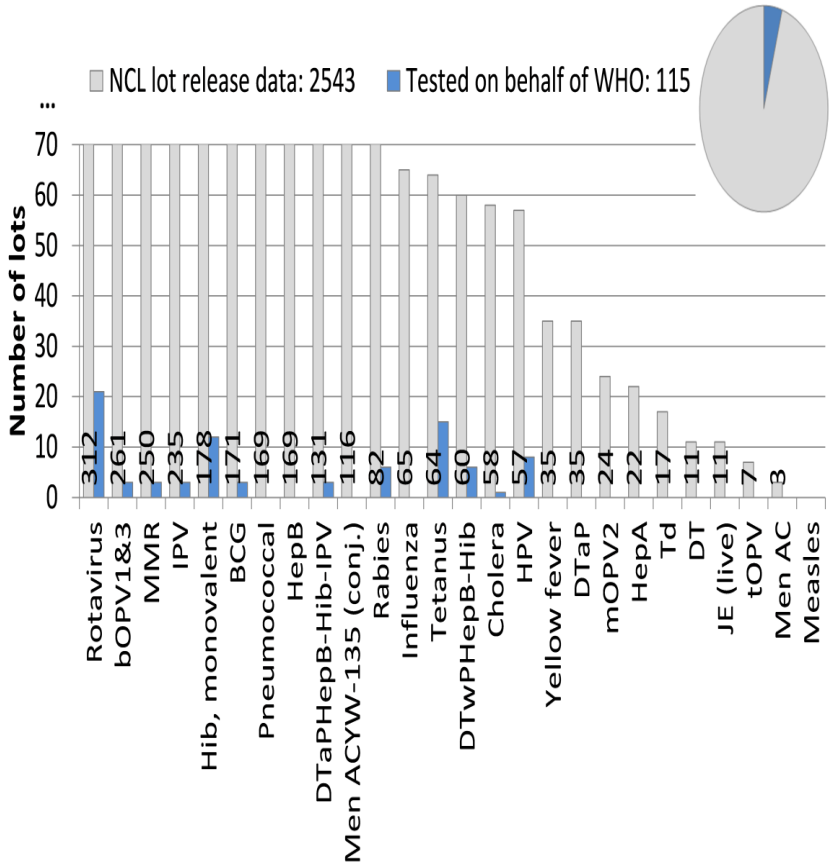
Information on:

- WHO-contracted testing (initial and post-PQ)
- National lot release data reported to WHO
- Related activities performed:
  - number of lab audits
  - test method harmonization
  - trainings: on-the-job, hands-on trainings
  - NCL network



Challenges

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General

- Globalization of vaccine industry: increasing number of production sites
- Increased complex regulation
- Limited resources of regulatory authorities (developed and developing countries)
- Duplication of efforts through redundant testing and approval of variations
- Non-compliances in test outcomes by importing countries: delay in vaccine access, disruption of vaccine delivery

WHO

- WHO contracted laboratories test vaccines of various manufacturers (differences in used methods)
- Increasing number of complex vaccines (test and cost intensive)
- Increasing number of applications for prequalification
- Increased number of prequalified vaccines to be monitored
- Limited resources (laboratories, WHO)

Target: Global access to vaccines – Sustainable Development Goal (SDG) 3.8

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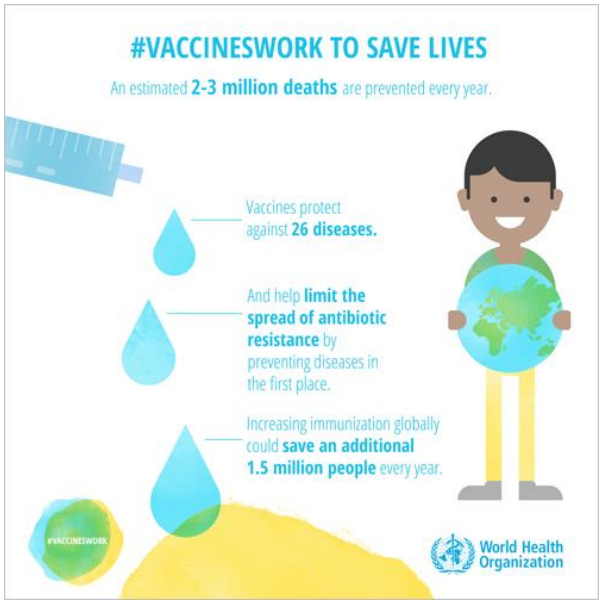

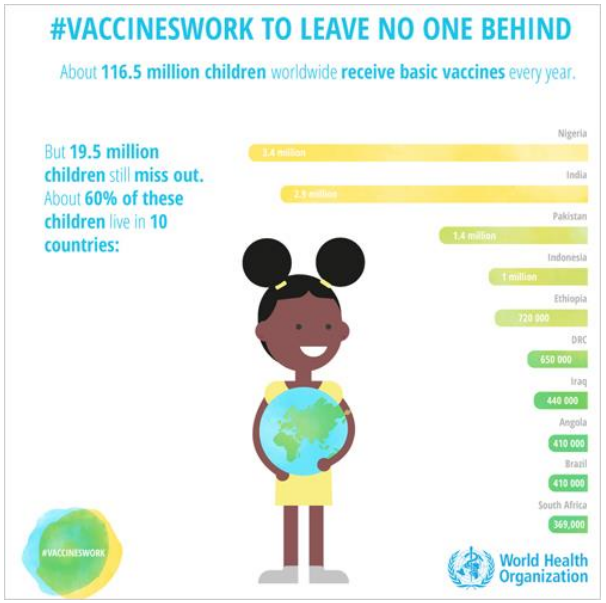

How to reach global access to needed safe and efficacious vaccines in a timely manner?

WHO responses to challenges – WHO test programme

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- Harmonization of test methodologies (performance of feasibility studies, collaborative studies and hands-on trainir courses)

- Change in PQ procedure section 3.4 (endorsed by ECBS meeting 2014):
  - Optimized logistics: Introduction direct shipmen vaccines to WHO test laboratories
  - Use of NCL of producing country (testing)

- Use of resources: lot release data gathered by the off national control laboratory (consent of manufacturers) and technical know-how

Networking meeting 2016

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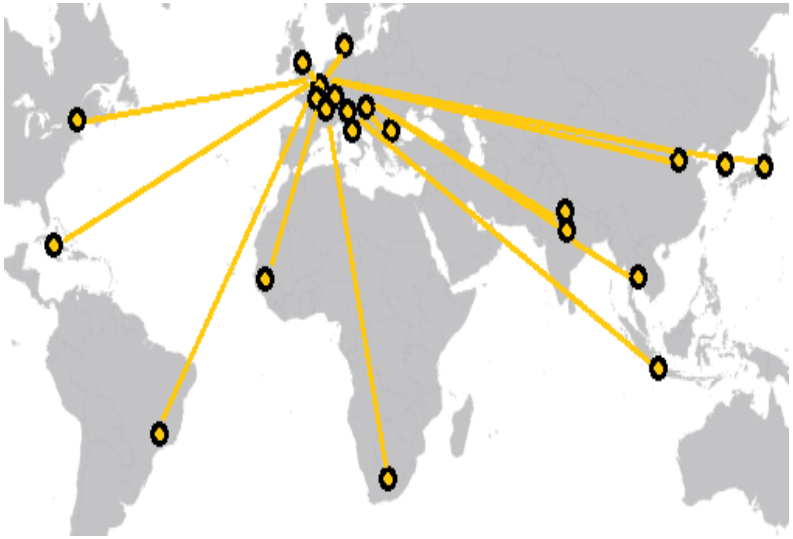
- 2016: WHO called for a national vaccine control laboratories (NCL) networking meeting
- Meeting co-hosted by RIVM, 30 August - 2 September 2016, The Netherlands
- Representatives from:

  21 NCLs involved in testing WHO- prequalified vaccines

  Manufacturers' associations

  European Directorate for the Quality of Medicines



- **Meeting participants agreed on the creation of a WHO national control laboratories network**

WHO response to challenges: WHO-National Control Laboratory Network for Biologicals

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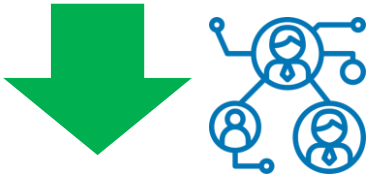
Creation of a structure to make information available to others, namely – receiving = importing countries.



Established WHO-National Control Laboratory Network for Biologicals (WHO-NNB)

In place:

Terms of Reference

Confidentiality and Participation Agreement

5. Operational arrangements

Confidentiality

Each Member (Head of the NRA/NCL) participating in the Network will sign a "Participation and Confidentiality Agreement", to be countersigned by the appointed focal point to confirm that he/she will respect the confidentiality of information exchanged during Network activities in accordance with that undertaking.

In addition, it is understood that each Network Member will respect the confidentiality of information submitted to it by, or originating from, vaccine (or other biological product) manufacturers. No discussion of confidential information regarding a specific manufacturer, its products and/or specific clinical trial data will take place during Network activities, without the express written permission given in advance by the manufacturer.

Membership

There are two types of **Members** of the Network, as follows:
a) **Full Members:** this classification is eligible to NCLs from countries producing WHO-prequalified vaccines (or other biological medicinal products), and WHO-contracted NCLs; and

b) **Associate Members:** this classification is eligible to NCLs or NRAs in countries that are recipients of UN-procured vaccines (or other biological products).

To be continued next page

2. ICDRA (continued)

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Achievement: Network-related ICDRA recommendations* (Workshop G, Vaccine regulation)

To WHO:

5. Establish a global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines.

To Member States:

2. For efficient lot release testing of vaccines, consider a risk-based approach or networking (reliance) approach.

Available at:
http://www..who.int/entity/medicines/areas/quality_safety/regulation_legislation/icdra/2016ICDRA_Recommendations.pdf

The Network – platform and basis for reliance: What each partner brings to the Network: National authorities

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- **Responsible NRAs/NCLs in producing countries have**
  - Best oversight of PQ'd vaccines and testing methods
  - Functional vaccine regulation and laboratories

Expert hub which assures quality and safety of vaccines

The Network – platform and basis for reliance: What each partner brings to the Network: WHO

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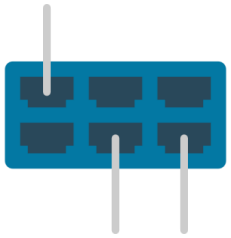
- International mandate of 194 Member States and WHA resolution 67.20 concerning networks
- Existing expert hub of qualified NCLs testing for WHO
- Reports on vaccine quality data = WHO test outcome (pre- and post-PQ)
- Reports on vaccine quality data through sharing of lot release data
- Established Terms of Reference & Participation Agreement
- Secured electronic platform



- Information and service center which collects, contributes and distributes quality information in a secure and confidential setting

The Network – Benefits and Impacts

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Reliance on responsible national control authority and laboratories' release testing and trust in WHO

➡ Benefits and impacts: manufacturers, vaccine procuring agencies and recipient countries

Reduce redundant testing

Save costs

Reduce the risk of inaccurate results

Accelerate access to vaccines

Network to optimize use of resources

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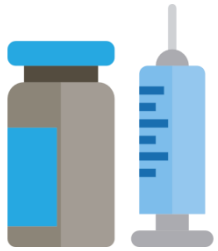
The Network works towards effective use of globally available resources, which is only possible through building of confidence, harmonization of requirements, exchange of information, collaboration, reliance and recognition of regulatory decisions.

Re-testing of already tested vaccines by recipient countries does not increase a product's quality but is heavily impacting access to needed vaccines and delivery to patients!

Reduce the risk of inaccurate results



Accelerate access to vaccines

Network memberships
Starting with < 20

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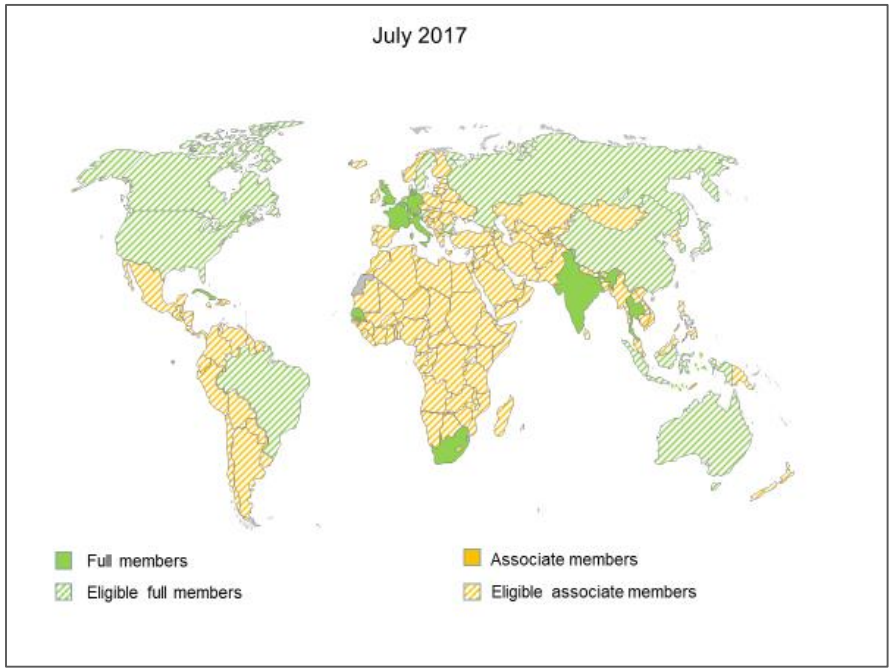

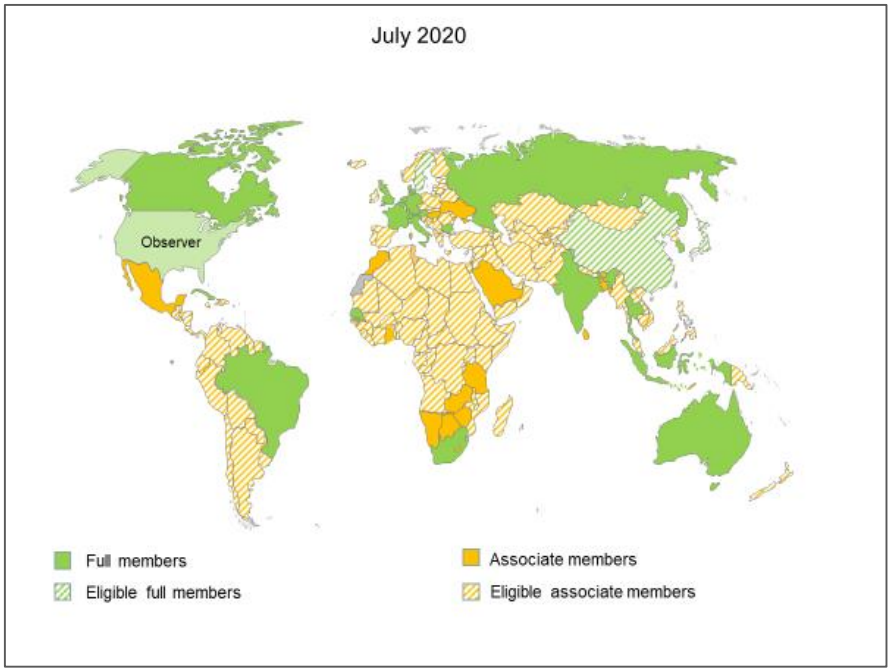

Current Network memberships (42)

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Australia
Austria
Bangladesh (AM)
Belgium
Bhutan (AM)
Botswana (AM)
Bulgaria
Brazil
Canada
Cuba
Denmark
Egypt (AM) signature imminent
France
Germany
Ghana (AM)
Hungary (AM)
India
Indonesia
Italy
Lesotho (AM)
Malaysia (AM)
Mexico (AM)
Morocco (AM)
Namibia (AM)
Oman (AM) signature imminent
Republic of Korea
Russian Federation
Saudi Arabia (AM)
Senegal
South Africa
Sri Lanka (AM)
Sweden
Switzerland
Thailand
Tunisia (AM)
The Netherlands
Uganda (AM)
Ukraine (AM)
United Kingdom
United Republic of Tanzania (AM)
Zambia (AM)
Zimbabwe (AM)

WHO-National Control Laboratory Network for Biologicals

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… aiming to

- share quality and technical information about prequalified products
- facilitate recognition of national lot release by recipient countries
- promote development of harmonized common standards and best practice, including use of the 3R principles
- contribute to and support: test harmonization & future development / revisions of WHO guidelines
- support strengthening of the NRAs and NCLs in the Network through technical assistance.
- promote recognition globally of WHO prequalified vaccines.

Network provides infrastructure:
➔ Electronic platform = SharePoint

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WHO-NCL Network for Biologicals SharePoint

The Network is a service to our member states by compiling and sharing of information regarding the quality and safety of vaccines and other biological medicinal products.

SharePoint
➔ Annual Quality Reports

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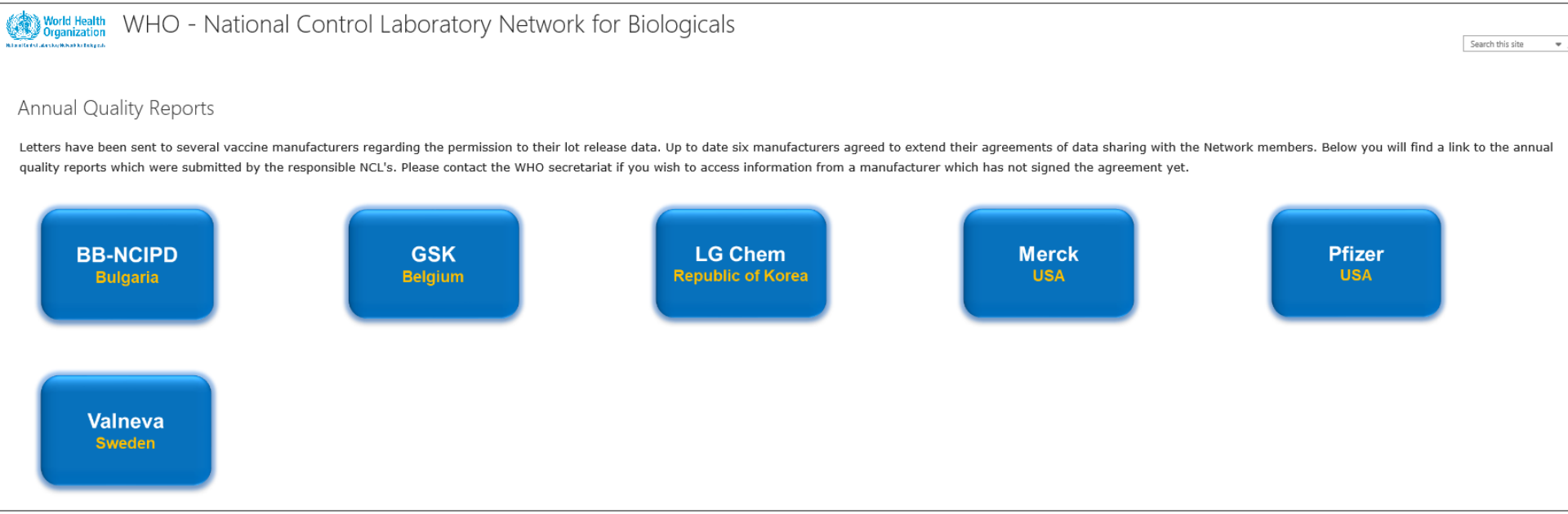

Six signed agreements for sharing information / quality data

with WHO and the Network members .

Conclusion: Network serves as…

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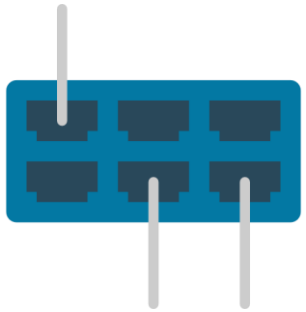

- an information and service center which collects, contributes and distributes quality information in a secure and confidential setting

- an expert hub which assures quality and safety of vaccines

Conclusion …

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… by consequence it facilitates and accelerates access to quality vaccines (….and other biological medicinal products)

- reach sustainable development goal (SDG 3.8):

"Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all".

The Network – vital part of WHO's work

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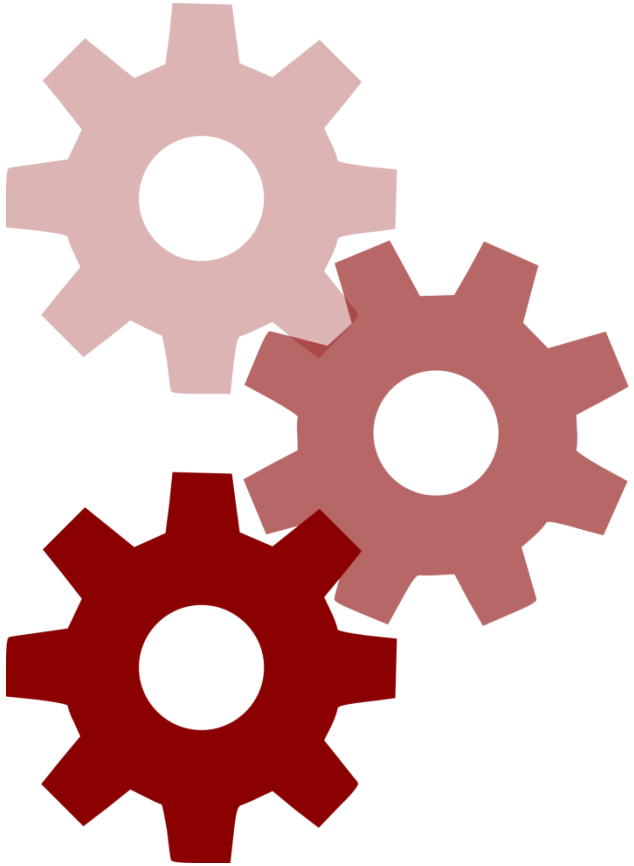

The WHO Network has great potential and is a unique model for collaboration, exchange of information and reliance on statutory as well as voluntary regulatory activities.

Use of the Network – member voices: COVID-19 pandemic

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"… also given that most manufacturers' have now agreed to share lot release data with your network, I see this as a perfect opportunity to start with real-time CoVID batch release data from the Sponsors (possibly including summary protocol information). Using this platform will result in a transparent and fair approach as all members will be able to access the information and would greatly contribute to increasing the profile and importance of the Network, a priority which was discussed at the last meeting."

"… also considers acceptance of other regulatory authority's lot release certificate in case that testing is not possible. Nevertheless, there is a voice that … should check at least the critical data tested by the responsible NCL. So I'm wondering if we can discuss the feasibility of sharing the critical data from lot release testing within this Network."

"I think this would be a unique opportunity…the relevance of having the WHO -National Control Laboratory Network.
The added value… would be to assure or at least facilitate the acceptance that the vaccine control performed by the NCL in one country of the Network be recognized by all the others."

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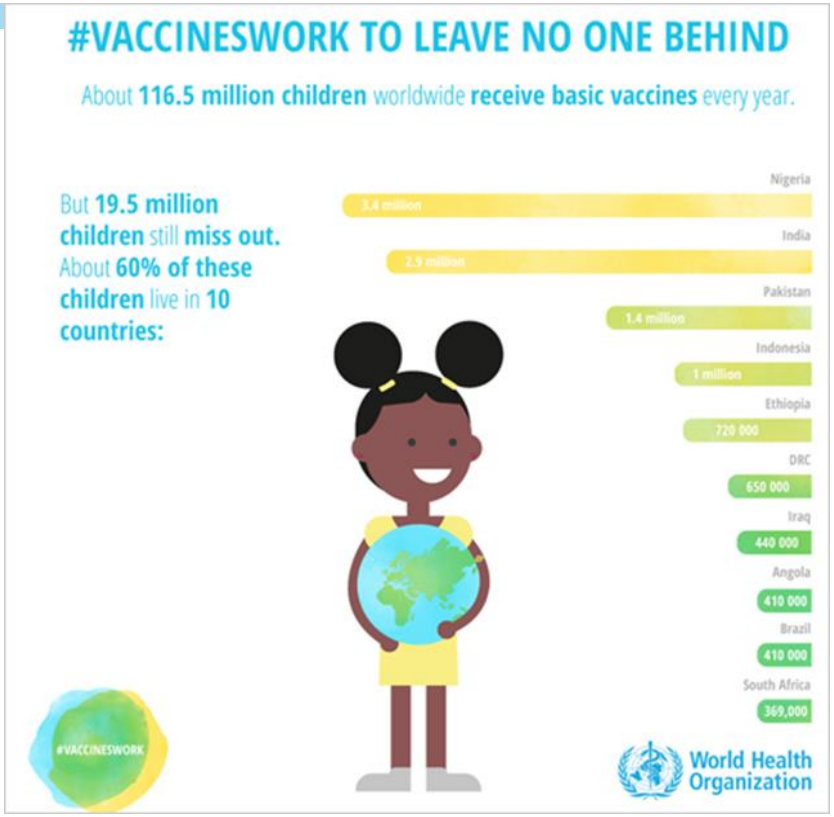
Thank you

for listening.



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Back-up

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