World Health Organization

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Foreword

The COVID-19 pandemic is the most severe health crisis in a century, exposing deep gaps in the world's defences against epidemics and pandemics, and teaching us painful lessons. One of them is that in our intimately connected world, pathogens can spread around the world very quickly, demanding systems that can respond equally quickly. That includes systems to facilitate the rapid exchange of biological materials and related data, to support the development of guidance and medical countermeasures including vaccines, tests and treatments.

Based on the lessons that COVID-19 was teaching us, World Health Organization announced the establishment of the WHO BioHub System at the height of the pandemic, in January 2021. Developed collaboratively and iteratively with the active engagement of Member States and other partners, the BioHub System has now been through a pilot-testing phase that has demonstrated its value as a multilateral model and a tangible asset that Member States can harness to bolster their preparedness against emergent viral threats. I thank those Member States who have contributed to the pilot-testing phase, especially Switzerland, which provided the inaugural facility in Spiez.

This report encapsulates the outcomes of the pilot testing phase, and charts the way forward. Importantly, we must see the BioHub System not in isolation, but as part of a strengthened architecture for health emergency prevention, preparedness and response, which also includes enhanced mechanisms for governance, financing, and accountability, as well as stronger systems for surveillance, emergency workforce, equitable access to countermeasures and more. It will also be tied to the new pandemic accord that Member States are negotiating, and to the amendments to International Health Regulations.

As the generation that endured the COVID-19 pandemic, we must be the generation to learn and apply its lessons, to honour those we lost, and to protect future generations from the devastating impacts of epidemics and pandemics. I am confident that the WHO BioHub System will play a vital role in making the world healthier, safer and fairer for our children, and our children's children.

Dr. Tedros Adhanom Ghebreyesus
Director-General
World Health Organization

Acknowledgements

WHO would like to extend its sincere gratitude to all the Member States who contributed to the pilot testing phase and transformed a concept of a multilateral voluntary system for sharing of biological materials into a reality. A special note of appreciation is extended to Switzerland and the team at Spiez Laboratory for their exceptional professionalism and collegiality throughout the process. WHO would also like to thank CSOs, representatives from the private sector, academia, other agencies, and other stakeholders that contributed to the Stream 2 activities.

The development of the WHO BioHub System has been a collaborative effort, under the leadership of the WHO Director General and the WHO Executive Director of the WHO Health Emergencies Programme, drawing upon the expertise and contributions of staff from various departments and divisions within WHO: the Epidemic and Pandemic Preparedness and Prevention Department, Legal Department, Science Division, Research for Health Department and the Office of the ADG for Preparedness. It also relied on support from the Regional Emergency Directors and laboratory focal points in all six WHO Regional Offices.

The WHO BioHub System development was supported by the following WHO staff throughout the pilot-testing phase: BRIAND, Sylvie; CROZET-FOURNEYRON, Sophie; ENDO, Yutaka; GHIGA, Ioana; HESS, Sarah; HUVOS, Anne Marie; JACOBS, Isabelle; KOJIMA, Kazunobu; HOUGENDOBLER, Daniel; LIM, Matthew Lawrence; MISSO Levina; PERKINS, Mark; PIERCY, Kenneth; ROVIRA VILAPLANA, Jose; SATHIYAMOORTHY, Vaseeharan; SHIDEED, Olla; SOLOMON Steven; SUBISSI, Lorenzo; VAN KERKHOVE, Maria; WAMBO, Marie-Ange.

Executive summary

- The COVID-19 pandemic highlighted the need for a multilateral system for sharing information and biological materials. Such a solution is represented by the WHO BioHub System, developed to promote, and foster international sharing of biological materials with pandemic or epidemic potential (BMEPP) and their genetic sequence data, which are critical for evidence-based responses and development of medical countermeasures. These are also the type of activities WHO was asked to engage in as part of the Member States (MS) requests under 2021 World Health Assembly (WHA) resolution 74.7.
- WHO proposed the BioHub System as a pilot project with two streams: Stream 1 focused on testing practical arrangements for sharing biological materials, while Stream 2 involved a consultative process to design the System. Stream 1 aimed to demonstrate the feasibility of standardized sharing agreements, establish procedures, and address logistical transport challenges. Stream 2 involved consultations with stakeholders to receive feedback on various aspects of the System. The approach respected the requests of Member States to provide input and to align with ongoing negotiating processes.
- The sharing of BMEPP is to be facilitated through WHO BioHub Facilities, that are laboratories that would operate under the WHO BioHub System's Guiding Principles and standard Terms of Reference. These Facilities would be responsible for receiving, storing, growing, sequencing, and preparing BMEPP for distribution to Qualified Entities (QE) or other Facilities. During the pilot-testing phase the WHO BioHub System established one WHO BioHub Facility – Spiez Laboratory – through the generous support of Switzerland.
- The main focus of Stream 1 was to evaluate the viability of multilateral sharing of a specific set of BMEPP: SARS-CoV-2 and its variants. Its primary objective was to demonstrate potential use of consistent and standardised Standard Material Transfer Agreements (SMTAs), Terms of Reference and Standard Operating Procedures that could be scaled up to different regions. Two SMTAs were used during the pilot-testing. SMTA1 is used by Member States for sharing BMEPP with the WHO BioHub System, whereas SMTA2 is employed for requests from Qualified Entities for access to such materials. Activities demonstrated the practicality of signing SMTAs and revealed the value of having these documents signed in advance. Additionally, this stream aimed to develop operational pathways and agreements to tackle the challenges posed by international logistical transport and introduce operational tools that enhanced transparency and efficiency while providing access to data to Member States and partners.
- Thus far (as of May 2023), the pilot phase has seen the participation, to varying extents, of the following countries, areas and territories: Australia, Austria, Brazil, China, Egypt, El Salvador, Germany, Ghana, Hong Kong SAR (China), India, Italy, Japan, Luxembourg, Netherlands (Kingdom of the), Portugal, Russian Federation, Singapore, South Africa, Switzerland, Thailand, United Arab Emirates, United Kingdom of Great Britain and Northern Ireland, United States of America. In total 23 SMTAs were signed: 8 countries signed SMTA1; 15 signed SMTA2; and 4 signed both SMTA1 and 2. Overall, 30 SARS-CoV-2 shipments were carried out to or from 18 Member States, comprising 10 shipments of BMEPP from 8 countries into the WHO BioHub System, and 20 BMEPP shipments to 14 countries. The number of shared BMEPP samples stood at 44, and over 100 are expected to be shared to Qualified Entities by the end of the pilot-testing phase.
- As part of Stream 2 activities, WHO conducted several technical consultations with stakeholders on critical subjects such as the management of research findings, genetic sequence data exchange, intellectual property, and access-and-benefit sharing.[1] The pilot-testing phase also involved bilateral engagements with Member States, conferences and meetings presentations, and Member State briefings conducted as part of WHO COVID-19 Information Sessions or standalone sessions, as well as briefings to the INB and International Health Regulations (IHR) working groups.

Overall, during its pilot-testing phase, the WHO BioHub System has accomplished several noteworthy achievements. It has ensured rapid and equitable access to BMEPP for all participating countries and qualified entities, regardless of their level of development or resources, upon request for non-commercial use. The System has facilitated increased collaboration and cooperation among Member States in the sharing of some specific pathogens. Moving forward the System could enhance pandemic preparedness and response, with its ability to aid countries to prevent, detect, and respond to public health emergencies.

1 These activities are described in detail in the WHO BioHub System 1 year progress report: May 2021 – May 2022. Geneva: World Health Organization; 2022

1. Introduction

1.1 Purpose of the pilot-testing report

The overall purpose of this report is to provide evidence-based information that can aid decision-making on how to proceed with future developments of the WHO BioHub System.

The report aims to offer an account on the feasibility, effectiveness, and potential limitations of the current form of the System and contains details on the approach that has been taken to its design, operations and policy related activities. The last section of the report summarises the potential way forward following the conclusion of the pilot-testing phase in the end of May 2023.

The report should be considered in connection to the one-year progress report on the WHO BioHub System. To facilitate comprehension, some aspects are captured in both reports.

1.2 Rationale, objectives and conceptual approach to the WHO BioHub System

The COVID-19 pandemic has had a profound impact on the approach to emergency preparedness and response, and consequently public health globally. The pandemic response has exposed several gaps in related systems and challenged assumptions on pandemic planning. However, the pandemic has also acted as a catalyst for change, as solutions had to be implemented urgently to mitigate its impact. Such a solution is represented by the WHO BioHub System, which emerged from a need to ensure a multilateral system to international sharing of biological materials with pandemic or epidemic potential (BMEPP), and their relevant genetic sequence data (GSD). The rapid access and analysis of the novel pathogen is critical for an evidence-informed response. Derived data is fundamental for implementing the appropriate public health and social measures as well as for the development of medical countermeasures such as diagnostics, vaccine and therapeutics solutions. However, for novel pathogens, where specialised laboratory networks may not be in place, sharing often occurs on a bilateral basis, reliant on different documentation, reviewed often for different sharing situations. This type of bilateral setup is further dependent on the limited resources of the laboratories involved. Ambiguous legal predictability and uncertain access-and-benefit sharing provisions, which rely on national legislations, are also challenges in a one-to-one type of system. Additionally, several global logistical constraints arise during a pandemic, including the need for special transport arrangements for highly infectious materials. Specialized couriers and well-managed processes are required to identify appropriate transport means, and pandemic-related constraints such as reduced availability of human resources, cessation of operations in certain areas, and lack of supplies can further complicate operations.

These are broadly the aspects that the WHO BioHub System set out to address, in the form of a voluntary service with the ultimate goal of bolstering pandemic preparedness worldwide and supporting the COVID-19 response. This initiative answered the Member State's request from May 2021, through World Health Assembly (WHA) resolution 74.7. which called on the WHO Director General to ensure that WHO undertakes activities to advance preparedness "*to work together with Member States, the medical and scientific community, and laboratory and surveillance networks, to promote early, safe, transparent and rapid sharing of samples and genetic sequence data of pathogens of pandemic and epidemic, or other high-risk, potential, taking into account relevant national and international laws, regulations, obligations and frameworks, including, as appropriate, the International Health Regulations (2005), the Convention on Biological Diversity and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization and the Pandemic Influenza Preparedness Framework and the importance of ensuring rapid access to human pathogens for public health preparedness and response purposes*".

Considering the foregoing, the following objectives have been formulated for the WHO BioHub System:

- Promote rapid and timely sharing of biological materials with epidemic or pandemic potential;
- Facilitate rapid access to such pathogens and their information by relevant, interested, and qualified entities for the development of effective and safe public health products including diagnostics, vaccines and therapeutics; and
- Ensure fair and equitable access to such products by all countries, based on public health needs.

A set of 10 Guiding Principles have been proposed to steer the activities. These are described in Box 1.

From a conceptual standpoint, the WHO BioHub System is designed to facilitate the sharing of BMEPP by means of WHO BioHub Facilities. These facilities are equipped with adequate capacities and capabilities to conform with guiding principles and standard terms of reference (ToR). Their primary function is to receive, preserve, cultivate, sequence, and prepare BMEPP for dispensation to Qualified Entities (QEs) or other appropriate facilities. The objective of this approach is to ensure prompt availability of BMEPP to laboratories worldwide to enable research to commence without undue delay.

The Standard Material Transfer Agreements (SMTAs) are utilized to list the terms and conditions under which BMEPP can be shared among countries within the WHO BioHub System. SMTA1 is used for placing BMEPP into the WHO BioHub System, whereas SMTA2 are employed for requesting such materials through the System. By signing SMTAs in advance, sharing timelines can be shortened during emergency responses. In the event that a SMTA1 is already established with a provider country, the shipment of a new BMEPP can be completed by only filling out a checklist-type form, called Annex 2 to SMTA1. This form specifies the details and permissions regarding the use of the specific BMEPP from the provider country. The provider country has the option to allow the BMEPP to be utilized for non-commercial, commercial, or both purposes. Similarly, Qualified Entities (QEs) can request BMEPP and sign SMTA2s in advance, which means that they only need to complete the Annex 2 to SMTA2 with information pertaining to that particular BMEPP and a biosafety and biosecurity checklist to allow WHO to assess the suitability of the laboratory to uphold the necessary safety practices.

WHO proposed that the BioHub System is considered as a pilot project, undertaking a phased development approach divided into two streams: Stream 1: Operationalization and Stream 2: System Design. This was thought to be an approach that would allow WHO to meet the requests of Member States (MS) under 2021 World Health Assembly (WHA) resolution 74.7, while concomitantly respecting MS requests to ensure ample opportunities for providing input and not getting ahead of other ongoing MS negotiating processes in particular the negotiations of the intergovernmental negotiating body (INB) to draft and negotiate a convention, agreement or other international instrument under the Constitution of the World Health Organization to strengthen pandemic prevention, preparedness and response.

Stream 1 activities focused on testing the practicality and operational arrangements for the multilateral sharing of BMEPP, specifically SARS-CoV-2 and its variants. The primary aim was to demonstrate the feasibility of signing SMTAs for the sharing of BMEPP, as well as establishing standardized ToRs and standard operating procedures (SOPs) that can be later scaled across various regions. This stream also involves developing operational pathways and agreements to overcome international logistical transport challenges and introducing operational tools that allow Member States and partners to transparently monitor and be informed of related operations, have access to data and ensure overall operational efficiency.

Stream 2, referred to as system design, consisted of activities carried out through a consultative and iterative process that provided an opportunity for WHO Member States and pertinent stakeholders to offer feedback on different aspects of the system. This involved a series of consultations and technical discussions with a diverse range of stakeholders, including public health organizations, research institutions, civil society organizations, biorepositories, industry, and Member States.

1.3 Overview of recent global developments to aide contextualization of report findings

During the pilot-testing phase of the WHO BioHub System, Member States began two significant intergovernmental processes that will have an impact on future health emergency responses: an Intergovernmental Negotiating Body to draft a WHO convention, agreement or other international instrument to strengthen pandemic prevention, preparedness and response, on the one hand, and a Member State Working Group to draft potential amendments to the International Health Regulations (2005), on the other. WHO will ensure that its work in connection with the BioHub remains aligned with the objectives of these 2 processes.

Following COVID-19 lessons learned, WHO produced the Strengthening the Global Architecture for Health Emergency Preparedness, Response, and Resilience (HEPR) framework, which seeks to enhance operational preparedness and readiness. This endeavour supports global health activities by proposing a set of capabilities that should be strengthened based on recent pandemic experience. It identifies five subsystems that should be strengthened, with two of them being Collaborative Surveillance and Access to Countermeasures. The WHO BioHub System has the potential to serve as an operational mechanism to maintain the necessary capabilities at a global level.

Box 1: Guiding principles for the WHO BioHub System

1. A voluntary system for the global public health
All contributions of BMEPP to the WHO BioHub will be entirely voluntary, based on the desire for rapid generation of information and other resources for global public health.

2. Timeliness
To enable an effective public health response, the end-to-end system from sample collection to shipping and generation of scientific information must function with urgency. Data and analyses will be made publicly available in a timely manner, while respecting all applicable WHO, international, and national regulations and standards, and communicated promptly to decision-makers in the affected countries as well as more broadly to all WHO Member States to support effective and timely response measures.

3. Equity and fairness
Equity and fairness, as well as public health risk and need, will govern access to BMEPP contributed to the WHO BioHub System, and the research, data, and other materials resulting from the WHO BioHub System.

4. Transparency
Terms and conditions with respect to the use of BMEPP, sequence data and information from the WHO BioHub System will be made publicly available, as will criteria to receive BMEPP.

5. Acknowledgement and co-authorship
The contributions of collaborators to the WHO BioHub System, including laboratories providing BMEPP or genetic sequence data, will be appropriately acknowledged in presentations and publications, using guidelines such as those outlined by the International Committee of Medical Journal Editors. To the extent possible, entities using BMEPP in scientific research projects will seek the participation of scientists from the originating laboratory or countries and make efforts to engage them in preparation of manuscripts for presentation and publication.

6. Sustainability and maximal preservation
The BMEPP and associated data (e.g epidemiological information) available through the WHO BioHub System will be critical for understanding diseases with epidemic or pandemic potential and developing tools to combat them. These important resources will need to be maintained and managed over the longer term. The WHO BioHub System will therefore be established and managed with longer term sustainability and maximal preservation in mind.

7. Collaboration and cooperation
The WHO BioHub System will promote collaboration and cooperation with existing networks, repositories, and scientific groups to strengthen knowledge and contribute to the advancement of effective, efficient, fair and equitable response to epidemic or pandemic public health events.

8. Best practices for safety and security
The WHO BioHub System will follow procedures that ensure that BMEPP which are shared have been properly characterized, usually through culture and sequencing for pathogen materials. They will be prepared, dispatched, received, processed, stored and shipped to qualified recipients according to current, applicable national and international biosafety and biosecurity standards.

9. Consistency with applicable law
The WHO BioHub System will be established and operated in a manner consistent with applicable law, regulations, rules, and standards, including under legal rules and regulations as well as national and international law.

10. Consistency with applicable ethical regulations, norms, and standards requirements
The WHO BioHub System will be established and operated in a manner consistent with applicable WHO, international, and national ethical regulations, norms, and standards.

2. Stream I – progress on operations

2.1 Overview of operations

Until May 2023, several countries, areas and territories - Australia, Austria, Brazil, China, Egypt, El Salvador, Germany, Ghana, Hong Kong SAR (China), India, Italy, Japan, Luxembourg, Netherlands (Kingdom of the), Portugal, Russian Federation, Singapore, South Africa, Switzerland, Thailand, United Arab Emirates, United Kingdom of Great Britain and Northern Ireland, United States of America – have joined the pilot phase in some capacity (e.g. contributing to discussions on drafting documentation, engaging in operational preparations, signing SMTAs, hosting a BioHub Facility, providing or requesting BMEPP). A total of 23 SMTAs have been signed with: 8 countries signing SMTA1, 15 signed SMTA2, and 4 signed both SMTA1 and 2. Please see Table 1.

Table 1: SMTA signatories

	Countries, areas, and territories	Signed SMTA type		
		SMTA 1	SMTA 2	Both
1	Australia		✓	
2	Austria		✓	
3	Brazil		✓	
4	China		In progress	
5	El Salvador	✓		
6	Germany		✓	
7	Ghana		✓	
8	Hong Kong SAR (China)		✓	
9	India	✓	✓	✓
10	Luxembourg	✓	✓	✓
11	Netherlands (Kingdom of the)		✓	
12	Portugal		✓	
13	Russian Federation		✓	
14	Singapore	✓		
15	South Africa	✓	✓	✓
16	Switzerland	✓	✓	✓
17	Thailand	✓		
18	United Arab Emirates		✓	
19	United Kingdom of Great Britain and Northern Ireland	✓		
20	United States of America		✓	
Total number signed SMTAs		**8**	**15**	**4**

As of May 2023, the 18 Member States engaged in 30 shipments of SARS-CoV-2, of these 10 shipments represented voluntary sharing of BMEPP from 8 countries into the WHO BioHub System, while 20 shipments were requests of BMEPP from 14 different countries. These are detailed in Table 2 and Table 3.

Table 2: BMEPP provided into the WHO BioHub Facility

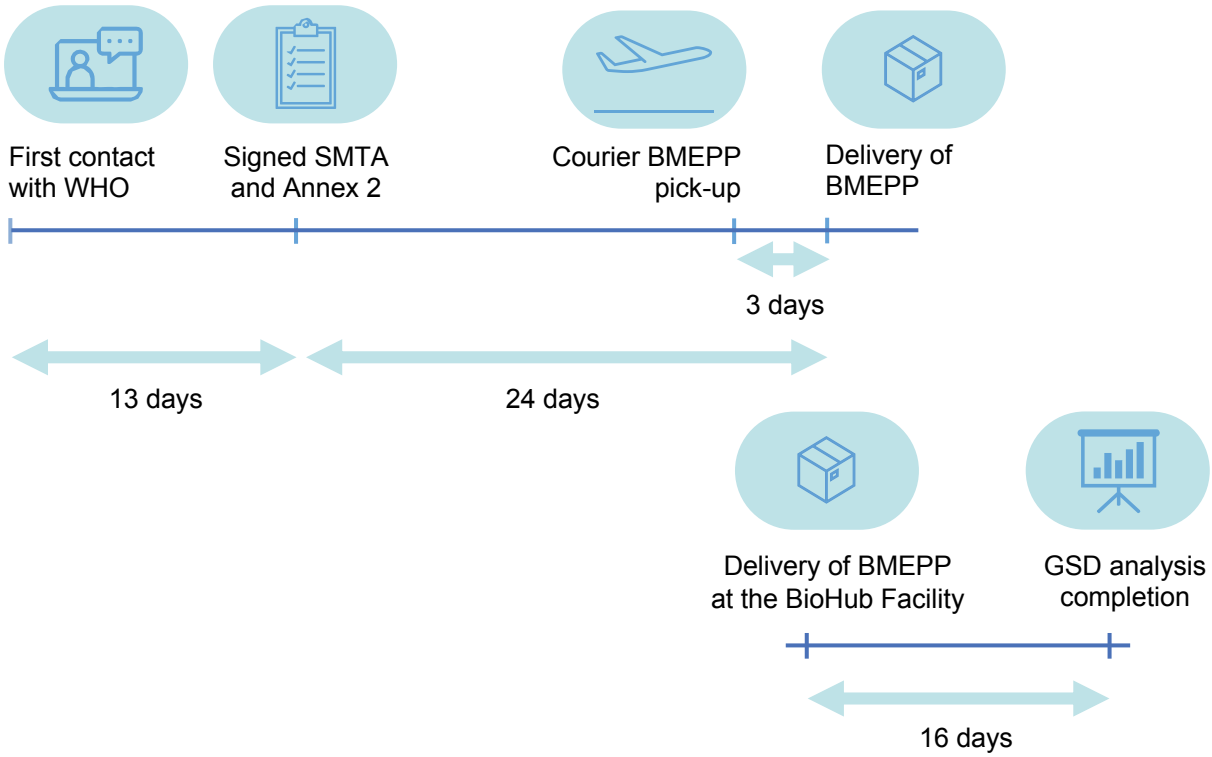
	BMEPP provider	Shared variant
1	El Salvador	Omicron (BA.2.12.1, BA.4.2, BA.5.1, BA.5.2.1, BA.5.5)
2	India (in progress)	Omicron (XBB.1.16)
3	Luxembourg	Alpha, Beta, Gamma, Delta
4	Singapore (some in progress)	Omicron (XBB.1, XBB.3, XBB.1.16.1, XBF, XBB.1.5, XBB.1.9.1, XBB.1.9.2)
5	South Africa	Omicron (B.1.1.529, BA.4, BA.5)
6	Switzerland	Omicron (XBB.1.5)
7	Thailand	Omicron (BA.1.1, BA.2)
8	United Kingdom of Great Britain and Northern Ireland	Omicron (B.1.1.529)

Table 3: BMEPP requested from the WHO BioHub Facility

	BMEPP recipient	Shared variant
1	Australia	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1, XBB.1.5)
2	Austria	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
3	Brazil	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
4	Germany	Alpha, Beta, Delta, Omicron (BA.1, BA.4, BA.5, XBB.1.5)
5	Ghana	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
6	Hong Kong SAR (China)	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
7	India	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
8	Luxembourg	Omicron (B.1.1.529)
9	Netherlands (Kingdom of the)	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
10	Portugal	Omicron (B.1.1.529)
11	South Africa	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
12	Switzerland	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
13	United Arab Emirates	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)
14	United States of America	Alpha, Beta, Delta, Omicron (BA.1, BA.5, XBB.1.5)

A set of key performance indicators (KPIs) were used to monitor operational progress made thus far. Figure 1 outlines a comprehensive set of KPIs that reflect the average time intervals between pivotal stages of the operation. Typically, the delivery of BMEPP is accomplished within an average of 35 days after a country has expressed its interest in collaborating with the BioHub System, with the total transportation time for BMEPP shipment averaging three (3) days. As a post-shipment benchmark, the analysis of GSD for the BMEPP received at the BioHub Facility is usually completed within a timeframe of approximately two (2) weeks following its arrival at the Facility.

Figure 1: Operational KPIs (average days)



In addition to normal BMEPP sharing, the WHO BioHub System has been involved in a pilot project to assess risk posed by emerging SARS-CoV-2 variants. The main objective of this immune evasion project is to study the reproducibility of neutralisation assays across various laboratories in all WHO regions using common reagents and protocol, and to estimate the reduction in neutralisation potency of control sera against the targeted variant (XBB.1.5), compared to reference variants (BA.1 and BA.5). As of the report's publication, this pilot is still underway. Participating laboratories are employing identical virus material supplied through the WHO BioHub System.

Costs associated with all the shipment operations amounted to USD 101,000, with shipments costs ranging from approximately USD 2,300 (Luxembourg shipment) to USD 6,400 (El Salvador shipment).

2.2 Development of the WHO operational platform

Work on a digital operational tool referred to as the WHO BioHub System operational platform has been ongoing since May 2022. The goal of the platform was to provide visibility on operational progress and on availability of BMEPP, as well as offer secure and automated interphases to facilitate timely and transparent operations within the WHO BioHub System.

The platform is undergoing final testing and will be offered for use subsequently depending on testing outcomes. It is envisioned that following further use, based on user feedback and analytics, additional improvements would be made.

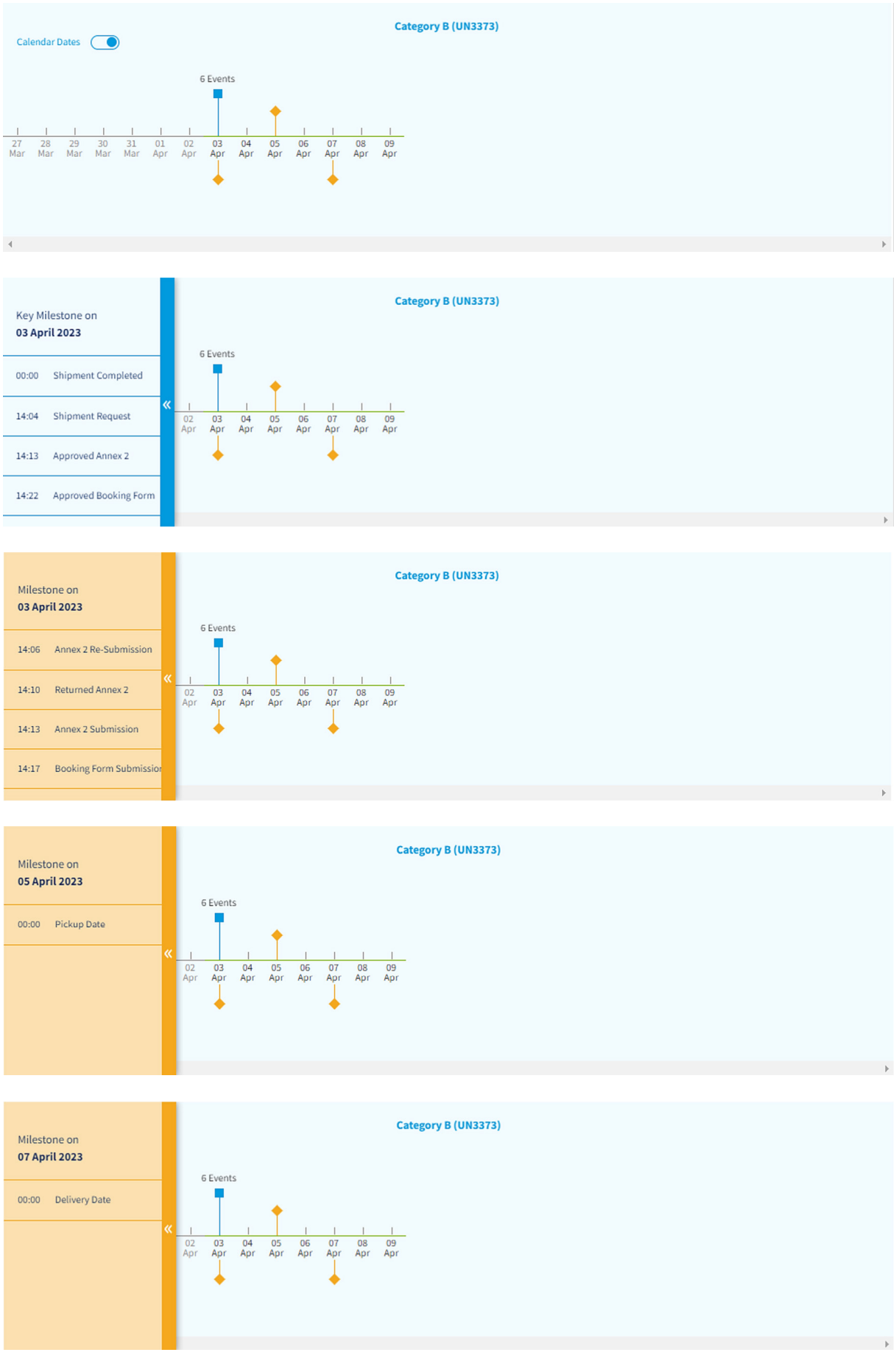
The WHO BioHub System operational platform comprises two distinct interfaces designed to cater to the different requirements of its users. The first interface, which is publicly available, features a range of functions such as key performance indicator metrics linked to the BioHub System's operations, an interactive map showcasing BioHub System users and previous shipments, a catalogue displaying the available BMEPP materials within the System, and a registration form for becoming a registered user.

The second interface is only accessible to registered users and provides additional functionalities that include requesting BMEPP sharing, managing documents and data related to BMEPP and shipments. Registered users submit various types of information, including personal and institute profile details. This may include their name, title, contact information, and the location/country of their institute. The information available to registered users includes detailed information about the BMEPP, provided by the user such their analysis results and GSD requisition number if available. It also contains information pertaining to shipment requests, both completed and in-progress. This includes specific details about the dates of each step in the shipment process and the submitted documents. Detailed information about the BMEPP analysis results performed at the Facility, is also accessible to registered users. This includes properties of materials and laboratory work analysis results as well as GSD. Registered users can upload completed documentation, such as SMTAs. The platform facilitates the online completion of Annex 2 to SMTAs', Biosafety and Biosecurity Checklists, as well as booking forms. Figure 2 shows an example of a shipment progress a user can visualize through the platform.

The BMEPP catalogue encompasses a range of information including BMEPP Name, BMEPP type (such as virus), provider laboratory name, product type at arrival at BioHub Facility (such as clinical specimen or cultured isolate), product type in sharing to QEs (such as cultured isolate), temperature in storage, usage permission (such as non-commercial use), lineage, variant, WHO variant assessment, database used for GSD sharing, BMEPP arrival date at BioHub Facility, International Taxonomy Classification, GMO status, and isolation host type.

The main laboratory data available following the BioHub Facility's BMEPP analysis include the following information: culturing results indicating success or failure and the corresponding date, the isolation technique employed such as cell culture, quality control results including the date, the infectivity and viral titer of cultured material, GSD analysis results along with the date of analysis, the status of GSD uploading and the date of upload, the GSD database used for uploading, the entity responsible for uploading, the accession ID to the GSD database, GSD information such as cell line, passage number, FASTA file, and strain designation at GSD database, the availability of aliquots in stock.

Figure 2: Example of shipment progress a user can visualize through the platform



2.3 WHO BioHub Facility

The current BioHub Facility, which is the initial and singular of its kind, is situated at the Spiez Laboratory and has been established with the support of Switzerland.

Numerous activities have been undertaken to develop a unified collection of documents and tools that will facilitate coordinated methodologies for the establishment and administration of operations in the event of supplementary BioHub Facilities.

These comprise of a Memorandum of Understanding, which should be endorsed by the host nation and the WHO, ToR that outline the activities of BioHub Facilities with regard to the BioHub System, and a compendium of SOPs for various operations. A selection of specific WHO BioHub System SOPs are presented in Box 2. The main type of operations conducted at the Facility are illustrated in Figure 3.

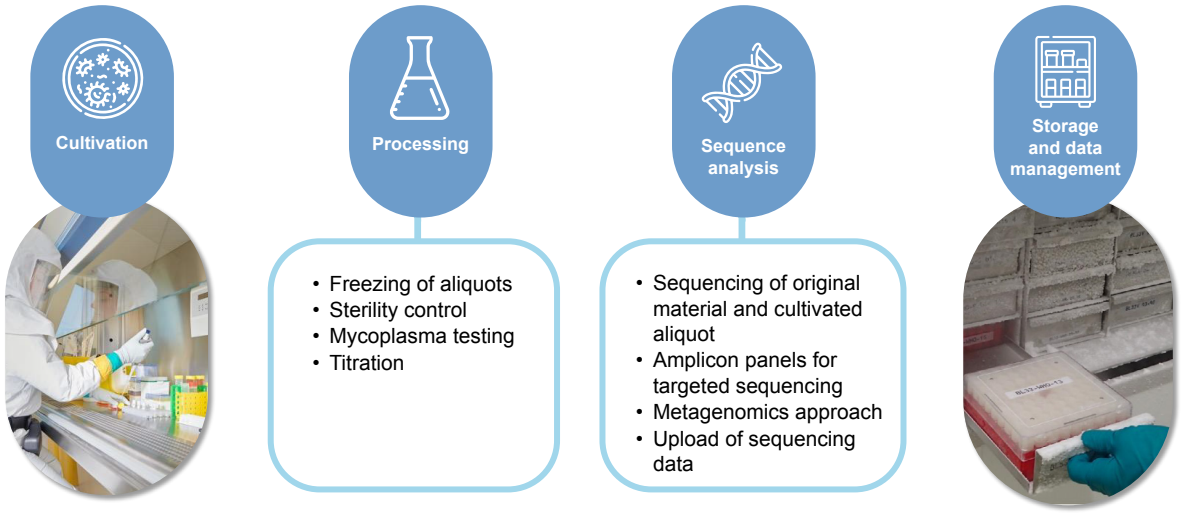
Box 2: Examples of SOPs available at the WHO BioHub Facility

- WHO BioHub: Data-monitoring and transfer to WHO (ad interim)
- WHO BioHub: Reception of WHO BioHub Samples
- WHO BioHub: Preparation of cell cultures for the cultivation of SARS-CoV-2 variants
- WHO BioHub: Culturing of SARS-CoV-2 variants
- WHO BioHub: Titer determination (TCID50) and sterility control of cultures of SARS-CoV-2 variants
- WHO BioHub: Storage and cataloguing of viral cultures
- WHO BioHub: Sequencing of SARS-CoV-2 samples with the Ion AmpliSeq™ SARS-CoV-2 Insight Research Assay
- WHO BioHub: Sequence Submission
- WHO BioHub: Mycoplasma detection using Myco-Sniff-Valid
- WHO BioHub: WHO sample management in LIMS
- WHO BioHub: Export of BMEPPs from BioHub Facility

During the course of operations, Spiez Laboratory has generously explored at no cost to WHO, the possibility of incorporating supplementary software that provides a sample workflow manager and would interface with their storage and cataloguing software as well as the WHO BioHub operational platform. This is an ongoing project, but it will provide transferable lessons learned for other Facilities.

Costs associated with the WHO BioHub Facility pertained to human resources, consumable costs (plastic ware, medium, extraction kits, real-time polymerase chain reaction, sequencing reagents etc), infrastructure related (cell culture facility, biosafety level 3 laboratory, biosafety level 4 laboratory, sequencing facility), laboratory information management system and back-up systems related as well as indirect costs. Costs varied depending on the intensity of work, however they could be approximated to about CHF 650 000 per year, with an approximate half and half split (between HR and non-HR costs).

Figure 3: Operations performed at the BioHub Facility once BMEPP is received



2.4 Approach to biosafety and biosecurity

To support upholding of biosafety and biosecurity operations by BMEPP receiving QEs, WHO has published the WHO BioHub Biosafety & Biosecurity: criteria and operational modalities[2]. This document details the requirements to which laboratories wishing to receive biological materials as part of this international exchange system should abide, to ensure safe and secure operations. These provisions are in accordance with the recommendations of the WHO Laboratory Biosafety Manual 4th edition (LBM4)[3], adopting an evidence- and risk-based approach to enable scalable and adaptable biosafety provisions and actions, proportionate to the assessed risk.

Based on these documents, WHO has created a biosecurity and biosafety checklist that is available either in document format or can be directly filled in electronically through the WHO BioHub operational platform.

Future developments of the WHO BioHub System may explore conformity with emergent accreditation options, spearheaded by WHO in connection to the wider biosafety and biosecurity capacity building activities.

2.5 WHO BioHub secretariat

The WHO BioHub System activities were supported by a WHO cross-departmental team under the leadership of the Director of the Epidemic and Pandemic Preparedness and Prevention Department. The type of functions different staff served were: i) coordination of workstreams, management and operational oversight, ii) overall project operations and cross-cutting work as well as iii) senior subject matter experts in R&D, science, GSD and Nagoya related issued, virology, laboratory and diagnostics, biosafety and biosecurity, operations and logistics, legal, INB and Pandemic Influenza Preparedness Framework (PIP) as well as iv) project support. Box 3 lists key concluding observations for Stream 1 activities.

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2 WHO BioHub system biosafety and biosecurity: criteria and operational modalities. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

3 Biological safety cabinets and other primary containment devices. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs). Licence: CC BY-NC-SA 3.0 IGO

Box 3: Stream 1 concluding observations

- Previously signed SMTAs result in reduced timelines in sharing of BMEPP.
- Evolving shipment prerequisites and modifications in import/export documentation underscore the essential nature of WHO's assistance in facilitating shipments.
- Development of SMTA3s was not done within Stream 1 due to the absence of a globally agreed access-and-benefit sharing mechanism.
- Substantial interest was received from the research community towards harnessing the capabilities of the WHO BioHub System.

3. Stream II – system design

Many of the efforts regarding the design of the system took place during the first year of the pilot testing operations. In 2021 and 2022, WHO held a succession of technical deliberations with an extensive array of stakeholders, in order to make preparations for and facilitate discussions among Member States concerning critical subjects. The subjects of these four technical and thematic consultations were as follows: i) the management of research findings, including the appropriate acknowledgement of contributions; ii) the exchange of GSD; iii) matters pertaining to Intellectual Property; and iv) Access-and-Benefit Sharing.

The previous WHO BioHub System report provides in-depth details on these consultations encompassing details on participation, feedback articulated by the participants, as well as the links to relevant documentation and video recordings of the consultation sessions.

Through the pilot-testing phase several bilateral engagements with Member States and other actors ranging from academia, biorepositories, civil society, and industry occurred. Additionally, presentations were delivered at various conferences and meetings to enhance awareness and promote the dissemination of the progress made thus far.

Crucially, a significant number of Member State Briefings were convened, either as an integral part of the WHO COVID-19 Information Sessions, or as standalone sessions, as well as briefings provided to the INB and the IHR working groups. Box 4 lists key concluding observations for Stream 2 activities.

Box 4: Stream 2 concluding observations

- The continuity of Stream 2 activities is essential for the establishment of a trusted WHO BioHub System.
- The WHO BioHub access-and-benefit sharing remains a work in progress. WHO will ensure that any advances in the work are aligned with the INB and WGIHR discussions.

4. Proposed way forward

In this section, we present considerations for the future development of the WHO BioHub System based on the experiences gathered during the pilot testing phase. Some proposals could be implemented in the interim phase - until conclusion of INB negotiations (i.e.until May 2024).

4.1 Expanding the networks of BioHub Facilities

WHO has received feedback and inquiries from several Member States during the pilot testing phase regarding the potential to host a BioHub Facility.

Regional expansion

In line with best practices observed in other networks, WHO suggests that having at least one BioHub Facility in each WHO region would bring significant benefits to the WHO BioHub System. Such facilities could serve as important resources for the regions during normal, inter-pandemic periods, as well as for localized outbreaks. During a pandemic, they could serve as the initial exchange points within the System. In effect, this would entail that a laboratory in each region would have BMEPP at its disposal for immediate sharing with other laboratories, thereby significantly enhancing regional BMEPP sharing. In situations where additional support is required, other Facilities, from different regions, can also provide assistance and help fill gaps in the event of limited capacity.

Diversification of WHO BioHub Facility functions

As the WHO BioHub System evolves into an interconnected network of networks, capitalizing on pre-existing arrangements (e.g. already existing WHO lab networks Terms of References), capacities, and capabilities, there is potential to expand the scope of each BioHub Facility's functions. This could involve specific Facilities concentrating on particular pathogens or distinct types of analysis. Please refer to the following paragraph concerning the introduction of a modular approach to the Terms of Reference (ToR).

4.2 Enhancing scope by broadening the spectrum of biological materials with pandemic or epidemic potential (BMEPP) shared

During the pilot-testing phase, the WHO BioHub System facilitated sharing of SARS-CoV-2 and its variants. In the 2022, during the Public Health Emergency of International Concern (PHEIC) caused by mpox, WHO received requests for the use of the System to share this virus. This was not considered possible due to the pilot-testing design that was communicated to MS, where it was established that the System would be used solely for SARS-CoV-2 during this period. Based on this experience, WHO suggests expanding the System to support all BMEPP that is covered by the R&D Blueprint, including Disease X as well as other pathogens causing outbreaks that become PHEICs. The WHO BioHub System would remain voluntary, with MS and QEs utilizing it at their discretion. The System should continue to aid the SARS-CoV-2 response, given the virus has not stabilized, continuous transmission, immune escape and potential emergence of more variants.

Moreover, the WHO BioHub System has garnered numerous requests for the sharing of sera. While sharing of sera was not performed during the pilot-testing phase, it could be taken into consideration for future developments.

4.3 Developing a code of practice

To foster trust within the WHO BioHub System, a code of practice is proposed to be developed. This will establish a comprehensive set of rules, values, principles and standards to guide the ethical, behavioural and legal expectations from all individuals and organizations involved in the governance and use of the WHO BioHub System, as well as their interactions with others. The Code would be adopted by the members of the WHO BioHub System and apply to various groups, including users such as provider countries, QEs, and BioHub Facility personnel, individuals or organizations involved in governance such as WHO, advisory groups, and financial contributors, and direct recipients of capacity building-related benefits provided through the WHO BioHub System. This document will be applicable globally, taking into consideration national and international legal and regulatory contexts, and would be continuously updated rather than having a specific expiration date.

4.4 Efforts towards optimization of documentation and supporting governance structures

Changes to the SMTAs

The completion of the pilot-testing phase necessitates minor adjustments to the SMTAs. The primary revisions involve eliminating all references to the 'pilot-testing' phase itself. Furthermore, Annex 2 to SMTA1 may be amended to offer additional alternatives for provider countries to choose from, regarding BMEPP and GSD usage, as presented in Figure 4. For BMEPP utilization, the options could include solely non-commercial use or both commercial and non-commercial uses.

SMTA3 considerations

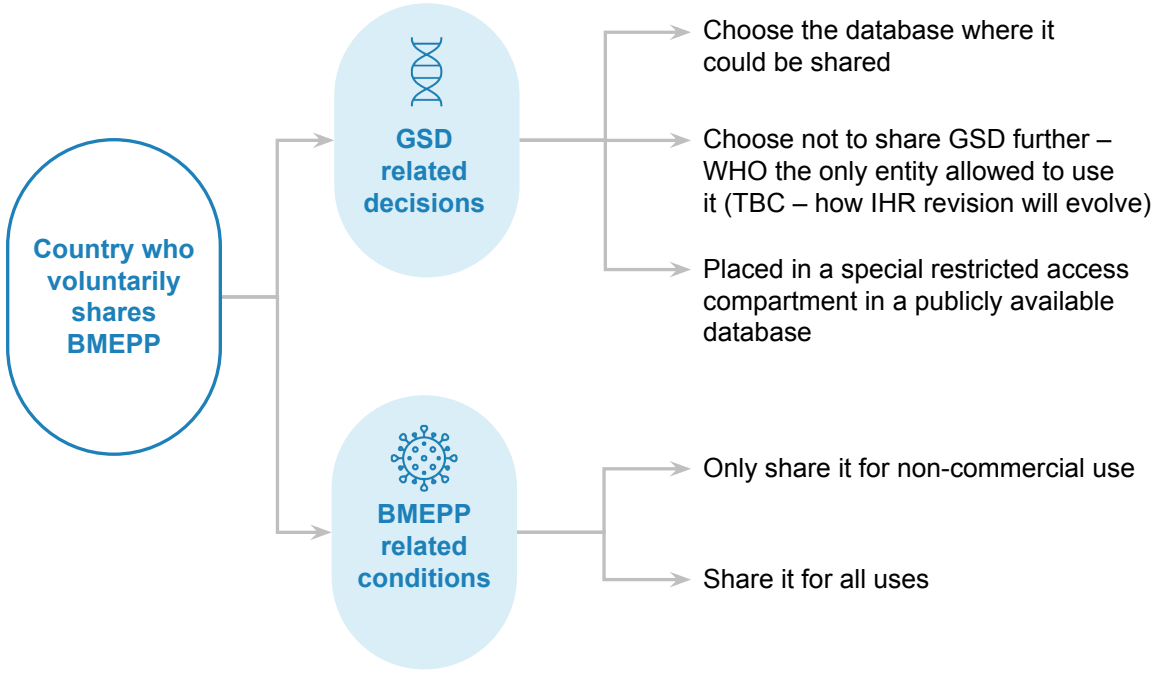
Presently, the WHO BioHub System does not offer commercial-use access. However, this could be further developed in the next phase of the initiative mindful of the outcome of the INB negotiations. Therefore, during the interim one year (until the adoption of the INB), the System will focus on exchanges based on SMTA1 and 2 only.

GSD sharing options

Whilst the INB and IHR negotiations are ongoing, for GSD sharing options, there may be three approaches: i)allowing immediate placement of the GSD in a publicly available database, ii) withholding permission for further GSD sharing while permitting WHO to use the GSD to inform public health-related analysis, or iii)exploring a new option to establish a secure compartment within a publicly available database where additional access conditions could be required (e.g., linked to the provision of certain benefits, an explanation of the research's importance to public health, etc.).

Currently the Annex 2 to SMTA1 relies on the consent of the provider to upload the GSD into a publicly accessible database stating that "the WHO BioHub Facility uploads BMEPP GSD that it generates, in a timely manner, to one or more publicly accessible genetic sequence databases, including for example GISAID or INSDC".

Figure 4: Potential options for providers to select different permissions for BMEPP and GSD use



SMTA1 signatories

To streamline operations and prevent undue strain on the resources of the WHO BioHub Facility, it is proposed that the SMTA1 will not be required to be signed by the Facility as well. The terms outlined in the SMTA1 will instead be incorporated into the Facility's existing ToR, which currently make reference to the SMTA1.

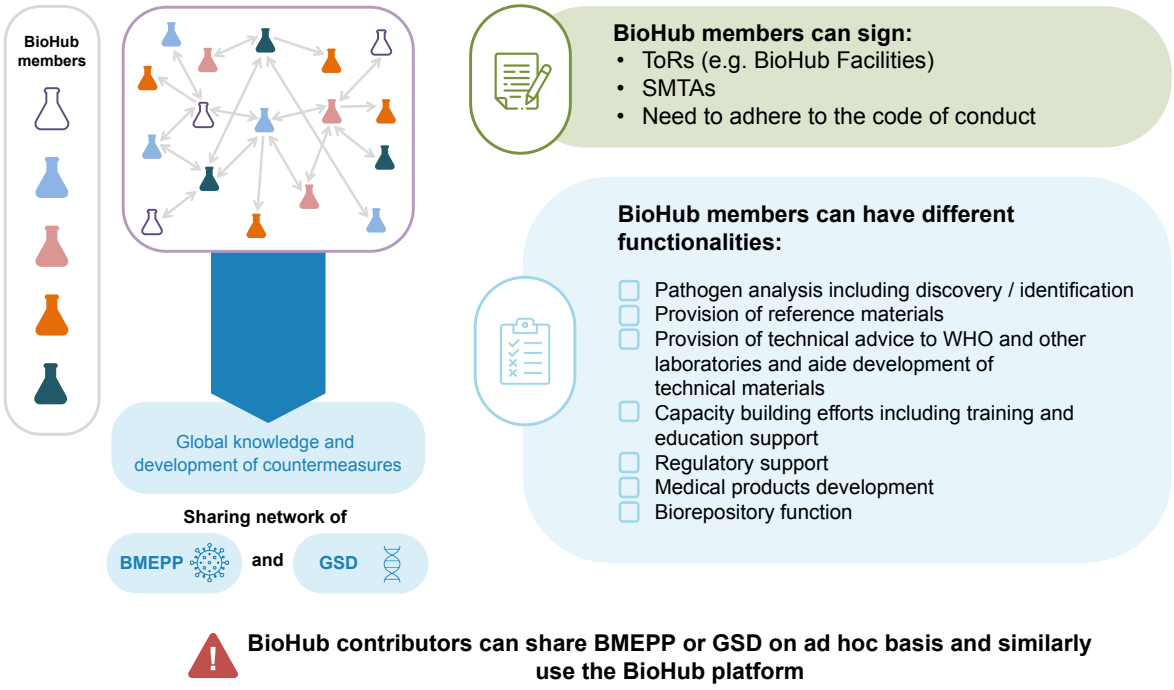
Introducing a modular approach to ToR

For laboratories that use the WHO BioHub System frequently, there may be opportunities to have an ever more standardized approach, and incorporate the standard provisions of the SMTAs into a consolidated ToR that contain functional modules. This would enable non-BioHub Facilities laboratories, that are frequent users of the System, to also contribute to the System should they wish to, by supporting different public health activities, even though they may not offer the full range of functions that a Facility provides. These new ToR, constructed in a modular approach, could easily be updated by selecting or de-selecting specific functional modules. Examples of such activities are presented in Figure 5.

Setting up a WHO BioHub System advisory group

To ensure an independent and public health driven approach to prioritisation of BMEPP sharing, in the event of numerous requests, an advisory group could be set-up. This group may also advise on who should receive access to GSD (please see next paragraph).

Figure 5: Overview of different functions of WHO BioHub members



4.5 Access-and-benefits

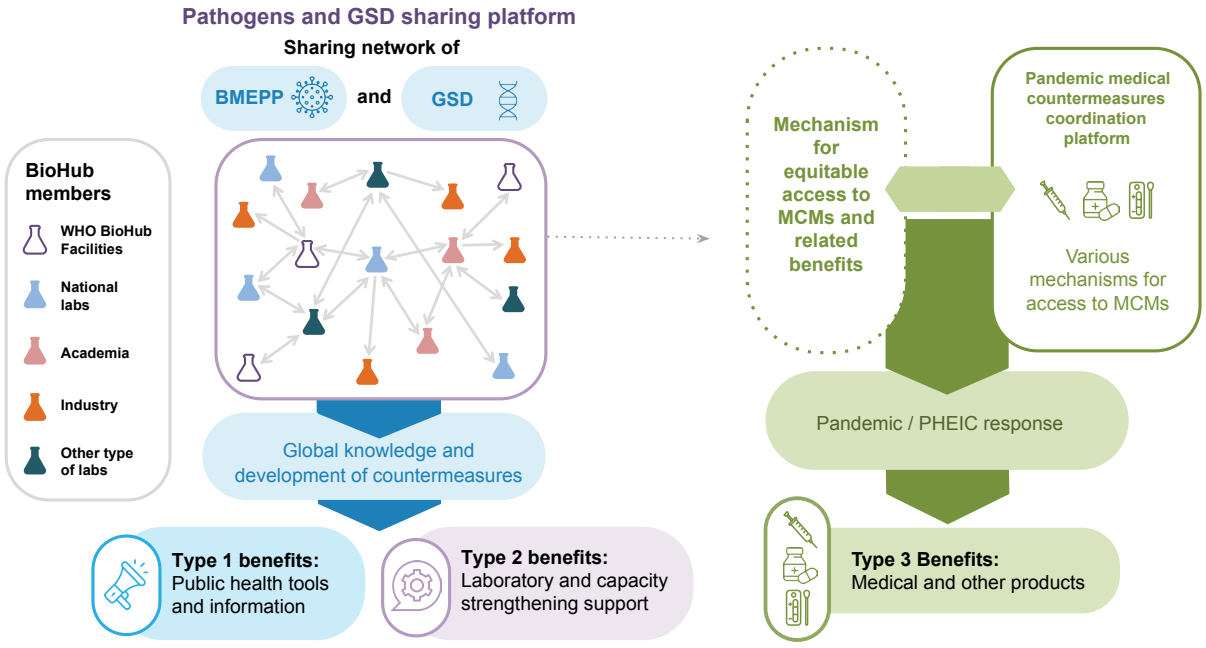
As discussed during Stream 2, there are three main type of benefits that may arise as part of the WHO Biohub System activities. These are:

1. Public health tools and information
2. Laboratory and capacity strengthening support
3. Access to medical (and other) products

In the interim period, while INB negotiations are ongoing, the WHO BioHub System could prioritize 2 types of benefits: i) public health information and tools, as well as ii) laboratory capacity building. This is until various policy-related developments regarding the commercial use of BMEPP and GSD are concluded. Another factor to consider when providing benefits is the operational initiatives that are currently underway in various fora to enhance access to medical countermeasures. All these should be synergistic and ensure they work in a coordinated fashion.

Please see Figure 6, for three main types of benefits and a potential integration within the evolving global health architecture.

Figure 6: A potential integration of the WHO BioHub System within a complex and evolving global health architecture



Conclusions

In its pilot-testing phase, the WHO BioHub System has achieved several notable successes:

- Rapid and equitable access to BMEPP: Rapid and equitable access to BMEPP was ensured for all countries and qualified entities that made a request for non-commercial use, regardless of their level of development or resources.
- Increased collaboration and cooperation: with greater sharing of knowledge, data, and expertise as demonstrated by the support of the WHO BioHub System to the pilot project to assess risk posed by emerging SARS-CoV-2 variants. This shows how the System can contribute to more effective and coordinated responses to public health emergencies. The knowledge generated will also lead to improved public health outcomes, aiding quicker scientific understanding of pathogen evolution and therefore calibration of public health, social and medical countermeasures.
- Enhanced pandemic preparedness and response: With the experience of Omicron, the WHO BioHub System proved it potential to aid countries to be better equipped to prevent, detect, and respond to public health emergencies. The QE country that received the first Omicron shipment through the BioHub Facility following the initial sharing from South Africa, managed to perform the necessary preparation based on the sample, prior to the official national detection of the first Omicron case.
- Predictive approaches and operational transparency to increase trust in a multilateral system: The WHO BioHub System has supported the creation of standardised documentation that led to increased operational efficiency as well as tools that support operations and data access in a transparent and secure way.

In the pilot testing phase, the WHO BioHub System focused on non-commercial sharing of BMEPP. In the future it is important to expand the sharing for commercial use mindful of discussions need to develop the comprehensive access-and-benefit sharing mechanism.

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