APPROACHES TO SEASONAL INFLUENZA AND GENETIC SEQUENCE DATA UNDER THE PIP FRAMEWORK

Analysis

Since the development of the draft Analysis (published in September 2018) two significant processes have taken place that are relevant to this Analysis:

- The 15-16 October 2018 WHO Consultation on Implementation of Decision WHA70(10)(8)(b), and
- The November 2018 meetings of the 14th Conference of the Parties (COP) to the Convention on Biological Diversity (CBD) and the 3rd Conference of the Parties serving as the Meeting of the Parties (COP-MOP) to the Nagoya Protocol.

This document has been revised in light of these developments, through the addition of three new annexes and edits to the draft Analysis document. The three new Annexes cover the following:

- Annex 1: *Summary of key outcomes from the November 2018 CBD COP and the Nagoya Protocol COP-MOP*
- Annex 2: *Implementation of the Nagoya Protocol and seasonal influenza virus sharing*, which presents some challenges with seasonal influenza virus sharing related to the implementation of the Nagoya Protocol.
- Annex 3: *Benefit-sharing under the PIP Framework*, which describes the two benefit-sharing mechanisms in the PIP Framework and current and potential future loopholes in the Framework.

Acknowledgments

WHO thanks Member States, GISRS laboratories, industry associations and their members, civil society organizations, databases and initiatives, the Secretariats of the Convention on Biological Diversity and the FAO International Treaty on Plant Genetic Resources for Food and Agriculture for their contribution to this Analysis. WHO would also like to give special thanks to the PIP Framework Advisory Group, GISRS Collaborating Centres and GISRS Essential Regulatory Laboratories for their invaluable guidance and support throughout the process to develop this Analysis.

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TABLE OF ACRONYMS AND ABBREVIATIONS

ABS	Access and benefit sharing
AHTEG	CBD Ad Hoc Technical Expert Group
CBD	Convention on Biological Diversity
cDNA	Complementary deoxyribonucleic acid
COP	Conference of the Parties to the Convention on Biological Diversity
COP-MOP	Conference of the Parties serving as the Meeting of the Parties to the Nagoya Protocol
CVV	Candidate vaccine virus
DSI	Digital sequence information
DNA	Deoxyribonucleic acid
FDA	United States Food and Drug Administration
GISRS	Global Influenza Surveillance and Response System
GSD	Genetic sequence data
IHR	International Health Regulations (2005)
ITPGRFA	International Treaty on Plant Genetic Resources for Food and Agriculture
IVPP	Influenza virus with human pandemic potential
IVPP GSD	Genetic sequence data from influenza viruses with human pandemic potential
IVTM	Influenza Virus Traceability Mechanism
NIC	WHO National Influenza Centre
MAT	Mutually agreed terms
MLS	Multilateral System of Access and Benefit-Sharing (of the ITPGRFA)
PC	PIP Framework Partnership Contribution
PIC	Prior informed consent
PIP AG	PIP Framework Advisory Group
PIP	Pandemic influenza preparedness
PIP BM	PIP Biological Materials
RNA	Ribonucleic acid
SBI	CBD Subsidiary Body on Implementation
SII	Specialized International Access and Benefit-sharing Instrument
SMTA	Standard Material Transfer Agreement
TORs	Terms of reference
VCM	Vaccine Composition Meeting
WHA	World Health Assembly
WHO	World Health Organization
WHO CC	WHO Collaborating Centre
WHO ERL	WHO Essential Regulatory Laboratory

INTRODUCTION

1. The Pandemic Influenza Preparedness (PIP) Framework, adopted in 2011, aims to improve pandemic influenza preparedness and response, and strengthen the protection against pandemic influenza, by improving and strengthening the WHO Global Influenza Surveillance and Response System (GISRS), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing: sharing of influenza viruses with human pandemic potential and access to vaccines and sharing of other benefits. In accord with section 7.4.2 of the Framework, WHO established the first PIP Framework Review Group (PIP Review Group) in 2016. The group of 8 independent experts was mandated to examine the Framework with a view to proposing revisions reflecting developments, as appropriate to the Seventieth World Health Assembly (2017).

2. The PIP Review Group found that the principles of the PIP Framework—especially that of placing virus sharing and benefit sharing on an equal footing—remain as relevant today as they were in 2011, given the unique threat that the ever-changing influenza virus presents for public health. Further, maintaining the contribution of the PIP Framework, and demonstrating the benefits of pandemic influenza preparedness, is especially important as countries with competing health priorities usually focus their attention on current local disease threats and therefore may be unprepared for an influenza pandemic.

3. However, the PIP Review Group also noted that "there are key issues that must urgently be addressed for the PIP Framework to remain relevant, including the issue of how [genetic sequence data] should be handled under the PIP Framework, and whether or not the PIP Framework could be expanded to include seasonal influenza."[1]

4. Although including seasonal influenza viruses was considered during negotiations of the PIP Framework, they were specifically excluded in the final text. However, seasonal and pandemic influenza viruses exist in a spectrum, involving humans, birds and other animals. Novel influenza viruses with pandemic potential (IVPP) emerge due to the evolving nature of the virus. Influenza viruses often pass between and among a variety of hosts including humans, birds and other animals. During this process an influenza virus can re-assort with other influenza viruses, resulting in a new IVPP.

5. The PIP Review Group noted that expanding the PIP Framework to include seasonal influenza viruses could lead to a significant increase in workload for GISRS laboratories, if seasonal viruses were tracked in the same way as IVPP. They also noted that the benefit sharing aspect of such expansion would also need to be addressed.

6. The PIP Review Group also considered genetic sequence data (GSD). The PIP Framework encourages all countries to share GSD; however, GSD is not included in the definition of PIP Biological Materials (BM)[2]. Therefore, the regime of benefit sharing that applies to PIP BM does not fully include GSD, although many IVPP genetic sequences are rapidly shared in accordance with relevant GISRS Terms of Reference. Therefore, the PIP Review Group concluded that clarity is urgently required on the handling of GSD under the PIP Framework to ensure that it is guided by the same principles as the sharing of PIP BM.

7. In May 2017, after considering the PIP Review Group's report, the World Health Assembly adopted decision WHA70(10), which requested the Director-General to, *inter alia*, conduct a thorough and deliberative analysis ('the Analysis') of the issues raised by the Review Group's recommendations on seasonal influenza and genetic sequence data (GSD), including the implications of pursuing or not pursuing possible approaches.

[1] PIP Framework Review Group. 2016 Review of the Pandemic Influenza Preparedness Framework, Report by the Director General. Geneva: World Health Organization; 2016 (EB140/16 (http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_16-en.pdf, accessed 14 May 2018)), p.13

[2] Pandemic Influenza Preparedness Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/resources/pip_framework/en/, accessed on 15 May 2018), section 4.1.

STRUCTURE OF THE ANALYSIS

8. Further to decision WHA70(10), this Analysis relies on the 2016 PIP Framework Review Group and the expertise of the PIP Advisory Group, and transparent consultation of Member States and relevant stakeholders, including GISRS.[3] A scoping paper, circulated and discussed in October and November of 2017, provided an annotated outline of the Analysis, including scope and preliminary considerations.[4] Further information on the methodology to develop the Analysis can be found in Annex 4.

9. Based on the feedback received at those consultations, the WHO Secretariat has developed the Analysis to have the following structure:

   a. Matters with overarching implications to the Analysis;

   b. Seasonal influenza in the context of the PIP Framework;

   c. GSD in the context of the PIP Framework; and,

   d. Relevant annexes.

10. In response to Member State request and to ensure that the Analysis is as useful as possible, fact sheets (and an accompanying Guide to the Fact Sheets) on a number of relevant topics that are mentioned in the Analysis have been developed and can be found at http://www.who.int/influenza/pip/Documents_WHA70108b/en/. These include:

    a. Purpose of the Analysis

    b. Process for amending the PIP Framework

    c. Biosafety and biosecurity

    d. Nagoya Protocol and public health

    e. WHO Global Influenza Surveillance and Response System (GISRS)

    f. Genetic sequence data and databases

    g. New technologies using genetic sequence data

11. The following are important considerations to this Analysis:

    a. This Analysis presents potential implications of possible approaches to seasonal influenza and GSD under the PIP Framework. It does not endorse a particular approach.

    b. The Analysis focuses on the most salient approaches and relevant potential implications. While it is as comprehensive as possible, other approaches may exist. In addition, while every effort was made to consider the breadth of implications, additional implications may exist. Finally, certain approaches may have broader implications that are not discussed in this Analysis.

    c. There are in some cases important interrelationships between the handling of IVPP GSD and seasonal influenza viruses. For example, the approach taken to the handling of IVPP GSD could potentially apply to GSD from seasonal influenza viruses if seasonal influenza viruses are included in the scope of the PIP Framework. The approaches presented below should be considered in light of these interrelationships.

    d. The Seventieth World Health Assembly in May 2017 "reaffirm[ed] the importance of the PIP Framework in addressing present or imminent threats to human health from influenza viruses with pandemic potential, and emphasize[d] its critical function as a specialized international instrument that facilitates expeditious access to influenza viruses of human pandemic potential, risk analysis and the expeditious, fair and equitable sharing of vaccines and other benefits"[5].

[3] Agenda item 12.5. Review of the Pandemic Influenza Preparedness Framework. Geneva: World Health Organization; 2017 (WHA70.10; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70(10)-en.pdf, accessed on 13 May 2018)
[4] Scoping Paper on approaches to seasonal influenza and genetic sequence data under the PIP Framework ("Scoping paper"). Geneva: World Health Organization; 2017 (WHA70.10; http://www.who.int/influenza/pip/scopingpaper.pdf, accessed on 13 May 2018)
[5] Agenda item 12.5. Review of the Pandemic Influenza Preparedness Framework. Geneva: World Health Organization; 2017 (WHA70.10; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70(10)-en.pdf, accessed on 13 May 2018)

e. There is great uncertainty about the outcomes of processes within the Convention on Biological Diversity and the Nagoya Protocol.

f. WHO is the leading authority on public health and considers leadership on issues related to the public health implications of the Nagoya Protocol to be of paramount importance. WHO will continue to engage with relevant organizations and processes related to access and benefit-sharing for pathogens in order to ensure the best possible outcomes for public health.

MATTERS WITH OVERARCHING IMPLICATIONS TO THE ANALYSIS

12. In this section, an overview is given of three matters that have overarching implications to the Analysis, both in the context of seasonal influenza and GSD: (1) The WHO Global Influenza Surveillance and Response System (GISRS); (2) new technologies; and (3) the Nagoya Protocol to the Convention on Biological Diversity.

The WHO Global Influenza Surveillance and Response System

13. Global influenza surveillance has been conducted through WHO's Global Influenza Surveillance and Response System (GISRS) for over 65 years. Formerly known as the Global Influenza Surveillance Network, GISRS currently comprises institutions in 114 WHO Member States. GISRS conducts year-round surveillance of seasonal, pandemic, and zoonotic influenza viruses and monitors virus evolution. A critical role of GISRS is providing a recommendation for the composition of seasonal influenza vaccines twice a year and the development of candidate vaccine viruses suitable for vaccine production and potency reagents, all of which depend on the rapid and unhindered sharing of seasonal influenza viruses for full characterization. In addition, GISRS provides recommendations in areas including laboratory diagnostics, antiviral susceptibility, and risk assessment. GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential.

14. GISRS comprises four different types of laboratories: National Influenza Centres (NICs), WHO Collaborating Centres (WHO CCs), WHO Essential Regulatory Laboratories (WHO ERLs), and WHO H5 Reference Laboratories, all of which operate under WHO Terms of Reference (TORs). Efficient influenza virus surveillance, pandemic risk assessment, and effective responses to seasonal influenza and influenza viruses with pandemic potential are based on collective efforts from all WHO GISRS members through rapid exchange of biological materials, reference reagents, epidemiological data, and other information. Below are descriptions of the roles and responsibilities of each type of laboratory part of GISRS:

a. National Influenza Centres (NICs) - NICs are designated by Member States and are recognized by WHO as being on the frontlines of surveillance and monitoring of influenza viruses. They collect and process more than 3 million clinical specimens globally every year and act as the reference laboratory in their country. They perform laboratory diagnosis and analysis, and ship in a timely manner, specimens or viruses to a WHO CC or H5 Reference Laboratory for advanced virological analysis. NICs play a key role in pandemic influenza risk assessment by alerting WHO to cases or outbreaks of novel influenza viruses with pandemic potential.

b. WHO Collaborating Centres (WHO CCs) – WHO CCs are designated by WHO as international centres of excellence on influenza. WHO CCs conduct year-round surveillance of seasonal influenza viruses and influenza viruses with pandemic potential, including pandemic risk assessment and development of candidate vaccine viruses to provide advice, expertise, and support to Member States, policy makers, and the WHO to facilitate activities in response to risks posed by influenza viruses. The WHO CCs also support outbreak investigation, conduct comprehensive virus analyses of seasonal influenza viruses and those with pandemic potential, and play a critical decision-making role in vaccine virus selection.

c. WHO Essential Regulatory Laboratories (WHO ERLs) – WHO ERLs are designated by WHO and operate at the interface of influenza surveillance and vaccine development. ERLs are formally associated with national regulatory agencies, and have a critical role in developing, regulating, and standardizing influenza vaccine potency reagents. WHO ERLs contribute to the production of safe and effective influenza vaccines through the selection and development of candidate vaccine viruses.

d. WHO H5 Reference Laboratories – WHO H5 Reference Laboratories are designated by WHO to support the WHO GISRS in response to the emergence and spread of highly pathogenic avian influenza H5 subtype viruses. These laboratories conduct rapid detection of novel influenza viruses as well as influenza risk assessment and response by providing reliable laboratory diagnosis of influenza infection in humans, especially those suspected of being associated with avian influenza A(H5) viruses or other influenza viruses with pandemic potential.

15. GISRS laboratories work on a wide range of influenza surveillance and response activities using a full spectrum of data, including GSD. Limiting access to and use of this data would negatively impact GISRS's ability to conduct influenza surveillance, which is essential to rapid and adequate response to and control of influenza.

16. More information is provided in the fact sheet on *Global Influenza Surveillance and Response System* (GISRS), developed by the WHO Global Influenza Programme: http://www.who.int/influenza/gisrs_laboratory/updates/gisrs_one_pager/en/.

New technologies

17. Surveillance and response to influenza requires state-of-the-art technological capacities, particularly with regard to genetic analysis. As the PIP Review Group noted, "technological developments mean that GSD can increasingly provide critical supplementary information and, in some cases, substitute for physical samples during pandemic risk assessment and the development of commercial products."[6] Forward-looking approaches to handling seasonal influenza viruses and GSD in the context of the PIP Framework will thus need to consider the implications of changing technology; this is more fully discussed below in the section "The PIP Framework and Genetic Sequence Data", below.

18. More information on new technologies is also provided in the Fact Sheet on *New technologies using genetic sequence data*[7], developed as a reference document for this Analysis.

The Nagoya Protocol to the Convention on Biological Diversity

19. The Nagoya Protocol to the Convention on Biological Diversity (CBD) is a legally binding instrument that supports the implementation of the CBD's third objective of fair and equitable sharing of the benefits[8] derived from the use of genetic resources.[9] It applies to genetic resources[10] covered by the CBD and the benefits arising from the utilization of such resources. Under the Protocol, Parties may require obtaining 'prior informed consent' (PIC) and reaching 'mutually agreed terms' (MAT)[11] before genetic materials may be accessed.[12] Together, PIC and MAT provide the terms and conditions for access and utilization of the resource as well as for the sharing of benefits arising from the resource's use. These principles are referred to as 'access and benefit-sharing' or 'ABS'. Under the Nagoya Protocol, ABS is often done through bilateral agreements[13] negotiated between the requesting entity and the country of origin.

20. In January 2016, the WHO Executive Board requested that the WHO Secretariat develop a study analysing how the implementation of the Nagoya Protocol might affect the sharing of pathogens, and

[6] PIP Framework Review Group. 2016 Review of the Pandemic Influenza Preparedness Framework, Report by the Director General. Geneva: World Health Organization; 2016 (EB140/16 (http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_16-en.pdf, accessed 14 May 2018).
[7] Fact Sheet on New Technologies using genetic sequence data, Version 1, Geneva: World Health Organization; 2018. (http://www.who.int/influenza/pip/NewTech_EN_3Apr2018.pdf, accessed on 15 August 2018)
[8] See "Benefits", Annex 5: Glossary of Terms
[9] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).
[10] See "Genetic Resource", Annex 5: Glossary of Terms
[11] See "Prior Informed Consent" and "Mutually Agreed Terms", Annex 5: Glossary of Terms
[12] Whether PIC and/or MAT are required—and the nature of such PIC and/or MAT requirements—is set out in the provider country's implementing legislation.
[13] See "Bilateral Approach", Annex 5: Glossary of Terms

the potential public health implications. As detailed in the Study,[14] "the Nagoya Protocol provides a foundation, based on core principles, such as fairness and equity, for a global common approach to accessing pathogens, and sharing benefits arising from their use."[15] On the other hand, concerns have been voiced that its implementation could slow or limit pathogen sharing due to the current uncertainty regarding the Protocol's scope and implementation, the high transactional cost of concluding bilateral ABS agreements, and the potential complexity of varying domestic ABS legislation.[16] This in turn could impact the comprehensiveness and speed of risk assessment as well as research and the timely development of vaccines, diagnostics and other medical countermeasures.[17]

21. In order to address the relationship with other international instruments, the Nagoya Protocol allows other specialized international instruments that address access and benefit-sharing for specific genetic resources[18] in a manner consistent with the objectives of the CBD and the Protocol – called "Specialized International ABS Instruments" (SII)[19] – to govern access and benefit-sharing for the resources in question.

22. At the moment, there is no consensus among Nagoya Protocol Parties about what constitutes an SII. Parties to the Protocol have established a process to determine criteria and a possible procedure for recognition under the Nagoya Protocol, which is on-going.[20]

23. The Nagoya Protocol applies to genetic resources not covered by an SII. For example, if the PIP Framework were not recognized as an SII, PIP BM (which includes IVPP) would also be covered by both the Nagoya Protocol and the PIP Framework. Depending on how the Nagoya Protocol is implemented, this could lead to cumbersome ABS obligations for GISRS laboratories, influenza manufacturers, and other entities participating in the PIP Framework and pose challenges to the effective implementation of the PIP Framework.

24. If an instrument is recognized as an SII, it becomes the single international instrument governing access to the resource in question (e.g. pathogens such as influenza viruses) and the sharing of benefits arising from its use. This would address the complexity of potentially overlapping ABS obligations and increase 'legal certainty'[21] for all who share and access this resource.

25. In the meantime, some Parties have recognized SII in their national implementing legislation.[22] For instance, the "European Union Regulation on compliance measures for users from the Nagoya Protocol" recognizes the PIP Framework as such for purposes of pandemic influenza.[23] However, this recognition applies only to the jurisdiction of the Party that has recognized the SII and for the scope and purpose of the legislation. Therefore, unless all Parties make this determination, national recognition may not offer a full solution to the legal complexity and uncertainty identified above.

26. This topic was discussed at the 14th CBD COP and 3rd Nagoya Protocol COP-MOP—the governing body meetings of the CBD and the Nagoya Protocol – in November 2018. A summary of the outcomes of these meetings is contained in Annex 1.

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[14] UN Convention on Biological Diversity and Public Health. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/un-collaboration/partners/UNCBD/en/, accessed 14 May 2018)

[15] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications. Geneva: World Health Organization; 2018 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).

[16] *Ibid.* See also, Annex 5: Glossary of Terms.

[17] *Ibid.*

[18] See "Genetic resource", Annex 5: Glossary of Terms.

[19] See "Specialized international access and benefit-sharing instrument", Annex 5: Glossary of Terms.

[20] Specialized International Access and Benefit Sharing Instruments in the Context of Article 4, Paragraph 4, of the Nagoya Protocol; CBD/NP-MOP/3/L.3 (22 November 2018, https://www.cbd.int/doc/c/7a3f/b000/f7c46f51a09dc6b9e2fc95a5/np-mop-03-l-03-en.pdf). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included..

[21] See "Legal certainty", Annex 5: Glossary of Terms, below.

[22] See "ABS legislation" Annex 5: Glossary of Terms.

[23] Regulation (EU) No. 511/2014 of the European Parliament and of the Council of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union, 2014 OJ L 150.

SEASONAL INFLUENZA VIRUSES IN THE CONTEXT OF THE PIP FRAMEWORK

27. Seasonal influenza viruses circulate in humans and cause seasonal epidemics of the disease. Annually, seasonal influenza results in an estimated 3 to 5 million cases of severe illness, and about 290 000 to 650 000 respiratory deaths.[24] In contrast, IVPP are influenza viruses that circulate in animal populations and are not yet capable of sustained transmission from human to human. IVPP have the potential to cause pandemics or large outbreaks outside of the normal influenza season.

28. The PIP Framework does not apply to seasonal influenza viruses (Article 3).

The Influenza Virus Traceability Mechanism (IVTM)

29. The PIP Framework requires that PIP biological materials be tracked in real-time through an electronic system known as the Influenza Virus Traceability Mechanism (IVTM). [25] GISRS laboratories are required to record shipments in this system, which creates additional workload for GISRS laboratories—especially WHO CCs.[26] It is important to note that PIP BM make up only a small percentage of total influenza viruses shared.[27] Seasonal virus sharing is not recorded in the IVTM.

The Nagoya Protocol and seasonal influenza viruses

30. Several Parties to the Nagoya Protocol have developed legislation to regulate ABS for genetic resources under their jurisdiction. This means that an individual or entity that wishes to use seasonal influenza viruses from such a country will have to comply with that country's national ABS legislation for access and use of that virus (see Fact Sheet on the *Nagoya Protocol and Public Health*).

31. The WHO study *Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications*[28] noted that implementation of the Nagoya Protocol could entail both opportunities and challenges to seasonal influenza virus sharing.

32. The study highlighted that implementation of the Nagoya Protocol has the potential to: strengthen GISRS by raising awareness of its core principles and highlight its fundamental importance as a global public health good; promote trust and encourage more countries to share seasonal influenza viruses; and promote the equitable sharing of benefits arising from the use of seasonal influenza viruses.

33. Depending on how it is done, however, implementation of the Nagoya Protocol could also lead to certain challenges, including: legal uncertainty and lack of clarity about the scope and obligations linked to access to viruses; complexity of varying domestic access and benefit-sharing legislations; and the potential for burdensome bilateral PIC and MAT procedures[29]. For instance, each year 40 000 seasonal influenza viruses are shared within GISRS, and between GISRS and non-GISRS laboratories. Obtaining timely, individual PIC and MAT for these viruses[30] may not be possible.

34. Currently, the implementation of the Nagoya Protocol is raising challenges with the sharing of seasonal influenza viruses. The WHO Nagoya study noted that if these challenges are not addressed in the implementation of the Protocol, the result could be to potentially slow or limit influenza virus sharing and delay or hinder the development of comprehensive and effective vaccines and other medical countermeasures. [31] (See Annex 2 for more information on recent examples of challenges related to implementation of the Nagoya Protocol and seasonal influenza virus sharing.)

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[24] Influenza (Seasonal). In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)), accessed on 26 October 2018).
[25] Pandemic Influenza Preparedness Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/resources/pip_framework/en/, accessed on 15 May 2018).
[26] Review of the Pandemic Influenza Preparedness Framework (2016), Report by the Director General. Geneva: World Health Organization; 2016 (EB140/16 (http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_16-en.pdf, accessed 14 May 2018).
[27] *Ibid.* More than 40 000 seasonal influenza viruses are shared each year through GISRS.
[28] UN Convention on Biological Diversity and Public Health. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/un-collaboration/partners/UNCBD/en/, accessed 15 May 2018)
[29] See "Bilateral approach", Annex 5: Glossary of Terms
[30] Not all GISRS laboratories are located in countries that are Parties to the Nagoya Protocol.
[31] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).

GISRS and influenza virus sharing

35. GISRS, an international network of public health laboratories and institutions coordinated by WHO, is among the oldest public health partnerships between WHO and Member States. In 2010, Member States requested an estimate of the running costs of GISRS in the context of the PIP Framework negotiations. The resulting estimate was US$ 56.5 million.

36. The process to become a GISRS NIC begins with a formal request to WHO from a Ministry of Health. WHO and the country work in partnership during the designation and recognition process to ensure that the laboratory meets specific capacity standards. These standards are reflected in detailed Terms of Reference (TORs) for the laboratory's work with both seasonal influenza viruses and IVPP. The formal designation letter from the WHO Director-General to the Minister of Health requires that the Member State accept the TORs. [32]

37. Under both seasonal influenza and IVPP TORs, Member States that are members of GISRS agree to share influenza viruses with GISRS in a timely manner. This enables GISRS to take all actions necessary to ensure comprehensive risk assessment and development of effective public health response measures including, but not limited to, vaccine development. In return, Member States receive some or all of the following[33]:

Table 1. Overview of the year-round benefits provided by GISRS

Laboratory testing, analysing and monitoring	Risk assessment	Reagents and viruses	Information and knowledge	National and global capacity building
Specimen testing	Detailed virus characterization	Annually-updated, free laboratory reagent kits	Genetic sequence data (GSD)	Annual external quality assessment
Virus characterization	Risk assessment for emerging viruses	Updated reference viruses	Situation updates	Validated laboratory protocols
Situation monitoring	Risk mitigation	Updated seasonal, zoonotic and pandemic candidate vaccine viruses (CVVs)	Better understanding of influenza	Timely guidance and advice
				Training & mentoring

38. It should be noted that many of the above benefits reflect the non-monetary benefits identified in the Annex of the Nagoya Protocol.[34]

39. In the case of IVPP, the PIP Framework provides several additional measures – through the Standard Material Transfer Agreement 1 (SMTA1) and the IVTM – which provide added legal certainty[35] with respect to those viruses. In addition, under the PIP Framework, two additional benefit-sharing mechanisms have been agreed:
    - Influenza vaccine, diagnostic and pharmaceutical manufacturers that use GISRS are expected to pay an annual partnership contribution (PC); and

[32] See National Influenza Centres. In: World Health Organization [website]. (http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/en/, accessed on 16 August 2018)
[33] See Global Influenza Surveillance and Response System (GISRS), Geneva: World Health Organization; 2018. (http://www.who.int/influenza/pip/Documents_WHA70108b/en/, accessed 15 August 2018)
[34] Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (adopted 29 October 2010, entered into force 12 October 2014) UNEP/CBD/COP/DEC/X/1 Annex.
[35] See "Legal certainty", Annex 5, Glossary of Terms.

- Non-GISRS entities that receive PIP BM must conclude a legally-binding agreement, known as a Standard Material Transfer Agreement 2 (SMTA 2) with WHO. Many of these SMTAs 2 will give WHO real-time access to pandemic supplies (e.g. vaccines, antivirals, diagnostics), which will be provided to countries in need at the time of a pandemic.

Approaches to and potential implications of expanding or not expanding the PIP Framework to include seasonal influenza viruses

40. In this section, potential implications of expanding or not expanding the PIP Framework to include seasonal influenza viruses will be explored by examining the opportunities and challenges of the following approaches:
    - Approach 1: Maintain the current PIP Framework scope (maintain *status quo*)
    - Approach 2: Expand the scope of the PIP Framework to include seasonal influenza viruses
    - Approach 3: Harmonize GISRS with the Nagoya Protocol
    - Approach 4: Develop a new international ABS instrument

Approach 1: Maintain the current PIP Framework scope (maintain *status quo*)

41. An approach to addressing seasonal influenza would be to maintain the current scope of the PIP Framework, which is limited to IVPP. Under this approach. the PIP Framework would remain focused on influenza viruses with human pandemic potential and access to seasonal influenza viruses would be governed by the Nagoya Protocol's ABS regime.

Potential Opportunity

42. *Would not require re-opening the PIP Framework text*. This approach would mean that WHO Member States would not have to discuss changes the scope of the PIP Framework.

Potential Challenges

43. *Implementation of a potential 196 different national legislations*[36] *will significantly increase the workload of GISRS with seasonal viruses, and as a result slow or limit the sharing of seasonal viruses.* Nagoya Parties may have widely differing approaches to ABS for seasonal influenza viruses. Depending on each country's approach, GISRS laboratories will have to comply with many different administrative requirements or processes of provider countries (e.g. obtaining the appropriate authorization and/or agreeing to mutually agreed terms).[37] This will significantly increase the burden on GISRS and other entities that share or receive influenza viruses.[38] If insufficient resources are provided, GISRS laboratories may be overwhelmed, hampering the network's capacity to identify newly emerging influenza variants that may have the potential to cause epidemics or pandemics. The result could be a reduction in the number of seasonal influenza viruses shared, or a slowing of sharing, which could in turn delay or hinder the development of effective vaccines and other medical countermeasures.[39]

Approach 2: Expand the scope of the PIP Framework to include seasonal influenza viruses

44. Under this approach, the PIP Framework would be expanded to include seasonal influenza viruses. This could be done in one of two ways. First, seasonal influenza viruses could be added under the same terms as PIP BM, with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing, the sharing of seasonal and pandemic potential influenza viruses, and access to vaccines and sharing of other benefits.[40] Alternatively, a new section or annex to the PIP Framework could be added to address access and benefit-sharing for seasonal influenza viruses. This

[36] Since there are currently 196 CBD parties, there are potentially 196 Nagoya Protocol parties.
[37] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018); see also Annex 2, below.
[38] *Ibid.*
[39] *Ibid.*
[40] This approach would require amending the PIP Framework; for options on how to this might be done, please see the fact sheet on Process for amending the PIP Framework.

new section or annex could be tailored to the specificities of seasonal influenza. For information on how this might occur, please see the Fact Sheet on *Process for amending the PIP Framework.*

Potential Opportunity

45. *Could address challenges related to the implementation of the Nagoya Protocol for seasonal influenza viruses*. If the PIP Framework is recognized as an SII[41], this means that access and benefit-sharing for IVPP are managed under the terms of the PIP Framework and the Nagoya Protocol does not apply for these viruses.[42] The inclusion of seasonal influenza viruses in the scope of the PIP Framework, if the Framework is recognized as an SII, would likewise mean that the Nagoya Protocol does not apply to those viruses. Therefore, this approach could help to address challenges related to implementing the Nagoya Protocol for seasonal influenza, including by increasing legal certainty.[43]

Potential Challenges

46. *Impact the workload and running costs for GISRS*. Tracing seasonal influenza virus sharing through the IVTM, as required for PIP BM under the PIP Framework[44], could—were such an approach to be taken—significantly increase the volume of data entry work and lead to a substantial increase in workload for GISRS laboratories. Based on the number of viruses shared in previous years, GISRS estimates that tracing the sharing of seasonal influenza viruses could increase the network's workload 100-fold as compared with the current system of tracing IVPP alone.[45] In addition, including seasonal influenza viruses in the scope of the PIP Framework would require putting in place additional procedures, such as those linked to benefit sharing, that could further increase the complexity of implementing such a system. Without a proportional increase in resources, this will overwhelm GISRS and adversely affect the timeliness and effectiveness of GISRS.[46] This could impact laboratories' capacity to share influenza viruses in a timely manner.[47] The result could be that the best candidate vaccine viruses are not available to manufacturers in time for vaccine production. This, in turn, could result in less effective vaccines and an increased burden of disease in countries that use influenza vaccines.

47. *Certain mechanisms of the PIP Framework are tailored to the pandemic context, rather than seasonal influenza and would need to be reconceptualised for the specificities of seasonal influenza*. Certain components of the Framework are specific to the pandemic context. For instance, an entity that signs a SMTA 2 agrees to share certain benefits in the case of a pandemic.[48] Were the PIP Framework to be expanded to include seasonal influenza viruses, consideration would need to be given to adapting these benefit-sharing mechanisms for operation in both the seasonal and pandemic contexts.

48. *Could require complex negotiations*. Reopening the text of the PIP Framework or adding a new benefit-sharing mechanism could be complex and require negotiations among WHO Member States, industry and stakeholders.

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[41] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).

[42] Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (adopted 29 October 2010, entered into force 12 October 2014) UNEP/CBD/COP/DEC/X/1 Article 4(4); https://www.cbd.int/doc/c/7a3f/b000/f7c46f51a09dc6b9e2fc95a5/np-mop-03-l-03-en.pdf, paragraph 6

[43] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).

[44] Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (http://www.who.int/influenza/resources/pip_framework/en/, accessed on 15 May 2018).

[45] The Inclusion of Seasonal Influenza Viruses and Genetic Sequence Data (GSD) in the Context of the Pandemic Influenza Preparedness (PIP) Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/resources/pip_framework/en/, accessed on 15 May 2018).

[46] *Ibid.*

[47] *Ibid.*

[48] Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (http://www.who.int/influenza/resources/pip_framework/en/, accessed on 15 May 2018). See also, SMTA2: Signed Agreements and benefits. In: World Health Organization [website]. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/pip/benefit_sharing/smta2_signed/en/, accessed on 15 August 2018).

Approach 3: Harmonize GISRS with the Nagoya Protocol

49. The Nagoya Protocol offers several mechanisms to address ABS for seasonal influenza while protecting public health.

(a) Adapt GISRS to be an international instrument with a view to its recognition as an SII under the Nagoya Protocol.[49] This would likely require formalizing the network's structure and practices[50] and adapting them to ensure consistency with the objectives of the CBD and the Nagoya Protocol. This formalization could take different forms and could potentially require going through an intergovernmental process in order for GISRS to be recognized as an SII.[51]

(b) Explore other Nagoya Protocol mechanisms such as:

i. Article 8(b): measures that pay due regard to cases of present or imminent emergencies that threaten or damage human, animal or plant health;

ii. Article 10: Global multilateral benefit-sharing mechanism; and

iii. Article 20: Codes of conduct, guidelines, best practices and/or standards.

50. Another option would be for Nagoya Parties to formally recognize that the current access and benefit-sharing approach to seasonal influenza under GISRS is consistent with the Nagoya Protocol (e.g. PIC and MAT principles) and their country's implementing legislation or measures.

51. Finally, Parties to the Nagoya Protocol could choose to waive PIC and/or MAT obligations for seasonal influenza viruses.

Potential Opportunities

52. *Could address implications of the Nagoya Protocol*. If GISRS, adapted as per above, was designated as a SII, it would govern access and benefit-sharing for seasonal influenza viruses.[52] This would avoid the challenges identified under Approach 1 (above). Another mechanism, such as a code of conduct (Article 20) or a global multilateral mechanism (Article 10) could provide a multilateral approach to ABS for seasonal influenza.

53. *Could increase resources for seasonal influenza prevention and control*. Harmonizing GISRS with the Nagoya Protocol could result in increased resources for seasonal influenza. In addition to the ones listed in Table 1, new monetary or non-monetary benefits supportive of seasonal influenza prevention and control could be implemented, notably from entities that are not part of GISRS. These benefits could include, e.g.: sharing of research and development results; collaboration, cooperation in and contribution to scientific research and development programmes, particularly in biotechnological research activities; technology transfer; and capacity-building.[53] This could, in turn, boost countries' preparedness and response capacities.[54]

54. *Would be tailored to the seasonal influenza context*. Unlike under Approach 2, the adapted GISRS instrument would address the specificities of seasonal influenza.

55. *Builds on an already functioning ABS system.* GISRS is a successful ABS system that has existed for more than 65 years. Member States that participate in GISRS agree to share their viruses through

[49] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).
[50] *Ibid*, p.25 "[…] some suggested recognition of GISRS itself as an Article 4.4 specialised international instrument, pointing to the provision of risk assessment and laboratory products (such as CVVs) as benefits generated by the network".
[51] See Specialized international access and benefit-sharing instruments in the context of Article 4, paragraph 4, of the Nagoya Protocol, Recommendation adopted by the Subsidiary Body on Implementation (adopted on 13 July 2018), CBD/SBI/REC/2/5) (https://www.cbd.int/doc/recommendations/sbi-02/sbi-02-rec-05-en.pdf, accessed on 15 August 2018)
[52] *Ibid.*
[53] The Nagoya Protocol contains a non-exhaustive list of monetary or non-monetary benefits that could be explored. See Nagoya Protocol Annex.
[54] The ten years of the Global Action Plan for Influenza Vaccines. Report to the Director-General from the GAP Advisory Group. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/GAP_AG_report_to_WHO_DG.pdf, accessed on 17 May 2018).

GISRS and in exchange receive many important benefits that support influenza surveillance, preparedness and response (as listed above in Table 1).

Potential Challenges

56. *May not take into account linkages between seasonal and pandemic influenza.* As found by the PIP Review Group, there are numerous linkages between preparedness and response activities for seasonal influenza viruses and IVPP.[55] There are also a number of linkages between seasonal and pandemic influenza in the PIP Framework, despite the fact that seasonal influenza viruses are outside its scope. For example, many pandemic influenza preparedness activities implemented through the Partnership Contribution rely on building capacity to respond to seasonal influenza. Moreover, both seasonal and pandemic influenza viruses are shared through the same network, GISRS. An approach in which two separate ABS instruments were to cover influenza may result in some duplication, and in less efficiency and coherence. Thus, attention would have to be given to harmonizing the relationship between them.

57. *Could increase complexity*. If a separate approach was taken for seasonal influenza, this would result in two different sets of rules and associated administrative burdens for handling seasonal and pandemic influenza viruses.

58. *The way the PIP Framework Partnership Contribution is operationalized may need to change*. While seasonal influenza viruses are outside the scope of the PIP Framework, seasonal influenza product sales are already used in calculating the PIP PC.[56] Depending on the benefit-sharing arrangements in the new instrument, it may be necessary to change the way the PIP PC is calculated to avoid overlapping benefit-sharing obligations. This could potentially impact PIP Framework implementation.

59. *Would require international consultations, including, potentially, a process to formalize or adapt GISRS*. Although public health mechanisms under the Nagoya Protocol could facilitate ABS for seasonal influenza, exploring such mechanisms would require significant international consultations, including within governments, across relevant ministries, and with other sectors involved in the implementation of the Nagoya Protocol. For example, implementing Articles 4.4 and 20 could require developing terms of reference for the GISRS network as a whole[57], and securing Member State adoption or agreement to those terms of reference. This process may require identifying and codifying benefit-sharing within GISRS. Because GISRS does not currently establish benefit-sharing expectations for sharing of seasonal influenza viruses outside of the network, this formalization or adaptation process may also require the negotiation of new benefit-sharing for non-GISRS entities.

Approach 4: Develop a new international ABS instrument

60. Another approach could be to develop a new instrument to address benefit-sharing.[58] Such an instrument could cover influenza viruses or a broader set of pathogens.

[55] Review of the Pandemic Influenza Preparedness Framework (2016), Report by the Director General. Geneva: World Health Organization; 2016 (EB140/16 (http://apps.who.int/gb/ebwha/pdf_files/EB140/B140_16-en.pdf), accessed 14 May 2018), Section 3.2.1.

[56] Pandemic Influenza Preparedness Framework: Distribution of Partnership Contribution among companies. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/pc_distribution.pdf, accessed on 15 May 2018).

[57] Currently, there are terms of reference for each category of GISRS laboratory, not for the whole network. See Terms of Reference for National Influenza Centers at http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/en/; Terms of reference for each WHO Collaborating Center and Essential Regulatory Laboratory at http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/; Terms of reference for WHO H5 reference laboratories at http://www.who.int/influenza/gisrs_laboratory/h5_reflabs/torh5reflab2006.pdf?ua=1;

[58] Facilitating Access and Benefit Sharing (ABS) for Pathogens to Support Public Health, Workshop Report. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/ABS_Workshop_Report_7Sep_hyperlinks.pdf, WHO/WHE/IHM/PIP2018.4).

61. This could be developed with a view to the instrument being recognized as an SII under the Nagoya Protocol.[59] Again, as discussions on this issue are still ongoing, it is not clear yet what form such an instrument should take (e.g. legally-binding or not, adopted through an intergovernmental process or not). This instrument however would need to be consistent with article 4(4) of the Protocol, which states that an SII must be "consistent with, and […] not run counter to the objectives of the [CBD] and [the Nagoya] Protocol".

Approach 4a: Develop a new international ABS instrument to cover all influenza viruses

62. One option would be for such a new international ABS instrument to be developed to cover all influenza viruses.

Potential opportunities

63. *Could address challenges related to the implementation of the Nagoya Protocol for seasonal influenza viruses.* If it was designated as an SII, this new instrument would govern access and benefit-sharing for both seasonal and pandemic influenza viruses.[60]

64. *Could be tailored to the specific needs of influenza.* Such a new instrument could be tailored to the influenza context and take into account the interlinkages between seasonal influenza and IVPP. It could allow for a harmonized approach to access and benefit-sharing for all influenza viruses.

Potential challenges

65. *Could be complex to negotiate.* Developing a new instrument would be technically complex, require input from a wide range of stakeholders, and potentially take substantial time.

66. *Would require addressing the status of the PIP Framework.* If a new instrument is developed for all influenza viruses, the status of the PIP Framework to this instrument would have to be considered, i.e whether the PIP Framework would fall under its umbrella or whether the instrument would replace the PIP Framework.

Approach 4b: Develop a new international ABS instrument to cover a broader set of pathogens affecting human health

67. Another option would be for a new international ABS instrument to cover a broader set of pathogens. For example, it could cover pathogens with human epidemic and pandemic potential, and those that are reportable under the International Health Regulations (2005).

68. Given that the pathogens included under the scope of this instrument would have different features (including different counter-measures, and product development processes), this new instrument could be developed as a high-level framework with sub-sections addressing the specificities of different pathogens.

Potential opportunity

69. *Avoid potential duplication or complexity of multiple international regimes.* Developing a new instrument to cover a broader range of pathogens could allow addressing the potential public health implications of the Nagoya Protocol more broadly.[61] This could reduce the legal complexity and administrative burden on entities that access a broader set of pathogens than influenza viruses while at the same time ensuring benefit-sharing.

Potential challenges

70. C*omplex to negotiate.* Developing a new instrument for benefit sharing would be technically complex, require input from a wide range of stakeholders, and potentially take substantial time.

[59] Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (adopted 29 October 2010, entered into force 12 October 2014) UNEP/CBD/COP/DEC/X/1 Article 4(4)
[60] *Ibid.*
[61] Facilitating Access and Benefit Sharing (ABS) for Pathogens to Support Public Health, Workshop Report. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/ABS_Workshop_Report_7Sep_hyperlinks.pdf, WHO/WHE/IHM/PIP2018.4).

GENETIC SEQUENCE DATA IN THE CONTEXT OF THE PIP FRAMEWORK

71. This section of the Analysis responds to the PIP Review Group recommendation that the WHO Director-General request Member States to consider amending the definition of PIP BM in section 4.1 of the PIP Framework to include GSD (recommendation 12). This section first provides background on IVPP GSD and the PIP Framework, and an overview of how recent developments within the CBD and the Nagoya Protocol may potentially impact the sharing of IVPP GSD. Second, it examines the potential implications of amending or not the definition of PIP BM to include IVPP GSD.

Genetic sequence data

72. The PIP Framework defines genetic sequences as follows:

> the order of nucleotides found in a molecule of DNA or RNA. They contain the genetic information that determines the biological characteristics of an organism or a virus. [PIP Framework, section 4.2] [62]

73. GSD can be used to conduct analyses or used to synthesize physical material to develop influenza products. However, in many ways GSD differ significantly from physical virus materials. For instance, like other types of information, GSD can be shared and moved electronically. In contrast, physical materials are shipped by carriers from one laboratory to the other. This difference makes it significantly easier to share GSD than materials. Moreover, there are many more IVPP sequences shared among many more users of GSD than recipients of PIP BM.

74. GSD is essential to both the work of GISRS and the development of influenza products. For more information on the product development process, please refer to the Fact Sheet on New Technologies available at: http://www.who.int/influenza/pip/NewTech_EN_3Apr2018-2.pdf?ua=1.

The PIP Framework and genetic sequence data

75. The PIP Framework is predicated on the foundational principle that sharing IVPPs should be placed on an equal footing with sharing the benefits arising from such sharing. While Member States did not explicitly extend this principle to GSD under the PIP Framework, recognizing instead that further work and analysis would be needed,[63] the PIP Framework did establish some principles for GSD, including the expectation that GSD will be shared in "a rapid, timely and systematic manner with the originating laboratory and among GISRS laboratories". It also "recogniz[es] that greater transparency and access concerning influenza virus genetic sequence data is important to public health and [that] there is a movement towards the use of public-domain or public-access databases such as Genbank and GISAID respectively" (Section 5.2.2).

76. IVPP GSD are included under the PIP Framework, but not in the definition of PIP BM. Under the Framework, benefit sharing for IVPP GSD is therefore handled differently than benefit sharing for physical viruses, such as wild-type viruses or candidate vaccines viruses. Indeed, while access to physical viruses ("PIP BM") requires signing an SMTA 2 and is linked to payment of the Partnership Contribution, access to IVPP GSD is only linked to payment of Partnership Contribution (see table 2 below).

77. This different treatment for PIP BM and IVPP GSD can be described as follows:

    a. Conclusion of an SMTA 2 with WHO is linked to receipt of PIP BM. Because IVPP GSD is not included in the definition of PIP BM, receipt of IVPP GSD does not trigger the obligation to conclude an SMTA 2 with WHO.

[62] Fact Sheet on Genetic Sequence Data and databases. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/pip/GSD_EN_V2_10Sep2018.pdf?ua=1, accessed on 14 December 2018)

[63] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (http://www.who.int/influenza/pip/en/, accessed 15 May 2018), Section 5.2.4

b. Use of IVPP GSD is considered "use of GISRS" in the context of the Partnership Contribution.[64] Influenza manufacturers that have used IVPP GSD produced by GISRS to develop, test or produce a licensed product to prevent, treat or diagnose infections from influenza viruses with human pandemic potential are expected to contribute an annual Partnership Contribution payment.

Table 2. Benefit sharing for PIP BM and IVPP GSD under the PIP Framework

	Partnership Contribution (PC)	SMTA 2
PIP BM	**Yes**	**Yes**
IVPP GSD	**Yes**	**No**

78. The difference in the way PIP BM and IVPP GSD are treated under the PIP Framework creates a potential benefit-sharing "loophole". Manufacturers that have never received a shipment of PIP BM and use IVPP GSD to develop a pandemic influenza product would be expected to pay the Partnership Contribution but would not have to share such product with WHO in the event of a pandemic. See Table 3 below, which provides an overview of the different benefits shared for access to PIP BM versus IVPP GSD.

79. All current major influenza vaccine manufacturers have signed SMTA 2s with WHO. These agreements would remain valid even if future vaccines were to be developed by these manufacturers using IVPP GSD only. Therefore, in case of a pandemic, WHO would have access to the vaccines developed by these manufacturers regardless of whether PIP BM or IVPP GSD were used in their development. In addition, almost all influenza vaccine production technologies currently require access to PIP BM at some point during the development, production or licensing process, notably for verification. Therefore, manufacturers that use such technologies need to access PIP BM.[65] In certain instances however, manufacturers engage other laboratories to conduct these activities and do not access PIP BM themselves. For more information on indirect use of PIP BM, please refer to Annex 3, *Benefit Sharing under the PIP Framework* and the 17-19 October 2018 PIP Advisory Group *Report to the Director-General*[66].

80. As technologies mature and reliance on IVPP GSD increases, physical material may no longer be necessary to conduct the activities described above. As new influenza manufacturers enter the market, this "loophole" may reduce WHO's access to certain benefits and potentially jeopardize PIP Framework implementation.

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[64] To determine implementation of the Partnership Contribution, WHO worked with industry partners and consulted with the Advisory Group to develop the concept of "using the WHO GISRS". It was decided that the scope of the PC should be broader than SMTA2 and include information, such as genetic sequence data. See PIP Partnership Contribution Questionnaire, available at: http://www.who.int/influenza/pip/pc_questionnaire/en/

"Use of GISRS" means your company/institution used or received:

- materials (e.g. virus materials, such as candidate vaccine viruses, wild-type viruses, cDNA, plasmids, or reagents); and/or
- services (e.g. antigenic and genetic characterization of candidate vaccine viruses/seed material, antiviral susceptibility assays); and/or
- **information (e.g. sequence information,** epidemiological data, antiviral susceptibility data, pre- and post-vaccine composition meeting reports); developed and/or provided by or through GISRS."

See also Pandemic Influenza Preparedness Framework: Distribution of Partnership Contribution among companies. In: World Health Organization [website]. Geneva: World Health Organization; 2013(http://www.who.int/influenza/pip/pc_distribution.pdf?ua=1 , accessed 18 May, 2018: "Data, information and analyses include virus characterization, sequence information, results of viral sensitivity tests as well as epidemiological patterns. Such materials and information have been and/or are currently used by manufacturing entities in many ways, including developing, testing, producing or marketing products. "Use of GISRS" is therefore understood to include receipt of physical materials, or use of data and/or information […]."

[65] This may be different for manufacturers of diagnostics or antivirals, who rely more on the use of data than on physical virus material to develop their products.

[66] Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 17-19 October 2018. Report to the Director-General. Geneva: World Health Organization; 2018 (available at https://www.who.int/influenza/pip/AGMR_Oct2018.pdf)

81. More information can be found in Annex 3 on *Benefit Sharing under the PIP Framework* and the Fact Sheet on *New Technologies using genetic sequence data*.

Table 3. Overview of benefits shared under the PIP Framework for PIP BM versus IVPP GSD

PIP BM	IVPP GSD
• Annual Partnership Contribution to WHO for strengthening influenza pandemic preparedness and response (see PIPF section 6.14.3)	• Annual Partnership Contribution to WHO for strengthening influenza pandemic preparedness and response (see PIPF section 6.14.3)
• Pandemic influenza response products (vaccines, diagnostics, antivirals); • Licenses to technology, know-how, processes or products needed for the production of influenza vaccines, antivirals, adjuvants; • Royalty-free license to developing country manufacturers or WHO; • Support laboratory and surveillance capacity building in developing countries (see PIPF Annex 2, Article 4)	

Equitable benefit sharing among users of genetic sequence data

82. Informing users that, if they choose to access or use IVPP GSD, they will be expected to participate in some form of benefit sharing is important for two reasons: first, it promotes the principle of equal footing that is at the core of the PIP Framework; and second it enables an entity such as WHO to approach users of GSD, as appropriate, for benefit sharing. For PIP BM, the issue is handled at the time a potential recipient requests a PIP BM from a GISRS laboratory. A Notice is included in the shipping documents, alerting the recipient that by accepting the materials it accepts to be contacted by WHO for SMTA2 and Partnership Contribution. Such notice will be far more complicated for GSD, given the many public and private ways that GSD may be shared.[67] The issue of notice creates an overarching complexity for benefit sharing from use of GSD. The document "*Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products*"[68] developed as part of the PIP Advisory Group's work on GSD, sets out options for providing such notice to users of GSD.

PIP Framework Advisory Group's work on genetic sequence data

83. The issues around the handling of IVPP GSD were discussed during PIP Framework negotiations. Recognizing that further work would be needed to resolve these issues, Member States requested that the Director-General consult with the PIP Advisory Group "on the best process for further discussion and resolution of issues relating to the handling of [IVPP GSD] as part of the PIP Framework."[69]

[67] In addition, the issue of notice can become challenging when aggregate data (generated from a large number of sequences) is used.

[68] Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/gsdoptionspaper_revised.pdf, (http://www.who.int/influenza/pip/advisory_group/gsdoptionspaper_revised.pdf, accessed on 15 August 2018)

[69] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (https://www.who.int/influenza/resources/pip_framework/en/, accessed 15 May 2018), Section 5.2.4

84. Since 2013 the PIP Advisory Group has been working to develop this guidance. To support its work, it established two technical working groups, and held several consultations with relevant stakeholders, all of which provided the bases for several recommendations to the Director-General.

85. Some of the main findings of the Advisory Group are as follows:

    a. In accordance with the fundamental principles of the PIP Framework, access to GSD and the sharing of benefits derived from their use are of equal importance. Thus, the sharing of GSD from influenza viruses with human pandemic potential should reflect the PIP Framework's fundamental objective of maintaining ABS on an equal footing.

    b. Due to technological development, the sharing of GSD is now as important as the sharing of virus material. GSD plays a critical role in influenza virus information sharing and it is likely that this role will further expand as technology advances. Strengthening and maintaining the rapid access to GSD is a priority to strengthen and enhance pandemic influenza preparedness.

    c. Four principles should be observed in connection with GSD and public health. There should be:

        1) Rapid sharing of high-quality GSD for timely risk assessment & response

        2) Sustainable, public access to IVPP GSD

        3) Fair and equitable sharing of benefits arising from the sharing of GSD

        4) Acknowledgement of data providers and active collaboration between data providers and users

    d. In cases where use of GSD directly leads to commercial products without the use of PIP Biological Materials, a potential process to address benefit sharing could include:

        1) The use of databases that enable identification of the GSD provider and flag the sequence as 'IVPP GSD';

        2) The use or development of appropriate data access agreements or identification of IVPP GSD as subject to certain terms and conditions for use;

        3) The development of a search engine to identify end-products developed using GSD.[70]

Discussions related to genetic sequence data in other fora

Discussions under the Convention on Biological Diversity and the Nagoya Protocol

86. The growing reliance on GSD for advancing knowledge or developing products, is not limited to public health. Other sectors are seeing similar trends, with related potential implications for access and benefit-sharing. In the context of CBD and its Nagoya Protocol, there are ongoing processes to examine these implications. The following section provides an overview of discussions and examines their relevance to this Analysis.

87. Parties to the CBD and Nagoya Protocol have established a process to consider the implications that the use of digital sequence information (DSI)[71] might have on the objectives of these treaties. In particular, Parties are currently considering whether or not digital sequence information (DSI) is or should be included in the scope of the Nagoya Protocol and subject to the same requirements as "physical" genetic resources[72]—and the implications of such inclusion.

88. The term "digital sequence information" is not defined in the CBD or the Nagoya Protocol. Views on the scope of the term vary widely: for example, certain Parties consider that DSI is limited to gene

[70] Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 8-10 November 2017. Report to the Director-General. Geneva: World Health Organization; 2017 (http://www.who.int/influenza/pip/AG_Nov2017.pdf, accessed on 15 August 2018)

[71] Parties to the CBD and Nagoya Protocol have not yet agreed on a definition of DSI. However, it generally refers to information associated to genetic sequencing. Genetic Sequence Data and Digital Sequence Information are sometimes used interchangeably.

[72] See "Genetic Resource", Annex 5: Glossary of Terms

sequences or whole genome sequences (e.g. sequences of RNA or DNA that form hereditary materials), while others believe that the term is much broader and include information associated with a genetic resource, such as information related to taxonomy or behavioural data.[73] The process established by the Parties will consider the concept and scope of DSI.

89. Parties' views on the status of DSI under the CBD and the Nagoya Protocol also vary widely.[74] Some Parties are of the view that DSI is not included in the scope of these instruments. Others believe that DSI is already included in the scope. As a result, these Parties believe that each Party can decide, through its national legislation, whether and how to regulate access and benefit-sharing for DSI.[75]

90. Some Parties consider that sequencing a genetic resource constitutes "utilization of genetic resources"[76], with DSI a product of such utilization. Under this view, a Party could regulate ABS for DSI through the same legal processes used for accessing physical genetic resources. Legal requirements can involve, for example, ensuring that mutually agreed terms (MAT) contain terms on publication of DSI and/or the use of DSI for commercial purposes.

91. Other Parties consider that DSI obtained from a genetic resource are another form of the genetic resource, meaning that DSI should be subject to their own PIC and MAT process. Under this view, ABS for DSI may require authorization to access and/or use DSI, a traceability mechanism, and benefit-sharing.

92. Consequently, Parties may potentially develop their own domestic bilateral approach[77] to access and benefit-sharing for DSI. This could result in a patchwork of different legislation and measures covering the sharing of DSI, including influenza GSD. The CBD Ad Hoc Technical Expert Group (AHTEG) on DSI found that "[a] multiplicity of national approaches to ABS relating to DSI may create cumbersome processes, and could lead to access restrictions, or to 'jurisdiction shopping'. […]".[78] In the context of influenza, access restrictions and jurisdiction shopping could potentially impact the timeliness and quality of risk assessments and/or the comprehensiveness of influenza

[73] Secretariat of the Convention on Biological Diversity, Synthesis of views and information on the potential implications of the use of digital sequence information on genetic resources for the three objectives of the Convention and the objective of the Nagoya Protocol. Montreal: Secretariat of the Convention on Biological Diversity; 2018 (https://www.cbd.int/doc/c/06dc/df41/cbbe0ff3d861dc4e45953973/dsi-ahteg-2018-01-02-en.pdf, accessed 17 May 2018); Report of the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources. Montreal, Canada; Secretariat 2018 (https://www.cbd.int/doc/c/4f53/a660/20273cadac313787b058a7b6/dsi-ahteg-2018-01-04-en.pdf , accessed 17 May, 2018); Digital Sequence Information on Genetic Resources; CBD/COP/14/L.36, paragraph 6 (29 November 2018, https://www.cbd.int/doc/c/1060/5367/b3ecb2f5ddea7ba9d154cc1d/cop-14-l-36-en.pdf). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included.

[74] Secretariat of the Convention on Biological Diversity, Synthesis of views and information on the potential implications of the use of digital sequence information on genetic resources for the three objectives of the Convention and the objective of the Nagoya Protocol. Montreal: Secretariat of the Convention on Biological Diversity; 2018 (https://www.cbd.int/doc/c/06dc/df41/cbbe0ff3d861dc4e45953973/dsi-ahteg-2018-01-02-en.pdf, accessed 17 May 2018); Digital Sequence Information on Genetic Resources; CBD/COP/14/L.36, paragraph 5 (29 November 2018, https://www.cbd.int/doc/c/1060/5367/b3ecb2f5ddea7ba9d154cc1d/cop-14-l-36-en.pdf).

[75] *Ibid.* See also for example: Brazil's Biodiversity Law 13,123/2015 provides that research utilizing GSD from genetic resources is to be carried out freely. Users of GSD must register at the time of publication of the results, or upon application for a patent, or before introduction of a product on the market. (see for further information, Ministry of Foreign Affairs of Brazil – Environment Division, Digital Sequence Information, as part of Submissions from Parties, other Governments, relevant organizations and stakeholders, views and relevant information to the Executive Secretary on any potential implications of the use of digital sequence information on genetic resources for the three objectives of the Convention, 2017, https://www.cbd.int/abs/DSI-views/Brazil-DSI.pdf, accessed 15 August 2018)

[76] See Government of Switzerland Submission in response to CBD Notification 2017-037 - Digital Sequence Information on Genetic Resources, 2017 (https://www.cbd.int/abs/DSI-views/Switzerland-DSI.pdf, accessed on 15 August 2018): "The specific conditions under which a particular genetic resource can be utilized, can be negotiated and defined in the mutually agreed terms (MAT) between the provider country and the user. This contract may also include provisions regarding digital sequence information resulting from the utilization of the particular genetic resource (e.g. provisions concerning the publication of digital sequence information on the genetic resource)."

[77] See "Bilateral Approach", Annex 5: Glossary of Terms.

[78] Report of the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources. Montreal, Canada; Secretariat 2018 (https://www.cbd.int/doc/c/4f53/a660/20273cadac313787b058a7b6/dsi-ahteg-2018-01-04-en.pdf , accessed 17 May, 2018). The AHTEG consider the Fact-Finding and Scoping Study on Digital Sequence Information on Genetic Resources in the Context of the Convention on Biological Diversity and the Nagoya Protocol, commissioned by the CBD Secretariat. The study is available at https://www.cbd.int/doc/c/079f/2dc5/2d20217d1cdacac787524d8e/dsi-ahteg-2018-01-03-en.pdf.

vaccines if laboratories are unable to rapidly access GSD from influenza viruses originating from certain countries.

93. Discussing issues related to this potential multiplicity of legal regimes, the AHTEG highlighted: "a multilateral approach for DSI could provide an alternative to requirements for prior informed consent and mutually agreed terms and therefore help to reduce transaction costs and facilitate equitable sharing of benefits." [79] In the context of influenza, a multilateral approach is more likely to support the global sharing of GSD.[80]

94. WHO provided comments as part of this process. The comments affirm that "DSI from pathogens is a global public health good that should benefit all" and highlight principles that WHO believes should govern DSI sharing.[81] These principles include:

    a. Supporting the rapid and broad sharing of DSI, and ensuring that countries in need have fair and equitable access to diagnostics, therapeutics and vaccines, as well as other technologies and information derived from their use;

    b. Promoting benefit-sharing without delaying the sharing of DSI;

    c. Creating clarity and transparency at the country-level, including fair and non-arbitrary rules as well as clear and expeditious processes for access and benefit-sharing to assist public health institutions and laboratories in carrying out their important work; and

    d. Reducing the administrative and financial burden on laboratories sharing and accessing DSI and on the databases that host the data.[82]

95. At the November 2018 CBD COP and Nagoya Protocol COP-MOP, Parties continued discussions on DSI and requested the development of four peer-reviewed studies on: (1) the concept of DSI; (2) the field of traceability; (3) DSI databases; and (4) domestic benefit-sharing measures.[83] They also established an extended AHTEG to, *inter alia*, develop options for operational terms and identify key areas for capacity-building.[84] The outcomes of the extended AHTEG will be considered by the open-ended intersessional working group established under the COP decision on the post-2020 biodiversity framework.[85] This open-ended working group is expected to make recommendations to the 15th CBD COP on how to address DSI in the context of the post-2020 global biodiversity framework.[86] Further detail on these discussions can be found in Annex 1.

Discussions under the FAO International Treaty on Plant Genetic Resources for Food and Agriculture

96. Related discussions are also taking place within the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA). WHO reached out to the Secretariat of the ITPGRFA, who provided the following text:

    - In 2013, the Governing Body of the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) established an intergovernmental process to discuss and develop

[79] Report of the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources. CBD/SBSTTA/22/INF/4. Montreal, Canada: Secretariat of the Convention on Biological Diversity; 2018 (https://www.cbd.int/doc/c/4f53/a660/20273cadac313787b058a7b6/dsi-ahteg-2018-01-04-en.pdf , accessed 17 May, 2018)
[80] See "Multilateral approach", Annex 5: Glossary of Terms.
[81] Comments by the World Health Organization on the draft Fact-Finding and Scoping Study "The Emergence and Growth of Digital Sequence Information in Research and Development: Implications for the Conservation and Sustainable Use of Biodiversity, and Fair and Equitable Benefit Sharing", dated 9 November 2017, Geneva: World Health Organization; 2017 (http://www.who.int/un-collaboration/partners/whocommentscbddsi.pdf, accessed on 15 August 2018)
[82] *Ibid.*
[83] Digital Sequence Information on Genetic Resources; CBD/COP/14/L.36, paragraph 11 (29 November 2018, https://www.cbd.int/doc/c/1060/5367/b3ecb2f5ddea7ba9d154cc1d/cop-14-l-36-en.pdf). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included.
[84] *Ibid.*
[85] *Ibid.* at paragraph 12; Proposals for a Comprehensive and Participatory Process for the Preparation of the Post-2020 Global Biodiversity Framework; CBD/COP/DEC/14/--, paragraph 2 (29 November 2018, https://www.cbd.int/doc/c/5c87/7ac5/ac448f13c71e2eb00fa0e556/cop-14-crp-04-en-dec-adv-en.pdf).
[86] Digital Sequence Information on Genetic Resources; CBD/SBSTTA/REC/22/1, paragraph 12 (7 July 2018, https://www.cbd.int/doc/recommendations/sbstta-22/sbstta-22-rec-01-en.pdf).

measures to enhance the functioning of the Multilateral System of Access and Benefit-Sharing (MLS)[87], including through the revision of the ITPGRFA's Standard Material Transfer Agreement (SMTA).

- These discussions have involved the use of digital sequence information in relation to plant germplasm under the MLS. In October 2017, the Governing Body discussed several proposals on this issue. Two are particularly relevant. The first was to establish a subscription system as an access option, with monetary benefit-sharing decoupled from access to individual germplasm samples. The second was to revise the definition of "genetic parts or components" found in article 2 of the SMTA to include "genetic information/traits". The Governing Body decided to consider the potential implications of the use of digital sequence information on genetic resources for the objectives of the International Treaty, including access and benefit-sharing and the MLS, at its next session in 2019. No consensus has yet been reached on whether and how to address digital sequence information in the revised SMTA. Discussions are ongoing.

Approaches to and potential implications of amending or not amending the definition of PIP Biological Materials to include genetic sequence data

97. This section explores the potential implications of amending or not the definition of PIP Biological Material to include GSD and examines how three possible approaches could: 1) support pandemic influenza preparedness and response; 2) promote PIP Framework implementation; and 3) address the considerations highlighted above. These three approaches are:
    - Approach 1: Maintain the current definition of PIP Biological Material (Maintain *status quo*)
    - Approach 2: Amend the definition of Biological Material to include GSD or synthetic materials
    - Approach 3: Address benefit-sharing for GSD through a new mechanism inside or outside the PIP Framework

Approach 1: Maintain the current definition of PIP Biological Material (Maintain *status quo*)

98. Under this first approach, the PIP Framework would remain unchanged. Therefore, benefit sharing for IVPP GSD would continue in its current form: use of IVPP GSD would continue to be linked to payment of Partnership Contribution, but access would not require signing an SMTA 2.

Potential opportunities

99. *Avoid negotiations*. Because the PIP Framework would remain unchanged, no negotiations would be necessary.

Potential challenges

100. *Uncertain access by WHO to vaccines and other influenza products produced by new companies that have used IVPP GSD and have not received PIP BM.* As explained above, companies that only access and/or use IVPP GSD do not have to sign an SMTA 2 or commit to provide access to some of their production to WHO in case of a pandemic (under the SMTA 2). Therefore, under approach 1, WHO would not have guaranteed access to vaccines developed by such new manufacturers in the event of a pandemic. Vaccines and other products developed through new technologies may potentially be more rapidly available and may be better matched to the pandemic virus (see Fact Sheet on *New technologies using genetic sequence data*). Without access to these products, WHO may have less capacity to promote an equitable response to an influenza pandemic.

101. *Could threaten the "equal footing" principle of the Framework.* One of the foundational principles of the PIP Framework is the equal footing between virus sharing and benefit sharing, which Member States have recognized as "equally important parts of the collective action for global public health".[88] As discussed above, this approach may undermine benefit sharing for certain vaccines and other benefits in the future. This, in turn, could weaken the equal footing principle.

[87] See "International Treaty on Plant Genetic Resources for Food and Agriculture's "Multilateral System", Annex 5: Glossary of Terms.

[88] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (http://www.who.int/influenza/pip/en/, accessed 15 May 2018), section 1, principle 3.

102. *May jeopardize IVPP and IVPP GSD sharing if Member States and stakeholders lose trust in the PIP Framework.* As noted by the WHO Technical Expert Working Group on GSD, without mechanisms to ensure fair and equitable benefit sharing for IVPP GSD "the attainment of essential objectives of the PIP Framework may be systematically frustrated"[89]. This could potentially impact Member State and stakeholder trust in the PIP Framework and their willingness to contribute to the objectives of the Framework. While this remains theoretical, some countries may be reluctant to share IVPP and IVPP GSD if they perceive the handling of IVPP GSD as inequitable.

103. *IVPP GSD could be regulated in a bilateral manner under domestic ABS legislation.* If the PIP Framework is recognized as an SII, such recognition applies only to IVPP. If GSD were not included, countries could consider IVPP GSD to be outside the scope of the Framework, meaning they could regulate IVPP GSD access and benefit-sharing bilaterally under their national legislation. This could have significant implications for the sharing of IVPP GSD as well as for pandemic influenza preparedness and response. In addition, products developed using both PIP BM and IVPP GSD could face a complex legal status.

Approach 2: Amend the definition of PIP Biological Material to include genetic sequence data or synthetic materials

104. In this second approach, the definition of PIP BM could be expanded to include the term "genetic sequence data" so that GSD and materials would be subject to the same terms and provisions. Alternatively, the definition could be amended so that materials generated using IVPP GSD ("synthetic materials") would be considered PIP BM.

105. Every provision of the Framework that applies to PIP BM would therefore apply in the same manner to IVPP GSD or to "synthetic materials". This would include, for example, section 5.1, which sets out expectations for virus sharing; section 5.3, which describes the traceability and reporting mechanisms (including the Influenza Virus Traceability Mechanism); and section 5.4 as well as Annexes 1 and 2 on Standard Material Transfer Agreements.

106. This approach would require amending the PIP Framework; for information on how this might be achieved, please refer to the Fact Sheet on *Process for amending the PIP Framework*.

Potential opportunities

107. *Enables a multilateral approach to access and benefit-sharing for GSD.* As explained above, several countries have adopted ABS legislation that covers GSD. Thus, unless IVPP GSD is specifically excluded from the scope of such legislation – or included under another mechanism, such as an SII – IVPP GSD could be subject to national ABS obligations. However, if the definition of PIP BM was expanded to include IVPP GSD, then access and benefit-sharing for IVPP GSD would be governed by the PIP Framework.

108. *Ensures that WHO has access to pandemic influenza products developed using GSD.* As described above, there is a potential future "loophole" in the Framework with respect to pandemic products developed solely through use of IVPP GSD. Including IVPP GSD in the definition of PIP BM could protect WHO's access to such products in the event of a pandemic.

109. *Establishes mechanisms to ensure that users of IVPP GSD are treated in the same manner as users of PIP BM with respect to benefit sharing*. GSD may, in certain cases, be used to replace or to synthesize PIP BM (see Fact Sheet on *New technologies using genetic sequence data*). Applying the same or similar benefit sharing terms to use of IVPP GSD would ensure that benefits arising from access to, or use of, IVPP GSD are shared in a fair and equitable manner.

Potential challenges

110. *Could be costly and resource intensive.* Certain PIP Framework requirements that apply to PIP BM could be cumbersome if applied to IVPP GSD. This could be the case, for instance, if all 'recipients' of IVPP GSD were asked to sign an SMTA 2. Due to the large number of entities/persons that access

[89] Technical Expert Working Group on genetic sequence data, Final Report to the PIP Advisory Group, 2014, Geneva: World Health Organization, (http://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf, accessed on 15 August 2018), p.3

IVPP GSD for academic, research and/or other non-commercial purposes, WHO might have to conclude thousands of SMTA 2s. Few of these users make profitable use of GSD. Thus, a requirement that recipients of IVPP GSD (like recipients of PIP BM) conclude an SMTA 2 with WHO could entail a high cost with few concrete benefits for public health. For information about GSD databases, please refer to the fact sheet *Genetic sequence data and databases*.

111. *Monitoring all access to GSD would not be feasible.* GSD are intangible and can be shared via public and private means including through databases, by email, in reports and publications. They pass through multiple hands and can be modified, combined or split. Under the SMTA 1, GISRS laboratories are asked to record shipments of PIP BM, both within and outside GISRS, in the IVTM. WHO uses IVTM data to identify entities that should be contacted for benefit sharing purposes. The IVTM is not adapted to the nature of GSD or the multiple ways in which it can be shared and used. For this reason, inclusion of IVPP GSD in the definition of PIP BM would likely require developing a different traceability mechanism tailored to IVPP GSD. However, such system is unlikely to be foolproof for two main reasons: (1) a significant amount of GSD is already available in databases that do not identify users; and (2) many sequences are shared bilaterally through private means. As a result, such a traceability mechanism may not enable WHO to ensure fairness and equity in identifying those who have accessed IVPP GSD.

112. *May be difficult to implement a fair and equitable benefit-sharing system.* If access to GSD triggered a requirement to sign a benefit-sharing agreement similar to an SMTA 2, entities and individuals would want assurances that all other others who have accessed IVPP GSD are contributing in a fair and equitable manner. However, for the reasons mentioned above, it does not seem possible to identify all who have accessed IVPP GSD.

113. In addition, not all instances of access and use of IVPP GSD are equivalent. For example, a GSD database entry can be viewed online like any other webpage or can be downloaded on a computer for further work and analysis. Some users may briefly look at a sequence online with no intent to use it further, others may download it for use in risk assessment or research, while others still will use it to reconstitute a protein or a virus and develop a commercial product. A benefit-sharing approach consistent with the PIP Framework's principles of fairness and equity would require distinguishing among these different types of uses. However, users may not always know at the time of download how the GSD will be used. Notice and information about benefit sharing expectations linked to IVPP GSD at the time of access are a possible solution. This could be done through a general statement on a database website or via a Data Access Agreement. The PIP Advisory Group has recommended this approach to the Director-General.[90]

114. *Could impact rapid sharing of IVPP GSD for pandemic preparedness and response.* Burdensome requirements associated with access to IVPP GSD could impact GISRS' capacity to share and analyse IVPP GSD, which are essential to rapid and effective response to and control of influenza.

115. *Could impact research and development using IVPP GSD.* Burdensome requirements on access and use of IVPP GSD could push companies and institutions away from research and development for pandemic influenza.

Approach 3: Address benefit-sharing for genetic sequence data through a new mechanism inside or outside the PIP Framework

Approach 3a: Develop a new benefit-sharing mechanism in the PIP Framework

116. In this approach, benefit sharing could be addressed by either expanding/modifying an existing mechanism in the Framework (e.g. an 'SMTA2-like' mechanism) or by developing a new mechanism within the PIP Framework.

117. For example, the PIP Advisory Group has explored the possibility of developing a traceability mechanism based on monitoring the development of commercial products using IVPP GSD, rather

[90] A Fact-Finding and Scoping Study on Digital Sequence Information on Genetic Resources in the Context of the Convention on Biological Diversity and the Nagoya Protocol. Montreal, Canada: Secretariat of the Convention on Biological Diversity; 2018 (https://www.cbd.int/doc/c/e95a/4ddd/4baea2ec772be28edcd10358/dsi-ahteg-2018-01-03-en.pdf, accessed 17 May 2018)

than tracking access to GSD. By searching patent databases, clinical trial registrations and regulatory approval files, this mechanism could identify entities that have used IVPP GSD to develop an influenza vaccine or diagnostics. Entities identified through this process could then be asked to contribute to benefit-sharing under the PIP Framework through, for example, a data access agreement.[91]

118. This could be done by developing a new annex or section to the PIP Framework. For options on how to this might take place, please see the Fact Sheet on *Process for amending the PIP Framework.*

Potential opportunities

119. *Could ensure that WHO has access to pandemic influenza products developed using GSD while providing an opportunity to tailor the mechanism to the unique features and context of GSD.* This approach provides an opportunity to ensure that IVPP GSD is handled in a way that takes into account its unique nature and features, and addresses the challenges identified under approach 2, including the development of an appropriate traceability mechanism and benefit-sharing tools.

120. *Enables a multilateral approach to access and benefit-sharing for GSD.* This could provide a solution to the complexities arising from multiple ABS legislation as described above.

Potential challenges

121. *Would require negotiations to develop a new mechanism.* Developing a new section or annex to the Framework for GSD would require negotiations and further technical work.

122. *Traceability system may be challenging to implement.* As highlighted above, it may be challenging to identify potential benefit-sharing contributors. However, this could be made easier by implementing a system that focuses on products developed using IVPP GSD, rather than on access to IVPP GSD.

Approach 3b: Develop/adapt another instrument to cover a broader set of pathogen GSD

123. Another approach could be to adapt an existing instrument or develop a new instrument, outside the PIP Framework, which could address ABS for IVPP GSD. This could be done by adapting/developing:

a. an instrument that covers GSD from a broader set of pathogens (e.g. all influenza GSD or GSD from pathogens with epidemic and pandemic potential); or

b. an instrument that covers both GSD and physical samples from a broader set of pathogens related to Approach 4, option B.

124. This could be done with a view to the instrument being recognized as an SII under the Nagoya Protocol, as discussed above.[92]

This approach entails the same opportunities and challenges as above as well as the ones below.

Potential opportunities

125. *Avoid potential duplication or complexity of multiple regimes.* Developing a new instrument could allow addressing benefit-sharing for GSD through one legal regime.[93] This could reduce the legal complexity and administrative burden on entities that access a broader set of GSD.

Potential challenges

126. C*omplex to negotiate.* Developing a new instrument of that scale would be technically complex, require input from a wide range of stakeholders, and take substantial time.

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[91] Advisory Group's work on handling Genetic Sequence Data under the PIP Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/advisory_group/gsd/en/, accessed 18 May 2018)

[92] Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (adopted 29 October 2010, entered into force 12 October 2014) UNEP/CBD/COP/DEC/X/1 Article 4(4).

[93] See Facilitating Access and Benefit Sharing (ABS) for Pathogens to Support Public Health, Workshop Report. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/ABS_Workshop_Report_7Sep_hyperlinks.pdf, WHO/WHE/IHM/PIP2018.4)

ANNEX 1: SUMMARY OF RELEVANT OUTCOMES FROM THE 14th CBD COP AND THE 3rd COP-MOP TO THE NAGOYA PROTOCOL

Parties to the Convention on Biological Diversity (CBD) and the Nagoya Protocol met from 17-29 November 2018 for their biennial governing bodies meetings, the COP and COP-MOP[94]. WHO participated as an observer. During the meetings, Parties discussed and adopted decisions on a number of topics relevant to this Analysis. Relevant parts of these decisions are discussed below.

Specialized international access and benefit-sharing instruments in the context of Article 4(4) of the Nagoya Protocol (SII)

At the Nagoya Protocol COP-MOP, Parties discussed the draft decision recommended by the Subsidiary Body on Implementation (SBI) and the CBD Secretariat's study on the topic, which included potential criteria for SII.[95]

During the discussions, WHO delivered a statement emphasizing the importance of both the rapid sharing of pathogens and equitable sharing of benefits arising from their use. WHO highlighted the potential of multilateral approaches to facilitate ABS for pathogens and presented the PIP Framework as a successful example of such an approach.

The decision on SII, *inter alia*, invites Parties and other Governments to submit "information on how specialized international access and benefit-sharing instruments are addressed in their domestic measures" and views on potential criteria for an SII for the consideration of the Subsidiary Body on Implementation (SBI).[96] SBI will hold its third meeting in May or June 2020 and has been requested to make a recommendation on this matter to the 4th COP-MOP, which will be held in the last quarter of 2020.[97]

Parties also decided to include a standing item on "cooperation with other international organizations" on the agenda of future meetings of the COP-MOP to "take stock of developments in relevant international forums, including any information on specialized international access and benefit-sharing instruments recognized by another intergovernmental body and/or by a Party or group of Parties, with a view to enhancing mutual supportiveness between the Protocol and specialized international access and benefit-sharing instruments".[98]

Parties and other Governments which are or may become Parties to the Nagoya Protocol and to an SII were also invited to take steps to implement both instruments in a mutually supportive manner.[99]

The decision also includes in annex the potential criteria identified in the CBD Secretariat's study.[100] The decision however clarified that these "are under discussion and have not been agreed by Parties to the Protocol."[101]

Digital Sequence Information on genetic resources

The COP and COP-MOP continued discussions on digital sequence information (DSI) on genetic resources and considered several documents, *inter alia*: (1) the Report of the AHTEG on DSI,[102] (2) the Fact-finding

[94] Conference of Parties to the CBD (COP) and Conference of Parties serving as the Meeting of the Parties (COP-MOP) to the Nagoya Protocol. For more information on these meetings, see https://www.cbd.int/conferences/2018 (accessed on 10 December 2018).
[95] "Study into criteria to identify a specialized international access and benefit-sharing instrument, and a possible process for its recognition" (CBD/SBI/2/INF/17).
[96] Specialized International Access and Benefit Sharing Instruments in the Context of Article 4, Paragraph 4, of the Nagoya Protocol (CBD/NP-MOP/3/L.3), paragraph 2 (https://www.cbd.int/doc/c/7a3f/b000/f7c46f51a09dc6b9e2fc95a5/np-mop-03-l-03-en.pdf, accessed on 10 December 2018). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included..
[97] *Ibid.* at paragraph 5.
[98] *Ibid.* at paragraph 6.
[99] *Ibid.* at paragraph 8.
[100] *Ibid.* at Annex.
[101] *Ibid.*
[102] Report of the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources; CBD/SBSTTA/22/INF/4; CBD/DSI/AHTEG/2018/1/4 (20 February 2018, https://www.cbd.int/doc/c/7ea1/36b3/7ccf849897a4c7abe49502b2/sbstta-22-inf-04-en.pdf).

and Scoping Study on DSI,[103] (3) Synthesis of views and information,[104] and (4) the draft decision taken by the Subsidiary Body on Scientific, Technical and Technological Advice.[105]

WHO delivered a statement on the need to develop approaches that support the rapid and broad sharing of DSI for disease prevention and control, and ensure that countries in need have fair and equitable access to diagnostics, therapeutics and vaccines, as well as to other technologies and information derived from use of DSI.

The decision on DSI recognized the importance of DSI for the three objectives of the CBD and its contribution "to scientific research as well as to other non-commercial and commercial activities in areas such as biological diversity, food security and human, animal and plant health".[106] It noted that the term "digital sequence information" may not be the most appropriate term and that it is used as a placeholder until an alternative term is agreed.[107]

The decision recognized that there is a divergence of views among Parties on benefit-sharing for DSI.[108] Parties committed to work towards resolving this divergence through a science and policy based process.[109] Noting ongoing work in other organizations, such as WHO, Parties requested the CBD Secretariat "to cooperate with other intergovernmental organizations to inform them of the process […] and to take into account the work, approaches and outcomes that these organizations generate in the area in question."[110]

The decision also discussed domestic measures that have been adopted by some Parties to regulate ABS for DSI and noted that mutually agreed terms governing access to genetic resources for their utilization can cover benefits arising from the commercial and/or non-commercial use of DSI.[111]

The decision acknowledged that many countries need to improve their capacity to access, use, generate and analyse DSI, and it therefore encouraged Parties, other Governments and relevant organizations to support capacity-building and technology transfers in such countries.[112]

[103] Fact-finding and Scoping Study on Digital Sequence Information on Genetic Resources in the Context of the Convention on Biological Diversity and the Nagoya Protocol; CBD/SBSTTA/22/INF/3; CBD/DSI/AHTEG/2018/1/3 (12 January 2018, https://www.cbd.int/doc/c/079f/2dc5/2d20217d1cdacac787524d8e/dsi-ahteg-2018-01-03-en.pdf).
[104] Synthesis of Views and Information on the Potential Implications of the Use of Digital Sequence Information on Genetic Resources for the Three Objectives of the Convention and the Objective of the Nagoya Protocol; CBD/SBSTTA/22/INF/2; CBD/DSI/AHTEG/2018/1/2 (9 January 2018, https://www.cbd.int/doc/c/49c9/06a7/0127fe7bc6f3bc5a8073a286/dsi-ahteg-2018-01-02-en.pdf).
[105] Digital Sequence Information on Genetic Resources; CBD/SBSTTA/REC/22/1 (7 July 2018, https://www.cbd.int/doc/recommendations/sbstta-22/sbstta-22-rec-01-en.pdf).
[106] Digital Sequence Information on Genetic Resources; CBD/COP/14/L.36 (29 November 2018, https://www.cbd.int/doc/c/1060/5367/b3ecb2f5ddea7ba9d154cc1d/cop-14-l-36-en.pdf). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included.
[107] *Ibid.* at Preamble.
[108] *Ibid.* at paragraph 6.
[109] The process outlined in the Decision is described in paragraph 95 of this Analysis, above.)
[110] Digital Sequence Information on Genetic Resources; CBD/COP/14/L.36, paragraph 13 (29 November 2018, https://www.cbd.int/doc/c/1060/5367/b3ecb2f5ddea7ba9d154cc1d/cop-14-l-36-en.pdf). Please note that, at the time of writing, the final decisions from the November 2018 COP and COP-MOP have not yet been published. Therefore, references to draft decisions ("L versions") have been included..
[111] *Ibid.* at paragraphs 5, 7.
[112] *Ibid.* at paragraph 3.

ANNEX 2: IMPLEMENTATION OF THE NAGOYA PROTOCOL AND SEASONAL INFLUENZA VIRUS SHARING

As highlighted in the WHO *Study on the public health implications of implementation of the Nagoya Protocol*[113], in time, implementation of the Nagoya Protocol has the potential to promote trust, improve access to affordable treatments and help build capacities. Until such time, however, concerns have been raised about its potential to slow down or limit the sharing of pathogen samples, including seasonal influenza viruses. Some challenges related to implementation of the Nagoya Protocol that have been reported to WHO include[114]:

- Lengthy administrative processes to comply with national ABS requirements;
- Complexity of non-standardized, national ABS requirements and processes;
- Uncertainty about the scope of application of national ABS measures (i.e. whether legislation applies to some or all pathogens);
- Difficulty of access to national regulations on implementation of the Nagoya Protocol, notwithstanding the CBD ABS Clearinghouse mechanism;
- National ABS focal points often taking a long time to reply to queries about national regulations under the Nagoya Protocol or not responding at all;
- Institutions not having the legal expertise and capacity to negotiate bilateral PIC and MAT agreements.

The GISRS Network

The Global Influenza Surveillance and Response System (GISRS) is a WHO-coordinated network of public health laboratories, now in 114 countries, that has been conducting global influenza surveillance, prevention and control for over 66 years.[115] GISRS is a voluntary network i.e. a WHO Member State initiates the official process for a laboratory to be recognized and designated by WHO. The official process starts with a request by a WHO Member State's Ministry of Health, with subsequent joint assessment by WHO and the proposed laboratory to ensure that the laboratory meets the requisite standards and criteria as defined in the relevant WHO Terms of Reference (ToRs), and ends with the commitment from the Ministry to fulfill the ToRs and an official designation/recognition letter from WHO.

National Influenza Centres (NICs) are national institutions authorized and designated by their national health ministry and subsequently recognized by WHO for the purpose of participating in the work of GISRS under the applicable WHO terms of reference (TORs). NIC TORs require NICs to send representative seasonal influenza virus isolates and/or samples to one or more WHO CCs of GISRS of their choice in time to inform decisions at the two Vaccine Composition meetings held in February and September each year. Using these isolates, as well as isolates or samples from IVPP, GISRS laboratories conduct risk assessments, monitor the evolution of seasonal influenza viruses, follow the epidemic spread of viruses, or evaluate the pandemic potential of novel influenza viruses. This system provides data and specimens to support twice annual WHO recommendations on the composition of seasonal influenza vaccines. In order to make the best possible recommendation, GISRS laboratories must test thousands of influenza virus samples from as many countries as possible. Without timely and broad access to influenza viruses, these crucial activities of GISRS cannot take place and countries cannot protect their populations from influenza.

The selection of viruses for development of CVVs are critical first steps every year, which must be completed before VCMs, to inform vaccine recommendations and subsequent seasonal vaccine production. The process is based on millions of samples tested by GISRS laboratories globally, tens of thousands of representative samples selected by NICs for shipping to and subsequent detailed characterization by WHO CCs. This

[113] Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications, Study by the Secretariat. Geneva: World Health Organization; 2016 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf, accessed on 14 May 2018).
[114] See Facilitating Access and Benefit Sharing (ABS) for Pathogens to Support Public Health, Workshop Report. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/ABS_Workshop_Report_7Sep_hyperlinks.pdf, WHO/WHE/IHM/PIP2018.4)
[115] *See* Fact Sheet: WHO Global Influenza Surveillance and Response System. (2018; https://www.who.int/influenza/gisrs_laboratory/updates/GISRS_one_pager_2018_EN.pdf)

collective work of GISRS laboratories globally allows the selection of CVVs for the best possible public health outcome.

Two situations, described in the section below, have arisen in recent months with respect to seasonal influenza virus sharing affecting, on the one hand, GISRS and on the other hand, vaccine manufacturers.

Example 1 – Sharing of seasonal influenza isolates from a National Influenza Centre

In July 2018, a NIC was preparing to send influenza virus isolates to a WHO CC in accordance with its TORs and in connection with preparations for the southern hemisphere VCM process. The NIC informed the WHO CC that there were additional requirements for sharing seasonal influenza viruses due to the country's Nagoya Protocol implementing legislation. These requirements included that the WHO CC provide an "acceptance letter" to the Ministry of Health and the Nagoya Protocol Competent National Authority providing details about the viruses to be shared, including certification that the samples would not be shared with third parties (including other GISRS laboratories) and would not be used for commercial purposes. In addition, the NIC informed the WHO CC that approval from the national Health Quarantine office would be required prior to shipment. All of these requirements prevented the sharing of these viruses with the WHO CC in time for the September 2018 VCM. Therefore, potential critical information contained in these virus samples was not included in the selection and development of CVVs for the southern hemisphere 2019 influenza season. Shipping of samples resumed after the VCM; the country has shipped recent samples to a WHOCC under NIC TORs. The WHO CC is in discussion with the country to understand if future shipments will be affected.

Example 2 – Access to the recommended virus strain

The second example relates to an influenza virus-positive clinical specimen that was freely shared for surveillance purposes by a country that has ratified the Nagoya Protocol and implemented it into national legislation. The virus isolated at the WHO CC was recommended as a prototype virus and developed into a CVV for inclusion in vaccines for the 2019 southern hemisphere influenza season. In light of this, vaccine manufacturers relayed concerns and questions about two matters that may affect the start of vaccine production:

1. Whether the use of this virus, which is named in the WHO CVV listing, requires the manufacturers to comply with any Nagoya requirements in the country of origin; and
2. Whether the regulatory agencies of the countries where the vaccines are manufactured and/or sold would require any additional ABS-related information (such as a "registration number" from the national authority).

The Nagoya Protocol Focal Point in the country of origin was consulted on the first question, provided a registration number for the virus and informed manufacturers that they would be required to notify the competent authorities of any products containing the virus and/or its derivatives prior to their commercialization, using the provided registration number as a reference. This created uncertainties at the beginning of a time-sensitive process.

With respect to the second question, the regulatory agency of the country of production confirmed that they would need an ABS registration number for the virus. The registration number was provided by the manufacturers to the regulatory agency but it took some time, creating uncertainties at the beginning of a time-sensitive process.

Since regulatory submissions in certain jurisdictions (e.g. FDA) are made several months ahead of market authorization, changes to or delays to the submissions can have a significant, detrimental impact on vaccine availability.

ANNEX 3: BENEFIT SHARING UNDER THE PIP FRAMEWORK

The PIP Framework places the sharing of viruses with pandemic potential on an equal footing with the sharing of benefits arising from such virus sharing. The Framework Benefit Sharing System operates to provide pandemic surveillance and risk assessment, prioritize important benefits, build capacity, and provide access to vaccines and other pandemic response products, to countries in need.

The PIP Framework has two distinct benefit sharing mechanisms: the Standard Material Transfer Agreement 2 (or 'SMTA2') and the PIP Partnership Contribution.

Standard Material Transfer Agreement 2 ('SMTA2')

The SMTA2 is a contract that WHO concludes with each non-GISRS recipient of PIP biological materials. Through that contract, WHO secures access to pandemic response products such as vaccines, antivirals, diagnostics, and other essential response products. These contracts are legally binding and enforceable in a court of law.

SMTA2s are contracts that are signed once, in connection with receipt of PIP Biological Materials; they remain in place until they are triggered by the declaration of a pandemic by WHO. At that time, WHO will contact the company that has signed the SMTA2 and discuss the modalities for delivery of the response products that have been secured.

The Influenza Virus Traceability Mechanism (or 'IVTM") is an internet-based, electronic database that provides transparency in the movement of PIP BM and enables providers and users of PIPBM to see summary reports of laboratory analyses conducted on the materials. Each shipment of PIP BM to a non-GISRS entity is recorded in the IVTM. The IVTM is the tool that enables WHO to find companies that have received PIP BM and must sign an SMTA2.

Current and Potential Future Loopholes

SMTA2s are based on receipt of physical PIP biological materials by a company. Two scenarios exist where a manufacturer of influenza products is not subject to SMTA2 benefit sharing:

a) Indirect use of PIP BM

In this first scenario, the recipient of PIPBM is a laboratory. As the recipient of PIP BM, the laboratory must sign an SMTA2 with WHO. In the scenario, a manufacturer engages the laboratory to test the manufacturer's product against the PIP BM. Since the manufacturer has not received PIP BM, the manufacturer does not have to sign an SMTA2. In that case, WHO will not have secured access to pandemic products developed by such a manufacturer. Examples of indirect use of PIP BM include:

- Products that require testing against PIP BM but for which the manufacturer has not requested PIP BM, such as diagnostic products, cleaning products, neutralizing antibodies, and herbal medicine.

- Products manufactured directly from IVPP GSD which require regulatory approval before they can be marketed, such as vaccines, diagnostics or other therapies. While the manufacturer accesses IVPP GSD to develop its product, it may engage another laboratory to access PIP BM to conduct the testing required for regulatory approval (as described above). In such cases, WHO will not have access to the products developed using IVPP GSD because the manufacturer never directly receives PIP BM.

b) Use of GSD only

In this second scenario, a manufacturer does not use any PIP BM, only IVPP GSD, throughout the full product development, manufacturing and marketing process. In such case, a manufacturer would not have to sign an SMTA 2 with WHO because it would not, directly or indirectly, receive PIP BM at any stage of its product development, manufacturing or marketing process.

Current technologies allow manufacturers to develop synthetic influenza viruses (including candidate vaccine viruses) using IVPP GSD only, without PIP BM.[116] There are already several examples of vaccines, diagnostics or other influenza products that have been developed using such technologies. However, manufacturers still currently require access to PIP BM to conduct testing of such products. Therefore, while scenario a) has already occurred, scenario b) is still theoretical and has not yet happened.

The PIP Partnership Contribution

The PIP Partnership Contribution is an annual payment to WHO by influenza vaccine, diagnostic and pharmaceutical manufacturers that use GISRS. "Use of GISRS" is understood to mean that the manufacturer used or received:

- materials (e.g. virus materials, such as candidate vaccine viruses, wild-type viruses, cDNA, plasmids, or reagents); and/or
- services (e.g. antigenic and genetic characterization of candidate vaccine viruses/seed material, antiviral susceptibility assays); and/or
- information (e.g. sequence information, epidemiological data, antiviral susceptibility data, pre- and post-vaccine composition meeting reports);

developed and/or provided by or through GISRS.

Under this definition, the companies identified in the current and potential future loopholes scenarios above could be captured and contribute to PIP Framework benefit sharing.

The annual amount of the Partnership Contribution is 50% of GISRS running costs. Those costs were estimated to be US$ 56.5 million in 2010 and thus the PC has been set at US$ 28 million per year.

Amounts to be paid by individual manufacturers are based on principles of transparency and equity, and take into account the manufacturers' nature and capacities (see PIP Framework, section 6.14.3).

The Framework defines "influenza vaccine, diagnostic and pharmaceutical manufacturers" as follows:

> public or private entities including academic institutions, government owned or government subsidized entities, non-profit organizations or commercial entities that develop and/or produce human influenza vaccines or other products derived from or using H5N1 or other influenza viruses of human pandemic potential" (see Framework, section 4.3).

The PIP Secretariat uses a set of standard operating procedures (SOPs) to identify manufacturers using GISRS and divide up the payment of the PC among companies.[117] The SOPs were developed in line with the WHO document on Distribution of Partnership Contribution among Companies.[118]

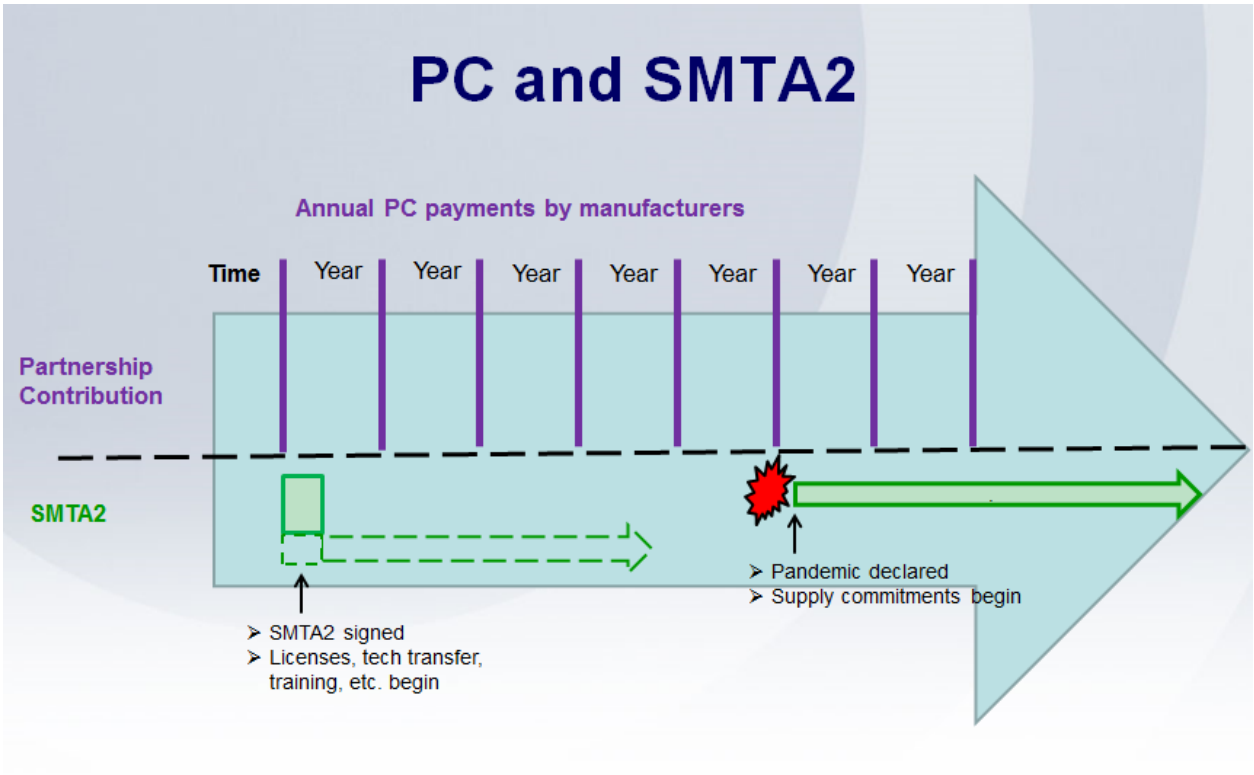
The funds collected through the Partnership Contribution are used by WHO to strengthen pandemic preparedness capacities in countries where they are weak and to build a reserve of funds that will be available for use at the time of the next pandemic. Some funds are also used to support the headquarters-based PIP Secretariat. Full transparency on the use of PIP PC funds may be found in the semi-annual Progress Report on use the of PIP Partnership Contributions (http://www.who.int/influenza/pip/pip_progressreport_30jun2018.PDF?ua=1) and on the WHO Programme Budget Portal (http://open.who.int/2018-19/our-work/category/20/about/about).

The diagram below illustrates the difference between the SMTA2 and the Partnership Contribution.

[116] See Fact sheet on New Technologies using GSD available at http://www.who.int/influenza/pip/NewTech_EN_3Apr2018-2.pdf?ua=1

[117] WHO. Partnership Contribution Standard Operating Procedures (June 2015, https://www.who.int/influenza/pip/benefit_sharing/pc_collection_sop.pdf, accessed on 11 December 2018).

[118] WHO. Pandemic Influenza Preparedness Framework: Distribution of Partnership Contribution among Companies (8 May 2013, https://www.who.int/influenza/pip/pc_distribution.pdf).


PC and SMTA2
Annual PC payments by manufacturers
Time
Year
Year
Year
Year
Year
Year
Year
Partnership Contribution
SMTA2
➢ SMTA2 signed
➢ Licenses, tech transfer, training, etc. begin
➢ Pandemic declared
➢ Supply commitments begin

ANNEX 4: METHODOLOGY

The Report of the 2016 PIP Framework Review Group was submitted to the Seventieth World Health Assembly (2017). At the Seventieth World Health Assembly, Member States adopted decision WHA70(10) which requested the Director-General, inter alia:

> 8(b) "Regarding the PIP Framework Review Group's recommendations concerning seasonal influenza and genetic sequence data (GSD), to conduct a thorough and deliberative analysis of the issues raised, including the implications of pursuing or not pursuing possible approaches, relying on the 2016 PIP Framework Review and the expertise of the PIP Advisory Group, and transparent consultation of Member States and relevant stakeholders, including the Global Influenza Surveillance and Response System [GISRS]."

This annex provides the methodology that WHO has used to conduct the Analysis requested in WHA70(10)(8)b.

As the Analysis must address two different topics (seasonal influenza viruses and GSD), two work streams have been undertaken in parallel. The process to conduct these two work streams has had three phases:

- Phase I: Scoping (June–October 2017)
- Phase II: Drafting (November 2017–September 2018)
- Phase III: Finalization (October–December 2018)

WHO has worked closely with the PIP Advisory Group and GISRS, notably the Collaborating Centres throughout the development of this Analysis. In addition, during each phase WHO has gathered evidence and views from Member States and stakeholders, including but not limited to: relevant international organizations, manufacturers and associations, civil society organizations, databases and initiatives.

Phase I: Scoping (June-October 2017)

Following the Seventieth World Health Assembly, WHO undertook a broad scoping exercise that resulted in a document that provided a highly annotated proposed outline of the Analysis, that included preliminary considerations related to seasonal influenza and GSD in the context of the PIP Framework. The *Scoping paper* was developed on the basis of the considerable evidence on seasonal influenza and GSD collected as part of the 2016 PIP Framework Review process; the PIP Advisory Group's work to provide guidance to the WHO Director-General on the handling of IVPP GSD under the PIP Framework; and the development of the WHO study on the public health implications of the implementation of the Nagoya Protocol.

The Scoping paper can be found at http://www.who.int/entity/influenza/pip/scopingpaper.pdf . It includes a methodology section.

The compilation of evidence on *seasonal influenza* can be found at :
http://www.who.int/influenza/pip/seasonalcompilation.pdf

The compilations of evidence on *genetic sequence data* and on *the PIP Advisory Group work on GSD under the Framework* can be found at :

- http://www.who.int/influenza/pip/GSDcompilation.pdf
- http://www.who.int/influenza/pip/AGcompilation.pdf

The draft scoping paper was reviewed by the PIP Framework Advisory Group and the GISRS Collaborating Centres. To gather broad stakeholder feedback on the revised scoping document, WHO held a multi-stakeholder Consultation on Implementation of Decision WHA70(10)8b) (Geneva, Switzerland: 6-7 November 2017) and conducted an online questionnaire to collect views on the scoping paper.

Phase II: Drafting (November 2017–September 2018)

During the Consultation, Member States and stakeholders raised a number of questions related to topics of importance to the Analysis and provided a number of recommendations. In addition, several Member States and stakeholders provided written submissions.[119]

[119] Submissions to the 8(b) process available at http://www.who.int/influenza/pip/8b_submissions/en/.

Taking into account this feedback, WHO expanded and adjusted the scoping paper to become draft zero of the Analysis. This draft zero was reviewed by the PIP Framework Advisory Group, GISRS Collaborating Centres and GISRS Essential Regulatory Laboratories.

To reduce the size of the Analysis and provide Member States and stakeholders with information about relevant topics, WHO also developed a set of Fact Sheets that can be found at http://www.who.int/influenza/pip/Documents_WHA70108b/en/.

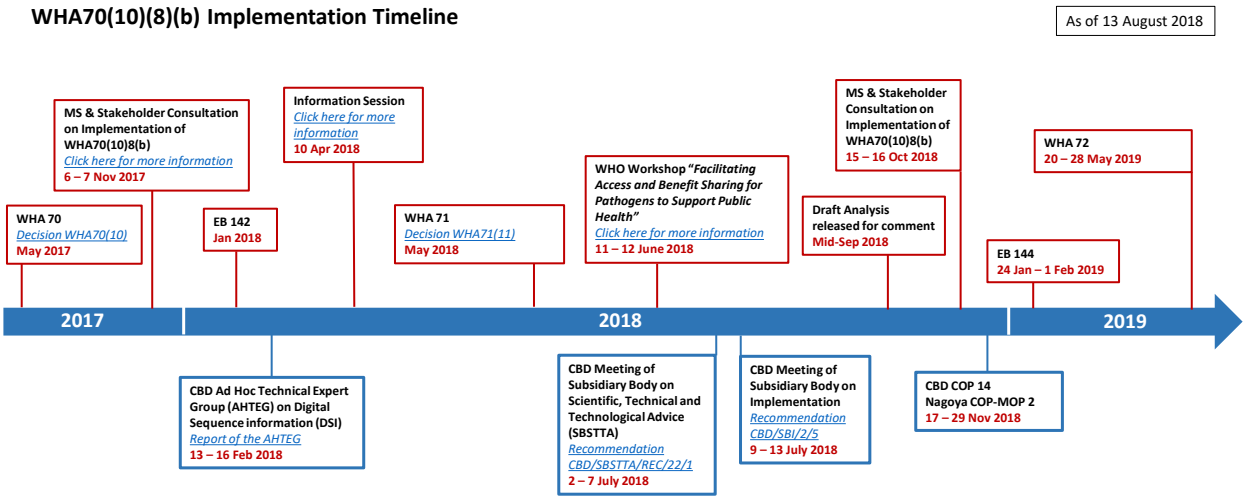
The first draft of the Analysis was developed taking into account: discussions of the Health Assembly in May 2018; feedback from the PIP Framework Advisory Group, GISRS Collaborating Centres and GISRS Essential Regulatory Laboratories; and relevant findings and outcomes of the CBD processes related to digital sequence information and specialized international access and benefit-sharing instruments under the Nagoya Protocol.

This first draft was shared with Member States and stakeholders in September 2018 in advance of the 15-16 October 2018 Consultation on implementation of WHA70(10)(8)(b).

Phase III. Finalization (October–December 2018)

As requested by the Seventy-first World Health Assembly through decision WHA71(11), the Secretariat has completed the Analysis, in order to submit the final text to WHA72 (2019) through EB144.[120] The document takes into account: views and comments received during the 15-16 October 2018 Consultation, written submissions received on the draft Analysis, and the decisions from the November 2018 14th CBD COP and 3rd Nagoya Protocol COP-MOP.

Timeline



[120] In May 2018, WHO provided the 71st World Health Assembly with an update on progress on implementing WHA70(10). Following consideration of the report, the Health Assembly adopted decision WHA71(11), which requested that "the final text of the analysis, requested under paragraph 8(b) of decision WHA70(10), be submitted to the Seventy-second World Health Assembly, through the Executive Board at its 144th session".

ANNEX 5: GLOSSARY OF TERMS

Access and Benefit-Sharing (ABS)
Access and benefit-sharing (ABS) refers to the way in which genetic resources may be accessed, and how the benefits that result from their use for research and development are shared between the people or countries using the resources (users) and the people or countries that provide them (providers).[121] This principle is based on the recognition that States have sovereign rights over genetic resources under their jurisdiction. As such, they can regulate access to and use of these resources, including the sharing of benefits derived from their use. This principle was developed under the Convention on Biological Diversity and is elaborated under the Nagoya Protocol.

ABS legislation
A set of laws or measures adopted by national governments to implement the ABS objective of the Convention on Biological Diversity or the Nagoya Protocol. ABS legislation can contain rules about how to access genetic resources, what benefits to share in exchange for using genetic resources and how to share them. All Parties are obligated to establish measures to ensure compliance with these rules.

Benefit
A benefit is "something that produces good or helpful results or effects or that promotes well-being"[122] which has been generated through the use of a genetic resource. The Nagoya Protocol provides in annex a list of monetary and non-monetary benefits [123], which include, for example, research funding or capacity-building. It also identifies "access to affordable treatments by those in need, especially in developing countries" as a benefit to be shared in the context of health emergencies. The PIP Framework also identifies in Annex 2 a list of benefits, which include donation of pandemic influenza vaccines or technology transfers.

Bilateral approach
Under the Nagoya Protocol, ABS for a genetic resource is negotiated between two entities – a provider country and a user – on a one-on-one, case-by-case basis. It can be contrasted with a multilateral approach (see below).

Genetic resource
As defined under the Convention on Biological Diversity, 'genetic resources' are defined in the CBD to mean "genetic material of actual or potential value" while the term 'genetic material' is defined as "any material of plant, animal, microbial or other origin containing functional units of heredity". The CBD and the Nagoya Protocol do not apply to human genetic resources.

Influenza virus with human pandemic potential
As defined in the PIP Framework, an 'influenza virus with human pandemic potential' (IVPP) is "any wild-type influenza virus that has been found to infect humans and that has a haemagglutinin antigen that is distinct from those in seasonal influenza viruses so as to indicate that the virus has potential to be associated with pandemic spread within human populations with reference to the International Health Regulations (2005) for defining characteristics."

International Treaty on Plant Genetic Resources for Food and Agriculture's "Multilateral System" (ITPGRFA – MLS)
The International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) is a treaty under the auspices of the Food and Agriculture Organization of the United Nations (FAO), which entered into force on 29 June 2004. Its objectives are "the conservation and sustainable use of all plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the Convention on Biological Diversity, for sustainable agriculture and food security" [124]. The ITPGRFA establishes a multilateral access and benefit-sharing system (MLS) for genetic resources from 64 major plant crops. Access is through "an easily accessible global pool of genetic resources that is freely

[121] Introduction to access and benefit-sharing, Montreal, Canada: Secretariat of the Convention on Biological Diversity; 2011 (https://www.cbd.int/abs/infokit/revised/web/all-files-en.pdf, accessed on 15 August 2018)
[122] Benefit. In: Merriam-Webster. [website] 2018 (https://www.merriam-webster.com/, accessed on 16 August 2018)
[123] Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (adopted 29 October 2010, entered into force 12 October 2014) UNEP/CBD/COP/DEC/X/1, Annex 1.
[124] ITPGRFA, article 1, (http://www.fao.org/3/a-i0510e.pdf, accessed on 16 August 2018)

available to potential users in the Treaty's ratifying nations for some uses"[125]. Those who access genetic materials through ITGRFA-MLS "agree to share any benefits from their use through four benefit-sharing mechanisms established by the Treaty"[126].

Legal certainty
Legal certainty is a fundamental principle of law which states that laws must be certain, clear and precise, and their effect must be reasonably foreseeable so that individuals and entities subject to those laws can take the necessary measures to comply with them.

Multilateral approach
In a multilateral approach, more than two entities agree on a common method for addressing an issue. The PIP Framework, which sets out guidelines for ABS for influenza viruses with human pandemic potential between all WHO Member States, is an example of a multilateral approach.

Mutually Agreed Terms
Mutually agreed terms "is an agreement reached between the providers of genetic resources and users on the conditions of access and use of the resources, and the benefits to be shared between both parties."[127]

PIP biological materials
The PIP Framework defines PIP biological materials (PIP BM) as including: "human clinical specimens, virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from H5N1 and/or other influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment."

Prior Informed Consent
Prior Informed Consent "is permission given by the Competent National Authority (CNA) of a country to an individual or institution seeking to obtain access to genetic resources, in line with an appropriate legal and institutional framework."[128]

Risk assessment
"Risk assessment is a systematic process for gathering, assessing and documenting information to assign a level of risk. Risk assessment aims to determine the likelihood and impact of events on public health so that action can be taken to manage and reduce the negative consequences."[129]

Specialized international access and benefit-sharing instrument
A specialized international access and benefit-sharing instrument (SII) is defined in Article 4, paragraph 4 of the Nagoya Protocol which states: "Where a specialized international access and benefit-sharing instrument applies that is consistent with, and does not run counter to the objectives of the Convention and this Protocol, this Protocol does not apply for the Party or Parties to the specialized instrument in respect of the specific genetic resource covered by and for the purpose of the specialized instrument."

Standard Material Transfer Agreement
A standard material transfer agreement (SMTA) is a standardized contract between two parties that governs the terms for sharing tangible materials. An example is the PIP Framework's SMTA 2, which covers the sharing of PIP biological materials outside of GISRS.

Traceability
In the context of influenza, traceability refers to the capability to identify the origin and to track the movement of an influenza virus. Traceability of influenza viruses with human pandemic potential is facilitated by the Influenza Virus Traceability Mechanism.

[125] Overview. In: International Plant Treaty on Plant Genetic Resources. [website] (http://www.fao.org/plant-treaty/overview/en/, accessed on 16 August 2018)
[126] *Ibid.*
[127] Introduction to access and benefit-sharing, Montreal, Canada: Secretariat of the Convention on Biological Diversity; 2011 (https://www.cbd.int/abs/infokit/revised/web/all-files-en.pdf, accessed on 15 August 2018)
[128] Introduction to access and benefit-sharing, Montreal, Canada: Secretariat of the Convention on Biological Diversity; 2011 (https://www.cbd.int/abs/infokit/revised/web/all-files-en.pdf, accessed on 15 August 2018)
[129] Tool for Influenza Pandemic Risk Assessment (TIPRA), Version 1 Release, Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/handle/10665/250130/WHO-OHE-PED-GIP-2016.2-eng.pdf?sequence=1, accessed on 15 August 2018), p.6

Use of GISRS
'Use of GISRS' means the receipt or use of materials, services and/or information from the Global Influenza Surveillance and Response System.[130]

[130] For more information, see: 2018 PIP Partnership Contribution Questionnaire. In: World Health Organization. [website] (2018) (http://origin.who.int/influenza/pip/pc_questionnaire/en, accessed on 16 August 2018)