Implementation of Decision WHA70(10)8(b)

Scoping Paper on approaches to seasonal influenza and genetic sequence data under the PIP Framework ("Scoping paper")

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, with the objective of fair, transparent, equitable, efficient and effective benefit sharing. In accord with section 7.4.2 of the Framework, WHO established the first PIP Framework Review Group ('PIP Review Group') in 2016, mandated to examine the Framework with a view to proposing revisions reflecting developments, as appropriate to the World Health Assembly.

2. After considering the PIP Review Group's report in May 2017, WHO Member States 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. Development of the Analysis will rely 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 WHO Global Influenza Surveillance and Response System (GISRS).[1]

3. This document provides an annotated outline of the requested Analysis, including background and preliminary considerations. It is divided into three sections:

- Matters with overarching implications to the Analysis;
- Seasonal influenza in the context of the PIP Framework; and
- GSD in the context of the PIP Framework.

4. The purpose of this document is to facilitate discussions during the 6-7 November 2017 consultations with Member States, the PIP Advisory Group, GISRS and stakeholders. Therefore, in addition to the annotated outline, this document includes proposed questions for discussion during the consultations.

5. This document has been developed on the basis of the considerable evidence on seasonal influenza and GSD collected by WHO in the course of implementation of the PIP Framework. The preliminary considerations identified in this document are taken from this evidence. For ease of reference, all sources used are listed in a *Guide to body of Evidence.*[2] Please note that many portions of this document are excerpted, in some cases verbatim, from various sources. While all sources are cited, in the interest of readability, quotation marks have in many cases been omitted.

MATTERS WITH OVERARCHING IMPLICATIONS TO THE ANALYSIS

6. In this section of the Analysis, the Secretariat will review three topics that have overarching implications for the Analysis, both in the context of seasonal influenza and GSD: (1) GISRS; (2) advancing technologies; and (3) the Nagoya Protocol to the Convention on Biological Diversity.

The WHO Global Influenza Surveillance and Response System.

7. Global influenza surveillance has been conducted through WHO's Global Influenza Surveillance and Response System (GISRS) for over half a century. Formerly known as the Global Influenza

[1] See decision WHA70(10). Review of the Pandemic Influenza Preparedness Framework. Seventieth World Health Assembly, 29 May 2017 (http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70(10)-en.pdf).

[2] See http://www.who.int/influenza/pip/evidencemap.pdf.

Surveillance Network (GISN), the new name came into effect following the adoption of the PIP Framework in May 2011.[3]

8. GISRS currently comprises 143 institutions in 113 WHO Member States, which are recognized by WHO as National Influenza Centres (NICs), 6 WHO Collaborating Centres (WHO CCs), 4 WHO Essential Regulatory Laboratories (ERLs), and 13 WHO H5 reference laboratories.[4] Each laboratory works under agreed Terms of Reference issued by WHO.[5] GISRS monitors the evolution of influenza viruses and provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment.[6] GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential.

9. In return for participating in GISRS, laboratories receive multiple benefits including, e.g.: technical training and support; the latest laboratory protocols and guidance documents; reagents and kits for molecular and antigenic testing; virus characterization reports on viruses submitted and access to associated genetic sequence data; and candidate vaccine viruses.[7]

10. GISRS provides influenza products, including candidate vaccine viruses (CVV) and reagents, and risk assessments, to GISRS and non-GISRS entities at no cost.[8] CVVs shared with industry are the basis for the development and production of seasonal and pandemic influenza vaccines.[9]

11. GISRS laboratories work across the spectrum of influenza surveillance and response, including with seasonal influenza viruses, influenza viruses with pandemic potential (IVPP), pandemic influenza viruses, and to some extent animal influenza viruses that are not currently perceived to have human pandemic potential. In this context, GISRS laboratories also work on various aspects of genetic analysis, producing, sharing and making use of GSD pertaining to all these viruses.

Advancing technologies

12. Surveillance and response to influenza requires state of the art technological capacities, particularly with regard to genetic analysis. As the PIP Framework 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."[10]

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[3] Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 25 September 2017).

[4] Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 25 September 2017).

[5] See, Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Annexes 4 and 5 (http://www.who.int/influenza/pip/en/); for WHO Collaborating Centres: Core Terms of Reference for WHO Collaborating Centres for Reference and Research on Influenza. In: World Health Organization [website]. Geneva: WHO; 2006 (http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/whocccoretor2006.pdf;); for National Influenza Centres (to be published) ; for WHO H5 Reference Laboratories: Terms of Reference for WHO H5 Reference Laboratories. In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/gisrs_laboratory/h5_reflabs/torh5reflab2006.pdf).

[6] Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 30 August 2017).

[7] See Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Annexes 4 and 5 (http://www.who.int/influenza/pip/en/); Core Terms of Reference for WHO Collaborating Centres for Reference and Research on Influenza. In: World Health Organization [website]. Geneva: WHO; 2006 (http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/whocccoretor2006.pdf); Terms of Reference for National Influenza Centres (to be published)

[8] Report of the 2016 PIP Framework Review Group. Geneva: World Health Organization; 2017: p. 40 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).

[9] Influenza vaccine viruses and reagents, . In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/vaccines/virus/en/, accessed 30 August 2017).

[10] Report of the 2016 PIP Framework Review Group, 10 April 2017. Geneva: World Health Organization; 2017: Finding 28, p. 48 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).

13. In recent years significant progress has been made in sequencing technologies (e.g. next generation sequencing and whole genome sequencing).[11] Some new technologies use GSD rather than physical virus materials in the development of vaccines and other pandemic influenza-related products ("synthetic genomics technologies").[12]

14. New technologies allow GSD derived from all influenza viruses to be used for an expanding range of purposes. Forward-looking approaches to seasonal influenza viruses and to GSD in the context of the PIP Framework will thus need to consider the implications of scientific and technological advances that are in progress and those that can be reasonably anticipated.

The Nagoya Protocol to the Convention on Biological Diversity

15. The Nagoya Protocol to the Convention on Biological Diversity (CBD) is a legally binding instrument with the fair and equitable sharing of the benefits derived from the use of genetic resources as one of its main goals.[13] Under the Protocol, genetic resources may be accessed once 'prior informed consent' and 'mutually agreed terms' have been reached, often through what are called bilateral access and benefit-sharing (ABS) agreements, negotiated between the requesting entity and the country of origin. In implementing the Protocol, some Parties have specified that pathogens fall within the scope of the Protocol.[14]

16. A WHO Study requested by the WHO Executive Board in January 2016, *Implementation of the Nagoya Protocol and Pathogen Sharing: Public Health Implications*, has found that implementation of the Nagoya Protocol may promote trust and encourage more countries to share genetic resources by improving fairness and equity.[15] However, 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, including negotiation of mutually agreed terms;
- the potential complexity of varying domestic ABS legislation.

17. This in turn could have public health implications, notably on the comprehensiveness and speed of risk assessment as well as the timely development of vaccines, diagnostics and other medical countermeasures.[16] Relevant to the Analysis, the Nagoya Protocol may have implications for implementation of the PIP Framework.

18. As the Analysis considers the implications of including seasonal influenza and GSD in the PIP Framework, it is useful to note that the Nagoya Protocol does address its relationship with other ABS instruments that cover specific genetic resources. Article 4.4 of the Protocol states that, where a specialized international access and benefit-sharing instrument (an 'SII') applies to a specific genetic resource and is recognized as consistent with the objectives of the CBD and the Nagoya Protocol, the Nagoya Protocol does not apply for the Parties to the SII for the resource in question and for the purpose of the SII.

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[11] Goodwin, S, McPherson JD, McCombie, WR. Coming of age: ten years of next-generation sequencing technologies. Nat Genetic Genet. 2016;17:333-351 (dx.doi.org/10.1038/nrg.2016.49).

[12] Dormitzer PR, Suphaphiphat P, Gibson DG, Wentworth DE, Stockwell TB et al. Synthetic Generation of Influenza Vaccine Viruses influenza vaccine viruses for Rapid Response to Pandemics, pandemics. Sci Transl Med, . 2013;5:185ra68 (dx.doi.org/10.1126/scitranslmed.3006368); See also: Suphaphiphat P, Whittaker L, De Souza I, Daniel RS, Dormitzer PR, McCauley JW et al., Antigenic characterization of influenza viruses produced using synthetic DNA and novel backbones. Vaccine. 2016;34:3641–3648 (http://dx.doi.org/10.1016/j.vaccine.2016.05.031).

[13] Nagoya Study, p. 4 Implementation of the Nagoya Protocol and pathogen sharing: Public health implications – Study by the Secretariat. Geneva: World Health Organization; 2016: p. 4 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf).

[14] This study is available in the 6 official languages of WHO at http://www.who.int/un-collaboration/partners/UNCBD/en/; See, e.g., European Union Regulation 511/2014 which states explicitly that pathogens fall within the scope of the Protocol.

[15] Nagoya Study, p. 18. Implementation of the Nagoya Protocol and pathogen sharing: Public health implications – Study by the Secretariat. Geneva: World Health Organization; 2016: p. 18 (http://www.who.int/un-collaboration/partners/Nagoya_Full_Study_English.pdf).

[16] *Ibid* at p. 14.

19. At the moment, there is no agreed definition of what constitutes an SII. This has implications for the PIP Framework, which – "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"[17]– may be eligible for consideration as an SII at some stage. The effects of the PIP Framework being an SII may be substantial and, should seasonal influenza and/or GSD be included in the Framework, these implications would extend to those areas, unless stipulations were made to the contrary.

Questions for Discussion

Overarching section (paras 1-19)

Does the overarching section of the Scoping Paper cover all of the overarching issues that are relevant to the Analysis? If not, what other issues should be addressed?

SEASONAL INFLUENZA IN THE CONTEXT OF THE PIP FRAMEWORK

20. This section of the Analysis will respond to the PIP Review Group recommendation that the WHO Director-General "undertake a study to determine the implications and desirability of including seasonal influenza viruses in the PIP Framework."

Background

21. Seasonal influenza is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world. Illness can range from mild to severe, and can result in death.[18] Seasonal and pandemic influenza viruses exist as a continuum,[19] making surveillance of seasonal influenza viruses an important part of pandemic preparedness.[20] Additionally, robust seasonal vaccine production is vital for pandemic vaccine production since the same facilities are used.[21]

22. Because influenza viruses constantly evolve, close monitoring is required to assess the risks they pose.[22] This monitoring, which drives decisions regarding the development of annual seasonal influenza vaccines as well as the response to epidemics, requires regular, timely and systematic access to virus samples.[23] GISRS uses such samples for risk assessment, monitoring viral evolution and following spread of the virus and disease.[24] GISRS laboratories provide recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment,[25] which in turn allow WHO to recommend risk management measures and development of influenza vaccines/countermeasures.[26]

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[17] See decision WHA70(10). Review of the Pandemic Influenza Preparedness Framework. Seventieth World Health Assembly, 29 May 2017 (http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70(10)-en.pdf).

[18] WHO Factsheet 211: Influenza (Seasonal), November 2016 http://www.who.int/mediacentre/factsheets/fs211/en/.. In: World Health Organization [website]. Geneva: WHO (2017; http://www.who.int/mediacentre/factsheets/fs211/en/).

[19] PIP Review Group, p. 34. Report of the 2016 PIP Framework Review Group. Geneva: World Health Organization; 2017: p. 34 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).

[20] "Fundamental to pandemic preparedness is the ongoing surveillance, epidemiologic, and laboratory activities that are undertaken to monitor and characterize both seasonal influenza, novel influenza A viruses and emerging influenza A viruses circulating in animals that have not yet infected humans." Influenza (Flu): Surveillance, Epidemiology and Laboratory . In: U.S. Centers for Disease Control and Prevention [website]. Atlanta: U.S. CDC (https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/surveillance-epidemiology-laboratory.html, accessed 31 August 2017).

[21] Report of the 2016 PIP Framework Review Group,. Geneva: World Health Organization; 2017: p. 34 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).

[22] WHO Factsheet 211: Influenza (Seasonal), November 2016. In: World Health Organization [website]. Geneva: WHO (http://www.who.int/mediacentre/factsheets/fs211/en/).

[23] [Nagoya Study] 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).

[24] *Ibid.*

[25] Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 30 August 2017).

[26] [Nagoya Study] 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).

The PIP Framework and seasonal influenza

23. Under the PIP Framework, pandemic influenza preparedness and response is promoted by improving and strengthening GISRS, with the objective of a fair, transparent, equitable, efficient, effective system for (i) the sharing of H5N1 and other influenza viruses with human pandemic potential; and (ii) access to vaccines and sharing of other benefits.[27] Member States are expected to provide PIP biological materials[28] from all cases of H5N1 and other influenza viruses with human pandemic potential, as feasible, to the WHO CC on Influenza or WHO H5 Reference Laboratory of the originating Member State's choice.[29] Standard material transfer agreements 2 (SMTA-2s) between WHO and non-GISRS recipients of PIP biological materials are put in place to ensure fair and equitable benefit sharing. In addition, influenza vaccine, diagnostic and pharmaceutical manufacturers using GISRS make an annual partnership contribution to WHO for improving global pandemic influenza preparedness and response.[30]

24. To a certain degree, seasonal influenza is already included in these benefit sharing arrangements. Under the Partnership Contribution, "using GISRS" is understood to "include receipt of physical materials, or use of data and/or information, some of which may not be routinely provided to the general public".[31] The Partnership Contribution formula is based on companies' average annual influenza product sales (seasonal and pandemic).[32] The sum of the annual Partnership Contributions [currently US$ 28 million per year] is designed to be equivalent to 50% of the running costs of GISRS.[33] GISRS running costs are borne by Member States and such monies support laboratory running costs for all influenza activities handled by a laboratory – not only those related to pandemic influenza.[34] Additionally, to improve global pandemic influenza preparedness and response, certain projects under Partnership Contribution Implementation focus on building countries' capacity to address all aspects of influenza, such as strengthening influenza laboratory surveillance and producing influenza disease burden estimates.[35]

25. Beyond the role seasonal influenza viruses play in the Partnership Contribution as described above, the PIP Framework does not specifically cover the sharing of seasonal influenza viruses. Thus, seasonal viruses are not included under the definition of PIP Biological Materials, and there are no SMTAs and related benefit sharing linked specifically to the sharing of seasonal influenza viruses.

Table A. Implications of pursuing three possible approaches to seasonal influenza viruses in the context of the PIP Framework

26. In this section, potential implications of expanding or not expanding the PIP Framework to include seasonal influenza will be explored by examining the opportunities and challenges of three approaches:

- Approach 1: Expand the PIP Framework to include seasonal influenza viruses
- Approach 2: Do not expand the PIP Framework so that national access and benefit-sharing regimes under the Nagoya Protocol apply to the sharing of seasonal influenza viruses

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[27] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Section 2 (http://www.who.int/influenza/pip/en/).

[28] PIP biological material "includes 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.." Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Section 4.1 (http://www.who.int/influenza/pip/en/).

[29] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Section 5.1.1 (http://www.who.int/influenza/pip/en/).

[30] *Ibid* at Section 6.14.3

[31] Pandemic Influenza Preparedness Framework: Distribution of Partnership Contribution among companies. In: World Health Organization [website]. Geneva: WHO; 2013 (http://www.who.int/influenza/pip/pc_distribution.pdf)

[32] *Ibid.*

[33] Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Section 6.14.3 (http://www.who.int/influenza/pip/en/).

[34] *Ibid.*

[35] Pandemic Influenza Preparedness Framework: Partnership Contribution Implementation Plan 2013-2016. In: World Health Organization [website]. Geneva: WHO; 2015 (http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf).

- Approach 3: Do not expand the PIP Framework and develop or adapt another instrument to cover seasonal influenza viruses, with a view to that instrument being recognized as an SII under the Nagoya Protocol

27. Opportunities and challenges for each approach have been consolidated in Table A. The Secretariat used the following methodology in generating this table:

1. Evidence was collected and compiled from the following sources:
    a. Report of the 2016 PIP Review Group[36];
    b. WHO study on the public health implications of the implementation of the Nagoya Protocol[37];
    c. Transcripts from interviews with GISRS laboratories and other stakeholders conducted by the 2016 PIP Review Group[38];
    d. Submissions from Member States, GISRS laboratories and other stakeholders to the 2016 PIP Review[39];
    e. Submissions from WHO Member States, GISRS laboratories, Parties to the Convention on Biological Diversity and the Nagoya Protocol and other stakeholders to the questions sent by the Secretariat in the context of the WHO study on the public health implications of the implementation of the Nagoya Protocol;[40]
    f. Interventions by Member States during the 140th Executive Board and the 70th World Health Assembly[41];
2. A review of this evidence highlighted three potential approaches to seasonal influenza under the Framework as well as potential opportunities and challenges for each of these approaches. These have been summarized in the table below. Where relevant, opportunities have been paired with corresponding challenges.
3. Sources have been anonymized and are included in the tables. Numbers in brackets correspond to the reference numbers in the appropriate evidence Compilation table. The letter "S" refers to information contained in Compilation I "Seasonal Analysis"; the letter "G" to evidence in Compilation II "GSD Analysis" and the letter "A" to evidence in Compilation III "PIP Advisory Group work on GSD under the Framework". Where possible, references in the tables below are hyperlinked to the appropriate Compilation or reference document.

[36] Report of the 2016 PIP Framework Review Group. Geneva: World Health Organization; 2017 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).
[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).
[38] Interviewees were asked "Should seasonal influenza viruses be included in the PIP Framework? What are the advantages and disadvantages as well as the opportunities and challenges of expanding the scope in this way?"
[39] 2016 [PIP Framework] Review Submissions. In: World Health Organization [website]. Geneva: WHO (2016; http://www.who.int/influenza/pip/2016-review/submissions/en/, accessed 13 September 2017).
[40] Questions asked were : What are the implications of implementing the Nagoya Protocol with respect to accessing seasonal influenza viruses? What actions do you think could be taken to ensure that, in countries where the Nagoya Protocol is being implemented, public health entities continue to have access to seasonal influenza viruses? Are there specific actions that you would recommend be taken to promote implementation of the Nagoya Protocol in harmony with public health programmes that require access to pathogens?"
[41] Submissions were not made public.

Table A. Implications of pursuing three possible approaches to seasonal influenza viruses in the context of the PIP Framework

	Opportunities			Challenges		
	Description of opportunities	**Summary of relevant information found in the evidence**	**References**	**Description of challenges**	**Summary of relevant information found in the evidence**	**References**
Approach 1: Expand the PIP Framework to include seasonal influenza viruses	Address challenges related to the implementation of the Nagoya Protocol for seasonal influenza viruses (and their GSD)	If the PIP Framework is designated as a specialized international access and benefit-sharing instrument under article 4(4) of the Nagoya Protocol ("SII"), the inclusion of seasonal influenza under the scope of the PIP Framework would mean that the Protocol would not apply to either IVPP or seasonal influenza viruses. This approach could help to address challenges related to the implementation of the Nagoya Protocol for seasonal influenza.	*See*: [Nagoya Study, p.23-25] [Collaboration with the Secretariat of the CBD and other relevant international organizations - Report by the Secretariat] See references number: [S1] [S3][S13] [S17] [S30] [S31]	Increases the workload for GISRS, costly and resource intensive	Tracing seasonal influenza virus sharing through the Influenza Virus Traceability Mechanism ("IVTM"), as required for IVPP under the PIP Framework, could significantly increase the volume of data entry work and lead to a substantial increase in workload for GISRS laboratories. Without a proportional increase in resources, this has the potential to overwhelm GISRS and impact the timeliness and effectiveness of GISRS.	*See*: [Report of the 2016 Review Group, p.35] See references number: [S1] [S2] [S3] [S5] [S6] [S13] [S16] [S21]
	Improve seasonal influenza virus sharing and development of seasonal vaccines	One main objective of the PIP Framework is to improve sharing of influenza viruses with pandemic potential. Including seasonal influenza could leverage PIP Framework mechanisms to improve seasonal influenza virus sharing, including ensuring that candidate vaccine viruses are provided to industry in time to make vaccines.	See references number: [S1] [S8]	Slows down seasonal influenza virus sharing and development of seasonal vaccines	The workload and increased complexity associated with tracing seasonal influenza virus sharing and other procedures associated with the inclusion of seasonal influenza under the PIP Framework (e.g. SMTAs) could potentially impact laboratories' capacity to share influenza viruses in a timely manner.	See reference number: [S5] [S6] [S19]
	Highlight linkages between seasonal and pandemic preparedness	Global influenza prevention and surveillance would be more effective if it were more comprehensive, encompassing seasonal and IVPP. Including seasonal influenza in the PIP Framework could facilitate a more holistic approach.	See: [Report of the 2016 Review Group, p.35] See references number: [S2] [S7] [S16] [S17] [S24] [S25]	PIP Framework is tailored to health emergencies, not adapted to seasonal influenza	The PIP Framework was developed to address a health emergency, so it is not tailored to seasonal influenza response. Certain components of the Framework are also specific to the pandemic context (eg, provision of benefits under the SMTA 2 is linked to the declaration of a pandemic).	See references number: [S11] [S19] [S20]

	Opportunities			Challenges		
	Description of opportunities	**Summary of relevant information found in the evidence**	**References**	**Description**	**Summary of relevant information found in the evidence**	**References**
Approach 1: Expand the PIP Framework to include seasonal influenza viruses (continued)	Promote seasonal influenza prevention and control	Inclusion of seasonal influenza in the Framework could highlight the importance of seasonal activities. This in turn could promote greater focus and investments in this sector, and lead to more resources to support developing countries. In addition, this could facilitate access to funds in cases of severe outbreaks of seasonal influenza.	See references number: [S5] [S9] [S17]	Impede pandemic influenza preparedness and response, and implementation of the PIP Framework	Inclusion of seasonal influenza in the Framework could detract from its health emergency focus and impact prioritization of pandemic preparedness activities by Member States. For instance, the added complexity and workload of an expanded Framework would make implementation of pandemic influenza preparedness and response activities more challenging, especially if sharing of seasonal influenza viruses is traced through the IVTM.	See references number: [S5] [S14] [S19] [S20]
	Increase the number of benefit-sharing contributors under the PIP Framework	Some manufacturers may develop seasonal influenza products or have licensed seasonal influenza products, but no licensed pandemic influenza products. In addition, there are a number of institutions (e.g. universities and other research institutions) that receive seasonal influenza virus materials only. These entities, which are not currently captured under the PIP Framework benefit-sharing mechanisms, could potentially be expected to participate in an expanded PIP Framework.		Increase the workload of the Secretariat	Because a larger number of entities receive seasonal influenza virus materials than PIP BM, the inclusion of seasonal influenza viruses in the Framework, especially if receipt is also linked to the conclusion of an SMTA 2, could increase the workload of the Secretariat considerably.	
	Address the handling of seasonal influenza GSD	Inclusion of seasonal influenza in the Framework could address the potential implications related to the inclusion of GSD under the Nagoya Protocol if the PIP Framework is designated as a specialized international access and benefit-sharing agreement under the Protocol.		Complex negotiations to amend the scope of the PIP Framework	Amending the scope of the PIP Framework could require long and complex negotiations. Reopening the text of the PIP Framework may lead to changes to the current text, which could jeopardize progress achieved so far.	See references number: [S11] [S14] [S19] [S20]

	Opportunities			Challenges		
	Description of opportunities	**Summary of relevant information found in the evidence**	**References**	**Description of challenges**	**Summary of relevant information found in the evidence**	**References**
Approach 2: Do not expand the PIP Framework so that national access and benefit-sharing regimes under the Nagoya Protocol apply to the sharing of seasonal influenza viruses	Clarify benefit-sharing obligations for seasonal influenza	The ABS agreement ("mutually agreed terms") negotiated between countries and entities that access seasonal influenza viruses may result in clear, predictable benefit-sharing obligations, which could improve access to affordable seasonal influenza vaccines and treatments, and aid in capacity building.	See: [Nagoya Study]	Slow down seasonal influenza virus sharing and delay development of seasonal vaccines	Increased workload and legal complexity due to variability among national access and benefit-sharing rules may slow or limit virus sharing and delay or hinder the development of comprehensive and effective vaccines and other medical countermeasures. This could constitute a significant global public health threat. This could hamper GISRS's capacity to identify newly emerging variants of influenza viruses that may have human pandemic potential.	See: [Nagoya Study] See references number: [S22] [S32]
	Allow PIP Framework to remain focused on pandemic preparedness and response	This could ensure that the PIP Framework maintains its focus on health emergency and that its implementation is not affected by its broader scope.	See references number: [S5] [S14] [S18] [S19] [S20]	Significant increased workload for GISRS due to additional negotiations and administrative requirements with potential negative impact on the timeliness of seasonal preparedness.	Implementation of the Nagoya Protocol will likely require that GISRS laboratories comply with administrative requirements of provider countries (e.g. obtaining the appropriate authorization and/or agreeing on mutually agreed terms).	See: [Nagoya Study] See reference number: [S5]
	No negotiations or re-opening the text of the PIP Framework	This would mean that WHO Member States do not have to go through long negotiations to change the scope of the PIP Framework or to adopt a new instrument.		Legal complexity	Conditions for access and benefit sharing in the context of seasonal influenza viruses may differ widely among Parties to the Nagoya Protocol. This would make the landscape of access and sharing complex. For example, provider country legislation may carry obligations related to third-party transfers, which would make sequential sharing events complicated.	See: [Nagoya Study] See reference number: [S23]
	Does not increase workload for WHO	Negotiations of access and benefit-sharing under the Nagoya Protocol are handled in a bilateral manner between the provider Party and the recipient laboratory.				
	Seasonal influenza genetic sequence data: Discussions about the handling of genetic sequence data under the Nagoya Protocol are ongoing. Depending on the outcome of these discussions, it is possible that the genetic sequence data of seasonal influenza are included under the scope of the Nagoya Protocol and subject to its access and benefit sharing obligations.					

	This could bring both opportunities and challenges.

	Opportunities			Challenges		
	Description of opportunities	**Summary of relevant information found in the evidence**	**References**	**Description of challenges**	**Summary of relevant information found in the evidence**	**References**
Approach 3: Develop or adapt another instrument to cover seasonal influenza viruses, with a view to that instrument being recognized as an SII under the Nagoya Protocol	Address implications of the Nagoya Protocol on seasonal influenza viruses (and their GSD)	If the new instrument were designated an SII, it could address Nagoya Protocol implementation challenges. Alternatively, it could be possible that GISRS could be an SII, if formalized, including articulating benefit-sharing vis-à-vis seasonal influenza (beyond that already addressed through the Partnership Contribution).	See: [Nagoya Study] See references number: [S15] [S18] [S19] [S28] [S29] [S30] [S33] [S34] [S36] [S38]	Increased complexity and duplication	A new instrument covering seasonal influenza could result in a multiplicity of rules governing access and benefit-sharing for influenza viruses, which could increase complexity for GISRS and stakeholders, notably manufacturers and institutions that receive virus material.	See references: [S38] See: International Law Commission. Fragmentation of international law: Difficulties arising from the diversification and expansion of international law: Report of the Study Group of the International Law Commission.2006.
	Improve seasonal influenza virus sharing and the development of seasonal vaccines	If a new instrument provided a clear and equitable system for access for access and benefit-sharing for seasonal influenza viruses, it could promote trust, and encourage more countries to share viruses, especially in the context of the Nagoya Protocol.		Could potentially increase workload for GISRS	Depending on the system implemented (e.g. if virus sharing is monitored), this could increase the workload for GISRS laboratories.	See: [S5] [S6]
	Raise profile of seasonal influenza prevention and control, increase resources	A new instrument could highlight the importance of seasonal activities and perhaps increase resources (e.g. better access to affordable vaccines and treatments) and aid for capacity building.	See references number: [S9] [S12]	Negotiating a new instrument or adapting and/or recognizing existing instrument would be complex	Negotiations will be time-consuming and resource-intensive. For instance, it took more than 4 years to negotiate the PIP Framework.	See: Taylor A, Dhillon I. An international legal strategy for alcohol control: not a framework convention—at least not yet. Addiction. 2013;108: 450-455, p. 452 See references

						number: [S38]
	Tailored to the seasonal influenza context	A new instrument could be tailored to the specificities of seasonal influenza.	See references number: [S11] [S30]	Implementation of a new instrument	Developing and implementing a new instrument requires resources and will have a period of uncertainty/inefficiency.	See references number: [S38]
	PIP Framework remains focused on pandemic preparedness and response	The PIP Framework would maintain its health-emergency focus, which may help to ensure that its implementation is not compromised.	See references number: [S5] [S14] [S18] [S19] [S20]	Does not consider linkages between seasonal and pandemic influenza; possible duplication	Several components of the PIP Framework already tacitly integrate seasonal influenza.	
	Addresses handling seasonal influenza GSD	A new instrument could address potential challenges related to GSD (in Nagoya Protocol and re: changes in technologies).		Increase workload for WHO and duplication	Implementation of the new instrument could potentially require a new Secretariat/dedicated staff.	

Questions for discussion

SEASONAL INFLUENZA IN THE CONTEXT OF THE PIP FRAMEWORK
Background to the seasonal influenza section (paras 20-25): Does the Scoping Paper cover all the issues that are relevant to the analysis of pursuing or not pursuing possible approaches to include seasonal influenza in the Framework? If not, what issues should be addressed?
Implications of pursuing three possible approaches to seasonal influenza viruses in the context of the PIP Framework
Approach 1: Expand the PIP Framework to include seasonal influenza viruses (paras 26-27 and Table A) What would be the implications of including seasonal influenza viruses in the PIP Framework for: • Pandemic influenza preparedness and response? • Seasonal influenza prevention and control? • The work of GISRS? • The development of influenza vaccines and other influenza products? Are there other implications to consider? How should the challenges identified under this approach be addressed?
Approach 2: Do not expand the PIP Framework so that national access and benefit-sharing regimes under the Nagoya Protocol apply to the sharing of seasonal influenza viruses (paras 26-27 and Table A) With reference to the findings contained in the WHO Nagoya Study, are there other opportunities or challenges that might arise from seasonal influenza viruses being covered by the Nagoya Protocol?
Approach 3: Develop or adapt another instrument to cover seasonal influenza viruses, with a view to that instrument being recognized as an SII under the Nagoya Protocol(paras 26-27 and Table A): What would be the implications of developing or adapting another instrument to cover seasonal influenza viruses for: • Pandemic influenza preparedness and response? • Seasonal influenza prevention and control? • The work of GISRS? • The development of influenza vaccines and other influenza products? Are there other implications to consider? How should the challenges identified under this approach be addressed?

GENETIC SEQUENCE DATA (GSD) IN THE CONTEXT OF THE PIP FRAMEWORK

28. This section of the Analysis will respond to the PIP Review Group recommendations that the WHO Director-General should request Member States to:

- consider amending the definition of PIP biological materials in section 4.1 of the PIP Framework to include GSD (recommendation 12);
- consider clarifying Annex 4, section 9, which currently states that "The WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement", by amending it to: "The WHO GISRS laboratories will submit genetic sequences data to one or more publicly accessible database of their choice in a timely manner consistent with the Standard Material Transfer Agreement" (recommendation 13); and
- consider updating and correcting the statement in section 5.2.2 of the PIP Framework, which currently states "Recognizing that greater transparency and access concerning influenza virus genetic sequence data is important to public health and there is a movement towards the use of public-domain or public-access databases such as Genbank and GISAID respectively;" by amending it to: "Recognizing that greater transparency and access concerning influenza virus genetic sequence data is important to public health and use is made of public domain or public-access databases such as GenBank and/or GISAID, respectively" (recommendation 14).

29. This section will also reflect recommendation 16, that the Director-General should enlist the support of Member States to ensure that influenza virus genetic sequence data remain publicly accessible in sustainable databases, to enable timely, accurate and accessible sharing of these data for pandemic risk assessment and rapid response.

Background

30. As technology advances, GSD is becoming increasingly critical in influenza research, and in some cases, GSD can now be used instead of physical material for pandemic risk assessment and the development of commercial products.[42]

31. Once a clinical specimen is collected from an influenza patient, the virus can be isolated and characterised. Genetic sequencing is one of the main ways in which viruses are characterised. GSD can be used to:

- monitor the emergence and evolution of variant seasonal viruses and make timely decisions and recommendations on the composition of influenza vaccines, antiviral medicine sensitivity and molecular diagnostic methods;
- develop novel predictive modeling algorithms that can facilitate WHO vaccine virus selection;
- improve risk assessment in candidate virus selection to avoid mismatch;
- develop more sensitive virus detection methods and generate candidate vaccine viruses;
- produce recombinant influenza vaccine and potentially also allow egg- and cell-based vaccine manufacturers to use synthetic genomics to construct candidate vaccine viruses.[43]

32. To ensure timely risk assessment and influenza product development, GSD should be shared rapidly after sample collection and sequencing.[44] For example, the *WHO Survey on the sharing of IVPP GSD*

[42] Under PIP Framework section 4.2, genetic sequences are defined as "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." Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011: Section 4.2 (http://www.who.int/influenza/pip/en/).

[43] United States Government Feedback for the 2016 Pandemic Influenza Preparedness Framework Review: Nagoya Protocol and Genetic Sequence Data, 5 August 2016. In: World Health Organization [website]. Geneva: WHO; 2017 (http://www.who.int/influenza/pip/2016-review/US_GSD_Nagoya_Aug2016.pdf).

found that almost all respondent data users "needed access to IVPP GSD at least within three months of their upload, with the majority needing access within two weeks, regardless of their intended use for the data".[45] The *Technical Working Group on the sharing of IVPP GSD* (TWG) recommended that data be uploaded no later than one month after sequencing is completed, with "draft preliminary or partial IVPP sequences […] submitted within 14 days".[46]

33. GSD of influenza viruses, both IVPP, seasonal, and other, are generated by GISRS laboratories and other laboratories around the world.[47] Many laboratories upload influenza GSD to databases, or share it by email, or through reports. GSD can be stored internally (e.g. in institutional databases) or stored in external databases, which include databases, such as GISAID EpiFlu™, the INSDC databases, the Influenza Research Database and OpenFlu. Most GISRS laboratories use GISAID EpiFlu™[48] and several providers use more than one platform to share IVPP GSD.[49]

The PIP Framework and GSD

34. 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 the use of those viruses. While Member States did not explicitly extend this principle to GSD under the PIP Framework, recognizing instead that that further work and analysis would be needed,[50] the PIP Framework did establish some principles for GSD. It "recogniz[ed] 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). Consistent with this, the Framework set out the following expectations:

- "[G]enetic sequence data, and analyses arising from that data, relating to H5N1 and other influenza viruses with human pandemic potential should be shared in a rapid, timely and systematic manner with the originating laboratory and among WHO GISRS laboratories" (Section 5.2.1).
- WHO CCs "upload available haemagglutinin, neuraminidase and other gene sequences of A(H5) and other influenza viruses with pandemic potential to a publicly accessible database in a timely manner but no later than three months after sequencing is completed, unless otherwise instructed by the laboratory or country providing the clinical specimens and/or viruses (Guiding Principle 9)" (see Annex 5 Terms of Reference for WHO Collaborating Centres, Core Term of Reference B.5).
- "WHO GISRS laboratories will submit genetic sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement."

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[44] The PIP Framework states under section 5.2.1 that: "Genetic sequence data, and analyses arising from that data, relating to H5N1 and other influenza viruses with human pandemic potential should be shared in a rapid, timely and systematic manner with the originating laboratory and among WHO GISRS laboratories." *Ibid.*

[45] WHO Survey on the Sharing of Genetic Sequence Data of Influenza Viruses with Human Pandemic Potential: Results and Analysis of data received. Geneva: World Health Organization; 2016: p. 16 (http://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf?ua=1.http://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf).

[46] PIP Framework Advisory Group Technical Working Group (TWG) on the sharing of influenza genetic sequence data, ". Optimal Characteristics of an Influenza Genetic Sequence Data Sharing Systemunder the PIP Framework",. Geneva: World Health Organization; 2016,: p. 8 (http://www.who.int/influenza/pip/advisory_group/twg_doc.pdf?ua=1.http://www.who.int/influenza/pip/advisory_group/twg_doc.pdf).

[47] PIP Framework Advisory Group Technical Expert Working Group (TEWG) on genetic sequence data. Final Report to the PIP Advisory Group. Geneva: World Health Organization; 2014: p.pp. 6-7 (http://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf).

[48] PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 9-11 April 2014, Geneva, Switzerland – Report to the Director-General. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_36Add1-en.pdf); WHO survey on the sharing of genetic sequence data of influenza viruses with human pandemic potential: Results and analysis of data received. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf).

[49] WHO survey on the sharing of genetic sequence data of influenza viruses with human pandemic potential: Results and analysis of data received. Geneva: World Health Organization; 2016: p. 16 (http://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf).

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

(see Annex 4, Guiding Principles for the development of Terms of Reference for current and potential future WHO global influenza surveillance and response system (GISRS) laboratories for H5N1 and other human pandemic influenza viruses, Principle 9)."

35. IVPP GSD are included under the PIP Framework, but not in the definition of PIP BM. Because conclusion of an SMTA 2 is linked to receipt of PIP BM, access to, or use of IVPP GSD does not trigger the obligation to conclude an SMTA 2 with WHO. However, use of IVPP GSD has been included as an example of "use of GISRS" in the context of the Partnership Contribution.

36. As noted by the Technical Expert Working Group on GSD, in the absence of mechanisms to ensure fair and equitable benefit sharing for GSD "the attainment of essential objectives of the PIP Framework may be systematically frustrated"[51], as only one element of the benefit sharing package – the Partnership Contribution is triggered by the use of GSD from GISRS.

PIP Framework Advisory Group and GSD

37. In the PIP Framework, Member States "request the Director-General to consult the Advisory Group on the best process for further discussion and resolution of issues relating to the handling of genetic sequence data under the PIP Framework." (Section 5.2.4).

38. To support the development of this guidance, the PIP Framework Advisory Group has: 1) provided several recommendations to WHO leadership on the matter of GSD under the Framework; 2) established two technical working groups; and 3) developed several documents on handling GSD under the Framework.[52]

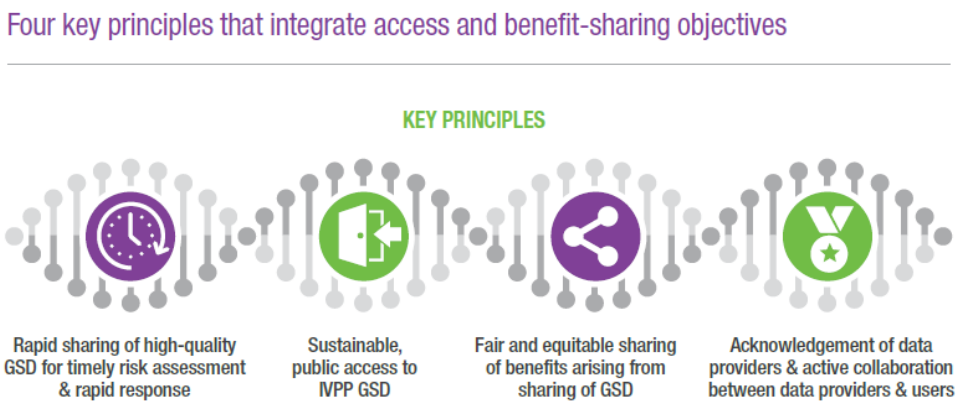
39. The Advisory Group's work contains considerable technical background materials to inform the Analysis, and articulates four key principles that could apply to the sharing of GSD under the Framework: (1) rapid sharing of high-quality GSD for timely risk assessment and rapid response, (2) sustainable, public access to IVPP, (3) fair and equitable sharing of benefits arising from the sharing of GSD and, (4) acknowledgment of data providers and active collaboration between data providers and users (see figure below).

40. Most recently, the Director-General accepted the Advisory Group's recommendation that it continue its work under section 5.2.4 by developing guidance on an approach to operationalize the handling of IVPP GSD under the PIP Framework for both data sharing and benefit sharing.[53] At its next meeting (8-10 November 2017), the Advisory Group will discuss how to take forward its work on GSD, taking into account the discussions and outcomes of the consultation of 6-7 November.

[51] Report of the Technical Expert Working Group on GSD PIP Framework Advisory Group Technical Expert Working Group (TEWG) on genetic sequence data. Final Report to the PIP Advisory Group. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf).

[52] An infographic of the timeline of the PIP AG's work on GSD is available online: GSD Timeline: Process for handling genetic sequence data under the PIP Framework. In: World Health Organization [website]. Geneva: WHO; 2017 http://www.who.int/influenza/pip/advisory_group/GSD_timeline.pdf(http://www.who.int/influenza/pip/advisory_group/GSD_timeline.pdf, accessed 13 October 2017).

[53] PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 28-31 March 2017, http://www.who.int/influenza/pip/AG_Mar2017.pdf, Geneva, Switzerland – Report to the Director-General. Geneva: World Health Organization; 2017: paragraph 32. (http://www.who.int/influenza/pip/AG_Mar2017.pdf).



Considerations in relation to GSD under the PIP Framework

41. Addressing the Review Group's recommendations on GSD requires consideration of a number of different factors. These may have implications for how GSD is handled under the PIP Framework. This section highlights some considerations and describes how they could affect approaches to GSD under the PIP Framework.

42. The considerations have been consolidated in Table B. WHO used the following methodology to develop this table:

1. Evidence was collected and compiled from the following sources:
    a. Report of the 2016 PIP Framework Review Group[54];
    b. Transcripts from interviews with GISRS laboratories and other stakeholders conducted by the 2016 PIP Framework Review Group[55];
    c. Submissions from Member States, GISRS laboratories and other stakeholders to the 2016 PIP Framework Review[56];
    d. WHO study on the public health implications of the implementation of the Nagoya Protocol[57];
    e. Submissions from WHO Member States, GISRS laboratories, Parties to the Convention on Biological Diversity and the Nagoya Protocol and other stakeholders to the questions sent by the Secretariat in the context of the WHO study on the public health implications of the implementation of the Nagoya Protocol;[58]
    f. Interventions by Member States during the 140th Executive Board and the 70th World Health Assembly[59];

[54] Report of the 2016 PIP Framework Review Group. Geneva: World Health Organization; 2017 (A70/17; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_17-en.pdf).
[55] Interviewees were asked "Should seasonal influenza viruses be included in the PIP Framework? What are the advantages and disadvantages as well as the opportunities and challenges of expanding the scope in this way?"
[56] 2016 [PIP Framework] Review Submissions. In: World Health Organization [website]. Geneva: WHO (2016; http://www.who.int/influenza/pip/2016-review/submissions/en/, accessed 13 September 2017).
[57] 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).
[58] Questions asked were : What are the implications of implementing the Nagoya Protocol with respect to accessing seasonal influenza viruses? What actions do you think could be taken to ensure that, in countries where the Nagoya Protocol is being implemented, public health entities continue to have access to seasonal influenza viruses? Are there specific actions that you would recommend be taken to promote implementation of the Nagoya Protocol in harmony with public health programmes that require access to pathogens?"
[59] Submissions were not made public.

g. Submissions from Member States, GISRS laboratories and other stakeholders to the Technical Expert Working Group on GSD[60];

h. Report of the Technical Expert Working Group on GSD[61];

i. Submissions from Member States, GISRS laboratories and other stakeholders to the Technical Working Group on sharing influenza GSD[62];

j. Report of the Technical Working Group on sharing influenza GSD[63];

k. Submissions to the Secretariat in relation to the paper *Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products*[64];

l. WHO Survey on the sharing of IVPP GSD [65];

m. WIPO Patent issues related to influenza viruses and their genes: working paper[66]

n. WIPO Patent search report on pandemic influenza preparedness (PIP) –related patents and patent applications[67]

o. Meeting reports of the PIP Advisory Group[68].

2. Review of this evidence highlighted a number of considerations that may affect approaches to GSD under the Framework. The table below summarizes these considerations and describes their potential implications for approaches to GSD under the PIP Framework.

3. Sources have been anonymized and are included in the tables. Numbers in brackets with the letter G correspond to the reference numbers in the appropriate evidence table in Compilation II (GSD Analysis). Where possible, references in the tables below are hyperlinked to the compilation or reference document . An additional table of evidence, Compilation III, contains relevant excerpts from Advisory Group works (e.g. meeting report findings, recommendations and guidance)[69]. References to Advisory Group works in the table below are hyperlinked to Compilation III.

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[60] PIP Framework Advisory Group Technical Expert Working Group (TEWG) on genetic sequence data. Final Report to the PIP Advisory Group. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf).

[61] *Ibid.*

[62] Handling of influenza genetic sequence data under the PIP Framework: Comments received on the draft document 'Optimal characteristics of an influenza genetic sequence data sharing system under the PIP Framework'. World Health Organization [website]. Geneva: WHO (http://www.who.int/influenza/pip/advisory_group/twg_comments/en/, accessed 13 October 2017).

[63] PIP Framework Advisory Group Technical Working Group (TWG) on the sharing of influenza genetic sequence data. Optimal characteristics of an influenza genetic sequence data sharing system under the PIP Framework. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/twg_doc.pdf).

[64] Handling genetic sequence data under the PIP Framework. In: World Health Organization [website]. Geneva: WHO (http://www.who.int/influenza/pip/advisory_group/gsd/en/, accessed 13 October 2017).

[65] WHO survey on the sharing of genetic sequence data of influenza viruses with human pandemic potential: Results and analysis of data received. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/GSDSurveyResults.pdf).

[66] WIPO Patent issues related to influenza viruses and their genes: working paper. World Intellectual Property Organization. Geneva: WIPO; 2007. (http://apps.who.int/medicinedocs/documents/s21417en/s21417en.pdf, accessed 15 October 2017)

[67] WIPO Patent search report on pandemic influenza preparedness (PIP) –related patents and patent applications. World Intellectual Property Organization. Geneva: WIPO; 2011. (http://www.wipo.int/export/sites/www/policy/en/global_health/pdf/report_influenza_2011.pdf, accessed 15 October 2017)

[68] PIP Framework Advisory Group Reports. In: World Health Organization [website]. Geneva: WHO (http://www.who.int/influenza/pip/pip_meetings_consultations/en/, accessed 13 October 2017).

[69] See Compilation III "*PIP Advisory Group work on GSD under the Framework*" http://www.who.int/influenza/pip/AGcompilation.pdf

Table B. Considerations in relation to GSD under the PIP Framework

Consideration	Description of consideration	Potential implications identified in the evidence	References
Challenges to sharing GSD	- Technical, motivational, economic, political, legal and other considerations affect the speed, breadth, and comprehensiveness of data sharing. These may include lack of human and technical resources needed to process GSD; cost of maintaining the infrastructure needed to generate, share and store data; data sharing agreements and policies; legal and/or administrative measures; publication policies; and other related factors such as acknowledgement and collaboration opportunities.	- It is important that influenza virus genetic sequence data remain publicly accessible in sustainable databases, to enable timely, accurate and accessible sharing of these data for pandemic risk assessment and rapid response. - Amending the PIP Framework could help to address some of these challenges to data sharing and could promote sharing.	*See*: [Report of the 2016 Review Group, recommendation 16, p.54] [October 2014 Advisory Group meeting report, par. 30-31][April 2016 Advisory Group meeting report, par. 49-51, 53][October 2016 Advisory Group meeting report, par. 13-14][Technical Working Group on the sharing of GSD, Optimal Characteristics of a data sharing system under the PIP Framework][WHO Survey on the sharing of IVPP GSD] See references number: [G1][G4][G10][G13][G27][G36]
Increasing usefulness of GSD for public health (e.g. risk assessment; product development)	- Advances in technology allow laboratories to do much more with GSD alone than was possible a few years ago. The need for physical samples is diminishing in some instances. For example, it is now possible to synthesize complete influenza viruses using GSD from isolated viruses. - An increasing number of vaccine manufacturers are using technologies relying on GSD as an alternative to conventional approaches making it possible to more rapidly develop vaccines.	- New technologies that facilitate risk assessment and vaccine production can improve influenza pandemic preparedness. - In the future, laboratories and manufacturers will rely increasingly on GSD to the exclusion of PIP biological materials. Companies that use GSD rather than PIP biological material to develop influenza-related products may not have signed an SMTA-2 with WHO. In that case, there will not be an obligation to provide WHO access to pandemic vaccines and other products that are generated using GSD only in the event of a pandemic. This has the potential to undermine the PIP Framework.	*See*: [Report of the 2016 Review Group, finding 28, p.48, recommendation 15, p.54] [October 2013 Advisory Group meeting report, par. 5-6][Report of the Technical Expert Working Group on GSD, October 2014][Suphaphiphat P, Whittaker L, De Souza ID, Daniel RS, Dormitzer PR, McCauley JW, et al. Antigenic characterization of influenza viruses produced using synthetic DNA and novel backbones. Vaccine. 2016;12:3641-3648]. See references number: [G2][G4][G6][G9][G10][G14][G16][G17][G19][G20][G22][G2

Consideration	Description of consideration	Potential implications identified in the evidence	References
			9][G36][G41]
Monitoring the sharing or use of IVPP GSD	- Unlike PIP BM, GSD is intangible and can be widely and rapidly disseminated. GSD can be shared via public and private means including through databases, by email, in reports, and such sharing is not necessarily easily trackable.	- It would be difficult to implement a traceability system for GSD, as exists for PIP biological materials under the PIP Framework. - The nature and extent of actual use of GSD that is accessed is extremely variable. - Monitoring all access to GSD is unlikely to be feasible and could result in significant workload for laboratories and/or WHO. - The objective of benefit-sharing may be met by mechanisms related to monitoring products generated using GSD, rather than by monitoring use of GSD and/or tracing GSD. - Equity would require that all users of GSD be subject to the same measures; if benefit sharing is to be expected from users of GSD, then users must have notice of this.	*See*: [April 2014 Advisory Group meeting report, par. 4][October 2014 Meeting Report, par. 29-31][April 2016 Advisory Group Meeting Report, par. 53] [Report of the Technical Expert Working Group, p.2] See references number: [G1][G6][G20][G30][G34][G37][G38][G40][G41]
GSD and the Nagoya Protocol	- GSD are not expressly included in the scope of the Nagoya Protocol. Parties to the Nagoya Protocol and the CBD will consider this issue in 2018. - At the most recent Conference of the Parties serving as the Meeting of the Parties to the Nagoya Protocol (COP-MOP), Parties agreed to establish an ad hoc technical expert group to consider the potential implications of the use of digital sequence information on genetic resources for the objective of the Nagoya Protocol. Outcomes of this process will be discussed by the Parties at the next COP-MOP in November 2018.	- The outcome of discussions on digital sequence information in the context of the Nagoya Protocol and the Convention on Biological Diversity may have an impact on the sharing of influenza GSD. - The outcome may also impact the handling of other human pathogens and potentially hinder response during a public health emergency.	*See*: [Nagoya Study, p.12] [Collaboration with the Secretariat of the Convention on Biological Diversity and other relevant international organizations, Report by the Secretariat, p2-3] See reference number: [G21]
Intellectual property rights and genetic sequences	- In most jurisdictions, naturally-occurring influenza GSD would not be considered patentable subject matter. However, innovations from the development of influenza-related products could be protected if patentability requirements are met (these are generally: novelty; patentability of the subject-matter; and an inventive step) - The early, open publication of gene sequences of newly-isolated influenza viruses may preclude obtaining patent protection for the genes as published.	- Several publicly-accessible IVPP sequences have been claimed as part of patent. - Early publication of IVPP GSD may affect patentability by placing sequences in the public domain.	*See:* [WIPO, "Patent issues related to influenza viruses and their genes: working paper"] [WIPO Patent search report on pandemic influenza preparedness (PIP) –related patents and patent applications] [Report of the Technical Expert Working Group on GSD, p.8-10]
Biosecurity and biosafety	- Biosecurity issues may arise due to the potential use of GSD to create a viable synthetic virus that could be used to infect	- The sharing of GSD rather than virus samples has potential advantages as it mitigates the risk of	*See*: [Report of the Technical Expert Working Group on

Consideration	Description of consideration	Potential implications identified in the evidence	References
	individuals or populations. - Biosafety issues may arise due to broader access to sequencing and other information about the virus by laboratories with inadequate containment or other biosafety precautions – that otherwise would not have had access to virus samples – potentially creating, or otherwise obtaining, biological materials derived from the sequencing data.	inadvertent release of the virus and reduces the need to transport virus materials. - It is easier to control custody of a physical virus than information, and GSD can be broadly and anonymously disseminated. However, it is more difficult to convert GSD into the physical virus needed for malicious use.	GSD, p.12-15] See references number: [G1][G4]
Benefit-sharing	- Currently, access to GSD does not trigger a requirement under the PIP Framework to sign an SMTA 2 with WHO. - Inclusion of GSD in the definition of PIP BM would require determining an appropriate benefit-sharing system, including the trigger for benefit-sharing and the types of benefits that could be shared. - Use of GSD is considered a use of GISRS and does trigger the Partnership Contribution.	- Benefit sharing from GSD would protect WHO's access to pandemic influenza products or technologies generated using GSD in the event of a pandemic. - Including GSD in the definition of PIP BM would allow maintaining an equal footing between data sharing and benefit sharing under the Framework and maintain relevance of the Framework. - Because a larger number of laboratories access GSD than PIP BM, inclusion of GSD in the definition of PIP BM could increase the number of benefit-sharing contributors leading to an increased workload for the Secretariat. - A considerably larger proportion of such laboratories make no profitable use of GSD. Thus, there is risk that broad pursuit of SMTA2s in this segment will constitute a large financial cost compared to the benefits solicited.	*See*: [Report of the Technical Expert Working Group, p.2][April 2014 Advisory Group meeting report, par. 4][October 2014 Advisory Group meeting report, par. 30-31][April 2016 Advisory Group Meeting Report, par. 50 and 53][March 2017 Advisory Group Meeting Report, par. 28] See references number: [G15][G19][G20][G21][G25][G33][G36]

Questions for Discussion

GENETIC SEQUENCE DATA (GSD) IN THE CONTEXT OF THE PIP FRAMEWORK (paras 28-42 and Table B)
Background to the GSD section (paras 28-40): Does the Scoping Paper cover all the issues that are relevant to the analysis of pursuing or not pursuing possible approaches to GSD under the PIP Framework? If not, what issues should be addressed?
Considerations in relation to GSD under the PIP Framework (paras 40-42 and Table B) How would implementation of the Review Group recommendations on GSD affect: • The work of GISRS? • The development of influenza vaccines and other influenza products? • The implementation of the PIP Framework? If the definition of PIP biological materials is not amended to include GSD, are there implications for: • Pandemic influenza preparedness and response? • Implementation of the PIP Framework? Are there additional considerations or implications?