The Inclusion of Seasonal Influenza Viruses and Genetic Sequence Data (GSD) in the Context of the Pandemic Influenza Preparedness (PIP) Framework

A position paper from the Directors of the GISRS WHO Collaborating Centers and Essential Regulatory Laboratories of GISRS

INTRODUCTION

During the May 2017 World Health Assembly (WHA), Member States adopted Decision WHA70(10), which in paragraph (8)(b) requests the Director-General conduct a thorough and deliberative analysis of the Review Group’s recommendations on seasonal influenza viruses and genetic sequence data (GSD), including the implications of pursuing or not pursuing possible approaches. As GISRS stakeholders and key decision-makers in the vaccine virus composition of influenza vaccines, the Directors of the WHO Collaborating Centers (CCs) and Essential Regulatory Laboratories (ERLs) for influenza surveillance and response provide here a collective position on the issues related to including seasonal influenza viruses and GSD in the context of the Pandemic Influenza Preparedness (PIP) Framework. These views are those of the individual directors of the CCs and ERLs and not necessarily those of their respective institutions.

BACKGROUND

The 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. Underpinning the success of pandemic influenza preparedness is a strong, reliable, and effective seasonal influenza virus sharing network and surveillance system as well as a time-tested platform for the development, evaluation, and recommendation of vaccine viruses for manufacturing seasonal influenza vaccines. For over half a century, these efforts have been performed and enhanced by the WHO Global Influenza Surveillance and Response System (GISRS). GISRS conducts year-round disease and virologic surveillance for influenza as well as genetic and antigenic characterization of circulating seasonal viruses, which provides the scientific evidence for the twice-annual vaccine composition decisions. The timely and open sharing of respiratory specimens, viruses, and GSD within GISRS are critical to ensure decision-makers have the most up-to-date information regarding circulating viruses to make the best vaccine virus recommendations. Timely and open sharing is also the cornerstone of the Terms of Reference under which GISRS laboratories operate.

The Nagoya Protocol (NP) on Access and Benefit Sharing (ABS) is a supplementary agreement to the 1992 Convention on Biological Diversity (CBD) that entered into force on 12 October 2014. The NP requires fair and equitable sharing of benefits from the utilization of non-human genetic resources and associated traditional knowledge, based upon mutually agreed terms, and specifies that access to genetic resources should be subject to prior informed consent unless otherwise determined by the Party with the genetic resource. Parties to the NP are required to take legislative, administrative, or policy measures as appropriate to implement their obligations. Article 4.4 of the NP provides that it “does not apply” to genetic resources covered by “a specialized international access and benefit-sharing instrument” (SII) that is consistent with the NP’s objectives for Parties to that specialized instrument.

In the context of influenza viruses, there is concern that implementation of the NP will affect influenza virus sharing within GISRS, particularly for the seasonal vaccine virus selection process, which relies on timely and open virus sharing among GISRS laboratories.

During the 70th World Health Assembly, the Delegates reaffirmed the critical role played by the PIP Framework as a specialized international instrument that facilitates expeditious access to influenza viruses of human
pandemic potential, risk analysis, and the fair and equitable sharing of vaccines and other benefits. One additional element of the PIP benefit sharing system is the Partnership Contribution (PC), which is an annual cash contribution to WHO by influenza vaccine, diagnostic, and pharmaceutical manufacturers who use the WHO GISRS. The inclusion of seasonal influenza viruses under the PIP Framework has been suggested as a means to providing access and benefit sharing required under the NP.

POSITION ON CONSIDERING SEASONAL INFLUENZA VIRUSES IN THE CONTEXT OF THE PIP FRAMEWORK

The GISRS is a unique and highly functioning global network that operates on the open and free sharing of seasonal influenza viruses to support surveillance efforts critical to informing the development of diagnostics, selection of viruses for vaccines, risk assessment, and preparedness and response strategies. The inclusion of seasonal influenza viruses under the PIP Framework would substantially affect logistical and operational processes within GISRS and would be counter to the terms on which GISRS operates. In addition to the identifiable issues surrounding the inclusion of seasonal viruses in the PIP Framework, there are no foreseeable benefits. For example, the PC already leverages the seasonal influenza business enterprise in determining the monetary contribution to WHO by industry stakeholders. As such, no additional monetary or benefit sharing requirement should be levied on industry and other stakeholders, and doing so would only negatively affect the global influenza vaccine manufacturing system and by extension, pandemic preparedness.

Our position is that seasonal viruses should not be included under the PIP Framework for the reasons outlined below:

1. The administrative burden placed on WHO CCs and National Influenza Centers (NICs) would be prohibitive should seasonal influenza viruses be treated as PIP Biological Materials (BM).
   - The time line within which GISRS operates to collect data on seasonal viruses has very little flexibility. Existing PIP Framework traceability requirements for sharing of PIP BM is labor-intensive and uses a complex reporting system. Inclusion of seasonal viruses into this system, or even a more simplified system, would add undue burden to GISRS laboratories and require extensive resources and time commitments, neither of which are available to GISRS laboratories. It is very likely that such a traceability system would reduce the numbers and timeliness of viruses shared within GISRS, resulting in more limited data available for vaccine composition decisions.
   - Any changes that hinder virus sharing will have deleterious consequences for the well-established seasonal influenza surveillance and vaccine manufacturing system, and would not be in the best interests of global public health.

2. Including seasonal viruses under the PIP Framework could indirectly undermine the standing of GISRS in the seasonal international influenza vaccine establishment.
   - Stakeholders may find it difficult and cumbersome to work with seasonal viruses under the umbrella of the PIP Framework and thus seek to establish a private laboratory network with sites at a few strategic locations whose sole purpose is to collect and analyze influenza viruses for commercial vaccine manufacturers. The PIP Framework may then see a substantial decrease in the Partnership Contribution (PC) funds if manufacturers are collecting their own viruses and generating vaccine virus lots.

3. Classifying seasonal influenza viruses as PIP BMs or imposing similar oversight could hinder Research and Development toward improved influenza prevention and control strategies.
GISRS provides a means for open access to seasonal influenza viruses for the influenza research and development community. Researchers developing vaccines, therapeutics, and diagnostics for influenza should have free access to seasonal influenza viruses to establish proof-of-concept and evaluate these potential products in pre-clinical and clinical settings, without the need to provide benefit sharing. Furthermore, research laboratories should be able to share viruses and their derivatives freely for maintaining scientific integrity. Inclusion of seasonal viruses in the PIP Framework would require that sharing of all seasonal viruses be controlled in some way, including tracking of virus sharing. This could negatively affect research and innovation with respect to both seasonal and pandemic influenza interventions and medical counter-measures.

- Optimal engagement with the research sector with respect to appropriate benefit sharing for influenza viruses of pandemic potential is already a challenge for the PIP Framework.
- Other Research and Development sectors to consider are small or start-up companies. Often, the key to a successful venture may be dependent on a company’s intellectual property having market value with few liabilities; the liabilities within the SMTA2 may deter future investment in novel technologies or treatments.

4. Inclusion of seasonal viruses would likely require renegotiation of the PIP Framework.
- The PIP Framework is a unique global public health agreement that is widely recognized to be a model for sharing of other pathogens of public health significance. The addition of seasonal viruses to the PIP Framework would open it up to renegotiations that may be lengthy, and ultimately disruptive to the originally negotiated framework. This could lead to uncertainty surrounding sharing of influenza viruses with pandemic potential.

5. There remains uncertainty as to whether the PIP Framework will be accepted as an SII by Parties of the NP.
- There is substantial legal uncertainty and lack of clarity regarding scope and application of the NP as well as how countries will implement legislation. Similarly, the criteria for what would constitute a SII are unknown. During the NP Conference of Parties at the Meeting of the Parties (COP-MOP) in December 2016, Parties requested the CBD Executive Secretariat conduct a study to define criteria outlining what constitutes a SII and a possible process for recognizing such an instrument. The outcomes of the study will be presented at the next NP COP-MOP in 2018. As such, any potential resolution on recognizing the PIP Framework as a SII under Article 4.4 of the NP would be delayed until such criteria and a process have been formally established.

**Preferred Course of Action**

Recognizing that there is a need to mitigate the potential impact of the NP on seasonal virus sharing, we support pursuing the recognition of GISRS, by the NP, as a Specialized International Access and Benefit Sharing Instrument (SII). To this end, we propose that the benefits of specimen and virus sharing within GISRS be clearly defined and codified along with the ongoing formalization of GISRS as the first steps to recognition of GISRS as a SII.

GISRS monitors the evolution of influenza viruses and provides recommendations regarding laboratory diagnostics and vaccines, analyzes antiviral susceptibility, conducts risk assessment, and serves as the global alert mechanism for the emergence of influenza viruses with pandemic potential. In return for participating in GISRS, laboratories receive multiple benefits including, but not limited to, technical training and support;
laboratory protocols and guidance documents; reagents and kits for molecular and antigenic testing, virus characterization reports on viruses submitted; access to associated GSD and candidate vaccine viruses (CVVs). In addition, GISRS provides influenza products (CVVs reagents, egg and cell-derived influenza virus isolates, risk assessments, etc.) to GISRS and non-GISRS entities at no cost and CVVs are shared with industry for the development and production of seasonal and pandemic influenza vaccines.

POSITION ON CONSIDERING GSD IN THE CONTEXT OF THE PIP FRAMEWORK

Given the many advances in synthetic biology technologies and the relative ease with which viruses or viral genetic components may be synthesized solely from GSD, we understand and appreciate the general need to address the sharing of GSD. However, similar to the issues surrounding the inclusion of seasonal viruses in the PIP Framework, we strongly believe that restrictions on the general use of GSD should not be enacted in any way that would hinder i) public health access to GSD for influenza virus risk assessment and preparedness and response purposes and ii) innovation for improved influenza vaccines and therapeutics as well as academic research and general scientific inquiry that promotes such innovation.

Our consensus position is that the sharing of GSD is a mechanism of benefit sharing of information. As such, general access and use of GSD should not be hindered in any way, and should not be classified as a PIP BM or subject to the liabilities associated with the legally binding SMTA2 requirements. In accordance with our general position on GSD as well as our position not to include seasonal viruses within the context of the PIP Framework, we posit that GSD related to seasonal influenza viruses also not fall within the scope of the PIP Framework.

Detailed below are potential issues we envision resulting from the consideration of GSD in the context of the PIP Framework:

1. The only apparent benefit to classifying GSD as PIP BM is to require benefit sharing by users of GSD.
   - GISRS laboratories already have well defined Terms of Reference with respect to virus and GSD sharing. GISRS laboratories use GISAID and/or other databases for sharing influenza virus sequences. Users of GISAID are bound by the terms of the Data Access Agreement (DAA) that requires acknowledgement of the data suppliers and encourages collaboration between data suppliers and data users. This has encouraged the open and timely sharing of data, particularly for novel influenza viruses of pandemic potential (e.g. H7N9), without the need for PIP BM classification of GSD. If GSD were considered as PIP BM, users would be required to enter into an agreement with WHO by signing either a SMTA1 or SMTA2. This would create an unreasonable requirement for most entities that simply use the data for general scientific purposes. In addition, the operational complexity of tracking GSD and/or navigating the requirements under the storage and access to GSD may significantly delay or eliminate posting of GSD onto available databases.

2. There is already a built-in mechanism for capturing commercialized influenza-related products generated from GSD.
   - If an entity uses IVPP GSD to synthesize a CVV, for example, the CVV is then treated as a PIP BM and subject to the same access and benefit sharing terms as any other PIP BM.
     - Recombinant vaccine or therapeutics developed through the use of GSD would also be readily identified
     - If an entity uses IVPP GSD to design a new diagnostic assay, any claims that the product detects a given novel virus would indicate use of the virus, the GSD, or both.
   - In reality, the companies currently identified as users of IVPP are also those that would use GSD, and should not be asked to provide additional PC.
If an entity opts to utilize GSD for strictly commercial purposes, this should be easy to track and identify; however, if the original GSD is modified by the end user in the development of a novel therapeutic, vaccine, etc., should it still be subject to the original agreement? How will this be enforced?

3. The legal enforcement of imposed sanctions on the use of GSD would be difficult and may diminish the willingness to use existing data sharing mechanisms.
   - GSD are held on public domain, open access, or other genetic sequence databases, all of which vary in their ability and/or willingness to track downloaded GSD. While GISAID is able to track downloaded GSD, GenBank, for example, is not. However, the tracking of all downloaded GSD seems to be unnecessary, would waste resources, and yield little or no benefit.
   - If access to and use of GSD were made too complicated, there is a risk that entities would set up surveillance systems to provide access to GSD independent of the WHO GiSRS system. This would, in turn, threaten the continued success of GiSRS.

Preferred Course of Action

We are supportive of the development of guidelines outlining the responsible and ethical use of GSD, including for development of a commercial product, as an annex to the PIP Framework.