5 October 2015

Briefing Note for the PIP Advisory Group Special Session

13-14 October 2015

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Background

1. The *Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access vaccines and other benefits* (the "PIP Framework" or "Framework") was adopted by the World Health Assembly in May 2011 through WHA64.5. The Framework 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 ("WHO GISRS"), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing:

a) the sharing of H5N1 and other influenza viruses with human pandemic potential; and
b) access to vaccines and sharing of other benefits[1].

2. In adopting the PIP Framework, the World Health Assembly "[r]equest[ed] the Director-General, in consultation with the Advisory Group: (1) to implement the Pandemic Influenza Preparedness Framework; (2) to monitor and review the operation of the Pandemic Influenza Preparedness Framework and all of its components, in accordance with its provisions."[2]

Framework Components

3. The Framework has three components

a) **Virus sharing.** Under the PIP Framework, Member States are expected to share PIP biological materials (PIPBM) which includes influenza viruses with human pandemic potential, with WHO's Global Influenza Surveillance & Response System (GISRS) in a rapid, systematic and timely manner.[3] GISRS is an international network of influenza laboratories that conduct year-round surveillance of influenza, assessing the risk of pandemic influenza and assisting in preparedness measures.

   Under the PIP Framework, GISRS laboratories are responsible for sequencing influenza viruses with pandemic potential and uploading those sequences to public-domain or public-access databases such as GISAID and Genbank or similar databases in a timely manner. While Genetic Sequence Data (GSD) is covered in the Framework,[4] handling of GSD remains unresolved and the Framework requested that the Director- General consult the Advisory Group on the best process for further discussion and resolution of issues relating to the handling of GSD from influenza viruses with human pandemic potential (IVPP) as part of the Framework.[5]

b) **Benefit Sharing.** The Framework has two principal benefit sharing mechanisms: a) the Standard Material Transfer Agreement 2 (SMTA 2); and b) the Partnership Contribution.

[1] See, PIP Framework Section 2 'Objective'. The PIP Framework and WHA64.5 may be downloaded from: http://apps.who.int/iris/bitstream/10665/44796/1/9789241503082_eng.pdf
[2] See WHA64.5 OP4(2).
[3] See PIP Framework Section 5.1.1
[4] See, for example, sections 5.2 and Annexes 4 and 5.
[5] See PIP Framework section 5.2.4

(i) An ***SMTA2*** is a legally binding contract between WHO and non-GISRS entities that receive PIP BM from GISRS. These include influenza vaccine, diagnostic and pharmaceutical manufacturers, as well as biotechnology firms, research institutions and academic institutions. Under the SMTA2 entities commit to share specified benefits based on the nature of their work and their capacities. Benefits include pandemic influenza vaccines, antiviral medicines or other pandemic-related products or technologies. The agreements specify that the products will be delivered at the time of the next pandemic to WHO for use in countries that need them.

(ii) ***Partnership Contribution*** is an annual contribution to WHO from influenza vaccine, pharmaceutical and diagnostic manufacturers that use the WHO GISRS. WHO uses the funds provided under the PC to strengthen influenza pandemic preparedness and response capacities in countries that require such support. In accordance with the Framework, the WHO Executive Board decided that for the period 2012-2016, 70% of the contributions should go to preparedness and 30% to response.[6]

c) **Governance.** Under the provisions of the Framework, the World Health Assembly oversees implementation; the Director-General advises the World Health Assembly and promotes implementation; and an Advisory Group monitors and evaluates implementation. In formulating its advice to the Director-General, the Advisory Group interacts with industry and other stakeholders.[7]

PIP Framework implementation progress to date

Virus sharing

4. The WHO GISRS[8], in collaboration with animal health partners, monitors and analyses a range of zoonotic and potentially pandemic influenza viruses as they emerge, and develops laboratory tests, reagents and candidate vaccine viruses.[9,10] This essential work for global pandemic preparedness is underpinned by timely sharing of influenza viruses as well as relevant virological, clinical and epidemiological information.

5. Risk assessments for non-seasonal influenza viruses are posted on a monthly or as-needed-basis to provide information about emerging threats. The current global situation is characterized by a number of trends including: an increase in the variety of animal influenza viruses co-circulating and

[6] See http://apps.who.int/gb/ebwha/pdf_files/EB131/B131_4-en.pdf?ua=1
[7] See PIP Framework Section 7.
[8] See the Appendix in this report for information on technical capacities and operational functioning of GISRS.
[9] See Warning signals from the volatile world of influenza viruses February 2015 http://www.who.int/influenza/publications/warningsignals201502/en/.
[10] See Summary and assessment of influenza at the human-animal interface, as of 17 July 2015 http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_17_July_2015.pdf?ua.

exchanging genetic material, giving rise to novel strains;[11] continuing cases of human H7N9 infections in China;[12] and a surge of human H5N1 cases in Egypt.[13]

6. Expanding the GISRS network to increase global coverage is vital. Since 2011, the network has grown from 136 laboratories in 106 countries to 143[14] laboratories in 113 countries. Expert working groups play a key role in improving GISRS' technical capacity and operational functioning. The WHO Working Group on Real-Time Polymerase Chain Reaction (RT-PCR) for the Detection and Subtyping of Influenza Viruses which began in 2007 is still vibrant and met in June 2015 to advise WHO on the best use of PCR testing in GISRS, taking into account new developments in PCR technology. The Working Group also provided guidance for the WHO External Quality Assessment Programme (EQAP), another program which has grown in participation since the PIP Framework was adopted. An Expert Working Group on Surveillance of Antiviral Susceptibility for GISRS met in June 2015 to provide advice on surveillance strategies and practical approaches taking into account current gaps and needs in the network.

7. WHO provides logistical, technical and financial support to facilitate efficient and timely sharing of influenza viruses and specimens. Since the Framework was adopted, hundreds of shipments of PIP Biological Materials have been shared with GISRS through the PIP Shipping Fund Project. Just in the past 12 months, (1 August 2014 through 31 July 2015), the WHO Shipping Fund Project supported 156 shipments from 83 laboratories in 74 countries, areas and territories to a GISRS Collaborating Centre or H5 Reference Laboratory at a cost of USD 192,341. As required under the Framework, shipments are recorded in the Influenza Virus Traceability Mechanism. GISRS has organized 11 training workshops in the proper handling and packaging of infectious substances for international shipment in four WHO regions for 259 laboratory staff from 69 countries, and certified 205 of the participants. A training course on infectious substances shipping comprised of eight modules and translated into three languages is now available[15] as is guidance on the transport of infectious substances[16] and influenza viruses.[17]

8. Epidemiological parameters are critical components of overall pandemic risk assessment. Beginning in late 2014, several countries pilot tested potential indicators of pandemic influenza severity based on information which is collected in routine influenza surveillance. An Expert Working Group on Pandemic Influenza Severity Assessment met in June 2105 to review findings and refine approaches to set severity-related thresholds.

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[11] See Warning signals from the volatile world of influenza viruses February 2015 http://www.who.int/influenza/publications/warningsignals201502/en/.

[12] See WHO risk assessment of human infection with avian influenza A(H7N9) virus http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7N9_23Feb20115.pdf?ua=1.

[13] See Egypt: upsurge in H5N1 human and poultry cases but no change in transmission pattern of infection http://www.emro.who.int/egy/egypt-news/upsurge-h5n1-human-poultry-cases-may-2015.html.

[14] The National Influenza Centre in Zambia has been recognized by WHO in September 2015.

[15] See Infectious substances shipping training - a course for shippers http://www.who.int/ihr/i_s_shipping_training/en/.

[16] See *Guidance on regulations for the transport of infectious substances 2015-2016* http://www.who.int/ihr/publications/who_hse_ihr_2015.2/en/.

[17] See Instructions for the classification of influenza viruses and candidate vaccine viruses (CVVs) for transport purposes, 1 December 2014 http://www.who.int/influenza/gisrs_laboratory/logistic_activities/20141201_shipment_cvvs.pdf?ua=1.

9. At the time of a pandemic, reliable estimates of the burden of influenza disease during annual epidemics can provide a baseline from which countries can gauge a pandemic's impact in vulnerable communities. To assist countries in measuring disease burden, WHO published *A manual for estimating disease burden associated with seasonal influenza*[18] in July 2015. With support from a technical advisory group, work is ongoing in this area. A consultation held in December 2014 considered how estimates of disease burden and the associated mortality and economic burden can be improved. Planning and training to support pilot testing of a tool to estimate economic burden occurred in July 2015.

Genetic sequence data (GSD) under the PIP Framework

10. In 2013, the PIP Advisory Group (AG) commenced work to provide guidance to the Director-General on the best process to handle genetic sequence data[19] under the PIP Framework[20]. This work is mandated by the PIP Framework. In October 2013, a Technical Expert Working Group (TEWG) was established to provide background and technical information to the AG. It submitted its final report to the AG in October 2014.[21] Upon consideration of this report as well as technical input from database representatives, the AG recommended that further work be undertaken to define the optimal characteristics of a GSD sharing system that would promote the objectives of the PIP Framework. To this end, the Advisory Group established a *Technical Working Group* (TWG) to develop optimal characteristics of a GSD sharing system which is best suited to meet the objectives of the Framework. In the coming weeks, a draft document will be shared with stakeholders for input

11. As part of this effort, in 2015, the Secretariat undertook the following:

a) *Collaboration with the World Federation for Culture Collections and the World Data Center for Microorganisms*. Through this collaboration, a prototype search engine was developed to allow monitoring of the use of GSD from influenza viruses with pandemic potential (IVPP) in end-products.
b) *Development of an Options paper on monitoring the use of IVPP GSD in end products*.
c) *Review of existing genetic sequence data sharing systems*, to gain a better understanding of how GSD for IVPP are generated, shared and used. A detailed questionnaire was sent to 150 data providers and users; analysis of the results is in process.

Benefit Sharing

Status of SMTAs2

12. The conclusion of Standard Material Transfer Agreements has been a priority of the Secretariat since the Framework was adopted in 2011. Using a strategic approach to plan negotiations with 35 vaccine producing companies, the Secretariat established a negotiation priority order based on a series of factors that included prequalification status; export capacity; regulatory

[18] See http://apps.who.int/iris/bitstream/10665/178801/1/9789241549301_eng.pdf?ua=1.
[19] Genetic sequence data is the digital "blueprint" of biological material. It is now possible to produce vaccines with this digital "blueprint" alone, i.e., without need for the actual biological material.
[20] See PIP Framework section 5.2.4
[21] See http://www.who.int/influenza/pip/advisory_group/PIP_AG_Rev_Final_TEWG_Report_10_Oct_2014.pdf.

approval; and status as a PC contributor. The overarching goal has been to quickly secure access to a predictable supply of pandemic influenza vaccine available in real time. To the extent possible, there is also the aim of striking a balance between developed and developing country manufacturers. The Secretariat also seeks to advance the conclusion of agreements with other types of entities, notably diagnostic companies and academic institutions.

13. In a relatively short period of time:

a) Three agreements were concluded, securing real-time access by WHO to approximately 7.8% of projected global pandemic vaccine influenza production capacity.[22]
b) One of these agreements secures access to antiviral medicines
c) Twenty-nine agreements were signed with academic institutions, several of which have indicated their willingness to provide training as a form of benefit sharing. Work is under way to operationalize these offers.

14. Discussions and negotiations are under way with many other manufacturers, notably:

a) Five Japanese vaccine manufacturers and one company that received a grant under the Global Action Plan for Influenza Vaccines (GAP).[23]
b) Twelve manufacturers of other products (diagnostics) needed during a pandemic. Discussions with six of these companies are well advanced and several proposals for the benefit sharing commitments have been submitted to the Advisory Group for review.
c) Three negotiations that had been under way – two of which were quite advanced – have been cancelled due to events beyond the control of the Secretariat (e.g. sale of the influenza part of the business or initial public offering)

15. The process has met with many challenges due to several factors, including:

- the novelty of the undertaking
- lack of awareness of the PIP Framework and its objectives
- lack of understanding about prequalification and other requirements for donation or sale of vaccine, medicines and other products to WHO
- parallel requests to the same companies for Partnership Contributions

16. All in all however, the process is yielding results even if the agreements have not yet been finalized. Knowledge of the PIP Framework is growing among a broad range of companies working in the influenza sector (vaccine, diagnostics and to a lesser extent medicines).

Partnership Contribution Collection

17. The Partnership Contribution is an annual payment – currently US$ 28M per year -- to WHO by influenza vaccine, diagnostic and pharmaceutical manufacturers that use GISRS.[24] A detailed

[22] Based on 2013 global seasonal vaccine production capacity of 1.5 billion. http://apps.who.int/iris/bitstream/10665/112307/1/9789241507011_eng.pdf?ua=1
[23] See http://www.who.int/influenza_vaccines_plan/objectives/en/; and http://www.who.int/influenza_vaccines_plan/objectives/projects/en/
[24] See Framework section 6.14.3

process and formula to identify companies and divide the annual payment among them, was developed in close consultation with manufacturers during 2012 and completed in May 2013. In a show of good faith and support for the Framework, many companies voluntarily paid a contribution in 2012 to enable it to start as required under the Framework. Since then, the formula has been applied and results for 2013 – 2014 are summarized in Table 1 below.

18. Experiences in collecting contributions have highlighted some challenges faced by companies, notably the ability to pay contributions in a single payment. Following guidance from the AG, the PIP Secretariat has given companies the option of paying in instalments. To improve understanding of the PC collection process, a new explanatory video was developed in 2015 and is available in all 6 WHO languages.[25]

Table 1. Summary of Partnership Contribution collection results, 2013-2014

Questionnaire year	No. of entities contacted	No. of Contributors identified	No. of Contributors that paid	Amount received (In US$)
2013	194	32	30	27,538,586 (as of 31 Aug 2015)
2014	250	43	37	26,964,062 (as of 31 Aug 2015)

Partnership Contribution Implementation[26]

Pandemic preparedness

19. The Framework states that PC resources shall be used to improve pandemic preparedness and response and that the WHO Executive Board will decide on the proportion that should be allocated to each area. In May 2012, the Executive Board decided that for the period 2012-2016, 70% of resources should go to preparedness and 30% to response. In January 2014, a high level implementation plan, developed through consultations with the Advisory, industry and stakeholders, was published. Work plans against available preparedness funds were developed to support capacity building in five priority areas of work: laboratory and surveillance; burden of disease; regulatory; planning for deployment; and risk communications. 2014 was a foundational year to build implementation systems across the three levels of the Organization. Since January 2015, the pace of implementation has increased and activities are beginning to show some results. Highlights of key implementation achievements to date are described in Annex 1.

20. PIP is a cross-cutting programme with strong synergies with other public health programmes. Ensuring that PIP outcomes are timely, effective and sustainable will require consolidation of PIP activities with renewed efforts to implement the International Health

[25] See http://www.who.int/influenza/pip/pc_questionnaire/en/.

[26] The Framework specifies that PC resources are to be used for improving pandemic preparedness and response. In May 2012, the Executive Board, based on advice to the Director-General from the PIP AG, decided that for the period 2012-2016, 70% of PC resources should go to preparedness and 30% to response.

Regulations (2005) following the Ebola crisis; an assessment of the possibilities for continuation of unfinished activities from the GAP initiative; and an alignment with the developing Global Health Security Agenda initiative for the 2016 PIP Framework review.

Pandemic response

21. Response funds are expected to be used to deploy vaccines, antivirals, diagnostics and other pandemic-related products secured through SMTA2s. The AG, with input from industry and other stakeholders, developed *Guiding Principles for the Use of PIP Partnership Contribution Response Funds* in October 2014.[27] The *Guiding Principles* were developed because during a pandemic there will be limited or no opportunities to convene the AG or hold interactions with industry and other stakeholders to discuss the use of response resources. The *Guiding Principles* will provide the basis for the Director-General to decide on the use of the PC for response purposes without further advice from the AG, or interaction with industry and other stakeholders.

PIP and the Global Action Plan for Vaccines (GAP)

22. The GAP Initiative is based on a comprehensive strategy to increase pandemic vaccines in the event of an influenza pandemic by catalyzing an increase in global seasonal vaccine production capacity. This manufacturing capacity has increased from 500 million doses in 2006 to 1503 million doses a year in 2013 and is anticipated to expand to at least 1700 million doses by 2016. This number of seasonal vaccine doses is equivalent to at least 4509 million doses of pandemic vaccine (assuming that 15ug of pandemic influenza antigen would be needed per dose).[28]

23. The number of developing countries with approved pandemic influenza vaccines has gone from zero in 2006 to seven in 2015. Experience shows that maintaining a sustainable influenza vaccine manufacturing capacity requires coherence in national policies on health, regulatory oversight, and industrial, science and technology development.

24. The projected global vaccine production capacity would still fall short of needs during a pandemic, based on currently available vaccines. Dose-sparing technologies are becoming increasingly available and may increase this number significantly. The emphasis is on accelerating research into more broadly protective vaccines.

25. The GAP will close in 2016.

Governance

26. Establishment of the Advisory Group was one of the first steps taken by the Secretariat after adoption of the PIP Framework. It consists of 18 members, drawn from three Member States in each WHO region, with a skill mix of internationally recognized policy makers, public health experts and technical experts in the field of influenza.[29] In the exercise of their functions the Members act as

[27] See http://www.who.int/influenza/pip/guiding_principles_pc_response_funds.pdf?ua=1.
[28] See http://apps.who.int/iris/bitstream/10665/112307/1/9789241507011_eng.pdf?ua=1
[29] See PIP Framework section 7.2.3 and Annex 3.

international experts serving WHO exclusively. The first rotation of members took place in October 2014 and each year, six members rotate out to be replaced by six new members.

27. During its first 4 years, the Advisory Group has provided to the Director-General significant recommendations to guide and improve implementation of the Framework, as well as annual reports on its evaluation of implementation of the Framework.[30]

2016 Review of the PIP Framework

28. In adopting the PIP Framework, the World Health Assembly requested the Director-General, in consultation with the Advisory Group, to monitor and review the operation of the Framework and all of its components, in accordance with its provisions. Section 7.4.2 provides that the PIP Framework and its annexes will be reviewed by 2016 with a view to proposing revisions reflecting developments as appropriate to the World Health Assembly in 2017, through the Executive Board. The Director-General has convened a Special Session of the PIP Advisory Group so this group can harvest the views of Member States and stakeholders on substantive issues and concerns regarding the PIP Framework and its implementation. The Advisory Group will submit a report from the meeting to the Director-General who will forward it to the 138th session of the Executive Board.

[30] See http://www.who.int/influenza/pip/advisory_group/en/

Annex 1

Key achievements from PIP Framework Partnership Contribution Implementation

Area of work	Programmatic results (January 2014- September 2015)
Laboratory & Surveillance **Target countries: 43** ***Improving national ability to detect, monitor and share novel influenza viruses***	• **9 countries** (21%) have functioning **event based surveillance**. • **28 countries** (65%) are reporting **virological data** to WHO global influenza database. • **9 countries** (21%) are reporting **epidemiological data** to WHO global influenza database. • **11 countries** (25%) are **sharing virus samples with GISRS.** • **27 countries** have scored **100% proficiency in PCR testing** of viral samples.
Burden of Disease **Target countries: 16** ***Defining national priorities for cost effective interventions for influenza***	• **A standard tool provided** by WHO to estimate economic burden and burden of disease in a standard way is being tested at the country level. • **5 target countries completed national burden estimates** and presented their work to national and/or international audiences.
Regulatory capacity building **Target countries: 16** ***Building national regulatory capacity so that vaccines, tests and treatments for influenza can be deployed safely***	• **5** (31%) target countries were **assessed for national regulatory capacity** in the areas of regulatory systems, marketing authorization, and pharmacovigilance. • 13 out of 48 countries[31] have accepted the **WHO collaborative procedure for accelerated approval** of influenza vaccines, antivirals and diagnostics.
Deployment **Target countries: 16** ***Planning for efficient deployment of vital supplies for pandemic influenza***	• **Deployment plans for 16 target country assessed** for ability to respond quickly in the event of a pandemic. • **Model agreement** between WHO and recipients of pandemic products completed in April 2015.
Risk Communications **Target countries: 30** ***Building capacity to provide accurate public information during health emergencies***	• **27** national and sub-regional **risk communications capacity building workshops**[32]-reaching-**911 participants**- were completed to prepare target countries for public health emergencies. • **6 risk communications trainings** for journalists[33] were completed in AFRO, EMRO, EURO, SEARO and WPRO. • **100% of requests for risk communications surge support** responded to within 72 hours through the ECN network of **101 members**.

[31] This is part of broader support to countries to agree to a common way of enabling the use of vital supplies by their populations during a pandemic.
[32] Started in March 2013
[33] Training builds capacity in journalists to report accurately on health emergencies and pandemics.