

Review of the Pandemic Influenza Preparedness Framework

Report by the Director-General

1. The Director-General has the honour to transmit to the Health Assembly the report of the 2016 Pandemic Influenza Preparedness (PIP) Framework Review Group (see Annex). An earlier version of the Director-General's report was considered by the Executive Board at its 140th session in January 2017.¹ The Board also adopted decision EB140(5) in which, inter alia, it decided to extend until 28 February 2018 the application of decision EB131(2) (2012) on the PIP Framework for the sharing of influenza viruses and access to vaccines and other benefits.² The Board's decision was consistent with the Advisory Group's recommendation to the Director-General,³ and will allow the Director-General and the Advisory Group to benefit from the discussions of the Seventieth World Health Assembly in developing the next proposal for the proportional division of funds between pandemic preparedness measures and response activities, to be submitted for consideration by the Executive Board at its 142nd session in January 2018.

ACTION BY THE HEALTH ASSEMBLY

2. The Health Assembly is invited to note the report.

¹ Document EB140/16; see also the summary records of the Executive Board at its 140th session, tenth meeting, section 3.

² See also document A70/57 for the report on the Secretariat's consultations with the secretariat of the Convention on Biological Diversity, as requested in decision EB140(5).

³ [http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1_paragraph 45](http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1_paragraph%2045) (accessed 17 March 2017).

ANNEX

Report of the 2016 PIP Framework Review Group

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Preface

The risk of another influenza pandemic is ever-present but its timing and impact is unpredictable. Advance planning and preparedness is key to mitigating the adverse outcomes of future influenza pandemics. This includes building capacity to detect and respond to a public health emergency of international concern.

In 2011, WHO and Member States set up the Pandemic Influenza Preparedness (PIP) Framework as a novel international instrument to strengthen the sharing of influenza viruses with human pandemic potential while increasing the preparedness of developing countries, and their access to vaccines and other pandemic related supplies in the event of a pandemic. All players – WHO, Member States, industry, civil society and other stakeholders – came together with a common purpose to better prepare the world to respond to the next pandemic and reduce uncertainty in our collective ability to share viruses and the benefits.

It has been five years since the PIP Framework was signed; while such new and complex initiatives take time to operationalise, it is now timely to review progress as to whether the PIP Framework has both achieved what was intended and continues to remain relevant looking forward.

As the world faces an increasing number of public health threats with international impact (e.g. Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus disease and Zika virus), global solidarity is more important than ever to address critical policy, operational and capacity barriers ahead of an emergency. The PIP Framework offers helpful insights for the sharing of other pathogens that require a rapid response and the equitable sharing of benefits. However, it is the view of the PIP Framework Review Group that the PIP Framework will only remain relevant if viruses continue to be shared and the need for clarification around the sharing of genetic sequence data and benefits is rapidly addressed. In addition, linkages to other efforts to strengthen capacity building (e.g. the International Health Regulations (2005)) and to increase influenza vaccine production are improved to maximise the impact of resources leveraged by the PIP Framework. In order to ensure the PIP Framework remains sustainable and maintains the interest of all major players, it is important that its delivery of results is regularly measured and widely communicated.

Dr Christine Kaseba-Sata (Chair), Dr Theresa Tam (acting Chair)

PIP Review Group

October 2016,

Geneva, Switzerland

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The following staff members of the WHO Secretariat at headquarters and in the regions provided input to the Review Group: Claudia Alfonso, Bruce Aylward, Jennifer Barragan, Terry Besselaar, Oona Bilbao, Anna Bowman, Sylvie Briand, Julia Fitzner, Keiji Fukuda, Gaya Gamhewage, Lisa Hedman, Anne Huvos, Marie-Paule Kieny, Alexandra Kontic, Maja Lievre, Jakob Quirin, Amelie Rioux, Guénaél Rodier, Paul Rogers, Peter Salama, Gina Samaan, Raphael Slattery, Steve Solomon, Kathleen Strong, Oliver Stucke, Katelijjn Vandemaele, Wenqing Zhang.

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In addition, the Review Group would especially like to thank the Review Group Secretariat: Gerhard Grohmann (lead), Daniel Hougendobler, Priya Joi, Teresa Poole, Magdalena Rabini and Alexandra Rosado-Miguel.

Glossary

AFRO	WHO Regional Office for Africa
AMRO	WHO Regional Office for the Americas
CDC	U.S. Centers for Disease Control and Prevention
CNBG	China National Biotec Group
COP	Conference of the Parties
CVV	Candidate vaccine virus
DDBJ	DNA Data Bank of Japan
ECN	WHO Emergency Communications Network
ECSP	WHO Expert Committee on Specifications for Pharmaceutical Preparations
EMRO	WHO Regional Office for the Eastern Mediterranean
ENA	European Nucleotide Archive
EQAP	WHO External Quality Assessment Project for the detection of influenza virus type A by polymerase chain reaction
EU	European Union
EURO	WHO Regional Office for Europe
FAO	Food and Agriculture Organization of the United Nations
FluID	Flu Informed Decisions
GAP	Global Action Plan for Influenza Vaccines
GDP	Gross domestic product
GHSA	Global Health Security Agenda
GIP	WHO Global Influenza Programme
GISAID	Global Initiative on Sharing All Influenza Data
GISN	Global Influenza Surveillance Network
GISRS	Global Influenza Surveillance and Response System
GSD	Genetic sequence data
GSK	GlaxoSmithKline
HQ	Headquarters
IDP	Institutional development plan
IHR (2005)	International Health Regulations (2005)
INSDC	International Nucleotide Sequence Database Collaboration
IRD	Influenza Research Database
IVPP	Influenza viruses with human pandemic potential
IVTM	Influenza Virus Traceability Mechanism
MAT	Mutually agreed terms
MERS-CoV	Middle East respiratory syndrome coronavirus
MOP	Meeting of the Parties
NIC	National Influenza Centre
NRA	National regulatory authority
OIE	World Organisation for Animal Health
PAHO	Pan American Health Organization
PC	Partnership Contribution
PCR	Polymerase chain reaction
PHEIC	Public health emergency of international concern
PIC	Prior informed consent
PIP	Pandemic Influenza Preparedness
PIP BM	PIP biological materials
PIRM	WHO Pandemic Influenza Risk Management
PSC	Programme support costs

SAGE	Strategic Advisory Group of Experts on Immunization
SARS	Severe acute respiratory syndrome
SDG	UN Sustainable Development Goal
SEARO	WHO South-East Asia Regional Office
SMTA	Standard material transfer agreement
SWOT	Strengths, weaknesses, opportunities and threats
TEWG	Technical Expert Working Group on Genetic Sequence Data
TWG	Technical Working Group on the Sharing of Influenza Genetic Sequence Data
TIPRA	Tool for Influenza Pandemic Risk Assessment
UN	United Nations
UNICEF	United Nations Children's Fund
WPRO	WHO Regional Office for the Western Pacific
WHO	World Health Organization
WHO CC	WHO Collaborating Centre
WHO ERL	WHO Essential Regulatory Laboratory
WHO H5RL	WHO H5 Reference Laboratory

Executive Summary

Global health security has become an international priority over the past decade, with the recognition that infectious diseases know no borders in a world of shifting populations and vastly expanded international travel. While the 2003 severe acute respiratory syndrome (SARS) outbreak provided a wake-up call, the specific global risks posed by influenza were highlighted by the re-emergence of influenza A(H5N1) in 2003 and the influenza A(H1N1) pdm09¹ pandemic in 2009. Almost a century after the deadly 1918 influenza pandemic swept the world with devastating consequences, the Report of the Review Committee on the Functioning of the International Health Regulations (2005) (IHR (2005)) in relation to the 2009 A(H1N1) outbreak concluded that the world remained “ill-prepared” to respond to a severe influenza pandemic and that “tens of millions” of people would be at risk of dying.²

After the influenza A(H5N1) outbreak in 2003, it became clear that an effective response to an influenza pandemic required closer international collaboration. Such collaboration not only needed to cover the sharing of information and of influenza viruses with human pandemic potential (IVPP), but also the distribution of the benefits that flow from such cooperation, including influenza vaccines and other medical products. Negotiations started on the creation of a new system and four years later, in 2011, an international instrument, the Pandemic Influenza Preparedness (PIP) Framework,³ was set up by 194 Member States.⁴ From the start, strong engagement with stakeholders – including Member States, industry and civil society – has been crucial to the implementation of the PIP Framework. Successful implementation of the PIP Framework remains as critical as ever given the continual emergence of new influenza viruses and the ever-present potential of a pandemic.

The PIP Framework aims to balance virus sharing with benefit sharing on an equal footing. Advances in vaccine, antiviral and diagnostic technology alone are not enough to protect a world against a pandemic. Whereas access to health services and products remains unequal around the world, the influenza virus is indiscriminate and all countries can be equally at risk. Consequently, it is vital that the influenza products produced through the rapid sharing of viruses are available to the most vulnerable populations in the time of a pandemic.

Viruses are shared through the Global Influenza Surveillance and Response System (GISRS) of 152 laboratories, including 143 National Influenza Centres (NICs) spread across 113 Member States, six WHO Collaborating Centres for Reference and Research on Influenza (WHO CCs), four WHO Essential Regulatory Laboratories (WHO ERLs), and 13 WHO H5

¹ Influenza A(H1N1)pdm09 is the virus responsible for the 2009 influenza pandemic that was declared the first Public Health Emergency of International Concern under the International Health Regulations (2005).

² Implementation of the International Health Regulations (2005), Report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009, Report by the Director-General. Geneva: World Health Organization; 2011 (A64/10; (http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf, accessed 20 September 2016).

³ Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 19 September 2016).

⁴ Agenda item 13.1. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. Sixty-fourth World Health Assembly. Geneva: World Health Organization; 2011 (WHA64.5; (http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_R5-en.pdf, accessed 21 September 2016).

Reference Laboratories (WHO H5RLs).^{1,2} The Standard Material Transfer Agreement 1 (SMTA1), contained in Annex 1 to the PIP Framework, is a binding contract that establishes the conditions under which GISRS laboratories exchange PIP biological materials (PIP BM) among themselves.

The PIP Framework's benefit sharing aspect occurs in two ways: SMTA2s and Partnership Contribution (PC).³ Non-GISRS entities, such as manufacturers or academic institutions, who receive physical virus samples sign an SMTA2, a legally binding agreement to provide products such as vaccines, antivirals and diagnostics in the event of a pandemic. Influenza vaccine, pharmaceutical and diagnostic manufacturers who use GISRS also pay annual PC funds totalling US\$ 28 million, which are used to bolster pandemic Preparedness and Response.

The first review of the PIP Framework

At the start of this Review, the PIP Framework had been implemented for five years. This first review was provided for under section 7.4.2 of the PIP Framework, which states that the PIP Framework and its Annexes should 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 PIP Framework Advisory Group (the "Advisory Group") met in a Special Session on 13-14 October 2015 with Member States, industry and other stakeholders, and recommended that an independent group of experts be established to review implementation of the PIP Framework.⁴ The Director-General convened the Review Group, consisting of eight experts with wide-ranging expertise, covering all WHO regions and with a good gender balance. As part of its terms of reference, the Review Group was asked to focus on three questions:⁵

1. What are the achievements since the PIP Framework was adopted?
2. Has implementation of the PIP Framework improved global pandemic influenza preparedness, including inter-pandemic surveillance, and capacity to respond?
3. What are the challenges, and possible ways of addressing them?

The Review Group was appointed in December 2015. In addition to analysing the sharing of influenza viruses with human pandemic potential (IVPP) through GISRS, the collection of PC

¹ Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 20 October 2016).

² Outside GISRS there are also influenza laboratories authorized and designated by a Member State to provide PIP BM to GISRS. These laboratories are either in Member States that do not have a NIC or are additional laboratories carrying out certain roles usually performed by NICs.

³ Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 19 September 2016), Annex 2 and section 6.14.

⁴ PIP Framework Advisory Group. Special session of the Pandemic influenza preparedness (PIP) Framework Advisory Group, 13-14 October 2015, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/advisory_group/ag_spec_session_report.pdf, accessed 24 September 2016).

⁵ *Ibid.*

and its implementation through five Areas of Work, the signing of SMTA2s, and the governance of the PIP Framework, the Review Group also looked at other key contextual and implementation issues including: the handling of genetic sequence data (GSD) under the PIP Framework; linkages with other programmes or instruments (specifically the Global Action Plan for Influenza Vaccines (GAP),¹ the IHR (2005),² the implementation of the Nagoya Protocol³); interactions with key partners in the PIP Framework, including industry, civil society and other stakeholders; and collateral benefits that may have resulted from implementation of the PIP Framework.

During 2016, the Review Group met several times face to face at WHO Headquarters in Geneva and held a number of teleconferences. To inform its deliberations, the Review Group actively sought input from WHO staff, Member States and many key stakeholders, including representatives of GISRS, industry, civil society organizations, and relevant databases. This engagement took place through individual interviews, written submissions, an electronic open consultation process that included questions for response, and two open consultation meetings at WHO Headquarters. Following several of the Review Group meetings, the Review Group held debriefing and question/answer sessions for Member States at WHO Headquarters that were open to all stakeholders and the public via a live webcast on the WHO website.⁴

The main report begins with an introduction to the PIP Framework and its component parts, followed by a brief description of the Review Group's Method of Work. The remainder of the report presents the Review Group's Findings and Recommendations. This Executive Summary summarizes the main Findings and reproduces all the Recommendations.

Findings and Recommendations

Overarching analysis

Summary of Findings:

The Review Group found that the PIP Framework is a bold and innovative tool for pandemic influenza preparedness, is being well implemented, and that the principle of the PIP Framework of placing virus sharing and benefit sharing on an equal footing remains relevant today. The implementation of the PIP Framework has led to greater confidence and predictability in the global capacity to respond to an influenza pandemic. The PIP Framework's success is due in part to the regular, committed engagement by WHO and Member States with key stakeholders including industry, civil society, and others. However, while there are regular reports on the implementation of the PIP Framework, the various elements could be better brought together to give a clearer picture of overall progress.

¹ Global Action Plan for Influenza Vaccines (GAP). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/en/, accessed 22 September 2016).

² International Health Regulations (2005), 2nd ed. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf, accessed 22 September 2016).

³ The Nagoya Protocol on Access and Benefit-sharing. In: Convention on Biological Diversity [website]. Montreal: Convention on Biological Diversity, United Nations; 2011 (<https://www.cbd.int/abs/>, accessed 4 October 2016).

⁴ PIP Framework Review Group. 2016 Review of the PIP Framework, PIP Review Group Meeting Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/pip/2016-review/meetings/en/>, accessed 20 September 2016).

It is also clear that there are key issues that must urgently be addressed for the PIP Framework to remain relevant, including the issue of how GSD should be handled under the PIP Framework, and whether or not the PIP Framework could be expanded to include seasonal influenza, or indeed be used as a model for the sharing of other pathogens.

Recommendations:

1. WHO should develop a comprehensive evaluation model, including overall success metrics for the Pandemic Influenza Preparedness (PIP) Framework for annual reporting. Such reporting should include an infographic that illustrates the status of overall progress in implementing the PIP Framework to allow for greater clarity on progress towards pandemic preparedness and response.
2. WHO should regularly and more effectively communicate the objectives and progress in the implementation of the PIP Framework to Member States, Global Influenza Surveillance and Response System (GISRS) laboratories, industry, civil society, and other stakeholders. In particular, it should better communicate:
 - a. Progress against the comprehensive evaluation model;
 - b. Partnership Contribution implementation measures; these should be highlighted in regular Advisory Group reports and post-meeting briefings so that progress is more visible and clearly recognized;
 - c. Communication and transparency should be enhanced around issues such as selection of countries to receive Partnership Contribution implementation support for improved understanding of the PIP Framework among Member States;
 - d. The significance of stakeholder voluntary contributions, and in-kind Member States' commitments, including support and maintenance of GISRS through provision of routine running costs of laboratories.
3. The Director-General should undertake a study to determine the implications and desirability of including seasonal influenza viruses in the PIP Framework.
4. The PIP Framework is a foundational model of reciprocity for global public health that could be applied to other pathogens; however, the current scope of the PIP Framework should remain focused on pandemic influenza at this time.
5. Member States should agree the timing of the next review of the PIP Framework, which should be before the end of 2021.

Virus Sharing

Summary of Findings:

GISRS has expanded in scope and been strengthened since the PIP Framework was adopted in 2011, and provides significant benefits to Member States, including risk assessment, candidate vaccine viruses (CVVs), diagnostic kits, reagents, training, capacity building and other expertise. Virus sharing via GISRS generally works well. However, despite a prompt and comprehensive response to the emergence of the H7N9 strain in 2013, there has since been a

reduced sharing of IVPP from some countries. At the Advisory's Group request, the Secretariat is studying the reasons for this reduced sharing.

GISRS collaborates closely with the animal sector to conduct risk assessment and develop CVVs; these links between the human and animal sectors are especially important when the sharing of human viruses is delayed, and include relationships with the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the OFFLU (the joint OIE-FAO network of animal influenza experts).

Although the Influenza Virus Traceability Mechanism (IVTM) is vital in tracking the sharing of viruses, and thereby triggering the PIP Framework's benefit sharing mechanisms, it is not consistently used by all laboratories.

Recommendations:

6. The Review Group welcomes the PIP Framework Secretariat's study of the reasons for the recent decline in the sharing of influenza viruses with human pandemic potential. The Advisory Group should, as a priority, follow-up on the results of this study in order to ensure the timely sharing of all viruses.
7. Given the recent decline in the sharing of influenza viruses with human pandemic potential, WHO should continue to provide technical operational guidance and training for National Influenza Centres to ensure that they are fully aware of their roles as agreed in the Standard Material Transfer Agreement 1, the effective use of the Influenza Virus Traceability Mechanism, and the importance of appropriate sharing of all PIP biological materials and genetic sequence data.
8. WHO should provide clarification to GISRS laboratories on the interpretation of the terms "timely" and "as feasible" with respect to the sharing of PIP biological materials from all cases of A(H5N1) and other influenza viruses with human pandemic potential (section 5.1.1 of the PIP Framework).
9. Although genetic sequence data do not fully substitute for the physical virus, in cases where it is not possible to ship PIP biological materials rapidly, genetic sequence data should, if available, be shared immediately.
10. The WHO Global Influenza Programme should strengthen contacts and linkages with, and processes between, the GISRS system and non-GISRS laboratories and other networks.
11. WHO, GISRS, the Food and Agricultural Organization of the United Nations, the World Organisation for Animal Health, the OFFLU and others should collaboratively establish guidance for GISRS and animal laboratories to strengthen their relationships and enhance surveillance and risk assessment of influenza viruses at the animal-human interface.

Genetic Sequence Data

Summary of Findings:

Due to the complexities of its handling under the PIP Framework, GSD was not included in the definition of PIP BM when the PIP Framework was set up. Thus, while the sharing of viruses is tracked via the IVTM, the sharing of GSD is not, and therefore does not trigger specific benefit sharing under the PIP Framework. However, as technology advances, GSD is becoming increasingly critical in influenza research, and can in some cases substitute for physical samples for pandemic risk assessment and the development of commercial products. Therefore, clarity is urgently required on the handling of GSD under the PIP Framework.

Some good progress has already been made by the Advisory Group in examining possible approaches to handling GSD under the PIP Framework. A key challenge has been the lack of agreement on what should be traced. Options could include tracking access to GSD or tracking the commercial products developed using such data. Transparency in both the sharing and traceability of GSD is crucial in order to identify any resulting benefit that should be shared.

There are a range of players involved in the discussion of how to handle GSD and diverse views about the optimal traceability and monitoring system. It is clear from the Review Group's interviews and wider discussions that there also remains some confusion among stakeholders as to the potential options for future sharing of GSD.

Recommendations:

12. The 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 genetic sequence data.

13. The Director-General should request Member States to 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".

14. The Director-General should request Member States to 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;"

15. It is critical that the PIP Framework adapts to technological developments, and that the Advisory Group produces with urgency recommendations to clarify the handling of genetic sequence data. The Advisory Group should consider asking WHO Collaborating Centres to report on how genetic sequence data are actually handled, with a view to providing information about the operational realities in GISRS in relation to the acquisition, sharing and use of such data, to inform the Advisory Group's recommendations on the optimal handling of genetic sequence data under the PIP Framework.

16. 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.

17. Noting that genetic sequence data may be generated from many entities outside of GISRS, and that there are diverse views on the optimal traceability and monitoring mechanism, the Advisory Group should give consideration to broadening and deepening engagement with all stakeholders.

Benefit Sharing

Standard Material Transfer Agreement 2 (SMTA2)

Summary of Findings:

The SMTA2s signed so far have secured access to approximately 350 million doses of pandemic vaccine to be delivered in real time during an influenza pandemic. However, PIP Framework options for SMTA2 commitments from manufacturers of other pandemic products (such as diagnostics, syringes, etc.) are too narrow, and need to include a wider choice of commitments.

Good progress on securing prequalified vaccines and antivirals has been achieved through the PIP Framework Secretariat's strategic approach of prioritizing agreements with large companies with prequalified vaccines before moving on to negotiations with medium to small companies. In order to facilitate negotiations of SMTA2s, the PIP Framework Secretariat has developed tools¹ that outline the technical requirements, such as prequalification, export procedures and regulatory approvals, which must be fulfilled by signatories to SMTA2s.

¹ Frequently asked questions about Standard Material Transfer Agreements 2. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/benefit_sharing/smta2_FAQs.pdf, accessed 26 September 2016).

The regularity and high quality of communication between the PIP Framework Secretariat and industry and other stakeholders has helped to facilitate the conclusion of SMTA2s. On the few occasions when negotiations have been complicated or have stalled, the PIP Framework Secretariat has successfully implemented the stepwise approach recommended by the Advisory Group to progress towards conclusion of the agreements.¹

The fulfilment of SMTA2 agreements at the time of a pandemic outbreak will be critical to pandemic response. Member States with in-country influenza vaccine production capacity need to recognize the SMTA2 commitments of the manufacturer(s) into their pandemic influenza response plans.

Recommendations:

18. The PIP Framework Secretariat should improve communication of progress and achievements in securing SMTA2s by better highlighting the rationale and prioritization strategy for concluding these agreements, and clarifying the intended use of the antivirals, vaccines and other products secured through these agreements.

19. The PIP Framework Secretariat should develop, for consideration by the Advisory Group, and ultimate decision-making by Member States, an approach to include the provision of financial contributions, specimen collection and processing materials as options for category B SMTA2 commitments in Annex 2.

20. The Director-General should consider requesting that Member States remove section 6.9 in the PIP Framework on pandemic influenza preparedness vaccine stockpiles, since it is no longer relevant.

21. The Director-General should request Member States with in-country vaccine production capacity to commit to allow manufacturers to release to WHO on a real-time basis, pandemic vaccines and other products secured by WHO under SMTA2s.

22. WHO should rapidly finalize and communicate the Interim Pandemic Influenza Risk Management (PIRM) Framework, which will provide clarity on the implementation of the switch from seasonal to pandemic vaccine production.

Partnership Contribution collection

Summary of Findings:

The involvement of industry in the collaborative development² of the PC formula has achieved its strong buy-in, and has resulted in early contribution payments being made in 2012, and the

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework (PIPF) Advisory Group, 15-16 October 2015, Geneva, Switzerland, Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_meetingreport_october2015.pdf, accessed 22 September 2015), paragraph 8.

² Partnership Contribution Standard Operating Procedures June 2015. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/benefit_sharing/pc_collection_sop.pdf?ua=1, accessed 24 September 2016), page 5, Annex 2.

collection of 96%¹ of the overall funds due for 2013 and 2014. However, not all companies pay their contributions by the expected deadline, which is of concern since the PC mechanism relies on all stakeholders fulfilling their obligations.

Several industry representatives have highlighted as an issue that the fluctuation in the amount of PC they are asked to pay each year poses budgetary challenges, and they would prefer to pay a set amount.² Consistent with the recommendation of the Advisory Group in April 2016,³ industry has begun a consultative process to review the PC formula, working with all relevant industry sectors (vaccine, diagnostics and pharmaceuticals) and the PIP Framework Secretariat.⁴

A survey of GISRS running costs was undertaken for this Review: the estimates from 41 laboratories are that their total annual running costs alone are approximately US\$ 39 million. Although this figure is preliminary, and should be studied further, this indicates that total running costs for the whole of the GISRS system are likely to have increased from the 2010 estimate.

Recommendations:

23. The Advisory Group should consider updating the 2010 estimate of GISRS running/operating costs, as input to a revision of the Partnership Contribution formula calculation, in collaboration with industry, to facilitate the timely payment of Partnership Contribution, and its sustainability as a financing mechanism for implementation of the PIP Framework.

24. Given the successful use, following a recommendation by the Advisory Group, of a stepwise approach for the agreement of SMTA2s, the Advisory Group should consider developing a similar escalation response to underpayment, late payment or default of Partnership Contribution.

Partnership Contribution implementation

Summary of Findings:

Since PC funds began to be distributed in 2014, the implementation of the PC mechanism has allowed countries to develop multi-year plans and has fostered sustained and meaningful capacity building in priority countries in each of the five Areas of Work for Preparedness (Laboratory and Surveillance; Burden of Disease; Regulatory Capacity building; Planning for

¹ Calculation based on data in Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf>, accessed 24 September 2016).

² PIP Framework Review Group. Report of the Third Meeting of the Pandemic Influenza Preparedness (PIP) Framework 2016 Review Group. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/2016-review/meeting30march_1april.pdf, accessed 4 October 2016).

³ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016).

⁴ PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

Deployment; and Risk Communication). A Response fund has also been established for use by WHO at the time of a pandemic outbreak.

However, expenditure does not always keep pace with collection, leading to a mistaken perception among some stakeholders that either additional Preparedness funds are not needed or that work plans are failing to be implemented according to planned timeframes.

The PIP Framework Secretariat communicates regularly about the achievements and challenges of PC implementation. Nevertheless, stakeholders regularly raise specific issues with WHO concerning: (1) dissatisfaction that PC funds continue to be collected while the Response funds are left untouched, which seemingly indicates a lack of understanding that the Response Fund is a contingency fund to enable rapid response at the start of a pandemic, and that the value of the Response funds is far below what will be needed at the time of a pandemic outbreak; (2) the basis on which recipient priority countries are selected, even though the criteria and process for selection have been published,¹ though this could indicate the desire of certain countries to be put on this list; and (3) a lack of understanding of how PC funds are building capacity in countries to increase preparedness for pandemic influenza.

Recommendations:

25. The Advisory Group should consider for inclusion in the 2018-2022 Partnership Contribution Implementation Plan, the development of process measures to enable better monitoring of progress for key Areas of Work.

26. The Advisory Group should request regular financial reports and audits and ensure that appropriate financial accountability mechanisms are in place; it should also request the PIP Framework Secretariat to illustrate how the Partnership Contribution Response funds will be severely inadequate in a pandemic.²

Governance

Summary of Findings:

The PIP Framework has a well-functioning governance structure that oversees how the PIP Framework is operationalized. It has benefited from strong commitment at each of WHO's three levels: Headquarters; Regional Offices; and Country Offices. The Advisory Group continues to play a key role in effective governance by providing impartial, committed, and pragmatic oversight and guidance, representing its independent deliberations. However, AG members usually leave after completing individual terms of three years, meaning that there can be gaps in knowledge continuity.

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimplan_update_31jan2015.pdf?ua=1, accessed 20 September 2016), pages 9-11.

² See Recommendation 2(b) of this report, which states: "WHO should regularly and more effectively communicate the objectives and progress in the implementation of the PIP Framework to Members States, Global Influenza Surveillance and Response System (GISRS) laboratories, industry, civil society, and other stakeholders. In particular, it should better communicate:

b. Partnership Contribution implementation measures; these should be highlighted in regular Advisory Group reports and post-meeting briefings so that progress is more visible and clearly recognized."

Although the AG's Annual Reports¹ to the Director-General and the Director-General's Biennial Reports² to the World Health Assembly are comprehensive and well-received, the formats and contents differ, leading to inefficient preparation of information.

Some GISRS members, notably WHO CCs, feel there should be greater interaction between themselves, the Advisory Group, and the PIP Framework Secretariat, including in the setting up of technical working groups and the subsequent selection of experts. The regular, direct contact that occurs between the Advisory Group and industry/civil society groups might also be helpful if it included GISRS representatives.

An objective of the PIP Framework (section 2) is to strengthen GISRS, and the geographical reach, scope and functioning of GISRS has expanded since 2011. However, the leadership of this network remains largely informal, with the system being coordinated through WHO's Global Influenza Programme (GIP). The lack of a formalized leadership structure from within GISRS has led to the absence of recognized representation for the entire GISRS network in PIP Framework operations.

Under the 2016 reform of WHO's work in health emergency management, all WHO's work in emergencies was brought under a new Health Emergencies Programme, including the Secretariat of the PIP Framework.³ WHO's commitment to the PIP Framework remains unchanged by this internal reorganization. The PIP Framework Secretariat is significantly dependent on close collaboration with many technical units of WHO, especially GIP, which is the technical influenza unit that coordinates GISRS, which in turn underpins the implementation of the PIP Framework.

Recommendations:

27. The Director-General should consider options for retaining continuity and knowledge in the Advisory Group, including members being able to serve a second term of flexible duration.
28. The structure of the Advisory Group's Annual Reports to the Director-General and the Director-General's Biennial Reports to the World Health Assembly should be harmonized to simplify reporting.
29. The PIP Framework Secretariat and Advisory Group should broaden and deepen engagement with civil society to a greater number of participating organizations.
30. Noting the critical role of the WHO Collaborating Centres in the GISRS network, the Advisory Group should undertake more regular engagement with the WHO Collaborating Centres and other key GISRS laboratories, including when setting up technical working groups.

¹ PIP Framework Advisory Group Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/pip_meetings_consultations/en/, accessed 22 September 2016).

² *Ibid.*

³ Reform of WHO's work in health emergency management, WHO Health Emergencies Programme, Report by the Director-General. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (A69/30; http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_30-en.pdf, accessed 22 September 2016).

31. The Director-General should address the issue of the lack of a formalized representation for the GISRS network, and encourage the WHO Global Influenza Programme and GISRS to establish such representation as soon as possible.

32. The Director-General should ensure that any internal reorganization of WHO departments under the new Health Emergencies Programmes should ensure that the activities of GISRS and the PIP Framework remain closely aligned and integrated with the WHO Global Influenza Programme to ensure stronger scientific and technical leadership in the implementation of the PIP Framework.

33. The Director-General should continue to make available the necessary human and financial resources to implement the growing activities of the PIP Framework and the Recommendations of this Review.

Linkages with WHO programmes and other legal instruments

Global Action Plan for Influenza Vaccines

Summary of Findings:

There are important synergies between the PIP Framework and the GAP programme.^{1,2} This includes the encouragement of technology transfers and capacity building for burden of disease studies, regulatory authorities and risk communications. However, technology transfer agreements are currently not being obtained through SMTA2s.

The November 2016 review of GAP will be available to feed into an assessment of which aspects of GAP (burden of disease studies, technical guidance to new vaccine manufacturers, vaccine deployment, or logistics), might be continued as part of the PIP Framework's implementation of PC.

The quantity of pandemic influenza vaccines secured by the PIP Framework, as well as global vaccine production capacity (including new vaccine capacity available through the GAP programme) currently remain insufficient to meet anticipated global demand at the time of an influenza pandemic.

Recommendation:

34. The PIP Framework Advisory Group should consider lessons learned from the Global Action Plan for Influenza Vaccines (GAP), which closes in November 2016, to identify any aspects that would support implementation of the PIP Framework.

¹ The objectives of the GAP programme centre around increasing influenza vaccine manufacturing capacity for developing countries, and include an increase in the manufacture and use of seasonal vaccine, an increase in vaccine production capacity for pandemic vaccine, and relevant research and development. The GAP was developed by WHO together with public health and academic experts, vaccine manufacturers and funding agencies from developed and developing countries. The third and final GAP consultation will take place in November 2016.

² Global Action Plan for Influenza Vaccines (GAP). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/en/, accessed 22 September 2016).

International Health Regulations (2005)

Summary of Findings:

PIP Framework PC funds may have additional benefits in improving IHR (2005)¹ core capacities, especially in the areas of laboratory and surveillance capacity. However, since PC funds only began to be distributed in 2014, data on the relationship between PC implementation funds and IHR (2005) core capacities are not yet available. An analysis of PC funds' impact on IHR (2005) core capacities could be undertaken in the next review of the PIP Framework.

Recommendation:

35. Activity under the PIP Framework should be undertaken with the provisions of the International Health Regulations (2005) (IHR (2005)) in mind, and capacity building efforts should be aligned, supportive and complementary to those under the IHR (2005). This could be addressed by closer interaction at all three levels of WHO regarding implementation of the IHR (2005) and the PIP Framework to maximise synergies and efficiencies.

Nagoya Protocol to the Convention on Biological Diversity

Summary of Findings:

The PIP Framework is a multilateral access and benefit sharing instrument that appears to be consistent with the objectives of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity.² The intergovernmental negotiation of the PIP Framework established rules for access to IVPP and sharing of benefits; by contrast, the implementation of the Nagoya Protocol may introduce uncertainty in relation to the sharing of influenza viruses, since numerous bilateral transactions could be required to be negotiated, which could delay the access to viruses. As more countries put in place domestic legislation to implement the Nagoya Protocol, the urgency increases to resolve this uncertainty and reduce the risk to global health security.

The public health implications of the implementation of the Nagoya Protocol are not yet widely understood. While the WHO Secretariat is producing a report to clarify these implications, better knowledge, understanding and awareness of the Protocol are required in the public health sector.

The Nagoya Protocol does not expressly identify a mechanism to recognize an instrument under its Article 4(4). The Review Group understands that an authoritative, formal and internationally credible entity such as the Meeting of the Parties (MOP) or World Health Assembly could make a decision that the PIP Framework constitutes a specialized international

¹ International Health Regulations (2005), 2nd ed. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf, accessed 22 September 2016).

² The Nagoya Protocol on Access and Benefit-sharing. In: Convention on Biological Diversity [website]. Montreal: Convention on Biological Diversity, United Nations; 2011 (<https://www.cbd.int/abs/>, accessed 4 October 2016).

instrument for pandemic influenza preparedness and response. In this case, the decision should facilitate fulfilment of the PIP Framework's access and benefit sharing objectives by ensuring that all countries would handle IVPP in the same way. IVPP access and sharing would be covered for Nagoya Protocol purposes by the PIP Framework, and therefore not require bilateral agreements on a case-by-case basis.

Recommendation:

36. The PIP Framework should be considered as a specialized international instrument to clarify the implementation of the Nagoya Protocol in relation to pandemic influenza preparedness and response:

- The December 2016 Meeting of the Parties of the Nagoya Protocol provides an opportunity to consider recognizing the PIP Framework as a specialized international instrument for pandemic influenza preparedness and response. In the view of the Review Group, it would serve the aims of the PIP Framework if the Meeting of the Parties took up this opportunity.
- Further, the 2017 World Health Assembly should address the recognition of the PIP Framework as a specialized international instrument under the Nagoya Protocol.

Chapter 1: Introduction and background

Ensuring the health security of all people is an overarching concern in public health today. The tremendous increase in international travel over the last 40 years or so means that diseases are no longer contained by geography alone. Health security became a prominent aspect of global health after the severe acute respiratory syndrome (SARS) outbreak in 2003, the re-emergence of influenza A(H5N1) beginning in 2003 and 2004, and the influenza A(H1N1) pdm09¹ pandemic in 2009. In 2011, the Report of the Review Committee on the Functioning of the International Health Regulations (2005) (IHR (2005)) in relation to the 2009 pandemic of influenza A(H1N1) concluded that the world was “ill-prepared” to respond to a severe influenza pandemic and that “the unavoidable reality is that tens of millions of people would be at risk of dying in a severe pandemic”.² These events taught the world a valuable lesson – an effective response to an outbreak of an infectious pathogen that can easily cross borders can only ever come about through close collaboration and information-sharing between countries.

After the re-emergence of influenza A(H5N1) with human pandemic potential, some developing countries were concerned that despite contributing virus samples to the Global Influenza Surveillance and Response System (GISRS) network of public health laboratories that collect, monitor and share influenza viruses, they were unable to afford vaccines and other medical products developed as a result of sharing viruses. It became clear that a new system was needed that lifted barriers to virus sharing among scientists, industry and countries, while ensuring that the products of such sharing could be fairly and easily accessed by those who need them most.

After four years of negotiation, this new system was embodied in the Pandemic Influenza Preparedness (PIP) Framework³ – an international instrument set up by 194 WHO Member States in 2011⁴ that brought together countries, industry and civil society to ready the world’s defences and strengthen its capacity to respond to an influenza pandemic. The PIP Framework does this by facilitating the sharing between countries of influenza viruses with human pandemic potential (IVPP), in order to develop antivirals, vaccines and diagnostics, while ensuring fair and equitable access to these products across the world. The PIP Framework also seeks to increase capacity for pandemic preparedness in all countries, and prioritizes support to those most in need. A fundamental tenet of the PIP Framework is that the sharing of viruses and benefits takes place on an equal footing, balancing public health and economic interests in a win-win model based on the principle of reciprocity (see Figure 1.1). The PIP Framework

¹ Influenza A(H1N1)pdm09 is the virus responsible for the 2009 influenza pandemic that was declared the first Public Health Emergency of International Concern under the International Health Regulations (2005).

² Implementation of the International Health Regulations (2005), Report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009, Report by the Director-General. Geneva: World Health Organization; 2011 (A64/10; (http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf, accessed 20 September 2016).

³ Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 19 September 2016).

⁴ Agenda item 13.1. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits. Sixty-fourth World Health Assembly. Geneva: World Health Organization; 2011 (WHA64.5; http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_R5-en.pdf, accessed 21 September 2016).

allows effective coordination without the need constantly to rewrite the rule book, which would cause delays that can be devastating to public health during a fast-moving pandemic.

Viruses are shared through the 152 GISRS laboratories, including 143 National Influenza Centres (NICs) spread across 113 Member States, six WHO Collaborating Centres (WHO CCs) for Reference and Research on Influenza, four WHO Essential Regulatory Laboratories (WHO ERLs), and 13 WHO H5 Reference Laboratories (WHO H5RLs).^{1,2} The Standard Material Transfer Agreement 1 (SMTA1), contained in Annex 1 to the PIP Framework, is a binding contract that establishes the conditions under which GISRS laboratories exchange PIP biological materials (PIP BM) among themselves. With the advent of technology to sequence and analyse genetic sequence data (GSD), an increasing proportion of viruses are shared electronically through their genetic sequences, although GSD is not included in the definition of PIP BM.

The PIP Framework's benefit sharing aspect occurs in two ways: Partnership Contribution (PC) funds and Standard Material Transfer Agreement 2s (SMTA2s). Influenza vaccine, pharmaceutical and diagnostic manufacturers who use GISRS pay annual PC funds totalling US\$ 28 million, which are used to bolster pandemic Preparedness and Response. Non-GISRS entities, such as manufacturers or academic institutions, who receive physical virus samples sign an STMA2, a legally binding agreement to provide products such as vaccines, antivirals and diagnostics in the event of a pandemic.

Why is the Framework being reviewed now?

This first review of the PIP Framework (the "Review") was provided for under section 7.4.2 of the PIP Framework, which states that the PIP Framework and its Annexes should 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 PIP Framework Advisory Group (the "Advisory Group") met in a Special Session on 13-14 October 2015 to seek views from Member States, industry and other stakeholders on the review. The outcome of that meeting was a recommendation that a small, independent group of experts be established to review implementation of the PIP Framework using a transparent and inclusive approach.³ In response, the Director-General convened the Review Group, consisting of eight experts with wide-ranging expertise and from across all WHO regions. The Review Group was charged with answering the following questions:⁴

¹ Global Influenza Surveillance and Response System (GISRS). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/gisrs_laboratory/en/, accessed 20 October 2016).

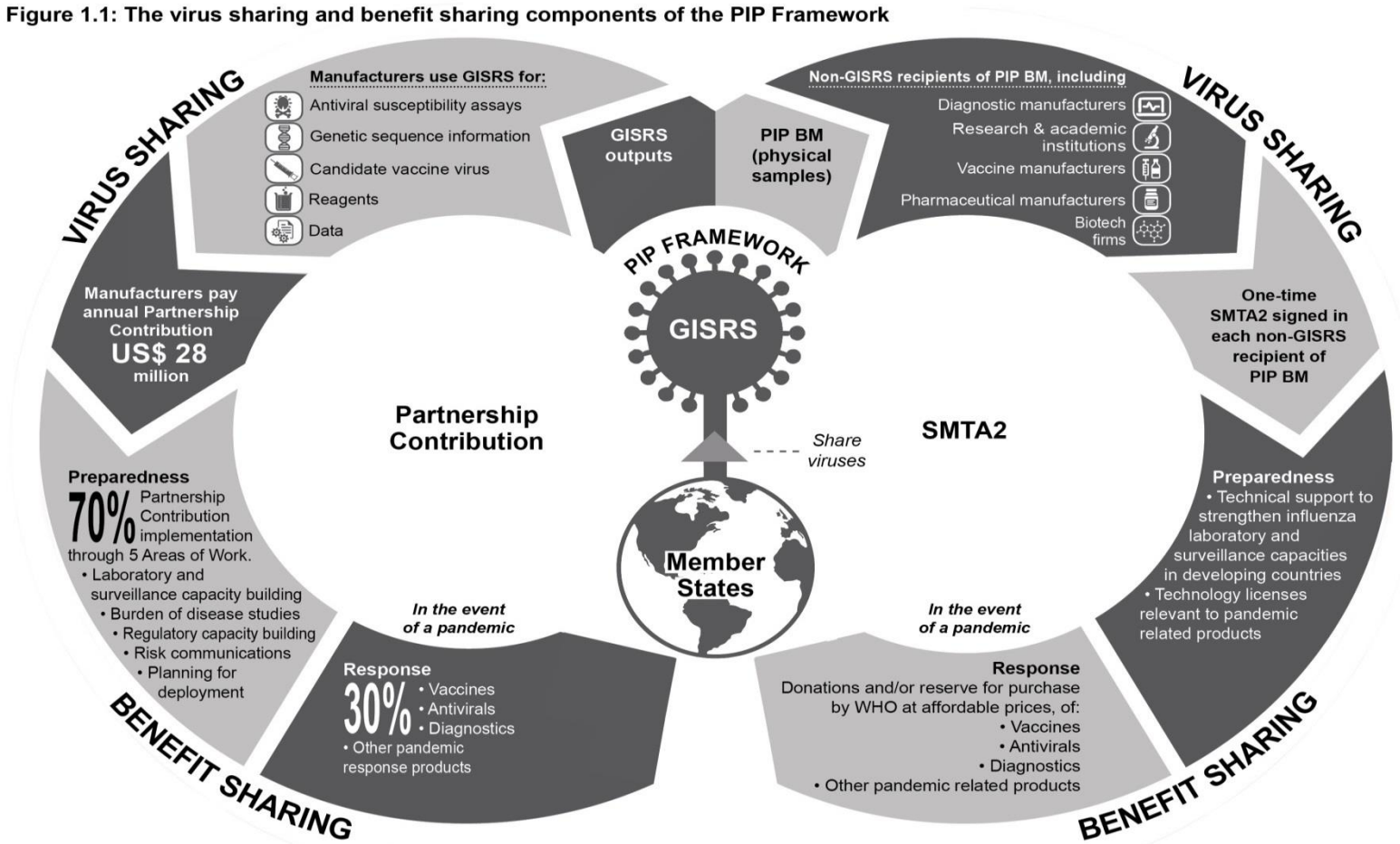
² Outside GISRS there are also influenza laboratories authorized and designated by a Member State to provide PIP BM to GISRS. These laboratories are either in Member States that do not have a NIC or are additional laboratories carrying out certain roles usually performed by NICs.

³ PIP Framework Advisory Group. Special session of the Pandemic influenza preparedness (PIP) Framework Advisory Group, 13-14 October 2015, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/advisory_group/ag_spec_session_report.pdf, accessed 24 September 2016).

⁴ *Ibid.*

1. What are the achievements since the PIP Framework was adopted?
2. Has implementation of the PIP Framework improved global pandemic influenza preparedness, including inter-pandemic surveillance, and capacity to respond?
3. What are the challenges, and possible ways of addressing them?

Figure 1.1: The virus sharing and benefit sharing components of the PIP Framework



GISRS: The Global Influenza Surveillance and Response System, made up of 143 National Influenza Centres (NIC) hosted by 113 Member States, 6 WHO Collaborating Centres (CCs), 4 WHO Essential Regulatory Laboratories (ERLs), and 13 WHO H5 Reference Laboratories (H5RLs)
 Manufacturers who pay Partnership Contribution may also be eligible to sign an SMTA2

PIP BM: PIP biological materials
SMTA2: Standard Material Transfer Agreement 2 (an SMTA1 is the agreement signed by NICs to be part of GISRS); an SMTA2 is valid until the next pandemic ends
 Source: WHO, 2016

Chapter 2: Method of Work

The Advisory Group's Special Session on 13-14 October 2015 sought views from Member States, industry and other stakeholders on the terms of reference and direction of the Review. Following the meeting, the Advisory Group reported to the Director-General, with recommendations on the organization, process, scope and terms of reference for the Review.¹

The Review Group was appointed in December 2015, and held four face-to-face meetings between March 2016 and September 2016 at WHO Headquarters in Geneva. These meetings were preceded by two teleconferences, in January and February 2016. The Review Group held deliberative sessions, open only to members of the Review Group and the WHO Review Group Secretariat. In addition, representatives of Member States were invited to attend a debriefing and question/answer session following the February 2016 teleconference and the March 2016, June 2016 and August/September 2016 meetings. These sessions were open to all stakeholders and the public via a live webcast on the WHO website.² In addition, the Review Group Chair, Dr Christine Mwelwa Kaseba-Sata, presented an update of the Review Group's work at the Sixty-ninth World Health Assembly on 25 May 2016.³

The methods of work of the Review Group are detailed in Appendix II and summarized briefly as follows. The Review Group began its work by conducting a systematic analysis of the PIP Framework, highlighting areas considered not to be functioning effectively and possible reasons for this. The Review Group reviewed key documents, including reports relating to the work of the Advisory Group, implementation of the PIP Framework, and a study on the implementation of the Nagoya Protocol.

To inform its deliberations, the Review Group actively sought input throughout the review from Member States and representatives of GISRS, industry, civil society organizations (s), relevant databases and other stakeholders, through both interviews and an electronic open consultation process that included questions for response. On 30 March 2016 and 29 August 2016, as part of Review Group meetings, open consultations were held at WHO HQ, with Member States, civil society and other stakeholders. Overall, the Review Group conducted 40 interviews with key informants; received several written submissions from Member States, industry, civil society, databases, and other stakeholders; examined other initiatives underway to protect global public health; and sought information from WHO staff at HQ and Regional Offices.

¹ *Ibid.*

² PIP Framework Review Group. 2016 Review of the PIP Framework, PIP Review Group Meeting Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/pip/2016-review/meetings/en/>, accessed 20 September 2016).

³ Dr Christine Mwelwa Kaseba-Sata, Review Group Chair. Update of the Review Group's work at the Sixty-ninth World Health Assembly. Committee A, Wednesday 25 May 2016, Late Session. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/mediacentre/events/2016/wha69/webstreaming/en/>, accessed 29 September, 2016).

The Review Group provided its final Report to the Director-General in October 2016, for transmission to the WHO Executive Board in January 2017 and the World Health Assembly in May 2017.

Chapter 3: Overarching Analysis

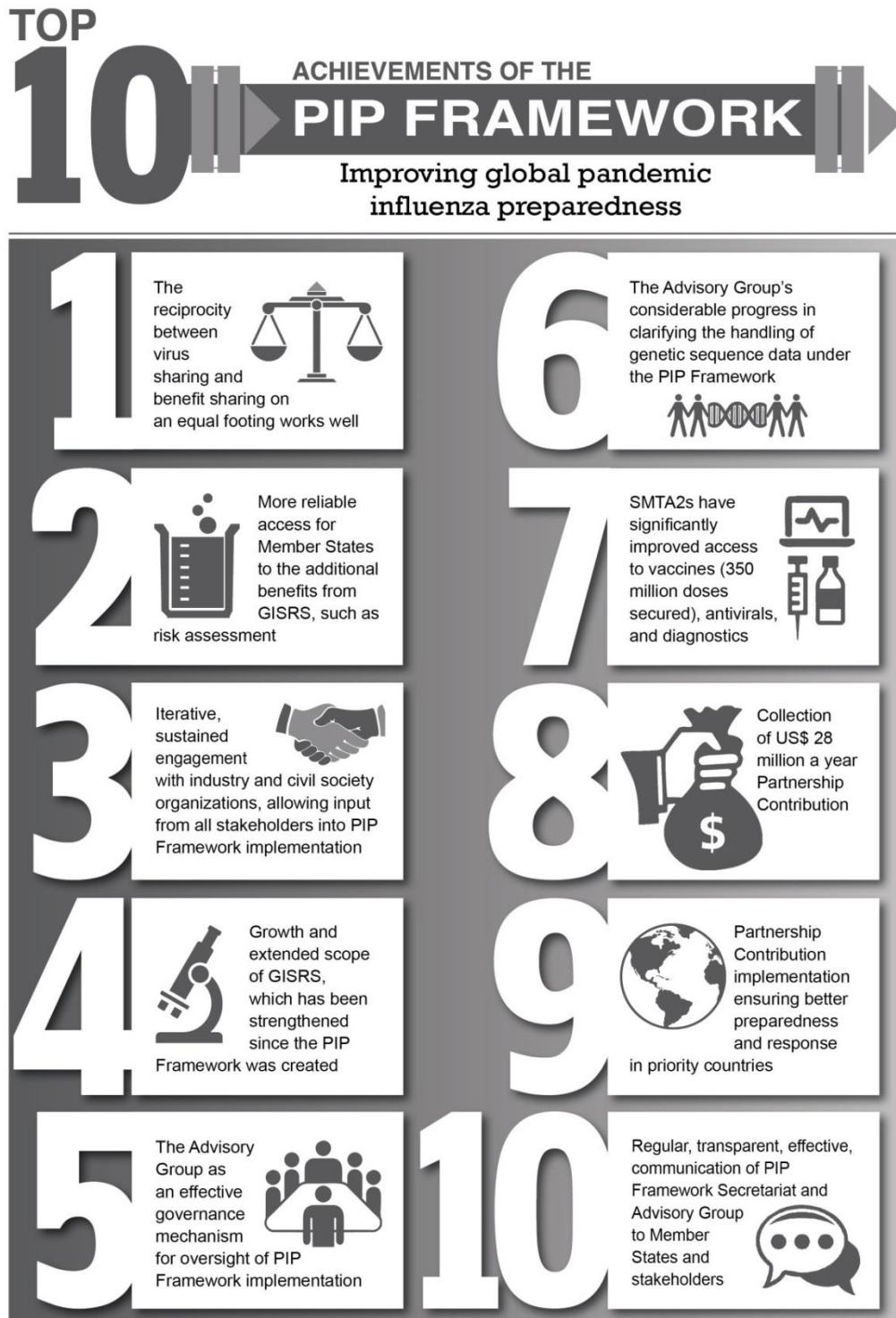
In this report, the Review Group responds to its terms of reference to:¹

1. Discuss achievements of the PIP Framework
2. Discuss whether implementation of the PIP Framework improved global pandemic influenza preparedness, including inter-pandemic surveillance, and capacity to respond
3. Discuss possible challenges and ways of addressing them.

This chapter addresses the first two points by taking an overarching perspective on the PIP Framework as a whole and the overall achievements (see Figure 3.1) and challenges; subsequent chapters 4 - 8 address the third point by considering achievements and challenges associated with specific elements of the PIP Framework and the ways in which challenges might be addressed.

¹ PIP Framework Advisory Group. Special session of the Pandemic influenza preparedness (PIP) Framework Advisory Group, 13-14 October 2015, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/advisory_group/ag_spec_session_report.pdf, accessed 24 September 2016).

Figure 3.1 Top 10 achievements of the PIP Framework



3.1 An innovative approach to improving pandemic preparedness

Key Findings

Finding 1: The PIP Framework, which was negotiated through an extensive intergovernmental process, is valued as a bold and innovative tool for pandemic influenza preparedness. It demonstrates that the balance of virus sharing and benefit sharing on an equal footing is a successful approach for improving pandemic influenza preparedness, which contributes to strengthening global health security.

Finding 2: The PIP Framework has improved global influenza pandemic preparedness through more reliable access to viruses, and its ongoing efforts in securing increased, real-time access to vaccines and antivirals in the event of an influenza pandemic. It has also improved preparedness by funding capacity building in priority countries with limited or no national ability to detect, monitor and share novel influenza viruses, and by ensuring that there is a reserved Response Fund for response. Through these activities, there is confidence and greater predictability in the global capacity to respond to an influenza pandemic as well as in the equity of that response.

Finding 3: The PIP Framework is a model within which Member States engage transparently and effectively, via WHO, with different stakeholders, including industry and civil society. WHO regularly brings industry and civil society to the table with Member States to operationalise different aspects of the PIP Framework and engages them at key decision making points. Given their varied perspectives, these stakeholders provide critical input that contribute to the success of the PIP Framework.

Finding 4: The ongoing risk assessment by GISRS of seasonal influenza viruses and periodic risk assessment of other zoonotic influenza viruses to ascertain pandemic potential provide key benefits for countries in strengthening core capacities for seasonal influenza response and pandemic preparedness.

Finding 5: While there is regular reporting on individual aspects of the PIP Framework, as provided for in sections 7.2.5 and 7.4.1, these elements are not currently brought together in a comprehensive evaluation model, and thus it is challenging for different stakeholders to gain a comprehensive picture of overall progress.

Finding 6: Contributions made to the PIP Framework could be given more visible recognition and acknowledgement, including the significant support by Member States for their GISRS laboratories. Such recognition could build on the PIP Framework Secretariat's existing practice of formally acknowledging PC payments.

The PIP Framework took an innovative approach to engaging stakeholders, especially industry, in a way that had not previously been achieved in public health. It brought key players in public and private health care together in a partnership that was challenging to negotiate, but has proven successful.

3.2 Ensuring the relevance of the PIP Framework

Finding 7: The principles of the PIP Framework, especially that of placing virus sharing and benefit sharing on an equal footing, remain as relevant today as they were five years ago, given the unique threat that the ever-changing influenza virus presents for public health, and the increasing number of health emergencies, such as the Ebola virus disease and Zika virus outbreaks.

Finding 8: Maintaining the contribution of the PIP Framework, and demonstrating the benefits of pandemic influenza preparedness, is especially important as countries with several competing health priorities usually focus their attention on current local disease threats and therefore may be unprepared for an influenza pandemic. The PIP Framework must continue to demonstrate its contribution towards increasing global health security in the context of a wider landscape of public health interventions in order to remain relevant to policymakers, government, industry and intergovernmental organizations.

Finding 9: Currently, the PIP Framework does not specify the timing of subsequent reviews. To ensure the continued relevance and optimal impact of the PIP Framework, regular review of its functioning is needed. There is a need for Member States to indicate how often future reviews should take place.

Finding 10: An increasingly urgent concern among Member States and other stakeholders has been how to address the impact of new technology, particularly relating to the handling of GSD under the PIP Framework.

While the text of the PIP Framework was formulated in a manner that was as forward-thinking as possible, it also reflects a particular political, scientific, technological and economic point in time. Preparing the world for an influenza pandemic remains a critical mission and it is important that the PIP Framework retains its relevancy by adapting to the ever-changing landscape of global health.

Global health, especially in relation to infectious pathogens, has become increasingly framed in the context of health security, where the various initiatives and key players extend beyond the health sector to include humanitarian actors, development agencies, UN agencies, and communities. The financing landscape is also wider, with funding for pandemics now including the new World Bank's Pandemic Emergency Facility.¹

The PIP Framework must also accommodate advances in technology that may change the way influenza viruses are shared or lead to the development of new products. These changes can include new methods of laboratory analysis, changes in influenza vaccine production technology, and novel communication technologies, as well as developments in the use of the genetic sequences of influenza viruses.

¹ Pandemic Emergency Facility: Frequently Asked Questions. In: The World Bank [website]. Geneva: World Bank; 2016 (<http://www.worldbank.org/en/topic/pandemics/brief/pandemic-emergency-facility-frequently-asked-questions>, accessed 26 October 2016).

3.2.1 Discussion on expanding the PIP Framework to seasonal influenza

Finding 11: The Review Group received wide-ranging views from key informants, including Member States, industry and civil society, on this complex and challenging issue, with strong views both for and against including seasonal influenza under the PIP Framework. The implications of including seasonal influenza need to be studied further.

The PIP Framework states in its scope (section 3.2) that the PIP Framework “does not apply to seasonal influenza viruses”. Such inclusion was considered but seasonal influenza viruses were not included in the final text of the PIP Framework. In reality, however, seasonal and pandemic influenza viruses exist as a continuum, involving humans, birds and other animals. Each of the novel IVPP is due to the continuously evolving nature of the virus, which can reassort with other influenza viruses. This is known as “antigenic shift”¹ and can rapidly lead to new viruses with pandemic potential.

The overwhelming majority of viruses shared through GISRS are seasonal viruses – annually, 28,000 seasonal viruses are shared with WHO CCs.² These viruses undergo “antigenic drift”³ through mutation, often requiring an update of the viruses in the seasonal vaccine. Moreover, this “drift” can be significant leading to more virulent seasonal viruses. The bulk of GISRS work is based on seasonal risk assessment, virus characterisation, the development of candidate vaccine viruses (CVVs), reagents and diagnostic kits, and vaccine virus recommendations for the seasonal vaccine. This is of critical importance to manufacturers and countries. Moreover, robust seasonal vaccine production is vital for pandemic vaccine production since the same facilities are used. Such facilities must be robust if there is to be a rapid and timely switch from seasonal vaccine to pandemic vaccine production at the right time.⁴

¹ According to the U.S. Centers for Disease Control and Prevention (CDC), “Antigenic shift is an abrupt, major change in the influenza A viruses, resulting in new hemagglutinin and/or new hemagglutinin and neuraminidase proteins in influenza viruses that infect humans. Shift results in a new influenza A subtype or a virus with a hemagglutinin or a hemagglutinin and neuraminidase combination that has emerged from an animal population that is so different from the same subtype in humans that most people do not have immunity to the new (e.g. novel) virus”. How the Flu Virus Can Change: “Drift” and “Shift”. Atlanta, GA: Centers for Disease Control and Prevention; 2016 (<http://www.cdc.gov/flu/about/viruses/change.htm>, accessed 19 September 2016).

² Global Influenza Programme, World Health Organization, unpublished data, October 2016.

³ The U.S. CDC further defines antigenic drift as “small changes in the genes of influenza viruses that happen continually over time as the virus replicates.” How the Flu Virus Can Change: “Drift” and “Shift”. Atlanta, GA: Centers for Disease Control and Prevention; 2016 (<http://www.cdc.gov/flu/about/viruses/change.htm>, accessed 19 September 2016).

⁴ Influenza Vaccine Response during the Start of a Pandemic, Report of a WHO Informal Consultation held in Geneva, Switzerland, 29 June-1 July 2015. Geneva: World Health Organization; 2016 http://apps.who.int/iris/bitstream/10665/207751/1/WHO_OHE_PED_GIP_2016.1_eng.pdf, accessed 20 September 2016).

It should be noted that in the implementation of the PIP Framework's PC mechanism, the value of seasonal vaccine production is the basis on which each of the vaccine producers using GISRS determines its "sales band", which in turn is the determining factor for calculating the amount each company is asked by WHO to contribute.

The distinction between seasonal and pandemic viruses can present challenges. This becomes particularly evident when a virus – such as the influenza A(H1N1) – causes a severe epidemic in a country well after the original pandemic has been declared over. This happened in May 2016 in Fiji, when influenza A(H1N1) caused several deaths in pregnant women,¹ well after the pandemic had been declared over.

However, expanding the PIP Framework to include seasonal influenza would lead to a significant increase in workload for GISRS laboratories if seasonal viruses were tracked in the same way as IVPP. The benefit sharing aspect would also need to be addressed.

3.2.2 Improved communication about the PIP Framework

Finding 12: Some stakeholders do not clearly understand key aspects of the PIP Framework, including priority country selection for PC implementation and the progress that is being achieved in PC-funded projects. While WHO and the Advisory Group already engage in regular, transparent communication with stakeholders, these gaps in understanding need to be addressed by enhancing communication about key aspects of the PIP Framework, its implementation and achievements.

The implementation of the PIP Framework would benefit from as wide an understanding as possible. Although the PIP Framework Secretariat communicates frequently through face-to-face meetings, teleconferences and newsletters, and the WHO's PIP Framework website,² the turnover of staff within Member State permanent missions in Geneva, WHO Regional Offices and stakeholder organizations leads to a loss of institutional memory, which means that they become less well engaged with the PIP Framework.

Communication about the importance of the PIP Framework for public health should also target a wider range of civil society organizations, since a lack of understanding about the seriousness of influenza can have wider impacts on health.

¹ Fiji Health & Nutrition Cluster. Bulletin #8: Covering Period 6 May-13 June, 2016. In: Fiji Ministry of Health and Medical Services [website] Toorak: Fiji Ministry of Health and Medical Services; 2016 (http://www.health.gov.fj/wp-content/uploads/2016/03/20160613_HNC_Bulletin8_final.pdf, accessed 4 October 2016).

² Pandemic Influenza Preparedness (PIP) Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/pip/en/>, accessed 20 September 2016).

3.3 Applying the PIP Framework to other pathogens

Finding 13: The success of the PIP Framework in ensuring better and more equitable access to viruses, vaccines, antivirals and diagnostics, has led some stakeholders to propose that the PIP Framework be expanded to include other infectious pathogens, whereas others have suggested applying the principles of the PIP Framework as a model.

Finding 14: Expanding the current PIP Framework to pathogens other than influenza viruses, as the 2016 report of the UN High Level Panel on the Global Response to Health Crises¹ has recommended, would be a very complicated process and may threaten its viability; no other disease has a system in which a network of public health laboratories and industry have such a long-standing interdependence.

Finding 15: Using the principles of the PIP Framework as a model for equity and reciprocity in other diseases, as recommended by the 2016 report of the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response,² is likely to be more feasible than expanding its scope, although this is still likely to be challenging.

The success of the PIP Framework has led some to consider how lessons from its implementation could be applied to other diseases. Some reports have gone as far as suggesting that the PIP Framework itself be expanded. The UN High Level Panel on the Global Response to Health Crises, which published its report in January 2016, recommended that “The WHO convenes its Member States to re-negotiate the Pandemic Influenza Preparedness Framework with a view to including other novel pathogens, making it legally binding, and achieving an appropriate balance between obligations and benefits, in accordance with the principles of the 2010 Nagoya Protocol to the Convention on Biological Diversity”.³

In the view of this Review Group, while the PIP Framework could serve as an effective model, an expansion of the PIP Framework itself to include other pathogens would be very challenging. A more pragmatic approach is reflected in the 2016 report of the IHR (2005) Review Committee, which recommended that WHO and States Parties should “consider using the PIP Framework or similar existing agreements as a template for creating new agreements or other infectious agents that have caused, or may potentially cause, [public health emergencies of international concern] PHEICs. These agreements should be based

¹ Protecting Humanity from Future Health Crises, Report of the High-level Panel on the Global Response to Health Crises, Recommendation 15. United Nations General Assembly, 9 February 2016. New York: United Nations; 2016 (A/70/723; http://www.un.org/ga/search/view_doc.asp?symbol=A/70/723, accessed 20 September; 2016).

² Implementation of the International Health Regulations (2005), Report of the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response, Report by the Director-General, 13 May 2016. Geneva: World Health Organization; 2016 (A69/21; http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_21-en.pdf?ua=1, accessed 20 September 2016).

³ Protecting Humanity from Future Health Crises, Report of the High-level Panel on the Global Response to Health Crises, Recommendation 15. United Nations General Assembly, 9 February 2016. New York: United Nations; 2016 (A/70/723; http://www.un.org/ga/search/view_doc.asp?symbol=A/70/723, accessed 20 September; 2016).

on the principle of balancing the sharing of samples and data with benefit sharing on an equal footing”.¹

Balancing the interests of different stakeholders to ensure equity in public health is complex. That the PIP Framework was the first global agreement of its kind has much to do with the uniqueness of the influenza virus itself – it mutates frequently and, because of the need for updated seasonal influenza vaccines, has a continuous product cycle, which therefore results in a consistent income stream for manufacturers, as well as a high quality production line that allows manufacturers to be ready to switch from seasonal to pandemic vaccine production. There is also a strong, established network of laboratories in GISRS, monitoring influenza, which provided the foundation for the PIP Framework.

However, for most new and emerging pathogens, there is no established laboratory network that regularly shares samples and expertise with an associated established vaccine (or other product) production capacity. Thus, while the sharing of viruses and benefits on an equal footing could be applied to other pathogens, using the PIP Framework as a template is likely to present significant implementational and operational challenges.

Recommendations: Overarching

1. WHO should develop a comprehensive evaluation model, including overall success metrics for the Pandemic Influenza Preparedness (PIP) Framework for annual reporting. Such reporting should include an infographic that illustrates the status of overall progress in implementing the PIP Framework to allow for greater clarity on progress towards pandemic preparedness and response.
2. WHO should regularly and more effectively communicate the objectives and progress in the implementation of the PIP Framework to Member States, Global Influenza Surveillance and Response System (GISRS) laboratories, industry, civil society, and other stakeholders. In particular, it should better communicate:
 - a. Progress against the comprehensive evaluation model;
 - b. Partnership Contribution implementation measures; these should be highlighted in regular Advisory Group reports and post-meeting briefings so that progress is more visible and clearly recognized;
 - c. Communication and transparency should be enhanced around issues such as selection of countries to receive Partnership Contribution implementation support for improved understanding of the PIP Framework among Member States;
 - d. The significance of stakeholder voluntary contributions, and in-kind Member States' commitments, including support and maintenance of GISRS through provision of routine running costs of laboratories.

¹ Implementation of the International Health Regulations (2005), Report of the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response, Report by the Director-General, 13 May 2016. Geneva: World Health Organization; 2016 (A69/21; http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_21-en.pdf?ua=1, accessed 20 September 2016).

3. The Director-General should undertake a study to determine the implications and desirability of including seasonal influenza viruses in the PIP Framework.
4. The PIP Framework is a foundational model of reciprocity for global public health that could be applied to other pathogens; however, the current scope of the PIP Framework should remain focused on pandemic influenza at this time.
5. Member States should agree the timing of the next review of the PIP Framework, which should be before the end of 2021.

Chapter 4: Virus sharing

4.1 Overview

Key Findings

Finding 16: The GISRS virus sharing system generally works well and is expanding to cover more geographical regions. Between 2011 and 2016, the number of NICs has increased from 136 to 143, the number of WHO H5RLs from 12 to 13; the number of WHO CCs remained at six and the number of WHO ERLs at four. At an operational level, there are platforms for the rapid exchange of information and strong interactions between different organizations. The WHO Shipping Fund Project (“Shipping Fund”) has increased laboratories’ ability to share viruses.

Finding 17: The PIP Framework (Annex 4) sets out guiding principles for the terms of reference for the WHO GISRS laboratories; assessment of whether those terms of reference are fulfilled is carried out through self-assessment by GISRS laboratories and surveys of NICs. The evidence is that laboratories comply with their SMTA1 obligations.

Finding 18: The Review Group’s discussions with key informants from laboratories indicated that they were unclear on how to interpret the definition of “timely” and “representative” with respect to the sharing of PIP BM and GSD, and on the meaning of “as feasible” with regard to the sharing of all cases of A(H5N1) and other IVPP in section 5.1.1 of the Framework.

Finding 19: GISRS provides significant benefits, including conducting critical risk assessment, and providing vaccine viruses and vaccine virus recommendations, diagnostic kits, reagents, reference viruses, expertise, training and capacity building. The laboratory capacity developed for influenza appears to have had collateral benefits for other pathogens, such as Middle East respiratory syndrome coronavirus (MERS-CoV).¹ The Review Group found, however, that there are some barriers (including political, regulatory and logistical) to the provision of reagents and diagnostic kits to some laboratories.

Finding 20: The GISRS self-assessment also revealed weaknesses, such as gaps in geographic coverage (particularly in Africa and the Middle East) along with insufficient national funding and a lack of prioritization of influenza surveillance.²

Finding 21: There are enduring links between GISRS and non-GISRS laboratories, especially those from the animal sector. However, some informants felt that there should be stronger linkages between the GISRS and non-GISRS parts of the system.

Finding 22: GISRS collaborates closely with the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the OFFLU (the

¹ Self-assessment of the WHO Global Influenza Surveillance and Response System (GISRS), Report to the Advisory Group. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/virus_sharing/gisrs_self_assessment.pdf, accessed 19 September 2016), section 4.1.

² *Ibid.*, section 4.2.

joint OIE-FAO network of animal influenza experts) to conduct risk assessment and development of CVVs. In some cases, where viruses from human infections are not shared (or their sharing is delayed) due to export controls, political hesitancy, or other reasons, animal viruses have been used for risk assessment and CVV development. However, there is a lack of clarity over when to share animal samples to GISRS, which could be improved.

Finding 23: In the event of an influenza pandemic, GISRS will face a surge of samples to process, and concerns have been raised that the network could become overwhelmed. WHO has provided guidance to prepare for this contingency, including prioritization of virus samples to be forwarded to WHO CCs for further analysis and development of CVVs.¹ This guidance proved valuable during the 2009 A(H1N1) pandemic, and it will be necessary to maintain or improve it as necessary, and continue to make it publicly available.

Finding 24: Following the recent launch of the Tool for Influenza Pandemic Risk Assessment (TIPRA),² there is an opportunity for WHO to work with Member States that have GISRS laboratories to strengthen risk assessment capacities for pandemic influenza.

Given the rapidly evolving nature of influenza and the potential threat it poses as a pandemic-prone disease, a robust, global system for sharing influenza viruses is vital to surveillance, preparedness and response. Monitoring global influenza virus evolution and spread helps public health officials perform risk assessment studies and identify potential pandemic viruses, while virus samples and genetic sequence information are indispensable for developing the diagnostics, vaccines and pharmaceuticals needed to detect, prevent and treat illness.

GISRS performs many of these functions and is the backbone of the PIP Framework. For more than 60 years a global network of public health laboratories, known as the Global Influenza Surveillance Network (GISN), had been collecting and monitoring influenza viruses. Its name was changed to GISRS when the PIP Framework was adopted in 2011, to reflect an expanded role for the network. This role is established in the SMTA1, in Annex 1 to the PIP Framework, which is a binding contract that sets out the conditions under which laboratories in GISRS exchange influenza viruses with human pandemic potential among themselves.

GISRS laboratories track the evolution of influenza viruses, providing vital risk assessment (see Box 4.1) and early warning to Member States, for instance through monthly risk assessment summaries.³ Although the PIP Framework (section 3) is limited to IVPP, the GISRS network handles all human influenza viruses and some animal influenza viruses that present a threat to humans (e.g. H3N2v and H5, H7, H9). All influenza viruses that are

¹ WHO checklist for influenza pandemic preparedness planning. Geneva: World Health Organization; 2005 (WHO/CDS/CSR/GIP/2005.4; <http://www.who.int/influenza/resources/documents/FluCheck6web.pdf>, accessed 19 September 2016).

² Tool for Influenza Pandemic Risk Assessment (TIPRA), Version 1 Release. Geneva: World Health Organization; 2016 (WHO/OHE/PED/GIP/2016.2; <http://apps.who.int/iris/bitstream/10665/250130/1/WHO-OHE-PED-GIP-2016.2-eng.pdf>, accessed 4 October 2016).

³ Monthly Risk Assessment Summary, Influenza at the Human-Animal Interface. In: World Health Organization [website]. Geneva: World Health Organization; 2011 to 2016 (http://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/, accessed 20 September 2016).

relevant for seasonal vaccines or pandemic preparedness should enter the GISRS network through an appropriate channel.

The GISRS network provides significant benefits to Member States and others, including specialist informal consultation on the improvement of influenza vaccine virus selection,¹ guidance on switching from seasonal to pandemic vaccine production,² training courses, specialist conferences for NICs, and increased collaborative scientific publications, such as on how WHO makes its vaccine virus recommendations.³ In some cases, the GISRS network has also been leveraged to respond to threats from non-influenza pathogens (e.g. for surveillance of respiratory syncytial virus (RSV))⁴ and some GISRS laboratories routinely detect other pathogens, such as measles and polio.⁵

NICs form the core of GISRS. They are responsible for gathering “clinical specimens from patients suspected to be infected with” IVPP, acting “as a collection point for virus isolates of suspected” IVPP, conducting preliminary testing, and shipping “within one week, clinical specimens and/or viruses” among other duties.⁶ Member States, through their NICs, are required to “provide PIP biological materials from all cases [of IVPP], as feasible” within one week to a WHO CC or WHO H5RL “of the originating Member State’s choice”.⁷

The WHO CCs conduct detailed analyses of IVPP, including “typing and subtyping”, virus isolation, “detailed antigenic and genetic analyses”, and “antiviral susceptibility testing” among other tasks.⁸ A key function of WHO CCs is the selection and creation of CVVs. A CVV is a virus that has been altered from the wild type⁹ to make it more suitable for the

¹ For example, 4th WHO Informal Consultation on Improving Influenza Vaccine Virus Selection. In: World Health Organization [website]. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/vaccines/virus/4thmtg_improve_vaccine_virus_selection/en/, accessed 19 September 2016).

² World Health Organization. Influenza vaccine response during the start of a pandemic, Report of a WHO Informal Consultation held in Geneva, Switzerland, 29 June-1 July 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/207751/1/WHO_OHE_PED_GIP_2016.1_eng.pdf, accessed 19 September 2016).

³ Ampofo W, Azziz-Baumgartner E, Bashir U, Cox NJ, Fasce R, Giovanni M, et al. Strengthening the influenza vaccine virus selection and development process: Report of the 3rd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at WHO headquarters, Geneva, Switzerland, 1-3 April 2014. *Vaccine*. 2014;36:4368-82. doi: 10.1016/j.vaccine.2015.06.090.

⁴ World Health Organization. WHO informal consultation on surveillance of respiratory syncytial virus on the WHO Global Influenza Surveillance and Response System (GISRS) platform, 25–27 March 2015. *Wkly Epidemiol Rec*. 2016;91:1 (<http://www.ncbi.nlm.nih.gov/pubmed/26753193>, accessed 19 September 2016).

⁵ Self-assessment of the WHO Global Influenza Surveillance and Response System (GISRS), Report to the Advisory Group. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/virus_sharing/girs_self_assessment.pdf, accessed 19 September 2016).

⁶ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), Annex 5, National Influenza Centres, Core Terms of Reference, B. Laboratory and related activities.

⁷ *Ibid.*, section 5.1.1.

⁸ *Ibid.*, Annex 5, WHO Collaborating Centres for Influenza, Core Terms of Reference, B. Laboratory analyses and related activities.

⁹ Wild type viruses are those in the field, naturally occurring in humans or animals. They are not modified or reassorted like many vaccine viruses.

production of vaccines, while retaining antigenic similarity.¹ This typically means: (1) attenuating (or weakening) the virus so it does not cause severe illness; (2) ensuring that it grows well in eggs and cell culture; and (3) ensuring that it still triggers the appropriate immune response.² Because they form the basis for vaccines, available and effective CVVs are critical both for the efficacy of seasonal vaccines and for a robust response to an influenza pandemic. WHO CCs are required to share widely all information gathered, along with CVVs and reagents.³ Between 1 August 2014 and 31 July 2015, WHO CCs characterized 123 IVPP coming from five countries (Bangladesh, Canada, China, Egypt, and the United States of America).⁴

WHO H5RLs are responsible for some of the same tasks as WHO CCs, but for a particular subset of influenza viruses with hemagglutinin antigen H5.⁵ WHO ERLs are tasked with “developing, regulating and standardizing influenza vaccines”, most significantly by developing CVVs⁶ and preparing reference reagents to standardize influenza vaccines.⁷

Box 4.1. Tool for Influenza Pandemic Risk Assessment (TIPRA)⁸

A central function of GISRS as a whole is to provide the data necessary for countries to develop an effective and meaningful response.⁹ Using this information along with other sources, according to the PIP Framework (section 6.2.3) it is the responsibility of the WHO Secretariat to “make available to all Member States, in a rapid, systematic and timely way,

¹ Antigenically similar viruses are those that induce equivalent antibody responses, as measured by serological tests.

² Making a Candidate Vaccine Virus (CVV) for a HPAI (Bird Flu) Virus. In: Centers for Disease Control and Prevention [website]. Atlanta: National Center for Immunization and Respiratory Diseases, U.S. Centers for Disease Control and Prevention; 2016 (<http://www.cdc.gov/flu/avianflu/candidate-vaccine-virus.htm>, accessed 19 September 2016).

³ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), Annex 5, WHO Collaborating Centres for Influenza, Core Terms of Reference, B. Laboratory analyses and related activities.

⁴ PIP Framework Advisory Group. Pandemic Influenza Preparedness Framework (“PIP Framework”) Advisory Group annual report to the Director-General under PIP Framework section 7.2.5: 2015 Annual Report. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_annual_report_2015.pdf, accessed 20 September 2016), page 17.

⁵ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), Annex 5, WHO H5 Reference Laboratories, Core Terms of Reference, B. Laboratory and other activities.

⁶ *Ibid.*, Annex 5, WHO Essential Regulatory Laboratories.

⁷ *Ibid.*, Annex 5, WHO Essential Regulatory Laboratories, Core Terms of Reference, B. Laboratory and related activities.

⁸ Tool for Influenza Pandemic Risk Assessment (TIPRA). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/areas_of_work/human_animal_interface/tipra/en/, accessed 20 October 2016).

⁹ Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 19 September 2016), section 6.2.1.

pandemic risk assessments". Recognizing the need for a specific risk assessment tool, the TIPRA has been developed to support a timely and updatable risk assessment for IVPP.¹ The tool focuses on a virus's qualitative pandemic potential, as evaluated by experts, based on different virus elements that are known to affect transmissibility and severity. It seeks to answer the question: What is the risk of sustained human-to-human transmission of the virus? To evaluate this risk it assesses two components: what is the likelihood of sustained human-to-human transmission of the virus; and what is the impact to the human population if the virus acquires sustained human-to-human transmissibility? Triggers for using the TIPRA may be epidemiological (for example, emergence of human cases of a non-seasonal or animal influenza virus) or virological (for example, studies in laboratory animals indicating that the virus has the capability to transmit to uninfected animals by either direct contact or respiratory droplets).²

The costs of virus sharing can be challenging for some laboratories. Started in 2005, the WHO Shipping Fund provides funding for the shipment by NICs (and in some cases other national influenza laboratories) of seasonal and pandemic virus specimens to WHO CCs and WHO H5RLs.³ Since 2015, PC contributions have financed the entire cost of the Shipping Fund. Beyond covering shipping costs, the Shipping Fund has also been used to streamline shipment procedures and to provide WHO technical and logistical support for shipping infectious substances.⁴ From 1 August 2015 to 31 July 2016, the Shipping Fund was used to facilitate 213 shipments of seasonal and pandemic influenza viruses.⁵

4.2 Virus sharing metrics

Key Findings

Finding 25: While the sharing of PIP BM initially increased after adoption of the PIP Framework, a decline has been noted over the past two years. The September 2014 GISRS self-assessment showed that the response to the emergence of the influenza A(H7N9) strain in 2013 was prompt and comprehensive, but virus sharing has declined since then.⁶ Overall, there has been a reduced sharing of IVPP from some countries. As requested by the Advisory Group, WHO is undertaking a study to understand the reasons for, and the significance of, this decline; this report is due to be provided to the Advisory Group in October 2016.

¹ TIPRA is based on the US CDC's Influenza Risk Assessment Tool tool: <http://www.cdc.gov/flu/pandemic-resources/tools/risk-assessment.htm>.

² Tool for Influenza Pandemic Risk Assessment (TIPRA), Version 1 Release. Geneva: World Health Organization; 2016 (WHO/OHE/PED/GIP/2016.2; <http://apps.who.int/iris/bitstream/10665/250130/1/WHO-OHE-PED-GIP-2016.2-eng.pdf>, accessed 4 October 2016).

³ Shipping and logistics activity. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/gisrs_laboratory/logistic_activities/en/, accessed 19 September 2016).

⁴ *Ibid.*

⁵ PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

⁶ Self-assessment of the WHO Global Influenza Surveillance and Response System (GISRS): Report to the Advisory Group. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/virus_sharing/gisrs_self_assessment.pdf, accessed 19 September 2016), section 4.1.

Despite the growth of the GISRS network and the assistance with shipping, there has been a worrying decline in virus sharing within GISRS since its peak of 370 IVPP between 1 August 2012 and 31 July 2013. The PIP Framework Advisory Group pointed out this trend at its April 2016 meeting:

While the sharing of PIP biological materials initially increased after adoption of the PIP Framework, recent data point to a decreasing trend in IVPP virus sharing. Detailed figures for H5N1, H7N9, H10N8 and H9N2 illustrated how in some specific countries the number of viruses shared was considerably lower than the number of confirmed human cases during 2011-16.¹

Figure 4.1 shows virus sharing with WHO CCs for part of 2016.

WHO and Influenza Virus Traceability Mechanism (IVTM) data show that:

- From 1 August 2014 to 31 July 2015, the IVTM recorded 156 shipments of IVPP from WHO CCs and WHO ERLs, 92 of which went to non-GISRS laboratories.² This represents a 71% drop in recorded IVPP sharing as compared with the previous year.³
- From 1 August 2015 through 31 July 2016, IVTM recorded the sharing of 84 IVPP from WHO CC's. Of these, 47 were shared with non-GISRS laboratories.⁴
- From March 2011 to February 2016, 79 CVVs were shared with GISRS laboratories and an additional 174 with non-GISRS laboratories.⁴
- In the one year period from March 2015 to February 2016, eight CVVs were shared with two GISRS laboratories and 13 CVVs were shared with eight non-GISRS laboratories.⁵

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016), paragraph 56.

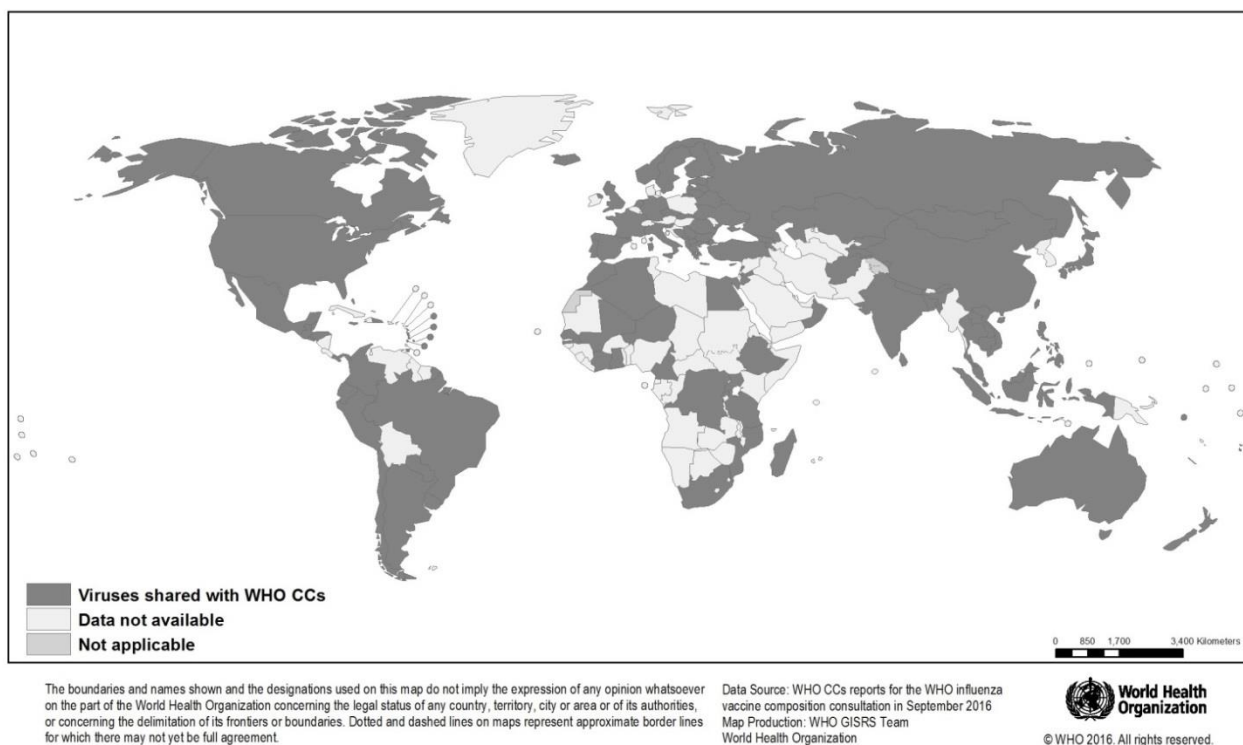
² PIP Framework Advisory Group. Pandemic Influenza Preparedness Framework ("PIP Framework") Advisory Group Annual Report to the Director-General Under PIP Framework section 7.2.5, 2015 Annual Report. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_annual_report_2015.pdf, accessed 20 September 2016), page 9.

³ *Ibid.*, page 9.

⁴ Global Influenza Programme, World Health Organization, unpublished data, October 2016.

⁵ *Ibid.*

Figure 4.1: Countries, areas and territories sharing viruses with WHO CCs from February to September 2016



During an outbreak, representative samples from each geographical location and point in time are critical to effective risk assessment and other GISRS activities. The decrease in virus sharing thus poses a potentially serious challenge to the PIP Framework's objective of improving pandemic influenza preparedness and response.

As requested by the Advisory Group, WHO is carrying out a study into the reasons for, and significance of, the decline in virus sharing and its impact on the PIP Framework's objectives.

Information from the WHO Global Influenza Programme (GIP) (which coordinates WHO's work on both pandemic and seasonal influenza, including overseeing GISRS) and interviews with key informants highlighted several areas where greater clarity might benefit virus sharing: a lack of understanding among NICs that sharing IVPP GSD does not replace the sharing of physical materials; different interpretations of the phrasing of the PIP Framework's requirement that all IVPP should be shared "as feasible"; export procedures that can be complex and involve Ministries other than Health; national concerns about a loss of control and sovereign rights; and uncertainty in countries with both a NIC and a WHO CC over whether sharing only between these two laboratories is enough to fulfil a literal interpretation of the PIP Framework's requirements, thereby not requiring the international sharing envisioned under the PIP Framework.

While the WHO study will help more fully to understand the apparent recent decline in virus sharing, implementation of the PIP Framework is putting in place many of the foundations needed to resume an upward trend. Capacity building activities funded under the PC's Laboratory and Surveillance work plans are targeting 43 priority countries to improve their

national ability to detect and share novel influenza viruses (see chapter 6, section 6.3.2.1). The PC investments are also improving countries' abilities to monitor evolution in IVPP and perform risk assessments.

4.3 Influenza Virus Traceability Mechanism

Key Findings

Finding 26: Consistent use of the IVTM among GISRS laboratories is vital for ensuring transparency and advancing the PIP Framework's goal of equitable benefit sharing.

Finding 27: IVTM recordkeeping is sporadic among NICs because many deal primarily and routinely with seasonal influenza viruses, whereas the IVTM is used specifically for specimens with pandemic potential. Many NICs therefore have had little exposure to this tool in day-to-day operations. While WHO CCs use the tool consistently, NICs generally fail to enter shipments of PIP BM. This appears to stem from a lack of knowledge, and training on the use of the IVTM could help address this problem.

The IVTM is a publicly accessible online tool for tracking IVPP "into, within, and out of" the GISRS network.¹ This information is used: by WHO to identify users of GISRS who are subject to signing SMTA2s; by Member States to see how the viruses they share are being used; and by other stakeholders to see how GISRS enhances pandemic influenza preparedness. The system relies on consistent reporting of the transfer and receipt of IVPP by GISRS laboratories.

Knowing who is receiving IVPP is vital for the PIP Framework's benefit sharing system as well as for its goal of transparency. Prior to the IVTM, Member States did not have a tracking system to inform them how the viruses they shared were subsequently passed on. The IVTM contains more than 1,000 records of IVPP and more than 1,100 shipment records, representing 19 influenza virus subtypes.² Transactions are meant to be recorded both when specimens are sent and when they are received. However, in practice many NICs fail to record their outgoing shipments, leaving WHO CCs retroactively to enter this information. This practice eliminates an important safeguard of data integrity and increases the workload on WHO CCs.

In discussions with GISRS laboratories, it became clear to the Review Group that an important reason for this failure was a lack of knowledge among NICs of the IVTM and the expectations for when it should be used. IVPP make up a relatively small proportion of total influenza virus specimens shared so IVPP procedures, such as the IVTM, are not routine for many NICs.

¹ Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 19 September 2016), section 5.3.1.

² Influenza Virus Traceability Mechanism [website]. Geneva: World Health Organization; 2016 (<https://extranet.who.int/ivtm/>, accessed 10 June 2016).

Recommendations: Virus Sharing

6. The Review Group welcomes the PIP Framework Secretariat's study of the reasons for the recent decline in the sharing of influenza viruses with human pandemic potential. The Advisory Group should, as a priority, follow-up on the results of this study in order to ensure the timely sharing of all viruses.
7. Given the recent decline in the sharing of influenza viruses with human pandemic potential, WHO should continue to provide technical operational guidance and training for National Influenza Centres to ensure that they are fully aware of their roles as agreed in the SMTA1, the effective use of the Influenza Virus Traceability Mechanism, and the importance of appropriate sharing of all PIP biological materials and genetic sequence data.
8. WHO should provide clarification to GISRS laboratories on the interpretation of the terms "timely" and "as feasible" with respect to the sharing of PIP biological materials from all cases of A(H5N1) and other influenza viruses with human pandemic potential (section 5.1.1 of the PIP Framework).
9. Although genetic sequence data do not fully substitute for the physical virus, in cases where it is not possible to ship PIP biological materials rapidly, genetic sequence data should, if available, be shared immediately.
10. The WHO Global Influenza Programme should strengthen contacts and linkages with, and processes between, the GISRS system and non-GISRS laboratories and other networks.
11. WHO, GISRS, the Food and Agricultural Organization of the United Nations, the World Organisation for Animal Health, the OFFLU and others should collaboratively establish guidance for GISRS and animal laboratories to strengthen their relationships and enhance surveillance and risk assessment of influenza viruses at the animal-human interface.

Chapter 5: Genetic Sequence Data

Key Findings

Finding 28: Due to the complexities of how best to handle GSD under the PIP Framework, GSD was not included in the definition of PIP BM in section 4.1. 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. Many IVPP sequences are already being shared; what is not currently clear under the PIP Framework is how GSD sharing should trigger benefit sharing, and what the trigger should be. Therefore, clarity is urgently required on the handling of GSD under the PIP Framework to ensure that it is guided by the same principles as the sharing of PIP BM.

Finding 29: There is confusion over language in the PIP Framework (Annex 4, section 9), which can read that WHO GISRS laboratories should submit genetic sequences to both the Global Initiative on Sharing All Influenza Data (GISAID) (Epiflu™) database and the GenBank database, rather than submitting to only one database if desired.

Finding 30: Some good progress has already been made by the Advisory Group on examining possible approaches to handling GSD under the PIP Framework, as requested by Member States in section 5.2.4.¹ A key challenge has been the lack of agreement on what should be traced. Options could include tracking access to GSD or tracing the commercial products developed using GSD. Transparency in both the sharing and traceability of GSD is crucial in order to identify any resulting benefit that should be shared.

Finding 31: Among stakeholders involved in the discussions around the handling of GSD, there are diverse views on how a traceability and monitoring system might best work. It was clear from the Review Group's interviews and wider discussions that there remains some confusion as to potential options for future data sharing and operating procedures.

Finding 32: WHO CCs have a key role in collating IVPP GSD through GISRS. Their understanding of the realities of how GSD is shared via GISRS will be critical in informing the ongoing deliberations about the optimal handling of GSD under the PIP Framework.

Finding 33: It is crucial for GISRS to have access to sustainable databases to enable uploading and timely sharing of sequence data, such as the rapid sharing of influenza A(H7N9) by China.

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016), paragraph 53.

5.1 Overview

GSD is important for surveillance and risk assessment because the sequences can reveal specific genetic changes in circulating influenza viruses that have been associated with pathogenicity and human-to-human transmission. GSD is also used to study influenza virus evolution, and segments of GSD can be used to design primers and probes for diagnostics. While GSD cannot fully substitute for physical virus samples in many areas, such as product development (mostly due to regulatory requirements), GSD is increasingly being used to develop several new types of vaccines without the need for physical virus.

GSD and physical materials are dealt with differently under the PIP Framework (see Figure 5.1). GSD is not included in the definition of PIP BM in section 4.1, and there is no mechanism (trigger) to operationalise the requirement for benefit sharing from GSD. Thus, there is a dissonance between the way the PIP Framework treats GSD and the reality in which it is used by scientists. This dissonance, if not resolved soon, could threaten the relevance of the PIP Framework since the sharing of GSD largely operates outside the virus sharing and benefit sharing rules of the PIP Framework.

The expectations on the sharing of IVPP GSD are laid out in Annex 5 of the PIP Framework. The core terms of reference of WHO CCs state that they should “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”.

The main genetic sequence databases that store influenza GSD include: GISAID’s EpiFlu™ database,¹ GenBank, the European Nucleotide Archive (ENA),² the DNA Data Bank of Japan (DDBJ)³ (GenBank, ENA and DDBJ participate in the International Nucleotide Sequence Database Collaboration (INSDC)),⁴ OpenFluDB,⁵ and Influenza Research Database (IRD).⁶

Member States and GISRS laboratories can choose the database or databases they want to use. Nevertheless, there remains some ambiguity over language in the PIP Framework (Annex 4, section 9), specifically over whether WHO GISRS laboratories should submit genetic sequences to both the GISAID (EpiFlu™) database and the GenBank database, or to only one database if desired: the guiding principles for the development of terms of reference for GISRS laboratories state that “The WHO GISRS laboratories will submit genetic

¹ EpiFlu™ Database. In: GISAID [website]. Bonn: GISAID; 2016 (<http://platform.gisaid.org/epi3/frontend#13da29>, accessed 29 September 2016).

² European Nucleotide Archive. In: European Nucleotide Archive [website]. Hinxton, UK: European Bioinformatics Institute (EMBL-EBI); 2016 (<http://www.ebi.ac.uk/ena>, accessed 29 September 2016).

³ Introduction of DDBJ. In: DNA Data Bank of Japan [website]. Shizuoka: DNA Data Bank of Japan; 2016 (<http://www.ddbj.nig.ac.jp/intro-e.html>, accessed 29 September 2016).

⁴ International Nucleotide Sequence Database Collaboration. In: INSDC [website]. Hinxton, UK: INSDC; 2016 (<http://www.insdc.org/>, accessed 29 September 2016).

⁵ OpenFlu Database. In: OpenFlu [website]. Lausanne: Swiss Institute of Bioinformatics; 2016 (<http://openflu.vital-it.ch/browse.php>, accessed 29 September 2016).

⁶ Influenza Research Database. In: Influenza Research Database [website]. Washington, DC: Influenza Research Database; 2016 (<https://www.fludb.org/brc/home.spg?decorator=influenza>, accessed 29 September 2016).

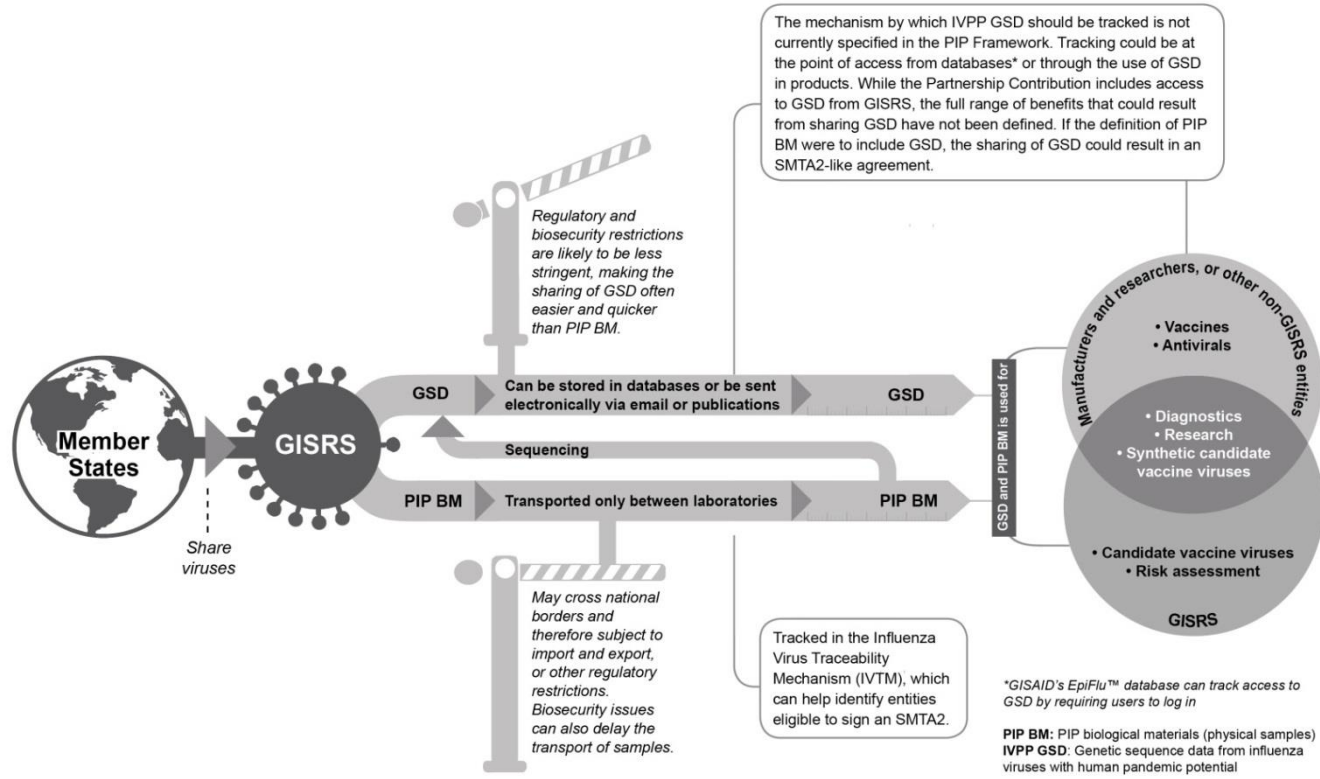
sequences data to GISAID and Genbank or similar databases in a timely manner consistent with the Standard Material Transfer Agreement.” The WHO CCs provide scientific oversight and, as noted by the Advisory Group in October 2014, “most GISRS laboratories use GISAID”.¹

While the IVTM tracks the sharing of PIP BM, resulting in SMTA2s being signed, there is no equivalent tracking (and therefore currently no benefit sharing mechanism) for GSD. This means that sequences that are shared are not tracked in the IVTM and that the benefits from such sharing of sequences are not covered under an SMTA2. When the PIP Framework (section 5.2.4) was agreed, Member States, recognizing that further work was needed, requested “the Director-General to consult the Advisory Group on the best process for further discussion and resolution of issues relating to the handling of” GSD for IVPP.

Since June 2013, the Advisory Group has been conducting technical work to better understand the issues related to GSD in order to advise the Director-General.

¹ PIP Framework Advisory Group. Meeting of the Pandemic influenza preparedness (PIP) Framework Advisory Group, 21-24 October 2014, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/advisory_group/oct2014_mr_consolidated.pdf?ua=1, accessed 24 September 2016), paragraph 29.

Figure 5.1 Sharing of physical samples (PIP BM) and genetic sequence data under the PIP Framework



5.1 Advisory Group's work on GSD

The Advisory Group's work on GSD began in June 2013 when GISAID requested clarification on the use of IVPP GSD under the PIP Framework.¹ In October 2013, the Advisory Group established the Technical Expert Working Group on Genetic Sequence Data (TEWG), tasked with assessing the "scientific, technical, operational and intellectual property implications" as well as "any other significant implications" of the shift from physical IVPP to IVPP GSD.²

The TEWG published its final report in October 2014, examining current uses of GSD, potential regulatory and intellectual property issues, the feasibility of monitoring and tracing GSD, and biosecurity and biosafety implications.³ In particular, it became apparent that a system for equitably sharing the benefits arising from GSD would need to take into account the unique characteristics of GSD and the way in which they are shared. Because easy and rapid sharing of GSD is needed for timely risk assessment, scientific research and product development, the TEWG recognized that "it is essential that any [benefit sharing] mechanisms do not slow down the sharing of genetic sequence data".⁴

After considering the TEWG report, and following consultation with database providers and other stakeholders, in October 2014 the Advisory Group formulated a recommendation to the Director-General on the best process to discuss further and resolve the issues related to the handling of IVPP GSD under the PIP Framework. The Advisory Group recommended a process to identify "the optimal characteristics of a system for the handling of IVPP GSD under the PIP Framework". To that end, the Advisory Group: (1) established a second expert group, the Technical Working Group on the Sharing of Influenza Genetic Sequence Data (TWG) to consider the optimal data sharing system, and; (2) commissioned a paper to consider possible benefit sharing options.⁵

In June 2016, the TWG issued its final report, which identified optimal characteristics of a data sharing system, and included some options within those characteristics.⁶ These covered such aspects as: expectations to submit IVPP GSD; timeliness of submission; ensuring

¹ GSD Timeline, Process for handling Genetic Sequence Data under the PIP Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/entity/influenza/pip/advisory_group/GSD_timeline.pdf?ua=1, accessed 22 September 2016).

² PIP Framework Advisory Group, Technical Expert Working Group (TEWG) on Genetic Sequence Data. Final Report to the 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, accessed 22 September 2016), page 2.

³ *Ibid.*

⁴ *Ibid.*, page 3.

⁵ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 21-24 October 2014, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/pip_ag_oct2014_meetingreport_final_7nov2014.pdf, accessed 22 September 2016), paragraph 32.

⁶ PIP Framework Advisory Group, Technical Working Group (TWG) on the sharing of influenza genetic sequence data. Optimal Characteristics of and 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?ua=1, accessed 22 September 2016).

quality; completeness of metadata; ease of access/use; sustainability/security of the system; source identification; and support to the regulatory process. The Review Group has heard concerns about the breadth and depth of engagement with stakeholders, in particular database providers, during the working group process.

On the benefit sharing system, the Advisory Group requested the PIP Framework Secretariat to develop a paper discussing benefit sharing mechanisms for IVPP GSD, and in particular options for monitoring use of IVPP GSD.¹ The paper identified two main types of monitoring: upstream and downstream. Upstream monitoring systems “are implemented at the point at which IVPP GSD is distributed and accessed” (e.g. when a sequence is downloaded from a database).² Downstream monitoring, on the other hand, is undertaken “after [IVPP GSD] has been shared and used to research and develop end-products”.³

At its April 2016 meeting, based on the work to then, the Advisory Group discussed key principles that should underpin the balance of virus sharing and benefit sharing for GSD.⁴ At its October 2016 meeting the Advisory Group considered the range of operational tools for the handling of GSD, as well as a strategy for the next steps.

Recommendations: Genetic Sequence Data

12. The 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 genetic sequence data.

13. The Director-General should request Member States to 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”.

14. The Director-General should request Member States to 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;”

¹ Best Process to Handle Genetic Sequence Data from Influenza Viruses with Human Pandemic Potential (IVPP GSD) under the PIP Framework, Options to monitor the use of genetic sequence data from influenza viruses with human pandemic potential (IVPP GSD) in end-products. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/gsoptionspaper_revised.pdf, accessed 22 September 2016).

² *Ibid.*, page 4.

³ *Ibid.*, page 6.

⁴ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016), paragraph 53.

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;”

15. It is critical that the PIP Framework adapts to technological developments, and that the Advisory Group produces with urgency recommendations to clarify the handling of genetic sequence data. The Advisory Group should consider asking WHO Collaborating Centres to report on how genetic sequence data are actually handled, with a view to providing information about the operational realities in GISRS in relation to the acquisition, sharing and use of such data, to inform the Advisory Group’s recommendations on the optimal handling of genetic sequence data under the PIP Framework.

16. 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.

17. Noting that genetic sequence data may be generated from many entities outside of GISRS, and that there are diverse views on the optimal traceability and monitoring mechanism, the Advisory Group should give consideration to broadening and deepening engagement with all stakeholders.

Chapter 6: Benefit sharing

6.1 Standard Material Transfer Agreement 2

Key Findings

Finding 34: By October 2016, four SMTA2s had been signed with vaccine manufacturers, one with a diagnostics manufacturer, and 47 with academic and research institutions.^{1,2} These agreements have secured access to approximately 350 million³ doses of pandemic influenza vaccine to be delivered in real time during an influenza pandemic. Further, two million⁴ antiviral treatment courses have been secured. Although some institutions have not yet been contacted to sign an SMTA2 and some negotiations are still under way, the Review Group considers that there has been good progress. The PIP Framework Secretariat has focused on addressing SMTA2s with those companies that offer the biggest gains – the agreements signed by October 2016 had already significantly improved WHO's future access to pandemic vaccine doses, antivirals and other products for distribution to countries in need should an influenza pandemic occur.

Finding 35: Good progress on securing prequalified vaccines and antivirals has been achieved through the PIP Framework Secretariat's strategic approach of prioritizing agreements with large companies with prequalified vaccines before moving on to negotiations with medium to small companies. Some Member States have queried whether the labour-intensive process of signing SMTA2s with small and medium companies is worth the resources required given the relatively modest additional volume of vaccines or other products secured. However, the PIP Framework's principle of fairness and equity in benefit sharing requires that all non-GISRS recipients of PIP BM sign an SMTA2 with WHO and provide benefits based on their nature and capacities. This principle is valued and WHO recognizes the importance of treating manufacturers equitably and of maintaining that goal despite the diminishing returns of additional products secured. The PIP Framework Secretariat has already made considerable effort to familiarise small and medium companies with the collateral benefits that are available, such as increased understanding of requirements for WHO prequalification status. The Review Group is of the opinion that the PIP Framework Secretariat, with support from the Advisory Group, should continue to take steps to prepare companies better for the SMTA2 negotiations.

Finding 36: The regularity and high quality of communication between the PIP Framework Secretariat and industry and other stakeholders has helped to facilitate the conclusion of SMTA2s. On several occasions when negotiations have been complicated or have stalled, the PIP Framework Secretariat has successfully implemented the stepwise approach recommended by the Advisory Group to progress towards conclusion of the agreements in a

¹ Standard Material Transfer Agreements 2 (SMTA2). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/benefit_sharing/smta2_signed/en/, accessed 19 October 2016).

² PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

³ *Ibid.*

⁴ *Ibid.*

timely manner.¹ There is nevertheless a perception that some eligible entities are not signing SMTA2s. The stepwise approach recognizes that a delicate balance needs to be maintained with the companies that are not facilitating completion of the negotiations; if these manufacturers are denied access to PIP BM because of failing to sign an SMTA2, this could be detrimental to public health.

Finding 37: Although SMTA2s were designed to be broad enough to accommodate a range of commitments, by October 2016 no companies had agreed to provide technology transfer. This is most likely because not many eligible manufacturers have patented technologies that could be made available for licence through WHO.

Finding 38: PIP Framework options for SMTA2 commitments from manufacturers of other pandemic products (such as diagnostics, syringes, etc.) are too narrow, and need to include a wider choice of commitments other than diagnostic materials that may not be beneficial in the case of a future influenza pandemic.

Finding 39: In November 2013, at the request of WHO, the Strategic Advisory Group of Experts on Immunization (SAGE) reviewed its 2007 recommended policies for the establishment and use of influenza A(H5N1) vaccine stockpiles during a pandemic. Recognizing the immediate access to pandemic vaccine production secured by the SMTA2 agreements under the PIP Framework and the unchanged global epidemiology of influenza A(H5N1) among other factors, SAGE recommended that WHO should no longer create a stockpile of influenza A(H5N1) vaccine. Instead, WHO should ensure immediate access to pandemic vaccines under the PIP Framework.^{2,3} This decision is not reflected in the PIP Framework (section 6.9).

Finding 40: Member States with in-country influenza vaccine production capacity need to include the SMTA2 requirements of the manufacturer(s) into their pandemic influenza response plans. It is essential that Member States ensure that the manufacturers can fulfil their SMTA2 commitments to provide WHO with real time access to pandemic vaccines and allow the export of these vaccines to other countries.

Finding 41: In order to facilitate negotiations of SMTA2s, the PIP Framework Secretariat has developed tools⁴ that outline the technical requirements, such as prequalification, export procedures and regulatory approvals that must be fulfilled by signatories to SMTA2s.

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework (PIPF) Advisory Group, 15-16 October 2015, Geneva, Switzerland, Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_meetingreport_october2015.pdf, accessed 22 September 2015), paragraph 8.

² PIP Framework Advisory Group. Annual report from the Advisory Group to the Director-General. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/ag_annual_report_2014.pdf, accessed 20 September 2016), section 3.5.

³ World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Wkly Epidemiol Rec. 2014;89:1-20 (<http://www.who.int/wer/2014/wer8901.pdf>, accessed 16 September 2016), page 10.

⁴ Frequently asked questions about Standard Material Transfer Agreements 2. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/benefit_sharing/smta2_FAQs.pdf, accessed 26 September 2016).

Finding 42: WHO has published a report on the rapid and timely switch¹ from seasonal vaccine to pandemic vaccine production, and the 2013 Interim Pandemic Influenza Risk Management (PIRM) Framework is being finalized.

SMTA2s ensure the availability and predictability of access to pandemic influenza vaccines, antivirals and other products at the time of a pandemic. SMTA2s are valid until the end of the next pandemic. There are three categories of SMTA2, corresponding to the different users of PIP BM. Category A are vaccine and antiviral manufacturers, category B are manufacturers of other products such as diagnostics test kits, and category C are academic and research institutions.

Under the concluded category A SMTA2s, it is expected that a total of 350 million² doses of pandemic vaccines from real time production will be donated or reserved for purchase by the WHO at affordable prices, representing 7 – 10% of global production capacity.^{3,4} In addition, two million⁵ treatment courses of antiviral medicine have been committed, with a further eight million courses reserved for purchase by WHO at affordable prices.⁶ The manufacturer Roche does not enter into SMTA2s as it does not use PIP BM but it has since 2005 voluntarily donated antiviral treatment courses for a WHO “rapid response stockpile”. There were an estimated five million treatment courses from Roche in the stockpile in October 2016.⁷ Among the category C research and academic entities that have entered into SMTA2s, almost half have offered to provide a benefit to WHO; these institutions are asked to consider but are not required to provide a benefit. Among these offers, the most common commitment selected up to October 2016 had been benefit sharing in the areas of improving laboratory and surveillance capacity; the PIP Framework Secretariat is working with WHO CCs and WHO Regional Offices to implement the training offers.

The first SMTA2 agreement with a vaccine manufacturer was signed in October 2012. As of 23 September 2016, four out of 32 vaccine manufacturers have signed SMTA2s, including two large multinational manufacturers: GlaxoSmithKline (GSK) (which also produces

¹ Influenza Vaccine Response during the Start of a Pandemic, Report of a WHO Informal Consultation held in Geneva, Switzerland, 29 June-1 July 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/207751/1/WHO_OHE_PED_GIP_2016.1_eng.pdf, accessed 20 September 2016).

² PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

³ Partridge J, Kieny MP. Global production capacity of seasonal influenza vaccine in 2011. *Vaccine*. 2012;31:728-31. doi: 10.1016/j.vaccine.2012.10.111.

⁴ Pandemic Influenza Preparedness Framework Partnership Contribution 2013-2016, Gap Analyses. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/pip_pc_ga.pdf, accessed 22 September 2016).

⁵ PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

⁶ Standard Material Transfer Agreement 2 between Glaxo Group Limited and WHO. In: World Health Organization [website]. Geneva: World Health Organization; 2012 (http://www.who.int/influenza/pip/benefit_sharing/gsk_smta2_dec_2012.pdf, accessed 22 September 2016).

⁷ Supporting pandemic preparedness. In: Roche [website]. Basel: Hoffman-La Roche; 2016 (http://www.roche.com/content/sustainability/what_we_do/for_patients/access_to_healthcare/making_innovation_accessible/tamiflu_corpres.htm, accessed 26 September 2016).

antivirals) and Sanofi Pasteur.¹ The two other SMTA2 signatories are Serum Institute of India (the largest developing country manufacturer) and China National Biotec Group (CNBG), a leading biotechnology company in China.² Eight other vaccine manufacturers have formally submitted benefit sharing proposals and thus are in formal negotiations.³ At the time of a pandemic, a decision will have to be made for vaccine producers to switch from seasonal to pandemic vaccine production (see Box 6.1). One category B SMTA2 has been signed with Quidel Corporation, and formal negotiations are taking place with one multinational company.⁴ A total of 47 agreements⁵ have been signed with category C research or academic institutions.

Box 6.1 Decision mechanisms for switching from seasonal to pandemic vaccine production

Influenza vaccine production facilities cannot produce pandemic vaccines at the same time as seasonal vaccines. Once risk assessment has indicated the start of an influenza pandemic, a decision has to be taken on whether and how to “switch” from seasonal vaccine to pandemic vaccine production, invoking the SMTA2 arrangements. A pandemic may be breaking out in one part of the world while elsewhere seasonal influenza is still circulating and/or manufacturers are mid-cycle in fulfilling contracts for the production of seasonal vaccines.⁶ Countries may also experience a pandemic at different times and with different levels of severity. So the decision to switch is a complex and time-sensitive process requiring the interaction and cooperation of many different public and private sector organizations, including WHO, GISRS, industry, Ministries of Health, providers of CVVs and regulatory agencies.⁷

In June-July 2015, WHO held an informal consultation to develop a global cooperative, risk-management approach to influenza vaccine response at the start of a pandemic. This consultation identified a number of key challenges, including the potentially severe public health consequences of switching to pandemic vaccine production either too early or too late.⁸ A premature decision to stop seasonal vaccine production may compromise seasonal vaccine availability and increase seasonal deaths; a late switch may delay response and

¹ Standard Material Transfer Agreements 2 (SMTA2). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/benefit_sharing/smta2_signed/en/, accessed 19 October 2016).

² WHO concludes SMTA2 with Chinese vaccine manufacturer CNBG. Pandemic Influenza Preparedness Framework eNewsletter [Internet]. July 2016. Geneva: World Health Organization; 2016 (<http://us8.campaign-archive1.com/?u=c35eb4938c7246655f6384192&id=5b4741cf8b>, accessed 26 September 2016).

³ PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

⁴ *Ibid.*

⁵ *Ibid.*

⁶ PIP Framework Advisory Group. Pandemic Influenza Preparedness Framework (“PIP Framework”) Advisory Group annual report to the Director-General under PIP Framework section 7.2.5, 2015 Annual Report. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_annual_report_2015.pdf, accessed 20 September 2016), page 8.

⁷ Influenza vaccine response during the start of a pandemic: Report of a WHO informal consultation held in Geneva, Switzerland, 29 June-1 July 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/207751/1/WHO_OHE_PED_GIP_2016.1_eng.pdf, accessed 19 September 2016).

⁸ *Ibid.*

increase the severity of a pandemic. Each stage of the complex vaccine development and manufacturing process presents the potential for a bottleneck or a delay, thereby creating a “domino effect” that can undermine a timely switch from seasonal vaccine production to pandemic vaccine production. For example, CVV development, reagent production, clinical trials, regulatory approvals and attaining adequate vaccine yields are all key sequential steps in the timeline of pandemic vaccine production.¹ Competing Advance Purchase Agreements between manufacturers and governments for seasonal vaccines may also affect WHO’s SMTA2 real-time access to vaccines at the beginning of the pandemic if manufacturers must first fulfil those contractual obligations.

Since the 2015 consultation, work has focussed on completing an Operational Framework for Pandemic Vaccine Response² and finalizing the 2013 Interim PIRM Framework, which will also address pandemic vaccine response. In July 2016 a second WHO informal consultation was held. While the key outcomes had not yet been published in October 2016, they included an update to the Operational Framework for Pandemic Vaccine Response, a recommendation to finalize the Interim PIRM Framework, the formation of working groups to solve the current bottleneck issues related to production and regulation, the formation of a policy group to identify the key principles of a decision to switch from seasonal to pandemic production, and a recommendation that a specialist committee be formed, involving GISRS experts, industry, civil society and other relevant stakeholders, to advise WHO in real time on the practical issues involved in switching from seasonal vaccine to pandemic vaccine production in the event of a pandemic declaration or emerging pandemic threat.

WHO’s strategy for Category A SMTA2s has been to focus on securing access to pandemic vaccines from large companies with an existing WHO prequalified vaccine. To ensure standards and safety concerns are met, UN organizations (such as WHO and UNICEF) can only accept prequalified vaccines. As the pandemic vaccine can only be produced when the novel pandemic strain arrives, all companies wanting to supply vaccine to WHO will have to prequalify their new vaccine. If a company has already previously prequalified an influenza vaccine (either seasonal or pandemic) then the time needed to prequalify a new pandemic vaccine when an outbreak occurs will usually be very much shorter. This is why the PIP Framework Secretariat encourages companies to prequalify a seasonal vaccine or a mock-up pandemic vaccine in advance of the next pandemic. As of October 2016, seven³ manufacturers of influenza vaccines had a prequalified vaccine. All the SMTA2 signatories had a prequalified vaccine except CNBG; WHO was in SMTA2 discussions or negotiations with the four other manufacturers with pre-qualified vaccines. As of October 2016, the Chinese vaccine manufacturing firms were all working to prequalify their seasonal vaccines.

Negotiations of SMTA2s are complex and lengthy, involving full-time staff or consultants, and so far WHO has successfully maximized the impact of the SMTA2 benefit sharing mechanism by initially focussing on the largest vaccine manufacturers. Additional effort and resources, such as travel and technical briefings, are required to finalize negotiations with medium and smaller manufacturers, as these manufacturers are usually less familiar with the

¹ *Ibid.*

² *Ibid.*

³ WHO Prequalified vaccines. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (https://extranet.who.int/gavi/PQ_Web/, accessed 26 September 2016).

technical requirements under the SMTA2 and for them an SMTA2 can represent a significant extra cost. If a company has only produced vaccines for its domestic market then as part of the SMTA2 negotiations it often needs to be informed about WHO prequalification, the UN vaccine procurement process, the requirements for exporting biological products,¹ labelling for export markets, and the need to license the vaccine in the recipient market. To this end, WHO has carried out a range of communications involving outreach and company briefings to improve knowledge about SMTA2s and the implications of benefit sharing.² Development of guidelines and protocols might assist smaller manufacturers to facilitate the process. In addition, companies can also communicate directly with the technical officers from the WHO Prequalification team, who are best placed to answer questions concerning packaging and labelling, shipping etc. However, it is difficult to see how the SMTA2 process can be completed significantly faster with smaller firms given all the complexities involved.

The PIP Framework Secretariat has approached medium sized manufacturers on a regional basis, as these companies have common profiles and issues.

Manufacturers with small production volumes can face additional challenges. The cost of achieving WHO prequalification status may not be perceived to bring any benefits if a company has no plans to export influenza vaccines, even though securing WHO prequalification could potentially open up new business markets. In addition, domestic manufacturers with government contracts accounting for the whole of their vaccine production capacity need to determine how to provide 10% of their production to meet SMTA2 requirements. For example, government contract holders may allow 10% of the vaccine reserved for them to be released to WHO, or companies may need to scale up production, which could increase costs and resources for some firms. This suggests the potential need for greater flexibility in the commitments required from small and medium sized manufacturers.

With category B diagnostic companies, WHO faces an additional challenge as the PIP Framework limits the donate/reserve option to just diagnostic kits. As there is no certainty as to which types of diagnostic kits will be useful in a future influenza pandemic, WHO risks signing SMTA2s for products that will not be needed. More benefit-sharing options could be made available for category B companies, such as supply of ancillary pandemic equipment (syringes, needles and applicators etc.), as well as materials needed for surveillance such as specimen collection and processing materials, in order to maximize the benefits from this category.

The need for technological support through the PIP Framework may increase after GAP ends in November 2016, and it may be necessary to put more effort into these wider SMTA2 options. Four of the GAP-supported companies are now producing vaccines and a further

¹ PIP Framework Advisory Group. Annual report from the Advisory Group to the Director-General. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/ag_annual_report_2014.pdf, accessed 20 September 2016), section 3.1.

² WHO Executive Board Resolution 138/21. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits: Report by the Director-General. Geneva: World Health Organization; 2016 (http://apps.who.int/gb/ebwha/pdf_files/EB138/B138_21-en.pdf, accessed 22 September 2016), paragraph 15.

five are expected to have capacity by 2019, but the sustainability of these early stage manufacturers is expected to require further technological support.¹

Since the PIP Framework was adopted, there have been some cases of companies delaying entering into an SMTA2 or not offering reasonable benefit sharing commitments despite being in receipt of PIP BM. In October 2015, in response to negotiations that were not progressing in a timely manner, the Advisory Group recommended to the Director-General that “where manufacturers engaged in SMTA2 negotiations maintain manifestly unreasonable positions, the PIP Framework Secretariat should use a stepwise approach” to remind them that access to PIP BM must be suspended to entities that do not have an SMTA2 with WHO.² The stepwise approach starts with informal and formal communications with industry and manufacturers’ associations but can then escalate to involve PIP Framework Secretariat dialogue with host governments and direct interventions by WHO senior officials with the manufacturer’s senior management. In recognition of the impact it could have on public health, only as a last resort will a company be cut off from access to PIP BM if all of the steps are exhausted and negotiations do not progress. The stepwise approach has already assisted negotiations with two manufacturers.

Looking ahead, there are still considerable gaps in the communication to a wider audience of the progress that has been achieved through SMTA2s. Better communication about benefit sharing and the associated processes will also help to ameliorate some of the criticisms of the SMTA2 system, including addressing the increasingly high costs to the PIP Framework Secretariat of concluding SMTA2s, given the diminishing returns of agreements with small and medium manufacturers and non-manufacturers.

Recommendations: SMTA2s

18. The PIP Framework Secretariat should improve communication of progress and achievements in securing SMTA2s by better highlighting the rationale and prioritization strategy for concluding these agreements, and clarifying the intended use of the antivirals, vaccines and other products secured through these agreements.

19. The PIP Framework Secretariat should develop, for consideration by the Advisory Group, and ultimate decision-making by Member States, an approach to include the provision of financial contributions, specimen collection and processing materials as options for category B SMTA2 commitments in Annex 2.

20. The Director-General should consider requesting that Member States remove section 6.9 in the PIP Framework on pandemic influenza preparedness vaccine stockpiles, since it is no longer relevant.

¹ Grohmann G, Francis DP, Sokhey J, Robertson J. Challenges and successes for the grantees and the Technical Advisory Group of WHO’s influenza vaccine technology transfer initiative. *Vaccine*. In press. doi: 10.1016/j.vaccine.2016.07.047.

² PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework (PIPF) Advisory Group: 15-16 October 2015, Geneva, Switzerland: Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/ag_meetingreport_october2015.pdf, accessed 22 September 2015), paragraph 8.

21. The Director-General should request Member States with in-country vaccine production capacity to commit to allow manufacturers to release to WHO on a real-time basis, pandemic vaccines and other products secured by WHO under SMTA2s.

22. WHO should rapidly finalize and communicate the Interim Pandemic Influenza Risk Management (PIRM) Framework, which will provide clarity on the implementation of the switch from seasonal to pandemic vaccine production.

6.2 Partnership Contribution collection

Key Findings

Finding 43: The involvement of industry in the collaborative development¹ of the PC formula has achieved strong buy-in, and has resulted in early contribution payments being made in 2012, and the collection of 96%² of the overall funds due for 2013 and 2014.

Finding 44: Collection of PC is a continuing challenge, however, as not all companies pay their contributions by the expected deadline, and a few have not paid in full. This is of concern since the PC mechanism relies on all stakeholders fulfilling their obligations. Unlike a contractual SMTA2, the PC system is not legally binding and there are no enforcement mechanisms available to WHO beyond skilful negotiation and the potential embarrassment for a company of public exposure. However, Member States have signed up to the PIP Framework and can hold their companies to account to fulfil these obligations.

Finding 45: Issues of concern that could adversely affect the PC process were identified. Some civil society organizations and industry representatives consider that not all entities qualifying to make contributions actually do so in practice, resulting in a perception of inequity. Some companies (mostly manufacturers of diagnostic products) that make infrequent use of GISRS, perceive unfairness in the requirement to make annual contributions, even though their product sales continue to benefit from past access to the network.

¹ Partnership Contribution Standard Operating Procedures June 2015. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/benefit_sharing/pc_collection_sop.pdf?ua=1, accessed 24 September 2016), page 5, Annex 2.

² Calculation based on data in Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 24 September 2016).

Finding 46: Several industry representatives have highlighted as an issue that the fluctuation in the amount of PC they are asked to pay each year poses budgetary challenges, and they would prefer to pay a set amount.¹ Consistent with the recommendation of the Advisory Group in April 2016, industry has begun a consultative process to review the PC formula, working with all relevant industry sectors (vaccine, diagnostics and pharmaceuticals) and the PIP Framework Secretariat.²

Finding 47: A survey of GISRS running costs was undertaken for this Review: the estimates from a sample of 41 laboratories indicates that GISRS total running costs are likely to have increased since 2010, and should be estimated more accurately (see Box 6.2 and Table 6.2).

By July 2016, 30 of the 32 contributor companies identified in 2013,³ and 38 of the 42 identified in 2014,⁴ had made their PC payments. The PC funds collected as of 2 March 2016 are shown in Table 6.1. The shortfall shown for 2015 is mostly accounted for by a payment from one major contributor that was not received by WHO until after that date.

Table 6.1: Partnership Contribution collection (2012-2015) (at 2 March 2016)^{1,2}

	2012	2013	2014	2015
Entities contacted	163	194	250	256
Questionnaire responses	43	89	102	90
Contributors identified	24	32	42	39
Funds received	US\$ 18 121 000	US\$ 27 538 586	US\$ 26 964 062	US\$ 18 813 522

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2014. Geneva: World Health Organization; 2015.

² Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016.

There are challenges for both industry and WHO regarding collection of the PC funds. Some companies find it difficult to pay the contributions in a single payment so they are permitted to pay in instalments.⁵ Contributors have also raised concerns about invoices arriving late in the financial year, the budgeting challenges that flow from the fluctuations in the required annual

¹ PIP Framework Review Group. Report of the Third Meeting of the Pandemic Influenza Preparedness (PIP) Framework 2016 Review Group. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/2016-review/meeting30march_1april.pdf, accessed 4 October 2016).

² PIP Framework Secretariat, World Health Organization, unpublished information, October 2016.

³ Provisional agenda item 8.2, Executive Board 138th session. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits, Report by the Director-General. Geneva: World Health Organization; 2016 (EB138/21; http://apps.who.int/gb/ebwha/pdf_files/EB138/B138_21-en.pdf?ua=1, accessed 22 October 2016), paragraph 16.

⁴ PIP Framework Secretariat, World Health Organization, unpublished data, October 2016.

⁵ 2015 PIP Partnership Contribution (PC) Collection, Results as of 1 April 2016. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/benefit_sharing/2015PCCollectionResults1APR2016.pdf?ua=1, accessed 24 September 2016).

contributions from each individual company, and the continuing inclusion of 2009, together with the three most recent years, in the calculation of the four-year average.^{1,2}

From WHO's perspective, there is often no response to the questionnaire, with replies from less than half of the entities contacted. Those replies are often slow to arrive and do not always include the necessary information for applying the formula, such as the "sales band" selection. Specifically, each company is asked to place itself in one of 23 bands, based on the average annual influenza product sales figure. Each band has an associated "weight" that, together with the sum of band weights for all entities, is required for the formula that calculates an individual company's PC.³ This means that the PIP Framework Secretariat cannot issue invoices until it has received adequate information from all the contributing organizations.

There is a cash-flow problem every year because the timing of receipt of PC funds is not well-aligned with the timetable for deciding and implementing the associated PC influenza preparedness work plans; any delays in payments by contributors further exacerbate this problem.⁴ For example, implementation of work plans and distribution of the 2016 PC funds had to be made in several tranches due to several contributions from manufacturers not being received by the end of 2015.⁵ In April 2016, the Advisory Group recommended that the Director-General explore mechanisms to advance funds to the Secretariat for preparedness projects based on projected contributions and that the PIP Framework Secretariat continue to explore, in consultation with industry, "modification and simplification" of the collection process.⁶ In addition, as the collection of PC funds operates on an annual cycle, some WHO Regional Offices said this can complicate efforts to make programmes sustainable, leading some regions to call for longer-term funding and/or forecasting.

When the PIP Framework was negotiated, it was decided that the total annual amount of PC should be equivalent to 50% of the running costs of the GISRS, based on 2010 costs of approximately US\$ 56.5 million.⁷ However, it was also stated that such running costs "may change over time and the partnership contribution will change accordingly".⁸

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016), paragraph 34.

² Pandemic Influenza Preparedness Framework: Distribution of Partnership Contribution among companies. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/pc_distribution.pdf?ua=1, accessed 24 September 2016), section III B.

³ *Ibid.*, pages 5 and 6.

⁴ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 24 September 2016), paragraph 34.

⁵ *Ibid.*, paragraphs 33 and 34.

⁶ *Ibid.*, paragraphs 36 and 37.

⁷ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 24 September 2016), section 6.14.3, footnote 1.

⁸ *Ibid.* section 6.14.3, footnote 1.

The Review Group requested that the PIP Framework Secretariat conduct a brief survey of GISRS laboratories to obtain estimated 2016 running costs, and to determine to what extent they may have changed since 2010 (see Box 6.2).

Box 6.2: GISRS running costs survey, June - September 2016

The Secretariat sent a survey to all GISRS laboratories including WHO CCs (6), NICs (143), WHO H5RLs laboratories (13) and WHO ERLs (4), noting that some laboratories provide dual functions.¹ Responses were received from only 41 laboratories, and only 19 provided complete datasets. The data provided had several limitations which made analysis difficult; it should be noted, that most responses were estimates of costs only, that data was often incomplete, and that in some cases the validity/accuracy of the data needed to be checked.

The estimated cost from only 41 laboratories totalled US\$ 39 million, indicating that GISRS total running costs most likely exceed the 2010 estimate of US\$ 56.5 million.

Given that WHO ERLs charge for their services, it was decided that their costs would not be included in this estimate. As running costs are different for WHO CCs, NICs and WHO H5RLs, they were grouped separately. Costs were then expressed as an average cost per laboratory (see Table 6.2) for each category and the 2016 total running costs then approximated for each category and then combined to reach an estimated overall total of US\$ 122 million.

There may be several reasons to explain why the running costs for GISRS have increased since 2010. The first estimate was based on little information, on only a few institutions, and did not contain all the running costs; for example, costs associated with training, accreditation, utilities, depreciation of equipment and in-kind contributions were not included. There are more laboratories in the GISRS network now than in 2011. Moreover, general costs and salaries would be expected to increase over the last five to six years. Industry's costs would also have increased over that time and while the Member State contribution to GISRS labs is a significant global investment and benefit, this contribution varies and is not equal among Member States.

Table 6.2: Preliminary estimated running costs of GISRS, 2016¹

Institution	Number of labs responding to survey*	Average cost per laboratory	Number of labs in GISRS	Estimated total cost
WHO CC	4	US\$ 10 875 769	5**	US\$ 54 million
NIC	13	US\$ 411 195	143	US\$ 58 million
WHO H5RL	2	US\$ 737 000	14**	US\$ 10 million ***
TOTAL				Approximately US\$ 122 million
* While 41 labs responded to the survey only 19 provided complete and reliable datasets; WHO ERLs are not included.				
** Note that the WHO CC for studies on the ecology of influenza in animals and birds has been added to the WHO H5RL group for averaging purposes as its costs were significantly lower than the WHO CCs working on seasonal and pandemic viruses, and similar to the data provided by a WHO H5RL.				
*** The dataset is too small to be meaningful and the average is likely to be exaggerated.				

¹ PIP Framework Review Group Secretariat, World Health Organization, unpublished data, October 2016.

Some stakeholders have suggested that the total PC should be linked to economic indicators, such as the gross domestic product (GDP) of the country in which the manufacturer is based. Industry representatives are working on some proposals for changes to the method for calculating the PC in order to improve stability and predictability and will submit these to WHO.

Recommendations: Partnership Contribution collection

23. The Advisory Group should consider updating the 2010 estimate of GISRS running/operating costs, as input to a revision of the Partnership Contribution formula calculation, in collaboration with industry, to facilitate the timely payment of Partnership Contribution, and its sustainability as a financing mechanism for implementation of the PIP Framework.

24. Given the successful use, following a recommendation by the Advisory Group, of a stepwise approach for the agreement of SMTA2s, the Advisory Group should consider developing a similar escalation response to underpayment, late payment or default of Partnership Contribution.

6.3 Partnership Contribution implementation

Key Findings

Finding 48: Since funds began to be distributed in 2014, the implementation of the PC benefit sharing mechanism has been transparent and well-aligned with the Partnership Contribution Implementation Plan 2013-2016, which has been extended, following a recommendation by the Advisory Group to the Director-General, to 2017.^{1,2} These PC resources have allowed countries to develop multi-year plans and have fostered sustained and meaningful capacity building.

Finding 49: Implementation of capacity development in each of the five Areas of Work (Laboratory and Surveillance; Burden of Disease; Regulatory Capacity building; Planning for Deployment; and Risk Communication) in priority countries started in 2014, with targets now due to be achieved by the end of 2017. Satisfactory progress has generally occurred although some regions have been delayed by necessary shifts in focus to outbreaks such as Ebola virus disease and Zika virus. Good progress has been made in supporting countries to improve capacity to detect and monitor novel influenza viruses, in burden of disease studies, risk communication, and the development of regulatory capacity. There has been some delay in the area of deployment capacity and there is now increased focus on national deployment plans.

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf?ua=1, accessed 20 September 2016), pages 9-11.

² PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 22 September 2016), paragraph 45.

Finding 50: Expenditure does not always keep pace with collection, leading to a mistaken perception among some stakeholders that either additional PC Preparedness funds are not needed or that work plans are failing to be implemented according to planned timeframes. This risks an erosion of support among the entities making PC payments and an unwillingness to make further contributions.

Finding 51: The PIP Framework Secretariat communicates regularly about the achievements and challenges of PC implementation. Nevertheless, stakeholders regularly raise specific issues with WHO concerning: (1) dissatisfaction that PC funds continue to be collected while the Response funds are left untouched, which seemingly indicates a lack of understanding that this is a contingency fund to enable rapid response at the start of a pandemic, and that the amount of the Response funds is far below what will be needed at the time of a pandemic outbreak; (2) the basis on which recipient priority countries are selected, even though the criteria and process for selection have been published,¹ though this could indicate the desire of certain countries to be put on this list; and (3) a lack of understanding of how PC funds are building capacity in countries to increase preparedness for pandemic influenza.

Finding 52: The second Gap Analysis (the assessment of gaps and needs, as well as PC strengths, weaknesses, opportunities and threats (SWOT)) to be carried out by the PIP Framework Secretariat will inform the Director-General's proposal to the WHO Executive Board on the proportional split of PC funds between Preparedness and Response, which currently stands at 70:30, respectively.

Finding 53: Industry and Member States remain highly interested in understanding the decision-making process for PC implementation, and providing input as appropriate. WHO Regional Offices, too, have requested opportunities for PC implementers to discuss lessons learned, and would like to be more engaged in planning, implementation and monitoring. However, it should be noted that WHO Regional Offices are invited to participate in all Advisory Group meetings.

Finding 54: PC implementation Areas of Work, especially Burden of Disease studies, Regulatory Capacity and Planning for Deployment, are fundamental for the introduction of seasonal influenza vaccine programmes, which in turn provide the critical foundations for pandemic preparedness.

Finding 55: Several WHO Regional Offices raised the issue of the limited PIP Framework funding that is available for staff costs involved in implementation of PIP Framework activities. The current operating principle is that the percentage used for WHO staff should be kept as low as possible to ensure that the maximum amount of PC funds goes to activities implemented by countries. Other sources of funds may be appropriate to assist with staffing costs, and the PIP Framework (section 6.14.3.1) does encourage other donors generally to provide additional funds.

The funds raised through PC collection are allocated and spent in line with decisions taken by Member States through the WHO Executive Board. An amount not exceeding 10% of total contributions is allocated to fund the operation of the PIP Framework Secretariat, which

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimplan_update_31jan2015.pdf?ua=1, accessed 20 September 2016), pages 9-11.

manages the implementation of the PIP Framework.¹ The balance is then split proportionately 70:30² between pandemic Preparedness activities and the PIP Response funds, with the indirect costs of WHO administrative support identified transparently as Programme Support Costs (PSC). A summary of total allocations relating to 2012-2015 PC is shown in Table 6.3 (receipts as of 30 June 2016).

Table 6.3: Total Partnership Contribution allocations (2012-2015^{*}) (as of 30 June 2016)¹

Total Partnership Contribution funds received	Allocations			
	Preparedness**	Response	PIP Framework Secretariat	Programme Support Costs
US\$ 92 800 499	US\$ 51 738 331	US\$ 23 416 948	US\$ 8 212 433	US\$ 9 432 786
* Year of invoice. **Includes funds not yet allocated to specific Preparedness activities.				
¹ Partnership Contribution Implementation Portal, Budget 2012-2016. In: World Health Organization (https://extranet.who.int/pip-pc-implementation/). Geneva: World Health Organization; 2016.				

6.3.1 Response

The Response funds are held in a reserve account that accumulates over time so that financial resources are immediately available to WHO at the time of a pandemic outbreak. A set of Guiding Principles was developed by the Advisory Group, in consultation with industry and other stakeholders, as the basis for the Director-General's decisions on how to use the Response funds.³ For example, it is expected that funds will be needed to distribute the pandemic influenza vaccines donated through the SMTA2s and to purchase the additional products that manufacturers have agreed to make available at affordable prices.

6.3.2 Preparedness

Under the Partnership Contribution Implementation Plan (2013-2016), the Preparedness funds are allocated across five Areas of Work: Laboratory and Surveillance; Burden of Disease; Regulatory Capacity building; Planning for Deployment; and Risk Communication.⁴ The activities selected for support under these five areas are directly linked to the findings of the 2013 Gap Analyses, which assessed where capacity building was most urgently needed to strengthen global pandemic preparedness.⁵ For each Area of Work there is a list of priority countries for action; regions were closely consulted in the selection of these countries, and the PIP Framework Partnership Contribution Implementation Plan 2013-2016 details the

¹ *Ibid.*, page 6.

² Guiding Principles for use of PIP Partnership Contribution "Response" Funds. In: World Health Organization [website]. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/pip/guiding_principles_pc_response_funds.pdf?ua=1, accessed 21 September 2016), paragraph 2(b).

³ *Ibid.*

⁴ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf?ua=1, accessed 22 September 2016).

⁵ Pandemic Influenza Preparedness Framework Partnership Contribution 2013-2016 Gap Analyses. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/pip_pc_ga.pdf?ua=1, accessed 22 September 2016).

country selection process for each Area of Work.¹ Since Laboratory and Surveillance capacity building would receive the majority of PC funds, a more detailed process of selection was undertaken (see Box 6.3).

Box 6.3: Selection of countries for Laboratory and Surveillance capacity building²

Regional lists of potential priority countries were created through technical assessment of influenza-specific laboratory and surveillance country capacity, using factors identified by the Advisory Group. These were: country development status; IHR (2005) core capacity implementation; country needs for influenza epidemiological and laboratory surveillance; and A(H5N1) vulnerability.

WHO Regional Offices refined these lists by taking into account additional elements including: the political situation of countries in the region, notably whether a country is in a complex emergency; ongoing donor funding and investments in a country; absorptive capacity of a country; country population size; geographical location of a country in the region/sub-region (notably for island states); level of interest within a country/Ministry of Health to work in influenza; ability of a country to build on existing capacities to produce influenza surveillance data that could be shared with neighbouring countries.

Regions prioritized countries according to their ability to receive PC funds to strengthen capacities to detect and monitor influenza outbreaks, and to share information on influenza, particularly through GISRS. The lists of recommended countries were then sent to the Director-General, via the Advisory Group.

During 2014, more than 50 work plans were developed across WHO. The first tranches of funding went out in April 2014 and by August 2014 some US\$ 17.4 million had been distributed to WHO HQ, Regional Offices and Country Offices to implement approved preparedness activities in the five areas.³ By the end of 2015 the total PC funds distributed had reached approximately US\$ 31 million, with Laboratory and Surveillance accounting for around 70% of the distributions (see Figure 6.1).⁴

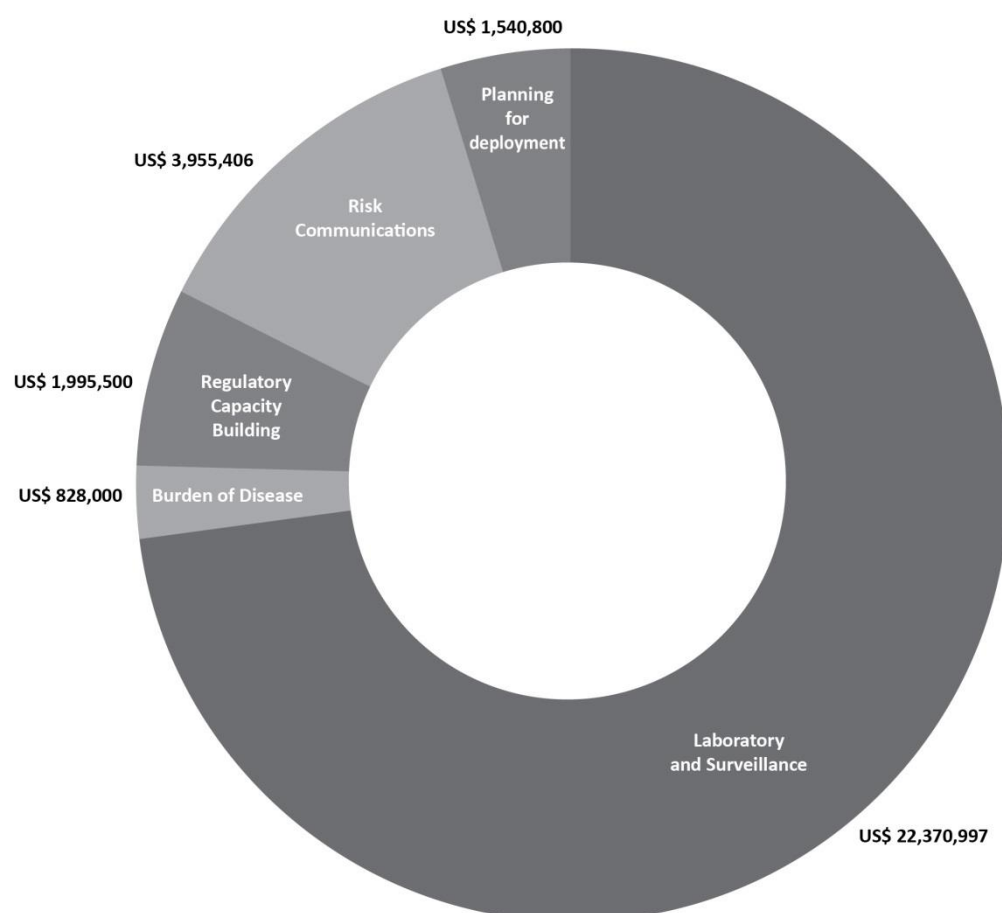
¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf?ua=1, accessed 22 September 2016), pages 9-11.

² *Ibid.*

³ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 8.

⁴ *Ibid.*, page 4.

Figure 6.1: Distribution of Preparedness funds by area of work (end December 2015)¹



¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 65.

PC Preparedness funds are distributed against approved work plans and expenditure (i.e. actual spending) is tracked and reported across WHO. This has shown that expenditure of PC funds has not always kept up with funds' distribution. Over the five Areas of Work, the proportion of distributed money (i.e. as shown in Figure 6.1) that had actually been spent by the end of 2015 for the different Areas of Work was: Laboratory and Surveillance (80%); Burden of Disease (76%); Regulatory Capacity building (56%); Planning for Deployment (44%); and Risk Communication (85%).¹ The overall expenditure rate for Preparedness for 2014 and 2015 combined was 77%.²

Although the five Areas of Work have guided PC implementation so far, WHO recognizes that additional work areas may become relevant and more low and middle-income countries than are currently supported will need PC support in the future.³ The Partnership Contribution

¹ *Ibid.*, page 67.

² *Ibid.*, page 65.

³ *Ibid.*, page 52.

Implementation Plan 2013-2016 has been extended to the end of 2017¹ while a new Gap Analysis is carried out to review progress in the existing Areas of Work and to define possible future Areas of Work. All this information will feed into the development of a new PC high level implementation plan. Aligned with this, the current 70:30² split of PC funds between Preparedness and Response has also been extended by one year to the end of 2017 and will, if appropriate, be revised in the new plan according to any recommendations from the Director-General and the WHO Executive Board that are ratified by Member States at the 2017 World Health Assembly.

Progress towards agreed implementation targets is monitored closely every six months using a set of indicators for each Area of Work in order to register achievements against initial baseline conditions.³ The targets set in the Partnership Contribution Implementation Plan 2013-2016 have been extended, with the Plan, to the end of 2017.⁴ A detailed update on performance, as measured by the indicators, has been published annually by WHO in a Partnership Contribution Annual Report, starting for 2014.^{5,6}

A summary of the main achievements under the five Areas of Work to end-2015 is presented in Table 6.4. Tables 6.5 – 6.10 present data for individual Areas of Work. While there are more recent data from 2016 for some of these indicators, different reporting periods mean that not all of Areas of Work have more recent data than the end of 2015; thus, to show progress in each Area of Work across the same period of time, the data used comes from the 2015 Partnership Contribution Annual Report.

¹ PIP Framework Advisory Group. Meeting of the Pandemic Influenza Preparedness Framework Advisory Group, 19-22 April 2016, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/ag_april2016_MeetingRpt.pdf?ua=1, accessed 22 September 2016), paragraph 45.

² This proportional split is after 10% of total PC income is allocated to the PIP Framework Secretariat.

³ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 11.

⁴ PIP Framework Secretariat, World Health Organization, unpublished information, October 2016.

⁵ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2014. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/161369/1/WHO_HSE_PED_GIP_PIP_2015.2_eng.pdf?ua=1&ua=1, accessed 22 September 2016).

⁶ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016).

Table 6.4: Highlights for 2014 and 2015 in the five Preparedness Areas of Work¹

	2014	2015
Laboratory and Surveillance capacity-building ^{2,3}	<p>21 capacity indicators were defined to measure progress towards outputs and outcomes. Baseline data were collected in the 43 countries prioritized for support in this area.</p>	<p>Established and functioning event-based surveillance for influenza in 12 of the 43 PIP priority countries.</p> <p>128 countries worldwide shared virus⁴ with WHO CCs, WHO H5RLs and WHO ERLs.</p> <p>66 countries consistently reported epidemiological data to regional or global platforms.</p> <p>114 countries consistently reported virological data to a regional or global platform.</p> <p>103 countries participated in the WHO External Quality Assessment Project for the detection of influenza virus type A by polymerase chain reaction (EQAP) and scored 100%.</p>
Burden of Disease	<p>Seven countries participated in a training to learn how to develop national disease burden estimates using a new WHO manual.</p>	<p>40 countries, including 19 PIP PC priority countries, are estimating the burden of influenza using WHO methodology and technical support.</p> <p>Three PIP priority countries completed robust national burden of influenza estimates.⁵</p> <p>Six countries are piloting the WHO economic burden tool.</p>
Regulatory capacity-building	<p>Work started to revise the expedited review procedure to facilitate licensing of pre-qualified antivirals and vaccines.</p> <p>The new Collaborative procedure to address assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines was developed and endorsed by the Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) in October 2014.</p>	<p>WHO collaborative procedure for accelerated regulatory approval of influenza products adopted by 14 countries.⁶</p> <p>14 of 16 priority countries assessed for regulatory capacity.</p>

	2014	2015
Planning for Deployment	Model agreements between WHO and recipient countries of pandemic products were drafted.	PIPDEPLOY tool to improve deployment of influenza products to countries was developed.
Risk Communications	Significant training materials were developed, translated and published online.	17 target countries had specific risk communication training and/or workshops. ⁷ The ECN has a roster of 150 people able to be deployed to health emergencies worldwide.

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 8.

² Data from regional and global databases.

³ Achievements for Laboratory & Surveillance at WHO Headquarters level were made with funds from PIP Partnership Contribution and other donors.

⁴ Refers to seasonal and pandemic potential influenza viruses.

⁵ Costa Rica, Chile and Egypt.

⁶ United Rep. of Tanzania, Uganda, Ethiopia, Ghana, Kenya, Mozambique, Burkina Faso, Cameroon, Benin, Mali, Armenia, Sri Lanka, Bhutan, and Myanmar.

⁷ Barbados, Cambodia, Dominica, Egypt, Kazakhstan, Kenya, Republic of Moldova, Mongolia, Nepal, Saint Lucia, Saint Vincent and the Grenadines, Senegal, Sudan, Turkey, Ukraine, Uzbekistan, Vietnam.

6.3.2.1 Area of work: Laboratory and Surveillance¹

The majority of activities in this Area of Work are under the responsibility of the Regional Offices that work through Country Offices to strengthen capacities for laboratory and surveillance where they are needed most. At the Regional level, the emphasis is placed on: 1) strengthening national capacities to detect respiratory disease outbreaks due to novel influenza virus (Output 1); and 2) strengthening national capacities to monitor trends in circulating influenza viruses (Output 2). In 2014, a total of 11 capacity indicators were defined to assess progress in national capacity to detect, monitor and share novel influenza viruses, and to judge the overall sustainability of the system in the 43 priority countries. Baseline data were collected from these priority countries in August 2014.

¹ *Ibid.*, pages 4, 8, 12-14, and 33–34.

At the global level, 10 capacity indicators focus on strengthening collaboration through the sharing of information and viruses with an emphasis on improving the quality of the GISRS system (Output 3). These global indicators reflect all 196 Member States that provide information on influenza viruses to the WHO global databases, Flu Informed Decisions (FluID) and FluNet, including the 43 priority countries. Together with the 11 indicators mentioned above, this makes a total of 21 capacity indicators for laboratory and surveillance. By the end of 2015, the number of PIP countries reporting to FluNet had increased from 26 to 30, and to FluID from five to 11.

Tables 6.5 and 6.6 present an overview as measured against indicators for the three Outputs, followed by summaries of progress in these areas.

Table 6.5: Laboratory and Surveillance indicators for Outputs 1 and 2 at the national level¹

Outcome: The capacity to detect and monitor influenza epidemics is strengthened in developing countries that have weak or no capacity.			
Support to WHO regions and countries			
Output indicators	Baseline*	Target	Status
Detention capacity (43 PIP priority countries) Number of countries with an established and functioning event-based surveillance system	8	43	12
Monitoring capacity (43 PIP priority countries) Number of countries able to consistently report and analyze virological data	26	35	30
Number of countries able to consistently report and analyze epidemiological data	5	17	9

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 13.

* 31 Aug 2014.

Summary of progress

Overall, good progress has been made across all regions in improving capacity to detect and monitor novel influenza viruses, share information about these viruses and sustain these actions over time.

- The 43 priority countries are distributed across six WHO Regional Offices as follows: WHO Regional Office for Africa (AFRO) (11 countries), WHO Regional Office for the Americas (AMRO)/Pan American Health Organization (PAHO) (8 countries), WHO Regional Office for the Eastern Mediterranean (EMRO) (7 countries), WHO Regional Office for Europe (EURO) (6 countries), WHO South-East Asia Regional Office (SEARO) (6 countries) and WHO Regional Office for the Western Pacific (WPRO) (5 countries).
- Not all priority countries are directly funded by PIP PC but they do benefit from training and workshops funded at the Regional and HQ levels of WHO. This means that countries may report full or partial capacity for an indicator where they have been supported indirectly, i.e. not through PIP PC funded work plans.

- AMRO, WPRO and EURO are expected to meet their country-level targets for the output indicators based on data collection round three in February 2016.
- AFRO, EMRO and SEARO have faced serious challenges to PIP PC implementation including outbreaks of Ebola virus disease, Yellow fever and Cholera (AFRO), civil unrest and refugee crises (EMRO), and staff turnover and reagent/equipment challenges (SEARO). These regions may struggle to reach their targets by 2017 but are still expected to improve capacity based on the data collection round three in February 2016.

Table 6.6: Laboratory and Surveillance indicators for Output 3 at the global level¹

Outcome: The capacity to detect and monitor influenza epidemics is strengthened in developing countries that have weak or no capacity.			
Output indicators	Baseline*	Target	Status
Sharing capacity (global) Number of countries that participate in EQAP and score 100%	109	120	103
Number of countries sharing virus with WHO CCs, H5 Reference Laboratories and Essential Regulatory Laboratories at least once a year in the past two years	90	108	128
Number of countries consistently reporting epidemiological data to regional or global platforms	55	71	66
Number of countries which consistently report virological data to a global platform	108	124	114
¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1 , accessed 22 September 2016), page 33. * 31 Aug 2014			

Summary of progress

Overall, good progress has been made at the global level with workshops and training regularly provided in WHO regions and countries.

- For the WHO External Quality Assessment Project for the detection of influenza virus type A by polymerase chain reaction (EQAP) indicator, there will be fluctuations in the number of participating laboratories scoring 100%. This reflects staff turnover in national laboratories and the need continuously to train laboratory technicians to maintain high quality use of polymerase chain reaction (PCR) to detect influenza viruses. The target for this indicator may need to be revised to capture the reality of training laboratory staff in countries. An appropriate target may be, for example, “no fewer than 100 countries participating and scoring 100%”.
- The results for sharing viruses with WHO CCs are positive and reflect the success of the influenza virus Shipping Fund (see chapter 4, section 4.1), which was established to improve sharing capacity for influenza viruses and clinical specimens.

- Results for global reporting of both epidemiological and virological data are positive and targets are expected to be met by the end of 2017. The results reflect improvements to make data entry easier when using the WHO/GIP global databases, FluNet (for epidemiological data) and FluID (for virological data).

6.3.2.2 Area of Work: Burden of Disease¹

Robust information on the national burden of disease for influenza is needed so that governments can decide whether to prioritize seasonal influenza prevention and control, including expansion of seasonal vaccine production capacity, which in turn is needed for pandemic vaccine preparedness. PC funds have supported GIP to develop tools for estimating the disease and economic burden of seasonal influenza. The biggest challenge in developing national burden of disease estimates is the lack of country-level data, which are often incomplete. In particular, robust data on influenza morbidity including hospitalization relies on laboratory confirmation, which is often unavailable in low income countries. Specific data are also needed on high risk groups and on the country-specific direct medical costs and indirect costs from loss of productivity. Considerable further work is needed to develop tools to estimate the cost-effectiveness of specific influenza interventions and to guide policy decisions on when and where to use seasonal vaccine. The goal is to create a global platform holding regularly updated global and regional data, economic data, and risk factor information for use in national influenza policy planning. Table 6.7 shows progress against this Area of Work's output indicators.

Table 6.7: Burden of Disease Output indicators¹

Outcome: National policy-makers will have influenza disease burden data needed for informed decision-making and prioritization of health resources			
	Baseline	Target	Status
All six WHO regions develop regional representative burden of disease data to guide developing countries' policy-making	NA	6	On track
Output 1: Derive regionally representative influenza disease burden estimates from selected countries Number of countries supported by Partnership Contribution with disease burden estimates by 2016	0	19	3*
Output 2: Derive a global estimate of influenza disease burden estimates from selected countries Global estimate of influenza disease burden derived from national estimates purchased	0	December 2016	On track

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), page 36.

* Costa Rica, Chile and Egypt have estimates pending publication in peer-reviewed journals. A further 12 countries are finalizing estimates

¹ *Ibid.*, pages 8 and 37-38.

Summary of progress

Overall good progress has been made in this Area of Work as a result of training workshops in countries and the Burden of Disease Expert Advisory Group for influenza, which was convened in 2014 to provide advice and support to countries carrying out influenza burden estimation. This group holds monthly teleconferences and by September 2016 had held two face-to-face meetings. There is also good synergy with the WHO economic burden of disease tool. This tool is being piloted in four PIP priority countries (Chile, Costa Rica, Lao PDR and Indonesia), plus two others. Process indicators may be helpful to track the amount of work that is going into the estimation process from WHO's side.

- By September 2016, 40 countries (including 19 PIP priority countries for this Area of Work) were engaged in estimating the burden of influenza using WHO methodology and technical support; three countries (Costa Rica, Chile and Egypt) had completed their burden of disease estimates.
- A workshop was held in July 2016 to bring together countries involved in the estimation process to share challenges, solutions and preliminary results. As a result of the workshop, more robust national estimates are expected to be produced by the end of 2016.
- The targets are expected to be met by the end of 2017. There have been some delays on certain inputs to the global burden of influenza estimation process (i.e. global mortality estimates) resulting from delays in finding the right organizations to contract for the estimates.

6.3.2.3 Area of Work: Regulatory Capacity Building¹

Non-vaccine-producing countries that do not have appropriately developed regulatory systems will be unable to ensure that incoming vaccines are swiftly approved for use in the event of a pandemic. During the 2009 A(H1N1) pandemic, lack of a common regulatory approval process hampered influenza product registration in over half of the countries that received donated pandemic A(H1N1) vaccines.² The outputs and targets for this Area of Work seek to address the regulatory gaps in countries that were unable to follow relevant WHO guidance documents for product registration (see Table 6.8). PC is being used by the WHO Essential Medicines and Health Products Department to strengthen regional/sub-regional/national regulatory systems in the regulation of influenza products and their national approval.

¹ *Ibid.*, pages 8 and 40-42.

² Main operational lessons learnt from the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative. WHO: Geneva; 2010 (http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiative_moll.pdf, accessed 4 October 2016).

Table 6.8: Regulatory Capacity Building Output indicators ¹

Outcome: Countries with weak or no regulatory capacity will be able to regulate influenza products including vaccines, antivirals and diagnostics, and to accelerate national approval of these commodities in case of an influenza pandemic			
	Baseline	Target	Status
By 2016, at least 16 countries will have improved their regulatory capacity to oversee influenza products including vaccines, antivirals and diagnostics and to accelerate national approval registration of these commodities in case of an influenza pandemic	NA	At least 16	On track
Output 1: Develop guidelines on regulatory preparedness of non-vaccine producing countries that enable them to expedite approval of influenza vaccines used in national immunization programmes Regulatory preparedness guidelines endorsed by the WHO Expert Committee on Biologicals Standardization (ECBS)	0	1	Awaiting ECBS endorsement
Output 2: NRA capacity to regulate influenza products including vaccines, antivirals and diagnostics is strengthened Number of countries which developed regulatory capacity to oversee influenza products including vaccines, antivirals and diagnostics in case of pandemic as per the WHO NRA assessment and IDP elaboration and implementation	0	16*	1**
Output 3: Regulatory processes to accelerate approval of influenza vaccines, antivirals and diagnostics during a public health emergency are incorporated into deployment plans for pandemic influenza products Number of countries with a common approach for accelerated regulatory approval of influenza products in a public health emergency	0	48***	14****
<p>¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1, accessed 22 September 2016), page 39.</p> <p>* Democratic Republic of the Congo, Ethiopia, Ghana, Kenya, United Republic of Tanzania, Uganda, Bolivia, Haiti, Pakistan, Sudan, Armenia, Georgia, Nepal, Sri Lanka, Cambodia, Lao PDR.</p> <p>** The NRA of 14 of 16 PIP priority countries were assessed. One country has acceptable capacity in the three areas of assessment: regulatory systems, marketing authorization and pharmacovigilance. Implementation of Institutional Development Plans (IDP) started in 14 of the 16 PIP countries. Enhancing regulatory capacity is a long-term investment and impact data is not yet available.</p> <p>*** Democratic Republic of Congo, Ethiopia, Ghana, Kenya, United Republic of Tanzania, Uganda, Mozambique, Cote d'Ivoire, South Africa, Angola, Burkina Faso, Gambia, Cameroon, Benin, Central African Republic, Guinea, Malawi, Mali, Bolivia, Haiti, Honduras, Nicaragua, Guyana, Peru, Pakistan, Sudan, Afghanistan, Yemen, Iraq, Morocco, Armenia, Georgia, Rep. of Moldova, Kazakhstan, Kyrgyzstan, Tajikistan, Nepal, Sri Lanka, Bangladesh, Bhutan, Myanmar, Timor-Leste, Cambodia, Lao PDR, Kiribati, Mongolia, Philippines, Papua New Guinea.</p> <p>**** United Republic of Tanzania, Uganda, Ethiopia, Ghana, Kenya, Mozambique, Burkina Faso, Cameroon, Benin, Mali, Armenia, Sri Lanka, Bhutan and Myanmar.</p>			

Summary of progress

Overall progress has been made in this Area of Work but the three outputs are closely linked and furthermore are designed to support countries at different stages of national regulatory authority (NRA) development. Since Outputs 2 and 3 require country buy-in, (i.e. countries committing to implementing institutional development plans (IDPs) and adopting the WHO collaborative approach), WHO spends time and money on workshops, training and advocacy, which go unreported due to the results-based indicators assigned to these outputs. Process indicators might be helpful to allow monitoring of the outputs at a more granular level.

- Guidelines have been produced on regulatory preparedness to assist non-vaccine producing countries to expedite approval of seasonal vaccines and/or pandemic vaccines deployed by a UN agency. The WHO Expert Committee on Biological Standardization approval is expected by October 2016 and the target for Output 1 is due to be met by the end of 2016.
- WHO is working with 16 priority countries to address critical gaps in regulatory systems and two other functions deemed essential for countries that procure vaccines through UN agencies: marketing authorization and pharmacovigilance. Progress has been made for this output, namely WHO has assessed 14 countries to identify gaps in these three critical areas. IDPs are in place in these countries to fix these gaps. The two remaining priority countries were due to be assessed by the end of 2016 and IDPs also put into place. By October 2016, only one of the 16 priority countries had met the “desired capacity” for regulatory preparedness in all three critical areas and it is unlikely that the remaining 15 countries will reach this stage by the end of 2017. Nonetheless progress has been made in moving countries from “below critical capacity” for regulatory capacity and into “acceptable capacity” as a result of in-country training activities.
- 14 out of 48 target countries have adopted the WHO common approach for accelerated regulatory approval of influenza products in a public health emergency. Acceptance of the WHO common approach is voluntary for countries, and is one of several options to improve regulatory capacity. Progress in this area has been made by holding advocacy workshops in SEARO and developing an addendum to the collaborative procedure to cover vaccines for emergency use. It is unlikely that all 48 target countries will adopt the collaborative procedure by 2017 but WHO continues to raise the profile of the collaborative procedure for pharmaceutical products and vaccines. A regional workshop in the WPRO region is due to take place by the end of 2016.

6.3.2.4 Area of Work: Planning for Deployment¹

System bottlenecks and lack of coordination between the large number of different organizations involved in deployment can severely delay the distribution and use of pandemic vaccines and other public health products at the time of an outbreak. In addition,

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 22 September 2016), pages 8 and 45.

low resourced countries need to be in a “ready” mode in order to receive and make optimal immediate use of an initial limited supply of pandemic vaccines and antivirals. Simulation exercises can be used to test operational deployment systems across countries and responding support agencies in a combined response. PC funds have helped to develop and test the PIPDEPLOY simulation tool, which is designed for countries to identify and help correct bottlenecks and failure points in vaccine delivery in public health emergencies. Table 6.9 shows progress against this Area of Work’s output indicators.

Table 6.9: Planning for Deployment Output indicators¹

Outcome: Plans for deployment of pandemic supplies includes vaccines, antivirals and diagnostics, will be developed and regularly updated			
	Baseline	Target	Status
Output 1: A common approach to manage deployment operations is developed and shared with stakeholders and deployment partners A common deployment approach is developed with multiple deployment stakeholder endorsement	0	1	Draft available
Number of training and simulation exercises with deployment stakeholders	0	8	Simulation exercise set for mid-2016*
Output 2: Country deployment readiness systems are simplified and updated Model country recipient agreement is revised and updated	0	1	In process
Countries and partners accessing web-based planning tools	0	16	Pending tools
¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1 , accessed 22 September 2016), page 44. * This simulation exercise was still pending as of 26 October 2016.			

Summary of progress

Overall this Area of Work has been delayed despite considerable work on developing the PIPDEPLOY simulation tool. National deployment plans are expected to be the focus of further development in 2016, with some process measures enabling progress to be monitored.

- For Output 1, a draft document on a common approach to manage deployment operations has been developed for endorsement by deployment stakeholders.
- The PIPDEPLOY simulation tool is delayed. The tool was expected to go live in early 2016 but the complexity of technological difficulties were underestimated, delaying the tool’s release. By the end of 2017, two or three simulation exercises are expected to be conducted with deployment stakeholders.
- For Output 2, the model country recipient agreement has been streamlined and updated. It will need to be adjusted for specific public health emergency circumstances as emergencies arise. The web-based planning tools have not yet

been developed. To support their development, current national deployment plans for the 16 target countries are being assessed and appropriate tools will be developed to fill any gaps identified in the plans.

- The 16 target countries for planning for deployment are the same as those for regulatory capacity building, creating a synergy between the linked activities of product registration and product deployment in countries.

6.3.2.5 Area of Work: Risk Communications¹

Effective risk communication is important for avoiding misinformation and panic that can hamper public health interventions. As was learned in 2014 and 2015, during the international response to Ebola virus disease in West Africa, national and international capacity for risk communication is a crucial element of effective emergency response. In this context, PC funds have been used to target the 30 priority countries, as well as supporting the global WHO Emergency Communications Network (ECN). A wide range of guidelines, tools, curricula and materials have been developed to build skills in pandemic influenza risk communication. These materials have been distributed through the WHO website, iLearn and through a contact database of more than 1,000 training participants. Materials to train journalists in responsible reporting during pandemic influenza have been finalized and sub-regional media workshops held. Simulation and “table-top” exercises hosted in eight countries were used to build and test risk communication capacity. Table 6.10 shows progress against this Area of Work’s output indicators.

Table 6.10: Risk Communication Output indicators¹

Outcome: Global risk communications capacities are strengthened with a specific focus on pandemic influenza communications			
	Baseline	Target	Status
Output 1: Access to risk communications training and platforms is increased enabling all countries to respond more effectively to a potential influenza pandemic Tools and web-based risk communications training material accessible to Member States in all language versions by December 2015	0	194	Available in English
Number of registered users of online material	0	500	513
Number of trainings completed on IHR risk communications training website*	0	200	96
Output 2: Risk communications capacity is established in priority countries with little or no capacity Targeted Member States will have benefitted from IHR risk communications programme by end of 2016	0	30	17

¹ *Ibid.*, pages 8 and 47.

<p>Output 3: Global Emergency Communications Network (ECN) operationalized to provide support to countries before, during and after public health emergencies</p> <p>Proportion of requests for risk communications surge support responded to within 72 hours by WHO in 2015/16</p>	0	80%	100%
<p>¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016, (http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1, accessed 22 September 2016), page 46.</p>			

Summary of progress

Overall this Area of Work has made good progress towards its targets and has exceeded expectations for Output 3 by meeting the target early. Work needs to continue to include all 30 priority countries in risk communications training and to make training materials available in languages other than English.

- Good progress has been made towards providing access to risk communication training, with introductory materials available in all UN languages and Portuguese and a wide range of more advanced materials available in English. Limitations of the material dissemination through iLearn, the WHO website, and contact lists will be addressed through the launch of www.openWHO.org platform, scheduled in October 2016. The new platform will facilitate access and a much wider dissemination and use of these training materials, and will enable better tracking of user numbers and feedback. With this platform, the target set for completed online training is likely to be met or exceeded by the end of 2017.
- The target of establishing risk communications capacity in the 30 priority countries is expected to be met by the end of 2017. Priority countries that are inaccessible for face-to-face training interventions will be supported through training initiatives hosted on the platform and supported through mentoring activities.
- Development of the ECN has met its target to provide support to countries before, after and during public health emergencies. By October 2016, this network had a roster of 150 staff, consultants, partners, government experts and officials able to be deployed for pandemic communications within 72 hours. The ECN is a benefit across WHO's Health Emergencies Programme because its capacities are available to all public health emergency operations, creating synergies between PIP and other areas. Regular deployment of trainees also ensures that existing capacity is maintained and exercised.

Operational challenges

Influenza pandemic preparedness activities naturally overlap with other public health initiatives and specifically with other influenza efforts. On the positive side, this means that PC funded programmes can produce collateral benefits, creating efficiencies and aligning with and providing support to other programmes. However, there is also the potential for duplication of effort if careful and detailed co-planning and monitoring are not performed. All influenza preparedness activities also have to deal with the reality that regions have

competing priorities and influenza is not high on policy makers' agendas all the time; in the case of the PIP Framework this contributes to variability across regions and countries in PC implementation.

There will always be a necessary balance between rapid disbursement of funds and the need for quality control of work plans. While WHO has been conservative in disbursement, attempts have also been made to streamline this process. However, as mentioned in chapter 6 section 6.2 (PC collection), the misalignment between the time period when PC funds are received and when they need to be distributed to work plans has been exacerbated by late payments from contributors and by some non-payments. Until this issue is addressed it will continue to have a knock-on impact in terms of delaying the start of work plans and hindering pandemic preparedness.

The PIP Framework Secretariat has commissioned an external independent evaluation of PC implementation, which is due to take place from October 2016 to April 2017. It will:

- Evaluate the progress of each Area of Work towards achieving the target outputs and outcomes set out in the high level Partnership Contribution Implementation Plan 2013-2016;¹
- Measure the short, medium and longer term impact generated by each of the Areas of Work to determine how these have helped prepared the global community for pandemic influenza;
- Identify lessons learnt that can improve the management of PIP PC funds in the future.

Recommendations: Partnership Contribution implementation

25. The Advisory Group should consider for inclusion in the 2018-2022 Partnership Contribution Implementation Plan, the development of process measures to enable better monitoring of progress for key Areas of Work.

26. The Advisory Group should request regular financial reports and audits and ensure that appropriate financial accountability mechanisms are in place; it should also request the PIP Framework Secretariat to illustrate how the Partnership Contribution Response funds will be severely inadequate in a pandemic.²

¹ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimplan_update_31jan2015.pdf?ua=1, accessed 22 September 2016).

² See Recommendation 2(b) of this report, which states: "WHO should regularly and more effectively communicate the objectives and progress in the implementation of the PIP Framework to Members States, Global Influenza Surveillance and Response System (GISRS) laboratories, industry, civil society, and other stakeholders. In particular, it should better communicate:

b. Partnership Contribution implementation measures; these should be highlighted in regular Advisory Group reports and post-meeting briefings so that progress is more visible and clearly recognized."

Chapter 7: Governance

Key Findings

Finding 56: Although it is relatively new, the PIP Framework overall has a well-functioning governance structure that oversees how the PIP Framework is operationalized. It has benefited from strong commitment at each of WHO's three levels: HQ; Regional Offices; and Country Offices.

Finding 57: The Advisory Group continues to play a key role in effective governance by providing impartial, committed, and pragmatic oversight and guidance, representing its independent deliberations.

Finding 58: The intended composition of the Advisory Group has been achieved in practice, with a good balance of skills and representation of the regions. The engagement of WHO Regional Offices in Advisory Group meetings has benefited all participants – and Regions should be encouraged to increase their participation. Where expert evidence and situational analysis has been required, the Advisory Group has initiated the establishment by the Director-General of technical and expert working groups on GSD.

Finding 59: The value of the Advisory Group has been enhanced by members' familiarity with the issues and the expertise that has developed over time. However, the fixed three-year term for Advisory Group members, with extensions only for a further full three-year term, means that the membership of the Advisory Group is usually completely renewed every three years. This regular turnover brings benefits in terms of fresh inputs from new members but also risks the loss of institutional memory with the exit of experienced members.

Finding 60: Based on evidence provided to the Review Group, since 2011 the Advisory Group's recommendations to the PIP Framework Secretariat and to the Director-General have been acted upon. The Advisory Group's Annual Reports and the Director-General's Biennial Reports have been completed and delivered on time and made available as publications on the PIP Framework website. The Director-General has reported each year on the PIP Framework to the WHO Executive Board and the World Health Assembly; therefore, Member States are well apprised of its actions and progress. However, harmonising the prescribed content of the Advisory Group Annual Reports and the Director-General's Biennial Reports would improve efficiency.

Finding 61: The regularity and transparency of communication and engagement between the Advisory Group and Member States, industry and civil society organizations was recognized and appreciated by a number of key informants interviewed by the Review Group. That said, only a relatively small number of civil society organizations engage consistently with the Secretariat; this may be because others are unclear about the relevance of the PIP Framework for their work. The Secretariat could reach out to a wider community of civil society groups in order to broaden and deepen engagement, which would bring new perspectives that could benefit the PIP Framework.

Finding 62: Some GISRS members, notably WHO CCs, feel there should be greater interaction between themselves, the Advisory Group, and the PIP Framework Secretariat,

including in the setting up of technical working groups. It might also be helpful if the regular, direct contact that occurs between the Advisory Group and industry and civil society organizations also included GISRS technical experts. However, it is important to note that the PIP Framework Secretariat and Advisory Group have had consistent engagement from only one or two civil society organizations.

Finding 63: An objective of the PIP Framework is to strengthen GISRS, and geographical reach, scope and functioning of GISRS has expanded; however, the leadership of this network remains largely informal and the system is coordinated through GIP. The lack of a formalized leadership structure from within GISRS has led to the absence of recognized representation for the entire GISRS network in PIP Framework operations.

Finding 64: Under the 2016 reform of WHO's work in health emergency management, all WHO's work in emergencies was brought under a new Health Emergencies Programme, including the PIP Framework Secretariat.¹ WHO's commitment to the PIP Framework remains unchanged by this internal reorganization. The PIP Framework Secretariat is significantly dependent on close collaboration with many technical units of WHO, especially the GIP. The GIP is the technical influenza unit that coordinates GISRS, which underpins the implementation of the PIP Framework. Thus any internal reorganization would need to ensure that the GIP technical input remains closely aligned with the PIP Framework Secretariat and informs its implementation.

Finding 65: The Review Group was advised that resources and staffing are stretched in many areas, at all three levels of WHO (HQ, Regional Offices and Country Offices) and across many areas of activity, such as virus sharing, PC implementation, and in the PIP Framework Secretariat's work with companies on the prequalification of vaccines. Some of this Review's Recommendations will require additional resources, for example to produce the studies that have been called for.

7.1 PIP Framework Advisory Group

The implementation of the PIP Framework is overseen by the World Health Assembly with advice from the Director-General, who also promotes implementation of the PIP Framework within WHO and among relevant WHO-related entities.² An independent Advisory Group, appointed by the Director-General, is the "third pillar" of the PIP Framework's Governance and Review structure.³ It provides expert monitoring and evaluation of implementation of the PIP Framework, with evidence-based reporting, assessment and recommendations to the Director-General on the functioning of the PIP Framework. The Advisory Group does not

¹ Reform of WHO's work in health emergency management, WHO Health Emergencies Programme,

Report by the Director-General. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (A69/30; http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_30-en.pdf, accessed 22 September 2016).

² Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), section 7.1.

³ Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits: report of the Advisory Group. Report by the Director-General. In: World Health Organization [website]. Geneva: World Health Organization; 2011 (EB130/18; http://apps.who.int/gb/ebwha/pdf_files/EB130/B130_18-en.pdf?ua=1, accessed 21 September 2016), paragraph 2.

itself engage in administrative functions.¹ When considered necessary, the Advisory Group can recommend that the Director-General set up a technical or expert working group to provide evidence an analysis on a specific issue, such as the handling of IVPP GSD under the PIP Framework.²

Since its first meeting in November 2011,³ the Advisory Group has convened twice a year at WHO HQ, Geneva. Reports of these meetings are published on the PIP Framework website, including recommendations to the Director-General. Member States' Permanent Missions in Geneva are briefed immediately after the meetings. Each Advisory Group meeting also includes an interaction with industry and other stakeholders to hear their views on the implementation of the PIP Framework. A PIP Framework e-Newsletter is published every two months to keep all stakeholders informed of events and new publications; regular teleconferences are held with industry and civil society groups for direct contact.

The 18 members of the Advisory Group are drawn from three Member States in each WHO region and are selected to provide a skill mix of internationally recognized policy makers, public health experts and technical experts in the field of influenza.⁴ The standard duration of appointment is three years, with members eligible to serve for two appointments. Members of the original Advisory Group all served until 2015 to maintain stability during the early years of PIP Framework implementation. Starting in 2015, one third of the Advisory Group (i.e. six of the 18 members) has been renewed each year after completing a three-year appointment, in line with the terms of reference.⁵ This pattern of staggered renewal over three years aims to preserve the continuity and institutional memory of the Advisory Group. The mix of geographical and skills is maintained when membership of the group changes.

Every April, the PIP Framework Secretariat puts considerable effort into educating the six new members of the group but the rotation means that at some meetings the most experienced members have only been on the Advisory Group for two years. The Review Group was encouraged to consider how an appropriate balance could be maintained between the positive impact of new members and the importance of institutional memory and continuity. While there would be ways to introduce more flexibility into the lengths of term served, many of these approaches would make it difficult to maintain the Advisory Group's geographic and skills mix that is required by the PIP Framework.

¹ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), section 7.1.2(iii).

² Handling Genetic Sequence Data under the PIP Framework. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/advisory_group/gsd/en/, accessed 20 September 2016).

³ Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits: report of the Advisory Group, Report by the Director-General. In: World Health Organization [website]. Geneva: World Health Organization; 2011 (EB130/18; http://apps.who.int/gb/ebwha/pdf_files/EB130/B130_18-en.pdf?ua=1, accessed 22 September 2016), paragraph 2.

⁴ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), Annex 3, Advisory Group, Terms of Reference, section 3.1.

⁵ *Ibid.* Annex 3, Advisory Group, Terms of Reference, section 3.2.

The Advisory Group presents an Annual Report to the Director-General describing progress and challenges to the PIP Framework's implementation. The report covers seven areas:¹ necessary technical capacities of WHO GISRS; operational functioning of WHO GISRS; WHO GISRS influenza pandemic preparedness priorities, guidelines and best practices (e.g. vaccine stockpiles, capacity building); increasing and enhancing surveillance for A(H5N1) and other IVPP; the IVTM; the sharing of influenza viruses and access to vaccines and other benefits; use of financial and non-financial contributions. The first separate Partnership Contribution Annual Report was published in April 2015.²

Every two years the Director-General presents a Biennial Report to inform the World Health Assembly, through the WHO Executive Board, about the status and progress in five areas of PIP Framework activity:³ laboratory and surveillance capacity; global influenza vaccine production capacity; the status of agreements entered into with industry, including information on access to vaccines, antivirals and other pandemic material; the financial report on the use of the PC; the experience arising from the use of the definition of PIP BM. All Annual Reports and Biennial Reports are available on the PIP Framework website.⁴

The subjects to be covered by the Annual Reports and Biennial Reports are specified in the PIP Framework and do not currently map well onto each other (see Table 7.1);⁵ this creates considerable additional work for the PIP Framework Secretariat when preparing the documents.

The PIP Framework also sets funding limits for WHO's own PIP Framework implementation related costs. The PIP Framework Secretariat is funded through an amount not exceeding 10% of total PC funds⁶ and a maximum of up to 20% of PC work plan funds can be used for staff in the regions. As a result, resources and staffing are stretched in many areas at all three levels of WHO work (HQ, Regional Offices and Country Offices), including for administering virus sharing, PC implementation, and in the GIP team working with companies on the prequalification of vaccines. Some of this Review's Recommendations will require additional resources, for example to produce the studies that have been called for.

¹ *Ibid.* section 7.2.5.

² Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2014. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/161369/1/WHO_HSE_PED_GIP_PIP_2015.2_eng.pdf?ua=1&ua=1, accessed 22 September 2016).

³ Pandemic influenza preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization; 2011 (<http://www.who.int/influenza/pip/en/>, accessed 21 September 2016), section 7.4.1.

⁴ PIP Framework Advisory Group. PIP Framework Advisory Group Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/pip_meetings_consultations/en/, accessed 22 September 2016).

⁵ http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf?ua=1, accessed 22 September 2016), page 6. The sequences in this table are out of numeric and alphabetical order as they follow that of the source publications.

⁶ Pandemic Influenza Preparedness Framework, Partnership Contribution Implementation Plan 2013-2016. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/pip_pcimpplan_update_31jan2015.pdf?ua=1, accessed 22 September 2016), page 6.

Table 7.1: PIP Framework Reporting Requirements

	Director-General's Biannual Report (section 7.4.1)	Advisory Group Annual Report (section 7.2.5 and Annex 3, section 2.6)¹
Virus Sharing	(i) Laboratory and Surveillance capacity	(f) The sharing of influenza viruses and access to vaccines and other benefits (e) The IVTM (a) Necessary technical capacities of WHO GISRS (b) Operational functioning of WHO GISRS (c) WHO GISRS influenza pandemic preparedness priorities, guidelines and best practices (e.g. vaccine stockpiles, capacity building) (d) Increasing and enhancing surveillance for A(H5N1) and other influenza viruses with human pandemic potential
	(v) The experience arising from the use of the definition of PIP BM	
Benefit Sharing	(ii) Global influenza vaccine production capacity	(f) The sharing of influenza viruses and access to vaccines and other benefits
	(iii) Status of agreements entered into with industry including information on access to vaccines, antivirals and other pandemic material	
	(iv) Financial report on the use of the PC	(g) Use of financial and non-financial contributions

7.2 Oversight of GISRS

The PIP Framework (Annexes 4 and 5) sets out core and specific guiding principles for the terms of reference for the different types of GISRS laboratories – WHO CCs, WHO NICs, WHO H5RLs and WHO ERLs. These terms of reference cover general operational requirements as well as PIP-specific clauses. All GISRS laboratories are under a system of continuous review by GIP to assess whether they are meeting their terms of reference; for example, WHO CCs are reviewed every four years.

NICS are sovereign national facilities with responsibilities as members of GISRS and under the PIP Framework but there is no contractual relationship and no payments for specific aspects of their PIP Framework and seasonal influenza work. Oversight by WHO of this voluntary network, for instance of their use of the IVTM, is therefore limited. The timeliness of the NICs' sharing of viruses with WHO CCs is key to any assessment their performance. Such sharing underpins the six-monthly WHO consultations that analyse the GISRS influenza virus surveillance data and issues recommendations on the composition of the influenza vaccines for the following influenza season. Among their tasks, these meetings review the antigenic and genetic characteristics of seasonal viruses and viruses presenting a pandemic threat such as A(H7N9), A(H5), A(H9) and other subtypes or variant influenza viruses detected and analysed by GISRS laboratories. They also review the need for the

¹ Section 7.2.5 and Annex 3, section 2.6 of the PIP Framework provide the same text.

development of new CVVs for pandemic preparedness purposes.¹ There are also regular updates on influenza virus global surveillance that show surveillance activity by region and the number of times updates are posted,^{2,3} all of which provides monitoring of the NICs' performance.

The PIP Framework Secretariat meets the WHO CC and WHO ERL directors every February and September at the vaccine virus selection meetings and works closely with GISRS. However, GISRS laboratories have had only limited involvement in the development of the high level PC implementation plans for capacity building for laboratories and surveillance. GISRS representatives also expressed to the Review Group their wish to have greater and regular engagement with the Advisory Group, along the same lines as that arranged for industry and civil society. Some concerns were also expressed about the selection of experts for the technical working groups.

An objective of the PIP Framework is to strengthen GISRS, and since 2011 the geographical reach, scope and functioning of GISRS has expanded; however, the leadership of this network remains largely informal and the system is coordinated through the GIP. The lack of a formalized leadership structure from within GISRS has led to the absence of recognized representation for the entire GISRS network in PIP Framework operations.

Recommendations: Governance

27. The Director-General should consider options for retaining continuity and knowledge in the Advisory Group, including members being able to serve a second term of flexible duration.
28. The structure of the Advisory Group's Annual Reports to the Director-General and the Director-General's Biennial Reports to the World Health Assembly should be harmonized to simplify reporting.
29. The PIP Framework Secretariat and Advisory Group should broaden and deepen engagement with civil society to a greater number of participating organizations.
30. Noting the critical role of the WHO Collaborating Centres in the GISRS network, the Advisory Group should undertake more regular engagement with the WHO Collaborating Centres and other key GISRS laboratories, including when setting up technical working groups.

¹ WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for the Northern Hemisphere 2016-2017. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/vaccines/virus/recommendations/consultation201602/en/>, accessed 22 September 2016).

² For example, Influenza update – 272. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/, accessed 22 September 2016).

³ FluNet Summary. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/gisrs_laboratory/updates/summaryreport, accessed 22 September 2016).

31. The Director-General should address the issue of the lack of a formalized representation for the GISRS network, and encourage the WHO Global Influenza Programme and GISRS to establish such representation as soon as possible.

32. The Director-General should ensure that any internal reorganization of WHO departments under the new Health Emergencies Programmes should ensure that the activities of GISRS and the PIP Framework remain closely aligned and integrated with the WHO Global Influenza Programme to ensure stronger scientific and technical leadership in the implementation of the PIP Framework.

33. The Director-General should continue to make available the necessary human and financial resources to implement the growing activities of the PIP Framework and the Recommendations of this Review.

Chapter 8: Linkages with WHO programmes and other legal instruments

Maximizing the impact of the PIP Framework requires looking beyond the specific scope of the agreement to the complex legal and institutional environment in which it operates. Aspects of the PIP Framework's mandate overlap with those of other legal instruments and WHO programmes. Three in particular – the GAP,¹ the IHR (2005),² and the Nagoya Protocol to the Convention on Biological Diversity³ (“Nagoya Protocol”) – intersect with the PIP Framework's scope (see Table 8.1).

The risk of an influenza pandemic is also relevant for the several major global health security initiatives to understand how to equip the world more generally against future emergencies. One of the most high-profile is the Global Health Security Agenda (GHSA),⁴ an effort by countries, international organizations, and civil society to enhance the capacity of the world to prevent, detect, and rapidly respond to infectious disease threats. The GHSA has 11 Action Packages, some of which support pandemic preparedness, including on zoonotic disease, immunization, national laboratory systems, and real-time surveillance.⁵ The third UN Sustainable Development Goal (SDG) is to ensure healthy lives and promote well-being for all at all ages. Its targets include the access to safe, effective, quality and affordable antivirals and vaccines for all, support for the research and development of antivirals and vaccines, and to strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks.⁶

Table 8.1: Summary of linkages between the PIP Framework the IHR (2005), GAP and Nagoya Protocol

Topic	PIP Framework	IHR (2005)	GAP	Nagoya
Improve pandemic preparedness	✓	✓	✓	
Improve pandemic response	✓	✓	✓	

¹ Global Action Plan for Influenza Vaccines (GAP). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/en/, accessed 22 September 2016).

² International Health Regulations (2005), 2nd ed. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf, accessed 22 September 2016).

³ The Nagoya Protocol on Access and Benefit-sharing. In: Convention on Biological Diversity [website]. Montreal: Convention on Biological Diversity, United Nations; 2011 (<https://www.cbd.int/abs/>, accessed 22 September 2016).

⁴ Global Health – CDC and the Global Health Security Agenda. In: Centers for Disease Control and Prevention [website]. Atlanta, GA: Centers for Disease Control and Prevention; 2016 (<http://www.cdc.gov/globalhealth/security/index.htm>, accessed 21 September 2016).

⁵ Global Health Security Agenda: Action Packages. In: Centers for Disease Control and Prevention [website]. Atlanta, GA: Centers for Disease Control and Prevention; 2016 (<http://www.cdc.gov/globalhealth/security/actionpackages/default.htm>, accessed 21 September 2016).

⁶ Sustainable Development Goals. In: Sustainable Development Knowledge Platform, United Nations Department of Economic and Social Affairs [website]. New York: United Nations; 2016 (<https://sustainabledevelopment.un.org/?menu=1300>, accessed 21 September 2016).

Topic	PIP Framework	IHR (2005)	GAP	Nagoya
Sharing of biological materials, including viruses	Section 5.1.1 Annex 5 terms of reference for NICs, WHO CCs			✓
Sharing of public health information	Section 5.1.3 (ii) Annex 5	Article 6.2		
Regulatory capacity building	Section 6.7		✓	
Increase access to vaccine	Sections 6.9, 6.10, 6.11 Annex 2, SMTA2		✓	
Strengthen laboratory and surveillance Capacities	Section 6.6 Section 6.14.4	Annex 1		
Develop influenza vaccine production capacity	Section 6.13 Annex 2, SMTA2 Article 4.1 A5, A6		✓	
Technology transfer	Section 6.13, Annex 2, SMTA2 Article 4.1A5, A6		✓	
Access to products, technology and information & benefit sharing	✓		✓	✓

8.1 Global Action Plan for Influenza Vaccines¹

Key Findings

Finding 66: There are important synergies between the PIP Framework and the GAP programme.² They include the encouragement of technology transfers and capacity building for burden of disease studies, regulatory authorities and risk communications. However, technology transfer agreements are currently not being obtained.

Finding 67: The November 2016 review of the GAP will be available to feed into an assessment on what aspects of the GAP (burden of disease studies/ technical guidance to new vaccine manufacturers/vaccine deployment/ logistics), might be continued as part of the PC implementation under the PIP Framework, and where these needs exist.

Finding 68: The quantity of pandemic influenza vaccines secured by the PIP Framework, as well as global vaccine production capacity, including new vaccine capacity available through the GAP, currently remain insufficient to meet anticipated global demand at the time of an influenza pandemic.

¹ Global Action Plan for Influenza Vaccines (GAP). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/en/, accessed 22 September 2016).

² The GAP was developed by WHO together with public health and academic experts, vaccine manufacturers and funding agencies from developed and developing countries. The third and final GAP consultation will take place in November 2016.

Some aspects of the PIP Framework intersect with those of other WHO programmes. GAP, which was set up in 2006 and further refined in 2011. Its objectives were increasing influenza vaccine manufacturing capacity for developing countries, and focused on an increase in the manufacture and use of seasonal vaccine, an increase in vaccine production capacity for pandemic vaccine, and relevant research and development.^{1,2}

Since GAP's inception, WHO has invested approximately US\$ 50 million and countries and other bodies have contributed nearly US\$ 1 billion.³ GAP funds have been used to support 14 manufacturers.⁴ As a result, between 2007 and 2017, the capacity to produce approximate additional 600 million doses of pandemic influenza was made possible by the GAP.⁵ In several cases, partnership with large pharmaceutical companies has facilitated vaccine production. By 2018/19, GAP-supported companies are expected to have expanded pandemic influenza vaccine capacity by a total of up to one billion doses.

The GAP's ten-year mandate ends in November 2016, and the Review Group has considered how the work of the programme could continue to be supported after its closure, for example through burden of disease studies or the provision to GAP-supported countries of technical assistance on vaccine manufacturing, registration and distribution. Where GAP-targeted vaccine manufacturers are still in the process of establishing themselves, PC funds could be used to strengthen their progress towards achieving sustainable seasonal and pandemic vaccine production capacity, including through training programmes and expert consultants. Such a proposal would benefit from discussions with established manufacturers to build support and collaboration. The SMTA2 mechanism could also be leveraged to fund such training if there were flexibility over the SMTA2 options for some categories of participants, such as diagnostic companies and category C entities. Along these lines, the PIP Framework Secretariat is assessing the introduction of laboratory and surveillance training as an option that category C SMTA2 contributors could support in order to complement PC Preparedness investment.

Recommendation: Global Action Plan for Influenza Vaccines

34. The PIP Framework Advisory Group should consider lessons learned from the Global Action Plan for Influenza Vaccines, which closes in November 2016, to identify any aspects that would support implementation of the PIP Framework.

¹ Global Action Plan for Influenza Vaccines (GAP). In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/en/, accessed 21 September 2016).

² Global action plan for influenza vaccines, GAP projects: capacity enhancement and technology transfer in developing countries. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza_vaccines_plan/objectives/projects/en/, accessed 21 September 2016).

³ Grohmann G, Francis DP, Sokhey J, Robertson J. Challenges and successes for the grantees and the Technical Advisory Group of WHO's influenza vaccine technology transfer initiative. *Vaccine*. In press. doi: 10.1016/j.vaccine.2016.07.047.

⁴ *Ibid.*

⁵ *Ibid.*

8.2 International Health Regulations (2005)¹

Key Findings

Finding 69: PIP Framework PC funds may have collateral benefits in improving IHR (2005) core capacities, especially in the areas of laboratory and surveillance capacity. However, since PC funds only began to be distributed in 2014, data on the relationship between PC funds and IHR (2005) core capacities are not yet available. An analysis of PC funds' impact on IHR (2005) core capacities could be undertaken in the next review of the PIP Framework.

The IHR (2005) are a legally binding instrument by which Member States “prevent, protect against, control and provide a public health response to the international spread of disease”.² Among other provisions, they require countries to ensure core capacities, such as laboratory and surveillance capacity, to detect, prevent and respond to an outbreak.³ States Parties to the IHR (2005) are likely to consider a case of human influenza with a new subtype as a potential PHEIC, and to notify WHO and share public health information related to such an event. An influenza pandemic is likely to be a PHEIC, as the 2009 pandemic was.

While discussions of the linkages between the PIP Framework and the IHR (2005) often focus on the synergies between the two instruments, there are also important differences. The IHR (2005)'s provisions are only legally binding on States Parties,^{4,5} and not on industry or other stakeholders. WHO collaborates with industry and other players in the implementation of the IHR (2005), but these actors are not legally obliged to adhere to the IHR (2005).

The PIP Framework encourages the sharing of physical samples between countries, while the IHR (2005) do not. The PIP Framework explicitly sets up a balance between virus sharing and benefit sharing, to ensure that commercial interest is balanced with equity in access to public health. While the IHR (2005) has provisions to encourage the rapid and timely sharing of data and other information, it does not have the PIP Framework's specific benefit sharing provisions – in the IHR (2005), the sharing of information and data is also the benefit, since this allows Member States and organizations such as WHO to detect disease more rapidly, alert populations at risk and implement public health actions earlier.

There are points of synergy between the IHR (2005) and the PIP Framework. Both were created to strengthen global health security by preparing the world to be able to detect and respond to health emergencies. Although the PIP Framework is specific to pandemic

¹ Strengthening health security by implementing the International Health Regulations (2005), About IHR. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/ihr/en/>, accessed 24 September 2016).

² International Health Regulations (2005), 2nd ed. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/43883/1/9789241580410_eng.pdf, accessed 22 September 2016).

³ *Ibid.*, Annex 1.

⁴ States Parties are States that are legally bound by the provisions of the IHR (2005). As of October 2016, the regulations have 196 States Parties.

⁵ States Parties to the International Health Regulations (2005). In: World Health Organization [website]. WHO: Geneva; 2016 (http://www.who.int/ihr/legal/legal_issues/states_parties/en/, accessed 4 October 2016).

influenza, both instruments have a common goal of supporting low-resource countries in building capacity to detect disease.

Indeed, IHR (2005) core capacities informed the initial process in the selection of countries for PC implementation. The Gap Analyses,¹ undertaken in 2013 to determine the most critical gaps in capacity for pandemic influenza preparedness and response, used the IHR (2005) core capacity indicators as a starting point, particularly for laboratory and surveillance capacity, to identify countries to be targeted for PC implementation funds. For instance, the scoring methodology for a country's capacity for "detection" of novel viruses included IHR (2005) indicator 3.2.1, which measures "event-based surveillance".²

It is likely that implementation of the PIP Framework, through capacity building in countries, has had a positive impact in helping countries establish IHR (2005) core capacities. However, it is important to note that these benefits may be challenging to pin down since the PC implementation funds strengthen only influenza laboratory and surveillance capacity, whereas the IHR (2005) core capacities relate to surveillance and laboratory capacity for all emerging health threats.

Recommendation: International Health Regulations

35. Activity under the PIP Framework should be undertaken with the provisions of the International Health Regulations (2005) (IHR (2005)) in mind, and capacity building efforts should be aligned, supportive and complementary to those under the IHR (2005). This could be addressed by closer interaction at all three levels of WHO regarding implementation of the IHR (2005) and the PIP Framework to maximise synergies and efficiencies.

8.3 Nagoya Protocol to the Convention on Biological Diversity³

Finding 70: The PIP Framework is a multilateral access and benefit sharing instrument that appears to be consistent with the objectives of the Nagoya Protocol.

Finding 71: The intergovernmental negotiation of the PIP Framework established rules for access to IVPP and sharing of benefits; by contrast, the implementation of the Nagoya Protocol may introduce uncertainty in relation to the sharing of influenza viruses, since numerous bilateral transactions could be required to be negotiated, which could delay the access to viruses. The European Union (EU) has already recognized the PIP Framework as a specialized instrument with respect to pandemic influenza, although other countries that have created legislation to implement the Nagoya Protocol have not taken this step yet. As

¹ Pandemic Influenza Preparedness Framework Partnership Contribution 2013-2016: Gap Analyses. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/pip/pip_pc_ga.pdf, accessed 22 September 2016), page 11.

² Checklist and indicators for monitoring progress in the development of IHR Core Capacities in States Parties. Geneva: World Health Organization; 2013 (WHO/HSE/GCR/2013.2; http://apps.who.int/iris/bitstream/10665/84933/1/WHO_HSE_GCR_2013.2_eng.pdf, accessed 4 October 2016).

³ In January 2016, the WHO Executive Board requested the Director-General undertake a study on the public health implications of implementation of the Nagoya Protocol. The Review Group's Findings have benefited from updates and data from that process.

more countries put in place domestic legislation to implement the Nagoya Protocol, the urgency increases to resolve this uncertainty and reduce the risk to global health security.

Finding 72: The public health implications of the implementation of the Nagoya Protocol are not widely understood. While the WHO Secretariat is producing a report to clarify these implications, better knowledge, understanding and awareness of the Protocol is required in the public health sector.

Finding 73: The Nagoya Protocol does not expressly identify a mechanism to recognize an instrument under its Article 4(4). An authoritative, formal and internationally credible entity such as the Meeting of the Parties (MOP) or World Health Assembly could make the decision that the PIP Framework constitutes a specialized international instrument for pandemic influenza preparedness and response. This decision would facilitate fulfilment of the PIP Framework's access and benefit sharing objectives by ensuring that all countries would handle IVPP in the same way. IVPP access and sharing would be covered for Nagoya Protocol purposes by the PIP Framework, and therefore not require bilateral agreements on a case-by-case basis.

The Convention on Biological Diversity¹ is a treaty among 196 states parties,² with three main objectives: (1) conserving biological diversity, (2) ensuring that biological resources are used sustainably and (3) the “fair and equitable sharing of the benefits arising out of the utilization of genetic resources”. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity³ is designed to help implement the Convention on Biological Diversity's third objective. It requires states to create a legal and regulatory environment that ensure benefits of genetic resources are shared equitably among states (particularly with countries of origin) and within states (indigenous or local communities who supply knowledge).

In January 2016, the WHO Executive Board asked the WHO Secretariat to explore the public health implications of the implementation of the Nagoya Protocol. In response, the WHO Secretariat commissioned a study focused on the impact of the Nagoya Protocol in two areas: (1) pathogen sharing broadly, including GSD and (2) the PIP Framework and GISRS, including options for “improved harmonization between the Nagoya Protocol and PIP Framework, in the context of the ongoing PIP Framework 2016 Review”.⁴ The Nagoya Protocol's provisions overlap considerably with the access and benefit sharing system under the PIP Framework. Of particular interest is whether the PIP Framework is a specialized instrument under the Nagoya Protocol.

¹ Convention on Biological Diversity. In: Convention on Biological Diversity [website]. Montreal: Convention on Biological Diversity, United Nations; 2016 (<https://www.cbd.int/convention/>, accessed 22 September 2016).

² States Parties to the Convention on Biological Diversity are not automatically bound by the Nagoya Protocol, but must rather ratify that agreement separately. As of 4 October 2016, the Nagoya Protocol had 78 states parties.

³ The Nagoya Protocol on Access and Benefit-sharing. In: Convention on Biological Diversity [website]. Montreal: Convention on Biological Diversity, United Nations; 2011 (<https://www.cbd.int/abs/>, accessed 4 October 2016).

⁴ Terms of Reference, Production of a study on how the implementation of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity might affect the sharing of pathogens and the potential public health implications. Geneva: World Health Organization; 2016 (<http://www.who.int/entity/influenza/pip/2016-review/NagoyaStudyTORs.pdf>, accessed 22 September 2016).

The Nagoya Protocol requires a would-be user of a genetic resource to obtain “prior informed consent” (PIC) from the provider. This will typically require negotiation between each party to reach “mutually agreed terms” (MAT) for the sharing of benefits. Like the Nagoya Protocol, the PIP Framework creates an access and benefit sharing system, but narrowly tailored to influenza viruses with human pandemic potential. The Nagoya Protocol recognizes that such agreements may exist, carving out an exception:

Where a specialized international access and benefit-sharing instrument applies that is consistent with, and does not run counter to the objectives of the Convention and this Protocol, this Protocol does not apply for the Party or Parties to the specialized instrument in respect of the specific genetic resource covered by and for the purpose of the specialized instrument.¹

Were virus sharing within GISRS to be subjected to both Nagoya’s PIC and MAT obligations (which might require negotiating terms for each virus sample) as well as the requirements of the PIP Framework, it would risk duplication and substantially slow down the sharing of viruses within the GISRS network. For instance, the Review Group heard concerns that requiring vaccine manufacturers to negotiate PIC and MAT with each originating country for individual CVVs could increase the cost and complexity of vaccine development, slowing development and in some cases resulting in less useful end products. So far, no instrument has been officially declared a “specialized instrument” under Nagoya and it remains unclear whether designation of the PIP Framework as a “specialized instrument” is accomplished by the States Parties collectively, e.g. through the Conference of the Parties (COP) to the Convention on Biological Diversity MOP to the Nagoya Protocol, by individual states through their implementing legislation, or by some other mechanism. Thus far, the COP and MOP have taken no action in this regard. And while the EU, in its legislation implementing the Nagoya Protocol, has recognized the PIP Framework as a specialized instrument,² other States Parties have not yet done so.

For the time being, the Review Group heard from key informants that there is still a lack of awareness of the Nagoya Protocol and that this is becoming an issue in pathogen sharing. For example, EU countries are seeking to abide by the protocol but have run into difficulties when they send pathogens to recipient states that are not familiar with the requirements of the protocol.

Recommendation: Nagoya Protocol

36. The PIP Framework should be considered as a specialized international instrument to clarify the implementation of the Nagoya Protocol in relation to pandemic influenza preparedness and response:

¹ Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity. Montreal: Convention on Biological Diversity, United Nations; 2011 (<https://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf>, accessed 22 September 2016), Article 4, paragraph 4.

² Regulation (EU) No. 511/2014 of the European Parliament and of the Council of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union. In: Official Journal of the European Union. Strasbourg: European Parliament; 2014 (L 150/59; <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32014R0511&from=EN>), paragraph 16.

- The December 2016 Meeting of the Parties of the Nagoya Protocol provides an opportunity to consider recognizing the PIP Framework as a specialized international instrument for pandemic influenza preparedness and response. In the view of the Review Group, it would serve the aims of the PIP Framework if the Meeting of the Parties took up this opportunity.
- Further, the 2017 World Health Assembly should address the recognition of the PIP Framework as a specialized international instrument under the Nagoya Protocol.

Appendix I: REVIEW GROUP MEMBERS

Professor William Kwabena Ampofo

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Prof William Ampofo holds the position of Associate Professor and Head of the Virology Department of the Noguchi Memorial Institute for Medical Research (NMIMR) at the University of Ghana in Accra, Ghana.

Prof Ampofo has held research fellowships at the NMIMR and headed its Department of Electron Microscopy and Histopathology. His work has focused on molecular and serological investigations of viral infections and anti-viral interventions.

Prof Ampofo is a member of the Academic Board at the University of Ghana's College of Health Sciences and of the Ghana Field Epidemiology and Laboratory Training Program Steering Committee of the School of Public Health. He also participates in the National Steering Committee for the IHR (2005) at Ghana's Ministry of Health and in the Ministry's National Technical Coordinating Committee for Ebola Virus Disease. He is a member of Ghana's National Ebola Emergency Operations Center.

Prof Ampofo has been a temporary advisor and consultant to WHO, including in support of the Ebola virus disease response, and is a former member of WHO's SAGE Working Group on Influenza Vaccines and Immunization. He recently chaired WHO's PIP Framework Advisory Group. He is a member of the WHO GAP Advisory Group and served as an advisor to the WHO IHR Emergency Committee for Ebola virus disease.

Dr Christine Mwelwa Kaseba-Sata (Chair)

Former WHO Goodwill Ambassador against Gender-based Violence, Zambia

Dr Christine Mwelwa Kaseba-Sata, is a renowned Zambian specialist in obstetrics and gynaecology. She has practiced as a physician at the University Teaching Hospital in Lusaka for more than 25 years, and lectured for the past 15 years at the University of Zambia, School of Medicine.

Dr Kaseba-Sata has broad experience in the area of sexual and reproductive health, from sexually transmitted infections including HIV/AIDS, to family planning, comprehensive abortion care, and malaria in pregnancy, reproductive health cancers, emergency obstetrics and newborn care.

Dr Kaseba-Sata is a committed advocate for improving maternal and newborn health and addressing issues around gender-based violence, and was appointed WHO's Goodwill Ambassador against Gender-based Violence from October 2012 to October 2014.

Dr Frances McGrath

Chief Advisor, Office of the Chief Medical Officer, Ministry of Health, New Zealand

Dr McGrath is a specialist public health physician, currently serving as the Chief Advisor in the Office of the Chief Medical Officer in the Ministry of Health, New Zealand. In this capacity, Dr McGrath advises ministers and colleagues on public health strategy and issues and, as required, serves as a key advisor on emergencies such as infectious disease outbreaks, notably the 2009 influenza pandemic, and the health impacts of contaminated environmental sites.

Dr McGrath has post-graduate qualifications and comprehensive experience in public health, public policy and senior management in many different parts of the health sector, including as Acting Director of Public Health, senior health advisor to a number of Ministers of Health, and has represented New Zealand at a number of meetings of the World Health Assembly, and at Regional Committee Meetings of the Western Pacific Region of WHO. She has worked in developing countries including Central America, Thailand, and worked for a year in the Cook Islands Ministry of Health.

Dr McGrath previously worked as a General Practitioner in rural and high need areas in New Zealand.

Dr Talat Mokhtari-Azad

Director, Iranian National Influenza Center

Dr Mokhtari-Azad has a degree in Veterinary Medicine from Tehran University, a Master of Public Health (MPH) and Ph.D. degree in Virology (1982) from Tehran University of Medical Sciences, and specialization degree in Clinical Medical Laboratory Sciences (1991) from the Iran University of Medical Sciences.

Dr Mokhtari-Azad is Professor of Virology and head of the Virology Department in the School of Public Health, Tehran University of Medical Sciences. Since 1985, she has been the Director of the NIC and since 2006 the head of the National Measles/Rubella laboratory. She has wide-ranging experience in research and higher education and has supervised MSc and Ph.D. students in different virology fields especially in sero-epidemiology, isolation and molecular diagnostics. She is currently a member of the National Influenza Committee and National Vaccination Committee in Iran. She serves as a temporary advisor with WHO on influenza vaccine composition.

Ms Johanne Newstead

Head of Food Policy, Public Health Directorate, Department of Health, United Kingdom

Ms Newstead is a UK civil servant with broad experience in public health and internationally. She currently heads the food policy work in the Department of Health in London, leading the work with the food industry, in particular on reducing obesity.

Prior to that she spent six years on pandemic flu preparedness and health security for the UK, much of that on the global issues both in the EU, within the WHO European Region, and more widely with WHO and other global partners. She led the UK delegation throughout the

PIP Framework negotiations, and chaired the WHO European Region meeting in the later stages of negotiations.

Ms Newstead has also led the Department of Health biotechnology policy development for England. She has worked at the Organisation for Economic Co-operation and Development and for five years represented the UK interests there on health, science and technology.

Dr Theresa Tam (acting Chair)

Assistant Deputy Minister, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada

Dr Theresa Tam is the Deputy Chief Public Health Officer of the Public Health Agency of Canada (the “Agency”). In this role, she provides support to Canada’s Chief Public Health Officer in day-to-day activities and responding to public health issues of high importance to Canadians.

She is also the Assistant Deputy Minister responsible for the Infectious Diseases Prevention and Control Branch at the Agency. In this role Dr Tam oversees Agency activities aimed at making Canadians less vulnerable to impacts of infectious diseases. This includes surveillance, laboratory diagnostics, science research, policy development and national leadership for a wide range of infectious disease threats. Dr Tam has previously provided senior leadership on key Agency initiatives and programmes on immunization, respiratory infections, health emergency preparedness and response; public health at Canada’s borders and on public conveyances; laboratory biosecurity; public health workforce, surveillance and other infrastructure capacities; and implementation of the IHR (2005).

Dr Tam is a paediatric infectious disease specialist and field epidemiologist with extensive experience in the management of outbreaks and complex health emergency situations, including the SARS outbreak; A(H1N1) influenza pandemic; and Ebola virus disease outbreak in West Africa. She has served as an international expert on a number of WHO committees and international missions, including the first WHO Influenza Pandemic Task Force. She has also served as a WHO consultant on multiple international missions related to influenza and polio eradication in Bangladesh.

Dr Viroj Tangcharoensathien

Senior Advisor, International Health Policy Program, Ministry of Public Health, Thailand

Dr Viroj Tangcharoensathien is a senior expert in Health Economics at the Ministry of Public Health, Thailand, and advisor to its International Health Policy Program, where he also heads the research hub for the Asia Pacific Observatory. He supports the implementation of universal health coverage in a number of countries. Trained in medicine, he served for nine years in rural district hospitals in a poor province of Thailand and received the ‘Best Rural Doctor’ award in 1986 from the Thai Medical Association.

In 1990 he received a PhD in health planning and financing at the London School of Hygiene & Tropical Medicine. He won the Woodruff Medal in 1991 for his PhD thesis on community health financing and the Edwin Chadwick Medal in 2011 for his contributions to improve health systems in the interests of the poor. He has published 155 scientific articles.

Dr Tangcharoensathien chaired the negotiations of the WHO Global Code of Practice on the International Recruitment of Health Personnel, adopted by the Sixty-third World Health Assembly.

Prof Dr Makarim Wibisono

Chairman, Governing Board of Indonesia Council of World Affairs

Prof Makarim Wibisono is a former Indonesian Ambassador and Permanent Representative to the United Nations in New York and Geneva. He served as Director-General for Foreign Affairs Economic Relations (2000-2002), and Director for Multilateral Economic Cooperation (1993-1994) of the Indonesian Ministry of Foreign Affairs. As Director-General for Asia Pacific and Africa (2002-2004), he helped finalize the Bali Concord II which created the Association of Southeast Asian Nations (ASEAN). He led the Indonesian Delegation to the Senior Officials Meetings of ASEAN, ASEAN+3, ASEAN Regional Forum (ARF) and Asia-Pacific Economic Cooperation (APEC). He has been the UN Special Rapporteur on the Occupied Palestinian Territory Since 1967, and General Coordinator of EuroPalia Indonesia, Ministry of Education and Culture, Republic of Indonesia.

He is the Chairman of the Governing Board of the Indonesian Council on World Affairs, Advisor to the National Commission of Human Rights, and Senior Advisor on International Affairs to the Speaker of the House of Representatives of Indonesia.

Prior to his post as Executive Director at the ASEAN Foundation, Prof Wibisono was Senior Advisor on International Cooperation to the Minister of Health of Indonesia. He also served as President of the UN Economic and Social Council and the UN Conference on Trade and Development. In addition, Prof Wibisono has served as a member and advisor to various UN Task Forces.

Prof Wibisono is a lecturer at the National Defense Institute, Paramadina University, Atma Jaya Catholic University, the University of Al Azhar, Indonesia and Gadjah Mada University. Prof Wibisono holds a Master's degree in International Political Economy and a PhD in Political Science from Ohio State University, USA. He also has an M.A. in International Relations from Johns Hopkins University, USA.

Appendix II: DETAILED METHODS OF WORK

Appointment of the Review Committee

The PIP Framework Advisory Group met in Special Session, 13-14 October 2015, shortly before the Review Group was convened, to seek views from Member States, industry, civil society and other stakeholders on the terms of reference and direction of the Review. The Advisory Group Report from the Special Session provided advice and recommendations to the WHO Director-General on the conduct of the Review, including four guiding principles: independence and impartiality; transparency; engagement with Member States and stakeholders; and an iterative process.¹

In response, the Director-General convened the Review Group and appointed eight members to the Review Group. In line with the Advisory Group's recommendations,² members were selected to provide a skill mix of internationally recognized policy makers, public health experts and technical experts in the field of influenza, and included two former members of the Advisory Group. All six WHO regions were represented and there was a good gender balance. The Review Group members are listed in Appendix I.

The Review Group selected Dr Kaseba-Sata as Chair, and Dr Tam served as acting Chair for the August meeting onwards. The Review Group has been supported by a dedicated Review Group Secretariat at WHO.

Meetings

The Review Group held four meetings at WHO HQ in Geneva: 30 March–1 April 2016; 9–11 May 2016; 27 June–1 July 2016; and 29 August–2 September 2016. The Review Group also held two meetings via teleconference: 7 January 2016 and 19 February 2016. Reports of all these meeting were published on the WHO website.³ Multiple consultations took place among the Review Group and the Review Group Secretariat by means of email exchanges.

Representatives of Member States were invited to attend a debriefing and question session at WHO HQ in Geneva following the February 2016 teleconference and the March 2016, June 2016 and August 2016 Review Group meetings. These sessions were open to all stakeholders and the public via a live webcast on the WHO website.⁴

¹ PIP Framework Advisory Group. Special session of the Pandemic influenza preparedness (PIP) Framework Advisory Group, 13-14 October 2015, Geneva, Switzerland. Report to the Director-General. Geneva: World Health Organization; 2015 (http://www.who.int/influenza/pip/advisory_group/ag_spec_session_report.pdf, accessed 24 September 2016).

² *Ibid.*

³ PIP Framework Review Group. 2016 Review of the PIP Framework, PIP Review Group Meeting Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/pip/2016-review/meetings/en/>, accessed 20 September 2016).

⁴ *Ibid.*

On 30 March 2016 and 29 August 2016, as part of Review Group meetings, the Review Group held open consultations at WHO HQ, Geneva, with Member States, civil society and other stakeholders, and these open sessions were also webcast live on the WHO website.¹ Participants were invited to make statements, ask questions and submit written memoranda at each open session.

In addition, the Review Group Chair, Dr Kaseba-Sata, presented an update of the Review Group's work at the Sixty-ninth World Health Assembly on 25 May 2016, which was also available via a live web stream.²

Information gathering

The Review Committee interviewed and/or received written inputs from key informants including Member States and representatives of GISRS, industry, civil society, relevant databases and other stakeholders. Overall, the Review Group conducted 40 interviews with key informants and received several written submissions. These key informants are listed in the Acknowledgements.

The Review Group reviewed key documents and reports including PIP Framework Advisory Group meeting reports;³ the Advisory Group Annual Reports to the Director-General;⁴ the Director-General's Biennial Reports on the PIP Framework to the WHO Executive Board;⁵ the Partnership Contribution 2014 and 2015 Annual Reports;^{6,7} the October 2014 final report of the TEWG;⁸ the 2016 final report of the TWG;⁹ the draft 2016 WHO study on the impact of

¹ *Ibid.*

² Dr Christine Mwelwa Kaseba-Sata, Review Group Chair. Update of the Review Group's work at the Sixty-ninth World Health Assembly. Committee A, Wednesday 25 May 2016, Late Session. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/mediacentre/events/2016/wha69/webstreaming/en/>, accessed 29 September 2016).

³ PIP Framework Advisory Group. PIP Framework Advisory Group Reports. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/pip_meetings_consultations/en/, accessed 22 September 2016).

⁴ *Ibid.*

⁵ *Ibid.*

⁶ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2014. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/161369/1/WHO_HSE_PED_GIP_PIP_2015.2_eng.pdf?ua=1&ua=1, accessed 24 September 2016).

⁷ Pandemic Influenza Preparedness Framework, Partnership Contribution Annual Report 2015. Geneva: World Health Organization; 2016 (<http://apps.who.int/iris/bitstream/10665/246229/1/WHO-OHE-PED-2016.01-eng.pdf?ua=1>, accessed 24 September 2016).

⁸ 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?ua=1, accessed 19 October 2016).

⁹ PIP Framework Advisory Group, Technical Working Group (TWG) on the sharing of influenza genetic sequence data. Optimal Characteristics of and 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?ua=1, accessed 22 September 2016).

the Nagoya Protocol implementation on public health; and the Report of a 2015 WHO informal consultation on influenza vaccine response during the start of a pandemic.¹

The Review Group actively sought input from Member States and other stakeholders. To this end, the Permanent Missions to the UN Office in Geneva and other relevant organizations were contacted by email and invited to contribute their views on the PIP Framework. The WHO website for the Review also published specific Review Group questions separately for Member States and stakeholders, with a request for responses and views on any other aspects of the implementation of the PIP Framework.²

During its deliberations the Review Group interviewed the Director-General, programme directors, technical and other staff and representatives of WHO Regional Offices. The key WHO informants are listed in Acknowledgements. The Review Group members received technical briefings on various aspects of the PIP Framework including: (1) SMTA 2 negotiations, (2) GISRS and virus sharing, (3) PC collection and implementation, (4) GSD. While operating independently, the Review Group sought information and requested the development of written technical documents from the PIP Framework Secretariat and the Review Group Secretariat. The Review Group also asked for clarification of issues that arose during the information-gathering and report-writing periods. WHO staff provided written responses to questions posed by the Review Group and spoke informally and openly with Review Group members.

The WHO Secretariat provided an overview of the progress of the GAP, linkages between the GAP and the PIP Framework, and how the work of the GAP could be continued after the GAP ended.

Assessment and development of recommendations

The Review Group began its work by conducting a thorough analysis of the PIP Framework and its implementation milestones and challenges. Review Group members established three sub-groups to cover the questions outlined in the terms of reference as they related to: 1) Virus Sharing, including GSD; 2) Benefit Sharing; and 3) Governance and Linkages with other instruments. Each of the sub-groups developed relevant questions and identified key informants to be interviewed whose input might inform the Review and the subsequent development of practical and feasible recommendations.

The Review Group conducted a SWOT analysis of various aspects of PIP Framework implementation, including virus sharing and GSD, SMTA2s, PC collection and implementation, governance, and linkages with other instruments such as the Nagoya Protocol, the IHR (2005) and the GHSA. This analysis assisted in identifying factors that promoted or inhibited successful implementation of the PIP Framework, as well as desirable outcomes and draft recommendations. Following a strategic analysis of each draft recommendation, preliminary recommendations were developed and subsequently refined.

¹ Influenza vaccine response during the start of a pandemic: Report of a WHO informal consultation held in Geneva, Switzerland 29 June-1 July 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/207751/1/WHO_OHE_PED_GIP_2016.1_eng.pdf, accessed 19 September 2016).

² 2016 Review of the PIP Framework, Questions to Member States, Questions to Stakeholders. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (<http://www.who.int/influenza/pip/2016-review/en/>, accessed 19 October 2016).

The Review Group's Preliminary Findings were circulated to Member States and published on the WHO website for response, dated 19 August 2016.¹

Review of recommendations

The Review Group provided its final Report to the Director-General in November 2016 for transmission to the WHO Executive Board in January 2017 and the World Health Assembly in May 2017.

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¹ PIP Framework Review Group 2016, Preliminary Findings. In: World Health Organization [website]. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/pip/2016-review/pip_review_group_prelim_findings.pdf?ua=1, accessed 19 October 2016).