D8 | ACCESS AND BENEFIT SHARING: THE PANDEMIC INFLUENZA PREPAREDNESS FRAMEWORK

In 2011, the members of the World Health Organization (WHO) adopted a ground-breaking agreement, the Pandemic Influenza Preparedness Framework (PIP Framework), for the first time linking access to pathogens to fair and equitable sharing of benefits arising from their use.

The right of governments to fair and equitable benefit-sharing was established in 1992, with the adoption of the Convention on Biological Diversity (CBD).[1] This right follows from the CBD's recognition of a state's sovereign right over its natural resources and the recognition that access to and use of genetic resource is subject to prior informed consent and mutually agreed terms.[2] The Nagoya Protocol on Access and Benefit-Sharing, which entered into force in 2014 further elaborates on these elements.[3]

The PIP Framework, adopted by the World Health Assembly Resolution WHA64.5, builds on the legal principles of the CBD and recognizes the sovereign right of states over their biological resources. It also recognizes that the members of the WHO have a commitment to virus-sharing and benefit-sharing on an "equal footing", as they are "equally important parts of the collective action for global public health".[4] Accordingly, the framework sets out international rules governing the access to influenza viruses of pandemic potential (IVPP) and the benefit-sharing obligations of the recipients of IVPP.

Five years of implementation reveals the framework to be a 'success story' in equitable pandemic preparedness and a significant precedent to be followed in relation to the WHO's handling of other pathogens and related epidemics and pandemics (Shashikant 2017).

PIP Framework: theorigins[5]

World attention focused on access and benefit-sharing in early 2007 when Indonesia's minister of health, Siti Fadilah Supari, announced that Indonesia would suspend the sharing of viruses with the WHO Collaborating Centres (WHO CCs) as the then WHO flu virus-sharing scheme, the Global Influenza Surveillance Network (GISN), was 'unfair' (Khor and Shashikant, 2007a, 2007b).

The affected countries would send potentially pandemic avian flu virus samples to certain national laboratories designated as WHO CCs and located in developed countries.[6] These laboratories would characterize the virus, develop candidate vaccine strains and, in violation of the WHO guidelines, send viruses

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Image D8.1 Viruses shared by countries are used by industry to develop vaccines (https://pixnio.com/)

to the commercial sector for vaccine development, without the consent of the contributing country. Worse still, the vaccines developed by the private sector, using viruses obtained from the GISN, were unavailable and/or not affordable to developing countries (Shashikant, 2010).

Indonesia, severely affected by the highly pathogenic H5N1 virus, found that its viruses shared with WHO CCs were used for vaccine development without its permission, and the same vaccines were being offered to Indonesia by an Australian drug company for US$ 20 a dose. As the country might need to vaccinate its entire population of over 200 million should a pandemic occur, the cost at this price level would be astronomical (Khor and Shashikant, 2007b).

Patent claims were also filed over influenza virus and virus parts, that is, viral gene segments and their sequences, shared in good faith with the GISN by avian influenza-affected countries such as Indonesia, Vietnam, China and Thailand (Hammond, 2009, 2011).

Thus the GISN virus-sharing system had a clear set of winners: the vaccine companies that gained access to flu viruses and developed proprietary flu vaccines to be sold at high prices; developed countries that entered into advance purchase agreements with vaccine manufacturers for the supply and stockpile of (pre) pandemic vaccines; and national laboratories in those countries that gained access to flu vaccines and claimed scientific recognition and patents. On the other hand were the losers: especially, developing countries facing dangerous outbreaks, astronomical bills for the purchase of vaccines and other treatments, and even difficulty in accessing such supplies at all, due to their limited availability. Technologies and know-how used in vaccine development and production (largely based in developed countries) are also protected as intellectual property, potentially creating more obstacles for developing countries seeking to build their own production capacity.

It also soon became apparent that the GISN's operations were inconsistent with the principles and provisions of the CBD, which subjects the

access to and use of genetic resources to prior informed consent and fair and equitable benefit-sharing on mutually agreed terms with the country providing the resource.

All of these issues came to a head at the World Health Assembly in 2007 as a number of developing countries led by Indonesia expressed outrage at the inequities and indifference of the then WHO GISN to the needs of developing countries and the lack of adherence to the principles of the CBD and sought to overhaul the system. The 2007 assembly adopted Resolution 60.28 titled 'Pandemic Influenza Preparedness: sharing of influenza viruses and access to vaccines and other benefits', which for the first time linked the sharing of viruses to benefit-sharing and kicked off four years of often tense negotiations that eventually led to the adoption of the PIP Framework.

Achievements and challenges of the PIP Framework

The PIP Framework overhauled the WHO's influenza virus-sharing system and the basis on which potentially pandemic flu viruses are accessed. It replaced the GISN with the Global Influenza Surveillance and Response System (GISRS) and set out the terms of references (TOR) for GISRS laboratories. The WHO GISRS is an international network of influenza laboratories coordinated by the WHO, which comprises 143 National Influenza Centres (NIC), 6 WHO Collaborating Centres (WHO CCs), 13 WHO H5 Reference Laboratories (H5RL) and 4 Essential Regulatory Laboratories (ERLs).

The objective of the PIP Framework is "to improve pandemic influenza preparedness and response, and strengthen protection against pandemic influenza by improving and strengthening WHO GISRS, with the objective of a fair, transparent, equitable, efficient, effective system for, on an *equal footing* [emphasis added]: (i) the sharing of H5N1 and other influenza viruses with human pandemic potential; and (ii) access to vaccines and sharing of other benefits."

The scope of the framework is limited to the IVPP (influenza viruses of pandemic potential) and does not extend to seasonal influenza viruses or any other pathogens. The framework subjects all transfers of IVPP (also known as PIP biological material) among the WHO GISRS laboratories and with entities outside the GISRS system to the Standard Material Transfer Agreements (SMTAs) and commits all recipients of PIP biological material to benefit-sharing. The framework also puts in place a transparent traceability mechanism, the Influenza Virus Tracking Mechanism (IVTM), which tracks in real time the movement of PIP biological material into, within and out of the WHO GISRS (WHO, 2017b).

Under the PIP Framework, WHO member states "should in a rapid, systematic and timely manner" through their NICs, or other authorized laboratories, provide PIP biological materials from "all cases" of IVPP "as feasible" to the WHO CCs or H5RL laboratories of their choice. By provid-

ing PIP biological materials "Member States provide their consent for the onward transfer and use of PIP biological materials" to entities outside of the GISRS "subject to provisions in the Standard Material Transfer Agreements [SMTA)]".

It is noteworthy that the framework does not prevent a WHO member state from providing PIP biological material "directly to any other party or body on a bilateral basis provided that the same materials are provided on a priority basis" to the WHO CC or the H5RL.

All transfers of PIP biological material within the WHO GISRS (for example, from an NIC to a WHO CC) are subject to mutually agreed terms contained in SMTA1.[7] This requires, inter alia, the following: the compliance of the recipient with its respective TOR for GISRS laboratories; the recording of any shipments of PIP biological materials to entities inside and outside WHO GISRS, in the IVTM; the active involvement of scientists from the originating laboratories, especially those from developing countries, in scientific projects on clinical specimens or influenza viruses and their active engagement in the preparation of manuscripts for presentation, and the publication and acknowledgement of their contributions. SMTA1 also makes it clear that neither the provider nor the recipient should seek to obtain any intellectual property right on the materials.

Disputes between the provider and the recipient are to be resolved through amicable means, or, if that fails, the matter is to be referred to the director general of the WHO, who may seek the advice of the Advisory Group (established to guide the implementation of the framework), with a view of settling it. The framework further provides the director general with the authority to suspend or revoke the WHO designation of the relevant GISRS laboratory in the event of a serious breach of its TOR.

All transfers of PIP biological material by the WHO GISRS to entities outside of the GISRS network are also subject to legally binding, mutually agreed terms contained in SMTA2.[8] This material transfer agreement is a one-time agreement between the WHO and the entity outside of the GISRS network. SMTA2 lists the different benefit-sharing options for different types of recipients. Box D8.1 shows the different options for different categories of recipients.[9]

As at March 2017, the WHO had signed nine agreements with vaccine and antiviral manufacturers (Table D8.1) providing the WHOreal-time access to an estimated 400 million doses of pandemic vaccine during the next pandemic (WHO, 2017a). However none of the agreements commit the manufacturers to technology transfer, as is possible under A5 and A6 benefit-sharing options of the SMTA2.

Box 8.1 Benefit-sharing options

Category A: Manufacturers of vaccines and antivirals are to commit to at least two of the following options:

- A1. Donate at least 10 per cent of real-time pandemic vaccine production to the WHO.
- A2. Reserve for the WHO at least 10 per cent of real-time pandemic vaccine production at affordable prices.
- A3. Donate at least X treatment courses of needed antiviral medicine for the pandemic to the WHO.
- A4. Reserve at least X treatment courses of needed antiviral medicine for the pandemic at affordable prices.
- A5. Grant to manufacturers in developing countries licences on mutually agreed terms that should be fair and reasonable, including in respect of affordable royalties, taking into account the development levels, in the country of end use of the products, of technology, know-how, products and processes for which it holds IPR for the production of (i) influenza vaccines, (ii) adjuvants, (iii) antivirals and/or (iv) diagnostics.
- A6. Grant royalty-free licences to manufacturers in developing countries or grant to WHO royalty-free, non-exclusive licences on IPR, which can be sublicensed, for the production of pandemic influenza vaccines, adjuvants, antivirals products and diagnostics needed in a pandemic. The WHO may sublicense these licences to manufacturers in developing countries on appropriate terms and conditions and in accordance with sound public health principles.

Category B: Manufacturers of other products relevant to pandemic influenza preparedness and response shall commit to one of the following options: A5, A6, B1, B2, B3 and B4.

- B1. Donate to the WHO at least X2 diagnostic kits needed for pandemics.
- B2. Reserve for WHO at least X2 diagnostic kits needed for pandemics at affordable prices.
- B3. Support, in coordination with the WHO, the strengthening of influenza-specific laboratoryand surveillance capacity in developing countries
- B4. Support, in coordination with the WHO, the transfer of technology, know-how and/or processes for pandemic influenza preparedness and response in developing countries.

Category C: The recipient shall, in addition to the commitments selected under A or B above, consider contributing to the measures listed below, as appropriate:

- donations of vaccines
- donations of pre-pandemic vaccines
- donations of antivirals
- donations of medical devices
- donations of diagnostic kits
- affordable pricing
- transfer of technology and processes
- granting of sublicences to the WHO
- laboratory and surveillance capacity-building.

TABLE D8.1: Agreements with vaccine and antiviral manufacturers

Company	Benefit-sharing commitments of influenza vaccines and antiviral manufacturers under SMTA2			
	Donation of real-time pandemic vaccine to the WHO (%)	Reservation of real-time pandemic vaccine for supply at affordable prices (%)	Antiviral donation	Antiviral reservation
China National Biotech Group (CNBG)	8.0	2.0		
Glaxo Group Limited	7.5	2.0	2 million treatment courses	3 million treatment courses
Kitasato Daiichi Sankyo Vaccine Co., Ltd	8.0	2.0		
MedImmune LLC	9.0	1.0		
The Research Foundation for Microbial Diseases of Osaka University (BIKEN)	8.0	2.0		
Sanofi	7.5	7.5		
Seqirius, UK	10.0	2.5		
Serum Institute of India	8.0	2.0		
Sinovac Biotech Ltd	8.0	2.0		

Source: World Health Organization, 2017, Manufacturers of vaccines & antivirals, current status, http://www.who.int/influenza/pip/benefit_sharing/SMTA2_pieChart_A.pdf?ua=1

The WHO has also concluded 50 SMTA2s with academic and research institutions and received 22 benefit-sharing offers. Most of these institutions have offered to provide laboratory and surveillance capacity-building as a benefit contribution. The WHO has also signed a SMTA2 with a diagnostic company.

In addition to SMTA2 commitments, the framework requires influenza vaccine, diagnostic and pharmaceutical manufacturers "using the WHO GISRS" to make an "annual partnership contribution to the WHO". The sum of annual contributions is set at "50 per cent of the running costs of the WHO GISRS", with the understanding that costs may change over time and the partnership contribution will change accordingly. At the point of the framework's adoption, these running costs were estimated to be US$ 56.5 million.

Thus, companies that access the GISRS are collectively responsible for contributing US$ 28 million annually. How much each company pays is based on a formula agreed among the industry representatives (WHO, 2013). Table D8.2 shows that from the start of 2012 to 31 January 2017, the total partnership contribution collected from 47 contributors stood at US$ 117,758,149 (WHO, 2015b). The use of the partnership contribution is decided by the director general, based on the advice from the Advisory Group, following consultations with manufacturers and other stakeholders.

The first high-level implementation plan approved for the period 2013 to 2016 was based on the allocation of 70 per cent of the contribution for preparedness, that is, for activities in the following categories: (i) laboratory and surveillance capacity, (ii) burden of disease, (iii) regulatory capacity, (iv) risk communications and (v) planning for deployment (WHO, 2015a). Thirty per cent of the contribution has been reserved for response activities in the event of a pandemic.

A five-year review In 2016, following five years of implementation, an Expert Review of the PIP Framework concluded that the framework is a "bold and innovative tool for pandemic influenza preparedness", and "its implementation has led to greater confidence and predictability in the global capacity to respond to an influenza pandemic" (WHO, 2017c). Noteworthy is the review's conclusion that "the principle of the Framework of placing virus-sharing and benefit-sharing on an equal footing remains relevant today".

The review also identified several on-going and new challenges specifically in relation to the PIP Framework and its relevance to other pathogens shared within the WHO. A particularly urgent challenge is the relevance of the framework in view of rapid technological developments. Viruses may be generated in whole or in part from the genetic sequence data (GSD), supplanting the need for the transfer of biological material, including for production of vaccine strains (Dormitzer et al., 2013). This development has brought to the forefront the issue of how the GSD should be handled and the importance

TABLE D8.2: Contributions by companies accessing GISRS (in US$)

Contributors	Total contributions (US$)	Contributors	Total contributions (US$)
GlaxoSmithKline	30,110,587	Scientific Research Institute of Vaccines and Sera	59,812
F.Hoffmann-La Roche AG	26,707,341	Serum Institute of India	33,168
Sanofi Pasteur	22,057,029	Diasorin Molecular LLC	29,692
Novartis Vaccines and Diagnostics, Inc.	15,292,743	China National Biotec Group (CNBG)	20,000
MedImmune, LLC	5,160,754	VABIOTECH	10,300
Seqirus	3,779,042	Cadila Healthcare	10,261
BioCSL Pty. Ltd	2,667,715	Fast-track Diagnostics	8,136
Kaketsuken	2,580,379	Princeton BioMeditech Corporation	8,136
The Research Foundation for Microbial Diseases of Osaka University (BIKEN)	2,369,318	Cepheid	8,130
Denka Seiken Co., Ltd	1,754,659	The Government Pharmaceutical Organization (GPO)	8,130
Kitasato Daiichi Sankyo Vaccine Co., Ltd	1,347,821	Quidel Corporation	8,130
Green Cross Corporation	1,347,781	Takeda	8,113
Sinovac Biotech Ltd	409,323	Institute of Vaccines & Medical Biologicals (IVAC), Vietnam	5,437
Shangai Institute of Biological Products Co., Ltd	409,317	Response Biomedical	5,417
Becton, Dickinson and Company	296,432	Nanotherapeutics	5,337
Baxter International Inc.	209,205	NPO Petrovax Pharm	5,337
Changchun Insitute of Biological Products Co., Ltd	208,231	InDevR, Inc.	4,984
Fluart Innovative Vaccines Kft	160,077	Medicago	4,984
Beijing TiantanBiological Products Co., Ltd	149,518	Nanosphere	4,984
Omninvest Vaccine Manufacturing, Researching and Trading Ltd.	149,443	PT Bio Farma	4,984
Alere Inc.	117,153	Protein Sciences Corporation	4,944
Focus Diagnostics, Inc.	83,844	UMN PharmaInc.	2,799
Adimmune Corporation	65,543	Lanzhou Institute of Biological Products Co., Ltd	2,173
Qiagen	61,506	Total receipts	117,758,149

Source: World Health Organization, 2017, Partnership Contribution Implementation Portal, https://extranet.who.int/pip-pc-implementation/budget.aspx?year=2012

of treating it in a manner equivalent to viral isolates, with access to the PIP GSD contingent on acceptance of benefit-sharing and other obligations of the framework.[10]

On the latter subject, the review also concluded that the framework 'is a foundational model of reciprocity for global public health that could be applied to other pathogens'.

An access and benefit-sharing model for other pathogens

In 2003, following the outbreak of SARS coronavirus, a major controversy broke out. Teams of scientists in Canada, Hong Kong and the USA, brought together by the WHO to address the outbreak, filed patent applications on all or part of the SARS virus genome and on the virus itself, which were reported to be sufficiently broad to allow their holders to claim rights in most diagnostic tests, drugs or vaccines that had been or would be developed to cope with the outbreak (NBCNEWS. com 2003; Simon et al., 2005, pp. 707–10).

In 2014, another dispute erupted, this time over the Middle East respiratory syndrome (MERS) virus. It emerged that Erasmus University in the Netherlands had filed patent applications over the MERS virus, which was sent to the Netherlands without permission from the country of origin, Saudi Arabia (Hammond, 2014).

These controversies are symptomatic of the inequities and bias prevailing in global health governance. The 2007 avian flu controversy led to a multilateral access and benefit-sharing with equity at the core of the arrangement, with the WHO financially and otherwise resourced to facilitate pandemic preparedness at the national and international levels. However a similar benefit-sharing arrangement does not exist for seasonal influenza viruses (although annually 28,000 such viruses are shared with the GISRS network and relevant strains with vaccine manufacturers) and other pathogens shared in situations of emergencies.

Even in the devastating outbreak of Ebola, the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response found that a number of states parties expressed concern that data-sharing was not be balanced by benefit-sharing (WHO, 2016). The same committee has recommended that the WHO Secretariat and member states consider using the PIP Framework or similar existing agreements as a template for creating new agreements for other infectious agents that have caused, or may potentially cause, a Public Health Emergency of International Concern (PHEIC), based on the principle of balancing the sharing of samples and data with benefit- sharing on an equal footing (ibid.).

Following the Ebola outbreak, the WHO is engaged in developing a blueprint for research and development preparedness and rapid research response covering 11 pathogens, which are likely to cause public health emergencies. The WHO's documentation suggests that it is involved in ad hoc activities with multiple actors – such as the Wellcome Trust, Chatham House, Institut

Pasteur and the Coalition for Epidemic Preparedness Innovation (CEPI), which includes initiatives linked to biological samples, such as developing global norms for sharing data and results, the development of bio-banks and capacity building on material transfer agreement. However, absent from the various activities of the blueprint is a transparent process engaging all the WHO members in the establishment of clear, equitable rules governing the use of pathogens or related GSD, and especially establishing fair and equitable benefit-sharing consistent with the objectives and provisions of the CBD and the Nagoya Protocol.

The lack of international rules governing access to pathogens and fair and equitable benefit-sharing is a major deficiency and risks the re-occurrence of controversies as seen in SARS, MERS and avian flu, with the consequence of erosion of trust and the weakening of pandemic preparedness and response.

Notes

1 The CBD has 196 parties.

2 See the Preamble and Article 15 of the CBD (United Nations 1992).

3 For the text of the Nagoya Protocol, see Secretariat of the Convention on Biological Diversity (2011).

4 For the Preamble (paras 3, 11 and 14) as well as the objectives of the PIP Framework, see WHO (2011).

5 See Shashikant (2010).

6 From 2003 to April 2007, 291 confirmed human cases (including 172 deaths) of avian influenza A(H5N1) were reported to the WHO. The most affected countries were Vietnam (93 confirmed human cases and 42 deaths in 2003–2005), Indonesia (81 cases, 63 deaths in 2005–2007), Egypt (34 cases, 14 deaths in 2006–2007), Thailand (25 cases, 17 deaths in 2004–2006), China (24 cases, 15 deaths in 2005–2007), Turkey (12 cases, 4 deaths in 2006), Azerbaijan (8 cases, 5 deaths in 2006), Cambodia (7 deaths in 2005–2007), Iraq (3 cases, 2 deaths in 2006), Laos (2 deaths in 2007), Nigeria (1 death in 2007) and Djibouti (1 case in 2006).

7 See Annex 1 of the PIP Framework (WHO 2011).

8 See Annex 2 of the PIP Framework (ibid.)

9 See ibid.

10 It is noteworthy that the Expert Review has recommended that the definition of PIP biological material in the PIP Framework be amended to explicitly include the genetic sequence data. The Advisory Group set up to monitor implementation of the PIP Framework is investigating the handling of the GSD.

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