The Pandemic Influenza Preparedness Framework: a viable procurement option for developing states?

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Abstract
In this paper I argue that the Pandemic Influenza Preparedness (PIP) Framework is unlikely to have a significant impact on procurement of pandemic influenza vaccines by developing states during the next pandemic. I argue this on the basis that the vaccine stockpile that the Framework has created is not sufficiently large to meet the demand from developing states. I also argue that the fact that so few pandemic influenza vaccine manufacturers have committed to supply the PIP stockpile, and those that have, have given commitments lower than those initially proposed by the WHO in the Framework, implies that the overall impact the PIP stockpile will have on procurement of PIV is even lower than initially anticipated within the literature.

Keywords
Access to medicine; pandemic influenza; PIP Framework; transfer of technology
Introduction

Prior to the Pandemic Influenza Preparedness (PIP) Framework being enacted by the World Health Organisation (WHO) in 2011, a considerable amount of discussion on access to pandemic influenza vaccines had centred on the fact that samples of the virus used to produce a pandemic influenza vaccine (henceforward PIV) were likely to have been supplied by developing states, which then struggled to purchase the resulting vaccine. Indeed, a major impetus for the creation of the Framework was the 2005-H5N1 virus sharing incident, during which Indonesia departed from the established norm of sharing pandemic influenza samples with the WHO, claiming that the samples were the sovereign property of the State of Indonesia, and they were under no obligation to share them with the wider international community. The Indonesian Government cited an unfair lack of correlation between sharing samples and the benefits obtained in return as the primary reason for refusing to share samples. This argument certainly has merit: an influenza pandemic is characterised by large inequalities between developed and developing states. During the 2009-H1N1 pandemic, there were significant disparities in vaccination coverage between developed and developing states: developed states were able to procure more vaccine, and procure it earlier in the pandemic, than developing states. Since 2009-H1N1 global manufacturing capacity for pandemic influenza vaccines has increased from nearly 800 million doses per annum in 2009 to 6.372 billion doses in 2015 doses per annum at the most recent estimation in 2015. However, 75% of the global influenza manufacturing capacity is dedicated to meeting the needs of developed states in the ‘Northern Hemisphere’. It is therefore unlikely that any increase in manufacturing capacity will have a beneficial effect on pandemic preparedness in developing states, meaning that developing states will continue to be reliant upon donations from the WHO for access to pandemic influenza vaccine.

Through the PIP Framework the WHO sought to create a more formal method of procurement of vaccines for onward donation to developing states, in order to alleviate some of the problems highlighted by 2005-H5N1 and 2009-H1N1 respectively. The Framework provides obligations and recommendations in two areas: first, the timely sharing of influenza viral samples with human pandemic potential between member States of the WHO Global Influenza Surveillance and Response System (GISRS); and second, the sharing of viral sam-
ples with entities that operate outside of GISRS, such as pharmaceutical and vaccine manufacturers, in return for these external entities sharing benefits with the WHO and its members. The Framework aims to improve the procurement of PIV by developing states by creating a more structured approach to collection and distribution of donated PIV than the ad-hoc manner in which the WHO has collected and donated vaccines in previous pandemics. This is intended to ensure that the PIV donated by manufacturers is not just given on an ad-hoc basis after orders from fee-paying states have been fulfilled, or once self-procuring states have determined they have excess PIV to meet their needs, as was the case with donations during 2009-H1N1. Instead, donations of pandemic influenza vaccine may be included within the company obligations within Standard Material Transfer Agreements (SMTA) completed via the PIP Framework, which mandate that a proportion of the real-time PIV production is reserved for, and transferred to, the PIP stockpile, for onward donation to developing states.

The PIP Framework and vaccine procurement

The PIP Framework enables the WHO to manage a stockpile of approximately 150 million doses of PIV. This stockpile is created by requiring vaccine manufacturers who receive pandemic influenza virus samples from the WHO for vaccine development to contribute to the stockpile, via an SMTA. In the event of an influenza pandemic, the WHO will then distribute PIV from the stockpile. The Framework provides that

50 million doses of the stockpile will be for use in ‘affected countries, according to public health risk and need, to assist in containing the first outbreak or outbreaks of an emerging pandemic and 100 million for distribution…to developing countries that have no or inadequate access to...influenza vaccines, on a per capita basis that can be distributed to affected and at risk developing states during a pandemic.

The fact that a stockpile will already be established at the outset of the pandemic, with real-time commitments from manufactures in place to contribute to the stockpile, should eliminate the delay in pledges being fulfilled by donor agencies that were noted during the 2009-H1N1 outbreak. Of particular note is the fact that the obligation that PIV manufactures have to contribute vaccine to the PIP stockpile is to be fulfilled at the same time as manufacturers’ contractual commitments to self-procuring states, including those with Advance Purchase
Agreements in place. This means that those developing states procuring vaccine from the PIP stockpile will receive their vaccine in the same timeframe as self-procuring states, thereby ensuring that developing states can vaccinate members of their population earlier in the pandemic, which is crucial in reducing disease transmission, and preventing mortality and morbidity from a pandemic influenza virus. The Pandemic Influenza Preparedness Framework can rightly be described as a ‘milestone for global health’ based solely on the fact that it is the first international agreement that has sought to address inequalities in virus sharing by developing states, and procurement of medical technologies stemming from such viruses. However, closer scrutiny of the terms and conditions the WHO has managed to secure in SMTA negotiations makes the Framework appear less impressive.

Within the literature, The Framework has been hailed as an innovative mechanism for guaranteeing access to vaccines and affordable life-saving drugs during an influenza pandemic. A number of papers has considered the PIP Framework, and attempted to determine the impact the stockpile it creates will have on procurement of PIV in developing states. In summary, much of the literature expresses concern that the Framework is unable to make any real changes to vaccine allocation due to its inability to close the gap between developed and developing states where procurement of PIV is concerned and that the Framework lacks sufficient legal powers in order to instigate positive changes to the manner in which developing states procure PIV. These papers considered the benefit sharing provisions of the Standard Material Transfer Agreements, as they were presented in the Appendix of the PIP Framework, as at the time, no SMTAs had been concluded with PIV manufacturers.

The major development since these articles were written is the fact that three SMTAs have been concluded between the WHO and pandemic influenza vaccine manufacturers. The WHO concluded an SMTA with GlaxoSmithKline in December 2012, the Serum Institute of India in October 2013, and Sanofi Pasteur in February 2014. Each of these agreements outlines ‘Obligations of the Company’, and it is the content of these obligations which gives a clearer indication of the true practical impact the PIP stockpile will have on procurement of PIV during the next pandemic.

**PIP commitments**
All vaccine, diagnostic and pharmaceutical manufacturers that use the WHO-GISRS system (Use of GISRS’ is understood to include receipt of physical materials, or use of data and/or information, some of which may not be routinely provided to the general public) are under an obligation to make an annual partnership contribution to WHO contributing an amount equivalent to 50% of the operational costs of GISRS, which in 2014 amounted to $26.9 million. Whilst securing commitments regarding running costs for the WHO-GISRS is clearly beneficial for the WHO, the focus of this research are the provisions of the PIP Framework which will impact upon the procurement of pandemic influenza vaccines by developing states. To this end, pandemic influenza vaccine manufacturers who wish to receive PIP biological materials by way of a Standard Material Transfer Agreement with the WHO must commit to at least two of the following options

A1. Donate at least 10% of real time pandemic vaccine production to WHO.
A2. Reserve at least 10% of real time pandemic vaccine production at affordable prices to WHO.
A3. Donate at least X treatment courses of needed antiviral medicine for the pandemic to WHO. A4. Reserve at least X treatment courses of needed antiviral medicine for the pandemic at affordable prices.
A4. Reserve at least X treatment courses of needed antiviral medicine for the pandemic at affordable prices.
A5. Grant to manufacturers in developing countries licenses on mutually agreed terms that should be fair and reasonable including in respect of affordable royalties, taking into account development levels in the country of end use of the products, on 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 licenses to manufacturers in developing countries or grant to WHO royalty-free, non-exclusive licenses on IPR, which can be sublicensed, for the production of pandemic influenza vaccines, adjuvants, antivirals products and diagnostics needed in a pandemic. WHO may sublicense these licenses to manufacturers in developing countries on appropriate terms and conditions and in accordance with sound public health principles.
These benefit sharing provisions of the Framework have been met with a good deal of support in the literature, on the basis that they will ensure increased access to vaccines for developing states during an influenza pandemic. This support is given on the basis that paragraphs 4.1.A.1 and 4.1.A.2 appear to commit manufacturers to provide at least 10% of their real time production to the WHO. However, the above provision has an accompanying footnote ‘[r]ecognizing that flexibility is important in negotiating with all manufacturers, in a range of 5–20%.’ Despite the fact that the Chair of the PIP negotiations envisioned that SMTAs would be ‘standardised, universal and globally applicable to all transfers of PIP biological materials and not subject to further negotiation’, there does appear to be a significant amount of flexibility within the SMTA provided in the Framework. These flexible terms afford PIV manufacturers scope to negotiate terms regarding the donation of vaccines, antivirals, the granting of licenses, and transfer of technology. In addition, the relevant articles on liability and indemnities, warranties, duration and termination of contracts, governing law, and dispute resolution are not standardised within the Framework and remain simply ‘to be agreed by the parties’.

This is concerning for a number of reasons. Firstly, the fact that so many terms within the SMTA need to be agreed upon by the parties is likely to elongate the negotiation process; and given the fact that influenza pandemics are sporadic in nature, it is not entirely clear to what extent such a delay in the negotiations will impact on procurement from the stockpile during an influenza pandemic. Secondly, if it is not possible to reach a consensus on all the flexible terms, the negotiations will fail, and the SMTA will not enter into force, thereby leading to fewer vaccines being available for the PIP vaccine stockpile. Moreover, the fact that so much of the SMTA is flexible and subject to negotiation will likely provide the manufacturer with a stronger negotiating position than the WHO, as the manufacturer will be one of a very limited number of providers of a product that is in very high demand, and the WHO will be one of a number of potential consumers of such products.

On the point of such flexible terms included within the SMTA, and the fact that so much of the SMTA content remains to be negotiated between the parties, Wilke has expressed the view that having WHO lead on such negotiations may actually lead to a more equitable and effective outcome for developing states.
Unlike before the PIP Framework, when negotiations were conducted on a bilateral basis (often involving developing countries), it is the WHO that negotiates the final SMTA which introduce further checks and balances, thereby increasing the effectiveness, and more importantly, the equity.\textsuperscript{38}

The extent to which these compromises in the wording of the standardised SMTA, along with flexibilities in the donations of vaccines provisions in the PIP Framework, will have on procurement of PIV by developing states is explored more fully later in this paper. Prior to considering the content of the SMTAs that have been concluded between the WHO and PIV manufacturers, it is necessary to note the low take-up of these agreements amongst PIV manufacturers, as the number of manufacturers with an SMTA will clearly impact upon the effectiveness of the PIP stockpile as a procurement method for developing states.

\textit{SMTA uptake amongst manufactures}

In the most recent review of PIV manufacturing capacity, Partridge & Kieny (on behalf of the WHO) identified twenty-four manufacturers that are active in manufacturing pandemic influenza vaccines\textsuperscript{39}. In addition to this categorisation of influenza manufacturers, the WHO, when calculating partnership contributions for the running costs of GISRS, identifies those influenza vaccine, diagnostic and pharmaceutical manufacturers using the WHO GISRS, in order for them to contribute to the running costs.\textsuperscript{40} Of those manufacturers identified by Partridge & Kieny, eighteen also make partnership contributions to the WHO, on the basis that they use the WHO-GISRS\textsuperscript{41}. Yet, despite the fact that eighteen active PIV manufactures have been identified as having benefited from the work of GISRS, only three of these manufactures have an SMTA in place.

Prior to the implementation of the PIP Framework Kamradt-Scott & Lee expressed concern that requiring PIV manufacturers to make partnership contributions for the running costs of GISRS could have the unintended consequence of forcing vaccine manufacturers out of the market, and thereby reducing the overall global vaccine capacity

The imposition of what effectively equates to user fees for pharmaceutical companies that access GISRS data and samples, either through directly funding the network or via commitments to provide at least 10 per cent of vaccines and diagnostics at re-
duced prices, raises the possibility that some manufacturers will exit what has traditionally been a low-profit industry.42

Whilst it does not appear that manufacturers are actively leaving the market in order to avoid making contributions to GISRS as Kamradt-Scott & Lee feared, the fact that so few PIV manufacturers have concluded an SMTA appears to suggest that the majority believe they can continue PIV production whilst operating outside of the PIP Framework, and GISRS. Presumably this would be achieved by concluding bilateral agreements with states that have relevant viral samples in their territory, in a similar fashion to the Indonesia-Baxter agreement.43 Indeed, nothing within the PIP Framework prevents states from transferring viral samples to GISRS via an SMTA, and concluding a bilateral agreement with a PIV manufacturer that operates outside of GISRS. It has further been noted that ‘A few manufacturers are using genetic sequence data to make vaccines and other influenza related products44’, a trend that allows manufacturers to make use of data generated via the WHO-GISRS network45 but not require access to the viral samples. This would allow them to easily operate within the PIV market without being party to an SMTA. This trend is ‘anticipated to increase’ amongst PIV manufacturers, due to the anticipated increase in the use of generic sequence data in pandemic influenza research and development.46 Both of these factors are particularly concerning from a procurement of PIV perspective as manufacturers, by avoiding the need to conclude an SMTA in order to gain viral samples, also avoid any obligations to contribute to the stockpile that PIP manages, which will reduce as a direct consequence.

*SMTA commitments by manufacturers*

With regard to the PIV manufacturers that have concluded an SMTA, the WHO uses a formula based upon the average annual influenza product sales per manufacturer, for the three past years, plus the most recent pandemic year when determining contributions towards the running costs of GISRS.47 On this basis, Sanofi Pasteur and GSK are the two largest PIV manufacturers in the world by sales value48, and the Serum Institute of India is the tenth largest, out of the eighteen PIV manufacturers that contribute to GISRS. Had these three manufacturers committed to donate 10% of their production capacity to the stockpile, (as the standardised SMTA provided at Annex 2) based on the company’s most recent estimates of production capacity for pandemic influenza vaccines49, this would amount to donations to the stockpile of
63.4 million doses of PIV, which is under half the amount of vaccine that the Framework was meant to raise. Moreover, considering the fact that two-thirds of this amount is to be allocated to developing countries on a per capita basis, this pledge would have covered approximately 1.4% of affected developing state’s populations, if a one-dose regime would suffice.\(^5^0\) In the event of a two-dose regime being necessary, population coverage from PIP donations within developing states would have dropped to 0.7%.

However, despite the fact that the standardised SMTA provided at Annex 2 provides that manufacturers of vaccines in receipt of viral samples from WHO-GISRS should donate at least 10% of real time pandemic vaccine production to WHO\(^5^1\), those SMTAs that have been concluded have industry commitments which are lower than this 10%. GSK has committed to ‘donate 7.5% of real-time pandemic influenza vaccines to the WHO’ and ‘reserve 2.5%....at affordable price to WHO’\(^5^2\). Sanofi has committed to donate 7.5% to WHO, and reserve an additional 7.5% at affordable purchase for purchase by WHO, and the Serum institute of India has committed to donate 8% of real-time production, and reserve 2% for purchase by the WHO. As the below table demonstrates, this means that the three manufacturers have committed to donate just under 48 million doses to the stockpile, a 25% decrease on the commitments provided in the example SMTA in the Framework, and over 100 million doses fewer than the Framework was intended to manage. The WHO has the option to purchase an additional 28 million doses at ‘affordable prices’.

*Table 1. Comparison of Commitments provided in example SMTA, with those provided in the signed Agreements*

<table>
<thead>
<tr>
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<th>Example SMTA: Donations</th>
<th>SMTA Commitments: Donations</th>
<th>SMTA Commitments: Purchase</th>
</tr>
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<tbody>
<tr>
<td>Sanofi</td>
<td>25</td>
<td>18.75</td>
<td>18.75</td>
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<tr>
<td>GSK</td>
<td>34</td>
<td>25</td>
<td>8.35</td>
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<tr>
<td>Serum</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total (million)</td>
<td>64</td>
<td>47.75</td>
<td>28.1</td>
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Such reductions in the obligations placed upon manufacturers that have SMTAs with the WHO significantly reduces the vaccination coverage within developing states using the stockpile as a procurement method. Based on the current production capacity of those manufacturers with an SMTA, 0.8% of the population of developing states could be vaccinated from the PIP Stockpile, based on the donation commitments contained within the enforceable SMTAs. This represents a 24% reduction in vaccination coverage when compared with the example commitments provided within the PIP Framework SMTA. Vaccination coverage increases to 1.26% if WHO purchases all those vaccines which are reserved by the manufacturers for purchase by the WHO. These vaccination coverage figures assume that that a one-dose strategy will suffice. If a two-dose vaccination strategy is required, vaccination coverage levels will halve.

The suitability of procurement via donations (making use of the PIP Framework) as a viable procurement method for developing states has actually reduced since the use of the VDI during 2009-H1N1, due to the low number of doses secured on behalf of the PIP stockpile. The stockpile the WHO managed during 2009-H1N1 distributed 78 million doses to the ninety-seven developing states that lacked domestic vaccine production and lacked the ability to purchase vaccine on the commercial market\textsuperscript{53}, whereas the PIP stockpile has firm commitments to receive donations of 47.75 million donations, and the option to purchase an additional 28 million doses. However, not all of this stockpile is reserved specifically for developing states that are unable to procure PIV on the open market. If the WHO maintains the proportions at which it intended to distribute the donated vaccine with

One-third to ‘for use in affected countries, according to public health risk and need, to assist in containing the first outbreak or outbreaks of an emerging pandemic’, two-thirds to ‘developing countries that have no or inadequate access to H5N1 influenza vaccines, on a per capita basis, with use to be determined by those countries’.\textsuperscript{54}

Only 31.8 million of those doses will be available to be procured by developing states that have no or inadequate access.
The shortcomings of the PIP stockpile as a procurement method for developing states are more clearly demonstrated with reference to vaccination coverage within developing states. The current PIP stockpile has 46 million doses committed to it, giving coverage of 0.76% on a one-dose strategy, and 0.38% on a two-dose, which is well below the vaccination coverage the VDI donations managed during 2009-H1N1, and significantly below the target of 33% needed to establish herd immunity within a population. While the PIP Stockpile was not explicitly created with the 33% vaccination target in mind (nowhere in the drafting or the final text was a vaccination coverage target set) the herd immunity level of 33% a minimum vaccination coverage of at least 33% has been required in all pandemics in order to establish community immunity and slow down the rate of infection. In relation to this target, clearly, the commitments provided in the example SMTA do not make procurement from the PIP stockpile a particularly attractive procurement option for developing states, particularly if a developing state is seeking to procure sufficient vaccine in order to establish herd immunity levels within their territory.

When comparing procurement of PIV from the PIP stockpile, with the procurement of PIV from the Vaccine Deployment Initiative stockpile the WHO created during 2009-H1N1, it is clear that the one major benefit of the PIP stockpile is the removal of the time delay of donated vaccine being committed to the WHO. Despite this apparent benefit, concern has been expressed by the industry that during an influenza pandemic, member states with domestic PIV production within their territory would place restrictions upon exports of PIV that have been committed to the PIP stockpile, until domestic demand had been fulfilled. This concern appears to be well founded, many developing states procured less vaccine, and procured it later, than their developed neighbours during 2009-H1N1. One reason noted for this was that governments of developed states with domestic manufacturing capacity (that would have benefited from virus sharing by developing states) restricted exports to other territories until domestic demand had been fulfilled. As Fidler noted Canada awarded its vaccine contract to a Canadian company because it feared that foreign governments might restrict exports to Canada because of vaccine shortages within their territories. The Australian government made it clear to the Australian manufacturer CSL that it must fulfil the government’s domestic needs before exporting vaccine to the United States. The United States [stated that the US] would not do-
nate H1N1 vaccine as promised until all at risk Americans had access, because pro-
duction problems had created shortages in the United States.\textsuperscript{60}

While the WHO Director-General is seeking periodic assurances from Member States that they would enable companies to fulfil their SMTA commitments to supply pandemic vaccine to WHO on a real-time basis\textsuperscript{61} it is not yet apparent if these assurances will be given by Member States, or indeed, even if they are given, whether they will be honoured during a future pandemic. The Director-General appears keen to obtain such assurances as the problem of governments of developed states with domestic manufacturing capacity being able to prevent the export of PIVs to the WHO or developing states until domestic demand has been satisfied has not been resolved by the PIP Framework. Article 14 of the SMTAs signed with PIV manufacturers states that ‘no Party shall be liable for any delay in the performance of or failure to perform its obligations under this Agreement, where such a delay or failure is caused by Force Majeure’\textsuperscript{62} and the definition provided for ‘Force Majeure’ includes ‘….embargo or requisition’ and ‘acts of government’\textsuperscript{63}, meaning that the PIP Framework does not prevent the nationalisation of pandemic influenza vaccination manufacturing, or the embargo or requisition of vaccinations by states with domestic manufacturing in their territory. Such an embargo or requisition occurring could have a significant impact on the viability of the PIP Stockpile by reducing the number of vaccines the Stockpile has to distribute, or by causing a significant delay in the delivery of the vaccines to the Stockpile, and onward transfer to recipient states. This suggests that it is unlikely the PIP Framework will have, in practice, a significant positive impact on the procurement of PIVs by developing states, or indeed, that the Framework has done anything to change the status quo that exists between developed and developing states during an influenza pandemic.

The low uptake of SMTAs amongst PIV manufacturers, combined with the reduced commitments being given by PIV manufacturers in those SMTAs that have been concluded, make the PIP stockpile a particularly undesirable procurement method for developing states. Moreover, even when all of the vaccine that has been committed to the WHO via SMTAs has been delivered, it is likely that the WHO will need to seek donations from PIV manufacturers (outside of SMTA commitments) and developed states, in order to be able to fulfil the procurement needs of developing states, in much the same way they did during 2009-H1N1. This is a particularly undesirable scenario because, when making appeals for donated vaccine the
WHO will again have ‘little leverage to influence developed countries [and PIV manufacturers] other than rhetoric about equity, justice, and solidarity’\textsuperscript{64}. If the WHO must again make appeals to equity and justice in order to procure vaccine to donate to developing states, as appears likely, it will highlight the significant shortcomings in the PIP Framework, which was designed specifically to minimise such a scenario during a pandemic.

This section has demonstrated that direct procurement from the PIP stockpile is not a viable option for developing states seeking to increase their access to pandemic influenza vaccines. Whilst procurement from the PIP Stockpile does have one distinct benefit: if developing states were to procure vaccines from the PIP Stockpile, then these vaccine would be distributed within the same timeframe as developed states\textsuperscript{65}. Whilst this is a clear benefit over procurement of the VDI during 2009-H1N1, relying upon the PIP Stockpile will not allow developing states to procure sufficient levels of vaccine on behalf of their population. Indeed, on the point of vaccination levels, it would appear that procurement from the PIP Framework will lead to lower vaccination levels in developing states, than procurement from the VDI did, unless the WHO can procure significantly more vaccines for onward donation to developing states by making use of ‘rhetoric about equity, justice, and solidarity’ in order to request donations from developed states and influenza manufacturers.

In addition to creating a stockpile for direct procurement, the PIP Framework also attempts to increase transfer of technology from established PIV manufacturers in developed states, to new manufacturers in developing states. Transfer of technology, if properly managed, can also improve the procurement of pandemic influenza vaccines by developing states. Transfer of technology can create a situation whereby developing states are able to contract with pandemic influenza vaccine manufacturers based in their own territory (possibly by way of an Advance Purchase Agreement), as opposed to being reliant upon the established manufacturers based in developed states. This would allow developing states to have rapid access to pandemic influenza vaccines, and would eliminate the risk of developed states with pandemic influenza vaccine manufacturers based in their territory restricting exports of vaccines until domestic demand has been fulfilled during a pandemic.

**Transfer of technology and vaccine procurement**
The importance of developing states having some degree of self-sufficiency in pandemic influenza vaccine procurement, by contracting with pandemic influenza vaccine manufacturers based in their own territory, as opposed to being reliant upon the established manufacturers based in developed states, was highlighted in a paper by Friede et al, in which they noted that

In 2006, 90% of influenza vaccine production was located in nine countries (largely in Europe and North America) that represented only 10% of the global population. Other countries, notably those in Africa, the Middle East and Asia, could witness a staggering death toll and a severe strain on their health services while waiting for producing countries and regions to have vaccinated their own populations.  

While pandemic influenza vaccine manufacturing capacity has increased since 2006, the proportions by which this capacity is divided between developing and developed states has remained largely the same, with capacity in developing states still being significantly lower than that which is required in order to adequately immunise the populations of developing states. Therefore there is a clear need for developing states, either standing alone or as part of regional groups, to move towards self-sufficient procurement of pandemic influenza vaccines. In order to do so, manufacturers based in developing states require access to specific technical knowledge that cannot be inferred from the patent, and is not available in the public domain, in order to manufacture a pandemic influenza vaccine. In the case of pandemic influenza vaccines, it has been noted that

[t]he technical know-how – even of conventional egg-derived influenza vaccines – is not readily found outside existing influenza vaccine production plants. Thus, even for procedures for which there are no patents, securing working partnerships with technology holders may be necessary.

Without access to such technical knowledge, developing states, or manufacturers in developing states, are unable to manufacture their own PIV as a method of procurement. Transfer of technology leading to increased self-procurement from domestic manufacturers is arguably the most effective manner by which developing states can sustainably and effectively procure sufficient doses of pandemic influenza vaccines, in an appropriate timeframe, during a pandemic. To this end, at a policy level, the World Health Organisation has often encouraged
transfer of technology from established manufacturers of pandemic influenza vaccines to new manufacturers in developing states, in order to improve pandemic preparedness within developing states. In the wake of growing concerns over the H5N1 strain of pandemic influenza in late 2005, the World Health Assembly passed Resolution WHA58.5, which focused upon strengthening pandemic influenza preparedness and response. Resolution WHA58.5 required the Director-General to

continue to develop WHO's plans and capacity to respond to an influenza pandemic, to be able to provide technical support, capacity building and technology transfer related to H5N1 influenza vaccines and diagnostics to developing countries.

While not specifically related to pandemic influenza vaccines, the next major policy development at the WHO regarding transfer of technology in order to improve access to and the procurement of medicines was the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) in 2008. The GSPA-PHI was ‘designed to promote innovation, build capacity [and] improve access to medicines’, and aimed to ‘promote new thinking on innovation and access to medicine’, as well as ‘provide a medium term framework for securing an enhanced and sustainable basis for needs driven essential health research and development relevant to diseases which disproportionally affect developing countries’.

GSPA-PHI aimed to promote transfer of technology and the production of health products in developing countries by

(a) exploring ‘possible new mechanisms and make better use of existing mechanisms to facilitate transfer of technology and technical support to build and improve innovative capacity for health-related research and development, particularly in developing countries’;
(b) promoting ‘transfer of technology and production of health products in developing countries through investment and capacity building’; and
(c) promoting ‘transfer of technology and production of health products in developing countries through identification of best practices, and investment and capacity building provided by developed and developing countries where appropriate.’
In relation to pandemic influenza vaccines, this policy of promoting transfer of technology to developing state manufacturers was largely facilitated though the WHO Influenza Vaccine Technology Transfer Initiative, a collaborative project between the WHO, some developed states and PIV manufactures. The Influenza Vaccine Technology Transfer Initiative aimed to create regionally based, independent, and sustainable pandemic influenza vaccine production capacity in developing countries, through financial support and technology transfer to manufacturers in developing states. Transfer of technology through the Influenza Vaccine Technology Transfer Initiative was facilitated through the creation of a ‘hub’ for the transfer of influenza vaccine technology. The Hub is a platform for transferring a complete manufacturing process at ‘pilot scale’ to a new manufacturer in a developing state by granting a non-exclusive license for use of the technology, along with providing information and training on using the technology, along with relevant safety and efficacy data, which allows the recipient to make use of a shortened regulatory pathway for licensing the PIV.

The WHO Hub was launched in 2007 and, to date, vaccine manufacturers in seventeen developing states have received financial grants, and technical knowledge and understanding from the hub, which has enabled them to produce pandemic influenza vaccine. Despite this success, it is reported that the WHO are concerned that ‘there is a great lack of interested technology providers’ wishing to contribute to the Hub; meaning that the Hub is limited in the amount, or level, of technology available to it to be transferred. The role of the technology provider is obviously key to the success of the hub model, as the ‘model can only be used with vaccines for which no intellectual property barriers exist in both the country hosting the hub and the country receiving the technology’. Therefore the active engagement of the technology holder to grant a license that effectively removes these barriers in host and reciprocal states, as well as providing the technology and know-how, is key to the success of the hub model. The result of this lack of interest from technology providers to provide new and updated technology to the hub is that recipient manufacturers are unlikely to benefit from any of the scientific advances which occur in the field of pandemic influenza vaccines. The impact of this is that the pandemic influenza vaccines produced by recipient manufactures will not be as effective, or produced in as efficient a manner, as the vaccine produced by established manufacturers in developed states.
Transfer of technology provisions and the PIP Framework

One of the most notable omissions from the SMTAs that have been signed with PIV manufacturers is that none of the agreements currently in place has secured any commitments from manufacturers regarding transfer of technology. This is despite the fact that during the negotiations of the PIP Framework, the importance of transfer of technology for pandemic preparedness and procurement was stressed in the reports of the Advisory Group on Pandemic influenza at the WHO and the WHO Director-General, which were integral to the development of the Framework. The Director-General noted that: ‘Preparedness requires long-term investment, particularly when capacity building requires training and transfer of knowledge’ whereas the Group stressed the need to achieve the greatest impact by building capacity in states where it is lowest and observed that preparedness requires long-term investment, particularly when capacity building requires training and transfer of knowledge.

Facilitating the transfer of technology from established PIV manufacturers to manufacturers in developing states is one of the clear aims of the PIP Framework. Paragraph 6.0.2(iv) states that ‘the PIP Benefit Sharing System will operate to: build capacity in receiving countries over time for and through technical assistance and transfer of technology, skills and know-how and expanded influenza vaccine production, tailored to their public health risk and needs’. Further detail on the WHO’s vision for transfer of technology via PIP is provided at 4.6.1-4.6.2, which states that

The Director-General will continue to work closely with Member States and influenza vaccine manufacturers to implement the WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply, including its strategies to build new production facilities in developing and/or industrialized countries and through transfer of technology, skills and know-how.

Member States should urge influenza vaccine, diagnostic and pharmaceutical manufacturers to make specific efforts to transfer these technologies to other countries, particularly developing countries, as appropriate.

Influenza vaccine manufacturers who receive PIP biological materials may grant, subject to any existing licensing restrictions, on mutually agreed terms, a non-exclusive, royalty-free license to any influenza vaccine manufacturer from a developing country, to use its intellectual property and other protected substances, products, technology,
It is clear that the WHO views increasing transfer of technology as an integral part of the plan to increase access to pandemic influenza vaccines and reduce the inequality between developing and developed states on this issue, therefore it is necessary to determine to what extent transfer of technology provisions have been incorporated into the PIP Framework. This is particularly relevant as the PIP Framework has been hailed as a ‘landmark in global governance for health, representing the first international agreement on influenza virus and benefit sharing’\textsuperscript{84}, it represents an ideal opportunity to increase transfer of technology to developing states manufacturers. However, despite the clear impetus within the WHO, both at a policy level, and in the development of the PIP Framework, the resulting obligations which were placed upon manufacturers in regard to transfer of technology via the PIP Framework appear particularly weak.

Within the ‘Obligations of the Company’ in the standardised SMTA provided in the Annex of the PIP Framework, the transfer of technology related provisions state that manufacturers of vaccines and/or antivirals can commit to

A5. Grant to manufacturers in developing countries licenses on mutually agreed terms that should be fair and reasonable including in respect of affordable royalties, taking into account development levels in the country of end use of the products, on 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\textsuperscript{85}

and/or:

A6. Grant royalty-free licenses to manufacturers in developing countries or grant to WHO royalty-free, non-exclusive licenses on IPR, which can be sublicensed, for the production of pandemic influenza vaccines, adjuvants, antivirals products and diagnostics needed in a pandemic. WHO may sublicense these licenses to manufacturers
in developing countries on appropriate terms and conditions and in accordance with sound public health principles.  

It seems bizarre that the WHO at a policy level, and within the aims of the PIP Framework, stressed the importance of transfer of technology for pandemic preparedness and procurement, and yet the relevant provisions addressing transfer of technology within the SMTA are so weak. There is a number of elements concerned with transfer of technology within these SMTA that are particularly concerning. Firstly, it seems unusual that, in creating the Framework, the WHO have chosen not to expressly link together the work of the WHO Influenza Vaccine Hub, and the PIP Framework. While Paragraph A.6 does provide the technology holder with the option to grant royalty-free, non-exclusive licenses on intellectual property rights to the WHO, who can then sublicensed these rights to manufacturers in developing states, it makes no reference to the transfer of technical knowhow required to work the invention covered by these intellectual property rights also being transferred to the WHO. This is concerning because it is not merely the intellectual property rights which pose a significant barrier to developing states being able to establish pandemic influenza vaccine manufacturing in their territory. While intellectual property rights can be a barrier to manufacturers in developing states establishing manufacturing capacity, it is the lack of technical knowhow amongst prospective manufacturers in developing states that has clearly been identified as the barrier to self-sufficient procurement of pandemic influenza vaccines by developing states.

Instead, PIV manufacturers that choose to engage with transfer of technology as part of their ‘Company Obligations’ are compelled only to transfer technology to a non-specific number of manufacturers in developing states, meaning the knowledge will only be transferred to a limited number of entities, at the technology holder’s discretion. Technology transfer which occurs on a bilateral basis between an established manufacturer acting as donor to a new manufacturer in a developing state has been noted as being ‘not readily feasible in cases where there is limited financial benefit for donor’ in the context of pandemic influenza vaccines. Therefore it is particularly concerning that this is the only transfer of technology option which is available as an ‘Obligation of the Company’ within an SMTA. Transfer of technology via the PIP Framework could have had significantly greater impact if the technology holder were compelled to transfer their knowledge to the WHO Influenza Vaccine Hub, along with the right for the hub to transfer this knowledge on again, to multiple relevant manufac-
urers in developing states. This would ensure maximum distribution of relevant technical knowledge, which in turn would help build pandemic preparedness by increasing vaccine manufacturing capacity in developing states.

In addition to the above, the wording in each of the transfer of technology provisions in the SMTA provisions is too vague. As noted above, if transfer of technology is to occur on a bilateral basis from one manufacturer to another, this will only occur when it is financially viable for the donor. The wording of paragraph A.5 specifies neither the number of recipient manufacturers, nor the number of recipient developing states that are to receive transferred technology in order to comply with the obligation. This is seemingly left to the PIV manufacturer transferring the technology to decide. Moreover, the wording ‘terms that should be fair and reasonable’ is again particularly subjective, with both ‘fair’ and ‘reasonable’ not being defined within the Framework, again, leaving it open to the interpretation of donor manufacturers. The vague wording of the transfer of technology related provisions within the SMTAs, particularly in relation to key terms, will inevitably lead to inconsistencies in the amount of technology transfer that will occur, and the terms of the transfer. This may lead to donor manufacturers determining that ‘fair’ and ‘reasonable’ has a particularly low threshold, and therefore, they are only obligation to undertake minimal transfer in order to meet this requirement. Whilst it may be the case that some particularly benevolent manufacturer will transfer more technology than is deemed ‘fair’ or ‘reasonable’ to a state, this will lead to an inequitable situation whereby some developing states have benefited significantly more than other recipient states.

Transfer of technology from an established pandemic influenza vaccine manufacturer to a new manufacturer in a developing states has been encouraged by the WHO through its policy initiatives, on the basis that it is not patents but access to knowledge that constitutes the most significant barrier for new manufacturers to begin pandemic influenza vaccine production. To this end, the WHO has seen some limited success in transferring technology related to the pandemic influenza vaccine manufacturing process from established manufacturers, to new ones. Despite this, and the fact that the PIP Framework represented a major opportunity for the WHO to strengthen the transfer of technology, it is clear that the WHO missed this opportunity.
None of the pandemic influenza vaccine manufacturers that have an SMTA in force has committed to transfer technology to the WHO as part of its company obligations. However, even if any manufacturer had committed to this, the transfer of technology related provisions contained within the Framework are too weak to have any real positive impact on the manner in which developing states can establish PIV manufacturing capacity within their territory, in order to achieve the sufficient access which is. This is a key failing of the Framework, as it is this ability to establish manufacturing capacity which looks to be the most suitable method to provide developing states with a sustainable and effective method of pandemic influenza vaccine procurement. Transfer of technology, along with the removal of intellectual property related barriers to production, is key to this being possible.

Conclusion

While the relevant academic literature has praised the PIP Framework as being an innovative model mechanism for guaranteeing access to vaccines and affordable life-saving drugs, this paper has argued that such praise appears to be misplaced. Indeed, while, the PIP Framework does provide one clear benefit to developing states that procure from it, in that those states that procure vaccine from the PIP Framework procure them in the same timeframe as self-procuring developed states. However, it is clear that the Framework is not appropriate tool by which developing states could procure enough vaccines to meet their public health needs.

Three predominant reasons for this can be identified. In the first instance, the provisions within the example Standard Material Transfer Agreement provided at the annex to the PIP Framework fail to maximise benefit sharing for developing states, largely due to the overly flexible benefit sharing obligations secured in the PIP Framework, and the lack of legal compulsion that requires relevant PIV manufacturers to commit to benefit sharing via a Standard Material Transfer Agreement. Secondly, the prospect of developing states using the PIP Stockpile as a procurement tool becomes even less viable when the SMTAs that pandemic influenza vaccine manufacturers have signed are taken into consideration. Too few of the pandemic influenza vaccine manufacturers currently active within the market have committed to share benefits with the WHO via an SMTA, with only 17% of manufacturers currently party to an SMTA. This clearly impacts undesirably on the number of doses which the PIP Stockpile has available to it for distribution to developing states that have been unable to pro-
cure vaccine via self-procurement methods. Thirdly, the viability of the PIP Stockpile as a procurement method is further reduced when the terms which have been secured with the three manufacturers that are party to a SMTA are evaluated.

Whilst the PIP Framework already contains provisions intended to improve transfer of technology from technology holders to developing states wishing to be in receipt of said technology, via SMTA2 Agreements, there is little incentive for technology holders to engage with SMTA2 generally, and even less incentive to engage with the specific transfer of technology provisions within the SMTAs. In respect of future reforms, it would be beneficial if the WHO tailored the PIP Framework, and the resulting SMTAs to facilitate transfer of technology and knowhow from vaccine manufacturers, to developing states, in order for developing states to become self-sufficient in their procurement of pandemic influenza vaccines. That is, to manufacture (either alone or in regional groups) sufficient levels of pandemic influenza vaccines in order to achieve herd immunity, without being reliant upon procurement from established pandemic influenza vaccine manufacturers in developed states, or receiving donations from the WHO - as these are demonstrably not viable options for developing states.


2 Since its inception the WHO has played a major role in the management of pandemic influenza outbreaks, even going as far as to procure vaccines, and distribute them to developing states that lack access during a pandemic, though this has been done on a largely ad-hoc basis. WHO, 'Main operational lessons learnt from the WHO pandemic influenza A(H1N1) vaccine deployment initiative' (2011) <http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiative_moll.pdf>; (accessed 14 June 2016);


4 Rachel Irwin, 'Indonesia, H5N1, and Global Health Diplomacy’ (2010) 3 Global Health Governance

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7 Jeffrey Partridge and Marie Paule Kieny, ‘Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets’ (2010) 28(30) Vaccine 4709


9 McLean, ‘2015 global production capacity’

10 It was subsequently acknowledged by the WHO Intergovernmental Meeting on Pandemic Influenza Preparedness that the pre-PIP system did not deliver fairness, transparency or equity to developing states, and disproportionately benefited developed states with their own vaccine manufacturing base, by allowing easy access to viral samples with which to develop a vaccine with no clear obligations to share the benefits - WHO, ‘Interim statement of the intergovernmental meeting on pandemic influenza preparedness: Sharing of influenza viruses and access to vaccine and other benefits’ (WHO) <http://apps.who.int/gb/pip/pdf_files/IGM_PIP-IntStatement-en.pdf>

11 ‘GISRS means the international network of influenza laboratories, coordinated by WHO, that conduct year-round surveillance of influenza, assessing the risk of pandemic influenza and assisting in preparedness measures. The WHO GISRS comprises National Influenza Centres, WHO Collaborating Centres on Influenza, WHO H5 Reference Laboratories and Essential Regulatory Laboratories’ – definition provided at 4.3, WHO, Pandemic Influenza Preparedness Framework For The Sharing Of Influenza Viruses And Access To Vaccines And Other Benefits (2011)

12 Article 1(9), PIP Framework these benefits, are considered in more detail later in this paper


14 Turner, ‘Vaccine’

15 Standard Material Transfer Agreements is the method by which the WHO enters into agreements with entities outside the WHO GISRS, such as pharmaceutical companies that manufacture pandemic influenza related products such as vaccines or antivirals. SMTA2’s have provisions related to benefit sharing included within them.

16 See for example the example SMTA2 provided at: Annex 2, SMTA2, Article 4.4.1.A, PIP Framework

17 6.9.2, PIP Framework

18 Turner, ‘Vaccine’

19 For more information on Advance Purchase Agreements, and the impact they have on procurement of pandemic influenza vaccines see: Turner, ‘Vaccine’


21 Fidler and Gostin, ‘Milestone’

23 Vezzani, ‘Preliminary’


26 Serum Institute of India-WHO SMTA2: A copy of the Agreement can be found at: http://www.who.int/influenza/pip/benefit_sharing/sii_smta2_oct_2013.pdf?ua=1 (accessed 22 May 2016)


29 6.14.3, PIP Framework


31 For the purposes of the Framework the terms PIP Biological Materials ‘includes human clinical specimens, virus isolates of wild type human H5N1 and other influenza viruses with human pandemic potential; and modified viruses prepared from…influenza viruses with human pandemic potential developed by WHO GISRS laboratories, these being candidate vaccine viruses generated by reverse genetics and/or high growth re-assortment… [and]… RNA extracted from wild-type H5N1 and other human influenza viruses with human pandemic potential and cDNA that encompass the entire coding region of one or more viral genes. 4.1 PIP Framework; These material are important as, in order to manufacture a pandemic influenza vaccine, the vaccine preparation must contain an element of the inactivated virus against which the vaccine inoculates: Catherine Gerdil, 'The Annual Production Cycle For Influenza Vaccine' *Vaccine* 21(16) (2003) P.1776

32 Annex 2, SMTA2, Article 4.4.1.A, PIP Framework

33 Jeffries, ‘Levelling’; Vezzani, ‘Preliminary’; Phelan and Gostin, 'Farewell’

34 Footnote 1, Annex 2, SMTA2, Article 4.1.A PIP Framework


36 Articles 5, 6, and 9-13 , Annex 2, SMTA2, PIP Framework
The complex and time-consuming work to negotiate and conclude SMTA2s as well as the lack of resources – both human and financial – to scale up the pace of negotiations was noted by the Pandemic Influenza Preparedness Framework Advisory Group, in May 2013. At this time One SMTA2 has been concluded with GSK, and pre-negotiation discussions were on-going with Sanofi and Novartis. Currently only two of these negotiations and pre-negotiations have led to an SMTA2 being concluded (Sanofi and the Serum Institute) WHO, 'Pandemic Influenza Preparedness: Sharing Of Influenza Viruses And Access To Vaccines And Other Benefits Report Of The Meeting Of The Pandemic Influenza Preparedness Framework Advisory Group Report by the Director-General' (WHO 2013) <http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_17-en.pdf> Add.1 (accessed 3 June 2016)


This figure was reached by cross-referencing the list provided in Partridge and Kieny ‘2011’ at Footnote.1 and WHO, ‘2013 PIP Partnership Contribution (PC) Collection: Results as of 1 August 2014’ (WHO 2014) <http://www.who.int/influenza/pip/benefit_sharing/2013_pc_collection_results_1aug2014.pdf?ua=1> Table.1. (accessed 22 March 2016)


During a period of not sharing viral samples with GISRS during 2005-H1N1 the Indonesian government entered into negotiations with Baxter International to develop a vaccine based on samples provided by Indonesia. The parties reached a Memorandum of Understanding that ‘provide[d] a framework for future discussions and negotiations related to any formal collaboration or supply agreements for pandemic vaccine’. These discussions eventually broke down, and Indonesia returned to consistently sharing viral samples with GISRS in mid-2007. See: David Fidler, ‘Negotiating Equitable Access to Influenza Vaccines: Global Health Diplomacy and the Controversies Surrounding Avian Influenza H5N1 and Pandemic Influenza H1N1’ PLoS Medicine 7(5) (2010) e1000247.


Op. cit., P.4

Op. cit., P.4

Op. cit., P.4

WHO, ‘Partnership Contributions’


This figure is reached based on the fact that Rhodes estimates that 100 million doses would cover 1.8% of the population of developing states that lack access, in Catherine Rhodes, ‘Sovereign Wrongs: Ethics in the Governance of Pathogenic Genetic Resources’ Ethics in Biology, Engineering and Medicine 3(1) (2012) P.97
Annex 2, SMTA2, Article 4.1.A.1, PIP Framework

‘Recognizing that flexibility is important in negotiating with all manufacturers, in a range of 5–20%.’


6.9.2, PIP Framework

Pedro Plans-Rubió, 'The Vaccination Coverage Required To Establish Herd Immunity Against Influenza Viruses' Preventive Medicine 55(1) (2012) P.72

As was noted in Turner, ‘Vaccine’ vaccine committed to the VDI stockpile by industry and developed states arrived in recipient developing states at least four months later than in self-procuring states.

WHO, ‘VDI’ 20

Turner, ‘Vaccine’


Fidler, 'Negotiating'


Fidler, 'Negotiating'

Providing none of the developed states in whose territory the manufacturing facilities are based place restrictions on the exports of pandemic influenza vaccines until domestic demands have been fulfilled. As noted above this is a very real possibility in the event of a severe pandemic.


World Health Assembly, ‘Resolution 58.5, Fifty-Eighth World Health Assembly’ (2005)


Op. cit., Article 34(4.1)

Friede, ‘Initiative’

G Torelli, 'WHO Technology Transfer Initiative: Progress Update (8th meeting with international partners on prospects for influenza vaccine technology transfer to developing country vaccine manufacturers)' (WHO 2015) <http://www.who.int/phi/DAY1_02_Torelli_PM_SaoPaulo2015.pdf> (accessed 15 May 2016)


Fidler and Gostin, ‘Milestone’

Annex 2, SMTA2, Article 4.4.1.A5, PIP Framework


Friede, ‘Initiative’