Pandemic Influenza Preparedness: In Search of a Global Health Ethos

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In early 2007, the Indonesian government made a controversial decision to withhold its H5N1 avian flu virus samples from World Health Organisation Collaborating Centres pending a new global mechanism for virus sharing that had better terms for developing countries. In doing so, it helped to reframe the discourse on international health cooperation and "global health citizenship" in relation to infectious diseases of pandemic potential. The 60th World Health Assembly in May 2007 resolved that the global alert and response system for pandemic influenza should go beyond the obligations and responsibilities of member states in infectious diseases surveillance, reporting of disease outbreaks, and sharing of viral isolates and information as its principal terms of reference. The sharing of other benefits from this global alert and response system, such as equitable access to affordable vaccines developed from these viral source materials, is now prominently on the agenda of global health diplomacy. Based on documentary sources and a re-reading of published materials, this paper argues that global infectious disease surveillance has largely catered to the priorities of developed countries, with little consideration for how the duties and obligations of these regimes might accord with the health priorities and needs of developing countries. In the absence of reciprocal benefits, the International Health Regulations (2005) for instance, which impose mandatory disease reporting obligations on signatory member states, could reduce poorer front-line states to the role of pandemic "canaries" in an early warning system for emergent flu pandemics.

Key Words: Pandemic influenza; disease surveillance; virus sharing; flu vaccines; health diplomacy; global health equity

Diseases without Borders

In 1992, the US National Academy of Sciences published a landmark report entitled *Emerging Infections: Microbial Threats to Health in the United States* (Lederberg, Shope & Oaks, 1992). This report was the fruit of an 18-month study undertaken by a multidisciplinary committee jointly chaired by the eminent microbiologists Joshua Lederberg (Nobel laureate in medicine or physiology, 1958) and Robert Shope. Notwithstanding its title, it was quite clear that these national concerns over emergent and re-emergent infectious diseases in an affluent country would inevitably take on an international dimension.

Indeed, the opening sentences of the first paragraph noted that *"in the context of infectious diseases, there is nowhere in the world from which we are remote and no one from whom we are disconnected. Consequently, some infectious diseases that now affect people in other parts of the world represent potential threats to the United States because of global interdependence, modern transportation, trade, and changing social and cultural patterns"*.

As if to reinforce these anxieties *vis-à-vis* the "diseased and infested threatening other" (Eichelberger, 2007), the Severe Acute Respiratory Syndrome (SARS) pandemic of 2002-2003 provided a vivid demonstration of the global reach of lethal pathogens emerging from local ecological perturbations (Li et al., 2005). With intercontinental air travel taking much less time than the incubation period of the disease (up to 10 days), it was fortunate that the highly pathogenic SARS coronavirus, while rapidly disseminated geographically, was not highly contagious.

By the time the chains of transmission were broken in July 2003, 774 persons had succumbed to the disease out of 8096 known infections. Parametric estimates of the case fatality rate (CFR, the ratio of deaths to infections) ranged from 13.2% (patients younger than 60 years) to 43·3% (patients aged 60 years and older) (Donnelly et al., 2003). Although the death toll was not extraordinary, the economic impact, largely driven by risk perception and risk avoidance behaviours, was estimated at $10-30 billion (Fan, 2003), thus ensuring that it would not be a "neglected disease".

In contrast, estimates of the death toll from the "Spanish" flu pandemic (March 1918 - June 1920) range from 20 million to 50 million (Johnson and Mueller, 2002). The case fatality rate of 2-3% was lower than that for SARS, but the "Spanish" flu virus was much more transmissible, infecting about a third of the world's population.

In May 1997, a highly pathogenic strain of H5N1 avian flu virus emerged in Hong Kong, which killed 6 out of 18 persons who were infected via exposure at live-poultry markets (Class et al., 1998). No human-to-human transmissions were detected and the outbreak was stamped out by a territory-wide culling of 1.3 million chickens. H5N1 avian flu re-emerged in human populations in 2003, and as of November 27, 2009, 444 human infections had been confirmed in 11 Asian countries plus Azerbaijan, Djibouti, Egypt, Nigeria, and Turkey, of whom 262 died. Indonesia recorded the highest cumulative total of 141 human infections and 115 deaths, followed by Vietnam (111 cases, 56 deaths) (WHO, 2009a). Efficient human-to-human transmissions were still not detected, thus affording some reassurance that it was still a "sequestrable" affliction.

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Potential Epicentres for Pandemic Flu

The East Asian region includes tropical and subtropical areas in southern China and Southeast Asia which are believed to harbour potential epicentres for pandemic influenza outbreaks. The natural reservoirs for a large variety of influenza A viruses are aquatic wild fowl which migrate in winter time to these warmer climes where high densities of human populations along with mixed farming practices (involving pigs, ducks, geese, and chickens) and live-poultry markets provide the opportunity for viral re-assortment between the migratory hosts' virus strains and established viral lineages circulating in poultry, pigs, and humans (Yen et al., 2008). Among the three pandemics that occurred during the 20th century, the 1957 Asian and 1968 Hong Kong pandemic viruses originated from this region.

The third pandemic however was misnamed as the "Spanish" flu. This came about because Spain, as a neutral country in the 1st World War was less subject to news censorship so that the pandemic there received much more coverage than in the belligerent countries. The first recorded case of "Spanish" flu in fact came to attention in March 1918 at Camp Funston (now Fort Riley)

in Kansas, after a Haskell County doctor Loring Miner had raised the alert on "an influenza of a severe type" circulating in the area (Barry, 2004). More recently, John Oxford (2002) has offered some presumptive evidence to argue that the flu pandemic may have emerged as early as the winter of 1916 at a huge British troop staging camp in Étaples, France, and that enabling circumstances for future pandemic outbreaks may not necessarily be confined to epicentres in the Far East.

Indeed, others have argued that while humans, pigs, and poultry may be in close proximity in backyard farming operations found in East Asia, it is the concentrated animal feeding operations (CAFOs), such as the massive pig farm near the Mexican epicentre of the 2009 H1N1 pandemic (operated by Granjas Carroll, a subsidiary of the US food giant Smithfield Foods), which bring together the huge numbers of pigs (or poultry) in industrial-scale operations along with an animal-human interface (Graham, et al., 2008; Schmidt, 2009). Constantly replenished with unexposed younger animals, these huge animal populations allow for the sustained transmissions, infections and viral replications which increase the likelihood of mutational events and genetic re-assortments between co-circulating viruses which could generate the feared combination of highly pathogenic and transmissible flu viruses.

Surveillance for Microbial Threats of Pandemic Potential

In 1995, mounting concerns over emergent and re-emergent infectious diseases prompted the 48th World Health Assembly to call for:

- the strengthening of regional, national and local programs for active surveillance, diagnostic capacities, outbreak investigation, timely communication, and research for the early detection and rapid response to emerging and re-emerging infectious diseases

- increasing cooperation among Member States, international organizations, bilateral development agencies and other groups in the recognition, prevention, and control of new, emerging and re-emerging infectious diseases

(World Health Assembly resolution WHA48.13, 1995)

The 2003 SARS pandemic provided further impetus for revisions to the International Health Regulations (IHR). Adopted by the 58th World Health Assembly in 2005, the International Health Regulations (2005) came into force on June 15, 2007 as a legally binding international agreement. In its revised form, its scope was no longer limited to specific diseases (prior to that, applicable to cholera, plague and yellow fever) or mode of transmission, but had been radically expanded to encompass any "illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans".

In particular, State Parties had obligations

- to develop certain minimum core public health capacities for surveillance and response
- to notify WHO of events that may constitute a public health emergency of international concern according to defined criteria
- to establish National IHR Focal Points for purposes of urgent communications with WHO's IHR Contact Points

IHR (2005) furthermore had provisions authorizing WHO to take into consideration unofficial reports of public health events and to obtain verification from States Parties concerning such events. There were also procedures allowing for the determination by the Director-General of a

"public health emergency of international concern" and the issuance of pandemic alerts and corresponding temporary recommendations, after taking into account the views of an Emergency Committee.

With regards to pandemic flu, the WHO's initiative in influenza surveillance had begun in 1952. Over the years, this evolved into the Global Influenza Surveillance Network (GISN) which relies on 128 National Influenza Centres from 99 countries which periodically send sampled viral isolates from patients with influenza-like illnesses to WHO Collaborating Centres for antigenic and genetic analyses. Sequencing of the viral genes encoding for the haemagglutinin and neuraminidase surface proteins is routinely carried out to ascertain the degree to which these viral markers may be evolving away from those of pre-existing or circulating strains.

These results allow the WHO to make annual recommendations for the antigenic composition of influenza vaccines for the northern and southern hemispheres for their respective flu seasons. The WHO GISN furthermore serves as a global alert and response system for the emergence of novel influenza viruses with pandemic potential.

There are currently five collaborating influenza laboratories located at:

- WHO Collaborating Centre for Reference and Research on Influenza (Melbourne)
- National Institute of Infectious Diseases (Tokyo)
- National Institute for Medical Research (London)
- Centres for Disease Control and Prevention (Atlanta)
- St. Jude Children's Research Hospital (Memphis)

Besides performing antigenic and genetic analyses on viral isolates, WHO's Collaborating Centres also prepare vaccine strains of the virus as well as reagents for testing the vaccines. These are made available to vaccine manufacturers who grow the viruses in bulk, usually by inoculating and incubating the seed viruses in the embryonic allantois of fertilized hen's eggs. The harvested virus is then inactivated with chemicals, and its outer proteins (antigens) are isolated and purified for use as the active ingredient in the vaccine.

The GISN in effect has been a system that caters principally to the needs of the affluent member states and their vaccine manufacturers, by facilitating the production of vaccines for commercial distribution and government procurement in wealthy countries. Prior to 2006, no one had questioned the system because seasonal influenza was typically not a high priority in poorer countries which have to contend with more pressing infectious threats and other disease burdens. But the smouldering possibility of a more lethal pandemic flu outbreak, with historical precedents which make it more than conjectural, has altered threat perceptions in the wake of H5N1 emergence. Even allowing for some scaremongering, a prudent approach towards a "low-likelihood, high consequence event" would try to secure some access to vaccines as one element of pandemic preparedness and response.

Donor Leverage for Access to Avian Flu Vaccines

In late 2006, the Indonesian government made a controversial decision to withhold its H5N1 avian flu virus samples from WHO's collaborating centres as leverage for a new global mechanism for virus sharing that had better terms for developing countries.

In breaking with the existing practice of freely sending flu virus samples to these laboratories, Indonesia expressed dissatisfaction with a system which obliged WHO member states to share

virus samples with WHO's collaborating centres, but which lacked mechanisms for equitable sharing of benefits, most importantly, affordable vaccines developed from these viral source materials (Jakarta Post, February 17, 2007).

The Indonesian decision, invoking provisions in the Convention on Biological Diversity (1992) for sovereign rights over biological resources, aroused indignation and accusations of irresponsibility which endangered global health. But there were also expressions of support and sympathy, including an editorial from *The Lancet (2007):*

> *"To protect the global population, 6.2 billion doses of pandemic vaccine will be needed, but current manufacturing capacity can only produce 500 million doses. Indonesia fears that vaccines produced from their viruses via the WHO system will not be affordable to them… In November 2004, a WHO consultation reached the depressing conclusion that most developing countries would have no access to vaccine during the first wave of a pandemic and possibly throughout its duration… The fairest way forward would be for WHO to seek an international agreement that would ensure that developing countries have equal access to a pandemic vaccine, at an affordable price".*

Indeed, this was an issue waiting to be articulated. On March 29, 2007, immediately following an interim agreement for Indonesia to resume sending flu virus samples to WHO, health ministers of eighteen Asia-Pacific countries issued a Jakarta Declaration (2007) which called upon WHO "*to convene the necessary meetings, initiate the critical processes and obtain the essential commitment of all stakeholders to establish the mechanisms for more open virus and information sharing and accessibility to avian influenza and other potential pandemic influenza vaccines for developing countries".* These proposals were tabled at the 60th World Health Assembly in

Geneva (May 14–23, 2007) as part of a resolution calling for new mechanisms for virus sharing and for more equitable access to vaccines developed from these viral source materials.

In the course of the deliberations, it emerged that WHO collaborating centres had not abided by the relevant guidelines on sharing of viruses which required the consent of donor countries before these collaborating centres could pass on the viruses (other than the vaccine strains) to third parties such as vaccine manufacturers (WHO, 2007). While discouraging the use of material transfer agreements (MTAs) at the point when donor countries transferred their virus samples to WHO, WHO's collaborating centres nonetheless resorted to MTAs when they transferred to third parties vaccine strains containing parts of the viruses supplied by developing countries such as Indonesia, Vietnam and China. Indeed WHO's collaborating centres themselves, as well as third parties, had sought patents covering parts of the source viruses used in developing vaccines and diagnostics (Third World Network, 2007). Possibly the most contentious item on the health assembly's agenda in 2007, the issue of virus sharing and access to avian flu vaccines remained unresolved until the final hours of the gathering when a resolution was adopted mandating WHO to establish an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential, and to formulate mechanisms and guidelines for equitable access to affordable pandemic flu vaccines (World Health Assembly, 2007). The resolution also requested a WHO working group to draft new Terms of Reference (TORs) for WHO collaborating centres and its H5 reference laboratories for the sharing of influenza viruses, to be submitted to a special intergovernmental meeting of WHO member states.

The Indonesian government's stance was notable on four counts:

- it called into question a system that had worked satisfactorily in routinely transferring viruses to manufacturers which produced seasonal flu vaccines that

were affordable in affluent countries, but whose (pre-)pandemic flu vaccines were beyond the reach of poorer countries

- it was explicitly a critique of WHO's balance of pragmatism which it felt was overly accommodative of structural inequities, to the detriment of the health and wellbeing of underserved communities among its member states
- it was an exercise of leverage by a source country of biological materials seeking to redress the inequities of access to what may be vitally important health inputs (avian flu vaccines) developed from these source materials
- it was seeking equitable benefits from commercial developers not just for its nationals but for other communities as well who were likely to be sidelined by commercially-driven product development and distribution.

Global Health Security, or Global Public Health?

In April 2003, as the SARS pandemic was unfolding, Ilona Kickbusch (2003), professor of global health at Yale University's School of Public Health lamented the weak enforcement mandate of international agencies such as the WHO for securing the cooperation of member states in safeguarding global health security. In parallel with *"an incentive system for countries who act as responsible global citizens"*, she issued an accompanying call *"to explore sanctions by the UN Security Council, the WTO and the IMF for countries that do not adhere to global health transparency and their obligations under the IHR".*

Similar sentiments, couched in terms of health security and health policing, were also expressed about Indonesia's refusal to dispatch H5N1 virus samples to the WHO's collaborating centres. In a strongly-worded op-ed in the Washington Post, Richard Holbrooke and Laurie Garrett (2008) castigated Indonesia's "dangerous folly" as "morally reprehensible" actions of a recalcitrant state which jeopardized global health security:

> *Here's a concept you've probably never heard of: "viral sovereignty." This extremely dangerous idea comes to us courtesy of Indonesia's minister of health, Siti Fadilah Supari, who asserts that deadly viruses are the sovereign property of individual nations - even though they cross borders and could pose a pandemic threat to all the peoples of the world… Disturbingly, the notion has morphed into a global movement, fueled by self-destructive, anti-Western sentiments. In May, Indian Health Minister A. Ramadoss endorsed the concept in a dispute with Bangladesh. The Non-Aligned Movement - a 112-nation organization that is a survivor of the Cold War era - has agreed to consider formally endorsing the concept of "viral sovereignty" at its November meeting… Political leaders around the world should take note - and take very strong action.*

A year later in July 2009, as the H1N1 pandemic was unfolding amidst efforts to boost vaccine production and widespread concerns over supply limitations and distribution, Garrett belatedly acknowledged the essential point about *"viral sovereignty",* that it was above all an exercise of sovereign leverage for more equitable access to lifesaving vaccines in a pandemic situation:

> *The Minister of Health of Indonesia, Dr. Siti Supari, has insisted for several years that it is not the duty of her country to share samples of H5N1 bird flu viruses. Supari's position all along has been that the drug companies will turn these viruses into vaccines, and then charge so much for their products that the poor countries will never be able to afford the life-saving products. What we now see unfolding with the H1N1 vaccine scenario would seem to validate her argument… when a pandemic comes, the rich world takes everything and saves itself* (Garrett, Science*Insider*, July 28, 2009)

Despite appeals to humanitarian solidarity and to enlightened self-interest, almost all of the first billion doses of H1N1 vaccine produced in 2009 were allotted to 12 wealthy nations which had made advance orders. Sanofi Pasteur and GlaxoSmithKline (GSK) pledged 120 million doses to the WHO for distribution to poor countries, but even those pledges could only be fulfilled months after the pandemic had waned.

In Mexico, the epicentre of the H1N1 pandemic where health authorities had promptly shared its viruses with the GISN, Health Secretary Jose Angel Cordova revealed that *"we had to wait in the second line to buy the vaccine, because obviously the first shipments were for the countries that make the vaccine"* (Associated Press, January 12, 2010). With no domestic production capacity at the time, Mexican officials had ordered 30 million doses of the vaccine from Sanofi Pasteur and GlaxoSmithKline, most of which could only be delivered in February or March 2010. Under the circumstances, they made an arrangement to borrow 5 million doses from Canada, as the pandemic waned in the northern hemisphere.

Access to Pandemic H1N1 Vaccines: A Worrisome Preview

As it turned out, the H1N1 pandemic peaked in October-November 2009 in the northern hemisphere, and it furthermore remained mild, more comparable in severity to the 1957 and 1968 pandemics than to the feared 1918 pandemic (Presanis et al., 2009).

Many nations cut back on their vaccine orders, while others attempted to sell off excess stock or pending deliveries as the threat perception receded and scepticism about the vaccine's safety resurfaced among the general public. France, for example, had ordered 94 million doses for its

65 million people and eventually reduced it by 50 million doses (Reuters, January 4, 2010). In Britain, the government likewise negotiated to reduce its prior contracts for 90 million doses (Guardian, April 6, 2010). The United States had contracts to buy 251 million doses from five companies. It reduced by 22 million doses an order of 36 million from CSL Ltd., an Australian manufacturer that fell behind on deliveries, while retaining the others (New York Times, February 2, 2010). As of early February 2010, only about 62 million doses had been administered to US residents. There had been earlier controversies over the reluctance of US health authorities to deploy adjuvanted vaccines, i.e. vaccines with booster additives which would have doubled the available doses at a time when vaccine need greatly exceeded vaccine supply.

In September 2009, President Obama's administration had brokered an agreement with eight other wealthy nations (Australia, Brazil, France, Italy, New Zealand, Norway, Switzerland, and the United Kingdom) to donate ten percent of their vaccine supplies to WHO for use in poor countries, on top of the pledges by Sanofi Pasteur and GlaxoSmithKline (White House press release, September 17, 2009). With accumulating evidence that a one-dose injection would be adequate in place of the anticipated two-dose regimen, three additional countries and four more manufacturers eventually came on board, raising the total pledges to 180 million doses of vaccine (WHO, 2009b).

As of early February 2010 however, only two of the 95 countries listed by World Health Organization as having no independent means of obtaining flu vaccines - Azerbaijan and Mongolia - had received any. WHO had earlier planned to deliver vaccines to 14 of these countries by then, and even then shipments were adequate to protect only 2 percent of the countries' populations (New York Times, February 2, 2010). Pledges and exhortations aside, few were really surprised that when faced with perceived national emergencies, countries that could

afford vaccines prioritized their own nationals first, and only when the worst had passed, transferred their leftovers to the poor using the WHO as a clearinghouse (Fidler, 2010).

In the wake of the mild pandemic, WHO's alert system for influenza pandemics was also subjected to scrutiny and criticism. Under WHO's existing six-stage approach, the highest (pandemic) stage is declared when a new flu strain that spreads easily among humans and causes serious illness, shows evidence of sustained community level spread in at least two regions of the world. The system however focuses more on transmissibility, while lacking an index of lethality. This causes confusion among people who equate "pandemic" with a high death rate, usually measured by the case-fatality rate (CFR, the ratio of deaths to infections). In truth, the CFR is an unstable parameter in the early stages of a novel outbreak, since it is usually the fatalities and severe cases that come to early attention, thus yielding an inflated CFR as an artefact of underreported mild or asymptomatic infections.

There were also allegations of scaremongering by parties with vested interests in vaccine manufacture and sales, squandering of scarce health resources and diversion of attention from more urgent priorities in global health. Adding to the unease was WHO's lack of transparency in handling the declared interests of its influential advisers on pandemic alert and response, many of whom had also acted as advisers and consultants for pharmaceutical companies or had investment interests in these companies (Cohen & Carter, 2010). The potential for conflict of interest was underscored by the fact that many of the advance purchase contracts for pandemic flu vaccines ("sleeping contracts") had trigger clauses which hinged upon the declaration of a level six flu pandemic by WHO. Prior to the H1N1 pandemic, other researchers had begun to question the efficacy of seasonal flu vaccines (Jackson et al., 2005; Jefferson, 2006).

In any case, whether one felt cheated by or relieved at the mild course of the pandemic, it provided a valuable preview of likely scenarios for vaccine supply and timely access, in the event of a more virulent pandemic. For developing countries, this dress rehearsal was uncomfortably close to the scenarios anticipated by Dr Siti Fadhilah Supari (Indonesia's health minister, 2004-2009), the Third World Network, and others.

Pathways to Access

Resolution WHA60.28 ("Pandemic Influenza Preparedness: Sharing of Influenza Viruses and Access to Vaccines and Other Benefits") which emerged from the 60th World Health Assembly (2007) was notable in declaring for the first time, at the highest levels of representative global health diplomacy, that affordable access to the benefits of virus sharing in such forms as vaccines, medicines, and diagnostics was the equitable *quid pro quo* of global virus sharing arrangements for pandemic alert and response.

Indeed the WHO Intergovernmental Meeting (IGM) on Pandemic Influenza Preparedness, a process mandated by WHA60.28, included by consensus the following paragraph in the draft framework for reforming the GISN that was tabled at the 62nd World Health Assembly (2009):

> *Recognise that member states have a commitment to share, on an equal footing, H5N1 and other influenza viruses of human pandemic potential and the benefits, considering these as equally important parts of the collective action for global public health.*

The wording of this text, with repetition for effect, clearly enunciated as an operative principle the parity of *virus sharing* and *access to benefits*.

In actuality though, WHA60.28 gave rise to two divergent approaches for achieving these reciprocal goals. Notwithstanding this resolution, developed countries in particular those heavily invested in pharmaceutical enterprises and associated intellectual property regimes, were opposed to the formal linking of virus sharing with the sharing of benefits, preferring instead *ad hoc* voluntary arrangements and case by case negotiations over technology transfer and contributions in cash or in kind. They were also opposed to any restrictions on patent claims over biological materials or parts thereof received through WHO's GISN system, as well as patent claims over the products developed from the use of these biological materials. Their posture was summed up thus by an observer at the sessions of the IGM on Pandemic Influenza Preparedness: *"We need their virus, they need our vaccine, nobody needs this framework"* (Hammond, 2009).

Developing countries on the other hand insisted on formalizing in an explicit and enforceable manner the reciprocal obligations of virus sharing and access to benefits. Their preferred instrument for achieving this was a formal Standard Material Transfer Agreement (SMTA) which would govern the terms of virus sharing as well as any intellectual property claims that may arise from this arrangement.

Among the terms proposed by developing countries for benefit sharing were the following (Third World Network, May 7, 2009):

- commercial entities that received virus samples should be required to contribute a portion of their production to WHO stockpiles and to reserve an allotment for developing countries which were to be affordably priced;
- royalty-free licenses should be granted to developing countries for the use of IP protected technology and know-how in the manufacture of vaccines and anti-virals in these countries;

- contributions of a portion of their profits to a fund, which could be used for purchasing the needed vaccines or anti-virals as well as building manufacturing and other relevant capacity in developing countries.

With regards to patents and equitable access to essential medicines, the following measures were proposed:

- recipients of virus samples that were designated as WHO centres (WHO Collaborating Centre, H5 Reference Laboratory, or Essential Regulatory Laboratory) should not claim patents over products or processes developed using these biological materials
- recipients of virus samples that were commercial entities should not claim patents over products or processes developed using these biological materials. Alternatively, they should grant on request royalty-free licenses to developing countries.

In an attempt to bridge these gaps, the WHO Director-General Dr Margaret Chan proposed a compromise along these lines at the 126th session of the WHO Executive Board which met from January18 to 23, 2010:

- an SMTA that governed the sharing, use and transfer of Pandemic Influenza Preparedness (PIP) biological materials *within the WHO network*. Through the SMTA, providers of PIP biological materials consent to the transfer of such materials within the WHO network of laboratories, which are in turn bound by the SMTA's terms for the use of PIP biological materials.

- guiding principles agreed to by Member States for the development of benefit sharing arrangements with influenza vaccine manufacturers and for handling intellectual property rights and dispute resolution. Based on these guiding principles, individual arrangements would be sought with influenza vaccine manufacturers which would allow for flexibility to recognise the differences between manufacturers.
- any entity receiving PIP biological materials (encompassing designated WHO Collaborating Centre, public, private, for-profit or non-profit entity) could pursue intellectual property rights derived from the use of these materials. Such entity should grant to WHO a non-exclusive, royalty-free, sub-licensable licence with respect to such rights, to the extent that such grant was not prohibited by law, regulation or third-party obligation which existed before the receipt of the biological materials. Licences to WHO would be subject to certain terms and conditions, including but not limited to: commitment, ability and readiness of a potential recipient to use the sub-license, and agreement on the territorial application of the sub-license (WHO, 2010).

Against the backdrop of the H1N1 pandemic and the evidently unequal access to pandemic vaccines, consensus remained elusive as a wide gulf persisted between the stances adopted by the developed and developing countries at the WHO Executive Board meeting. Given these widely divergent positions on the PIP framework, it was agreed that an Open-Ended Working Group (OWG) would be convened for further negotiations between Member States, building on the outcome of the PIP Intergovernmental Meeting (Third World Network, January 27, 2010).

Building National Capacities

In October 2006, WHO invited proposals from vaccine manufacturers in developing countries to establish domestic production capacity for (seasonal) influenza vaccines which could be converted to pandemic vaccine production if the need arose. In return for grants and facilitated access to vaccine production technologies, the grantees would undertake to make available up to 10% of their production to United Nations purchasers in the event of a pandemic.

By late 2008, six developing country manufacturers had received grants of US$ 2.0−2.7 million each to establish pilot facilities for the production of influenza vaccines (WHO, 2009c):

- *Brazil (Instituto Butantan):* Egg-based inactivated split and/or whole-virion H5N1 vaccine with adjuvant. Pandemic vaccine pilot plant established, 10 experimental lots produced (seven H3N2, three recombinant H5N1 vaccines).
- *India (Serum Institute of India):* Cell-based inactivated split virus and egg-based live attenuated influenza vaccines. H1N1 and H3N2 strains successfully grown in laboratory conditions.
- *Indonesia (BioFarma):* Fill and finish operations for egg-based split seasonal vaccine. Facility established, three clinical-grade lots produced and a clinical trial completed.
- *Mexico (Birmex):* Blending, filling, packaging of egg-based inactivated split seasonal vaccine. Construction and equipping of pilot facility in progress.
- *Thailand (Government Pharmaceutical Organization):* Egg-based split inactivated vaccine and live attenuated influenza vaccine production. Trivalent seasonal vaccine ready for tests in pilot-plant conditions. (In December 2009, Mahidol University's Faculty of Tropical Medicine began clinical trials on the safety, efficacy and immunogenicity of an H1N1 nasal spray vaccine produced by GPO).

- *Viet Nam (IVAC):* Egg-based whole-virion, alum adjuvanted vaccine. Pilot facility under construction. Three recombinant H5N1 experimental lots tested for antigen content.

As of February 2009, WHO was also processing proposals from five additional establishments: Vacsera (Egypt), Green Cross (Korea), Cantacuzino (Romania), Torlak (Serbia), and Razi (Iran).

These modest initiatives will in time augment the existing flu vaccine manufacturing capacity in developing countries. But the gulf between potential need and existing capacity remained daunting. In the Asia-Pacific region, Singapore was among the minority of affluent countries that were able to acquire sufficient doses of vaccines to meet domestic need and demand during the H1N1 pandemic. In June 2009, GlaxoSmithKline's first Asian vaccine plant began commercial operations in Singapore, initially to produce pneumococcal conjugate vaccine, with a planned expansion of the product range over the next five years to include a (seasonal) flu vaccine for the elderly. Japan, in its response to the H1N1 pandemic, produced 54 million doses of pandemic flu vaccine, and imported a further 50 million doses (Watanabe, 2010). By contrast, a regional stockpile of personal protective equipment and anti-virals for the Asean region (pop. 580 million) could cater for all of 500,000 individuals (Noda, 2009).

A Parallel Regional Initiative for Pandemic Preparedness?

A month after the 60th WHA in 2007, Dr Margaret Chan, the Director-General of WHO called for thinking-outside-the-box for an innovative financing scheme for the international stockpile of avian flu vaccines *(Reuters, June 13, 2007).*

One proposal for risk management that was floated - since the stockpiled pre-pandemic vaccines have a shelf-life and potential donors might balk at the recurrent costs of continual replenishments - was to use the donated cash resources to buy insurance coverage instead from a willing underwriter. If and when an outbreak of pandemic flu emerged, the financial payout could then be used to bid for existing stocks of pre-pandemic vaccines that had not already been committed, and to make immediate advance purchase orders for supplies of the pandemic strain vaccine.

Quite apart from the chaotic scramble for vaccines in a pandemic outbreak, this improbable scheme would have been a casualty of the turmoil and severe stresses currently afflicting the global financial and risk management markets.

Taking Dr Chan's call to heart, and stepping outside the box of obsessive bias against public enterprises, we might call upon the WHO to explore the feasibility of an international public enterprise that could produce, acquire, and manage an international stockpile of avian flu vaccines that could be made available as critical essential goods on a rational and transparent priority needs basis.

More realistically, and noting that WHO's efforts at brokering new terms of agreement for virus sharing were still bogged down by disagreements over material transfer agreements and intellectual property claims, it might be wise to also consider parallel regional initiatives that could be set in motion without undue delay within an institutional framework with a functional track record.

The Asian financial crisis in 1997 gave impetus to a regional effort at managing financial instability caused by volatile capital flows and speculative currency attacks. Recognizing the increasing integration of East and Southeast Asian economies, a Chiang Mai Initiative emerged in

May 2000, initially as a network of bilateral swap agreements among ASEAN+3 member states, which might yet evolve into a *de facto* Asian Monetary Fund following a May 2007 decision to multi-lateralize an $80 billion (risk) pool of foreign exchange reserves of ASEAN+3 member states (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Viet Nam, plus China, Japan, South Korea).

Beyond the risk of *financial contagion* in globalised capital markets, the SARS epidemic of 2002-2003 forcefully demonstrated the regional economic consequences of a life-threatening infectious epidemic, effects which would pale in comparison with the devastating human and economic impact of an outbreak of highly transmissible and lethal human flu on the scale of the 1918-1919 pandemic.

A persuasive case could therefore be made that (ASEAN+3) might provide an institutional framework, building upon the Chiang Mai Initiative, for a regional public sector-led initiative to mobilize the financial and technological capabilities in Asia to enhance regional preparedness in a likely epicentre for future flu pandemics. This would go beyond the existing co-ordination of pandemic surveillance networks and informational exchanges and virus sharing to also include the development or expansion of manufacturing capabilities for vaccines, anti-virals and diagnostics.

Concluding Remarks

Amartya Sen once observed that if poverty itself were contagious, it would speedily dispel the nonchalance and indifference of the privileged and the sequestered. By analogy, we might perhaps equate “neglected diseases” (Trouiller et al., 2002) with “sequestrable diseases”, while

the less sequestrable diseases become "emergent and re-emergent" diseases worthy of surveillance, alert and response.

In a 2003 report on migration and health, WHO acknowledged that *"investing in improving health in poor countries is not a question of altruism but of long-term self-interest. For example, it has been shown by mathematical modelling for hepatitis B that the resources needed to prevent one carrier in the United Kingdom could prevent 4,000 carriers in Bangladesh of whom, statistically, four might be expected to migrate to the UK. Thus, it would be four times more cost effective for the UK to sponsor a vaccination programme against hepatitis B in Bangladesh than to introduce its own universal vaccination programme."* (citing Gay & Edmunds, 1998).

Notwithstanding this well-meaning appeal to enlightened self-interest, how does hepatitis B rank as a national health priority within Bangladesh? Bangladesh has been categorized as an intermediate endemic zone for hepatitis B virus (WHO, 2002). *WaterAid***,** a London-based NGO which advocates for safe domestic water supplies and sanitation for the world's poorest communities, worries more about diarrhea, which accounted for 17% of under-5 mortality worldwide in 2005, more than that for HIV/AIDS and malaria combined, and second only to acute respiratory infections (19%). In Bangladesh, diarrhea (in synergy with under-nutrition) is the leading cause of death among children under 5 (excluding neonates) (WHO, 2006), and it topped the list for hospital admissions (WHO/SEARO, 1997).

Foreign assistance therefore can be skewed towards specific diseases and can be driven by the health priorities of affluent countries rather than those of the recipient countries. Is there a similar potential for donor-driven global surveillance initiatives to distort national health priorities of aid recipients and possibly weaken national health systems via disease-specific funding mechanisms? Calain (2007) concludes from his review of disease surveillance experiences in Uganda, India,

Laos, and Cambodia that among the attributes that underpin a successful surveillance system in developing countries are simplicity, community participation, ownership, feedback and timely interventions, and personal relationships with field surveillance agents. On the other hand, donor-driven, poorly coordinated and redundant surveillance networks which siphon off scarce human resources from already fragile health systems can further fragment and distort national health capacities of developing countries. In such circumstances, *"global surveillance strategies seem bound to benefit mainly the most industrially developed nations through the provision of early warning information or scientific data".*

There is clearly an asymmetry in the global system for pandemic influenza alert and response, which asserts a global *need* for surveillance, information exchanges, and virus sharing (essential "global public goods" to be made available via enforceable international regimes), but accepts a *demand-based* allocation of key elements of pandemic response (such as vaccines, anti-virals, protective equipment) with all the inequities this entails.

The International Health Regulations (2005) in particular, which impose mandatory disease reporting obligations on signatory member states, in the absence of reciprocal benefits, could reduce poorer front-line states to the role of pandemic "canaries" in an early warning system for emergent flu pandemics (Chan & de Wildt, 2007).

In many instances, developing countries lack the leverage to rebalance these inequities which are rooted in existing power configurations. Paradoxically, the commodification of life forms and the extension of property rights and patent claims to cover their derived entities as well allowed Indonesia to invoke sovereign claims on biological resources such as H5N1 viral strains, citing provisions in the Convention on Biological Diversity.

Beyond the immediate concerns of timely and affordable access to pandemic flu vaccines, the Indonesian initiative has also raised the intriguing possibility of other analogous instances where donors of biological materials and personal data could utilize the leverage of their gift relationship in furtherance of the common good (Chan & de Wildt, 2007).

Indeed, PXE International in the US emerged in the late 1990s as a prototype along these lines, a novel advocacy group for patients with *pseudoxanthoma elasticum* (PXE). PXE is a Mendelian autosomal recessive genetic disorder which is characterized by the calcification and fragmentation of elastic fibres in the skin, eyes, the cardiovascular system and gastrointestinal system. Over the last two decades, parents and family members of affected individuals have established through PXE International a *modus vivendi* with researchers, to whom they have provided financial and material support, and most importantly, access to biological materials for research. In return, PXE International obtained authorship rights in papers that were published, as well as ownership rights in any patents that may be granted, through the use of material transfer agreements.

We look forward to a time when research volunteers and communities will be able to specify prior conditionalities for their participation in clinical trials, laboratory investigations, field trials, or other research settings, to require that meaningful and verifiable efforts be made to ensure that the research output would be deployed in a manner which serves the public good on an equitable needs basis.

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