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# THE UNCERTAIN FUTURE OF VACCINE DEVELOPMENT AND DEPLOYMENT FOR INFLUENZA PANDEMICS

## O'NEILL INSTITUTE

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On December 13, 2013, a joint communique issued by seven European and North American governments, Japan, and the European Commission noted three influenza viruses now circulating globally that with unpredictable ease may become large-scale pandemics. They affirmed their commitment to “support open sharing [of influenza samples], as endorsed through the World Health Organization (WHO) Pandemic Influenza Preparedness (PIP) Framework and the International Health Regulations (2005) (IHR)” and recognized “the importance of pathogen sample sharing in strengthening our capabilities to respond to emerging public health threats of international concern.”<sup>1</sup> The communique did not specifically mention the ultimate aim of sharing samples – the development of pandemic vaccines – nor how the medical discoveries achieved through international cooperation might be distributed to those countries and people who lacked the advanced technical capacity to produce

<sup>1</sup> [http://ec.europa.eu/health/preparedness\\_response/docs/ghsi\\_communique\\_2013\\_en.pdf](http://ec.europa.eu/health/preparedness_response/docs/ghsi_communique_2013_en.pdf)



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vaccines. Indeed, they could not; no such system exists. In the wake of the world's 2009 experience with H1N1 pandemic influenza A (so-called "swine flu"), high-, middle-, and low-income countries, the World Health Organization, and the major vaccine manufacturers (which are overwhelmingly located in the countries issuing the communique) have made only halting progress in ensuring that pandemic vaccines are developed, approved, and distributed consistently with approaches that maximize their public health impact. This briefing paper assesses the obstacles to vaccination donation and distribution faced by the major global pharmaceutical companies, the World Health Organization, donor and recipient governments during the 2009 H1N1 pandemic and outlines some features of an effective system to deal with vaccine access when the next pandemic strikes.

### BACKGROUND

When researchers in Mexico and the United States concluded that influenza-related hospitalizations in separate, non-contiguous areas of Mexico, southern California, and New York City uniquely affected children and young adults, they were alerted to the possibility that a new pandemic viral subtype of influenza had emerged.<sup>2</sup> After the U.S. Centers for Disease Control and Prevention (CDC) received samples from two early H1N1 patients in mid-April, 2009, researchers exposed banked blood samples taken before and after vaccinations from 2005 to the new virus. Samples from children produced no antibodies, while samples from adults vaccinated against seasonal flu showed a slight increase in antibodies against the pH1N1 virus. Because it did not appear that the seasonal vaccine would adequately protect adults against infection, the CDC recommended development of a vaccine specific to the new strain. This recommendation was echoed in WHO's June 11, 2009 declaration of a Phase 6 pandemic. Under the WHO classificatory scheme operating in 2009 (it has been revised in light of the H1N1 experience), in Phases 1-3 of a pandemic, influenza circulates predominantly in animals and there are few human infections. In Phase 4, there is sustained human-to-human transmission and in Phases 5 and 6, sustained human transmission spreads to at least two WHO regions.<sup>3</sup>

Vaccines are the first line of defense against influenza to prevent infection and control spread of the disease because they are more effective and burden society less than non-pharmaceutical measures like masks, closing of public gathering places, and isolation of patients. The CDC's recommendation and WHO's declaration triggered a race by a small number of vaccine manufacturers to develop and then put into production a pandemic-specific vaccine both because a market had instantaneously developed and because some manufacturers already had in place agreements with governments that required them to shift to pandemic vaccine production. Aside from the governments that had already put procurement policies and contracts in place, the vast majority of the world's governments and the populations they represented lacked access to vaccines and looked to WHO to work with firms and potential donor governments to facilitate access. The gene sequence of wild-type pandemic pH1N1 was

<sup>2</sup> Jose A. Cordova Villalobos et. al., *The Influenza A(H1N1) Epidemic in Mexico:: Lessons Learned Health Research Policy and Systems* 2009, 7:21 .

<sup>3</sup> Doshi, P (2011). *The Elusive Definition of Pandemic Influenza. Bull. World Health Organ.* 2011;89:532-538.



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made publicly available on 27 April 2009. By 8 May 2009 samples of wild-type virus had been sent from reference laboratories to vaccine manufacturers, all of which were in Europe and the USA because they had the necessary high-level biological containment facilities.

After researchers concluded that the seasonal flu vaccine did not protect against pH1N1, pharmaceutical firms, five of which control approximately 80% of the influenza vaccine market, found themselves negotiating with WHO over conditions for donation, shipment, and distribution of vaccines. Governments with preexisting contracts sought to preserve as much of their firms' capacity – that is, firms located within the territorial borders of the procuring governments – as would be necessary to inoculate their populations first before giving or selling to others; and a much larger than usual number of procurement officials, regulators, and other health care providers and vaccine distributors.

From the manufacturers' perspective, these negotiations occurred in the shadow of potentially large liabilities related to their existing contractual arrangements with governments, detailed processes for vaccine approval, distribution and marketing, as well as more general exposure should quickly-developed vaccines generate unexpected adverse reactions or safety problems. Regulatory approval for marketing and use is dependent on laboratory-generated evidence and clinical trial outcomes. Even safe and effective vaccines generate adverse events among those inoculated, ranging from (common) soreness at the injection site to fever, discomfort and muscle pain to (rare) anaphylaxis and oculo-respiratory syndrome (WHO 2012). One of the vaccines produced specifically for pH1N1 by GlaxoSmithKline has been associated with an increased risk of narcolepsy (CDC 2013). In many jurisdictions, manufacturers bear legal responsibility for these adverse events, although many states change these liabilities in cases of public health emergencies. Nevertheless, manufacturers faced a range of legal barriers to production, donation and discounted sale of pandemic vaccines like the process by which vaccines may be approved and registered with national regulatory authorities, protection from and indemnification for liability, preexisting advanced market commitment agreements which affect the ability to enter into additional contracts once a pandemic has been declared.

### THE LEGAL FRAMEWORK FOR PH1N1 PANDEMIC INFLUENZA VACCINE DISTRIBUTION

Development, approval, and distribution of the 2009 pH1N1 vaccine was shaped by pre-existing frameworks that had been established to address the outbreak of H5N1 avian flu in Southeast Asia.<sup>4</sup> That subtype spread quickly around the globe but did not (and has not to date) evolved to become easily transmissible to humans. The concern that H5N1 may become easily transmissible to and then between humans resulted in both divergent (if accelerated) regulatory approval processes as well as a set of agreements entered into between two manufacturers – GlaxoSmithKline (GSK) and Sanofi Pasteur (Sanofi) – and the World Health Organization for donations of prepandemic H5N1 vaccine doses. After the pN1H1 influenza strain was identified, WHO immediately began negotiations with “all known” influenza vaccine

<sup>4</sup> McConnell J. (2010). Pandemic influenza: learning from the present. *Public Health*; 124(1):3-4.



manufacturers. Those discussions were shaped by planning for H5N1.

When the World Health Organization declared a Phase 6 pandemic, GSK and Sanofi had pledged 50 million and 60 million doses of H5N1 vaccine respectively, although no legal agreements for donations were in place. GSK and Sanofi agreed to convert those commitments to pandemic influenza A pH1N1 vaccine and to increase the number of doses to 150 million. GSK and WHO signed an agreement for the donations on 10 November 2009 which resulted in just over 24 million doses actually donated. Sanofi announced a “flexible” donation of up to 100 million doses on 17 June 2009 but the donation agreement was not signed until December 2009. Novartis specifically eschewed donations, favoring pricing mechanisms to establish a “sustainable way” to deliver vaccines to developing countries.

Despite the small number of players, negotiations over all aspects of procurement were difficult and protracted, revealing a near total lack of planning to move vaccines from their private sector developers and manufacturers to the populations that needed them. Negotiations involved at least 4 manufacturers and 12 governments on the donor side and nearly 100 governments on the beneficiary side.<sup>5</sup> WHO’s negotiation with GSK served as a template for agreements with CSL Australia, MedImmune, and Sanofi, which concluded in December 2009. Novartis signed an agreement in January 2010, although a 2011 WHO assessment of its response to the pandemic strongly suggests that the Novartis agreement differed from the other four. Legal agreements with governments followed those with firms: the USA (16 December), Australia (22 December), France (15 January 2010), Belgium (29 January 2010), Switzerland (16 March 2010), Norway (19 March 2010), Italy (16 April 2010), the UK (28 May 2010) and Singapore (21 June 2010). Some states perceived that WHO “shopped” different agreements with different legal terms to different governments, a practice that generated suspicion among the donor governments and further delay in finalizing terms.

The delay in placing agreements between firms, governments, and WHO was attributable to at least two causes. First, both firms and governments had entered into advance purchase agreements that constrained the ability of firms to donate or otherwise provide vaccines to WHO or governments directly. Second, vaccine manufacturers insisted on strong protections from liability should the pandemic influenza vaccine result in adverse health events in populations as well as coverage for interests affected by specific title-transfer arrangements.

## **ADVANCE PURCHASE AGREEMENTS AND TERRITORIAL RESTRAINTS**

Long before WHO declared a pandemic, many countries including Belgium, Canada, Finland, France, Germany, Italy, Switzerland, The Netherlands, the United States, and the United Kingdom had already placed large orders of pH1N1 vaccine or had advanced agreements in place.<sup>6</sup> In advance purchase agreements, a vaccine manufacturer agrees to supply its pandemic

<sup>5</sup> World Health Organization. Implementation of the International Health Regulations (2005). Report of the Review Committee on the Functioning of the International Health Regulations (2005) in Relation to Pandemic (H1N1) 2009 (2011). Geneva: World Health Organization.

<sup>6</sup> Doshi P, Jefferson T. (2010). Another question for GSK, BMJ: 340(June):c3455.



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influenza vaccine as soon as possible after a pandemic has been declared and agrees to reserve a specified number of doses for the country or to more openly meet that country's orders first. When it commenced negotiations with manufacturers, WHO did not know about key aspects of the agreements. When asked whether they would be willing to reserve (not donate) 10% of real-time production for purchase by UN agencies, many vaccine manufacturers cited advance purchase agreements with high-income countries as a barrier. Contracting states noted the relatively inflexible terms of those agreements, which required orders for pandemic vaccine not tailored to severity or ultimate need.

Even aside from advance purchase agreements, the decision to dedicate physical infrastructure and human resources to pandemic influenza vaccine production is, from the manufacturers' view, a business decision. In a 2010 WHO report examining operational successes and failures of the WHO Deployment Initiative (the umbrella term WHO used to describe its effort to procure vaccines from firms and governments and distribute them to needy countries) pharmaceutical firms noted that "support for the WHO Deployment Initiative may have disrupted business in other areas and reduced their competitive strength."<sup>7</sup> Vaccine manufacturers, therefore, desire stockpiling agreements as a solution to business uncertainty, while procuring governments demand flexibility to fit the severity of the pandemic. The 2009 pH1N1 influenza pandemic has exacerbated this tension between firms and the governments wealthy enough to procure advanced vaccine production, and, therefore, what is left for populations in lesser developed or middle income states. After the pH1N1 threat diminished, more governments entered into advance purchase agreements with unknown divergence (or convergence) in legal terms for doses of pandemic or prepandemic vaccine.

In addition to and accompanying advance purchase agreements, domestic law may nevertheless constrain the production and shipment environment of vaccine manufacturers. For example, GSK's facility in Sainte Foy, Quebec must fill Canada's orders first before supplying to others and Canada awarded its pandemic influenza vaccine contract to a Canadian company precisely because it feared foreign governments would restrict exports of vaccine doses.<sup>8</sup> The Australian government made it clear to the Australian manufacturer CSL that it must fulfill the government's domestic needs before exporting pH1N1 vaccine.<sup>9</sup> Despite clear acknowledgment that the 2009 outbreak originated in Mexico and leveled its most significant toll there, Mexico had "a terrifically difficult time getting access to the pandemic vaccine" as a result of the difficulties in assessing needs and distributing vaccines to target populations across the globe.<sup>10</sup>

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<sup>7</sup> World Health Organization (2010), Main operational lessons learnt from the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative. Accessed January 28, 2014 at [http://www.who.int/influenza\\_vaccines\\_plan/resources/h1n1\\_vaccine\\_deployment\\_initiative\\_moll.pdf](http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiative_moll.pdf).

<sup>8</sup> Fidler DP (2010) Negotiating Equitable Access to Influenza Vaccines: Global Health Diplomacy and the Controversies Surrounding Avian Influenza H5N1 and Pandemic Influenza H1N1. *PLoS Med* 7(5): e1000247. doi:10.1371/journal.pmed.1000247

<sup>9</sup> *Id.*

<sup>10</sup> Halabi, S. (2014). Multipolarity, Intellectual Property, and the Internationalization of Public Health Law, 35 *Mich J. Int'l. L.* 1.



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## REGULATORY APPROVAL AND LEGAL LIABILITIES

Each country's national regulatory authority responding to the pandemic imposed its own regulatory process for approving pH1N1 vaccines, authorizing their importation, and overseeing their distribution. These processes ranged, on the one hand, from one-time waivers of certain rules to, on the other, detailed requirements for pediatric subgroup data, regulatory assessments capacity, quality control preparedness and capacity, and post marketing safety surveillance and field assessment of efficacy and immunogenicity. Some regulatory agencies approved pandemic vaccines as a type of seasonal influenza vaccine, while others adapted an approval process in place for candidate H5N1 (avian flu) vaccines. The biochemistry of pH1N1 vaccines varied widely, with adjuvanted vaccines (an adjuvant is an inorganic or organic chemical, macromolecule or entire cell of certain killed bacteria used to enhance the immune response to an antigen) and vaccines produced using cell- rather than egg-based technology facing more significant regulatory review. In over half of the beneficiary countries, prequalification of a vaccine by WHO was not sufficient to obtain regulatory approval and relatively few countries' national laws stated that products donated by the United Nations did not require national registration.

These requirements, in turn, adversely affected efficacious donation and distribution. Even where a manufacturer agreed in principle to donate to WHO or other UN agencies, it may not agree to do so if the vaccine might be distributed in a country where that vaccine is not licensed. Since at least 2006, industry representatives have stated that manufacturers would need advance assurance that governments would provide liability protection in order to donate vaccines. Indeed, some manufacturers will not even authorize use of the vaccine for clinical trials if not insured against legal liabilities. Because the initial urgency of the pandemic response required an unprecedented number of doses of a new vaccine to be deployed globally in a period of only a few months, vaccine manufacturers required that all purchasers or recipients (many of which were European and North American governments) indemnify them for adverse events resulting from the use of the pandemic H1N1 vaccine, with exceptions allowed for failure to follow current good manufacturing processes or other discrete specifications.

Manufacturers required access to information on country regulatory processes that was often difficult to obtain. Reallocating products once this work had begun led to additional work for manufacturers and delayed delivery to countries. In one instance, a change in the delivery schedule necessitated switching to the product of a different manufacturer, which triggered a de novo review of all aspects of vaccine approval. The delays caused by this legal wrangling were substantial. For countries in WHO's African Region, vaccines were deployed on average 261 days after a country expressed interest in donated vaccine. Delays were exacerbated by some governments' failure to submit effective deployment plans. "For those countries that were first hit by the emerging pandemic, like those in the Southern Hemisphere, but also for some countries in the Northern Hemisphere, the vaccines clearly came too late and well after the pandemic struck."<sup>11</sup>

<sup>11</sup> Osterhaus, Ab, Ron Fouchier, and Guus Rimmelzwaan, Towards Universal Influenza Vaccines. *Phil. Trans. R. Soc. B* (2011) 366, 2766–2773



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The complexity of this contracting universe explains, in part, discrepancies in pledged versus contractually committed vaccines. Availability of supply and differing appreciation of available safety and efficacy data influenced where and under what circumstances certain vaccines could be deployed to certain countries. Because some countries would authorize one vaccine but not another, WHO was in a constant process of matching available vaccines to countries where approval could be obtained. By the end of the WHO Deployment Initiative in September 2010, 200 million doses of pandemic influenza A (pH1N1) 2009 vaccine had been pledged for donation but only 122.5 million doses had been contractually committed. In total, 78 million doses of pandemic influenza A (pH1N1) 2009 were deployed to 77 countries.

### THE UNCERTAIN FUTURE OF VACCINE DEVELOPMENT AND DEPLOYMENT

Manufacturers faced differing regulatory and approval processes, uncertain protection from legal liabilities, constraints imposed by advance purchase agreements in place with mostly European and North American countries, and equally uncertain and undeveloped systems for distribution even if they could manufacture a limitless number of doses. In short, the global public health response to pandemic influenza in 2009 was dependent on private sector actors who, under the circumstances then prevailing, demanded both legal assurances and relief from legal requirements in order to participate fully in that response. There were few effective mechanisms for dealing with that reality. An effective global strategy for the next influenza pandemic will require the identification of these contracting and regulatory obstacles, anticipation of new ones, and the creation of ex ante agreements and negotiation fora which may facilitate vaccine development and distribution.

While efforts are underway to increase vaccine manufacturing capacity in developing states, capability remains overwhelmingly centered in large pharmaceutical firms located in Australia, Japan, Europe and North America. There is a substantial consensus that capacity for vaccine production is tiny compared to the number of doses required in the event of the next pandemic. The WHO, as well as North American and European governments, are funding programs to increase the supply of seasonal and pandemic influenza vaccines by expanding global coverage of seasonal flu vaccine, promoting new development sites (including in developing states) and enhancing research and development for novel influenza vaccines.

WHO is optimistic that the agreements put in place between donor governments and firms between November 2009 and March 2010 will provide a time-saving legal framework for production and distribution of vaccines or other medicines during the next pandemic.<sup>12</sup> But there are reasons to doubt that this will be the case based on system-wide response changes. For example, one of the controversial aspects of vaccine development and distribution between 2009 and 2010 was WHO's criteria for identifying a pandemic. Those criteria were based in some measure on geographic spread rather than severity. WHO has agreed to revise these criteria so that the next time WHO declares a pandemic, it will reflect a more severe public health event on a widespread scale, a scenario likely to render existing legal agreements less

<sup>12</sup> World Health Organization (2010), Main operational lessons learnt from the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative. Accessed January 28, 2014 at [http://www.who.int/influenza\\_vaccines\\_plan/resources/h1n1\\_vaccine\\_deployment\\_initiative\\_moll.pdf](http://www.who.int/influenza_vaccines_plan/resources/h1n1_vaccine_deployment_initiative_moll.pdf).



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applicable than WHO now hopes.<sup>13</sup> Similarly, many European governments now have similar if not identical terms in their advance purchase agreements with vaccine manufacturers, but there is no way of knowing whether those terms have been drafted in light of system-wide pressures.

So far as the 2009 pH1N1 experience goes, building capacity without a consistently updated framework for efficiently moving pandemic vaccines from the private sector to the public sphere may simply aggravate the legal and regulatory bottlenecks experienced between 2009 and 2010. The expansion of capacity in middle income or developing countries enhances the contracting complexity that will likely be faced during the next pandemic. No agreements were reached with firms that are not members of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), which does not include the small but growing number of manufacturers in developing countries. For the most part, vaccine manufacturers and major purchasers still decide whether to suspend seasonal influenza vaccine production so that all production capacity can be used for pandemic vaccine. Manufacturers also decide whether production of pandemic vaccine can be safely scaled down or suspended in favor of seasonal vaccine. Advance agreements should exist between industry, WHO and countries as to these decisions or at least create ongoing forums that regularly keep relevant stakeholders current on how vaccine manufacturers' commitments affect overall capacity for production in the case of a pandemic.

Approval processes for national regulatory authorities created a major obstacle not just for initial agreements to donate, but for logistical practicalities that favored deployment of pandemic vaccines as quickly as possible to countries that needed them as soon as possible. As with the vaccine framework developed for H1N1, regulatory harmonization has been largely shaped by pre-2009 preparations for emergence of a pandemic H5N1 influenza virus strain. WHO in collaboration with health authorities from Canada, Japan, Spain, and the U.S., convened three technical workshops between 2006 and 2007 to examine regulatory harmonization, but the results are shaped by detailed examination of countries with clear regulatory mandates and at least one major vaccine manufacturer. The 2009 H1N1 pandemic has not resulted in a measurable increase in agreements between national regulatory authorities or with WHO on data sharing, mutual recognition of some or all aspects of vaccine approval.

Moreover, the difficulty lesser developed and middle income countries experienced in obtaining pandemic H1N1 vaccine exacerbated already existing tensions over the process of developing medicines and vaccines (which frequently involves the use of flu samples obtained in developing countries) and making them available at affordable prices. In 2007, Indonesia withheld samples of influenza A (H5N1) from WHO, arguing that developing countries typically shared such samples for free only to have North American and European firms patent derivative medicines and vaccines for sale in richer states, out of reach (in financial and other terms) from developing countries. In response, WHO and the World Health Assembly adopted the Pandemic Influenza Preparedness Framework, under which member states and vaccine

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<sup>13</sup> Doshi, P (2011). The Elusive Definition of Pandemic Influenza. *Bull. World Health Organ.* 2011;89:532–538.



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manufacturers have agreed on a standard material transfer agreement (STMA) that regulates the terms under which countries agree to donate influenza samples, the entities authorized to receive and research them, and the corresponding sharing of resulting vaccines and other intellectual properties. These agreements provide several options to manufacturers as to the contributions they must make in exchange for virus access. Some of these options involve pandemic vaccine donation, while others involve antiviral donations and still others authorize licensing of intellectual property to developing country manufacturers. These agreements, especially the options manufacturers choose, must coexist with the advance purchase agreements and, presumably, liability issues outlined above. Together with the proliferation of advance purchase agreements and the unknown extent of vaccine stockpiling agreements, the commitments made by manufacturers under the WHO's Pandemic Influenza Preparedness Framework may render obsolete the legal framework used in 2009. A far preferable course, which I develop at length elsewhere, is to authorize the PIP Framework to become a clearinghouse in which manufacturers, WHO, donor and beneficiary governments survey global capacity and make preparations for pandemic vaccine production and distribution.

### CONCLUSION

Vaccines are the fundamental core of the global response to the next pandemic influenza outbreak and thus their manufacturers, together with public health agencies, form a critical public-private partnership. The seasonal-pandemic influenza vaccine production balance; the process by which vaccines are developed, researched and approved for use by regulatory agencies, the potential liability manufacturers face and the contractual limitations imposed by advance purchase agreements all portend potential delays for the necessary global health response. WHO has already noted that advance agreements between itself, countries and industries should be negotiated without regard to virus subtype, for a specified period of time (e.g. three to five years) and should be regularly reviewed and renewed. Countries that receive donated vaccine, as any purchaser of the vaccine, should adhere to the same practices of releasing and indemnifying manufacturers from certain legal liabilities. Whether donated or purchased, vaccine manufacturers have emphasized that liability protection is a crucial part of their participation in the broader response to pandemic influenza. So, the commitment of the member countries of the Global Health Security Initiative to international cooperation as to global health threats, while important, demands a clearer, more focused framework for bringing the critical stakeholders to the table, more regularly, to put in place the necessary mechanisms ensure that safe and effective vaccines reach the people who need them as quickly as possible.

Additional briefings from the O'Neill Institute on the ACA can be found at <http://www.law.georgetown.edu/oneillinstitute/resources/briefings.html>.