Market incentives for pandemic influenza vaccines

by

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Abstract

It has been estimated that 100 million plus individuals could perish if a virulent influenza pandemic were to occur. In wake of the 2009-10 H1N1 pandemic and in an era of economic austerity, however, industry lacks clear incentives to invest in vaccines for other high-risk strains. The cyclic nature of pandemics also means we can expect another influenza pandemic within the next 20 years. In this environment, design of incentive mechanisms for funding development of vaccines against strains with known pandemic potential, but for whom vaccine technology is currently lacking, would be welcomed. This research explores which novel incentive mechanisms could induce investment in and development of processes for production of vaccines for these high risk strains. Interviews with vaccine developers and funding agencies and analysis of the pipeline of influenza vaccines in development were conducted.

This thesis finds that there is a dearth of vaccines against influenza strains of known pandemic potential, such as H2, H7 and H9; that current pandemic preparedness efforts are not focused on these strains; that funding for pandemic preparedness efforts in H2, H7 and H9 would help incentivize development of vaccines against these strains; and that support for seasonal influenza, regulatory changes, alignment of public and private sector goals, and increased vaccine acceptance are also required to incentivize the development of vaccines against strains of known pandemic potential such as H2, H7 and H9.

Furthermore, this thesis recommends that policy makers increase funding for pandemic preparedness so that programs may be initiated or expanded to include additional high risk influenza strains; that US and EU regulatory regimes for pandemic influenza vaccines be harmonized; and that governments promote public awareness of the importance of influenza vaccination.

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Chapter 1: Introduction

The idea for this thesis arose during a business school summer internship at Novartis Vaccines and Diagnostics in the pandemic influenza group. My two primary objectives for the summer were to draw lessons from the 2009-10 H1N1 influenza pandemic, and to help launch a pre-pandemic vaccine in Europe for the H5N1 influenza strain. As I learned more about these topics and influenza in general over the summer, I noticed something troubling: vaccines against certain strains of influenza with known pandemic potential (H2, H7 and H9) were not in the portfolio of Novartis or other major vaccine developers such as GlaxoSmithKline (GSK). Moreover, based on European government disinterest in the H5 pre-pandemic vaccine, the market potential for such vaccines seemed limited to nonexistent.

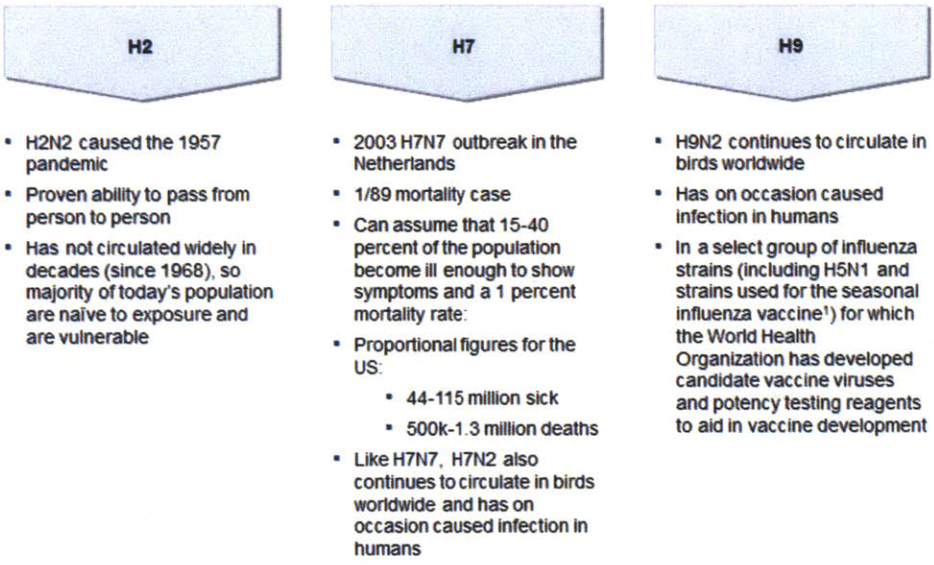
This is surprising and troubling. Following the 2009-10 H1N1 pandemic, the World Health Organization (WHO)'s chairwoman, Margaret Chan, was widely quoted acknowledging that the world dodged a bullet and was lucky to have experience such a mild influenza pandemic: "This time around, we have been aided by pure good luck. The virus did not mutate during the pandemic to a more lethal form. Widespread resistance to oseltamivir [an antiviral] did not develop. The vaccine proved to be a good match with circulating viruses and showed an excellent safety profile (WHO 2012)."[a]

Next time the world may not be so lucky. The Bill and Melinda Gates Foundation estimates that 100 million plus individuals could perish in an influenza pandemic, with those most at risk in the developing world (PATH 2007). Even much more conservative estimates would be devastating in term of: deaths, life years lost (since the young are often most vulnerable to new circulating strains of influenza) (Viboud, et al. 2010) and economic losses in the form of disruption of trade, transportation, etc.

[a]While antivirals are used in instances of pandemic influenza, vaccination is considered the preferred method for disease control.

The case for concern about these strains is very real. For example, in the Netherlands in 2003, there was an outbreak of H7N7 outbreak that resulted in a 1/89 mortality rate. Along with H7, the WHO deems H2 and H9 strains of influenza with pandemic potential:

Figure 1: The Case for Concern (Author's analysis) (Barry 2004) (Yong 2012) (WHO n.d.)



[1] Influenza A H1N1, H3N2, and influenza B; currently there are also candidate vaccine viruses and potency testing reagents for a variant of H3N2

Given the unfavorable environment to invest in vaccines against these strains, the question of how to design incentive mechanisms to encourage development is an important one.

The motivating question of this thesis is: What novel sets of incentives can induce investment in and development of processes for production of H2, H7 and H9 influenza vaccines?

Answering this question could benefit numerous stakeholders, including the public health community, vaccine developers, governments, their citizens, physicians, scientists working in influenza and economist interested in incentive mechanism design.

The ultimate goal in pandemic influenza vaccine preparedness is a universal vaccine. These are vaccines that can target multiple strains of pandemic influenza and could provide broad protection. Current universal vaccines in development are years away and some scientists even view their development as impossible. Until they are, strain-matched vaccines against neglected, high risk strains are urgently needed.

Chapter 2: Background

Pandemic influenza

There are two strains of pandemic influenza that are well known to the general public: there is H5N1, which received widespread attention following outbreaks in 1997 and 2003, and has garnered renewed attention in recent months as researchers have sought to publish the mechanism involved in human to human transmission (Saey 2012) (An Engineered Doomsday 2012); and there is H1N1, which spread rapidly across the globe in 2009-10.

As mentioned earlier, other strains of influenza are also considered to be of pandemic potential. The WHO has three criteria that are used to make a determination that a form of influenza is a pandemic (WHO 2006):

1) "a new virus emerges with a new [haemagglutinin antigen (HA) on the influenza virus] to which there is almost universal susceptibility;
2) this virus is capable of causing significant disease in humans;
3) this virus is efficiently transmitted from human to human."

Viruses that newly emerge thus are of concern according to this criterion; such viruses that cause morbidity and/or mortality in humans are of even greater concern; and those that also are able to make the leap from animal to human transmission to human to human transmission are considered pandemic viruses.

Such viruses become possible according to the WHO (WHO 2006), when there is an antigenic shift in the [HA] of an influenza virus to a new type – a type to which virtually the entire human population lacks immunity. "

The exact time when a given strain of influenza might emerge in pandemic form is unknown. Experts agree that there is a cyclic nature to influenza pandemics but are divided on the predicted length of time between pandemics. Historical trends, as illustrated below, lead many to believe that an influenza pandemic is likely every 20-50 years.

Figure 2: Timeline of Human Flu Pandemics (Author's analysis) (Clyde Crumpacker 2011) (U.S. Department of Health & Human Services n.d.)

Year	Strain	Mortality	Additional impact
1889-90	Russian influenza H2N2		
1898-00	Old Hong Kong influenza H3N8		
1918-19	Spanish influenza H1N1	• 50+ million worldwide • 675,000 US	• 20% to 40% of the worldwide population became ill • Illness and mortality rates were highest among adults 20 to 50 years old • H1N1 continued to circulate, causing epidemics from 1927-43
1957-58	Asian influenza H2N2	• 69,800 US	• Elderly had the highest rates of death • Second wave of illness in 1958
1968-69	Hong Kong influenza H3N2	• 33,800 US	• Similar to '57 strain, hit during school break • Those over the age of 65 were most likely to die • Same virus in '70, and '72
2009-10	Pandemic influenza H1N1	• 8,870 - 18,300 deaths worldwide	• 43-89 million cases implies a very low mortality rate

Moreover, new strains continue to emerge in humans.

Figure 3: Appearance of New Influenza Strains in Humans (Author's analysis)

(Clyde Crumpacker 2011) (U.S. Department of Health & Human Services n.d.)

Year	Strain	Impact
1976	HswN1	• Four soldiers in a US army base in New Jersey are infected with swine influenza, resulting in one death. • Concerns that the virus was similar to the 1918 Spanish flu were unfounded
1977	Russian Influenza H1N1	• This virus was similar to the virus that spread before 1957, and individuals born before 1957 were generally protected. However, children and young adults born after that year were not because they had no prior immunity. • Not considered a pandemic because most patients were children.
1997, 2003-	H5N1	• The first time an influenza virus was found to be transmitted directly from birds to people, with infections linked to exposure to poultry markets. • To date, there are 606 laboratory confirmed cases from patients in: Azerbaijan, Bangladesh, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Laos, Myanmar, Nigeria, Pakistan, Thailand, Turkey and Vietnam • Of these, there 357 patients have died (59%)
1999, 2003	H9N2	• Appeared for the first time in humans in 1999, causing illness in two children in Hong Kong, with poultry being the probable source. In 2003, caused illness in one child in Hong Kong.
2002, 2003	H7N2	• In 2002, evidence of infection is found in one person in Virginia following a poultry outbreak. In 2003, caused a person to be hospitalized in New York.
2003, 2007	H7N7	• The first reported cases of this strain in humans were in 2003, when 89 people in the Netherlands, most of whom were poultry workers, became ill with eye infections or flu-like symptoms. A veterinarian who visited one of the affected poultry farms died. • In May 2007, four cases of H7N7 avian influenza were confirmed in the United Kingdom among individuals exposed to infected poultry.
2004	H7N3	• In 2004, infection is reported for the first time in humans after two poultry workers in Canada fall ill.
2004	H10N7	• In 2004, infection is reported for the first time in humans after two infants in Egypt fall ill. One child's father is a poultry merchant.

Incentives for neglected diseases

Neglected diseases are ones for which drugs, vaccines and diagnostics are needed but the economic incentives for companies to develop these technologies are lacking. Traditionally, incentives to create these technologies have focused on diseases afflicting primarily patients in the developing world, such as HIV, malaria, pneumonia and diarrheal disease.

By creating "push" mechanisms that reduce the risks and costs of technology developers, or "pull" mechanisms that increase the technology developer's return on investment, incentives for neglected diseases create an economic environment in which desired technologies can be developed that otherwise would not.

With the advent of the Gates Foundation and the help of donor governments and other foundations, a plethora of types of incentives for neglected diseases have arisen. (Please see Figure 4 below for a schematic of types of incentives for neglected diseases.)

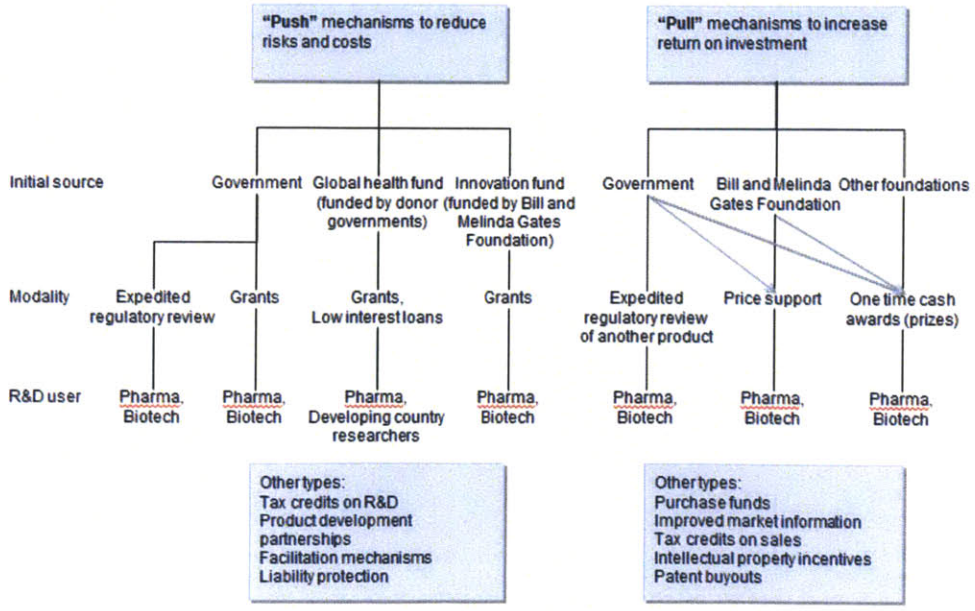
Push mechanisms in general focus on the pre-clinical and clinical phases of the research and development process. These can be funded directly by governments, global health funds (which are funded by donor governments; examples include the GAVI Alliance) or innovation funds (these include the Gates-supported International AIDS Vaccine Initiative Innovation Fund). Governments have offered expedited regulatory review of the technology in development and grant funding to pharmaceutical (pharma) and biotechnology (biotech) companies. Global health funds have offered grants and low interest loans to pharma companies and developing country researchers. Innovations funds have also offered grants to pharma and biotech companies.

Other types of push mechanisms include tax credits for R&D; product development partnerships; facilitation mechanisms; and liability protection.

Pull mechanisms increase the rewards for successful R&D investments and are rewarded to products that are fully developed and/or marketed. These have been funded directly by governments and foundations as Gates. Governments have offered a credit for expedited regulatory review of a different technology in development (i.e. FDA priority review vouchers); price guarantees; and one time cash awards (prizes) for pharma and biotech companies. The Gates Foundation and other organizations have also participated in offering prizes to pharma and biotech companies, and Gates has been instrumental in funding the advance market commitment to support prices for neglected disease technologies.

Other types of pull mechanisms include purchase funds; improved market information; tax credits on sales; intellectual property incentives; and patent buyouts.

Figure 4: Types of Incentives for Neglected Diseases (Author's analysis) (Hecht 2009)



Current incentives for pandemic influenza vaccines: Introduction

Pandemic influenza represents another type of disease neglected by for-profit vaccine developers. Given the need for protection against pandemic influenza, the US government has stepped in with multiple programs to incent desired activity. These programs are laid out in Table 1 and described in detail below.

Table 1: Current Incentives for Pandemic Influenza Vaccines

Funding agency	Program	Type of incentive	Influenza strain	Stage of development	Technology
BARDA	Cell-based influenza vaccine development	Push	Not strain specific	Clinical	Cell-based
BARDA	Year round egg supply guarantee for influenza vaccine manufacturing	Push	Not strain specific	Clinical	Egg-based
BARDA	Pre-pandemic vaccine stockpiles	Pull	H5	Developed	Egg-based
BARDA	Antigen-sparing technology development	Push	Not strain specific	Clinical	Adjuvant
BARDA	Retrofitting to enhance manufacturing capacity	Push	Not strain specific	Clinical	Egg-based
BARDA	Cell-based facility construction	Push	Not strain specific	Clinical	Cell-based
BARDA	Recombinant vaccines development	Push	Not strain specific	Clinical	Next generation technology
BARDA	Next generation assay development	Push	Not strain specific	Clinical	Next generation technology
DARPA	Quick plant-based manufacturing proof of concept	Push	H1	Clinical	Next generation technology
DARPA	Large scale plant-based manufacturing	Push	H1	Clinical	Next generation technology
DARPA	*In vitro* assessment of immune responses	Push	Not strain specific	Clinical	Next generation technology
DARPA	Extending the value of the antigen	Push	Not strain specific	Clinical	Adjuvant
NIAID	Research	Push	Not strain specific	Pre-clinical	Multiple
PATH	Supporting development of live attenuated influenza	Push	H1, H2, H5, H7	Pre-clinical/clinical	Next generation technology

	vaccines (LIAV)				
PATH	Developing recombinant influenza vaccines	Push	Not strain specific	Pre-clinical	Next generation technology
PATH	Developing vaccines with non-propriety adjuvants	Push	Not strain specific	Pre-clinical/clinical	Adjuvant
PATH	Broadly reactive (universal) vaccines	Push	Not strain specific	Pre-clinical	Next generation technology

Current incentives for pandemic influenza vaccines: BARDA

The US Department of Health and Human Services (HHS) Biomedical Advanced Research and Development Authority's (BARDA's) efforts are focused on products that are in the clinical phases of development or in some cases are already marketed. The HHS entity views itself as an advanced development organization. Companies at earlier stages of development are directed to the NIAID to develop the technology. Most of the work is done by contract, with multiple contracts granted for most programs.

BARDA's main pandemic preparedness programs include:

1) **Cell-based influenza vaccine development**. In 2005-06, six contracts were awarded to Sanofi Pasteur, MedImmune, GSK, Solvay, DynPort Vaccine Company LLC (DVC)/Baxter and Novartis to develop influenza vaccines manufactured using cell culture technology. Three of these programs remain active today: DVC/Baxter, GSK and Novartis. Developing manufacturing capabilities in cell culture is a BARDA priority since the traditional method of manufacturing influenza vaccines is egg-based, and the egg supply could become endangered in the event of an avian influenza outbreak.

2) **Year round egg supply guarantee for influenza vaccine manufacturing**. In that same vein, in 2005 BARDA launched a program to ensure that egg-producing flocks birds of would be available year-round to supply influenza vaccine manufacturers in the event of a pandemic. Traditionally, influenza vaccine manufacturers procure eggs only for the window of the year when they are producing seasonal influenza vaccine. Were a pandemic to emerge, sufficient eggs supplies to produce vaccine would also need to be available.

3) **Pre-pandemic vaccine stockpiles.** In 2005, BARDA initiated the first contracts to produce H5 vaccine for stockpiles. This program was originally with Sanofi Pasteur and has been expanded to include contracts with Novartis and GSK for procurement of both antigen as well as adjuvant for the stockpiles. BARDA is stockpiling with the goal of having enough vaccine for 20 million people in the critical workforce, should there be an influenza pandemic, and currently has enough vaccine to do that for a multiple high risk strain of H5.

4) **Antigen-sparing technology development.** This program has awarded contracts to InterCell, GSK and Novartis, with the GSK and Novartis programs remaining active. The goal is to expand the supply of pre-pandemic and pandemic influenza vaccines available at onset and during an influenza pandemic by optimization of antigen content using available adjuvants. GSK filed for a Biologics License Application for US Food and Drug Administration (FDA) approval of their adjuvants with pandemic vaccines in February of this year.

5) **Retrofitting to enhance manufacturing capacity**. This program awarded contracts to MedImmune and Sanofi to retrofit existing facilities in the US to enhance their influenza vaccine manufacturing capacity. In the case of MedImmune, there is sufficient production of its live attenuated vaccine and the BARDA contracts seeks to overcome the rate limiting step of filling the vaccine. In the case of Sanofi, BARDA is helping to double the influenza vaccine manufacturing capacity by building a new facility.

6) **Cell-based facility construction**. This program's largest single award is to Novartis, to support the building of a domestic US facility that can produce 150 million doses of cell-based influenza vaccine within six months of a pandemic declaration.

7) **Recombinant vaccines development**. BARDA has also awarded contracts to support the development of recombinant influenza vaccines at Protein Sciences, Novavax and VaxInnate. The next-generation technology platforms these companies are developing could produce influenza vaccine faster and possibly with higher efficacy than existing egg- and cell-based manufacturing methods.

8) **Next generation assay development**. BARDA is also sponsoring efforts to develop next-generation assays for influenza manufacturing with the goal of reducing manufacturing time for pandemic influenza vaccines by 1-2 weeks. In particular, there is interest in reducing the time associated with the Single Radial Immunodiffusion (SRID) assay, which determines the specific antigen concentration in the vaccine, and the sterility assay, which tests for vaccine sterility.

Current incentives for pandemic influenza vaccines: DARPA

The US Department of Defense (DOD) Advanced Research Projects Agency's (DARPA's) efforts are focused on developing basic platform technologies and working on problems of importance to national defense that are hard and high risk and therefore unattractive to industry, but if solved could beget both defense and commercial applications.

DARPA's main pandemic preparedness programs, all under the aegis of Blue Angel, are focused on development of a recombinant DNA plant-based expression platform. Influenza is a proof of concept for this platform, which DARPA is also considering for manufacture of a recombinant nerve agent, monoclonal antibodies, and other products that could demonstrate the versatility of the platform.

These programs include:

1) **Quick plant-based manufacturing proof of concept**. DARPA awarded contracts to four companies with plant-based manufacturing platforms: Fraunhofer USA Center for Molecular Biotechnology in Delaware, Kentucky Bioprocessing in Owensboro, a consortium called Project GreenVax, whose partners are the Texas A&M University system and a Texas company called G-Con, and Medicago USA in North Carolina (Pellerin 2012), and asked them to demonstrate that they can manufacture an H1 protein.

2) **Large scale plant-based manufacturing**. All of these companies then advanced to demonstrate their large scale manufacturing capabilities at scale and under GMP. Companies are tasked with producing 1 kilogram of antigen in 30 days, or 10 million doses in one month of recombinant protein.

3) ***In vitro* assessment of immune responses**. DARPA contracted with VaxDesign (now a subsidiary of Sanofi) in Florida to develop a cell-based antibody readout system that determines if an antigen will be immunogenic in humans. The goal of the program is to help select lead candidates for clinical trials and reduce unnecessary development expenses.

4) **Extending the value of the antigen**. Like BARDA, DARPA is also interested in exploring the use of adjuvant technologies. DARPA has contracted with the Infectious Disease Research Institute (IDRI) in Seattle to use its GLA adjuvant, which has a mechanism of action similar to others the FDA has approved.

Current incentives for pandemic influenza vaccines: NIAID

According to the US National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID), developing new and improved vaccines is a high priority. The NIAID influenza vaccine program supports research activities in the following areas (NIAID 2012):

- Innovative technologies to improve production flexibility
- New, more broadly protective vaccines
- Vaccines effective against newly emerging influenza viruses
- Adjuvant development, from early discovery to clinical evaluation
- Safety and efficacy in special populations

Current incentives for pandemic influenza vaccines: PATH

The Program for Appropriate Technology in Health (PATH) sees itself as complementing what pharma companies and governments may do to combat pandemic influenza, and vaccine development is a relatively new part of PATH's portfolio. Funding for PATH's operations is provided primarily by the Gates Foundation. One exception is a rare international program funded by BARDA, whereby PATH is helping a vaccine manufacturer in Vietnam produce a pandemic vaccine.

PATH's main influenza vaccine project (IVP) has four components:

1) **Supporting development of live attenuated influenza vaccines (LAIV).** PATH is partnering with Russia's Institute of Experimental Medicine (IEM) to develop LAIVs, similar in technology to MedImmune's FluMist, for avian influenza viruses. LAIVs hold the potential to be produced inexpensively, quickly, and in large quantities, which could lead to a more efficient response in

both pandemic and seasonal outbreaks, and generally delivered through droppers or nasal spray devices, which can reduce reliance on needles and enable non-medical personnel to administer the vaccine in a global outbreak.

PATH has supported IEM's efforts to develop an H7N3 vaccine, which is now in phase I clinical trials in Russia, and funds identification of seed strains for other viruses of pandemic potential, including H1N1 (developed in 2009), H5N1 (three candidates completed preclinical testing, one phase I trial is ongoing and there are plans for a potential second trial), and H2N2 (preclinical development in progress). (Kathleen M. Neuzil 2012)

All LAIVs developed under this partnership agreement can be sublicensed by the WHO to companies in developing countries.

2) **Developing recombinant influenza vaccines**. Like BARDA and DARPA, PATH is also interested in developing recombinant influenza vaccines. PATH's contract is with Gaithersburg, Maryland-based Lentigen and is currently at the preclinical stage of testing for avian influenza subtypes. PATH believes that unique advantages to this approach could include high production yields of VLPs in a portable and disposable manufacturing system, which could lead to heightened real-time response capacity in a pandemic. (PATH, Influenza vaccine development n.d.)

3) **Developing vaccines with non-propriety adjuvants**. As like BARDA and DARPA, PATH has recognized that adjuvants will likely be a requirement to achieve sufficient pandemic influenza vaccine immunogenicity in people who are immunologically naïve to the circulating strain. As such, PATH is collaborating with Seattle's IDRI (which is also working with DARPA on a separate

initiative) to develop adjuvants that are not proprietary and can be licensed broadly by companies in the developing world. A second phase of this collaboration will involve studies of developed adjuvants with vaccine candidates to identify leading vaccine-adjuvant candidates (Infectious Disease Research Institute 2010).

4) **Broadly reactive (universal) vaccines**. For this initiative, PATH is partnering with Medicago to use its plant-based virus-like particle (VLP) manufacturing platform to produce antigen based on research from the University of Pittsburgh, which has a computational approach to design broadly reactive hemagluttinin (HA) antigen on the surface of VLPs. The Pittsburgh approach modifies a sequence of HA to create a synthetic molecule that can then be recognized and create the immunity against all previous historic strains of influenza, and perhaps create immunity against emerging strains as well. (PATH, Agreements signed to advance research for broad-coverage influenza vaccines 2010)

Chapter 3: Research design

Hypotheses and key questions

The apparent dearth of vaccines in development for known strains of pandemic potential is extremely concerning. This thesis seeks to understand what incentives would effectively encourage the private sector to invest greater resources in developing vaccines for these strains. Specifically, this thesis aims to answer three sets of questions:

1) What are the corporate goals of influenza companies? What are the goals of government agencies that work together with these companies on pandemic influenza programs?
2) What is the decision-making process for initiation of influenza vaccine programs within for-profit companies, particularly for strains of pandemic potential? What is the role of any outside incentives or partnerships in vaccine development?
3) What incentive mechanisms, financial or otherwise, could induce additional private investment in vaccines for strains of pandemic potential? (see Figure 4: Types of Incentives for Neglected Diseases)

This thesis sought to test six hypotheses related to the above questions. These hypotheses are:

1) There is a dearth of vaccines against known influenza strains of pandemic potential H2, H7 and H9
2) Funding agencies for pandemic influenza have not focused efforts on H2, H7 and/or H9
3) For-profit vaccine developers require an economic rationale to develop and commercialize a vaccine
4) Developing vaccines against H2, H7 and /or H9 is not a profoundly difficult scientific problem

5) Developing vaccines against H2, H7 and /or H9 is uneconomic for for-profit vaccine developers under current conditions
6) New financial incentive mechanisms will induce investment in and development of H2, H7 and H9 influenza vaccines

Methods

To answer these questions and test these hypotheses, I first performed a descriptive analysis of the ADIS R&D Insight drug pipeline database (ADIS R&D Insight 2012) to quantify and characterize the extent of influenza vaccine development. I then conducted primary qualitative research with key stakeholders in pandemic influenza, using the ADIS database to identify target interviewees. Two sets of companies were characterized:

1) Those with programs in H2, H7, and/or H9.
2) Those with programs for other strains of influenza. This group was sorted and prioritized according to the number of programs ongoing.

I initially deemed only the latter group "at risk" because companies in that group could choose to pursue vaccine development for high risk strains under the right conditions. However, I later realized that all companies in my sample were "at risk," since none were working on vaccines for all strains of known pandemic potential.

In addition, I noted that many of these companies had significant operations in the US and had received funding from outside entities. US government agencies and non-profits providing significant funding in influenza were then also added to the target list:

- US Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA)

- US Department of Defense Advanced Research Projects Agency (DARPA)
- US National Institutes of Health National Institute of Allergy and Infectious Diseases (NIAID)
- Program for Appropriate Technology in Health (PATH)

Furthermore, in an attempt to capture broad industry insights, I sought to speak with known influenza industry experts.

The target list for interviews was as follows:

Table 2: Target Company Interview List

Company	Type	Recent influenza vaccine company acquisitions	Neglected high risk strains	Other pandemic influenza strains
Sanofi Pasteur	Pharma	Acambis	H7	H1, H5
Novartis	Pharma		H9	H1, H5
Baxter	Pharma		H9	H1, H5
GlaxoSmithKline (GSK)	Pharma	ID Biomedical Corporation	H2	H1, H5
Crucell (a Johnson & Johnson subsidiary)	Biotech	Berna Biotech	H7, H9	H1, H5
Abbott	Pharma	Solvay	N/A	H5
CSL	Pharma		N/A	H1, H5
Merck	Pharma		N/A	N/A
AlphaVax	Biotech		N/A	H1, H5
Medicago	Biotech		N/A	H1, H5
MedImmune (a subsidiary of AstraZeneca)	Biotech		N/A	H1, H5
Novavax	Biotech		N/A	H1, H5
PowderMed (a subsidiary of Pfizer)	Biotech		N/A	H5
Protein Sciences Corporation	Biotech		N/A	H1, H5
Serum Institute of India	Biotech		N/A	H1, H5
Sinovac Biotech	Biotech		N/A	H1, H5
Vaxart	Biotech		N/A	H1, H5
Vaxine	Biotech		N/A	H1
VaxInnate	Biotech		N/A	H1, H5
Visterra	Biotech		N/A	H1, H5

Interviews were conducted primarily over the phone (with selected interviews were in person), with all but a few conducted between March and May 2012. The duration was typically 45 minutes to one hour. Interviews were scheduled through personal introductions and LinkedIn expertise requests. Interviewees included individuals from senior management, program management, regulatory affairs,

marketing, business development, and other functions. Some answers to questions were prompted, and some were unprompted.

In total, I conducted 20 interviews with current or recent former employees of the following 18 organizations:

Figure 5: Interviewees

	Clinical stage programs in H2, H7 and/or H9	Clinical stage programs in other influenza
Pharma	-GlaxoSmithKline -Novartis -Sanofi Pasteur	-Abbott / Solvay -Merck
Biotech	-Crucell (now a Johnson & Johnson subsidiary)	-Medicago -MedImmune (now an AstraZeneca subsidiary) -Protein Sciences Corporation -Novavax -VaxInnate -Visterra
Funding agency	-U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) -U.S. Department of Defense's Defense Advanced Research Projects Agency (DARPA) -Program for Appropriate Technology in Health (PATH)	

Additional discussions with:

-Biotechnology Industry Organization Biodefense and Pandemic Working Group

-Center for Infectious Disease Research and Policy

-Kleiner Perkins Caufield & Byers Pandemic and Biodefense Fund

Chapter 4: Results

Hypothesis 1: There is a dearth of vaccines against known influenza strains of pandemic potential H2, H7 and H9

Influenza vaccines in development

I found that clinical development in influenza strains H2, H7 and H9 is currently lacking. Of the 119 influenza vaccines in preclinical or clinical development, only three target strains of H2, H7, or H9. In contrast, there are 25 projects for H1 and 30 projects for H5 at the same stages of development. In addition, among vaccines that are registered or marketed, the sole H2, H7 or H9 vaccine is an H9 mockup registered in Europe by Novartis following co-development with the NIAID. In contrast, there are 13 vaccines marketed or registered for H1 and ten for H5 in the US.

Figure 6 below provides an overview of influenza vaccines in development. This clearly demonstrates that, relative to other strains of pandemic potential H1 and H5, the strains H2, H7 and H9 are not a focus of vaccine development. This provides strong evidence to support my first hypothesis that there is a dearth of vaccines against known influenza strains of pandemic potential H2, H7 and H9.

Figure 6: Influenza Vaccines in Development (Author's analysis) (ADIS R&D Insight 2012)

	Discontinued Suspended	Preclinical	Phase I	Phase II	Phase III	Registered Marketed
H2	SKF 106160 - GlaxoSmithKline					
H7	Influenza monoclonal antibodies – Kirin Pharma	Influenza monoclonal antibodies – Crucell	H7N1 influenza virus A vaccine – sanofi pasteur/FLUPAN			
H9	Influenza virus H9N2 vaccine - Crucell		Influenza A virus vaccine H9N2 - Baxter			Pandemic influenza A virus vaccines - Novartis/NIAID
H1	2	11	10	4	0	13
H5	4	14	13	3	0	10
All other	40	44	7	6	2	15

Hypothesis 2: Funding agencies for pandemic influenza have not focused efforts on H2, H7 and/or H9

Funding agency goals

The goals of funding agencies tend to be specific and clearly elucidated. Selected goals are listed below.

BARDA:

1) Establish and maintain dynamic pre-pandemic influenza vaccine stockpiles available for 20 million people (two doses per person). So far, this program is limited to H5N1.
2) Provide pandemic vaccine to all US citizens within 6 months of a pandemic declaration (600 million doses, assuming two doses per person and 300 million US citizens), with the first doses available by week 12 of the pandemic.

DARPA: DARPA's pandemic influenza efforts were initiated in 2009 and are known as the Blue Angel program. Vaccine-related goals for Blue Angel are to develop a surge capacity, and include:

1) Identifying new ways to produce large amounts of high-quality vaccine-grade protein in less than two months in response to emerging and novel biologic threats, including pandemic influenza.
2) Developing a Modular IMmune In vitro Constructs (MIMIC) system to test vaccine produced using plant-based manufacturing methods to ensure it is safe and immunogenic.

To ensure successful contract completion, DARPA also tells awardees that the long term goal of projects is an FDA-approved product. This is driven by a belief that companies with commercially viable products are more stable partners for the Department of Defense in the long run. Thus, DARPA seeks to fund companies with dual use for their technologies—both a biodefense purpose that DARPA can fund (i.e. pandemic influenza) and another purpose that a commercial market can support (i.e. seasonal influenza).

PATH: PATH's stated goal is to advance the development of promising new vaccine technologies that the global population, including people in low-resource countries, can access and afford in influenza outbreaks.

Funding agency decision-making

BARDA: BARDA relies heavily on colleagues at the Centers for Disease Control (CDC) to do surveillance on the viruses in circulation. Depending on the perceived threat of a circulating strain (i.e. how many cases there are in humans, severity of illness, rate of person-to-person transmission), BARDA then

consults with agencies from across the US government, including the FDA, CDC, NIH, DOD and HHS to determine the next best course of action.

Requests for proposals or task orders would then be issued in a stepwise approach:

1) Determine whether a vaccine candidate for the strain of concerns exists. If so, this is given to a vaccine manufacturer. If not, one is developed.
2) Production of a batch of vaccine candidate antigens to determine compatibility with the manufacturing platform.
3) Production of reagents to determine the antigen yield, the amount of antigen the manufacturing platform is able to produce.
4) Clinical trials to determine immunogenicity (provoked immune response) of the antigen in various age groups and dosing regimens, and to determine whether addition of an adjuvant is warranted.
5) Full scale manufacture.

DARPA: DARPA chose to focus on influenza for two reasons:

1) It became a target of opportunity in the wake of the 2009 H1N1 pandemic, and was fundable (Blue Angel began in May 2009 when the pandemic was in full force).
2) With influenza, unlike other biodefense and countermeasures threats, it is possible to conduct human clinical studies. This allows DARPA to understand if a technology platform works, and if it does, the technology or platform is deemed less risky and can become viable for industry to further develop.

Given the timing and reasoning for the launch of Blue Angel, H1 was a logical choice among influenza strains to demonstrate that the technology platforms could produce proteins in the necessary time frame.

PATH: PATH believes in the importance of identifying seed strains and candidate vaccines for pandemic viruses, noting that, with influenza, no one really knows which strain will cause a pandemic. PATH believes in creating several potential vaccine candidates, testing them for safety at minimum, and keeping them in reserve, so if a particular strain does start a pandemic, there is a quicker way to develop vaccine. Accordingly, PATH has pursed development of H7N3 and H2N2 candidate vaccines. PATH works closely with the WHO and uses the WHO surveillance network to identify strains of concern.

We see from a review of key funding agencies that H2, H7 and H9 are not an area of specific emphasis. Their programs, as laid out in Table 1, also demonstrate that the H2, H7 and H9 strains are not the targets of current programs. In addition, we see from funding agency decision-making processes that, with the exception of PATH, there is not a clean path to funding a vaccine for a high-risk strain prior to escalated pandemic potential. This supports my second hypothesis that funding agencies for pandemic influenza have not focused efforts on H2, H7 and/or H9.

Hypothesis 3: For-profit vaccine developers require an economic rationale to develop and commercialize a vaccine

Vaccine developer goals

The goals of pandemic influenza manufacturers are typically two-fold:

- Return on investment
- Broader corporate citizenship

According to one company executive, "The business case for a pandemic vaccine has always been a difficult one. A company has to put a lot of effort, resources and money into a product that may never be marketed. There has always been a lot of discussion around it. The other side of the coin is the corporate citizenship and social responsibility. Companies have an obligation to prepare the world for a pandemic, such as the one that occurred in 1918. But it's always a balance between that and a reasonable business model."

The relative prioritization of these two attributes varies by company. Some interviewees suggested that influenza vaccine manufacturers may not seek to profit off of vaccine development for pandemic influenza to support the public good, though these companies would not want to lose money either. However, interviewees associated with venture-backed companies indicated a need to create a return on investment for shareholders, but argued that creating value for patients and governments by producing safe and efficacious vaccines is a means to that end.

Representatives from companies that are not active in developing pandemic influenza technologies cited the inability to achieve a sufficient return on investment as the reason. This is due to:

- Need for further investments to achieve uncertain revenues
- Inability to differentiate technology and to capture a price premium

These interviewees considered the market for seasonal influenza vaccines to be crowded and commoditized, and cited these reasons for their companies' decisions not to participate. Because they do not have facilities and manpower available from their seasonal programs, these companies have significantly higher costs (personnel, manufacturing technology, etc.) associated with entering pandemic influenza, and also choose not to participate there.

Vaccine developer decision-making

Companies' decisions to initiate programs are aligned with their corporate citizenship and return on investment goals.

- **Many companies take initiative in beginning work with new seed strains.** When there is a potential pandemic strain identified by the WHO or CDC, a company might start experimenting with it without waiting for a specific government request. Company representatives in general did not want to discuss their criteria for deciding when to initiate work with given seed strains, viewing it as trade secrets.
- **In the absence of government involvement, vaccine candidates will not advance.** Some company representatives lamented that they could do more in terms of producing theoretical pandemic strains. Though these manufacturers do work on theoretical strains, funds devoted to such work divert resources from programs with clearer revenue potential. Again, the point at which a developer might stop working with a seed strain in the absence of a specific government request was viewed as a trade secret by interviewees.
- **Decision to initiate a vaccine program against a strain of concern is driven by a specific government request.** A request from BARDA, however, would significantly improve the chances of advancing a vaccine candidate. This request is in effect a hybrid "pull" mechanism that reduces the market risks associated with pandemic influenza vaccine development, as the developers know that the US government is interested in purchase of such a vaccine.

Most interviewees described similar rationales for their companies' business decision-making: There are roughly four pandemics per century, which amounts to about one every 25 years. All companies are looking for a viable business opportunity in a shorter time frame. They do not

know which strain form the pandemic may take, or if a competitor vaccine will emerge in the interim before the pandemic arises. In that environment, who is going to invest a lot of money in developing a vaccine for a pandemic that may never happen in our lifetime? Unless there is a worried government with funding, they likely will not.

Companies do believe there are benefits in working with pandemic candidate strains prior to a pandemic. These include:

- Developing comfort with compatibility of strains to manufacturing platforms. This includes both the ability to produce the antigen as well as the antigen yield.
- Developing understanding of the possible dosing required for an immunogenic vaccine. Particularly if a strain has not circulated in the population for a while, a large dose, an adjuvanted dose (antigen plus an adjuvant that that enhances the body's immune response to the antigen), and/or two doses may be required to achieve an immune response
- Providing an opportunity to study different adjuvant approaches
- Providing an opportunity to do an efficacy study in the event of a pandemic. Seasonal influenza vaccine clinical trials are expensive to run because of the large numbers of patients needed to show efficacy. At time of a pandemic, fewer patients are needed for such a clinical trial. So, a company that has advanced a candidate far enough along to run a clinical trial with it in a pandemic setting will have a dataset it can take away and use to support the efficacy of its platform technology.

Employees of vaccine developers note that most pandemic influenza programs are focused on H1N1 and H5N1, the two highest profile strains in recent years. The following reasons are cited for this focus:

- H1N1's speed of spread in 2009-10

- H5N1's continued circulation and high mortality rate when it crosses over into humans

Other strains of pandemic potential have not garnered the same level of attention from BARDA, DARPA, NIAID and PATH and thus have not generated significant attention among vaccine developers. This is directly reflected in the paucity of programs for strains of H2, H7 and H9. I found that vaccine developers require a return on investment to advance a clinical program, and that without a specific government request establishing a market for a developed vaccine, vaccine candidates will languish. This clearly supports my third hypothesis that for-profit vaccine developers require an economic rationale to develop and commercialize a vaccine.

Hypothesis 4: Developing vaccines against H2, H7 and /or H9 is not a profoundly difficult scientific problem

One possible explanation for the lack of vaccines against H2, H7 and H9 is that developing such vaccines poses a great technical challenge to vaccine developers. Interviewees report that influenza vaccine developers use their manufacturing technologies as platforms for producing seasonal and pandemic vaccines. These platforms are capable of producing various strains of pandemic potential. Moreover, it is not uncommon for vaccine developers to test this capability to see if various influenza strains can be incubated in a firm's manufacturing platform (such as eggs), and whether a reasonable yield of antigen can be obtained.

Given the absence of evidence to the contrary, interviewees confirmed that producing vaccine against other strains is not significantly more difficult than producing vaccine against seasonal strains, H5N1 or H1N1.

Another possibility is that this is a futile effort for companies. Current and even next-generation influenza vaccine technologies require a specific seed strain to be identified before vaccine production can commence. Thus, in the absence of WHO/CDC efforts to identify seed strains and associated reagents, development of a candidate vaccine cannot commence.

Neither of these points suggests that development of pandemic influenza vaccines is impeded by a gap in scientific knowledge, supporting my fourth hypothesis that developing vaccines against H2, H7 and /or H9 is not a profoundly difficult scientific problem.

Hypothesis 5: Developing vaccines against H2, H7 and /or H9 is uneconomic for vaccine developers under current conditions

Yet another possibility to explain the dearth of vaccines against H2, H7 and H9 is that manufacturers lack the proper economic incentives to invest in vaccines. Given the uncertainty surrounding the timing, severity and strain of the next pandemic; the time of manufacture vaccine; and the public acceptance of vaccines, this seems a logical explanation. The market for pandemic influenza vaccines is complex and, as in any market with uncertain demand, market failure remains a distinct possibility.

Barring future financial incentives from BARDA, DARPA, PATH or another entity, interviewees view the further development of vaccines for strains of pandemic potential as unlikely.

Many companies will continue to experiment with seed strains, but actual development of candidate vaccines will continue to languish in the current funding environment.

This clearly supports my fifth hypothesis that developing vaccines against H2, H7 and /or H9 is uneconomic for vaccine developers under current conditions.

Hypothesis 6: A new financial incentive mechanism will induce investment in and development of H2, H7 and H9 influenza vaccines

Financial incentives

As mentioned earlier, interviewees in general are positive about the current incentives for pandemic preparedness that are illustrated in Table 1. However, they view these incentives, which are almost exclusively "push" mechanisms (the one "pull" mechanism noted is for strains of H5) as insufficient to create the desired investment in vaccines against neglected, high risk pandemic influenza strains.

There is also a need for top-line, revenue support, executives said. "If look at simple things like NPV [net present value] calculations, commercial forecasts, any kind you make for pandemic is going to be wrong. It is completely unpredictable when a pandemic will occur and how big it will be. In terms of business decisions, in terms of a business case, pandemic will always be at the end of the line—so you need some financial support," one pharma executive noted.

Interviewees from vaccine developers proposed several ways in which governments or non-profits like PATH could financially support pandemic influenza preparedness efforts.

Pharma companies with pandemic influenza programs benefit from built up manufacturing capacity and regulatory known-how, and viewed themselves as best equipped to benefit from the programs to address neglected, high risk pandemic influenza strains.

However, smaller biotechs also suggested some programs and indicated a willingness to participate when their manufacturing capacity and in-house knowledge made feasible. One interviewee from a biotech expressed a "need to focus" on flagship programs. Like H5 has for some biotechs, however, other neglected, high risk strain could be elevated in importance with the right government incentive.

Interviewees' proposals are all for "pull" mechanisms, and include:

Developing pandemic capacity reservation systems. Multiple companies have used these in the past or are currently exploring them with partner governments, particularly in Europe where many countries lack dedicated influenza vaccine manufacturing capacity.

Government subscriptions for pandemic capacity can help to subsidize the cost of maintaining personnel and infrastructure that might not be needed for normal seasonal production; this is known as maintenance of a "warm base."

According to interviewees, the concept of pandemic capacity reservation systems—also known as advance purchase agreements, or APAs—was developed in 2005. These were directed at a possible H5N1 pandemic which was of particular concern in 2005. According to interviewees, several EU countries (France, Germany, Italy, the United Kingdom and some Nordic countries) entered into APAs that paid companies a one-time fee to reserve manufacturing capacity for them that would be triggered by a declaration of a pandemic. Some of these agreements were structured as call options, and at the time of an H5N1 pandemic, countries could "call" their option to have priority manufacturing capacity and pay the vaccine manufacturer to produce vaccine for them.

Importantly, one executive reports that the current renewals of such APAs may have two fundamental differences: 1) they will not be restricted to H5 and so could require companies to be prepared for the other strains that could have pandemic potential, such as H2, H7 and H9; and 2) they should pay the companies a reservation fee annually for maintaining pandemic preparedness.

"A few countries are moving in this direction but others will need to follow in order to create the necessary incentives," the executive stated.

Specific government request such as an APA agreement that provides annual funding for being pandemic ready and reserving capacity for the government that pays the annual fees could provide the "pull" needed for investment in vaccines for neglected, high risk strains. Companies with existing manufacturing capacity and regulatory known-how (primarily pharma) suggested this incentive and viewed themselves as best equipped to benefit from it.

Priming a population against strains of known pandemic potential. This is an approach that multiple companies mentioned could be financially attractive and is something they have considered internally, but they see it as less feasible in the current environment of funding and public vaccine acceptance. The benefit of vaccination with a strain prior to a pandemic could be considerable if a strain does circulate at a later date. Doing so would prime the immunized population, giving them immune system exposure. Later, if the strain were to circulate, immunized individuals might only need one, not two doses to gain immune protection, particularly if the priming vaccine included an adjuvant. Priming could also potentially reduce the severity of disease upon exposure.

Priming could entail multiple forms, such as including a potential pandemic strain every year in the seasonal formulation; developing a vaccine that is a cocktail of antigens, not unlike the annual seasonal vaccine that combines multiple strains of influenza; and developing single antigen pre-pandemic vaccines (Klaus Stohr 2010).

Again, companies with existing manufacturing capacity and regulatory known-how (primarily pharma) suggested this incentive and viewed themselves as best equipped to benefit from it.

Creating national antigen stockpiles with a variety of influenza strains. Currently, the US stockpile that BARDA funds includes multiple strains of H5 but none of other influenza types. Interviewees suggested that, with funding, BARDA (or other governments) could expand this program to include other strains of known pandemic potential.

These stockpiled antigens will likely not be strain-matched perfectly with whatever strain may circulate in the future. However, a government could use the best matched strain to vaccine during the first wave of a pandemic, when manufacturing of strain-matched vaccine is ramping up.

Both pharma and biotech influenza vaccine developers viewed themselves as appropriate for this incentive. The recurring costs (to the government, otherwise known as revenue to the vaccine developer) were viewed as attractive.

Creating national adjuvant stockpiles. Similarly, interviewees noted that adjuvants will very likely be needed to render manufactured pandemic influenza vaccines immunogenic, and stockpiling adjuvants

to ensure sufficient national supplies thus makes a lot of sense. Through BARDA, the US government is currently doing this, and other governments could as well.

The stockpiled adjuvant could be used in combination with stockpiled antigen to broaden the immune response of the pandemic influenza vaccinations.

Though potentially financially attractive, interviewees noted that this approach is fraught with regulatory issues. Two important ones include: 1) Shelf-life of the bulk antigens and adjuvants; and 2) Compatibility of the adjuvant and the various stockpiled antigens.

Regulatory hurdles aside, both pharma and biotech influenza vaccine developers viewed themselves as appropriate for this incentive.

Other types of incentives

This thesis initially sought to focus only on the financial incentives that companies require to increase investment in pandemic influenza efforts. However, it was clear from all interviewees that financial incentives alone are necessary but not sufficient to change the existing industry dynamic. The chief non-directly financial concerns cited by representatives from industry relate to:

1) Seasonal influenza
2) Regulatory processes
3) Public awareness and vaccine acceptance
4) Public and private sector goal alignment

Seasonal influenza

Among interviewees, there was near universal recognition of the important of seasonal influenza programs to the health of pandemic influenza preparedness. It is a complementary product line that provides a cross-subsidy to pandemic influenza.

One interviewee put it succinctly: "Seasonal is a business, and pandemic is a public health emergency."

The benefits of strong seasonal influenza programs are two-fold, according to interviewees:

1) **Maintenance of a "warm base" of production capacity, skilled personnel and regulatory infrastructure**. Interviewees noted that these attributes are often underappreciated by countries that seek to build pandemic influenza vaccine manufacturing capabilities but lack the seasonal influenza vaccination rates to support utilization of the plant. A "warm base" allows manufacturers to rapidly switch from seasonal to pandemic vaccine production when necessary; interviewees said that lacking the seasonal component can negate the benefit of local pandemic manufacturing capacity.
2) **Regular, recurring revenues to influenza manufacturers.** This benefit is seen as tenuous, many interviewees noted, since historical capacity fluctuations have led to marked changes in the economics of the seasonal business in the US. Some interviewees noted that they thought the US was entering another phase of overcapacity in seasonal influenza and noted that, in the recent past, manufacturers have exited the seasonal business because they could not achieve a sufficient return on investment. Interviewees noted that sufficient pricing and volume (through seasonal vaccination rates) is important to the health of the seasonal influenza businesses at their companies.

Regulatory processes

Interviewees were quick to laud the US Food and Drug Administration (FDA) for its work with Medical Countermeasures (MCMs) initiative that President Obama announced in his 2010 State of the Union address. To help the nation better respond to bioterrorism and infectious disease threats, the FDA developed an action plan based on a three part strategy (FDA n.d.):

1) **Review process**. The FDA seeks to enhance the review process for MCMs by establishing teams to ensure consistent and efficient regulatory approaches.
2) **Regulatory science**. To support MCM development and evaluation, the FDA will explore solutions to complex scientific regulatory problems and identify situations in which the application of new science could simplify or speed product development and/or the regulatory process.
3) **Legal, regulatory, and policy framework**. The FDA will assure that laws and policies support preparedness and response, and will work with partner agencies to develop new approaches where changes are needed.

Despite strides made by the FDA with its MCM initiative, however, there was still a near-universal view among interviewees that regulatory processes for pandemic influenza have significant opportunity for improvement. Interviewees had many suggestions for regulatory reform, including:

Introduction of mock dossiers in the US. The mock-up procedure allows a vaccine to be developed and authorized in advance of a pandemic, based on clinical studies generated with a virus strain that could potentially cause a pandemic. Once the actual virus strain causing a pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for it to be authorized as a final pandemic vaccine (EMA 2012).

This is a feature of the European Medicines Agency (EMA) approval process that many interviewees mentioned would facilitate pandemic influenza vaccine licensure in the US if it was brought here.

Were a manufacturer to follow this procedure, a small immunogenicity study might be the only additional step needed upon pandemic declaration before licensure and marketing of the vaccine.

By contrast, in the US, interviewees expressed frustration with the regulatory processes for pandemic influenza vaccine approval. This has led to the development of influenza vaccines in Europe but not the US, such as Novartis' Aflunov for pre-pandemic H5N1[b].

Non-emergency approval processes for pandemic influenza vaccines. In particular, interviewees were concerned about licensure of pandemic influenza vaccines for strains that are not part of the annual seasonal vaccine, which currently includes influenza A(H1N1) and A(H3N2) subtypes and influenza B subtypes.

Were another strain to emerge with pandemic potential, manufacturers would have two options for approval of a vaccine: licensure as a new vaccine under current FDA rules; or emergency access granted by HHS under the Public Readiness and Emergency Preparedness (PREP) Act. Many interviewees expressed a desire for a sufficiently fast, non-emergency path to approval.

In addition, companies that do not currently have approved seasonal influenza vaccines currently would have to apply for licensure as a new vaccine or appeal to HHS to manufacture vaccine for an H1N1 or

[b] I worked on pre-launch activities for this vaccine

H3N2 pandemic. Interviewees from these companies noted that the PREP act procedure may work, but was not as efficient as the European process for mockups.

FDA/EMA regulatory harmonization. Many interviewees also noted that harmonizing regulatory processes in the US, Europe and other markets could facilitate broader access to pandemic influenza vaccines, particularly in the event of a pandemic.

The mock-up procedure in Europe was very popular with interviewees, as was the relatively easy process for filing for annual strain change updates to the seasonal influenza vaccine in the US.

One idea an interviewee offered was for a hybrid EU/US approach, whereby mockup vaccine candidates would be licensed and their dossiers updated annually to reflect any strain changes. In this way, the mockup would be treated similarly to the annual strain change for the seasonal influenza vaccine, and strain changes that happened over time would carry through to the product.

Clarification of criteria for licensure of new technologies. This is an area lacking clarity from regulatory authorities currently, and is a great source of uncertainty for companies developing new technologies and for big companies looking to acquire them. Interviewees developing recombinant influenza vaccines in particular expressed significant concern that the approval process for their technologies is not yet clarified.

Current regulatory requirements for an efficacy study create what interviewees dubbed a "Catch-22". The requirement for an efficacy study at the time of a pandemic by definition sets them up to fail, interviewees from vaccine developers said. If a pandemic influenza vaccine is studied versus a placebo

or other control in clinical trials, then the vaccine may be approved but people will likely face unnecessary morbidity and mortality. Or, if vaccine developer studies the vaccine versus a known efficacious alternative (this could include another vaccine in development if available or a broad spectrum antiviral), it will be difficult to show a statistical efficacy improvement, and the new vaccine will fail its clinical trial.

Regulatory acceptance and consensus on next generation assay technologies. In addition, many interviewees noted that there is a need to develop next-generation assay technologies that can both speed up vaccine manufacturing technology with current technologies and also be capable of measuring immunogenicity of vaccine produced using new technology platforms.

All interviewees commenting on this issue said they remain unclear on what the regulatory acceptance of these assays will be.

Until current assay technology is phased out, development of reagents for strains of pandemic potential. Interviewees noted that until next generation assays are developed, strain-matched reagents will still be needed to test the immunogenicity of candidate vaccines. Currently, reagents are available for some but not all strains of pandemic potential, and interviewees said that this is a rate-limiting step for companies that seek to develop vaccine candidates for strains of pandemic potential, as they are reliant on the WHO in this regard.

Interviewees noted that additional reagents for other strains of pandemic potential to the WHO's repertoire need not be updated as regularly as seasonal strains. Particularly if a virus of pandemic

potential does not mutate while circulating, then a reagent could remain viable and would not require regular updating.

Public awareness and vaccine acceptance

There is a sense among many interviewees that the US general public does not sufficiently appreciate the public health value of seasonal and pandemic influenza vaccines, and this is reflected in the annual seasonal influenza vaccination rates, which remain less than 50% for the general population despite an HHS target of 80% for persons 6 months–64 years and 90% for adults ≥65 years and adults 18–64 years with high-risk conditions (CDC n.d.).

Public willingness to receive vaccines is essential to any pandemic influenza public health effort, and the need for media and public awareness ranks high on interviewees' lists of concerns.

According to one executive, "The public understanding of severity of the flu; misperceptions about the safety and efficacy of the vaccine; the fact that many adults don't view vaccination as part of their life – view it as something you do to children—all of these are issues for influenza manufacturers."

In addition, since adjuvants may be needed at the time of a pandemic, public concerns around these will also need to be addressed. Concerns about adjuvants safety and adverse effects could be addressed with additional clinical trials, post marketing surveillance, and patient education. However, many interviewees noted that "vaccine phobia," sparked in part by retracted research linking vaccines to autism (CNN 2011), remains a serious concern for industry.

Private-public sector goal alignment

Lastly, some interviewees noted that given the interdependent nature of industry and government in combatting pandemic influenza, there remains a need to ensure that public and private sector goals are aligned.

A BARDA interviewee clearly expressed an understanding of this need, saying: "We will help you [vaccine companies] with your seasonal vaccine business. But you have to help us on pandemic preparedness. It is two groups working together for the public good: more and better seasonal vaccine in the short term, and longer term, pandemic preparedness."

Most interviewees from companies lauded BARDA and its role in creating financial conditions that help private companies invest in public-private goals. As one interviewee from industry noted, "BARDA is a great example of a public private government partnership. Without this funding, it would not be a viable business opportunity. It would not make financial sense for organizations to take that up."

Other interviewees from industry noted that BARDA is working in a rapidly changing industry as new technologies are developed, and that they see a need to clarify what the agency's long term goals are and to align these with the goals of companies.

One executive asked: "In the US, what challenge are we trying to solve? It is supply? [This] may have been addressed. Is it speed? This is going to require new technology. How can this be expedited?"

Interviewees from industry also noted that the government would be the main purchaser of new technologies, and until there is greater clarity on governments' willingness to pay for next-generation technologies, that uncertainty deters further private investment in these technologies.

"If there were some clarity that people would be willing to pay for a product with certain characteristics; that they'll shift from older technologies to newer," claimed one interviewee.

Some interviewees cited the US government's appreciation of the importance of indemnifying vaccine manufacturers as a positive example of public-private sector goal alignment. Under the PREP Act, the US government indemnifies the manufacturers. If there is an untoward side effect profile that no one anticipated during a pandemic, the US government will carry the risk.

Interviewees noted that the US government appreciated this risk during the H1N1 pandemic, and had the NIH run some of the riskier clinical trials on special populations like pregnant women. However, interviewees also noted the risk that not all governments will always accept the notion that vaccine manufacturers require indemnification to deliver pandemic influenza vaccine. "They have short memories," one executive said, "and do not have an understanding of all the risks that could bring a company down."

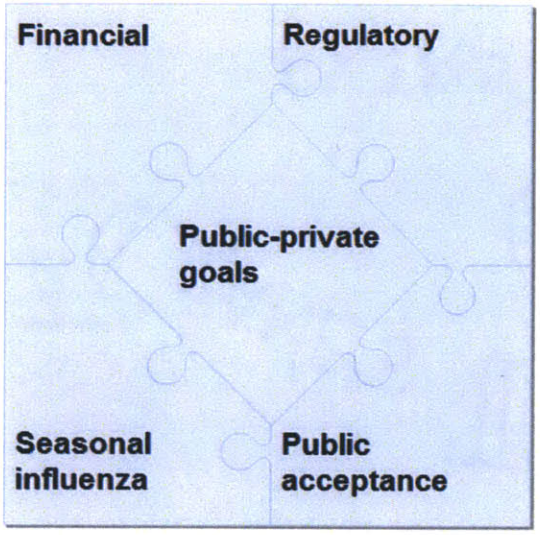
Given the finding that financial incentives alone are necessary but not sufficient to induce investment in H2, H7 and H9 vaccines, there is evidence to conditionally reject my sixth hypothesis that new financial incentive mechanisms will induce investment in and development of H2, H7 and H9 influenza vaccines, with the caveat that financial incentives *plus* other factors (regulatory, seasonal influenza, public

acceptance and public private goals) are needed to change the current pandemic influenza vaccine development paradigm.

Chapter 5: Impact

In the past, when incentive mechanisms for development of treatments for neglected diseases were designed, the policymakers did not speak to the people and organizations intended to be incented. In this thesis, I have not only laid out possible mechanisms for pandemic influenza vaccines as proposed by the intended targets of such incentives, but also a broader framework to support them (please see Figure 7 below):

Figure 7: Incentives Framework for Pandemic Influenza Vaccines



This framework is important for a simple reason: the US, and the world, is not ready for the next influenza pandemic, and despite significant efforts and resources expended to improve preparedness, there is still more to be done.

The laudable efforts by BARDA, DARPA, NIAID and PATH, with a few exceptions, have not focused on developing vaccines for the H2, H7 and H9 strains that are known to be of pandemic potential.

Areas for future research

This thesis could serve as the basis for additional research in a number of areas. Ideally, it can be used to encourage research to better understand the unique challenges facing programs targeting pandemic influenza and biodefense threats, as well as other pandemic threats such as dengue.

At BARDA, one former employee told me that influenza was considered a success story on which to model other programs. She noted that other threats (i.e. biological, radiological, chemical) did not have the seasonal component help establish them as businesses with regular, recurring revenues, and, as a result, there were also not companies presently working in the space with which to partner.

Future research could explore whether lessons from pandemic influenza (e.g. that a seasonal influenza program creates a complementary business line that cross subsidizes the public health emergency efforts in pandemic influenza) are applicable to understanding other biodefense threats, and whether the incentives framework laid out here has broader applicability to these threats.

Chapter 6: Policy recommendations

Three policy recommendations arise from this work:

1) Increase funding for pandemic preparedness to support programs tailored to neglected high risk influenza strains such as H2, H7 and H9

   In 2011, GSK had sales of 248M GBP, approximately 400M USD, across its influenza brands (Annual Report 2011). Novartis Vaccines and Diagnostics had net sales of nearly 2B USD and core operating income of 135M USD across all brands including influenza in 2011 (Annual Report 2011).

   In the context of these financial figures, it stands to reason that additional pandemic preparedness funding in the hundreds of millions of dollars annually would be meaningful to the bottom line of influenza vaccine developers. If this took the form of the "pull" mechanisms described in the Chapter 4 section on financial incentives, it would incent the desired investment in vaccines for neglected, high risk strains.

   In light of predicted BARDA funding shortfalls for technology development (Matheny, Mair and Smith 2008), economic austerity in the euro zone, and the lack of a perceived imminent threat in pandemic influenza, however, this additional funding may languish in the absence of strong political leadership.

2) Harmonize EU and US influenza vaccine regulatory regimes to reduce dis-incentives to pandemic influenza vaccine investment

Back in 2004 at a WHO meeting for pandemic influenza vaccines, one of the conclusions was that "coordination at the regulatory level is needed to improve the regulatory environment and facilitate international marketing of vaccines (WHO 2004)."

As of yet, the FDA and EMA still have important difference in their regulatory processes that were reviewed earlier in Chapter 4. The US has not yet introduced "mock-up" pandemic vaccines as was encouraged in the WHO 2004 meeting (WHO 2004): "All manufacturers should develop internal contingency plans to expedite the switch from production of seasonal vaccines to pandemic vaccines. Such plans should include the testing of "mock-up" pandemic-like vaccines according to established regulatory procedures."

Though harmonization has not been achieved in the past eight years, US and EU authorities should work together to forge a consensus on pandemic influenza vaccine regulatory requirements. Doing so would reduce the cost of developing pandemic influenza vaccines and could help increase global access to them (WHO 2004) (Gronvall and Borio 2006).

3) Promote public awareness of the importance of influenza vaccination to support uptake of the seasonal influenza vaccine and, when necessary, pandemic influenza vaccine as well

This is difficult in light of the barriers to vaccination individuals face—among them fear of needles, convenience, costs, concern about side effects from social media and now-refuted autism scares. Public awareness campaigns about the importance of influenza vaccination, subsidies for seasonal influenza vaccines and accessible vaccination facilities all could help improve the seasonal vaccination rates so they get closer to the CDC's Health People 2020 goals.

Chapter 7: Conclusion

This work has produced the following key observations:

1) There is a dearth of vaccines against influenza strains of known pandemic potential such as H2, H7 and H9
2) Current pandemic preparedness efforts are not focused on these strains
3) Funding for pandemic preparedness efforts in H2, H7 and H9 would help incentivize development of vaccines against these strains
4) Support for seasonal influenza, regulatory changes, alignment of public and private sector goals, and increased vaccine acceptance are also required

In a world of limited public health and biodefense funding, it is not illogical that BARDA, DARPA, NIAID and PATH have focused on the higher priority H1 and H5 strains of influenza. They have also done important work to ensure the health of the domestic seasonal influenza business and made considerable progress in diversifying away from egg-based influenza vaccine production and into cell-based and possibly recombinant technologies. The stockpiles of H5 antigen and various adjuvants that BARDA has funded could also prove to be tremendous value in the event a strain of an H5 with human-to-human transmission capabilities emerges and a pandemic strikes.

This is not enough. The suggestions that the interviewees from industry proffered should be seriously considered to support the health of the industry and protection of the population from the next influenza pandemic.

Stockpiles of influenza antigen, the key ingredient in vaccine that provokes an immune response, and adjuvant, which would likely be needed with pandemic influenza and increases the immune response,

against the latest circulating strains could save lives; regulatory mockups for pandemic influenza vaccines could speed approval; and building familiarity and comfort with manufacturing techniques for these strains can aid in a time of immense strain. Even in an age when we do not yet have universal vaccines that can provide broad protection against many strains of influenza, there are steps we can take to protect against pandemic strains.

Pandemic and biodefense threats are a unique challenge to the traditional public health framework, in which resources are commonly allocated according to the probability of an event and its possible impact. This mentality may be effective for cancer or HIV but is wrong for pandemic influenza.

The consequences of the latter are staggering, even though the probabilities of such events are difficult or impossible to estimate. They are the black swans, the low probability but high impact events that can change history, of public health.

Addressing them requires not only the financial incentives for therapeutic development but also an integrated framework of incentives that:

1) maintains a recurring revenue stream and skilled workforce
2) supports the approval and regulation of therapeutics for diseases that are rare and create challenging clinical trial settings
3) facilitates public acceptance of therapeutics not studied in randomized controlled trials
4) aligns public and private sector goals so that the right treatments for important threats are developed according to agreed criteria

Following this framework is a key step towards protecting the public from not only pandemic influenza, but also the chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, and

emerging infectious diseases that it is BARDA's mission to develop and procure medical countermeasures against.

A comment on H3N2v

At the time of this thesis submission (September 4, 2012), a variant of H3N2 had been recently found responsible for limited person to person transmission. Since July, this strain has sickened almost 300 individuals across ten US states (CDC n.d.) and at the end of August led to its first death (McNeil Jr. 2012).

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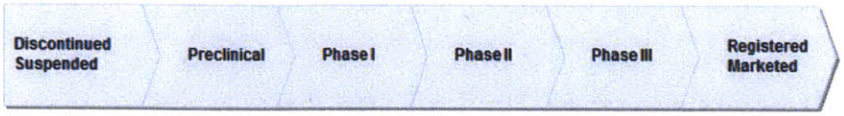
Appendix

Influenza vaccines portfolios

Figure 8: Influenza Vaccines Portfolio – Abbott (Author's analysis) (ADIS R&D Insight 2012)

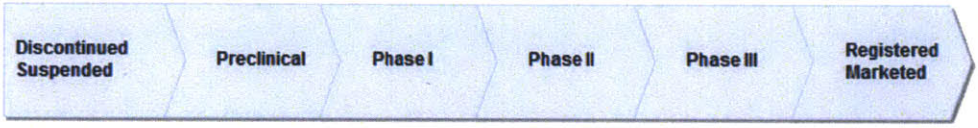
	Discontinued Suspended	Preclinical	Phase I	Phase II	Phase III	Registered Marketed
H5	Influenza A virus H5N1 vaccine - Solvay					
All other					Cell culture-derived influenza vaccine (Influvac TC) - Abbott	Cell cultured-derived adjuvanted influenza vaccine (Grippol TC) - Abbott Egg-derived adjuvanted influenza vaccine (Grippol Plus) - Abbott Influenza virus vaccine liposomal - Crucell [Market Licensee]

Figure 9: Influenza Vaccines Portfolio – GlaxoSmithKline (Author's analysis) (ADIS R&D Insight 2012)



H2	SKF 106160			
H1			Influenza A virus H5N1 cell culture based vaccine	Influenza A virus vaccines
H5				H5N1 (pre-)pandemic influenza virus vaccine
				H5N1 whole virus influenza vaccine (Daronrix)
All other	Research programme: influenza vaccines – with MedImmune	Research programme: influenza vaccines – with Kaketsuken		Influenza vaccine
				Influenza virus vaccine - Sinovac Biotech [Market Licensee]
				Influenza virus vaccine GSK 2282512A
	Inactivated split-trivalent seasonal	Research programme: influenza vaccines – with Shenzhen Neptunus Interlong Bio-Technique		Influenza virus vaccine GSK 2321138A
				Influenza virus vaccine-Fluarix

Figure 10: Influenza Vaccines Portfolio – Merck (Author's analysis) (ADIS R&D Insight 2012)



All other	V 512 Influenza virus vaccine - Merck				Influenza vaccine - CSL Biotherapies [Market Licensee]

Figure 11: Influenza Vaccines Portfolio – Novartis (Author's analysis) (ADIS R&D Insight 2012)

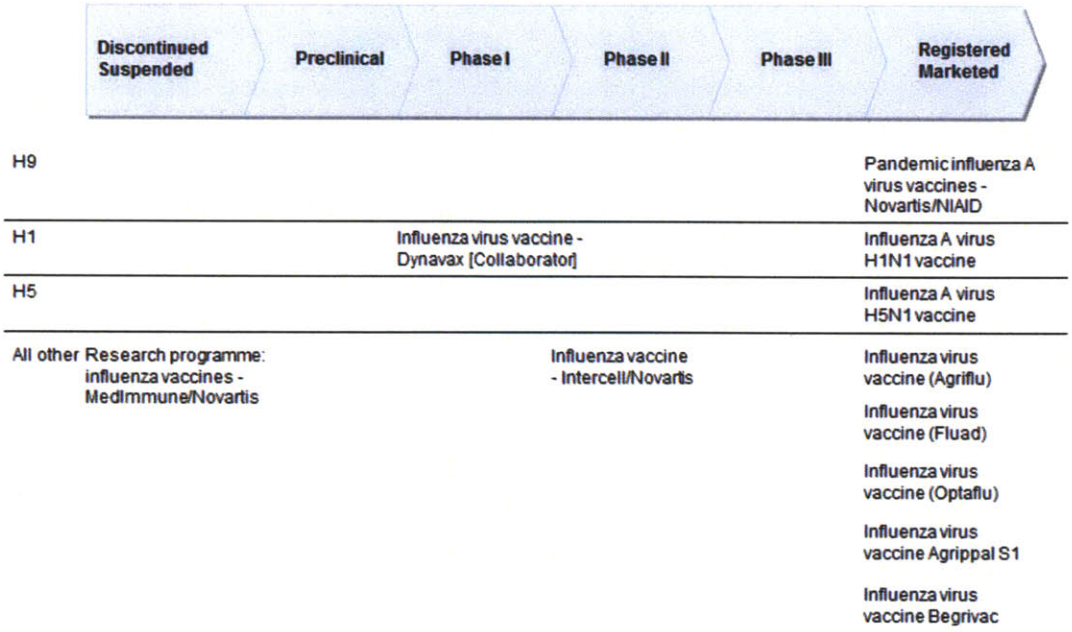
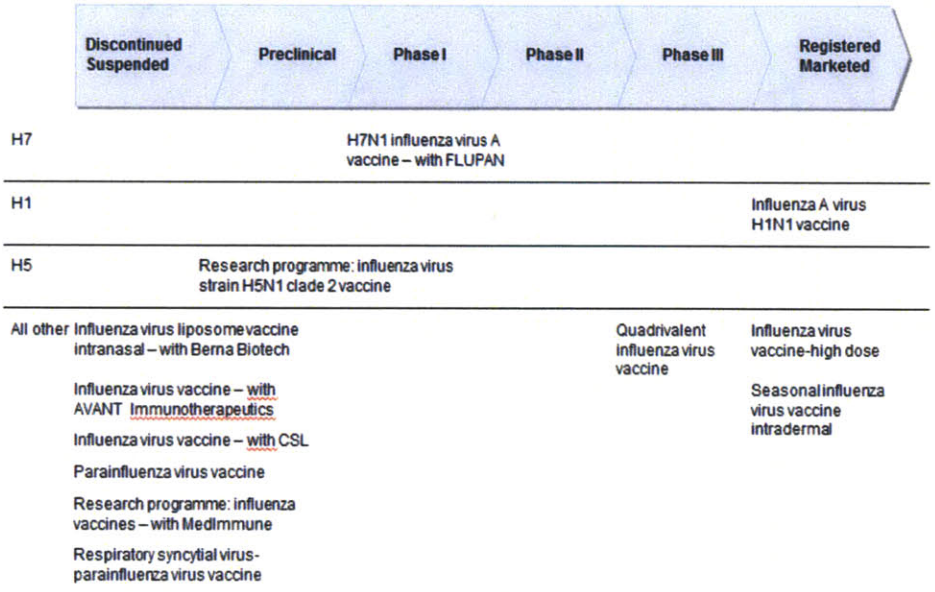


Figure 12: Influenza Vaccines Portfolio – Sanofi Pasteur (Author's analysis) (ADIS R&D Insight 2012)



Influenza vaccines in development: H1N1

Table 3: Influenza Vaccines In Development: H1N1 (Author's analysis) (ADIS R&D Insight 2012)

Drug	Phase	Originator	Other Organizations
Influenza A virus H1N1 vaccine - CEL-SCI	Discontinued/Suspended/No development reported	CEL-SCI Corporation	Johns Hopkins University (Collaborator)
SKF 106160	Discontinued/Suspended/No development reported	GlaxoSmithKline	
Research program: pandemic influenza virus vaccines – AlphaVax	Preclinical	AlphaVax	
Research program: Ii-Key peptide hybrid vaccines - Antigen Express	Preclinical	Antigen Express	Generex Biotechnology Corporation (Owner), Mayo Clinic (Collaborator), Pevion Biotech (Collaborator)
Research program: influenza A H1N1 vaccine - BioAlliance Pharma	Preclinical	BioAlliance Pharma	
CR 6261	Preclinical	Crucell	Janssen Pharmaceuticals (Collaborator)
Research program: influenza A H1N1 vaccine - Etubics	Preclinical	Etubics Corporation	
Research program: substance P derivative - ImmuneRegen	Preclinical	ImmuneRegen BioSciences	BioCure (Collaborator), GenPhar (Collaborator), Hyperion Biotechnology (Collaborator), Lovelace Respiratory Research Institute (Collaborator), National Cancer Institute (USA)

			(Collaborator), Radboud-University-Nijmegen-Medical-Centre (Collaborator), Scancell (Technology Provider), Translational Genomics Research Institute (Collaborator), ULURU (Collaborator), University of Rochester (Collaborator), Virion Systems (Collaborator)
Research program: influenza DNA vaccines - Inovio	Preclinical	Inovio Biomedical Corporation, VGX International	Public Health Agency of Canada (Collaborator), University of Pennsylvania (Collaborator), Vaccine Research Center (Collaborator)
Research program: influenza A virus H1N1 vaccine – Inviragen	Preclinical	Inviragen	
Research program: viral vaccines - Variation Biotechnologies	Preclinical	Variation Biotechnologies	
Research program: H1N1 influenza virus vaccine - Vaxart	Preclinical	Vaxart	
Research program: infectious disease vaccines – VaxInnate	Preclinical	VaxInnate	3M Drug Delivery Systems (Technology Provider)
Influenza A virus H1N1 vaccine -	Phase I	Antigen Express	Generex Biotechnology

Antigen Express			Corporation (Owner)
Influenza virus vaccine - Dynavax	Phase I	Dynavax Technologies	Novartis (Collaborator)
Influenza A virus H5N1 cell culture based vaccine - GlaxoSmithKline	Phase I	GlaxoSmithKline	Intercell (Collaborator)
Influenza A virus H1N1 vaccine - iBio/Fraunhofer USA Center for Molecular Biotechnology	Phase I	iBio Inc	Fraunhofer USA Center for Molecular Biotechnology (Collaborator)
Influenza A virus vaccine H1N1 – Medicago	Phase I	Medicago	
VRC-FLUDNA057-00-VP	Phase I	National Institute of Allergy and Infectious Diseases, Vaccine Research Center	
INO 3510	Phase I	University of Pennsylvania	Inovio Pharmaceuticals (Technology Provider)
H1N1 influenza virus vaccine – Vaxine	Phase I	Vaxine	Protein Sciences Corporation (Collaborator)
VAX 128	Phase I	VaxInnate	
Influenza virus DNA vaccine – Vical	Phase I	Vical	
Influenza virus delta NS1 vaccine	Phase II	Green Hills Biotechnology	
Influenza virus-like particle vaccine (trivalent) – Novavax	Phase II	Novavax	
Attenuated influenza A virus H1N1 vaccine - Serum Institute of India	Phase II	Serum Institute of India	
Inactivated influenza A virus H1N1 vaccine - Serum Institute of	Phase II	Serum Institute of India	

India			
Influenza A virus H1N1 vaccine - Baxter International	Marketed/Registered/Preregistration	Baxter International	
Influenza A H1N1 vaccine - Bharat Biotech	Marketed/Registered/Preregistration	Bharat Biotech	
Pandemic influenza virus vaccine – BioDiem	Marketed/Registered/Preregistration	BioDiem, Nobilon International	Centers for Disease Control and Prevention (Collaborator), Institute of Experimental Medicine of the Russian Academy of Medical Sciences (Collaborator), Serum Institute of India (Collaborator)
Influenza A virus H1N1 vaccine (CSL 425) - CSL Biotherapies	Marketed/Registered/Preregistration	CSL	National Institute of Allergy and Infectious Diseases (Collaborator)
Influenza A virus vaccines - GlaxoSmithKline	Marketed/Registered/Preregistration	GlaxoSmithKline	
Influenza A virus H1N1 vaccine - Hard To Treat Diseases	Marketed/Registered/Preregistration	Hard To Treat Diseases	Zhejiang Tianyuan Bio-pharmaceutical (Collaborator)
Influenza A virus H1N1 vaccine - Hualan	Marketed/Registered/Preregistration	Hualan Biological Engineering	
MEDI 3414	Marketed/Registered/Preregistration	MedImmune, National Institute of Allergy and Infectious Diseases	
Pandemic influenza A virus vaccines - Novartis/NIAID	Marketed/Registered/Preregistration	National Institute of Allergy and Infectious Diseases, Novartis	
Influenza A virus H1N1 vaccine - Novartis	Marketed/Registered/Preregistration	Novartis	
Influenza A H1N1 vaccine - Novavax	Marketed/Registered/Preregistration	Novavax	Centers for Disease Control and

			Prevention (Collaborator), GE Healthcare (Collaborator), National Institute of Allergy and Infectious Diseases (Collaborator), Novavax (Owner), University of Pittsburgh (Collaborator)
Influenza A virus H1N1 vaccine - Sanofi Pasteur	Marketed/Registered/Preregistration	Sanofi Pasteur	National Institute of Allergy and Infectious Diseases (Collaborator)
H1N1 pandemic influenza virus vaccine - Sinovac Biotech	Marketed/Registered/Preregistration	Sinovac Biotech	

Influenza vaccines in development: H5N1

Table 4: Influenza Vaccines In Development: H5N1 (Author's analysis) (ADIS R&D Insight 2012)

Drug	Phase	Originator	Other Organizations
Research program: influenza monoclonal antibodies - Kirin Pharma	Discontinued/Suspended/No development reported	Kirin Brewery	Kyowa Hakko Kirin (Owner)
H5N1 influenza A virus vaccine - Protein Sciences	Discontinued/Suspended/No development reported	National Institute of Allergy and Infectious Diseases	Protein Sciences Corporation (Collaborator)
Research program: H5N1 avian influenza virus vaccine - PowderMed	Discontinued/Suspended/No development reported	PowderMed	
Influenza A virus H5N1 vaccine - Solvay	Discontinued/Suspended/No development reported	Solvay Pharmaceuticals	
Research program: pandemic influenza virus vaccines - AlphaVax	Preclinical	AlphaVax	
Research program: influenza A virus H5N1 vaccines - AmVac	Preclinical	AmVac	
Research program: CEL 1000 - CEL-SCI	Preclinical	CEL-SCI Corporation	National Institute of Allergy and Infectious Diseases (Collaborator), Naval Medical Research Center (Collaborator), Northeastern Ohio Universities College of Medicine (Collaborator), Proxima Concepts (Technology Provider), United

			States Army Medical Research Institute of Infectious Diseases (Collaborator), University of Nebraska Medical Center (Collaborator)
CR 6261	Preclinical	Crucell	Janssen Pharmaceuticals (Collaborator)
Research program: influenza monoclonal antibodies - Crucell	Preclinical	Crucell	Janssen Pharmaceuticals (Collaborator)
Research program: DNA vaccines - CytoGenix	Preclinical	CytoGenix	United States Army Medical Research Institute of Infectious Diseases (Collaborator)
Research program: influenza antibodies and vaccines - EPIC BIO	Preclinical	EPIC BIO	
Research program: influenza DNA vaccines - Inovio	Preclinical	Inovio Biomedical Corporation, VGX International	Public Health Agency of Canada (Collaborator), University of Pennsylvania (Collaborator), Vaccine Research Center (Collaborator)
Research program: H5N1 avian influenza vaccine - Inviragen/University of Wisconsin	Preclinical	InViragen LLC, University of Wisconsin-Madison	
Research program: influenza virus vaccine - MediVas	Preclinical	MediVas-LLC	
Research program: influenza virus strain H5N1 clade 2	Preclinical	Sanofi Pasteur	

vaccine - Sanofi Pasteur			
Research program: infectious disease vaccines - Tetragenetics	Preclinical	Tetragenetics	National Institute of Allergy and Infectious Diseases (Funder)
Research program: viral vaccines - Variation Biotechnologies	Preclinical	Variation Biotechnologies	
Research program: infectious disease vaccines - VaxInnate	Preclinical	VaxInnate	3M Drug Delivery Systems (Technology Provider)
Influenza A virus H5N1 vaccine - Antigen Express	Phase I	Antigen Express	University of Rochester (Collaborator)
Intranasal influenza A virus H5N1 vaccine - Archimedes Pharma	Phase I	Archimedes Pharma	
H5N1 influenza virus vaccine intranasal - Nanotherapeutics	Phase I	DelSite Biotechnologies	Nanotherapeutics (Owner)
Influenza A virus H5N1 cell culture based vaccine - GlaxoSmithKline	Phase I	GlaxoSmithKline	Intercell (Collaborator)
Influenza A virus vaccine H5N1 - Green Cross/Mogam Biotechnology Institute	Phase I	Green Cross	Mogam Biotechnology Research Institute (Collaborator)
Influenza A virus vaccine H5N1 - iBio	Phase I	INB:Biotechnologies	Fraunhofer USA Center for Molecular Biotechnology (Collaborator), iBio Inc (Owner)
H5N1 avian influenza vaccine intranasal - MedImmune/NIAID	Phase I	MedImmune Vaccines, National Institute of Allergy and Infectious Diseases	
H5N1 influenza virus vaccine - Novavax	Phase I	Novavax	Centers for Disease Control and Prevention

			(Collaborator), Southern Research Institute (Collaborator), University of Hong Kong (Collaborator), University of Pittsburgh (Collaborator)
Influenza A virus vaccine H5N1 - PaxVax	Phase I	PaxVax	Purdue Research Foundation (Technology Provider)
INO 3510	Phase I	University of Pennsylvania	Inovio Pharmaceuticals (Technology Provider)
VGX 3400	Phase I	University of Pennsylvania	
H5N1 influenza virus vaccine - Vaxart	Phase I	Vaxart	
Influenza virus DNA vaccine - Vical	Phase I	Vical	
Influenza virus delta NS1 vaccine	Phase II	Green Hills Biotechnology	
Influenza A virus H5N1 vaccine - Medicago	Phase II	Medicago	Infectious Disease Research Institute (Collaborator)
Influenza A virus H5N1 vaccine - Protein Sciences Corporation	Phase II	Protein Sciences Corporation	
Influenza A virus H5N1 vaccines - Baxter International	Marketed/Registered/Preregistration	Baxter International	DynPort Vaccine Company (Collaborator), National Institute of Allergy and Infectious Diseases (Collaborator), US Department of Health and Human Services (Collaborator)
Pandemic influenza virus vaccine -	Marketed/Registered/Preregistration	BioDiem, Nobilon International	Centers for Disease Control

BioDiem			and Prevention (Collaborator), Institute of Experimental Medicine of the Russian Academy of Medical Sciences (Collaborator), Serum Institute of India (Collaborator)
Influenza A virus H5N1 vaccine - CSL	Marketed/Registered/Preregistration	CSL	
H5N1 (pre-)pandemic influenza virus vaccine - GlaxoSmithKline	Marketed/Registered/Preregistration	GlaxoSmithKline	
Influenza A virus vaccines - GlaxoSmithKline	Marketed/Registered/Preregistration	GlaxoSmithKline	
H5N1 whole virus influenza vaccine (Daronrix) - GlaxoSmithKline	Marketed/Registered/Preregistration	ID Biomedical Corporation	GlaxoSmithKline (Owner)
Pandemic influenza A virus vaccines - Novartis/NIAID	Marketed/Registered/Preregistration	National Institute of Allergy and Infectious Diseases, Novartis	
Influenza A virus H5N1 vaccine - Novartis	Marketed/Registered/Preregistration	Novartis, Novartis Vaccines	
Influenza A H1N1 vaccine - Novavax	Marketed/Registered/Preregistration	Novavax	Centers for Disease Control and Prevention (Collaborator), GE Healthcare (Collaborator), National Institute of Allergy and Infectious Diseases (Collaborator), Novavax (Owner), University of Pittsburgh (Collaborator)

Influenza A virus H5N1 vaccine - Sinovac Biotech	Marketed/Registered/Preregistration	Sinovac Biotech	