

Pandemic Preparedness

The Issue

The 2009/2010 H1N1 influenza (“flu”) pandemic provided a wake-up call regarding pandemic preparedness. It highlighted and “stress tested” the key components that need to be addressed to ensure an effective pandemic response – and demonstrated a wide variation in pandemic preparedness between countries.

Despite the recent H1N1 pandemic, the potential for a severe flu pandemic with significant global impact remains, whilst our ability to predict its appearance is limited. The World Bank estimates¹ that a flu pandemic could kill 71 million people worldwide, and for every death there would be many more people with mild, moderate or very severe illness. The accumulative effect could be to push the global economy into a major recession costing more than \$3 trillion. A slump in tourism, transportation and retail sales, as well as workplace absenteeism and lower productivity caused by a severe outbreak, may cut global gross domestic product by 4.8 percent.

It is therefore vital that the global community learns from the H1N1 experience. Appropriate steps need to be taken to prepare for, and where possible mitigate, the impact of the next pandemic – whether it occurs this year, this decade, or several decades into the future. No one organisation, country, or group, can meet the pandemic challenge alone. All partners - multilateral organisations such as the UN, developed countries, developing countries, public-private partnerships and industry – must work together to put in place a robust and effective global response.

GlaxoSmithKline (GSK) is committed to playing our part in pandemic preparedness. This paper sets out the key components of this commitment and our views on essential policy elements of pandemic flu preparedness.

GSK's Public Position

Clear and Operational Preparedness Plans

- National pandemic preparedness plans are key to mitigating the public health consequences and social and economic disruption of a pandemic. It is, therefore, critical that any Guidance from bodies such as the WHO, FDA, CDC, EMA and ECDC and those issued at a national level, incorporate lessons learnt from the H1N1 pandemic and accurately reflect ongoing scientific developments in the vaccines and antivirals fields.
- Member States need to be aware of all the policy options available to them. These include the value of stockpiling antivirals and pre-pandemic vaccines, as well as Advance Purchase Agreements (APAs) which can help to reduce supply timelines in the event of extreme demand in a pandemic. Governments should be encouraged to update or develop comprehensive preparedness plans in response.
- To fulfil their own public health mandates and to support capacity-building for pandemic vaccines, Governments should fully implement seasonal flu vaccination programmes in line with WHO recommendations.

¹ http://siteresources.worldbank.org/EXTAVIANFLU/Resources/EvaluatingAHleconomics_2008.pdf

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

GSK's Role

- GSK is fully committed to playing our part in supporting pandemic preparedness. Our main contribution is via the research, development and provision of pre-pandemic and pandemic vaccines, along with antivirals and other medical interventions such as antibiotics.
- GSK's portfolio of antivirals, pre-pandemic and pandemic vaccines are available to developed and developing countries at tiered (reduced) prices based on gross national income (as defined by the World Bank). This offer includes a commitment to provide our antiviral, *Relenza™*, to the world's 48 Least Developed Countries on a not-for-profit basis.
- Given the unpredictable nature of a flu pandemic, GSK's pandemic preparedness strategy running up to the H1N1 pandemic and since, involved significant financial risks, including substantial upfront investment, to ensure we would be in a position to support Governments with their own plans. Our pandemic portfolio tiered pricing strategy reflects this risk, allowing us to recoup our investment, make provision for an ongoing state of readiness and to generate a return for shareholders.
- Antiviral stockpile provision should be reviewed by national authorities to assess desired levels of population coverage and diversification of stockpiles. Taking these measures will improve advance planning and is the most effective way to ensure availability of antiviral medication at the onset of a pandemic. The recent experience with H1N1 demonstrated that demand quickly outstripped supply in the initial months of the pandemic.
- GSK supports the Pandemic Influenza Preparedness (PIP) Agreement adopted by WHO member states at the 2011 World Health Assembly. This includes a commitment from manufacturers to support developing country pandemic preparedness plans via such measures as 1) allocation of 10% of production of vaccines and antivirals for supply to developing countries at tiered prices or via donation 2) technology transfer and 3) provision of 50% of the funding of the GISN (the Global Influenza Surveillance Network).
- Technology transfer of production capacity is considered by some as key to ensuring adequate protection for developing world populations. GSK is prepared to explore the feasibility of technology transfer with individual countries on a case-by-case basis and has committed to do so under the PIP Agreement of 2011.

International Co-operation

- International agreement is needed to ensure that, during a pandemic, governments will not close borders or nationalise medicine manufacturing facilities, preventing the free movement of vaccines, antivirals and other essential goods. Fortunately this did not occur during the recent H1N1 pandemic but such an occurrence in future would have highly negative effects on controlling the impact of the pandemic.
- Rapid access to new viruses for research and development and vaccine production is essential if the international community and individual governments are to protect their populations. It is therefore vital that new influenza viruses with pandemic potential are shared without restrictions with the WHO and vaccine manufacturers, irrespective of the country in which they are identified. The 2011 PIP Agreement should help to ensure this is the case.
- The international community, including multinational organisations, charities and donor governments should work together to provide financial support to the world's poorest countries for the creation and implementation of pandemic preparedness plans, including building adequate stockpiles of recommended and approved medical interventions.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- A robust patent system is essential to support global pandemic preparedness. It provides the incentives required for the ongoing risky and costly development of the key technologies needed to ensure sufficient, timely and effective vaccine provision running up to and in the event of a pandemic.
- GSK is willing to support and actively participate in multidisciplinary research and funding consortia (e.g. through PPPs) designed to plan and co-ordinate clinical studies on the use of vaccines and antivirals in a pandemic setting in order to improve the global preparedness for the next pandemic. Such studies - initiated at the earliest opportunity – would provide important information on the effectiveness and safety of different medical interventions in different target groups and under different conditions in the early stages of a new pandemic.

BACKGROUND

The Pandemic Threat

“An influenza pandemic is a unique event. I know of no other health emergency that can spread to every corner of the globe within a few months. Once a fully transmissible pandemic virus emerges, its international spread is considered unstoppable.”

Margaret Chan, DG WHO ²

A pandemic occurs when a new influenza virus emerges and starts spreading readily between humans – by coughing and sneezing. Because the virus is new, the human immune system will have little or no pre-existing immunity. Experience with previous flu pandemics has shown that a pandemic spreads in two or three waves over a total period of 13–23 months.³

Morbidity associated with pandemic flu may be far more severe than seasonal flu. Mortality may also be significantly greater, with an overall case fatality rate of 2.5% for the 1918 pandemic versus 0.01% for typical seasonal flu. The H5N1 strain now prevalent in many poultry and wildfowl species across the world and considered by many experts to be a potential candidate pandemic strain, has a reported mortality rate of approximately 60% amongst humans infected with it.

Fortunately the 2009 H1N1 strain did not possess the severity associated with the 1918 Spanish flu pandemic or the expected severity of a future H5N1 pandemic, should it emerge. It certainly exhibited the transmissibility characteristics noted by Dr Margaret Chan of the WHO in her above quote, spreading globally within weeks and became the dominant circulating human influenza virus. For most people, illness caused by the 2009 H1N1 influenza virus was mild and similar to a normal seasonal flu infection. However, some people were very severely infected and the disease disproportionately affected young children and young adults, as well as pregnant women and those with pre-existing illnesses that placed them at greater risk from infection. As a result, although the number of people who are known to have died is in the same range as for a normal flu season, the average age of those who died is considerably lower than that in seasonal flu outbreaks. Moreover, the very severe acute respiratory distress syndromes seen in severe cases placed considerable strain on hospitals and critical care facilities in particular during peak periods of disease transmission.

It is impossible to anticipate when the next pandemic might occur or how severe its consequences might be⁴. On average, three pandemics per century have been documented since the 16th century, occurring at intervals of 10–50 years. In the 20th century, flu pandemics occurred in 1918, 1957 and 1968.

² Address to the Pacific Health Summit, Seattle, Washington, 13 June 2007

³ Daems R, Del Giudice G, Rappuoli R. Anticipating crisis: towards a pandemic flu vaccination strategy through alignment of public health and industrial policy, *Vaccine* December 2005

⁴ WHO Global Influenza Pandemic Preparedness Plan 2005

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GlaxoSmithKline's Position

The pandemic of 1918 is estimated to have killed more than 40 million people, with peak mortality rates occurring in people aged 20–45 years. The pandemics of 1957 and 1968 were less severe (nevertheless accounting for between 1–4 million estimated deaths, primarily in traditional risk groups such as the elderly and those with pre-existing conditions), and many countries experienced severe strains on healthcare resources. Modern medical technologies and critical care facilities may help to reduce the mortality rate of a future pandemic, but demand for these limited resources will likely be greater than the capacity available to deliver them.

The Role of National Pandemic Preparedness Plans

In 2009 the WHO issued a series of recommended strategic actions for responding to the pandemic threat. The recommendations are designed to reduce opportunities for human infection; strengthen the early warning system; contain or delay the spread at the source; and reduce morbidity, mortality, and social and economic disruption. They are periodically updated to reflect scientific and other developments.

Many countries are reviewing their preparedness plans following the H1N1 Pandemic and in doing so, they should be encouraged to note WHO Europe's Report; *"Recommendations for Good Practice in Pandemic Preparedness identified through evaluation of the response to pandemic (H1N1) 2009"* which concluded that whilst the response of EU Member States to H1N1 was proportionate, planning ahead, certain areas could benefit from further attention, including:

- risk communication in general, especially regarding vaccination;
- vertical communication within the health care system (with greater emphasis on frontline health care workers);
- vaccine procurement planning;
- operational planning for vaccine distribution/logistics;
- increased flexibility/adaptability in planning across a wider range of impact scenarios (mild to severe), especially at local and regional tiers;
- optimisation and best use of scarce diagnostic capacity;
- improved acceptance of flu vaccination by health care workers.

GSK and Pandemic Preparedness

To date, GSK has invested \$2 billion to conduct research and expand production capacity for both our antiviral, *Relenza™*, and pre-pandemic and pandemic vaccines. We were the first company to obtain a European Marketing Authorisation for a pre-pandemic vaccine, *Prepandrix™* and we secured licences and special authorisations during the H1N1 pandemic for our pandemic vaccines, *Pandemrix™* and *Arepanrix™* in more than 100 countries. In the event, we delivered 344 million doses of our adjuvanted H1N1 pandemic vaccines to governments and the World Health Organisation (WHO) and our vaccines were administered in over 47 countries.

GSK's portfolio of antivirals, pre-pandemic and pandemic vaccines are available to governments of developed and developing countries at tiered prices based on gross national income of the nation (as defined by the World Bank). This offer includes a commitment to provide our antiviral, *Relenza™*, to the world's 48 Least Developed Countries on a not-for-profit basis. This undertaking includes a not-for-profit pandemic price for all three products for the world's 48 Least Developed Countries (LDCs).

Additionally, we have granted a voluntary licence to Simcere, a Chinese manufacturer, giving them the right to manufacture and sell zanamivir (the active ingredient of *Relenza™*) containing products in China, and to sell in a number of other countries including LDCs.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Internally, GSK has developed plans to ensure security of product supply for our customers to GSK essential medicines and vaccines. Our approach includes business continuity planning, product stockpiling and use of travel protocols.

The Role of “Pre-pandemic” Vaccines

There are multiple complex steps associated with virus isolation and characterisation, development and testing of strains suitable for vaccine manufacture, and production scale-up. This means that, in reality, the first batches of vaccine based on the actual pandemic virus strain (i.e. pandemic vaccines) will not start to become available for at least 12 weeks after the pandemic declaration and receipt of the appropriate seed virus from the WHO reference laboratories. This may be too late to have a significant impact on the first wave of pandemic infections, while according to the Oliver Wyman report⁵ supplies to cover *entire* global populations are unlikely to be available for 18 to 48 months.

Therefore, although manufacturers and scientists around the world are working on new approaches and technologies to reduce this delay, there will inevitably be a period at the beginning of a pandemic when vaccines based on the causative strain are not available.

To address this issue, GSK has committed significant efforts to the development of “pre-pandemic” vaccines, based on currently circulating avian strains, such as H5N1, which are considered by the WHO to pose a risk of adapting or mutating into viruses capable of causing a human pandemic. These pre-pandemic vaccines incorporate technologies that aim to provide a level of cross-protection against virus strains related to the one contained in the vaccine. This makes them potentially useful for stockpiling for use immediately when a pandemic caused by a related virus strain is declared to provide protection against the first pandemic wave, or for broader use to ‘prime’ populations during the inter-pandemic period against a future pandemic virus of the viral subtype incorporated in the vaccine.

If it appears that an H5N1 variant is adapting to human-to-human transmission, then current data, reflected in ECDC Recommendations from 2007⁶, suggests that human pre-pandemic vaccines should be deployed as early as Phase 4 (as per current WHO phasing) – targeting people at greater risk of exposure to avian flu (vets, poultry workers and laboratory workers). This should then be followed by more extensive, prioritised coverage of further risk groups and the general population during Phases 5 and 6.

The Role of Pandemic Vaccines

As stated above, the development and manufacturing processes around producing a vaccine that matches the actual pandemic strain mean that a vaccine will not start to become available for a minimum of 12 weeks after the strain has been identified and supplied to manufacturers by the WHO.

In an effort to shorten the regulatory approval timelines associated with pandemic vaccines as much as possible the EMA (European Medicines Agency) has established the “mock up” approval process. Under this system, the approval is first granted upon data produced on a currently circulating strain (e.g. H5N1), then supplemented, whilst the vaccine is actually being manufactured, with data on the vaccine using the actual pandemic strain when it is identified. GSK followed this process with its “mock” pandemic vaccine *Pandemrix™*, obtaining approval with data based on the H5N1 sub-type in May 2008, and facilitating rapid regulatory approval in many countries early in the H1N1 pandemic.

Governments can ensure access to GSK’s Pandemic Vaccines in the event of a future flu pandemic via an APA. APAs improve advance planning and can reduce supply timelines in the event of extreme demand in a pandemic – as was the recent experience with H1N1.

⁵ Authoritative New Study Reveals Global Pandemic Influenza Capacity, IFPMA, 24Feb2009

⁶ Technical Report - Expert Advisory Groups on Human H5N1 Vaccines, August 2007.

Stockpiling and Use of Antivirals

Whilst pre-pandemic vaccines could potentially offer the most effective medical intervention in the early stages of a pandemic caused by a virus related to that contained within the vaccine, antivirals will play an important role in treating pandemic flu whatever the virus type involved. This was acknowledged in the WHO's 2009 Pandemic Planning Guidance which recommends stockpiling antivirals.

While countries should obviously decide for themselves the optimum level of population coverage requiring antiviral provision, mathematical modelling predicts that approximately 25% of the population may become infected during a flu pandemic.

In terms of deciding which antivirals to include in preparedness planning, national authorities are advised to consider the need for diversified stockpiles to mitigate against the risk of drug resistance. The EMA's Guidance of December 2007 on the use of antivirals in a flu pandemic concluded that the development of widespread antiviral resistance may have a substantial impact on the clinical usefulness of oseltamivir and therefore, stockpiling more than one antiviral would be useful in preparing for a flu pandemic. Both zanamivir (*Relenza™*) and oseltamivir (*Tamiflu™*) are recommended as candidates for stockpiling.

Seasonal Vaccination and Capacity Building

Increased coverage with seasonal vaccination will reduce illness and death; cut healthcare costs associated with hospitalisation of severe cases; and, for economies, reduce work days lost. Importantly, however, it will help to establish mechanisms by which vaccination can be delivered to large sections of the population in the event of a pandemic and will also support provision of additional manufacturing capacity for pandemic vaccines. This is because the inherent similarity between the two vaccines is such that pandemic vaccines will be produced in the same facilities that currently make seasonal flu vaccines. With global manufacturing capacity for pandemic vaccines currently inadequate to meet the needs of the entire global population, it is important that seasonal flu vaccine immunisation recommendations are in place and implemented. Countries should, therefore, be encouraged to achieve the current WHO recommended seasonal vaccine coverage level of 75% of targeted risk groups.

In Europe, the EU Health Council agreed in December 2009 a Resolution calling on all EU Member States to achieve the WHO target of 75% coverage of risk groups and to increase coverage of health care workers by 2015. Other Governments should follow the EU's lead in emphasising the importance of the WHO target.

Ensuring Free Movement of Essential Medicines

One of the biggest risks to public health and economic prosperity during a pandemic will be if Governments close borders. This will hamper global supply chains and will severely compromise the production and distribution of medicines and vaccines. International agreement is therefore needed to ensure that during a pandemic, Governments will not close borders since the benefit, if any, will be massively outweighed by the cost. Medicine manufacturing facilities also need to be protected against nationalisation. Advanced planning by Governments and multinational agencies which ensures that appropriate provisions are in place in advance of a pandemic, coupled with open borders, should ensure that such dramatic actions are not resorted to.

Protecting Public Health via Unrestricted Virus Sharing

The WHO Global Influenza Surveillance Network (GISN) was established in 1952 to advise WHO Member States on “what influenza control measures are useful, useless or harmful”. It comprises more than 100 National Influenza Centres, five Collaborating Centres based in Australia, Japan, the UK and US and three reference Laboratories in Australia, the UK and US. Twice annually the Network recommends the content of the flu vaccines for the subsequent flu seasons in the Northern and Southern hemispheres.

Importantly, the network also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. In early 2007, however, Indonesia stopped sharing influenza viruses with the WHO, saying they wanted some “benefits” in exchange for viruses. This was a dangerous situation, because the free and timely sharing of influenza viruses is vital in protecting global public health. The influenza virus can mutate quickly. Vigilance and rapid access to new viruses for research and development and vaccine production is therefore essential.

Fortunately this situation has now been resolved via the PIP (Pandemic Influenza Preparedness) Agreement, which was adopted by Member States at the World Health Assembly in 2011. The agreement covers the terms under which Member States share influenza viruses of pandemic potential with the WHO labs and their onward provision to industry for vaccine manufacture. In return, industry has agreed to cover 50% of the GISN running costs and provide other benefits, including production allocations of vaccines and antivirals for supply to developing countries via donation or at tiered prices.

Influenza Vaccines and Patenting

Influenza viruses are naturally occurring infectious agents and as such, are not patentable. Patents have, therefore, not previously prevented the free exchange and use of influenza viruses. In addition, WIPO (World Intellectual Property Organisation) has pointed out that conventional flu vaccine manufacturing technology is mature and free of patents blocking potential new manufacturers from entering the field.

Patents in the flu vaccines field instead tend to apply to novel production technologies or to ways of making the vaccines more potent. Examples of patented technologies are:

- *Cell-culture systems to replace classical egg-based production:* Cell-culture technology is being developed to reduce the historic reliance on chicken eggs for the production of flu vaccines.
- *New types of adjuvants:* These compounds, when added to vaccines, create a more efficient immunisation response often from a reduced antigen dose, thereby allowing more doses to be produced.
- *Reverse genetics technology:* This technology allows a highly pathogenic virus (such as avian H5N1) to be genetically modified to reduce its pathogenicity. This enables it to be safely used in a manufacturing environment, whilst still providing a strong immune response against the original virus.

Particular challenges associated with 1) ensuring sufficient global capacity of pre-pandemic and pandemic vaccines 2) achieving cross protection against drifting influenza strains and 3) improving efficacy in the very young as well as in very old populations, are such that the technologies detailed above are key to effective pandemic preparedness. All these developments involve substantial risk and huge investment. A robust patent system to protect intellectual property is therefore essential.

Global Access to Pandemic Vaccines

Developing countries are understandably concerned about securing access to pre-pandemic and pandemic vaccines for their citizens, but some may lack the resources to mount an effective response. This important issue was addressed by WHO via the PIP (Pandemic Influenza Preparedness) agreement, adopted by Member States at the 2011 World Health Assembly. GSK fully supports this agreement and the commitment made by manufacturers to support pandemic preparedness through such measures as allocation of 10% of production of vaccines and antivirals for supply to developing countries at tiered prices or via donation, technology transfer and provision of 50% of the funding of the GISN (global influenza surveillance network).

Noting that many developed countries have secured their supply of pandemic vaccines through APAs, the 2011 International Health Regulations (IHR) Committee Report on the H1N1 pandemic recommends similar APA arrangements to ensure pandemic vaccines are available early for the world's poorest in the event of another pandemic. Individual developing countries could also enter into APAs. GSK would supply at tiered prices, based on the gross national income of the nation (as defined by the World Bank).

Financial Support for Developing Country Pandemic Plans

The need for funding support for pandemic preparedness for the world's poorest countries is increasingly recognised. This now requires firm financial commitments by multilateral organisations, donor governments and charities. Through sustainable funding initiatives, the world's poorest countries should be better able to put in place robust preparedness plans.

Technology Transfer and Local Manufacturing

Technology transfer of production capacity is often presented as the solution to the access challenges faced by developing countries. Indeed industry, including GSK, is undertaking technology transfer in relation to flu vaccines. However, because it depends upon an underlying annual demand for seasonal flu vaccines to sustain the viability of the manufacturing operation between pandemics (which may be a number of years apart), it is not always the optimal approach to ensuring adequate protection for developing world populations in the event of a pandemic.

As with other biological products, design, setup and approval of vaccine manufacturing facilities are highly complex and consume large amounts of time, as well as financial and human capital. In the case of partnerships, key factors for success will be the alliance of an experienced GMP (good manufacturing practice) - qualified research-based vaccine manufacturer and of a suitably qualified local partner.

Importantly, local production will not address the lack of availability of vaccines early in a pandemic due to production timelines. And it is unrealistic to establish facilities that would only be 'switched on' in the event of a pandemic. As noted above, local production of flu vaccines must be coupled with implementation of a seasonal flu vaccination programme.

Arguably, the most appropriate way of ensuring protection for developing world populations is via the development of appropriate pandemic preparedness plans including the provision of affordable pre-pandemic vaccines, arrangement of APAs for supply of pandemic specific vaccines and stockpiling of antivirals, all via tiered prices.

For the longer term and in countries investing in seasonal capacity that could be switched to pandemic vaccine production, GSK is open to explore the feasibility of technology transfer with individual countries.

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