

GSK Public policy positions

Pandemic Preparedness

The Issue

The 2009 H1N1 influenza (“flu”) pandemic provided an insight into what it takes to prepare for a pandemic. 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 preparedness between countries.

Despite the 2009 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 that for every death there would be many more people with mild, moderate or very severe illness. The cumulative 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 remains vigilant after the 2009 H1N1 pandemic. 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 WHO, developed countries, developing countries, public-private partnerships and industry – must work together to put in place a robust and effective global response.

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 Position

Clear and Operational Preparedness Plans

- National pandemic preparedness plans are central 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 2009 H1N1 pandemic and accurately reflect ongoing scientific developments in the vaccines and antivirals fields.
- Governments 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) for pandemic vaccines, which can help to build comfort about product availability in the event of extreme demand in a pandemic as well as assist manufacturers in forecasting demand and preparedness requirements. Governments should be encouraged to update or develop comprehensive preparedness plans.
- To fulfil their own public health mandates and to support capacity-building amongst manufacturers for pandemic vaccines, Governments should fully implement seasonal flu vaccination programmes in line with WHO recommendations.
- Antiviral stockpile provision should be reviewed by national authorities to assess desired levels of population coverage and diversification of stockpiles. This will improve advance planning and is the most effective way to ensure availability of antiviral medication at the onset of a pandemic. Experience during the 2009 H1N1 pandemic demonstrated that demand quickly out-stripped supply in the initial months of the pandemic.

GSK's Role

- GSK is 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.

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



- GSK’s portfolio of antivirals, pre-pandemic and pandemic vaccines is 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™*(zanamivir), to the world’s 50 Least Developed Countries on a not-for-profit basis.
- GSK supports the Pandemic Influenza Preparedness (PIP) Agreement adopted by WHO member states in 2011. In December 2012 we were the first company to formalise an Agreement under the PIP Framework by undertaking to provide the WHO with access to up to 10% of pandemic influenza vaccines as they come off the production line as well as access to up to 10 million treatment courses of *Relenza™*. These commitments are a combination of donations and reservations for potential purchase at tiered prices. They are in addition to GSK’s contribution to the industry-wide undertaking to provide 50% of the Partnership Funding for the Global Influenza Surveillance and Response System (GISRS).
- 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.
- 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. GSK is also exploring partnerships to develop new technologies to support pandemic preparedness, such as manufacturing influenza vaccines based on a cell-culture line.

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, which would significantly impair efforts to mitigate the impact of a pandemic.
- Rapid access to new viruses for research and development and vaccine production is essential to protect people. It is therefore vital that new influenza viruses with pandemic potential are shared without restrictions with the WHO and vaccine manufacturers. 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 beyond what is provided for under the PIP Framework.
- 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.

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

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

Morbidity associated with pandemic flu may be far more severe than seasonal flu. Mortality may also be significantly greater. 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 pandemic strain did not possess the severity associated with the 1918 Spanish flu pandemic or that of current human H5N1 influenza infections. However it spread globally within weeks and became the dominant circulating human influenza virus. For most people, the illness was mild and similar to a normal seasonal flu infection. However, some people were severely ill 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 was in the same range as for a normal flu season, the average age of those who died was considerably lower than that in seasonal flu outbreaks. Moreover, the acute respiratory distress syndromes seen in severe cases placed considerable strain on hospitals and critical care facilities.

The pandemic of 1918 is estimated to have killed more than 40 million people while the pandemics of 1957 and 1968 were less severe accounting for between 1–4 million estimated deaths. 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. It is impossible to anticipate when the next pandemic might occur or how severe its consequences might be. 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.

The Role of National Pandemic Preparedness Plans

Many countries are reviewing their preparedness plans following the 2009 H1N1 Pandemic. 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, certain areas could benefit from further attention, including:

- risk communication in general, especially regarding vaccination;
- vertical communication within the health care system ;
- 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

In recent years, 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 2009 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 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 50 Least Developed Countries on a not-for-profit basis.

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 Least Developed Countries.



Internally, GSK has developed plans to support 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 pandemic vaccine manufacture and production scale-up. Following the declaration of a pandemic by the WHO and GSK’s subsequent switch to pandemic vaccine manufacture, supply timelines are subject to a number of factors, some of which are outside our control, such as availability of the pandemic virus strain and calibrated reagents. It is difficult to predict the exact time at which the first batches of vaccine based on the actual pandemic virus strain (i.e. pandemic vaccines) will become available. It is possible that availability of large volumes of pandemic vaccine may be too late to have a significant impact on the first wave of pandemic infections, while according to the Oliver Wyman report³ 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, GSK has committed significant efforts to the development of a “pre-pandemic” vaccine based on currently circulating avian strains which are considered by the WHO to pose a risk of adapting or mutating into viruses capable of causing a human pandemic, H5N1 for example. 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 in response to a pandemic caused by a related virus strain, to provide protection against the first pandemic wave.

Accessing Pandemic Vaccines

As stated above, the development and manufacturing processes concerning the production of a vaccine that matches the actual pandemic strain, and its regulatory approval, mean that a vaccine will not start to become available for a period of time after the strain has been identified and supplied to manufacturers by the WHO.

Governments can ensure access to GSK’s Pandemic Vaccines in the event of a future flu pandemic via an APA. APAs improve advance planning in the event of extreme demand in a pandemic – as was the experience with 2009 H1N1 pandemic.

Monitoring and Identifying Adverse Events Related to Mass Vaccination

Global experience with previous large scale immunisation programmes has shown that adverse events will be reported. These events may be the result of underlying conditions, new conditions that occur in temporal association with the vaccination or environmental factors, or events that may be related to the vaccine used. GSK takes patient safety seriously, and monitors and evaluates all adverse events reported to the company according to regulations. GSK employs a full range of rigorous pharmacovigilance activities in monitoring the safety of all its products.

By July 2013, a total of 989 cases of narcolepsy in people reported to have been vaccinated with Pandemrix™ (H1N1) or Arepanrix™ (H1N1) during and after the 2009 pandemic had been received by GSK. Due to limitations imposed by local privacy law, sufficient information cannot be obtained on many reports to ensure they do not represent duplicate reports and/or that they describe confirmed cases of narcolepsy. Over 90 million doses of Pandemrix™ (H1N1) or Arepanrix™ (H1N1) have been administered worldwide. Of the reported cases, approximately 69% are from Finland and Sweden.

³ Authoritative New Study Reveals Global Pandemic Influenza Capacity, IFPMA, 24Feb2009

Epidemiological data currently available to GSK suggest an increased risk of narcolepsy following vaccination with Pandemrix™ (H1N1). Due to the methodological limitations of the studies, which are retrospective observational studies, further research is needed to determine whether the observed risk is related to the vaccine, environmental effects, genetic factors, other factors or a combination of them. Further research is also needed to evaluate whether there are biologically plausible mechanisms by which vaccination with Pandemrix™ (H1N1) may have triggered narcolepsy in some individuals as no such mechanism has been demonstrated to date.

Pandemrix™ (H1N1) went through a rigorous approval process and underwent all safety and efficacy testing required for registration by national regulatory bodies. Throughout the development of our pandemic vaccines there were no data that suggested a potential for an increased risk of narcolepsy among those vaccinated. However, rare adverse events often cannot be detected during clinical trials.

GSK remains committed to the pursuit of additional research to understand the potential role of Pandemrix™ (H1N1) in those who developed narcolepsy after vaccination and continues to support the research of others who are investigating the reported cases of narcolepsy.

Stockpiling and Use of Antivirals

Antivirals 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 determine the optimum level of antiviral coverage for their population, mathematical modelling predicts that approximately 25% of the population may become infected during a flu pandemic. National authorities are advised to consider the need for diversified antiviral 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 and reduce work days lost. It helps 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 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 at least to achieve the current WHO recommended seasonal vaccine coverage level of 75% of targeted risk groups.

Ensuring Free Movement of Essential Medicines

One of the biggest risks to public health during a pandemic will be border closures. This hampers global supply chains and severely compromises the production and distribution of medicines and vaccines. International agreement is needed to avoid such closures since the benefit, if any, will be significantly 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 and Response System (GISRS) (formerly the Global Influenza Surveillance Network) was established in 1952 to advise WHO Member States on "what influenza control measures are useful, useless or harmful". It comprises more than 130 National Influenza Centres, six Collaborating Centres and four Essential Regulatory Laboratories. Twice annually the Network recommends the virus strains for the seasonal flu vaccines.

The network also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. To secure this role in the long term, in 2011 the World Health Assembly reached an agreement under which Member States share influenza viruses of pandemic potential with the WHO labs for their onward provision to industry for vaccine manufacture. In return, industry agreed to cover 50% of the GISRS running costs and to provide other benefits, including production allocations of vaccines and antivirals for supply to developing countries via donation or at tiered prices.

In December 2012 GSK was the first company to sign an Agreement with the WHO under the 2011 *Pandemic Influenza Preparedness* (PIP) Framework. Under this Agreement, we have agreed to **donate** 7.5% of our 'real time' pandemic influenza vaccine production and 2 million treatment courses of our antiviral, *Relenza*TM for distribution by the WHO to countries in need in the event of a future pandemic. In addition to the donation, GSK also agreed to **reserve** further volumes of pandemic vaccine (2.5% of 'real time' production) and antiviral medicine (8 million treatment courses) for developing countries to purchase at tiered prices.

Global Access to Pandemic Vaccines

The 2011 International Health Regulations (IHR) Committee Report on the 2009 H1N1 pandemic recommends APA arrangements are made available to developing countries to enable them to secure pandemic vaccines early in the event of another pandemic. Individual developing countries can enter into APAs with GSK at tiered prices, based on multiple factors including 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 above and beyond provisions under the PIP Framework.

Technology Transfer and Local Manufacturing

Technology transfer of production capacity is often presented as the solution to the access challenges faced by developing countries. However, because it depends upon an underlying annual demand for seasonal flu vaccines to sustain the viability of the manufacturing operation between pandemics, it is not always the optimal approach. It is unrealistic to establish facilities that would only be 'switched on' in the event of a pandemic. Sustainable local production must therefore be coupled with implementation of a seasonal flu vaccination programme.

The design, setup and approval of GMP (Good Manufacturing Practice) vaccine manufacturing facilities are highly complex and require significant time, financial and human capital.

Importantly, local production will not address the lack of availability of vaccines early in a pandemic due to production timelines. 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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