



***Preparing for and responding to influenza pandemics:
roles and responsibilities of Roche***

Revised September 2009

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Introduction

The purpose of this document is to articulate in an open and transparent manner the roles and responsibilities of Roche and other stakeholders during pre-pandemic and pandemic time periods. The audience for this document includes international agencies, governments, the business community, and any other person or organization involved with an interest in pandemic preparedness.

The document was first written and made publicly available in January 2008. It has since been updated following the outbreak of Pandemic (H1N1) 2009 in April 2009.

It is important to note that the revision of this document in no way reflects any material changes to how Roche views or articulates what it believes to be its role in the multi-agency response to a pandemic. Rather, Roche has taken the opportunity to reflect on its experiences from the 21st century's first global pandemic.

Executive summary

Overview

Pandemic influenza must be viewed not just as a government public health emergency but as a possible global catastrophe with a potentially serious impact on human health and well-being, the global economy and social infrastructure.

Global pandemic preparedness is a critical element for the protection of global society and its economy. Influenza pandemics have occurred approximately every thirty years. There were three pandemics in the 20th century, the last of which originated in Hong Kong in 1968-1969 and resulted in 800,000 deaths.

The World Health Organization (WHO) warned that the next pandemic was imminent and estimated 2 to 7 million people worldwide could die as a result of it.

On April 27th 2009, the WHO moved the pandemic phase alert from Phase 3 to 4. On April 29th, the WHO raised the alert from Phase 4 to 5. On June 11th, the WHO raised the alert to Phase 6, and the 21st century's first pandemic was declared.

By June 2009, 95 governments worldwide had purchased or ordered pandemic Tamiflu stockpiles, which cumulatively is sufficient to treat only 5% of the world's population.

It is important to note that despite these levels of stockpiling, there is a belief that the world has never been better placed to manage a global pandemic. The diverse range of national and supra-national bodies involved in the response must work together cohesively and manage the situation effectively.

But, what specifically is Roche's role in the response?

Roche's role

As the manufacturer of Tamiflu (oseltamivir), an oral antiviral (not a vaccine) active in the prevention and treatment of all influenza viruses, including Pandemic (H1N1) 2009 and avian influenza A (H5N1), Roche has an important role in pandemic preparedness.

The company recognises that healthcare is a shared responsibility and that medicines are only one component of healthcare. However, we believe that our primary role is the research, development and registration of innovative drugs for serious illnesses including influenza.

Roche will undertake specific activities in the pre-pandemic and pandemic phases. These include:

- ensuring we have a supply chain which can be modified to meet surges in demand thereby satisfying as many orders as possible in a timely manner
- securely delivering Tamiflu which meets stringent quality standards

- acting in a socially responsible manner by:
 - contributing to WHO stockpiles (the company has donated over 10 million packs of Tamiflu so far)
 - ensuring that developing economies have access to Tamiflu through its recently launched Tamiflu Reserves Programme (TRPs)
 - tiered pricing for developed and developing economies
 - holding no patents for Tamiflu in Least Developed Countries (LDCs)
- prioritising orders effectively and following defined business practices in the event of scarce supplies of Tamiflu. Roche is/will fill orders in the following priority:
 - 1) delivery of the Rapid Response Stockpile donated by Roche to the WHO
 - 2) government and corporate orders already placed
 - 3) new orders from governments
- working collaboratively with non-governmental organisations and industry associations to research and share clinical intelligence gathered on the virus' development
- advising governments on how Tamiflu fits within their own national pandemic preparedness plans.

Roche is committed to executing these activities to the very best of its abilities.

However, it is also important that Roche is transparent about the roles that do not fall under its responsibility. These include:

- manufacturing and stockpiling high levels of Tamiflu in the absence of firm orders but rather in anticipation of possible orders in the pre-pandemic phase. This is not sustainable for us nor a reliable way for governments to appropriately prepare for national populations. Governments must recognise that Roche will require six to nine months to increase supply to full capacity and a vaccine will take some time to produce. Hence, governments having sufficient antiviral stockpiles in place becomes even more critical
- taking on the role of government in health care delivery. Once Tamiflu has been delivered to governments it is their responsibility to ensure that the infrastructure exists to deliver it to patients. It is also governments' responsibility to educate citizens on measures they should take (e.g. social distancing) to prevent the spread of the virus
- determining which countries become recipients of the donation of Tamiflu from the WHO stockpiles. This is the responsibility of the WHO
- undertaking the global co-ordination of surveillance and tracking the development of the virus. This is also the role of the WHO and other bodies such as the Centre for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and national laboratories.

Roche's role

1) Ensuring a sustainable manufacturing supply

Pre-pandemic

As the manufacturer of Tamiflu, Roche's responsibility is to ensure that production of Tamiflu meets the demand for the management of seasonal influenza and for pandemic stockpiling.

Roche is committed to being clear and transparent about its production capacity.

At the end of 2004, Roche had capacity to produce 28 million courses of Tamiflu treatment per year. Since that time, Roche has invested in the development of a global manufacturing network for Tamiflu that can establish a production capacity of 400 million courses of treatment annually if required.

In addition, Roche has provided manufacturing sub-licenses to generic manufacturers in China and India – allowing them to produce generic versions of oseltamivir to further increase the global availability of the drug for pandemic use. Roche has also signed an agreement with a South African manufacturer to produce a generic version for Africa.

However, it should be noted that over-production is not sustainable from a business perspective and production output will be modified to meet real demand.

Pandemic

Upon the declaration of a pandemic by WHO, Roche will immediately upscale the complex manufacturing process for Tamiflu to activate its total annual production capacity of up to 400 million treatments. However, it will take six to nine months before additional supply from the enhanced manufacturing process is available.

In early May 2009, shortly after WHO declared Phase 5 of Pandemic (H1N1) 2009, Roche announced it would ramp up its production immediately with the intention of reaching its maximum production capacity by the end of 2009 or early 2010. The company is currently on track to meet that target.

This increased production, will allow Roche to increase the amount of orders it can satisfy. However, in countries where Roche does not hold patents, governments are free to pursue the production of oseltamivir through generic manufacturers if they feel this is in the best interests of their country.

2) Filling orders for stockpiles

During an influenza pandemic, and despite our increased production capabilities, resources are likely to be in short supply. For this reason, Roche, in line with WHO recommendations, has advocated advance stockpiling of antivirals by governments as a pandemic preparedness measure.

However, it is recognized that not all governments would respond to this advice and intelligence suggested that ahead of the Pandemic (H1N1) 2009, global stockpiles of antivirals secured by governments was enough to treat only 5% of the world's population.

In recognition of this and to support governments, Roche has a series of protocols which outline how it would allocate limited supplies of Tamiflu during a pandemic.

Objective

Roche has determined that its policy for allocating Tamiflu during a pandemic should be consistent with the WHO publication, *Ethical considerations in developing a public health response to pandemic influenza*, which states that "resources should be used to provide the maximum possible health benefit".

Principles

As a global company and recognizing the role Tamiflu will play in the event of a pandemic, Roche's policy regarding the allocation of Tamiflu during a pandemic is guided by the following key principles:

- maximizing the health benefit to society during a pandemic, by supporting WHO's and national governments' containment, treatment and transmission reduction efforts
- balancing the needs of society, employees and Roche's shareholders
- basing decisions on the strength and integrity of the scientific and medical information available
- communicating Roche's approach in a transparent manner and providing a transparent delivery schedule
- maintaining a dialogue with WHO and other international agencies regarding the areas and populations in need of antiviral allocation.

Policy for the allocation of Tamiflu

It is these objectives and principles – as well as input which Roche has sought from a variety of stakeholders representing different interests including ethicists, physicians, government and non-governmental organizations, policymakers and the private sector – which underpin the company’s policy for Tamiflu allocation.

The policy, which applies to the extent permitted under local emergency legislation affecting Roche’s manufacturing and supply capabilities, is outlined below and is aligned with WHO’s pandemic alert levels.

Phase 3 – Focus on pandemic preparedness and prevention

- WHO stockpiles – 5 million packs of Tamiflu donated by Roche between 2003 and 2006, established for rapid containment and for management of current outbreaks as a preventative measure
- governments will be prioritized over the private sector
- any further orders will be fulfilled on a “first come, first served” basis.

Phase 4 – Focus on implementation of pandemic containment measures

- delivery of WHO rapid response stockpile – 3 million packs, stored by Roche US and Europe. (During the Pandemic (H1N1) 2009, these were replaced by a further donation of 5.65 million packs)
- fulfillment of existing pandemic orders, from both governments and other groups
- increase rapid response effort for containment in collaboration with WHO and other international agencies
- It is important to note that at this point Roche will prioritize new WHO and government orders over those from other groups.

Phase 5/6 – Containment measures have failed

- Roche will continue to seek the input of international agencies such as WHO as well as other advisors to ensure the allocation of Tamiflu “ provides maximum possible health benefit”
- in the absence of international input and advice, and where clear priorities for allocation cannot be developed and agreed upon, Roche will consider the “first come, first served” principle for government orders (a letter of intent or firm order determines the date of the first in a schedule of deliveries)
- however, Roche retains the right to prioritize some orders if the spread of the virus provides a clear indication that there is public health need to deliver to one country before another i.e. epidemiological evidence or concentration of the outbreak would indicate that one country may be in greater need than another.

It is also important to note that:

- while Roche will take responsibility for the delivery of orders to governments, Roche cannot take responsibility for the distribution of Tamiflu in country. This will be the responsibility of the competent health authorities
- to ensure an efficient supply chain, Roche will agree a date for delivery of the first installment of the order for Tamiflu once a firm letter of intent has been received from an ordering government. A contract must be signed shortly afterwards to secure the delivery date for the remainder of the order. Roche will not provide any one country all of their Tamiflu order at once which could cause delays for other countries to also receive the first installment of their order.
- Roche will supply Tamiflu to all governments placing an order. The company will not discriminate, by refusing to allocate Tamiflu, against citizens of specific countries based on the economic, political or social record of their government
- Roche will not release information about which governments have placed orders. It is for those governments to make public their purchase of Tamiflu.

Roche has adhered to this policy throughout its response to Pandemic (H1N1) 2009.

3) Donations

Pre-pandemic

Roche has undertaken a number of donations to the WHO to assist and support it in its global role for countries in need.

These donations include:

- 2004 – donation of 125,000 treatments which were used by the WHO in affected countries (Asia and Eastern Europe)
- 2005 – donation of a rapid response stockpile of 3 million treatments – 1.5 million treatments stored in Switzerland and another 1.5 million treatments stored in the United States. In both cases, these stockpiles were ready to go immediately to the airport closest to the outbreak and to be used as a *fire blanket* to contain the pandemic at the place of outbreak
- 2006 – donation of 2 million treatments to the WHO as regional stockpiles for use primarily in those developing countries which are most likely to be affected by avian influenza A (H5N1) in humans and unable to purchase the drug for economic reasons. These treatments are stored by the WHO in the regions.

Pandemic

When the WHO announced its intention to deploy stockpiles in early May 2009, to help fight Pandemic (H1N1) 2009, Roche announced a further donation of 5.65 million packs to:

- replenish the regional stockpile of 2 million packs of Tamiflu
- replenish the rapid response stockpile of 3 million packs of Tamiflu
- establish a new paediatric stockpile of 650,000 treatment courses of Tamiflu small (30mg and 45mg) capsules.

It is important to note that while Roche will ensure it meets its stated obligations to deliver stockpiles to the WHO, the decision on which country will be offered access to the stockpiles rests with WHO. Roche is also unable to take responsibility for the subsequent delivery of Tamiflu to patients in the countries receiving treatment stockpile. This also rests with the WHO and the national governments involved.

4) Tamiflu pricing policy

Roche is committed to combining and balancing its pursuit of innovation with corporate social responsibility.

In relation to pandemic preparedness, the company will act in a socially responsible manner by helping the world's poorest countries through differential pricing. Roche has offered Tamiflu at a reduced price for government orders, with further reduced pricing offered to developing countries, since stockpiling began in 2004.

In July 2009 and in response to Pandemic (H1N1) 2009, Roche launched its Tamiflu Reserve Programme (TRP) to ensure Tamiflu is available to governments and patients in developing nations. This is for use when the WHO has declared an influenza pandemic, or for the management of a novel influenza strain defined by WHO that has significant and current pandemic potential.

Under the TRP programme which is available to GAVI¹ countries (excluding India²), Roche will produce and store Tamiflu pandemic stockpiles for specified developing countries at a significantly reduced price with the cost spread over a number of years. Roche will then ship the stockpile to the governments of countries involved when an influenza pandemic has been announced, or in the event of a public health emergency, upon request from that governments. The countries can exercise their option to purchase the product at any time.

Roche will not raise its prices during a pandemic unless an increased cost for raw materials, contract manufacturing, transportation or applicable taxes and duties are raised forcing it to do so.

¹ The Global Alliance for Vaccines and Immunisation is a global health partnership representing stakeholders in immunisation from both private and public sectors: developing world and donor governments, private sector philanthropists, the financial community, developed and developing country vaccine manufacturers, research and technical institutes, civil society organisations and multilateral organisations.

² India is not included in the programme as a sub-licence for the production of generic oseltamivir was granted to the Indian company Hetero by Roche in 2005.

5) Data collection on real-life utilization of Tamiflu

Pre-pandemic

Roche has a number of ongoing clinical research programs. In 2007, the company collaborated with a clinical research organization for the development of a patient registry to collect clinical and virology information from people infected with influenza.

The purpose of this registry is to better understand the clinical course of the disease. Also whether changes in treatment duration and dosing of Tamiflu are warranted in the management of these cases, based on different strain virulence. Roche wishes to ensure appropriate use of Tamiflu and this data collection will provide valuable insight into real-life use.

Pandemic

The registry study has continued into the outbreak of Pandemic (H1N1) 2009 and Roche will share any intelligence gathered through it that will help international organizations and national governments respond to the public health threat posed by the outbreak.

It should, however, be understood that although Roche is undertaking this study and has a pharmacovigilance process for Tamiflu during a pandemic, the role of monitoring the development and spread of a pandemic is best carried out by supra-national organizations and co-ordinated by the WHO. It is not the role of Roche to co-ordinate global surveillance.

6) Company pandemic preparedness

Roche has a company pandemic preparedness plan to enable it to fulfill its obligations in a pandemic. This plan includes prioritizing products and services to be maintained during a pandemic such as the supply of previously specified life-saving medicines, but also identifying medical and non-medical interventions to minimize the risk of spread of the virus in the workplace, and the provision of Tamiflu to Roche employees and their families during a pandemic.

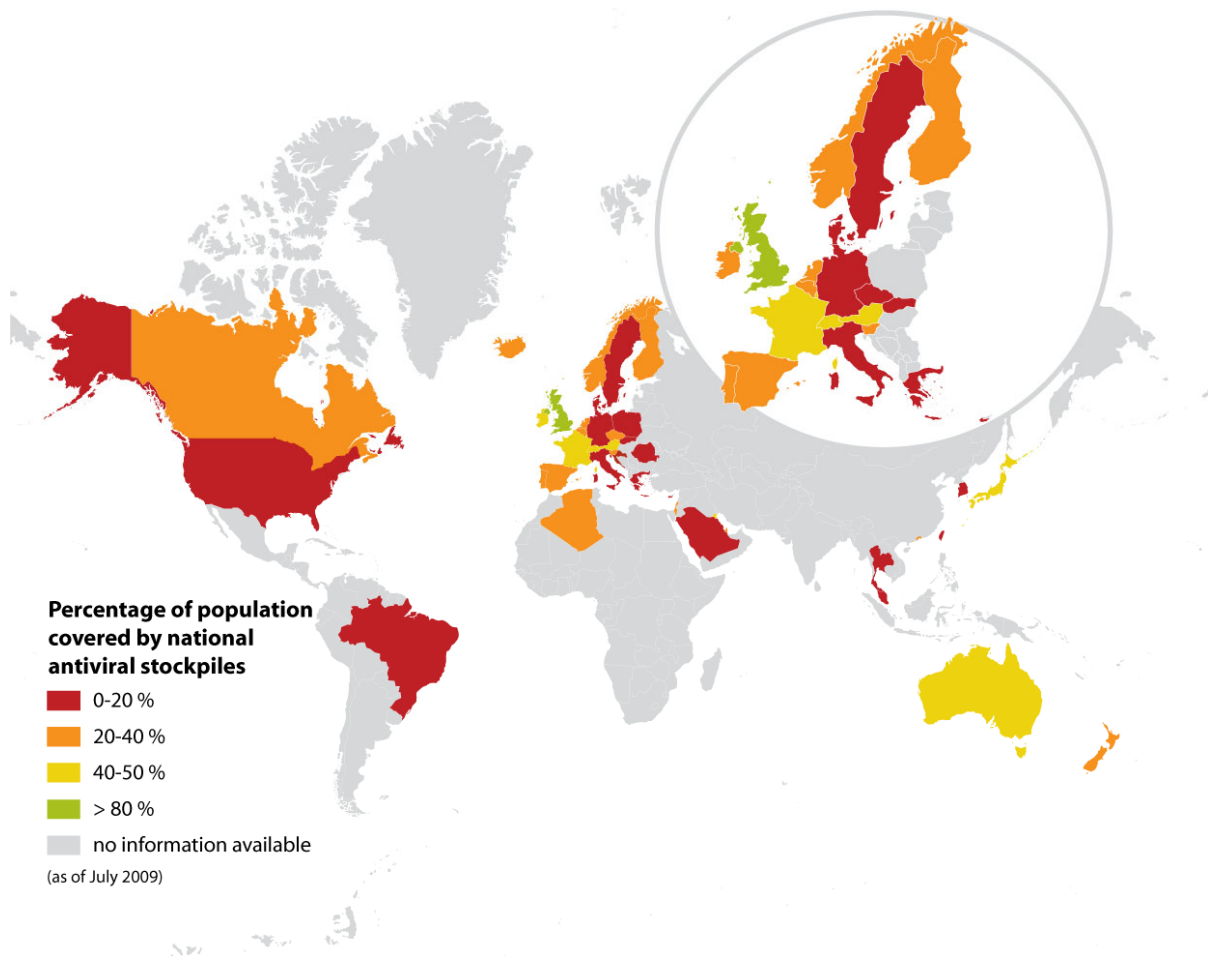
The role of governments, international agencies and corporations

1) Respective responsibilities regarding pandemic preparedness

Pre-pandemic – governments

Governments have a responsibility to deliver public health care to their citizens. It is therefore governments' responsibility to plan for a pandemic, to put strategic and operational pandemic plans in place. This includes ensuring adequate stockpiles of antivirals, to prioritize patients (if needed), and to set up systems and measures ensuring rapid distribution and effective delivery in order for their population to receive urgent and timely access to antivirals. The importance of timely delivery (within two days) to ensure maximum efficacy of Tamiflu needs to be considered in the planning for delivery.

When the WHO declared Pandemic (H1N1) 2009, statistics showed that stockpile levels had wide variability, with some governments having sufficient antiviral stockpiles to treat up to 50-80% of their national population, while others would only be able to cover a small fraction. The total antiviral (oseltamivir or zanamivir; including generic forms) stockpile by governments around the world would have provided treatment for around 9% of the world's population.



Source: Roche, July 2009

This lack of stockpiling in some countries has therefore led to a huge surge in demand on Roche which the company is now trying to manage through its increased production capacity.

Pre-Pandemic – international agencies

International agencies also have a responsibility to put in place pandemic plans for their employees. The World Health Organization (WHO) has been the most active international agency in this regard.

For a number of years, the WHO has been urging all countries to develop pandemic preparedness plans and developed a checklist to assist governments in their preparations. In the face of a pandemic threat, the WHO stated in January 2005 that, “stockpiling antiviral drugs in advance is presently the only way to ensure that sufficient supplies are available at the start of a pandemic.”

In 2005 WHO also issued guidance on the management of patients with avian influenza A (H5N1), the strain that WHO and other bodies feared would lead to the next global pandemic, and strongly recommended oseltamivir for the treatment and prevention of it.

Roche worked closely with WHO during the pre-pandemic donating some 5 million courses which it was ready to deploy in April 2009 for Pandemic (H1N1) 2009.

Once donated stockpiles reach these countries, the distribution of Tamiflu to populations affected becomes the sole responsibility of the WHO and of national governments concerned.

Pre-pandemic – corporations

Corporations must also consider the impact of a pandemic on the continuity of their business operations, both on the short and long term, in order to appropriately assess and manage the risk of a pandemic. For instance, many corporations have pandemic planning committees to combine strategic planning, operational continuity procedures, human resources and stockpiling of antivirals, so that the impact of a pandemic on their employees, products and/or services can be contained or even reduced.

2) Managing the current Pandemic (H1N1) 2009: the need for interaction and cooperation

In any pre-pandemic phase, governments and international agencies must work together to plan and prepare, to ensure that they can cooperate effectively for the good of society and the global economy once a pandemic is declared.

Prior to the Pandemic (H1N1) 2009 outbreak, many felt that despite the calls from the WHO there had been a lack of interaction between these agencies and key individuals at the international, national and regional/local levels.

Dr. Margaret Chan, Director General of the WHO has stated, despite this, the world is better placed than it ever has been to fight a pandemic. And, now that the world is encountering its first pandemic of the 21st century, it is imperative that these

agencies work closely together to manage the situation effectively, executing their roles in a responsible fashion:

- governments must mobilize their national pandemic plans, provide access to antivirals and ensure that their citizens are educated on the spread of the disease and how they can mitigate their chances of infection
- international agencies such as the WHO must continue to provide a coordinating role, providing broad guidance on the use of antivirals and helping to distribute stockpiles. Other bodies such as the Centre for Disease Control (CDC) and European Centre for Disease Control and Prevention (ECDC) – as well as the WHO – must continue to undertake global surveillance of the Pandemic's progress and provide intelligence to the other actors
- corporations must ensure their organizations continue to operate and meet the needs of society. At the same time, they must exercise their duty of care over their employees and, where possible, implement policies that help slow the Pandemic's development through responsible working practices
- antiviral manufacturers such as Roche, must continue to try and meet the surge in demand and deliver drugs safely to national governments and competent health authorities.

Finally, it is imperative that these agencies don't end their cooperation too soon and that they work together to learn the lessons of Pandemic (H1N1) 2009 to ensure that society is even more prepared to meet inevitable future pandemic threats.

Conclusion

This position paper describes Roche's roles, responsibilities and contributions, both in a pre-pandemic and a pandemic setting, and addresses the expectations of the global community.

Responsibility for pandemic preparedness has to be shared between governments and international agencies/non governmental organizations (NGOs) as well as manufacturers of antivirals and vaccines.

While Roche is not in a position to lead this response it acknowledges the key role it has to play as a partner in it.

In this respect, Roche calls upon all stakeholders involved to understand their responsibility, to work together cohesively to respond to Pandemic (H1N1) 2009 and to further refine and develop future pandemic preparedness plans.
