

# Pandemic influenza vaccines: meeting the supply, distribution and deployment challenges

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## Abstract

An influenza pandemic will place an enormous strain on the world's vaccine production, distribution and administration systems. Following a pandemic declaration, industry's priority will be to deliver as much vaccine in as short a timeframe as possible. In respect to this challenge, manufacturers have successfully developed antigen-sparing strategies and significantly increased production capacity, with further growth planned assuming ongoing rising demand for seasonal vaccines. The combination of these factors has the potential to closer meet global needs for vaccine supply than ever before through increased availability of pandemic and pre-pandemic vaccines. The demonstration of cross-clade reactivity with H5N1 viruses makes the concept of pre-pandemic stockpiling and vaccination a reality for this subtype. Ensuring these vaccines are made available in a timely fashion to those who need them will present significant challenges. For local authorities, national governments and international organisations this means defining vaccine allocation and procurement processes as well as strengthening, and where necessary establishing, the critical health systems and infrastructure required for vaccine deployment. For vaccine

producers this means addressing the technical and logistical issues associated with supply. This includes working with regulators to streamline key procedures, including generic labelling and batch release, while establishing flexibility in supply formats, including bulk and finished products, to maximise the speed of delivery. Similarly, the deployment of large quantities of vaccines in an emergency situation requires appropriate transport infrastructure and the distribution of associated medical supplies. As well as addressing these issues, specific consideration must be given to the logistics and storage aspects associated with stockpiling pre-pandemic vaccines. Finally, mutually agreed contractual arrangements between manufacturers and governments or international institutions represent the best approach toward addressing supply challenges and assisting vaccine producers meet national and international demand. To be effective, these contracts should be based on accurate forecasts, clearly defined vaccination strategies and the capabilities of public health infrastructure.

**Keywords** Influenza, infrastructure, logistic, pandemic, supply, vaccine.

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## Introduction

As a result of its unpredictability, rapid spread and the immune naivety of its victims, an influenza pandemic would represent a global public health emergency. Such an event would present health authorities, governments, international institutions and vaccine producers with a series of challenges, all of which must be addressed for pandemic preparations to prove effective. While much commentary has focused on industrial vaccine production capacity and pandemic immunisation strategies, many other logistical, practical and operational issues must also be addressed to effectively and rapidly deploy such vaccines during a period of intense pressure on health services. Therefore this paper,

which is based on a presentation given at the Third European Influenza Conference held in Vilamoura, Portugal from 14–17 September 2008, briefly summarises progress in vaccine development and production before focusing predominantly on these important additional factors, exploring the many systematic aspects of pandemic planning that will ultimately determine the success or otherwise of preparedness activities.

## Addressing the pandemic and pre-pandemic vaccine supply challenge

An influenza pandemic would present industry with a major challenge: to produce sufficient high-quality and

effective vaccines in a time frame that would permit the rapid immunisation of whole communities around the world. In an effort to address this, industry has adopted a twin-track approach:

- *Building timely supply.* By focusing its R&D efforts and working closely with regulatory authorities, vaccine producers have developed a number of prototype pandemic vaccines. These products are based on model influenza strains and those with pandemic potential, and allow manufacturers to establish the clinical and regulatory profile of the vaccines prior to an outbreak. Producers can then update the vaccines once a pandemic-causing strain is identified and characterised. In the period before these pandemic vaccines become available, stockpiled pre-pandemic vaccines can be deployed.

- *Building sufficient supply.* Despite the similarities with seasonal manufacturing, the production of pandemic vaccines in established plants requires a number of facility modifications and technical adjustments to meet biosecurity/biosafety requirements.

In addition to these measures, and following a number of years of investment, industry has made much progress toward meeting the pandemic vaccine supply challenge.

- *Antigen-sparing technologies and cross-strain immunity.* Manufacturers have developed adjuvantation and whole virion approaches that greatly reduce the antigen level required to induce neutralising antibody responses and provide cross-strain reactivity between different clades of avian viruses with pandemic potential.<sup>1–8</sup> These technologies offer the prospect of multiplying production capacity many times over and make the concept of pre-pandemic immunisation a realistic option.

- *Expansion of seasonal vaccine production capacity.* In addition, producers have greatly expanded overall capacity, with the number of seasonal vaccine doses distributed increasing from approximately 300 million in 2003<sup>9</sup> to over 400 million in 2007,<sup>10</sup> and potentially growing substantially further by 2010 if demand continues to rise.<sup>11</sup>

When these measures are combined with efficiencies that could be achieved through continuous plant operation, and based on continued and rising use of seasonal vaccines and taking advantage of antigen-sparing technologies, annual industrial capacity may rise to billions of pandemic vaccine doses by 2010.<sup>11</sup> Indeed, if successfully implemented, and although the first doses of pandemic will only be available 4–6 months after the pandemic virus has been identified, i.e. missing the first wave of the pandemic, these advances have the potential to cover a large part of the global population in a reasonable time-frame.

**Table 1.** Key areas for pre- and pandemic vaccine optimisation and policy focus

#### Pandemic vaccine supply ongoing challenges

##### Vaccine optimisation

Defining optimal product formulations  
 Clarifying immunisation schedules  
 Establishing duration of protection  
 Determining cross-reactivity/cross-protection against newly drifted strains  
 Defining prime/boost strategies based on homologous/heterologous vaccine strains  
 Developing standardised immunological tools and animal challenge models

##### Policy focus

Implementing appropriate seasonal vaccination policies to protect local populations and expand vaccine production capacity  
 Defining pandemic vaccination strategies including the use of pre-pandemic vaccines  
 Defining processes for vaccine allocation and procurement around the world  
 Strengthening/establishing essential health and distribution infrastructure to enable population-wide immunisation

## Continuing challenges for pandemic vaccine supply

While much has been achieved in securing vaccine supply, industry, governments and international public health organisations continue to face hurdles that require resolution. Manufacturers must build on the success achieved to date in optimising vaccine performance (Table 1), and in completing the development and licensing process. In addition, producers should address the technical and logistical issues that can impact vaccine supply. These include ensuring the appropriate product stability, storage and supply chain are in place, as well as vaccine filling and packaging capabilities. In parallel with these industrial activities, health authorities and international organisations must focus on the policy and strategic processes required to define and secure supply (Table 1). This article will specifically focus on the critical factors of the equitable availability of vaccines in a pandemic situation and the technical issues linked to the supply and logistics.

## Success factors for ensuring vaccine availability

For populations to access vaccines during a pandemic several key processes must be completed well in advance to ensure availability.

- *Developing/finalising immunisation strategies.* To be effective pandemic vaccination strategies must be clearly

defined, agreed by key stakeholders, widely communicated and appropriate training given to all relevant personnel. These plans must detail the deployment of pandemic vaccines and describe the role of pre-pandemic vaccines at key points in the pandemic cycle: prior to an outbreak, in the intermediate period when a pandemic appears imminent and early in the first wave when vaccines matched to the causative strain will not be available.

- *Forecasting demand.* With robust vaccination strategies in place, health authorities can establish realistic demand forecasts. These are essential for the planning of vaccine production, deployment and supply.
- *Ensuring appropriate regulatory processes.* Defining the regulatory pathway for products targeting a virus that does not yet exist is challenging. However, this process must not become a barrier to vaccine supply, and should be clear, timely and workable.
- *Strengthening public health infrastructure.* Undertaking vaccination programmes across entire populations will challenge even the most developed healthcare systems. Consequently, authorities should critically examine existing capabilities and ensure that the appropriate infrastructure is in place.
- *Securing vaccine supplies.* Finally, governments should utilise demand forecasts to enter contractual arrangements for pre-pandemic vaccines and to reserve the supply of vaccines during an pandemic. Completing this well in advance of an outbreak is important to avoid the need for negotiations during a period when time pressures will be intense for all parties.

## Vaccine supply, deployment and administration during a pandemic

The process of pandemic influenza immunisation will prove highly challenging during a period when health services will be under intense pressure and may be disrupted by public fear and societal upheaval. Vaccine manufacturers are likely to produce millions of doses each day, which will place unprecedented strains on distribution and administration systems. Consequently, transforming existing infrastructure and establishing additional capabilities is essential to overcome the constraints of the traditional models currently employed to distribute and administer vaccines.<sup>12</sup>

To address this challenge industry, health authorities, regulators and international organisations must work together. As health systems vary from country to country, planners must adopt locally-appropriate solutions to avoid the imposition of a 'one-size-fits-all' approach. Health authorities must deploy vaccination services efficiently, and this can only be achieved if many practical issues are resolved in advance.

- *Shipping capabilities.* Pandemic vaccine supply will require robust cold chain infrastructure with central management and appropriate monitoring and tracking to allow rapid shipping from producers, through local distribution systems, and ultimately to immunisation centres. A pandemic will severely stretch existing capabilities and therefore logistics plans must be established and tested beforehand.
- *Warehousing.* As an integral component of vaccine distribution systems, warehousing must also meet strict quality and regulatory requirements. Temperature control (2–8°C), Good Manufacturing Practice (GMP) compliance, protection against unauthorised access, pests and environmental hazards, and operation by appropriately trained employees under the control of a 'Qualified Person' are all essential.
- *Security.* Pandemic influenza is likely to cause panic and disruption. As a consequence, measures must be in place to safeguard vaccines and personnel throughout the supply chain, including at manufacturing facilities and immunisation centres. In addition, contingencies must be put in place to ensure sufficient and appropriate human resources at each point in the distribution system, allowing for a significant level of work place absences. Equally, counterfeit vaccines must be eliminated from the supply chain and measures established to prevent the introduction of fake products, particularly via the internet.
- *Ensuring the free movement of goods.* With influenza vaccine production based in a limited number of countries, logistical considerations will present challenges to both producers and health authorities. To ease this burden governments should pre-establish procedures for the smooth transit of vaccines across borders.
- *Material requirements.* In addition to establishing vaccine supply agreements, authorities should pre-source the associated materials required for immunisation, including needles and syringes to avoid bottlenecks; for example, as may be the case for certain products the administration of and vaccine adjuvanted at the point of care from a 10-dose vial, would require 12 needles and 11 syringes.
- *Establishing vaccination infrastructure.* Existing immunisation centres are likely to be overwhelmed by the demand for and supply of pandemic vaccines, and the establishment of public vaccination venues in non-traditional settings such as schools or leisure facilities may be required.<sup>13</sup> This infrastructure must be capable of managing the complexity of vaccination schedules potentially requiring two immunisations over a period of time and the use of adjuvants supplied in separate and varying presentations. As for other pandemic preparedness approaches, computer modelling could help health agencies to design and assess their plans.<sup>13</sup>

- *Communication and training.* Even the most effective plans and robust infrastructure will prove unsuccessful if communications are unclear. Communications must encompass comprehensive training for immunisers and vaccination centre workers, and include patient invitation and recall systems and vaccination information. These 'internal' elements must be supported by public information campaigns, which will run in close collaboration with local media. These can include novel methods for providing updates and warnings.
- *Contingency and testing.* With any event on the scale of a global influenza pandemic, unexpected situations will arise. Consequently, preparations should incorporate contingency measures and flexible processes designed to address unplanned outcomes.
- *Simulation exercises.* Tests should be conducted to assess the effectiveness of all these procedures, and national/local preparedness plans should be adapted to address any issues that are identified.  
As well as addressing these operational requirements for successful vaccine deployment during an emergency, public health authorities and industry must give special consideration to processes that can support pandemic preparedness strategies.
- *Prioritisation and targeting.* Plans must clarify target groups for immunisation, including those to receive pre-pandemic vaccines, and the order in which to vaccinate specific populations when the supply of 'true' pandemic vaccines begins. The defining of these groups and their relative prioritisation may prove controversial and require public consultation; for example, this process was adopted by the US government, which refined its plans based on public input.<sup>14</sup>
- *Discouraging disease transmission.* When putting in place vaccination venues, planners should aim to resolve the conflict between encouraging social distancing and voluntary quarantining, and bringing people to a central point for immunisation. Alternative vaccine administration points should cater to this requirement where possible, for instance when establishing patient flows, recall systems and waiting areas.
- *Learning from established practice.* While an influenza pandemic would be an unprecedented event for many healthcare professionals, processes are in place on an international scale to address natural disasters, including the roll out of broad immunisation programmes such as those targeting measles or polio in developing countries. Consequently, by working with organisations such as the Red Cross, UNICEF, Médecins sans Frontières and other non-governmental organisations, those responsible for public health can build on existing best practice.
- *Efficient regulatory processes.* Regulatory approaches must support the rapid supply of high-quality and effective

vaccines, without presenting unwarranted barriers and duplication of processes. This is particularly true in the developing world where the introduction of a fast-track WHO pre-qualification process would enhance pandemic preparations. Equally, regulatory systems should streamline batch release and adapt product profiles to meet the characteristics of delivery systems needed in an emergency situation, e.g. harmonised/generic labelling.

- *Flexible production.* Manufacturers and health authorities should take a flexible approach to supply to maximise the speed of delivery. This should incorporate a range of supply formats (bulk antigen and vaccines in multi-dose vials or single syringes) and the use of local plants for filling and packaging where appropriate.
- *Liability.* Immunising entire populations with vaccines with limited clinical experience, often based on pre-licensure studies, is likely to raise liability issues that must be resolved as part of the negotiation of supply contracts. With vaccination likely to occur under government mandated programmes, overall liability is likely to be retained by national authorities.

### Pre-pandemic vaccines: special considerations

The availability of vaccines with the ability to provide cross-strain immunity offers the potential of an early defence against pandemic influenza, via pre-pandemic priming or the rapid deployment of stockpiled doses at the start of an outbreak, provided the pandemic strain is actually closely related to avian strains used in vaccine development. While this approach relies on a positive benefit/risk assessment of cross-reactivity against potential future pandemic strains, the WHO and a number of national governments have adopted stockpiling strategies for H5N1 vaccines, including Australia, Finland, France, Italy, Japan, Switzerland, the UK and the USA.<sup>11</sup>

A number of studies with whole-virus<sup>3</sup> and adjuvanted vaccines<sup>4-7</sup> have demonstrated the generation of antibodies that are cross-reactive against H5N1 viruses from a variety of different clades and strains, as well as the induction of robust immune responses following prime and boost doses separated by months or even years, and with vaccines based on heterologous viruses.<sup>6,8</sup> These results open up the prospect of pre-pandemic immunisation offering early protection during the 3-4 months when pandemic vaccine production is ongoing. Similarly, priming portions of the population beforehand would ease the burden on pandemic vaccine deployment. Beyond scientific and regulatory aspects, several issues must be addressed before implementing pre-pandemic vaccination strategies outside of a pandemic emergency. This includes the decision to immunise individuals against a non-human disease and safety aspects linked to the extensive use of vaccine formulations (whole virus and new adjuvants)

with limited clinical experience, and subsequent public acceptance and potential liability.

However, to reap these potential benefits, appropriate logistical and operational systems are required.

- Management systems to handle vaccines from multiple suppliers with a range of packaging, product identification and presentations, including vials containing different numbers of doses.
- Warehousing and stock management systems with qualified buildings and operators and appropriate security.
- Stock management systems to manage product expiries and replacements.
- Stockpiling systems for associated supplies, including needles and syringes and packaging materials for distribution.

## Conclusion

In recent years preparations to protect against pandemic influenza have advanced considerably. Rapid R&D progress has resulted in a new generation of vaccines, and in parallel manufacturers have dramatically expanded production capacity.

To capitalise on these capabilities, planners must continue efforts to address the significant number of operational, logistical and distribution challenges presented by population-wide immunisation. This includes the adoption of vaccination strategies that anticipate immunisation needs and define delivery processes, as well the adaptation of vaccine deployment systems to enable the efficient distribution and administration of pre- and pandemic vaccines in an emergency situation.

Appropriate contractual agreements are the most appropriate way to address many of these challenges to assist vaccine manufacturers in meeting national and international demands in accordance with global public health needs. This will help facilitate supply based on reasonable forecasts, and in a manner that is relevant to specific vaccination strategies, infrastructure and regulatory considerations.

Securing vaccine supply and the associated deployment capabilities is an urgent concern and should be incorporated in local, national and international pandemic plans as well as in WHO guidance.

Finally, successfully protecting communities around the world against an influenza pandemic will require strong co-ordination amongst public health partners. This essential process must be initiated where it is not already in place, and nurtured and maintained in the interests of everyone's future health.

## Conflict of interest

Dr. Luc Hessel is an employee of Sanofi Pasteur MSD, a provider of influenza vaccine in Europe.

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