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Review

Lessons from pandemic influenza A(H1N1): The research-based vaccine industry's perspective

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ABSTRACT

As A(H1N1) influenza enters the post-pandemic phase, health authorities around the world are reviewing the response to the pandemic. To ensure this process enhances future preparations, it is essential that perspectives are included from all relevant stakeholders, including vaccine manufacturers. This paper outlines the contribution of R&D-based influenza vaccine producers to the pandemic response, and explores lessons that can be learned to improve future preparedness.

The emergence of 2009 A(H1N1) influenza led to unprecedented collaboration between global health authorities, scientists and manufacturers, resulting in the most comprehensive pandemic response ever undertaken, with a number of vaccines approved for use three months after the pandemic declaration. This response was only possible because of the extensive preparations undertaken during the last decade.

During this period, manufacturers greatly increased influenza vaccine production capacity, and estimates suggest a further doubling of capacity by 2014. Producers also introduced cell-culture technology, while adjuvant and whole virion technologies significantly reduced pandemic vaccine antigen content. This substantially increased pandemic vaccine production capacity, which in July 2009 WHO estimated reached 4.9 billion doses per annum. Manufacturers also worked with health authorities to establish risk management plans for robust vaccine surveillance during the pandemic. Individual producers pledged significant donations of vaccine doses and tiered-pricing approaches for developing country supply.

Based on the pandemic experience, a number of improvements would strengthen future preparedness. Technical improvements to rapidly select optimal vaccine viruses, and processes to speed up vaccine standardization, could accelerate and extend vaccine availability. Establishing vaccine supply agreements beforehand would avoid the need for complex discussions during a period of intense time pressure.

Enhancing international regulatory co-operation and mutual recognition of approvals could accelerate vaccine supply, while maintaining safety standards. Strengthening communications with the public and healthcare workers using new approaches and new channels could help improve vaccine uptake. Finally, increasing seasonal vaccine coverage will be particularly important to extend and sustain pandemic vaccine production capacity.

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1. Introduction

In June 2009, WHO declared the first influenza pandemic in over 40 years. The emergence of this new influenza virus initiated a robust and rapid response from public health partners around the world, including the research-based vaccine industry. As the 2009 A(H1N1) virus enters its post-pandemic phase, international institutions, national governments and individual manufacturers are conducting reviews to identify which aspects of the response were successful, and which can be improved. As part of this global assessment process, the international and European organizations that represent the world's major influenza vaccine manufacturers (the IFPMA IVS taskforce and EVM respectively) have worked together to compile an industry perspective. This is intended to complement the reviews conducted by other organizations, and ultimately to help inform future preparedness activities.

2. The vaccine industry's role

Vaccines are a crucial tool in the fight against pandemic influenza, and consequently the vaccine industry has an essential role to play when called on by public health authorities. In answering this call, the manufacturers' role is clear: the rapid development, production and supply of safe and effective pandemic vaccines to enable the immunization of local populations. However, fulfilling this role is challenging. Influenza vaccine manufacture is complex and time consuming, and requires specialist facilities and highly trained personnel. In addition, the timely provision of vaccines is not entirely controlled by manufacturers, and involves the collaboration of other organizations, for instance to ensure efficient regulatory review or provide logistical infrastructure.

Following the emergence of the 2009 A(H1N1) pandemic strain, a broad collaboration of international institutions, governments, public health authorities, scientists and vaccine producers came together to address these challenges. These partners went on to mount the most complete pandemic response ever undertaken.

- *Rapid supply of pandemic vaccines*. Three months after the June 2009 pandemic declaration, several manufacturers of inactivated and live attenuated vaccines had completed vaccine development, received regulatory authorization and undertaken production scale-up (see Fig. 1). Soon afterwards, a number of health authorities initiated immunization programs, with others following in the subsequent weeks and months. By December, over 30 vaccines had received approval, and more than 50 countries had started vaccination programs [1]. Manufacturers went on to supply significant quantities of pandemic vaccines to many countries around the world, while also supplying seasonal influenza vaccines to meet local needs in both the Northern and Southern hemispheres. The speed of this response was only possible because of the preparations undertaken in the years preceding the 2009 pandemic.
- *Safe supply of pandemic vaccines*. Prior to the A(H1N1) pandemic, manufacturers had amassed many decades of experience producing seasonal influenza vaccines, and had also developed and tested many prototype pandemic vaccines. Building on these preparations, manufacturers conducted clinical trials with new A(H1N1) vaccines, to ensure they met regulatory and public health authorities' safety requirements. Subsequently, the vaccines' safety was confirmed by extensive surveillance of vaccine use in millions of people, including the more than 40 million vaccinated in Europe and nearly 127 million doses distributed in the US by the end of March 2010 [2,3].
- *Meeting health authorities' needs*. As the pandemic progressed, vaccine demand changed and in many countries uptake was lower than anticipated. As a result, a number of governments revised their vaccine needs downwards, and manufacturers worked with these countries to meet the new requirements where possible.

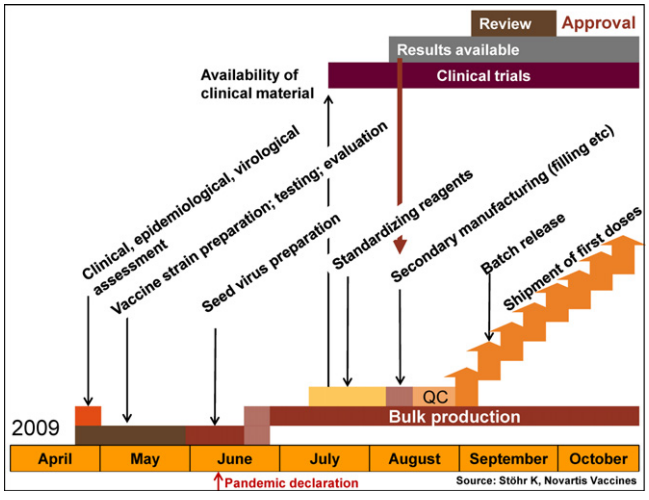

Fig. 1. Production process for initial batches of 2009 A(H1N1) influenza vaccines.

3. A decade of pandemic preparations

For many years, international institutions, such as WHO and the European Union, called for pandemic preparations [4,5]. Manufacturers answered this call, and over the last 10 years committed significant resources to preparedness despite uncertain financial returns, and as a result enhanced the world's response capabilities.

- *Substantial increase in vaccine production capacity*. Over a period of years, manufacturers steadily increased seasonal influenza vaccine supply. Independent estimates suggest capacity could continue to expand to approximately 1.4 billion seasonal doses per annum by 2014 [6]. In addition, manufacturers developed live attenuated, adjuvanted and whole virion inactivated pandemic vaccines, which met regulatory requirements with far lower antigen contents than are used in seasonal inactivated vaccines. By utilizing 3.75 μg–7.5 μg of antigen per monovalent dose [7–11], rather than the 45 μg typically contained in inactivated trivalent seasonal vaccines [12,13], these pandemic vaccines in effect stretched antigen utilization 600–1200%. The combination of these advances increased pandemic vaccine production capacity significantly, with WHO estimating in July 2009 that it had reached 4.9 billion doses per year [14].
- *Advanced technologies enhanced preparedness*. Earlier research with other influenza viruses, such as A(H5N1) and seasonal strains, suggested that vaccine strategies incorporating adjuvant technologies, whole virion inactivated vaccines and live attenuated vaccine approaches may also offer broader immunity [15–17]. Additionally, manufacturers developed new generation adjuvanted and non-adjuvanted pandemic vaccines using cell culture biotechnologies, and these were supplied to a number of countries during the A(H1N1) pandemic, alongside wide-scale provision of traditional egg-produced vaccines.
- *Vaccination monitoring systems ensured safety*. Prior to the pandemic outbreak, manufacturers established risk management plans as part of their vaccine development activities. These enabled the wide-scale safety surveillance of pandemic vaccination programs.

4. Industry's contribution to a global response

During the 2009 pandemic, vaccine manufacturers provided further contributions in addition to responding to requests for vaccine development and supply. Recognizing the importance of broad vaccine access, individual manufacturers put in place a number of measures to enhance global access. Producers also provided clinical data and production information to enable the timely development of vaccination policies by public health authorities.

- *Significant vaccine donations*. Individual producers pledged 166 million doses of A(H1N1) vaccines to help meet the WHO's 200 million dose target for developing country supply [18].
- *Reserved production capacity and tiered-pricing*. In recognition of countries' differing levels of economic development, a number of manufacturers put in place approaches to assist supply to developing countries.
- *Financial and technical support for the WHO system*. Manufacturers worked closely with WHO network laboratories to accelerate production initiation and scale up. These laboratories, supported financially by manufacturers, produced isolates and high-growth reassortant vaccine viruses, which inactivated-vaccine producers rapidly tested and provided data on growth characteristics to help yield improvement efforts. Producers also supplied concentrated antigen to the WHO network for vaccine standardization. These measures helped accelerate and ultimately increase vaccine availability.
- *Data provision for health authority policy development*. Manufacturers undertook extensive clinical studies with A(H1N1) vaccines, and provided public health authorities with clinical data to enable the timely development of immunization policies. This included the provision of preliminary data to the WHO Strategic Advisory Group of Experts on Immunization to enable the Group to formulate independent advice on pandemic vaccine use [19]. Throughout the production of pandemic vaccines, manufacturers provided supply data to assist authorities' planning activities, as well as establishing distribution mechanisms to enhance availability.

5. Lessons from the 2009 pandemic

It is clear that the emergence and subsequent global spread of 2009 A(H1N1) influenza prompted the largest pandemic response ever mounted. Many aspects of this undertaking were highly positive. However, not surprisingly, the response also revealed a number of areas where improvements could be made.

Assessments by health authorities and other stakeholders will play an important role in determining the lessons that can be learned from the 2009 pandemic. The review undertaken by the IFPMA IVS and EVM groups can complement this process, providing a perspective from the vaccine industry.

- *Record levels of preparedness*. Over many years, public health partners, including vaccine manufacturers, undertook extensive preparations to combat future influenza pandemics. This process accelerated significantly following the rapid spread of A(H5N1) avian viruses. Without this level of preparedness, the 2009 response would not have been possible. This situation clearly demonstrates the need for pandemic preparations to continue as a high priority.
- *Scientific and technical collaboration*. The initial stages of A(H1N1) inactivated vaccine virus development and production scale-up proved highly challenging. As a result, industry scientists worked closely with WHO network colleagues to improve yields from the viruses and to provide materials for vaccine standardization. In addition, methods for the rapid development of high-yielding reverse genetics vaccine virus strains were shared with public health agencies and made available via journal publications. This spirit of voluntary collaboration and flexibility amongst public health partners can be built upon to strengthen future preparedness.
- *Vaccine safety monitoring*. The implementation of previously established monitoring plans allowed the rapid confirmation of A(H1N1) vaccine safety. Future preparedness efforts should focus on ensuring vaccine safety through the use of flexible and efficient surveillance systems.
- A number of improvements could complement the positive elements outlined above.
- *Technical enhancements*. Initial A(H1N1) inactivated vaccine virus production yields were only 1/3–1/2 of those achieved with good seasonal strains [20]. Overcoming this major issue impacted on early inactivated vaccine availability. Consequently, systems that would allow the WHO network to evaluate multiple vaccine viruses in parallel and select those with optimal growth characteristics could both speed up and increase vaccine supply. Similarly, the introduction of alternative vaccine standardization technologies, such as HPLC or mass spectrometry, could enable earlier clinical testing and vaccine availability.
- *Enhancing decision-making processes*. The further development of rapid pandemic epidemiological research capabilities could help underpin assessments of the likely course and impact of future outbreaks. This could help inform policy decision making and enhance modeling of vaccine demand.
- *Pre-establishing supply agreements*. At the outbreak of the A(H1N1) pandemic, many countries did not have vaccine supply agreements in place. As a result, large numbers of complex negotiations had to be undertaken in parallel with significant time pressures on all parties. The establishment of appropriate agreements prior to a pandemic would avoid this situation, and assist health departments and manufacturers with logistical planning.
- *Streamlining regulatory processes*. A number of regulatory procedures introduced to accelerate pandemic vaccine assessment worked well. However, others resulted in duplication and additional bureaucracy. For instance, some authorities requested duplicate lot release testing, and WHO pre-qualification required production site visits even when these had been completed by local regulatory agencies or previously by WHO for seasonal vaccines. Consequently, the recognition of existing regulatory authorizations and enhanced co-operation could speed up vaccine supply, while continuing to ensure robust safety standards.
- *Regional collaboration*. The occurrence of the first pandemic in decades provided a number of opportunities for supra-national co-operation that were not seized upon. For instance, although Europe-wide effectiveness studies were conducted, the opportunity was not taken to combine these in a centralized, co-ordinated manner with European safety studies; similarly, co-ordinated pan-European safety studies should be conducted as an integral component of future vaccine surveillance. The pandemic also reinforced the need to enhance regional virus surveillance and epidemiology capabilities, particularly in developing regions such as Africa.
- *Overcoming communications challenges*. For the first time during a pandemic, modern electronic communications played a high profile role. New channels greatly speed up and broaden communications, but they also enable the rapid spread of unscientific and unbalanced information. During the 2009 pandemic, this may have amplified public concern regarding pandemic vaccines, and in some instances the use of social media may have eroded public confidence in vaccine safety. The impact of these new communication methods may have played a role in the low uptake of A(H1N1) vaccines. Even amongst key target groups, vaccina-

tion rates remained low (for example, in the US only 37.1% of healthcare workers were vaccinated by mid-January 2010 [21]). In future, it will be important to utilize new communication approaches to address concerns over vaccine safety, build public trust and convince those at risk of the importance of vaccination. In addition, further transparency about the different roles of all stakeholders involved in the process of immunization assessment and policy making could help avoid misconceptions about the nature of the collaboration required to protect against pandemic influenza.

6. Conclusions

For many years, the vaccine industry has been committed to pandemic preparations, and has contributed major resources to the field as requested by health authorities. Record levels of preparedness and collaboration between public health partners enabled manufacturers to answer the call for safe and effective A(H1N1) vaccines, and to go on to supply significant quantities starting just three months after the pandemic declaration.

However, despite the magnitude and speed of the 2009 pandemic response, there remain areas for improvement. Amongst the issues likely to be explored by ongoing reviews, is the potential scale of future vaccine provision. Although the severity of the recent pandemic was relatively mild, and vaccine demand was low, this cannot be relied on in future. WHO estimated that production capacity stood at 4.9 billion doses per annum, but while this represents a step change in global capabilities it may be insufficient for global populations in future. Many solutions have been suggested to fill the gap, such as local capacity building and technology transfer, and initiatives are progressing in both of these areas. However, pandemic vaccine production capacity can only be increased and sustained through the wider use of seasonal vaccines. During recent years, seasonal vaccine usage has failed to match the growth in production capacity, and uptake has remained low even amongst a number of high risk groups. By providing strong policy support and implementing existing vaccination recommendations, governments can help protect local populations against the ongoing threat posed by seasonal influenza, while simultaneously extending and sustaining the world's ability to combat the next, inevitable pandemic.

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References

[1] WHO. Statement from WHO global advisory committee on vaccine safety about the safety profile of pandemic influenza A(H1N1) 2009 vaccines. 18 December 2009. http://www.who.int/csr/resources/publications/swineflu/cp164_2009_1612_gacvs_h1n1_vaccine_safety.pdf.
[2] European Medicines Agency. 15th pandemic pharmacovigilance update. 8 April 2010. http://www.ema.europa.eu/pdfs/influenza/21323810en.pdf.
[3] US Centers for Disease Control and Prevention. Summary of 2009 monovalent H1N1 influenza vaccine data – vaccine adverse event reporting system. Data through March 26; 2010. http://vaers.hhs.gov/resources/2010H1N1Summary_Apr01.pdf.
[4] Fifty-eighth World Health Assembly resolution WHA58.5. Strengthening pandemic-influenza preparedness and response. http://apps.who.int/gb/ebwha/pdf_files/WHA58/WHA58_5-en.pdf.
[5] European Parliament resolution on the strategy against an influenza pandemic. 26 October 2005. http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P6-TA-2005-0406&language=EN.
[6] Oliver Wyman. Influenza vaccine supply and demand. March 2009. http://www.oliverwyman.com/ow/pdf_files/Influenza_Vaccine_Supply__Demand_Study_-_Summary_of_Findings_.pdf.
[7] Arepanrix Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001201/WC500089737.pdf.
[8] Celvapan Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000982/WC500022670.pdf.
[9] Focetria Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000710/WC500023749.pdf.
[10] Humenza Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001202/WC500094348.pdf.
[11] Pandemrix Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000832/WC500038121.pdf.
[12] Ph. Eur. 7th ed. 2011. European pharmacopoeia 7.0, 08 vaccines, vaccines for human use, European pharmacopoeia Monograph 01/2008:0869, influenza vaccine (surface antigen, inactivated). p. 789–91.
[13] Ph. Eur. 7th ed. 2011. European pharmacopoeia 7.0, 08 vaccines, vaccines for human use, European pharmacopoeia monograph 04/2009:2149, influenza vaccine (surface antigen, inactivated, prepared in cell cultures). p. 791–93.
[14] WHO. Update on A(H1N1) pandemic and seasonal vaccine availability. 7 July 2009. http://www.who.int/immunization/sage/3.MPK-SAGE_7_July.pdf.
[15] WHO. Wkly Epidemiol Rec 2009;30(84):301–8, http://www.who.int/wer/2009/wer8430.pdf.
[16] Ehrlich H, Mv̈ller M, Oh H, Tambyah P, Joukhadar C, Montomoli E, et al. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture. N Engl J Med 2008;358:2573–84, http://content.nejm.org/cgi/reprint/358/24/2573.pdf.
[17] Rhorer J, Ambrose C, Dickinson S, Hamilton H, Oleka N, Malinoski F, et al. Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. Vaccine 2009;27:1101–10.
[18] WHO. Pandemic (H1N1) 2009 vaccine deployment update – 1 March 2010. http://www.who.int/csr/disease/swineflu/vaccines/h1n1_vaccine_deployment_update20100301.pdf.
[19] WHO. Wkly Epidemiol Rec 2009;49(84):505–8, http://www.who.int/wer/2009/wer8449.pdf.
[20] WHO. Transcript of WHO virtual press conference of 6 August 2009. http://www.who.int/mediacentre/pandemic_h1n1_presstranscript_2009_08_06.pdf.
[21] US Centers for Disease Control and Prevention. MMWR 2010;59(April (12)):357–62, http://www.cdc.gov/mmwr/pdf/wk/mm5912.pdf.