Royal Society/Academy of Medical Science Study on Pandemic Influenza

Call for Evidence

How to ensure availability of effective vaccines in case of influenza pandemic

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Vaccination represents the most effective medical way of controlling influenza during annual seasonal epidemic periods and is expected to play a critical role during a pandemic. In the event of a pandemic, a specific monovalent vaccine will have to be developed rapidly, and then produced in very large quantities. The global demand for pandemic vaccine will result in increased pressure from health authorities, the medical community and the general public, all seeking access. There is a substantial risk of inadequate, inequitable and delayed supply, including possible measures by countries with production facilities to limit or prevent export to countries without such facilities.

In order to assist medical and public health leaders to optimise the response to the potential threat of pandemic influenza, the World Health Organisation (WHO) and the European Union (EU) as well as several individual Member States have developed or are developing Influenza Pandemic Preparedness plans. WHO has provided detailed guidance on the content of such plans. The 56th World Health Assembly adopted a specific resolution on May 28, 2003 to ensure that all WHO Member States give priority to influenza pandemic preparedness planning. This includes paying particular attention to the need to ensure adequate supplies of pandemic vaccine.

The vaccine industry is committed to addressing the challenges posed by the threat of influenza pandemic worldwide. The successful handling of these issues will rely upon common understanding of the roles and responsibilities of each partner. Collaboration between governments, health authorities, international institutions, industry and academia is needed to overcome the obstacles and to guarantee the most rapid development, production and use of pandemic vaccine candidates. The unique features of vaccination use and prevention policies (compared to therapeutic drugs) justify specific approaches.

The key figures and elements that need to be taken in account as well as concrete proposals for building a long-term commitment vaccine manufacturers and Member States have been addressed by the vaccine industry both at the European and global levels (http://www.evm-vaccines.org, http://www.ifpma.org/Health/other_cont/health_other_influenza.aspx). Since then, some significant progress has been made in managing some of these issues. Others still need to be addressed for which science should play an important role directly or in influencing vaccination policies.

For the vaccine industry, properly addressing the pandemic threat relies on three main pillars:

1. R&D activities
2. Vaccine production and supply
3. Appropriate vaccination strategies

1. Strengthen R&D activities

The development of prototype influenza pandemic vaccines is a fundamental step in influenza pandemic preparedness. It is aimed at shortening the lead-time to license pandemic vaccines. In the EU, the EMEA issued in March 2004 guidelines on submission of marketing authorization applications and dossier structure and content for pandemic influenza vaccine. The EMEA guidelines provide a route for accelerated regulatory approval through the submission of the prototype pandemic vaccine files before the pandemic arrives.

Based on current scientific knowledge and industrial know how, the vaccine industry has been undertaking an intensive research drive to develop prototype pandemic vaccines. The vaccine industry is currently engaged in the development of 28 prototype vaccines. These prototype vaccines cover a range of potential pandemic strains (H5N1, H5N3, H7N1, H2N2 and H9N2) and different types of vaccine (inactivated whole virions, inactivated split virus and purified surface antigen) (Ref IFPMA). Two mock-up dossiers have already been submitted to EMEA and several others will follow during the course of this year.

In addition to the achievement of these short-term objectives, medium and long-term R&D activities are ongoing:

- to speed up the development of pandemic vaccine, based on existing know how;
- to develop novel, scientifically sound approaches to pandemic vaccine formulations with the aim of improving vaccine efficacy and antigen sparing;

In support of these activities, support & incentives from public health authorities would be needed to contribute to additional but necessary scientific approaches, such as those mentioned below:

- to ensure that all potential candidates are developed and registered;
- to conduct non-competitive research on immunological and virological methods to assess the protective efficacy of pandemic vaccines and on the cross-protection of prototype vaccines against mutated forms of the virus;
- to encourage research into new influenza pandemic vaccines concepts.
- to develop standardised clinical assay methods for evaluation of pandemic/pre-pandemic vaccines.

2. Adapt and prepare production of pandemic vaccines

Pandemic vaccines will be manufactured in facilities dedicated to seasonal flu vaccine manufacture, so the current capacity for seasonal flu vaccines is an important determinant of pandemic vaccine capacity. Hence the scientific community and policy makers focus on the additional advantage of encouraging everyone who will benefit from seasonal influenza vaccination to actually receive a vaccine. Not only is there an immediate health benefit, but over time the global capacity to produce pandemic vaccines will increase as well. In this respect WHO is recommending a vaccine coverage objective of 75% of people at risk by 2010.

The timing and availability of pandemic vaccines is linked to several scientific, regulatory and industrial factors:

- the amount of antigen per dose, a lower level will enable more doses to be produced;
- the production yield of the pandemic virus strain, which could be inferior, equal or superior to seasonal influenza production yield;
- timing for availability of vaccine candidate strains and reagents;

- fast-track release mechanisms by regulatory authorities (batch-release, universal packaging material).

Vaccine manufacturers are currently working on:

- producing H5N1 vaccines on pilot and industrial scale;
- securing the supply of eggs and/or adjuvants;
- developing vaccines in cell culture production;
- developing new vaccine formulations, and
- increasing capacity in bulk manufacturing facilities.

Some countries are already increasing vaccination coverage for the annual flu vaccine in at risk groups in order to reach the defined WHO coverage targets of 75% in elderly and other at risk groups. Keeping in mind that it takes 3 to 5 years to build and validate a new production site, Member States should plan in advance their interpandemic needs and share with manufacturers a 3 years perspective.

In addition, some European MSs are anticipating their pandemic needs through advanced purchase agreements (APAs) with vaccine manufacturers requesting pandemic vaccines, with the aim to cover their entire population. Therefore, the cumulated demand of doses requested is likely to outstrip current capacity. This could have an impact on the allocation of pandemic vaccines within and outside the EU and there is a danger that large segments of population would be unable to obtain access to vaccines in the event of a pandemic. More scientific evidence, including a better analysis / understanding of how a pandemic will occur and spread across the population, target populations or optimal strategic approach of vaccination programmes (see below), should support the legitimate objective of governments to protect their population while ensuring the best use of limited vaccine supply.

3. Evaluate complementary vaccination strategic approaches

The increased knowledge acquired in the past few months and the growing understanding of the situation suggests several approaches to complement the developments already underway, which are currently discussed at WHO level with experts and public health representatives.

The current strategy to combat pandemics relies on developing specific vaccines which will only be available several months after the pandemic has already begun, e.g. will not cover the first phase of the pandemic. It is almost certain that, two doses of vaccine will be required because of the “immunological naivety” of the population, whereas in seasonal influenza epidemics a single dose of the vaccine is usually enough to induce specific immune responses. It is thought that this is due to previous contacts with circulating flu viruses sharing an antigenic heritage with new annual strain. This means that people are already “primed” and the vaccine acts as a booster of natural immunity. This is not the case in younger children who need two doses of vaccines, a rather similar situation to what will be observed in the general population in the face of a pandemic strain,

By analogy, it is sensible to consider a similar approach when preparing for a pandemic. If it happens that vaccine using avian “pre-pandemic” strains, like currently the H5N1 Viet Nam strain, could elicit an immune response with a certain degree of cross reactivity with future human mutants, three strategies could be considered:

1. Using the stockpile of prototype vaccines in selected populations (those directly in charge of taking care of infected people, i.e. health care professionals) immediately at the start of the pandemic, without waiting for the final pandemic vaccine, which would only be available 3 to 6 months after the pandemic virus has been identified. This would represent a first line of defence.

2. A “prime-boost” approach consisting of a “primo vaccination” with monovalent “pre-pandemic” vaccines, containing potentially pandemic avian strains during the in inter-pandemic periods. One could then expect that, at the time of a pandemic, one single “booster” injection of the specific pandemic vaccine may be needed. This would mean more doses would be available and that the situation could be brought more quickly under control. One could also speculate that the wild-type pandemic virus could act as a natural booster in people having received a dose of an antigenically close virus, providing protection of this population against the most severe forms of the disease or against death. Scientific knowledge from other fields of vaccinology should be used to support this approach.
3. A step further would even consist of systematically including a “pre-pandemic” virus strain in the seasonal vaccine in addition to the three A H1 and H3 and B strains or instead of one of the strains.

It is important that these approaches are scientifically validated since it has major implications for public health and vaccination policies. This would also have an impact on the regulatory approach, as this means adding the actual license of "pre-pandemic" vaccines to the "mock-up" approach, with a more comprehensive pre- and post-licensure clinical development."

The value of these strategies requests on several elements, three of them relying on scientific approaches:

1. Developing appropriate immunological and virological methods to assess the protective efficacy of pandemic vaccines;
2. Assessing the cross-protection of prototype vaccines against mutated forms of the virus, for example between the prototype vaccines using the H5N1 Viet Nam 2004 strain and the clade 2 strains isolated in Turkey or Indonesia.
3. Confirmation of the “prime-boost” effect observed in current studies when prototype (adjuvanted or non adjuvanted) are given several months apart;

Conclusion

During recent years, the vaccine industry has moved forward with the development of prototype pandemic vaccines and research is ongoing to optimise pandemic vaccines.

At the same time, there have been several initiatives by the national and international institutions, but few concrete proposals and actions have materialised in the EU so far, mainly focused on regulatory aspects. Some governments, however, are actively supporting the development of pandemic vaccines, which include contractual arrangements with manufacturers to develop vaccine formulations and increase manufacturing capacity.

Additional aspects, probably out of the scope of the call for evidence should also be considered, such as equitable allocation of pandemic vaccine and liability linked to the use in large vaccination campaigns of vaccine which will not have undergone the usual regulatory process.

Finally, consistent scientific evidence as well as political leadership is needed to properly address this expected public health threat.