New Decade of Vaccines 3

Vaccine production, distribution, access, and uptake

Jon Smith, Marc Lipsitch, Jeffrey W Almond

For human vaccines to be available on a global scale, complex production methods, meticulous quality control, and reliable distribution channels are needed to ensure that the products are potent and effective at the point of use. The technologies used to manufacture different types of vaccines can strongly affect vaccine cost, ease of industrial scale-up, stability, and, ultimately, worldwide availability. The complexity of manufacturing is compounded by the need for different formulations in different countries and age-groups. Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies. However, to ensure optimum access and uptake, strong partnerships are needed between private manufacturers, regulatory authorities, and national and international public health services. For vaccines whose supply is insufficient to meet demand, prioritisation of target groups can increase the effect of these vaccines. In this report, we draw from our experience of vaccine development and focus on influenza vaccines as an example to consider production, distribution, access, and other factors that affect vaccine uptake and population-level effectiveness.

Introduction

Licensed vaccines are available to prevent human infections caused by about 25 microbes. The actual number of vaccine products is, however, much higher because many combination vaccines and formulations are aimed at different age-groups and geographical regions, and both private and public markets. Although vaccines differ in effectiveness, as explained in the fourth paper in this Series,1 most have contributed substantially to the improvements in human health across the past century. Among the large multinational pharmaceutical companies, only Sanofi Pasteur (part of the Sanofi-Aventis group) and GlaxoSmithKline manufacture a broad range of vaccines generally licensed for worldwide use. Others, such as Merck, Pfizer, and Novartis, offer a narrower range of products addressing particular disease indications or market niches.

This situation is changing with the growing number of manufacturers with headquarters in developing countries and the large new investment by multinational companies in vaccine research and development. As recently as 2005, only three of the present top ten pharmaceutical companies had substantial activities in vaccines. After recent mergers and acquisitions, the figure is now eight of the top ten. Vaccines are seen as an attractive and sustainable business for several reasons; vaccine demand has grown rapidly over the past decade and looks certain to grow further; many medical needs are unmet and vaccines do not exist for a range of important disease targets; innovative financing methods have greatly expanded markets, particularly in developing countries; advances in immunology and microbiology and our understanding of pathogenesis mean that previously intractable targets might now be within reach; and the vaccine sector has not been subject to the sharp revenue declines from expiry of patents that are plaguing much of the rest of the pharmaceuticals industry. Part of the reason for this last point is that vaccines are not as easy to produce and license generically as are small drug molecules, because it is the production processes as well as the products themselves that are licensed by regulatory authorities. Therefore, research and development, industrial know-how, and the associated costs provide high barriers to entry for potential new players, even for non-patented vaccines. Additionally, established manufacturers with a range of licensed antigens available are better able than small manufacturers to produce combination vaccines. Nevertheless, the drive for countries to be self-sufficient in production of essential vaccines, often with governmental support, has led to the expansion and technological advancement of several local

Key messages

- Manufacture of vaccines uses complex production methods, meticulous quality control, and reliable distribution channels
- Manufacturing technologies strongly affect vaccine cost, ease of industrial scale-up, stability, and, ultimately, worldwide availability
- Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies
- For vaccines with constrained supplies, such as influenza in a pandemic situation, prioritisation of target groups can increase vaccine protection
- As a result of strong growth, multinational pharmaceutical companies have recently returned to vaccine research and development with substantial investment
- Partnership organisations such as the GAVI Alliance have a powerful part to play in ensuring access to vaccines and future research and development
- New manufacturing technologies for influenza vaccine are being developed, but are likely to complement, rather than replace, egg-based production in the medium term
Examples of vaccine classes and associated industrial challenges

<table>
<thead>
<tr>
<th>Vaccine Class</th>
<th>Active Component</th>
<th>Main Manufacturing Challenge</th>
</tr>
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<tbody>
<tr>
<td>Rabies vaccine</td>
<td>Inactivated cell culture grown virus (e.g., on Vero cells)</td>
<td>Ensure complete inactivation, but maintain immunogenic potency and avoid reactogenicity; achieve appropriate biosafety level containment of live virus steps</td>
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<tr>
<td>Acellular pertussis vaccine</td>
<td>Purified proteins from Bordetella pertussis</td>
<td>Consistency of production and detoxification of components; maintain stability and quality control</td>
</tr>
<tr>
<td>Multivalent pneumococcal conjugate vaccines</td>
<td>Glycoconjugates of polysaccharides on a suitable carrier protein</td>
<td>Use of complex chemical conjugation chemistries tailored and done separately for each valency; yields; formulation to avoid immunological interferences between valencies; quality control of complex mixtures</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>Recombinant protein</td>
<td>Consistency of manufacturing, with reproducible immunogenicity and low contamination by host protein</td>
</tr>
<tr>
<td>Japanese encephalitis vaccine</td>
<td>Vectored vaccine</td>
<td>Need to show absence of potential for reversion or genetic rearrangement; robustness of process; freeze drying process and stability of product</td>
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Table 1: Examples of vaccine classes and associated industrial challenges

<table>
<thead>
<tr>
<th>Vaccine Class</th>
<th>Active Component</th>
<th>Production method</th>
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<tbody>
<tr>
<td>Oral polio vaccine</td>
<td>Three live attenuated viruses</td>
<td>Live attenuated virus grown in non-human cell culture (e.g., primary monkey kidney culture or Vero cell line)</td>
</tr>
<tr>
<td>Tetanus vaccine</td>
<td>Tetanus toxoid extracted from fermentations of Clostridium tetani, inactivated with formaldehyde and adsorbed onto an adjuvant such as alum</td>
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<tr>
<td>Measles vaccine</td>
<td>Live attenuated virus grown in cell culture of human diploid cells or chick embryo fibroblasts</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Influenza virus propagated in eggs, inactivated and further treated to give either split or subunit vaccines</td>
<td></td>
</tr>
<tr>
<td>Diphtheria vaccine</td>
<td>Diphtheria toxoid extracted from fermentations of Corynebacterium diphtheriae, inactivated with formalin and adsorbed onto alum adjuvant</td>
<td></td>
</tr>
<tr>
<td>Whole-cell pertussis</td>
<td>Whole Bordetella pertussis grown in fermenters, heat killed, and inactivated with formalin</td>
<td></td>
</tr>
<tr>
<td>BCG vaccine</td>
<td>Live attenuated Mycobacterium bovis produced in static surface culture</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>Recombinant expression of HBsAg protein, as virus-like particles, in yeast species</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>Polysaccharide purified from culture of Haemophilus influenzae and conjugated to a carrier protein such as inactivated tetanus toxoid, diphtheria toxoid, tetanospanmin, mutant diphtheria protein, or the outer membrane vesicle protein of Nissensia meningitis serogroup B</td>
<td></td>
</tr>
<tr>
<td>MMR vaccine</td>
<td>Live attenuated virus grown in chick embryo fibroblast culture for mumps vaccine, live attenuated virus grown in human diploid fibroblast culture for rubella vaccine</td>
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</tr>
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</table>

The production methods listed might not be exhaustive for each antigen type. MMR=measles, mumps, and rubella.

Table 2: Production systems for the top ten human vaccine antigens by doses produced

producers. These producers have achieved WHO prequalification to assure a consistent standard of quality, safety, and efficacy of medicinal products, and have built sufficient capacity to supply markets in developing countries at competitive prices, either directly or via organisations such as UNICEF and the GAVI Alliance.

Vaccine production by major suppliers

A wide range of technologies participate in manufacture of a comprehensive portfolio of vaccines. Table 1 provides examples of the main vaccine types and identifies associated industrial and technical challenges. Technologies are needed not only for bulk production but also for vaccine formulation and stabilisation, addition of adjuvants, design of delivery devices, and to provide the capacity and logistics for worldwide supply and distribution.

The production method used for a particular vaccine can greatly affect manufacturing capacity and cost of goods and, hence, availability (table 2). For example, the oral polio vaccine Sabin strains grow well in culture to titres in excess of $10^8$ plaque-forming units (pfu) per mL and are used at a dose of about $10^5–10^6$ pfu per mL in human beings. Preparation of the live attenuated oral polio vaccine can be achieved at high capacity, albeit with complex and lengthy quality control, with hundreds of millions of doses produced at a low cost, making possible the national immunisation days that have been the driver of WHO’s poliomyelitis eradication programmes. By contrast, complex vaccines—such as multivalent glycoconjugates for pneumococcus or meningococcus, the multivalent virus-like particles for human papillomavirus, and purified multicomponents of acellular pertussis vaccines—can have substantially lower yields of individual components, a less robust production process (leading to batch production failure), and lengthier and more expensive quality control, requiring much more investment in resources and facilities, resulting in substantially lower global capacities and higher cost of goods.
Vaccine production includes a high level of quality control at every stage of the process and compliance in a wide range of assays is essential for batch release. Assays include precise definition of physicochemical properties such as pH and osmolality, component identity and stability analyses for antigens, excipients, and adjuvants, microbiological testing for sterility, concentration and potency testing, and animal-based testing for toxic effects. The testing process for a vaccine can be further complicated by different regulatory agencies using different release criteria and requiring different testing methods for release in their specific jurisdiction. Thus, the quality control test profile is specific to each vaccine and to each country of release. For example, quality control testing for diphtheria toxoid vaccine bulk includes all essential assays plus animal testing for at least 6 weeks to show absence of residual toxicity. However, diphtheria toxoid is routinely used in combination vaccines, such as the diphtheria, tetanus, and acellular pertussis vaccine, and therefore a further series of quality control tests have to be done after blending of the additional antigens. The manufacturer again has to show sterility, that the physicochemical properties are correct and stable and that all components in the combination are identifiable and at the correct concentration and potency. Further testing of residual toxic effects in animals has to be done at this stage, adding at least a further 6 weeks to the release time.

Complexity in the worldwide supply of vaccines is caused by variations in the manufacture of different vaccines, including batch size, quality control release tests, shelf life, filling into single-dose or multidose vials or syringes, production of freeze dried or stabilised liquid formulation, cold-chain requirements, and packaging and labelling in different languages for different markets. For example, Sanofi Pasteur manufactures two versions of the inactivated polio vaccine, but the main difference between the versions is the cell substrate on which they are grown (MRC-5 cells vs Vero cells), leading to two specific and different licensed production processes. These two inactivated polio vaccines are included in 16 different standalone or combination vaccine formulations, which are dispensed into 32 different filled products, packaged into 64 presentations, and, when boxed and labelled according to requirements of specific country markets, result in more than 300 different final products being distributed across the world. Furthermore, products licensed in, and destined for, one particular market cannot usually be diverted to another in response to fluctuations in demand or problems with shipments or inventory control. Organised distribution of vaccine products is therefore a crucial part of the overall supply chain to ensure vaccines eventually reach their target.

Inevitably the complexities in manufacturing lead to occasional disruption of supply caused by, for example, batch or production failure, quality control issues with bulk or finished products, breakdown of the cold chain in delivery, and failure to predict variations in demand. However, for the most part, such disruptions are not a serious long-term impediment to vaccine access. The remedy to short-term supply interruptions is to develop and formulate vaccines with a long shelf life so that inventories can be established to anticipate occasional delivery failure. Manufacturers also benefit from individual countries and organisations (eg, UNICEF) making long-term procurement arrangements on the basis of accurate demand forecasting and budgeting across several years. With reasonable assurances or guarantees of purchase, the industry can confidently make the investments needed to ensure long-term supply and be prepared to deal with occasional fluctuations in demand, while maintaining fair pricing policies.

**Distribution and supply**

Distribution and supply is dependent on licensure of vaccines in particular national markets. Vaccines can be licensed directly in countries with highly developed regulatory authorities, whereas other countries rely on licensure in the country of manufacture, followed by review and approval in the final country of use. In all cases, licensing includes approval of the manufacturing process and facilities, and some countries also require inspections. For procurement of vaccines by UN agencies, products need WHO prequalification to assure a consistent standard of quality for countries with poorly developed regulatory agencies. Prequalification is reliant on the vaccine having been previously licensed in the country of manufacture by an authority that is regarded as functional by WHO. Additionally, for vaccines that are manufactured but not used in the country of origin, mechanisms exist, such as the Article 58 regulation in the European Union (EU) and rapid review by the US Food and Drug Administration under the investigational new drug process, to expedite availability of new vaccines that address a primary medical need in emerging nations.

Therefore, the complex production and product range, licensure, and methods of distribution are country dependent and affected by national vaccination policies. In the USA, for example, access to vaccines is usually via a physician who orders directly from a manufacturer or distributor (Sanofi Pasteur operate a direct-to-physician policy with dispatch within 24 h of ordering). Vaccines can be advertised directly to the customer through the media, and the influenza vaccine is widely available to the public from a range of retail outlets where immunisation by a professional can be directly purchased. In the EU, member states have varying distribution policies, but typically manufacturers ship to distribution centres and wholesalers. In some EU countries, price controls are imposed by government and vaccines are procured by government tender (Italy, France, and the UK), whereas in other countries, sales are predominantly to the private market where price control and bulk...
purchasing are reduced (eg, Germany). These buying models determine how manufacturers supply vaccines to each country. Publicity and advocacy typically target both the consumer (eg, via wellbeing clinics and primary care centres) and medical professionals, especially paediatricians and general practitioners.

Other countries can be supplied after direct orders from public health departments, sometimes private customers on a case-by-case basis, or international non-governmental organisations. Public markets are usually served by tenders, where international manufacturers compete with each other and with local suppliers on price, volume, and, importantly, reliability of supply. For developing countries that qualify for support from the GAVI Alliance, the advantages of bulk purchasing are provided by long-term agreements negotiated by organisations such as UNICEF. The model for these agreements was provided by the Pan American Health Organization, which established the revolving fund for vaccine procurement in 1979. The purpose of the fund was to provide participating member states with a means to assures the smooth and constant flow of high-quality vaccines, syringes, and cold-chain equipment at affordable prices, initially for the implementation of immunisation programmes in Latin America and the Caribbean.16

Vaccines vary in stability and, thus, shelf life in their final container. An essential part of the supply process is maintenance of a cold chain that is robust, reliable, and routinely monitored for possible deviations between the manufacturer and end user.

Access and uptake
In almost all countries, a primary series of vaccination of infants is well established and the vaccines included are readily available. Although the precise vaccines and schedules vary between countries, programmes regularly include vaccination against diphtheria, tetanus, and pertussis (DTP vaccine), measles, poliomyelitis (inactivated or oral vaccine), and, dependent on the geographical region, hepatitis B, *Haemophilus influenzae* type b infection, and tuberculosis (BCG vaccine). In some countries, the BCG, oral polio, and hepatitis B vaccines are given at birth, and the remaining vaccines are typically given in a three-dose schedule from 6 weeks to 6 months of age, with fourth and sometimes fifth booster doses given in the second year of life and before school, but this practice varies between countries. In the past decade, pneumococcal conjugate vaccines (initially seven-valent formulations and subsequently ten-valent and 13-valent formulations) and, in some countries, the rotavirus vaccine have been added to the vaccination schedule from 6 weeks to 6 months of age. Hepatitis A vaccine can also be given to children as early as 1 year of age. The live attenuated measles vaccine is given subsequently, typically at about 12–15 months of age, to avoid the effect of maternally acquired antibodies. In most developed countries, measles vaccination is provided as part of a trivalent formulation that includes live attenuated mumps and rubella vaccines or even a tetravalent formulation with added varicella. Usually vaccination is a single dose followed by a preschool booster. Thus, through infancy, most children acquire immunity through vaccination to diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, measles, and, in some countries, mumps, rubella, pneumococcal infection, rotavirus infection, varicella, tuberculosis, *H influenzae* type b infection, and hepatitis A. Vaccination campaigns against specific pathogens, such as cholera, typhoid, or influenza, can extend this list.24–28

Differences in vaccine use between developed and low-income countries mainly relate to the combination vaccines licensed and the type of a specific vaccine. For example, whole-cell pertussis vaccine is easier to manufacture and has a lower cost of goods than do the multicomponent acellular pertussis vaccines preferred by developed countries. Hence developing countries tend to use the DTP vaccine with whole-cell rather than acellular pertussis. For reasons of cost and vaccine availability, many developing countries also use the measles standalone vaccine rather than combined vaccines including protection against mumps, rubella, and varicella, and the oral rather than the inactivated polio vaccine.

Particularly in developed countries, vaccines have been developed for adolescent populations, with specific formulations of the DTP vaccine and combined DTP and inactivated polio vaccines to boost childhood-acquired immunity. These boosters are regarded as important to provide herd immunity, particularly to pertussis.29 Other adolescent vaccines available include the human papillomavirus vaccine28 for protection against cervical cancer (Cervarix, GlaxoSmithKline, Rixensart, Belgium) or cervical cancer plus genital warts (Gardasil, Sanofi Pasteur, Lyon, France), and several meningococcal meningitis vaccines that can be either polysaccharide or glycoconjugate based and monovalent, bivalent, or tetravalent. However, the threat of infection in adolescents also includes hepatitis C virus, *Neisseria gonorrhoeae* (gonorrhoea), *Treponema pallidum* (syphilis), *Chlamydia trachomatis* (chlamydia), Epstein-Barr virus, herpes simplex virus type 2, cytomegalovirus, and HIV, against which we do not have licensed vaccines. A range of vaccines are also available for specific geographical or environmental risks, including rabies, Japanese encephalitis, tick-borne encephalitis, yellow fever, typhoid, and cholera.

In developing countries, access to and uptake of vaccines have been hugely improved in the past decade by the launch of the GAVI Alliance, which aims to save children’s lives and protect people’s health by increasing access to immunisation in poor countries. The 72 countries that can apply for support from the GAVI Alliance are home to about half the world’s population.29
The GAVI Alliance estimates that between 2000 and 2009, more than 257 million children were immunised with vaccines funded by the GAVI Alliance, and by the end of 2009, more than 5 million future deaths had been prevented through routine immunisation against hepatitis B, *H influenzae* type b infection, and pertussis and one-off investments in immunisation against measles, poliomyelitis, and yellow fever. In these 72 countries, immunisation coverage has climbed steadily and about 80% of children now receive three doses of DTP vaccine. For the basic vaccines in the Expanded Programme on Immunization (EPI), global manufacturing capacity is adequate. Thus, incomplete coverage with these traditional vaccines is mainly a result of the need for better delivery infrastructure.

By contrast with the EPI vaccines, availability of new and more complex vaccines in developing countries lags substantially behind that in wealthier countries. This situation is partly caused by manufacturing capacities that are seldom sufficient to satisfy global demand in the early years of licensure, and is partly due to the economic reality that companies need to recoup research and development investment (which can be in the region of US$1 billion for a new vaccine) by prioritisation of supply to markets that can sustain a high price. In the absence of specific purchasing and supply agreements, new vaccines are often unavailable or unaffordable for many countries for extended periods. As a result, for the 2008 global birth cohort of about 129 million children, the GAVI Alliance estimates that 34% of children did not receive the hepatitis B vaccine, 71% did not receive the *H influenzae* type b vaccine, 92% did not receive the rotavirus vaccine, and 93% did not receive the pneumococcal conjugate vaccines. Major funders, such as the GAVI Alliance, donor countries, the Bill & Melinda Gates Foundation, and international organisations, have recognised this challenge and have designed innovative financing schemes and other measures to accelerate introduction and to support the purchase of new vaccines for developing countries.

The GAVI Alliance is also undertaking efforts to strengthen and fund health systems to overcome barriers to vaccine access. In view of the continuing cholera epidemic in Haiti, the supply of cholera vaccine merits special mention. Although three vaccines are approved for cholera in individual countries, only one (Dukoral, Crucell, Stockholm, Sweden) has been prequalified by WHO. For the other two vaccines, only an estimated 400 000 doses are available worldwide for shipment from manufacturers, which is far from adequate for the Haitian population of about 10 million who each need two or three doses of each vaccine for immunisation. As several groups have argued, a global stockpile of cholera vaccines is needed to respond to emergencies, such as that in Haiti, because routine demand has not ensured adequate supplies for such a surge in need. The effort to provide adequate and timely supplies of pandemic influenza vaccines—either in advance, for the possible pandemic of influenza A H5N1 that has raised concerns in the past decade, or as a pandemic emerges, as in the case of swine influenza A H1N1 in 2009—provides a different example of the economic and scientific challenges of vaccine supply and access that affect both developing and developed countries, though to different extents. In a case study of influenza, we discuss influenza manufacture and the opportunities to use new methods of production, and how vaccine access might be managed to achieve maximum protection.

**Production and supply of influenza vaccine**

**Seasonal influenza vaccine**

As discussed in the first paper in this Series, influenza viruses continuously undergo antigenic drift, resulting in the need to routinely monitor circulating strains and update the annual influenza vaccine formulation. Monitoring of human influenza is a truly global effort: a network of over 120 national influenza centres in more than 90 countries work with sentinel medical professionals to gather clinical swabs for virus isolation. The clinical isolates are supplied to the four WHO collaborating centres, located in Atlanta (GA, USA), Tokyo (Japan), Melbourne (VIC, Australia), and London (UK), for antigenic and genetic analysis to assist WHO in preparing the two annual influenza strains recommendations: in February, for manufacturers to produce the northern hemisphere vaccine to be used from September onwards of the same year; and in September, for manufacturers to produce the southern hemisphere vaccine to be used from March onwards of the following year.

The timing of vaccine production and release is a crucial factor, especially in the northern hemisphere because capacity is typically more constrained, relative to demand, than in the southern hemisphere. About 400 million doses are manufactured, formulated, filled, packaged, and released in the autumn, which is a substantial logistical challenge. Producers routinely try to get a head start by starting manufacture “at risk” in January with the vaccine seed strain judged most likely to be retained from the previous year. The remaining two bulks of monovalent vaccine are then manufactured as the WHO-recommended vaccine seed strains become available. Large multinational companies manufacture bulk vaccine for about 180 days, of which potentially 60 days are “at risk”.

The point at which manufacturers can start the final production steps, formulation and filling, is not within their own control, but is dependent on the availability of specific antisera for use in the regulatory-approved potency and release assay—single radial immunodiffusion. Antisera are prepared, calibrated, and distributed by the National Institute for Biological Sciences and Control in the UK, the Center for Biologics
Evaluation and Research in the USA, the Therapeutic Goods Administration in Australia, and the National Institute of Infectious Diseases in Japan. Receipt in late May allows formulation and filling of the vaccine batches to start and then run concurrently with production of the final monovalent bulk. Final product release follows different routes dependent on specific regulatory requirements, but submission of a variation to the licensed process can lead to accelerated approval by regulators. In the USA, the master seed lots are checked for antigenic similarity to the WHO-recommended strains, and then five monovalent batches of each strain and all trivalent batches are tested for antigenicity and released. The final packaged product has no formal release process and typically the first vaccine doses begin to ship to customers in mid-July. In Europe, the master seed lots are not assessed in the same way but there is a regulatory requirement for an annual clinical trial to assess safety and immunogenicity. Each component has to fulfil established immunogenicity endpoints before the vaccine is approved for distribution and sale. This process adds risk for the manufacturers because by the time the clinical results become available, nearly all the doses have been manufactured and the formulation and filling campaigns are well underway. The seasonal clinical trial affects timing, especially because the trial cannot normally begin until reagents for single radial immunodiffusion are available to allow correct formulation of the clinical trial batches. Consequently, vaccine doses are not usually ready for shipment in Europe until mid-August, about 4 weeks later than in the USA.

**Pandemic influenza vaccine**

The egg-based manufacturing system has been reliably supplying influenza vaccine for several decades. However, this system has clear timing and capacity constraints and, following the influenza H1N1 pandemic in 2009, a perception has arisen that it needs to be updated. The virus could be grown in cell cultures such as MDCK, Vero, or PER.C6, or recombinant DNA technology could be used to express haemagglutinin and potentially other viral proteins in, for example, insect cells (Protein Sciences, Novavax), tobacco plants (GreenVax, Medicago), or the fungus Neurospora crassa (Neugenesis). Such technologies are potentially better able to respond to global demand in a pandemic because of more rapid production and greater surge capacity than in egg-based manufacturing. But which of these options can bring benefits while performing as reliably as the existing system? Several criteria should be used to assess the response of new technologies to seasonal and pandemic demand (panel).

Economic factors also affect the choice of replacement technology, especially considering the already substantial investment in egg-based production that has been made globally by producers. First, the research and development cost of a new influenza vaccine will be high because the novel approaches will probably need full clinical development, potentially including large efficacy studies across several years. The cost from the research idea to product launch is likely to be several €100 million plus the cost of new production facilities. Second, growth of the market for influenza vaccination has led to investments that have increased global capacity for seasonal influenza vaccine to about 600 million doses for the northern hemisphere. Capacity is expected to increase to about 1 billion doses by 2018. However, market demand is not expected to increase at the same rate, potentially leading to an excess supply. This situation will lead to further pressure on pricing and reduce return on investment, thereby reducing incentives for investment in new technologies.

For manufacturers to justify the replacement of existing production technology from an economic point of view, any new technology will need to deliver within the required regulatory and supply environment, and also offer substantial advantages over egg-based manufacturing. Among the new systems under assessment, at this stage none clearly has all the characteristics needed to fundamentally alter manufacturing. In 2013, when the first large-scale cell culture facility is due to start market supply, production capacity for the northern hemisphere is expected to be about 750–800 million doses per year, of which about 74 million doses are planned to be from cell culture and the remainder (about 90% of world production) will be from egg-based production. Although the switch to alternative technologies is likely to gather momentum, the timescales needed to license new production systems, secure capital investment, and develop infrastructure for manufacturing will mean that egg-based manufacture of influenza vaccines will be used for some time to come.

Capacity for seasonal influenza vaccine is expected to exceed global demand, but in the event of a pandemic, substantial further capacity is needed very quickly. From a commercial perspective, investment in further capacity is not easy to justify without a concomitant annual market expansion to use all of the supply. Therefore alternative approaches to expand influenza vaccine supply in a pandemic need to be considered. One such approach is dose sparing provided by addition of adjuvants. During the swine influenza H1N1 pandemic in 2009, Novartis released a vaccine containing 7·5 μg of antigen adjuvanted with MF59 \(^\text{52}\) and GlaxoSmithKline released a vaccine with 3·75 μg of antigen adjuvanted with AS03 (the unadjuvanted dose is 15 μg). \(^\text{53}\) This process allows an increase in vaccine supply from the same industrial base, assuming that supply of the adjuvant is not restricted. By contrast, the use of adjuvants in seasonal influenza vaccines is much debated and the need for adjuvants is less obvious, certainly from a dose-sparing perspective.
Development of pandemic vaccines for emergency use also requires some flexibility in the regulatory pathway because time is not sufficient for full clinical development. For Europe, the European Medicines Agency has developed a guideline to allow rapid market authorisation of a variation of a vaccine against a reference virus via an application containing only the new production data for a vaccine against a potentially pandemic strain. The eventual pandemic vaccine would have to be produced in the same way, including formulation and addition of adjuvants. This process was used during the swine influenza H1N1 outbreak to release pandemic vaccines in the EU.

**Principles for allocation of restricted supplies of vaccines**

The quantity of vaccines available and affordable for many countries is often less than that needed to cover the entire population. As the 2009 pandemic of influenza H1N1 showed, existing technology cannot be used to scale up production of vaccine fast enough to immunise even populations of the wealthiest countries in the timeframe needed to ensure protection. In this type of situation, vaccine use should be prioritised to achieve the greatest benefit for public health. A major problem at present is that the most potent force in prioritisation of pandemic influenza vaccination is the market: through advance contract commitments, wealthy countries had a claim on virtually the entire available supply in the 2009 pandemic.

In jurisdictions that do have access to vaccines for pandemic influenza, theoretical models provide some principles for allocation of restricted supplies that will best achieve various public health objectives. Vaccines serve two related but distinct functions: to protect vaccinated people against infection and severe disease; and to reduce transmission, thereby offering indirect protection to those not vaccinated via herd immunity. With few vaccines available, a fundamental question for allocation is how to balance these goals. Vaccines most effectively reduce transmission if they are given to the groups that are most likely to be infected and most likely to transmit the infection onward, which in practice often means children. However, the groups most likely to get severe disease if they are not vaccinated can be a very different group, specifically adults and people with certain predisposing disorders. Therefore, achievement of one of these goals typically comes at the expense of the other.

Models have shown that vaccination of transmission groups is most likely to be effective when large quantities of vaccine are available early in the epidemic. By contrast, direct immunisation of individuals at highest risk will probably be best when vaccine supplies are small or arrive late because such vaccination programmes can only make a slight dent in transmission, hence the protection offered to unvaccinated individuals is small, and the core transmission groups, such as children, tend to become less important to transmission as the epidemic progresses, because many of them are already immune. One caveat should be noted, however: many individuals who are at high risk of severe outcome, such as elderly or immunocompromised people, might have suboptimal immune responses to the vaccine. Even in seasonal influenza, vaccination of elderly people is not totally effective. The decision to target vaccination at high-risk groups should ideally be based on evidence that the vaccine is effective in these

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**Panel: Criteria for assessment of new technologies for pandemic and seasonal influenza**

**Time to availability of the first doses**

The speed of the industry response from receipt of the WHO-recommended strains to release of the first fully controlled and formulated batch is crucial for the pandemic response.

**Time to availability of the last doses**

The success of a campaign is determined by how quickly all doses can be supplied. Most manufacturers release their initial batches within days of each other, but their different logistics and capacities mean that their overall contributions to global supply are very different.

**Scalability**

Any new manufacturing system needs to be readily scalable to the large production volumes needed for global supply. Appropriate scale-up is not established for most of the technologies that could potentially replace egg-based production. Moreover, manufacturing needs to be efficient to keep cost of goods to a minimum, and rapid formulation and filling on the appropriate scale are an essential part of this process.

**Regulatory aspects**

Any new technology needs to be robust and applicable to all influenza types, subtypes, and strains, in a way that allows approval by regulators via variations to the licensed process, on time and with the lowest possible risk.

**Surge capacity**

The ability to quickly scale and deliver a substantial increase in production from that used for routine seasonal vaccination is quite difficult to build into an industrial system. Generally, capacity is sized and built on routine demand, and manufacturers cannot afford to build facilities for an event that might occur only three or four times per century. The notion of a warm-base facility funded in partnership with government and ready for use in case of a pandemic has been much discussed and is a laudable goal. However, the logistics are not straightforward. Highly trained staff would need to be permanently available to manage and maintain the facility. Moreover, sufficient raw materials to meet surge requirements would need to be available at short notice.

**Flexible manufacturing platform**

A technology with reduced time to final dose would shorten the total time needed for manufacturing. Thus, the facility could be used to make other products if the production system is flexible enough and constructed in a way relevant to other vaccines or biologicals, which would reduce cost of goods.

**Dispersed manufacturing capability**

During the 2009 influenza H1N1 pandemic, the need for national self-sufficiency was discussed extensively, especially by countries which noted inequality in the distribution of pandemic vaccine. Thus, a further criterion is how adaptable the new technologies are to distributed production.
groups, which is difficult to obtain in the urgent setting of a pandemic.

With existing technology, vaccine supply is likely to be restricted and delayed relative to the spread of an influenza pandemic; the timescale of present vaccine manufacturing is simply slower than the timescale in which influenza spreads. However, consideration of how vaccines can be used to reduce spread of influenza is worthwhile because this goal is achievable for seasonal (non-pandemic) influenza, and an understanding of this approach can help to define what would be needed from an increased capacity to manufacture pandemic vaccine. Theoretical models provide some basic principles, but, as always, these principles need to be interpreted in view of available data because they do not apply uniformly to all settings.

First, growth of an epidemic can be substantially reduced or even stopped by vaccination of less than the entire population.\textsuperscript{41} Epidemics grow when, on average, each infectious person infects more than one additional person.\textsuperscript{41} In the early phase of past influenza pandemics, the number of secondary cases per infected case—the reproductive number (R)—was estimated to be 1·3–1·8 for 2009\textsuperscript{62–65} and 1·8–2·0 for 1918,\textsuperscript{66,67} but was possibly even higher in the spring of 1918.\textsuperscript{68} In seasonal influenza, the reproductive number is much lower because a proportion of the population has partial immunity. Immunisation can slow the spread of infection by reducing the reproductive number, and can essentially halt spread by bringing the number below one.\textsuperscript{61} If immunisation occurs at random, the proportion of people who need to be vaccinated to halt transmission is about:

\[
p_c \approx \frac{R - 1}{R_f}
\]

where \(f\) is the efficacy of the vaccine.\textsuperscript{61} For a vaccine of 90% efficacy and a reproductive number of five, vaccine coverage of about 89% would be needed to halt transmission.\textsuperscript{61} This estimate is merely illustrative and can be improved by detailed simulation or analytical models,\textsuperscript{68–72} but in all situations, coverage need not be 100%.

Second, other interventions, such as reduction in contact and use of antiviral prophylaxis and treatment, can reduce transmission by working in concert with vaccination and allowing major reductions in the epidemic growth rate with less coverage than would otherwise be needed.\textsuperscript{62–73}

Last, the benefits of vaccination can be maximised by identification of the groups that are most crucial to transmission.\textsuperscript{74} One approach is to identify in advance the most likely core transmission groups on the basis of behavioural data\textsuperscript{75} or other information about contact patterns; these data can then be used to predict the relative reduction in transmission from vaccination of various groups.\textsuperscript{76} If these data are not available, patterns of disease incidence and immunity in the population can be used to estimate, with certain assumptions, which groups should be vaccinated.\textsuperscript{77} All such methods suggest that for seasonal and pandemic influenza, the greatest reduction in transmission would be achieved by vaccination of school children, a conclusion that is consistent with data from observational studies\textsuperscript{78} and a randomised trial.\textsuperscript{79} Such strategies are particularly appealing for seasonal influenza, for which vaccine is generally available early, in view of concerns about the direct benefits of vaccination of elderly people\textsuperscript{80} who suffer the vast majority of severe morbidity and mortality in seasonal influenza.\textsuperscript{78} Indeed, the USA has recently recommended near-universal seasonal influenza vaccination.

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<td>Production and updating of estimates of vaccine effectiveness outside of phase 3 trials</td>
<td>Improve surveillance for disease outcomes and intermediates (eg, carriage) in developing countries where vaccine is introduced;\textsuperscript{81} maintain surveillance where it already exists to assess long-term effects of vaccine</td>
</tr>
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Table 3: Major issues for the next decade and beyond on vaccine production, distribution, access, and uptake
Progress on this front, although still preclinical, warrants influenza vaccines that provide broad protection across possible technical solutions, including development of supplies in the meantime. This problem has other supply and the principles to optimise use of restricted the challenges to improvement of pandemic vaccine wisely to achieve maximum protection. We have described even with improvements, vaccine will need to be used pandemic vaccine in a timely and equitable manner and, industry is not yet sufficient to meet the full need for, at any time. Unfortunately, the response of global way reduces the risk of a more virulent pandemic arising occurrence of the 2009 influenza H1N1 pandemic in no decade (table 3).

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Conclusions and perspectives

Capacity for global manufacturing of vaccines has substantially improved in the past decade and looks set to continue to do so because investment in research and development and industrial production methods is rapidly increasing. These improvements have led to increased access to vaccines in many nations, resulting in high population coverage with established vaccines and positive initiatives to introduce new vaccines as they are developed and launched. Non-governmental organisations, such as the GAVI Alliance, continue to play an extremely important part, especially for the developing world, via policies on advocacy, creative financing to provide incentives to manufacturers, and procurement strategies. However, several new and underused vaccines have the potential to save many lives if they can be delivered to populations at risk. This objective, together with the research and development challenges associated with pathogens that are difficult to develop vaccines against, as described in the first part of this Series,86 sets the agenda for the next decade (table 3).

The threat of pandemic influenza is ever present and occurrence of the 2009 influenza H1N1 pandemic in no way reduces the risk of a more virulent pandemic arising at any time. Unfortunately, the response of global industry is not yet sufficient to meet the full need for pandemic vaccine in a timely and equitable manner and, even with improvements, vaccine will need to be used wisely to achieve maximum protection. We have described the challenges to improvement of pandemic vaccine supply and the principles to optimise use of restricted supplies in the meantime. This problem has other possible technical solutions, including development of influenza vaccines that provide broad protection across subtypes and could be manufactured in advance. Recent progress on this front, although still preclinical, warrants further investigation.86-87

In the past decade, expanded markets, realistic pricing, improved advocacy, and wise health priorities have attracted substantial new investment into the industry, generating a so-called vaccine renaissance.88 Although much work is ahead, the next decade of vaccines is well placed to maintain this momentum and to allow the full benefit of vaccination to be felt by all the world’s population.

Contributors

All authors contributed to the writing and editing of the report.

Conflicts of interest

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