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Vaccine production, distribution, access and uptake

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Abstract

Making human vaccines available on a global scale requires the use of complex production methods, meticulous quality control and reliable distribution channels that ensure the products are potent and effective at their point of use. The technologies involved in manufacturing different types of vaccines may strongly influence vaccine cost, ease of industrial scale-up, stability and ultimately world-wide availability. Manufacturing complexity is compounded by the need for different formulations for different countries and age groups. Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies. However, ensuring optimal access and uptake also requires strong partnerships between private manufacturers, regulatory authorities and national and international public health services. For vaccines whose supplies are limited, either due to rapidly emerging diseases or longer-term mismatch of supply and demand, prioritizing target groups can increase vaccine impact. Focusing on influenza vaccines as an example that well illustrates many of the relevant points, this article considers current production, distribution, access and other factors that ultimately impact on vaccine uptake and population-level effectiveness.

Introduction

Today there are licensed vaccines available to prevent human infections caused by approximately 25 microbes. The actual number of vaccine products is however considerably higher, there being many combination vaccines and formulations aimed at different age groups, different geographical regions and both private and public markets. Although there are differences in effectiveness among vaccines, as explained elsewhere in this series (Chapter by Greenwood et al.), most have contributed significantly to the improvements in human health that we have witnessed over the past century. Among the large multinational pharmaceutical companies currently only two, 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 particular market niches. This situation is changing with the growth of manufacturers headquartered in developing countries and with the significant new investment by multinationals in vaccine R&D. As recently as 2005, only three of today's top ten pharmaceutical companies had significant activities in vaccines. Following recent mergers and acquisitions that figure is now eight of the top ten. Vaccines are seen as an attractive and sustainable business for a number of reasons that include:

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vaccine demand has grown rapidly over the past decade and looks certain to grow further; there are still significant unmet medical needs and a range of important disease targets for which vaccines do not currently exist; innovative financing methods have significantly expanded markets, particularly in the developing world; advances in immunology and microbiology and our understanding of pathogenesis mean that previously intractable targets may now be within reach; and last but not least, the vaccine sector has not been subject to the sharp revenue declines upon patent expiry currently plaguing much of the rest of the pharmaceuticals industry. Part of the reason for this last point is that vaccines as biologicals are not as easy to produce and license “generically” as small drug molecules, as the production processes, as well as the products themselves, are licensed by the regulatory authorities. Therefore R&D and industrial “know-how” and the associated costs provide high barriers to entry for potential new players, even for non-patented vaccines. In addition, the ability to offer combination vaccines also favours established manufacturers who have a range of licensed antigens available. Nevertheless, the drive for countries to be self-sufficient in essential vaccines, often with government support, has led to the expansion and technological advancement of a number of local producers who have achieved both WHO pre-qualification and have built sufficient capacity to supply developing world markets at competitive prices, either directly or via such organizations as UNICEF and GAVI.

Vaccine Production by Major Suppliers

In considering manufacturing and R&D know-how, it is important to recognize the wide range of technologies that are involved in the manufacture of a comprehensive portfolio of vaccines. Table 1 provides examples of the main vaccine types and identifies associated industrial and technical challenges. To the technologies used for bulk production must be added the specifics of vaccine formulation and stabilization, adjuvantation, delivery device design, and the capacity and logistics to supply and distribute across the globe.

The particular production method of a given vaccine can significantly influence manufacturing capacity and cost of goods (COGs) and hence availability. At one end of the spectrum is the production of a live-attenuated vaccine such as oral polio vaccine (OPV). The OPV Sabin vaccine strains grow well in culture to titres in excess of 10⁸ pfu/ml and are used at a human dose of around 10⁵ – 10⁶ pfu. Preparation can be achieved at high capacity (albeit with complex and lengthy quality control) of hundreds of millions of doses at low COGs, making possible low cost supply to the national immunization days that have been the driver of WHO’s polio eradication programmes [1]. At the other end are the more complex vaccines such as multivalent glycoconjugates for pneumococcus [2] or meningococcus[3], the multivalent virus-like particles (VLPs) for human papilloma virus [4] and purified multi-components of acellular pertussis vaccines[5], where yields of individual components may be considerably lower, robustness of the process poorer (leading to write-offs), quality control lengthier and more expensive, so that production requires much more investment in both resources and facilities, resulting in significantly lower global capacities and higher COGs.

Vaccine production of course includes a high level of quality control (QC) at every stage of the process and compliance in a wide range of assays is essential for batch release. Assays include precise definition of physico-chemical 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 toxicity. The testing process for a given vaccine may be further complicated by different Regulatory Agencies using different release criteria and requiring different testing methods for release in their specific jurisdiction. Thus, although there are common concepts, the QC test profile is specific to each vaccine and to each country of release. As an example

the QC testing for diphtheria toxoid vaccine bulk includes tests for all the properties mentioned above including animal testing over at least 6 weeks, to show absence of residual toxicity. However, diphtheria toxoid is routinely used in combination vaccines such as DTaP, and therefore a further series of QC tests are required after blending of the additional antigens. The manufacturer is again required to demonstrate sterility, that the physico-chemical properties are correct and stable, and that all components in the combination are identifiable and are at the correct concentration and potency. Further residual toxicity testing in animals is required at this stage adding at least a further 6 weeks to the release time.

The complexity of manufacture for different vaccines with the large differences in batch size, QC release tests, shelf-life, filling into single and/or multi-dose vials or syringes, freeze dried or stabilized liquid formulation, cold-chain requirements, packaging and labelling in different languages for different markets, makes the worldwide supply of vaccines very complex. To take a single example; Sanofi Pasteur manufactures 2 versions (for legacy reasons) of the inactivated polio vaccine (IPV) whose only principal difference lies in 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 IPVs are included in 16 different stand-alone or combination vaccine formulations which are dispensed into 32 different filled products, packaged into 64 presentations which, when boxed and labelled according to specific country market requirements, result in over 300 different final products being distributed to different parts of the world. Further, products licensed in, and destined for, one particular market cannot usually be diverted to another if there are fluctuations in demand or problems with shipments or inventory control. Organized distribution of vaccine products is therefore a crucial part of the overall supply chain if the vaccines are to eventually reach their target.

Inevitably the complexities in manufacturing lead to occasional disruption of supply caused by for example, batch or production failure, QC 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 that anticipate occasional delivery failure. It is also extremely helpful to manufacturers if individual countries and organizations such as UNICEF have long term procurement arrangements based on accurate demand forecasting and multi-year budgets. With reasonable assurances or guarantees of purchase, the industry can confidently make the investments necessary to ensure long term supply and be better prepared to deal with occasional fluctuations in demand, while maintaining fair pricing policies

Distribution and Supply

Distribution and supply is of course dependent on licensure of vaccines in particular national markets. Vaccines can be licensed directly in those countries that have highly developed regulatory authorities, while other countries rely on licensure in the country of manufacture, followed by review and approval by the final country of use. In all cases, licensing includes approval of the manufacturing process and facilities and some countries also require inspections. Procurement of vaccines by United Nations agencies requires that the product has WHO pre-qualification. This assures a consistent product quality standard for countries with less developed regulatory agencies and is reliant on the vaccine having been previously licensed in the country of manufacture by an authority that is regarded as 'functional' by the WHO. In addition, mechanisms exist, such as the "Article 58" regulation in the EU, and rapid review under IND by FDA to expedite availability of new vaccines that address a

primary medical need in emerging nations for a vaccine that is manufactured but not used in the country of origin.

The picture therefore is one of complex production and product range, licensure, and methods of distribution that are country-dependent and influenced by national vaccination policies. In the USA, for example, access to vaccine 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 hours of an order being placed). Vaccines may be advertised directly to the customer through the media and the influenza vaccine is available from retail drugstores in an “almost OTC” mode, though always administered by medical professionals. In the European Union, member states vary in their distribution policies, though 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, UK) whereas in others sales are predominantly to the private market where there is less price-control and less bulk purchasing (e.g. Germany). It is these buying models that determine how manufacturers supply vaccine to each country. Publicity and advocacy typically targets both the consumer (via well-being clinics, primary care centres, etc.) and the medical professionals, especially paediatricians and general practitioners. Vaccines vary in stability and thus shelf-life in their final container. An essential part of the supply process is the maintenance of a cold-chain between the manufacturer and end-user that must be robust, reliable and routinely monitored for possible deviations all along its length.

Other countries of the world may be supplied following direct order from public health departments and sometimes private customers on a case by case basis, or via international NGOs. 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 the GAVI qualified developing countries (see below), the advantages of bulk purchasing are provided by long term agreements negotiated by such organizations as UNICEF. Indeed the model here was provided by PAHO who established the Revolving Fund for Vaccine Procurement in 1979. The purpose of the Fund was to provide participating Member States with a means of assuring the smooth and constant flow of high quality vaccines, syringes and cold-chain equipment at affordable prices, initially for the implementation of immunization programs in Latin America and the Caribbean. [6] and see http://www.paho.org/english/hvp/hvi/revol_fund.htm.

Access and Uptake

In almost all countries, a “primary series” of vaccination of infants is well established and the vaccines involved are readily available. Although there is some country to country variation in the precise vaccines and schedules used, they regularly include measles, diphtheria, tetanus and pertussis (DTP), polio (IPV or OPV) and, depending on the geographical region, Hepatitis B, Haemophilus influenzae type b (Hib) and Tuberculosis (BCG). In some countries BCG, OPV and HepB may be given at birth but the remaining vaccines are typically given in a 3-dose schedule, between 6 weeks and 6 months of age, with a 4th and sometimes 5th dose booster in the second year of life and pre-school, but this varies from country to country. Over recent years, pneumococcal conjugate vaccines (initially, 7-valent, and more recently 10- and 13-valent formulations), and in some countries Rotavirus vaccine have been superimposed on the same schedule between 6 weeks and 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 later (typically around 12–15 months) to avoid the impact 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 tetravalent with added Varicella. Usually this is a single dose

followed by a pre-school booster. Thus, most children through infancy acquire immunity through vaccination to D, P, T, Hep B, polio, measles, and in some countries mumps, rubella, pneumococcus, rotavirus, Varicella, TB, Hib and Hepatitis A. Vaccination campaigns against specific pathogens such as cholera, typhoid or influenza can extend this list.

Differences in vaccine use between developed and lower income countries mainly relate to the combination vaccines licensed and the particular type of a given vaccine. For example, whole cell pertussis vaccine (wP) is easier to manufacture and has a lower COGs than the multi-component acellular pertussis (aP) vaccines preferred by developed countries. Hence developing countries tend to use DTwP rather than DTaP combinations. For reasons of cost and vaccine availability, many developing countries also use measles stand-alone (M) rather than MMR or MMRV, and OPV above IPV.

Particularly in the developed world there are vaccines developed for adolescent populations, with specific formulations of DTP and DTP/IPV for boosting childhood acquired immunity [7]. These boosters are considered to be important for providing herd immunity, particularly to pertussis. Other adolescent vaccines available include Human Papillomavirus vaccine (HPV) [8] as protection against cervical cancer (Cervarix) or cervical cancer plus genital warts (Gardasil) and several meningococcal meningitis vaccines that may be either polysaccharide or glyco-conjugate based and mono-, bi- or tetravalent. However, the threat of infection in adolescents also includes Hepatitis C virus, *Neisseria gonorrhoeae*, syphilis, *Chlamydia trachomatis*, Epstein-Barr Virus, Herpes Simplex type 2, Cytomegalovirus and Human Immunodeficiency Virus, against which we currently 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 the developing world, access to and uptake of vaccines has been hugely improved over the past decade by the launch of the Global Alliance for Vaccines and Immunization (GAVI) whose mission is to save children's lives and protect people's health by increasing access to immunisation in poor countries. There are 72 countries that can apply for GAVI support which together make up about half the world's population. GAVI estimates that between 2000 and 2009, more than 257 million children have been immunised with GAVI-funded vaccines and that as of the end of 2009, 5.4 million future deaths have been prevented through routine immunisation against HepB, Hib and pertussis and one-off investments in immunisation against measles, polio and yellow fever [9]. In the GAVI countries immunisation coverage has climbed steadily and around 80% of children now receive three doses of DTP vaccine. At least for the basic vaccines of the Expanded Programme of Immunization (EPI) series, global manufacturing capacity is adequate. Thus, incomplete coverage with these "traditional vaccines" primarily results from the need for better delivery infrastructure [10].

In contrast to the EPI vaccines, it is a reality that for the new and more complex vaccines, availability in developing countries lags substantially behind that in wealthier countries. At present, the reasons are partly due to manufacturing capacities which, due to investment cost, are seldom sufficient to satisfy global demand in the early years of licensure, and partly due to the economic realities of companies needing to recoup R&D investment (which may be in the region of 1B \$US for a new vaccine) by prioritizing supply to markets that can sustain a high price. In the absence of specific purchasing and supply agreements, newer vaccines are thus often unavailable or unaffordable for many countries for extended periods. As a result, for the 2008 global birth cohort of around 129 million children, GAVI estimates that 34% 71%, 92% and 93% of children were not vaccinated with HepB, Hib, rotavirus,

and pneumococcal conjugate vaccines respectively. This particular challenge for newer vaccines has been recognized by major funders such as GAVI, donor countries, the Bill and Melinda Gates Foundation, and international organizations, which have designed innovative financing schemes and other measures to accelerate introduction and support purchase of these vaccines for developing countries. GAVI is also undertaking efforts to strengthen and fund health systems to overcome barriers to vaccine delivery [9].

In light of the ongoing cholera epidemic in Haiti, the supply of cholera vaccine merits special mention. Although there are three vaccines approved for cholera in individual countries, only one (Dukoral) has been prequalified by WHO, and there are only an estimated 400,000 doses of the two vaccines worldwide available for shipping from manufacturers [11], far from adequate given a Haitian population of about 10 million and the need for two or three doses of each vaccine to immunize an individual. As several groups have argued, a global stockpile of cholera vaccines is needed to respond to emergencies like the Haitian outbreak, because routine demand has not ensured adequate supplies for such a surge in need [11, 12].

The effort to provide adequate and timely supplies of pandemic influenza vaccines –either in advance, for the possible pandemic of influenza H5N1 that raised concerns over the last decade, or as a pandemic emerges, as in the case of 2009 H1N1 – provides a still different example of the economic and scientific challenges of vaccine supply and access, one that affects both developing and developed countries, though to different extents. Below we discuss the particulars of influenza manufacture and the opportunities for using new methods of production that might bring benefits and how vaccine access might be managed to achieve maximum impact.

Exemplar: Influenza vaccine production and supply

As discussed elsewhere 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. The monitoring of human influenza is a truly global effort with a network of over 120 National Influenza Centres in more than 90 countries [13, 14], working 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, Tokyo, Melbourne and London, for antigenic and genetic analysis which assists the WHO in preparing the two annual influenza strains recommendations:

1. In February – for preparation of the northern hemisphere vaccine to be used from September onwards of the same year.
2. In September – for preparation of the southern hemisphere vaccine to be used from March onwards of the following year.

The timing of vaccine production and release is a critical factor, especially for the northern hemisphere where there is typically more capacity constraint, relative to demand, than for the southern. Approximately 400 million doses are manufactured, formulated, filled, packaged and released over the autumn. This is a significant logistical challenge, which routinely begins with producers trying to get a head start by commencing manufacture ‘at risk’ in January using the vaccine seed strain judged most likely to be retained from the previous year. The remaining two mono-valent bulks are then manufactured as the WHO recommended vaccine seeds become available. In total, large multinational companies manufacture bulk vaccine for approximately 180 days of which potentially 60 are ‘at risk’.

The point at which manufacturers can commence the final production steps, formulation and filling, is also not within their own control, being dependent on the availability of specific

anti-sera for use in the regulatory approved potency and release assay – single radial immunodiffusion (SRID). These anti-sera are prepared, calibrated and distributed by NIBSC in the United Kingdom, CBER in the United States, TGA in Australia and NIID in Japan. Receipt in late May allows formulation and filling of the vaccine batches to commence, which then run concurrently with the production of the final monovalent bulk. Final product release follows different routes depending on specific regulatory requirements but accelerated approval pathways exist with all regulators based on the submission of a “variation” to the licensed process. For the US, the master seed lots are checked for antigenic similarity to the WHO recommended strains and then 5 monovalent batches of each strain, and all trivalent batches are tested for antigenicity and released. There is no formal release test on the final packaged product and typically the first vaccine doses begin to ship to customers in mid-July. In Europe, the master seeds are not evaluated in the same way but there is a regulatory requirement for an annual clinical trial to evaluate safety and immunogenicity. Each component must fulfil established immunogenicity endpoints before the vaccine is approved for distribution and sale. This process adds risk for the manufacturers as 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 of course impacts on timing especially since the trial cannot normally begin until SRID reagents are available to allow for the correct formulation of the clinical trial batches. Consequently vaccine doses are not usually ready for shipment in Europe until mid-August, approximately 4 weeks later than in the US.

The Challenge of Pandemics

The current egg manufacturing system has been reliably supplying influenza vaccine for several decades. However, as discussed above, there are clearly timing and capacity constraints and following the 2009 H1N1 pandemic, a perception has arisen that egg-based manufacturing needs to be updated. Possibilities include growing the virus in cell cultures such as MDCK[15], Vero[16] or PER.C6 [17], or by using recombinant DNA technology to express HA and potentially other viral proteins in for example, insect cells (Protein Sciences [18], Novovax [19]), tobacco plants (GreenVax[20], Medicago [21, 22]) or the fungus *Neurospora crassa* (Neugenesis [22]). Such technologies are potentially better able to respond to the global demand in a pandemic with a more rapid production process and a considerably enhanced surge capacity (see below). But which of these options can bring benefits while at the same time performing as reliably as the current system? With both seasonal and pandemic demand in mind, there are several criteria by which the new technologies should be assessed including:

- Time to first dose availability: how fast could the industry respond from receiving the WHO recommendation on strain(s) to releasing the first fully controlled and formulated batch? This is obviously critical for pandemic response.
- Time to last dose availability or how ‘powerful’ is the manufacturing system? It is not just the availability of the first doses that will determine success of a campaign, but how quickly all of the required doses can be supplied. Currently, most manufacturers release their initial batches within days of each other, yet 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 currently established for most of the technologies mentioned above. Moreover, manufacturing must be efficient to minimize COGs and rapid formulation and filling on the appropriate scale are an essential part of this process.

- Regulatory aspects: in addition to being fast, any new technology must be robust and applicable to all influenza types, sub-types and strains, in a way that allows approval by regulators via variations to the licensed process, on time and with minimal risk.
- Surge capacity - the ability to quickly scale and deliver a significant increase in production over that used for routine seasonal vaccination is a relatively difficult capability 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 may occur only 3 or 4 times per century. The notion of a 'warm-base' facility funded in partnership with Government and ready to go 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 the facility and maintain it in an operational state. Moreover sufficient raw materials to meet the surge requirements need to be available at short notice.
- Flexible manufacturing platform. With a reduction in time to final dose the total time required for manufacturing will be shorter. 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. This would impact favourably on COGs.
- Dispersed manufacturing capability. During the H1N1 pandemic there was considerable discussion on national self-sufficiency, especially in countries who noted inequality in the distribution of pandemic vaccine. Thus, a further criterion is how adaptable the new technologies are to distributed production.

There are also economic factors that impact on the choice of replacement technology, especially considering the already considerable investment in egg production that has been made globally by producers. These include:

- The R&D cost of a new influenza vaccine will be considerable as it is likely that the novel approaches will require full clinical development, potentially including large, multi-year efficacy studies. The cost from research concept to product launch is likely to be several hundred million Euros plus the additional cost of new production facilities.
- Recent growth of the influenza market has led to investments that have increased current global capacity for seasonal influenza vaccine to around 600M northern hemisphere doses. The capacity is expected to continue increasing to a base of approximately 1 billion doses by 2018. However, market demand is not expected to increase at the same rate, potentially leading to an excess supply. This will lead to further pressure on pricing and hence return on investment that will de-incentivise investment in new technologies.

Consequently it will be difficult for manufacturers to justify the replacement of current production technology from an economic point of view, and any new technology needs to not just be capable of delivering within the required regulatory and supply environment, but must offer significant advantages over egg manufacturing to persuade manufacturers to engage in the change. Among the new systems being assessed it is not clear at this stage that any of them have all of the characteristics to fundamentally alter the manufacturing paradigm. It is also worth noting that in 2013, when the first "large scale" cell culture facility is due to start market supply, the Northern Hemisphere production capacity is expected to be approx 750–800M doses per year. Of this approximately 74M doses is planned to be of cell culture origin, and the remainder (approx 90% of world production) will be from eggs. Although the switch to alternative technologies is likely to gather

momentum, the time scales required for the licensure of new production systems, and the capital investment and infrastructure development that will be needed, will mean that egg manufacture of flu vaccines will be with us for some considerable time to come.

As discussed above, the existing and planned seasonal influenza capacity is likely to exceed global demand in the years ahead. However in the event of a pandemic considerable further capacity is required very quickly. From a commercial perspective it is not easy to justify investment in further capacity without a concomitant annual market expansion to utilise all of the supply. Therefore alternative approaches to expand influenza vaccine supply in the times of a pandemic need to be considered. One such approach is dose sparing provided by adjuvantation. During the recent H1N1 swine flu pandemic both Novartis and GSK released vaccines containing 7.5ug of antigen adjuvanted with MF59 and 3.75ug of antigen adjuvanted with AS03 respectively (the unadjuvanted dose is 15ug), thus allowing an increase in supply from the same industrial base, assuming that supply of the adjuvant itself is not limiting (the use of adjuvants in seasonal influenza vaccines is much debated but the need is less obvious; certainly from a dose sparing perspective).

The development of 'emergency use' pandemic vaccines also requires some flexibility in the regulatory pathway, as there is insufficient time to conduct the full clinical development required for a new vaccine. For Europe the EMA has developed a guideline (EMA/CPMP/VEG/4717/2003- Rev.1) that allows licensure via creation of a 'mock-up' dossier using all relevant data on the production process, clinical and non-clinical safety etc. on a vaccine prepared from a reference virus similar to a potential pandemic strain. The eventual pandemic vaccine must be produced in the same way, including formulation, and adjuvantation. This allows rapid market authorisation via a "variation" application containing only the new production data for the actual pandemic vaccine. This process was used during the recent H1N1 swine pandemic to release pandemic vaccines in the EU.

Principles for allocating limited vaccines

For the reasons described above, the quantity of vaccines available and affordable to many countries is often less than that required to cover the entire population. For pandemic influenza, it is not possible using current technology to scale up production fast enough to immunize even the populations of the wealthiest countries in time frame that would ensure protection, as the 2009 pandemic showed. In this type of situation it may be appropriate to prioritize the use of vaccines to achieve the greatest public health impact. A major problem at present is that the most potent force in prioritizing pandemic influenza vaccination is the market; through advance contract commitments, wealthy countries had a claim on virtually the entire available supply [29, 30]

In jurisdictions that do have access to vaccines for pandemic influenza, theoretical models provide some principles for allocations of limited supplies that will best achieve various public health objectives. Vaccines serve two related but distinct functions: they protect the vaccinated persons against infection and severe disease, and they reduce transmission, thereby offering indirect protection to those not vaccinated via herd immunity. With limited vaccines available, a fundamental question for vaccine 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 [31], which in practice often means children, whereas the individuals most likely to get severe disease if they are not vaccinated may be a very different group, specifically adults and those with certain predisposing conditions [32]. Therefore, achieving one of these goals typically comes at the expense of achieving the other.

Theoretical work has shown that vaccination of the transmitters is most likely to be effective if large quantities of vaccine are available early in the epidemic [32], while if vaccine supplies are small or arrive late, then they are likely better used to immunize directly those at highest risk. The latter is true, first because small or delayed vaccination programs can only make a modest dent in transmission (hence the protection offered to those not vaccinated is modest) [32], but also because 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 [31]. One caveat should be noted, however: many of those at highest risk of severe outcome, such as older adults and immunocompromised persons, experience these risk precisely because their immune function is suboptimal. Even in seasonal influenza, there is evidence that vaccination of elderly persons has limited effectiveness [33]. A decision to target vaccination at high-risk groups should ideally be based on evidence that the vaccine is effective in these groups – a sort of evidence that is difficult to obtain in the urgent setting of a pandemic.

With current technology, vaccine supply is likely to be limited and delayed relative to the spread of an influenza pandemic; the time scale of present vaccine manufacturing is simply slower than the time scale on which influenza spreads. However, it is worth considering how vaccines can be used to reduce spread of influenza, both because this is an achievable goal for seasonal (non-pandemic) influenza, and because an understanding of this approach can help to define what would be needed from an improved pandemic vaccine manufacturing capacity. Again, theoretical models provide some basic principles; as always, these principles need to be interpreted in light of available data as they do not apply uniformly to all scenarios.

First, growth of an epidemic can be substantially reduced or even stopped by vaccination of less than the entire population.⁶¹ Epidemics grow when, on average, each infectious person infects more than one additional person.⁶¹ 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^{63–65} and 1.8–2.0 for 1918,^{66,67} but was possibly even higher in the spring of 1918.⁶⁸ 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.⁶¹ If immunisation occurs at random, the proportion of people who need to be vaccinated to halt transmission is about:

$$P_c \approx \frac{R - 1}{Rf}$$

where *f* is the efficacy of the vaccine.⁶¹ For a vaccine of 90% efficacy and a reproductive number of five, vaccine coverage of about 89% would be needed to halt transmission.⁶¹ This estimate is merely illustrative and can be improved by detailed simulation or analytical models,^{69–72} but in all situations, coverage need not be 100%.

A second principle is that other interventions, such as reductions in contact and use of antiviral prophylaxis and treatment, can themselves reduce transmission, working in concert with vaccination and allowing major reductions in epidemic growth rate with less coverage than would otherwise be needed [42, 44].

Finally, theoretical work has shown how to maximize the benefits of vaccination to reduce transmission by identifying the groups who are most crucial to transmission. One approach is to identify in advance those groups most likely to be core transmitters, based on

behavioural data [46] or other information about contact patterns; using such data, it is possible to predict the relative reduction in transmission from vaccinating various groups [47]. If such data are not available, methods now exist to estimate (with certain assumptions) which groups should be vaccinated to maximize the impact on transmission just from the patterns of disease incidence and immunity in the population [31]. All such methods suggest for influenza (both seasonal and pandemic) that the maximum benefit in reducing transmission would come from vaccinating schoolchildren, a conclusion consistent with data from observational studies [48] and a recent randomized trial [49]. Such strategies are particularly appealing for seasonal influenza (for which vaccine is generally available early on), given concerns about the direct benefits of vaccinating the elderly [33], who suffer the vast majority of severe morbidity and mortality in seasonal flu [50, 51]. Indeed, the US has recently recommended near-universal seasonal influenza vaccination.

Conclusions and Perspectives

The significant improvements in the global manufacturing capacity of vaccines made in the past decade looks set to continue as investment in vaccine R&D and industrial production methods increases apace. These improvements have led to better access to vaccines for the populations of many nations resulting in high population coverage with established vaccines and positive initiatives to introduce new vaccines as they are developed and launched. Non-Government Organizations such as GAVI, continue to play an extremely important role, especially for the developing world, via policies on advocacy, creative financing to provide incentives to manufacturers, and procurement strategies. However, there are several new and underused vaccines that have the potential to save many lives if they can be delivered to the populations at risk. This, along with the R&D challenges of developing vaccines against some of the more difficult infectious disease agents as described elsewhere in this series, sets the agenda for the next decade.

The threat of pandemic influenza is ever present and the events of 2009 with H1N1 in no way diminish the risk of a more virulent pandemic arising at any time. Unfortunately the global industry is not yet at a level where it can respond to meet the full pandemic vaccine need in a timely and equitable manner and even with improvements we will need to use vaccine in the wisest possible way to achieve maximum impact. We have described the challenges of improving pandemic vaccine supply and the principles for optimizing use of limited supplies in the mean time. It should be noted that there are other possible technical solutions to this problem, including the invention of influenza vaccines that provide broad protection across subtypes, which could be manufactured in advance. Recent progress on this front, though still preclinical, warrants further investigation [26, 27, 52].

More broadly, we are fortunate that over the past decade the expanded markets, more realistic pricing, better advocacy and wiser health priorities, have attracted significant new investment into this industry, generating what has been called a “vaccine renaissance” [53]. Although there is much work to do 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 of the world’s population.

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Box

Major issues for the next decade and beyond on “Vaccine production, distribution, access and uptake”

Issues	Challenge	Potential Impact and Options for Improvement
Anti vaccine propaganda.	To counteract misleading and false messages that discourage uptake of safe vaccines	Improve public health messaging and advocacy.
Crowded immunization schedule	Introduction of new childhood vaccines	New manufacturing and blending technologies to allow easier development of combinations
Improve global vaccine infrastructure	Maintaining vaccine quality while driving down costs. Strengthen National Regulatory Authorities in developing world Increase development of vaccines with primary launch in developing countries.	Harmonisation of regulatory and quality requirements to allow simplified and simultaneous licensure across the globe.
Influenza vaccine uptake	Increase protection against influenza by driving global uptake	Expand industrial base and diversify production technologies in a commodity vaccine market Expand seasonal demand by stronger advocacy, thereby increasing available capacity for pandemic response Drive establishment and achievement of national influenza vaccine recommendations
Improve global vaccine infrastructure	Maintaining vaccine quality while driving down costs. Strengthen National Regulatory Authorities in developing world Increase development of vaccines with primary launch in developing countries.	Harmonisation of regulatory and quality requirements to allow simplified and simultaneous licensure across the globe.
Equity and timeliness of global vaccine access	Ensuring access of new vaccines to developed and developing countries simultaneously	Securing advanced market commitments, external funding, and other mechanisms
Breadth of vaccine coverage	Development of vaccines that are effective against a wide range of antigenic variants (e.g. universal flu vaccines [54])	Increased valency of multivalent vaccines. Development of vaccines against conserved antigens, including sets of conserved antigens. Possibly, also improved adjuvants [28].
Producing and updating estimates of vaccine effectiveness outside of Phase III trials	Measuring the effect of vaccine introduction on morbidity and mortality in settings where no clinical trial was performed, and/or as the pathogen population evolves [55]	Improved surveillance for disease outcomes and intermediates (e.g. carriage) in developing countries where vaccine is introduced [56]; maintaining surveillance where it already exists to assess long-term effects of vaccine.

Key Messages

- Making vaccines uses complex production methods, meticulous quality control and reliable distribution channels
- Manufacturing technologies strongly influence vaccine cost, ease of industrial scale-up, stability and ultimately world-wide availability.
- Reliable vaccine production in appropriate quantities and at affordable prices is the cornerstone of developing global vaccination policies.
- For vaccines whose supplies are limited, such as influenza in a pandemic situation, prioritizing target groups can increase vaccine impact.
- As a result of strong growth, there is a recent return to vaccines and strong investment by multinational pharmaceutical companies.
- NGOs such as GAVI have a powerful role to play in ensuring access to vaccines and future R&D.
- New manufacturing technologies for influenza vaccine are being developed, but are likely to complement rather than replace, egg based production in the medium term.

Table 1

Examples of classes of vaccines and the industrial challenges associated.

	Vaccine Active Component	Main Manufacturing Challenge
Oral Polio vaccine	Live-attenuated viruses x3	Maintaining phenotypic and genotypic stability of each of the 3 strains during production, and viability from blending through the supply cold-chain.
Rabies	Inactivated cell culture grown virus (e.g. on Vero cells)	Ensuring complete inactivation while maintaining immunogenic potency and avoiding reactogenicity. Appropriate BSL containment of live virus steps.
Acellular Pertussis	Purified proteins from B. pertussis	Consistency of production, detoxification of components. Stability and quality control.
Multivalent Pneumococcal conjugate vaccines	Glycoconjugates of polysaccharides on a suitable carrier protein.	Use of complex chemical conjugation chemistries tailored and performed separately for each individual valency. Yields. Formulation to avoid immunological interferences between valencies. QC on complex mixtures
Hepatitis B Vaccine	Recombinant protein	Consistency of manufacturing, with reproducible immunogenicity and minimal host protein contaminant profiles
Japanese Encephalitis e.g. ImmunoJev	Vectored vaccine	Need to demonstrate absence of potential for reversion or genetic rearrangement. Robustness of process. Freeze drying process and stability of product.

Production systems for the top 10 human Vaccine Antigens (by Doses produced)

Vaccine	Production Method
Oral Polio Vaccine	Live attenuated virus grown in non-human cell culture eg primary monkey kidney culture or Vero cell line.
Tetanus	Tetanus toxin extracted from fermentations of <i>Clostridium tetani</i> , inactivated with formaldehyde and adsorbed onto an adjuvant such as alum.
Measles (standalone & MMR)	Live attenuated virus grown cell culture of human diploid cells or chick embryo fibroblasts
Influenza (intramuscular)	Influenza virus propagated in eggs, inactivated and further treated to give either split or subunit vaccines.
Diphtheria	Diphtheria toxin extracted from fermentations of <i>Corynebacterium diphtheriae</i> , inactivated with formalin and adsorbed onto alum adjuvant.
Whole cell Pertussis	Heat killed and formalin inactivated whole <i>Bordetella pertussis</i> bacteria grown in fermenters.
BCG Vaccine	Live attenuated <i>Mycobacterium bovis</i> produced in static surface culture.
Hepatitis B	Recombinant expression of the HBsAG protein, as VLPs, in yeast species.
<i>Haemophilus influenzae</i> b (Hib)	Polysaccharide purified from fermenter culture of <i>Haemophilus influenzae</i> and conjugated to a carrier protein such as inactivated tetanus toxoid, diphtheria CRM protein, tetanospasmin, mutant diphtheria protein, or Group B <i>Neisseria meningitidis</i> outer membrane vesicle protein
MMR	Mumps: Live attenuated virus cultured in chick embryo fibroblast culture. Rubella: live attenuated virus cultured in human diploid fibroblast culture.

Note: the above production methods may not be exhaustive for each antigen type