Preparing for Pandemic Vaccination: An International Policy Agenda for Vaccine Development

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ABSTRACT

The international use of influenza vaccine is growing, especially in developing countries. Since 1997, avian H5N1 influenza in Southeast Asia has caused several human infections and high mortality. Experts warn that the next influenza pandemic is imminent and could be severe. Prevention and control will depend on the rapid production and worldwide distribution of specific pandemic vaccines. If the vaccine supply is to be sufficient to meet global demand, issues related to the intellectual property rights for the reverse genetics technology essential for vaccine production must be resolved. In addition, candidate "pandemic-like" vaccines must be developed and tested in clinical trials to determine the most antigen sparing formulation and the best vaccination schedule. These studies must involve all vaccine companies and will require international coordination and public funding. Whether this international policy agenda for pandemic vaccine development will succeed is uncertain, but it will provide a good indication of whether "good governance" for global public health can be achieved.

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INTRODUCTION

On November 27, 2001, the European Commission held a conference in Brussels on "Pandemic Preparedness in the Community". In its preliminary conclusions, the conference noted:

> The next pandemic is imminent … (and we) … are not prepared. Vaccine availability is not secured. Antiviral stocks do not exist and will not be under the current market forces. In the event of a pandemic millions of people could die, economies will be affected and … (medical and civil) … services could

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> collapse. Members of the public will not excuse authorities, who will be held responsible for not having put in place up-to-date preparedness(1).

This article reviews several policy issues that are central to the development of vaccines for the next influenza pandemic. It begins with a brief overview of influenza viruses, followed by a concise statement on the dimensions of the pandemic threat. A discussion of the effectiveness of influenza vaccination is next, followed by a summary of the global use of influenza vaccines. Then comes a discussion of basic considerations for producing adequate supplies of pandemic vaccines, a review of the scientific basis for their development and registration and an outline of current activities in the United States and Europe. The closely related issue of reverse genetics (RG) and intellectual property is also considered. The article closes with suggestions for an international policy agenda for pandemic vaccine development.

Antiviral agents will be important for the prevention and control of pandemic influenza, but they are outside the scope of this article and will not be discussed.

THE INFLUENZA VIRUS

Influenza viruses are negative-stranded RNA viruses, of which type A is the most pathogenic for humans (2). The influenza virus genome consists of eight RNA segments that code for 10 proteins: two envelope glycoproteins–the hemagglutinin (HA) and neuraminidase (NA) antigens–matrix protein (M1), nucleoprotein (NP), three polymerases (PB1, PB2 and PA), an ion channel protein (M2) and two non-structural proteins (NS1 and NS2). Type A viruses that cause epidemics in man are classified according to the HA (H1, H2 and H3) and NA (N1 and N2) antigens. Point mutations in the HA and less frequently NA antigens lead to antigenic drift that is characteristic of interpandemic years. Sudden substitutions of whole genes from one subtype to another lead to the antigenic shifts that are the hallmark of new pandemics.

THE NEXT INFLUENZA PANDEMIC AND ITS POTENTIAL IMPACT ON THE WORLD

The influenza pandemic of 1918 was one of the most significant disease outbreaks in all of recorded history (3). Within a two-year

period, it killed an estimated 50–100 million people worldwide, 2.5 to 5% of the world's population (4). The number of people who died was far greater than the number who died in World War I. Two later pandemics–Asian influenza in 1957–1959 and Hong Kong influenza in 1968–were much milder, but nonetheless caused widespread social disruption and substantial excess mortality (3).

In 1997, avian H5N1 influenza appeared in the poultry markets of Hong Kong and infection spread to 18 people, six of whom died (5). Human cases of H5N1 influenza reappeared in 1999 and again in early 2003. In late 2003 and early 2004, unprecedented outbreaks of avian H5N1 influenza swept through poultry flocks in many countries in East and Southeast Asia, leading to the deaths or culling of more than 100 million chickens. Again, human cases of H5N1 infection occurred, and this time 24 (68%) of the 34 who were infected died (6). In autumn 2004, human cases of H5N1 influenza reappeared, with similarly high fatality rates.

Other regions of the world have also experienced human infections with avian influenza viruses. In early 2003, a highly pathogenic avian influenza H7N7 outbreak affected commercial poultry farms in the Netherlands and infection was transmitted to humans. As a result, more than 400 poultry workers and their family members developed conjunctivitis and influenza-like illness and one, a previously healthy veterinarian, died (7). This is not the only documented instance of the transmission of an avian influenza virus to mammals. In the early 1980s, an H7N7 avian virus infected harbor seals on Cape Cod in New England, and within 2 months approximately 20% had died (8).

The World Health Organization (WHO) and infectious disease experts throughout the world are concerned that events such as the recent avian influenza outbreaks in Asia could lead to a new human influenza pandemic. Given the more than three-fold increase in the world's population since 1918, a reappearance of a 1918-like pandemic could kill as many as 175 to 350 million people. This is greater than the number of people killed in all wars and by the most murderous governments throughout the twentieth century (9). Deaths from a flu pandemic would not be spread over 100 years but happen in one or two.

Several years ago, a noted influenza expert cautioned against what he called "influenza extrapolitis", that is, the assumption that the

next pandemic will be as severe as the one in 1918 (10). No one can know with certainty how severe the next pandemic will be. However, we do know that this year ~70% of human cases of avian H5N1 influenza died, far worse than the case-fatality rate seen in the 1918 pandemic. If a pandemic virus with similar virulence were to acquire the transmission characteristics of the usual pandemic influenza virus, the consequences for human populations everywhere would be catastrophic. Given this possibility, it would be prudent to anticipate the "worst case scenario" and make preparations to manage it.

THE EFFECTIVENESS OF INFLUENZA VACCINATION

Influenza vaccines are the mainstay of efforts to prevent and control outbreaks of influenza that occur almost every year (2). Trivalent vaccines currently available contain inactivated (killed) viruses representing three different strains of circulating influenza viruses– the A/H3N2, A/H1N1 and B subtypes. The strains selected for each year's vaccine are chosen by WHO experts who attempt to match them with those expected to cause outbreaks of disease.

Influenza vaccines are safe and immunogenic. Following vaccination, serum antibody responses to the HA antigen of the influenza virus correlate well with clinical protection (11). Vaccination stimulates an increase in anti-NA antibodies (12,13), and these antibodies are also protective (14). If there is a good antigenic match between the vaccine virus and the circulating virus causing disease, vaccination reliably reduces influenza-related hospitalizations for cardiopulmonary and cerebrovascular conditions and deaths (15). In addition to being clinically effective, influenza vaccination has also been shown to be cost-effective (16). Vaccination of children is also clinically effective (17) and high levels of coverage among schoolchildren induce herd immunity and prevent deaths in older adults (18). Pregnant women are at increased risk of hospitalization for influenza-related illness (19), and vaccination during pregnancy has the potential to benefit not only mothers themselves but also their newborn infants (20).

When the next pandemic emerges, pandemic vaccines will not be immediately available. The new virus can be expected to spread to many parts of the world in a few weeks or months. Nonetheless, the pandemics of the twentieth century showed that many parts of the

world were affected only after several months had passed; that several waves of infection affected individual regions, and that later waves had a greater impact on morbidity and mortality than did the initial wave. Thus, the health and social consequences of even a severe pandemic may be reduced if large numbers of doses of effective pandemic vaccines can be quickly produced and equitably distributed to countries that need them.

THE GLOBAL USE OF INFLUENZA VACCINES DURING THE INTERPANDEMIC PERIOD

Supplies of vaccine for the next pandemic will be critically dependent on annual levels of trivalent vaccine use during the interpandemic period. Thus, planning for pandemic vaccine supply requires an understanding of the global epidemiology of influenza vaccination (21).

An overview of the global production and distribution of trivalent influenza vaccines during the period 2000–2003 was recently published by WHO (22). In 2003, at least 292 million doses of influenza vaccine were distributed worldwide, (Table 1). This was more than twice the 135 million doses distributed a decade earlier (DS Fedson, unpublished observation). Almost all of the world's influenza vaccine is produced in nine countries–Australia, Canada, France, Germany, Italy, Japan, The Netherlands, the United Kingdom and the United States. (In Europe, a Swiss company markets influenza vaccine, but it obtains its bulk vaccine virus from a vaccine company located in Australia.) In 2003, these nine countries had only 12% of the world's population, yet they used 62% and produced $\geqslant$95% of the world's influenza vaccine. Almost none of the vaccine produced in Canada, Japan and the United States was exported to other countries. Four companies located in the five Western European countries produced 190 million doses, 65% of the world's supply. Excluding 13.8 million doses produced in Hungary, Romania and Russia (all of which were distributed domestically), these five countries produced almost all of the 79 million doses of influenza vaccine that were used in countries outside Western Europe, Canada, the United States, Australia and Japan (Table 1).

Recent information gathered from almost 60 countries documents the increasing use of influenza vaccine throughout the world (Macroepidemiology of Influenza Vaccination (MIV) Study Group,

TABLE 1: Global distribution of influenza vaccine, 2003

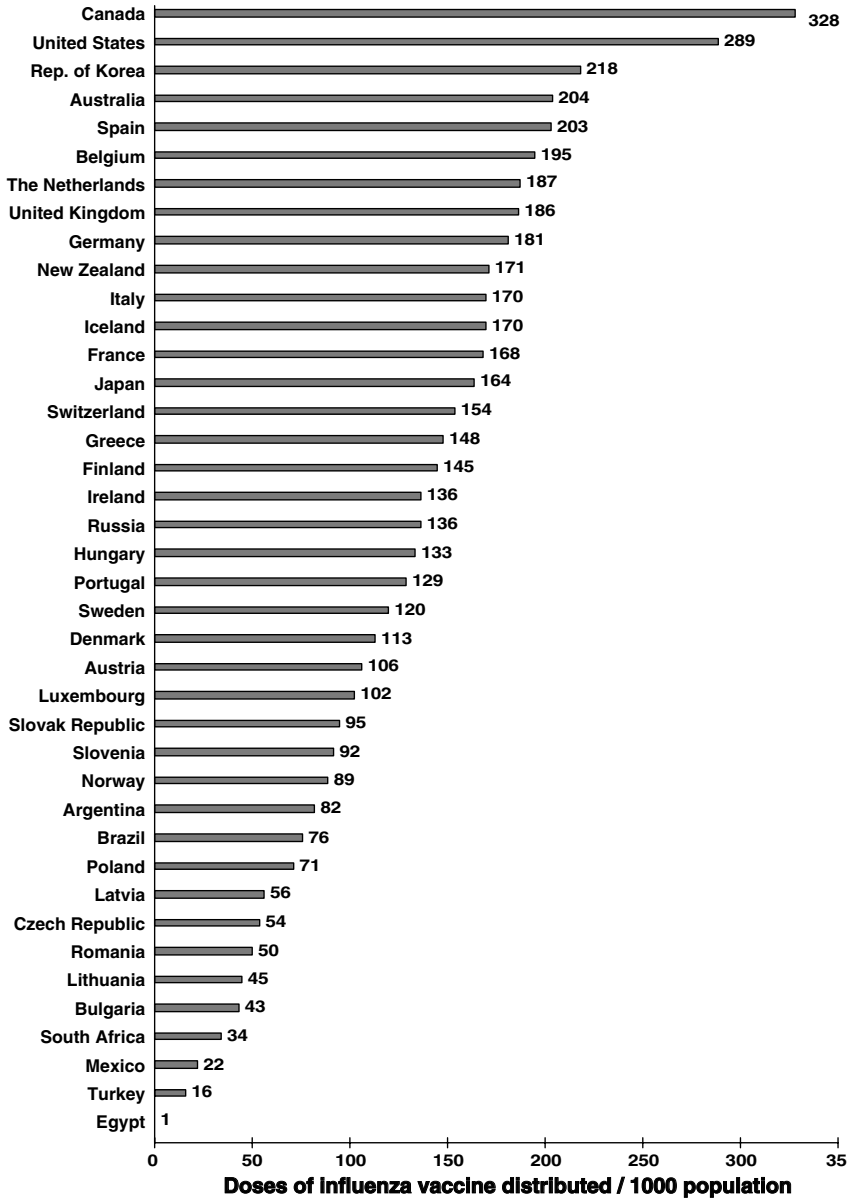
WHO region	*Total doses distributed, 2003 (000s)*[*]
Europe	102,891
Western Europe	76,523
Central and Eastern Europe	26,368
Americas	123,578
Canada	11,100
United States	84,913[†]
Mexico, Central and South America	27,565
Western Pacific	61,189
Australia	4,357
Japan	29,253
New Zealand	715
Other countries	26,864
Southeast Asia	253
Eastern Mediterranean	1,540
Africa	1,230
Global total	291,979

[*] See reference (22). Individual reports on the numbers of doses of influenza vaccine distributed each year were submitted by all Influenza Vaccine Supply (IVS) Task Force companies: Aventis Pasteur, Aventis Pasteur MSD, Berna Biotech, Ltd., Chiron/Powderject, CSL Limited, GSK Biological, Medimmune, Inc., Shire Biologicals, Solvay Pharmaceuticals B.V. and Wyeth Vaccines. The Association of Japanese Biologicals Manufacturers reported data on behalf of four Japanese vaccine companies. In addition, data were gathered from non-IVS Task Force companies located in Hungary, the Russian Federation, and Romania. The Task Force was unable to obtain information on doses produced and distributed in other counties. The data were reported for calendar years according to WHO regions. For some regions, additional information was obtained on vaccine distribution in countries within the regions.

[†] The data for the United States do not include doses of cold-adapted, live-attenuated trivalent influenza vaccine distributed by Medimmune. In 2003, Medimmune produced ~4–5 million doses of CAIV-T and distributed ~830,000 doses, but only ~250,000 doses were actually sold.

unpublished observations). Figure 1 shows the level of vaccine distribution in 40 countries in 2002. The following year (2003), the country with the largest per capita use of influenza vaccine was Canada (344 doses distributed/1000 total population). This level of

FIGURE 1
Influenza vaccine distribution in 40 countries in 2002



vaccine use was achieved primarily because Canada's largest province, Ontario, has a universal influenza vaccination program. The Republic of Korea ranked second (311), in part, because a vigorous program for vaccination was undertaken in the wake of the SARS outbreak in early 2003. The United States ranked third (286) and Japan was fourth (231). Countries within the European Union (EU) showed widely varying levels of vaccine use, with countries in Western Europe generally having higher levels than the new Member States of Central and Eastern Europe (see data for 2002 in Figure 1). The Russian Federation, Hungary and several countries in South America, however, had higher levels of vaccine use than did several Western European countries.

Almost all developed and rapidly developing countries have national recommendations to vaccinate elderly people and others with high-risk medical conditions (23). Variations in vaccine use seen among these countries are due to several factors, including the availability of public reimbursement for vaccination, the views of small groups of policy-makers, and probably broader historical and cultural reasons.

The epidemiology of influenza vaccination documents a reality of enormous logistical and political importance. Almost 40% of the world's supply of interpandemic influenza vaccines is used in countries that do not produce their own vaccines. Virtually all of these "have not" countries are critically dependent on supplies of vaccines produced in only five Western European countries. This dependence will profoundly affect the global availability of pandemic vaccines.

BASIC CONSIDERATIONS FOR PRODUCING ADEQUATE SUPPLIES OF PANDEMIC VACCINES

No one can predict when the next influenza pandemic will appear (24). If it does not come for another 15 or 20 years, it is likely that several companies will have begun producing influenza vaccines in cell culture and will be marketing newer vaccines and vaccine delivery systems. In most countries there will be a continued increase in the interpandemic use of influenza vaccines. These developments will increase the likelihood that greater supplies of vaccines could be available to confront the pandemic. However, it would be prudent to

assume that the pandemic will emerge not in 15–20 years but within the next 5 years. If this principle is accepted for purposes of planning, several potential limitations in the global supply of pandemic vaccines immediately become apparent.

Pandemic vaccination will be almost totally dependent on the production facilities of companies located in the nine vaccine-producing countries. All of these companies currently produce their vaccines in embryonated eggs (25). If interpandemic vaccine use increases in the next few years, the production capacities of these companies will increase in parallel, but this incremental increase will not be large. One new European-based company plans to enter the market within the next few years and intends to produce 40–50 million doses of cell culture-produced inactivated influenza vaccine each year. However, none of the other vaccine companies is expected to have an appreciable capacity to produce cell culture vaccines within the next 5 years because it takes at least that long to build and obtain regulatory approval for a new vaccine production facility.

When the next pandemic virus emerges, it will replace the influenza viruses that have been circulating until then. Thus, a pandemic vaccine will need to contain only the pandemic virus; in other words, it will be a monovalent not trivalent vaccine. Given the current global production capacity of ~300 million doses of trivalent vaccine (and assuming a production cycle similar to that for current trivalent vaccines), it is theoretically possible that up to 900 million doses of same-strength (15 μg HA) monovalent pandemic vaccine could be produced.

Most if not all people will never have been infected with an influenza virus like the pandemic virus. As they will be immunologically naïve, they will require two doses of vaccine to be fully protected (21). This means that only 450 million people could be vaccinated with two doses of a "same strength" monovalent vaccine.

In many countries, public health officials will want to vaccinate everyone in their populations. For this reason, when a pandemic virus appears, government leaders in countries that have vaccine companies will probably "nationalize" their vaccine production facilities to ensure that there is enough vaccine to vaccinate their populations. This could mean that millions of people living in countries without vaccine companies will have to wait several months or more for supplies of pandemic vaccines. It also means that

millions of people living in many "have not" countries that have traditionally been supplied with interpandemic vaccines will not be a able to obtain any supplies of pandemic vaccines.

THE SCIENTIFIC BASIS FOR DEVELOPING AND REGISTERING A PANDEMIC VACCINE

Within the past few years, several groups of European investigators have carefully worked out a promising strategy for developing "pandemic-like" vaccines that 1) induce protective levels of antibodies when two doses are given to immunologically naïve subjects and 2) can be produced in abundant supply by vaccine companies in their existing facilities (21). The strategy is based on using a lower dose of HA antigen and including an adjuvant in the vaccine. The initial studies were conducted using a proprietary MF59 adjuvant (26–29), but later studies used a simple alum adjuvant–the kind widely available and used by all vaccine companies that produce childhood vaccines (30,31). Vaccines against H2, H5 and H9 "pandemic-like" viruses have been tested. Both adjuvanted and non-adjuvanted vaccines have been produced using both whole virus and subunit virus preparations (32,33). They have been formulated with concentrations of HA antigen as low as 1.875 μg per dose (30,31). A single injection of one of these low-dose vaccines primes the recipient and a second dose, usually given 3 weeks later, leads to the development of protective levels of antibodies when measured after another 3 weeks.

How low the HA content of a pandemic vaccine can be set is uncertain, but this "antigen sparing" strategy has critical implications for the amounts of vaccine that can be produced at any given time during the course of a pandemic. Consider, for example, a monovalent alum-adjuvanted pandemic vaccine containing only 1.875 μg HA per dose. If all of the world's vaccine companies were instructed to produce this antigen sparing vaccine, in less than 6 months from the time production started, they could in theory produce 7.2 billion doses (300 million $\times$ 3 $\times$ 8). This would be enough to vaccinate 3.6 billion people, more than half the world's population. This amount of vaccine would probably exceed the combined capacities of the world's health-care systems to deliver it. Most influenza experts believe that an antigen sparing formulation

offers the greatest promise for producing supplies of pandemic vaccines that are adequate to meet global demand.

THE US APPROACH TO DEVELOPING A PANDEMIC VACCINE

In May 2004, the US government awarded contracts to two US-based companies–Aventis Pasteur and Chiron Vaccines–to produce pilot lots of monovalent H5N1 "pandemic-like" vaccines. These vaccines will be formulated at two dosage strengths–15 and 45 μg of HA antigen (standard- and high-dose, respectively)–in order to comply with FDA requirements for currently licensed influenza vaccines. They will be tested in the NIH Vaccine Trial and Evaluation Units. Public funding will support the full costs of the clinical trials.

In the fall of 2004, difficulties in Chiron's influenza vaccine production facility in the UK led to the sudden loss of approximately half of the normal US supply of trivalent influenza vaccine. Aventis Pasteur (now Sanofi Pasteur) has the only influenza vaccine production facility that is located in the United States and its capacity is limited to approximately 50–60 million doses of trivalent vaccine per year. If a pandemic virus emerges in the next year or two and the governments of vaccine-producing countries refuse to allow their companies to export pandemic vaccines, the United States will be forced to rely on its sole domestic vaccine company for its supply of pandemic vaccine.

According to the NIH pandemic vaccine development strategy, 60 million doses of domestically produced trivalent inactivated vaccine would be equivalent to 180 million doses of standard-dose (15 μg HA) monovalent pandemic vaccine and 60 million doses of high-dose (45 μg HA) vaccine. Given the usual 6-month trivalent vaccine production cycle, the United States would be able to vaccinate (with two doses) 90 million people using the standard-dose (15 μg HA) vaccine and only 30 million people using a high-dose (45 μg HA) vaccine. This is the same or fewer than the annual number of people vaccinated with the trivalent vaccine in recent years. If domestic production capacity could be increased to 100 million doses of trivalent vaccine per year (an unlikely event), then 150 million people could be vaccinated with two doses of the standard-strength pandemic vaccine, and 50 million people with the high-dose vaccine.

The United States government hopes to increase domestic capacity for producing influenza vaccines by accelerating the introduction of cell culture-based production, but this will have little effect on capacity within the next 5 years. Thus, for the United States to be able to offer two doses of monovalent standard-dose (15 μg HA) pandemic vaccine to every person in the country (600 doses, assuming 300 million people), domestic egg-based production of trivalent vaccine would have to increase four-fold to 200 million doses per year. To provide everyone with two doses of high-dose (45 μg HA) pandemic vaccine, domestic production would have to increase 12-fold to 600 million doses of trivalent vaccine per year. Within the next 5 years, increases in US vaccine production capacity this large will simply not be possible.

The current NIH strategy for developing an H5N1 "pandemic-like" non-adjuvanted vaccine appears to be based on 1) the goal of determining the optimal dose of HA antigen for an individual rather than an acceptably immunogenic dose for a population and 2) the assumption that a new pandemic virus will not emerge for 5 or more years. Previous studies have shown that vaccinating healthy younger (34) and older (35) adults with non-adjuvanted vaccines containing increasing amounts of HA antigen (up to 135 μg HA per dose) is associated with higher and more persistent antibody levels, albeit with more frequent local adverse reactions. Although higher doses of HA antigen offer better immunogenicity for individuals, these studies were conducted in subjects who already had had immunological experience with the virus subtypes included in the trial vaccines. Consequently, the results cannot be extrapolated to the circumstances of a new pandemic. Moreover, a recent study in immunologically naive younger adults showed that two doses of a non-adjuvanted "pandemic-like" H9N2 vaccine containing 30 μg HA was poorly immunogenic and would leave most people unprotected in the event of an H9N2 pandemic (32).

Simple arithmetic shows that the number of doses of pandemic vaccine that could be supplied if formulated according to the current NIH clinical trial strategy for H5N1 vaccines will fall far short of providing two doses for every American. Also, it is unlikely that two doses of non-adjuvanted vaccine (either 15 or 45 μg HA) will be acceptably immunogenic in people who have not previously experienced infection with a similar pandemic-type virus. Moreover,

if this strategy is followed, the United States will have no pandemic vaccine to offer people in other countries.

The US strategy for pandemic vaccine development needs to change. It should focus on ensuring that the largest possible supply of pandemic vaccine can be made available as quickly as possible. It must be based on current domestic egg-based production capacity. Its goal should be to determine the lowest amount of HA antigen that can be included in an adjuvanted vaccine that will be acceptably immunogenic when given in a two-dose schedule to a population. If successful, this alternative strategy would meet the needs of the American people. It would also provide millions of doses of pandemic vaccine to people in other countries.

THE EUROPEAN APPROACH TO PANDEMIC VACCINE DEVELOPMENT

Within the European Union the annual updating of a marketing authorization for an interpandemic vaccine is handled by a "fast track" variation of a decentralized registration procedure (36). Unlike registering influenza vaccines in the United States, the registration requirements of the European Medicines Evaluation Agency (EMEA) entail a demonstration of safety and satisfactory serum antibody responses for each company's vaccine each year. This process can take as long as 73 days.

For a pandemic vaccine, registration in the EU will need a different procedure (37). The vaccine will not be a variation of a current vaccine but an entirely new vaccine, and thus the EMEA centralized procedure will have to be used. The pressure of time will be severe. Current EU regulations allow national authorities to "exceptionally and temporarily consider the variation to be accepted after a complete application has been lodged and *before* the end of the procedure …" (38). This regulation provides the legal basis for the EU approach to developing and registering pandemic vaccines.

In September 2002, an EMEA representative met with staff of WHO and its Collaborating Centers and with representatives of several vaccine companies to explore steps needed to develop and register pandemic vaccines in Europe. Over the next 18 months, two "Notes for Guidance" were drafted, one dealing with the structure of the dossier and the content of the marketing authorization

application for pandemic vaccines (scientific guidance) (39), and the other providing guidelines on submission of marketing authorization applications for pandemic vaccines through the EMEA centralized procedure (procedural guidance) (40).

The Notes for Guidance were published in final form in April 2004. They set forth requirements for demonstrating the quality, safety and immunogenicity of what is called a "mock-up" (i.e., candidate) pandemic vaccine. Companies have been asked to develop prototype "mock-up" vaccines during the interpandemic period. These vaccines must contain viral antigens to which humans have not been previously exposed (e.g., H5N1). Each company must conduct clinical trials of its "mock-up" vaccine to determine the antigen dosage and vaccination schedule for its vaccine and establish its safety. The core dossier must document the production process for the vaccine and its final formulation. Once this is done, the company can obtain a marketing authorization for its "mock-up" vaccine. When a pandemic threat is declared and a true pandemic vaccine needs to be produced, only quality data related to the pandemic variation need to be submitted to the EMEA. Each pandemic variation will receive a "fast track" assessment and approval within 3 days and an EU decision within another 24 h (39,40). Approval will be given with the understanding that companies will gather safety, immunogenicity and effectiveness data on their pandemic vaccines during clinical use (39). Precise details on how this will be done have yet to be worked out.

The EMEA has not published a clinical development plan for a "mock-up" pandemic vaccine. However, the Clinical Working Group of the European Vaccine Manufacturers has proposed a step-wise clinical development plan that is based on earlier experience with pandemic-like vaccines (26–33).

EMEA staff and vaccine experts, working closely with their colleagues in European vaccine companies, have put together an integrated "roadmap" that outlines most of the steps for developing and registering a "mock-up" pandemic vaccine. Once a company obtains a marketing authorization for its core dossier, regulatory approval for a true pandemic vaccine can be quickly obtained. Regulatory authorities in several non-European countries have indicated that they will probably follow the EMEA approach.

Despite this remarkably detailed approach to developing and registering a pandemic vaccine, it is uncertain whether any European vaccine company will carry out a full development program for a "mock-up" vaccine on its own (37). Vaccine companies will be understandably reluctant to pay the costs for developing vaccines that may never be marketed. Expectations that the "sunk" costs of developing a "mock-up" vaccine could be quickly recovered when a pandemic arrives will be tempered by uncertainty over vaccine prices, purchasing guarantees and liability coverage, and by the prospect of national takeovers of pandemic vaccine production. Although one or two companies have indicated they might be willing to develop "mock-up" vaccines on their own, their early development costs will be small compared with the much larger costs that will be required for full-scale clinical trials later on.

EU officials and European vaccine companies have yet to enter into specific discussions about whether EU funding could be made available for the more expensive later stages of "mock-up" vaccine clinical development. If the emergence of the next pandemic virus is delayed for several years, EU officials might have enough time to work through these difficult problems. However, if a pandemic virus should emerge within the next year or two, EU officials and their counterparts in the United States and elsewhere will be forced to make decisions about a pandemic vaccine formulation and vaccination schedule based on existing clinical data. These data clearly indicate that only an antigen sparing pandemic vaccine will meet the population needs of Europeans and of people in other countries that depend on European vaccine companies.

REVERSE GENETICS (RG), INTELLECTUAL PROPERTY RIGHTS AND PANDEMIC VACCINE DEVELOPMENT

Each year, the production of influenza vaccines begins when reference strains are provided to vaccine companies by WHO. Since the early 1970s, these reference strains have been prepared using the technique of genetic reassortment. With this technique, embryonated eggs are coinfected with an influenza virus considered most likely to cause epidemic disease and a high-growth strain of influenza A/PR8 virus. Following subsequent cloning, a progeny genetic reassortant virus is isolated that has two genes coding for the surface (HA and

NA) antigens of the epidemic virus and six genes derived from the PR8 virus that are associated with high growth. These reference strains become the seed strains used by companies to produce their vaccines (25,36).

Genetic reassortants have been essential to the success of influenza vaccine production for more than 30 years, but they have several disadvantages. The time needed to isolate a genetic reassortant suitable for commercial vaccine production can take many weeks. The reassortants do not always grow efficiently in egg-based production systems. Importantly, the avian H5N1 viruses recently associated with human disease are lethal for embryonated eggs. Largely for this reason, no viable H5N1 seed strain suitable for commercial vaccine production has yet been prepared using genetic reassortment.

In the past few years, reference strains suitable for producing human H5N1 influenza vaccines have been prepared in several laboratories using the techniques of RG (41–43). With this technique, the polybasic amino-acid sequences associated with H5N1 virulence are removed from the HA cleavage site. Plasmids containing the genes for the avian virus HA and NA antigens are then cloned and transfected into Vero cells along with plasmids containing the six PR8 genes. The progeny virus is rescued from cell culture, purified, propagated in embryonated eggs, and tested for stability and pathogenicity. The methods for preparing RG-engineered viruses are straightforward, the results are predictable, and the process can take as little as 10–20 days. Moreover, when used with avian viruses, the resultant RG-engineered reference strains can be used as seed strains for egg-based vaccine production.

The techniques of RG differ from genetic reassortment in one important respect; they are associated with patents. The intellectual property (IP) rights for RG are divided into four portfolios (44). Three portfolios for what is known as the 8-plasmid system (43) are held by MedImmune, Inc., an American pharmaceutical company. The fourth portfolio for what is known as the 12-plasmid system (41) is held by the Mount Sinai Medical Center in New York City. MedImmune has agreed that its 8-plasmid RG technology can be used to prepare reference strains for vaccine research and development and that no royalty payments will be required (44). Mount Sinai Medical Center has yet to indicate whether RG-engineered reference strains prepared using its 12-plasmid system can be used

for research purposes without royalty payments. However, if either one of these RG-engineered viruses is used for commercial vaccine production, the patent holder expects to be paid reasonable royalties for the use of its RG technology.

An H5N1 reference strain prepared using the MedImmune 8-plasmid RG system will be used by Aventis Pasteur and Chiron to produce research lots of H5N1 vaccines for clinical testing in the United States. However, if a true H5N1 pandemic virus should emerge and H5N1 vaccines are needed to respond to this threat, vaccine companies would still be uncertain about the precise ownership of the IP rights for the RG-engineered seed strains they would be called upon to use. The US Department of Health and Human Services and several companies have already undertaken their own analyses of the patent status of the 8- and 12-plasmid RG systems, but their findings and policy options are not publicly known. Even if they were, the US patent rights would apply only to the United States, because patent rights in Europe and Japan are independent of those in the United States. The status of European and Japanese patents for the two RG technologies is not publicly known.

The importance of the uncertainty over the patent status for the two RG technologies has recently been highlighted by developments in Europe. An H5N1 reference strain was produced by the National Institute of Biological Standards and Control (NIBSC) in the United Kingdom using the 12-plasmid RG system (33). This reference strain was offered to four Western European companies, but three refused to accept it, in some measure because of persisting uncertainty over the patent status of the RG technology used to produce it.

In addition to uncertainty in the research setting, in the absence of knowing who owns the intellectual property for RG, it will be difficult for a vaccine company to enter into negotiations on royalty payments for commercial pandemic vaccine production. If negotiations with one patent holder should be attempted, litigation by the other could follow. Given these uncertainties, when presented with an immediate pandemic threat, the governments of countries with vaccine companies might be forced to exercise compulsory use licenses for RG technology. Royalty payments would be determined by governments and not be negotiated between patent holders and patent users. Moreover, European companies with no previous experience using RG-engineered viruses might find it difficult to

obtain regulatory approval to use them to make pandemic vaccines because these viruses are considered to be "genetically modified organisms" (GMOs) and can be used only in facilities that meet high-level biosafety requirements that not all companies currently have.

A strong argument can be made for resolving RG-IP ownership before the next pandemic threat appears (21,45). This would allow companies to determine whether using RG-engineered seed strains would offer advantages over genetic reassortants for both interpandemic and pandemic vaccine production. Companies in Europe would have time to resolve uncertainties over GMO issues with their national regulatory authorities and, if necessary, upgrade their production facilities. Royalty payments for commercial sale of these vaccines could be negotiated with the RG patent holders. The possibility of establishing a patent pool (single licensing authority) among all patent holders could be explored.

One obstacle still stands in the way. In interpandemic years, companies have enough time to produce their vaccines using genetic reassortants. If they were to use RG-engineered seed strains, their vaccines could not command higher prices in the market and paying royalties would erode their profit margins. Thus, companies have no compelling commercial reason to use RG-engineered viruses for producing interpandemic vaccines. Coupled with the possibility of national takeovers of all important aspects of pandemic vaccine production and distribution, it is not surprising that individual vaccine companies have had little incentive to seek resolution of the intellectual property rights issues for influenza virus RG. Experts in intellectual property would describe this as a classic example of market failure.

AN INTERNATIONAL POLICY AGENDA FOR PANDEMIC VACCINE DEVELOPMENT

International efforts to develop pandemic vaccines are being undertaken within the context of several major WHO initiatives. These include the publication of the WHO Influenza Pandemic Preparedness Plan in 1999 (46) and the WHO Global Agenda on Influenza (47,48) and position paper on influenza vaccine in 2002 (49). In May 2003, the World Health Assembly passed a resolution on the "Prevention and Control of Influenza Pandemics and Annual Epidemics" (50). More recently, WHO published its "Guidelines

on the Use of Vaccines and Antivirals During Influenza Pandemics" (51) and its "Consultation on Priority Public Health Interventions Before and During an Influenza Pandemic" (52). In November 2004, WHO held an important meeting with representatives of influenza vaccine manufacturers, national licensing agencies and governments to review the current status of pandemic vaccine development (53).

Vaccine experts agree that RG must be used to prepare reference strains that will be used as seed strains for pandemic vaccine production. Most also agree that an antigen sparing vaccine formulation will be essential if adequate supplies of pandemic vaccines are to be produced for worldwide use. An international solution to both of these problems will be required and WHO leadership will be essential.

Companies may not be adequately prepared to produce pandemic vaccines using RG-engineered viruses unless the public sector provides a framework for RG-IP negotiations during interpandemic years. As patent issues are governed by national patent laws, any negotiating framework that is established must be international in scope, and this has been acknowledged by the World Health Assembly (51) and WHO (52). WHO can address technical issues such as the safety of using RG-engineered viruses (54), but WHO may not be able to play a central role in resolving RG-IP issues. Nonetheless, because of the importance of RG to the development of "pandemic-like" vaccines during the interpandemic period, efforts must be undertaken immediately to remove the uncertainties regarding the status of its patents.

An international solution is not readily apparent. European (37) and other national governments (55) that plan to organize pandemic vaccination programs must take an interest. The intellectual property rules of the World Trade Organization and the needs of international public health must be reconciled (56). Political and technical support might be sought from the EU and other international institutions such as the Organization for Economic Cooperation and Development (almost all countries with vaccine companies are OECD Member States) and the World Bank. Non-governmental institutions such as the Bill and Melinda Gates Foundation could play a vital role in supporting this process. The technical support of the World Intellectual Property Organization and the WIPO Arbitration and Mediation Center could be especially helpful (57). The report of WHO's Commission on Intellectual Property Rights, Innovation,

and Public Health expected in 2005 might offer guidance on what should be done (58). Whatever process is chosen, resolving the uncertainties related to intellectual property rights for RG will be essential if companies are to be fully prepared to produce pandemic vaccines when the next pandemic emerges.

There is also a growing awareness of the need for multicenter international clinical trials of candidate "pandemic-like" vaccines produced by all companies that intend to produce true pandemic vaccines (21,45). This "dress rehearsal" strategy would challenge vaccine companies and national regulatory agencies on whether RG-engineered viruses could be used in their production facilities. Both would gain the practical experience needed to prepare them for pandemic vaccine production. However, questions still remain on how to formulate the vaccines and how to fund the clinical trials.

Currently, all vaccine companies produce trivalent influenza vaccines according to a common formulation. Similarly, the protocol for the international trials should be designed to determine a common formulation for an optimal antigen sparing vaccine, one that can be produced by all companies that intend to produce a true pandemic vaccine. Unfortunately, the current NIH clinical trial strategy for its H5N1 vaccines involves only two companies and will provide no information on how to formulate an antigen sparing pandemic vaccine. Likewise, the EMEA Notes for Guidance make no mention of the need for international clinical trials or the need for a common formulation for an antigen sparing vaccine. If companies are to be permitted to develop their own unique formulations for their pandemic vaccines, they might choose simple variations of the formulations used for their current non-adjuvanted interpandemic vaccines and forego the possibility of producing the much greater number of doses of antigen sparing vaccines that will be needed if "have not" countries are to be supplied with pandemic vaccines. This must not be allowed to happen. WHO must take a leading role in drafting an international clinical trial protocol for "pandemic-like" vaccine and the protocol must be endorsed by the public health officials of all vaccine-producing countries.

A consensus is developing among vaccine companies and national and international health officials that public funding will be needed to conduct clinical trials of candidate "pandemic-like" vaccines (21,45). In the United States, the absolute requirement for public funding has

been recognized and acted upon by the NIH in its trials of H5N1 vaccines. Europeans are also becoming convinced that public funding will be necessary if clinical trials of "mock-up" pandemic vaccines are to become a reality. However, Europeans have yet to come up with a Europe-wide mechanism for funding such trials, although efforts are under way to change this (59). For the time being, it seems that individual national governments will be the only source of public funding for the clinical trials that will be conducted by their domestic vaccine companies. In the short run, this may be an efficient way of getting the trials under way. In the long run, however, such funding could link the production and distribution of future pandemic vaccines more closely with meeting the domestic needs of each vaccine-producing country and compromise their willingness to share their vaccines with "have not" countries. The "have not" countries might improve their chances of obtaining supplies of a future pandemic vaccine if they could find a way to help fund these clinical trials.

Thus far, most discussions on RG intellectual property rights and clinical trials of "pandemic-like" vaccines have involved only US and European health authorities and vaccine companies. Vaccine companies in Australia, Canada and Japan are actively planning to develop these vaccines and companies in China, Hungary, the Russian Federation, and Romania will sooner or later do the same. (In future years, companies located in Brazil and other developing countries will also begin to produce influenza vaccines.) Considered together, the companies in these countries currently provide ~20% of the world's trivalent influenza vaccines, and this proportion is likely to increase. International discussions on pandemic vaccine development must include these companies.

CONCLUSIONS

If pandemic vaccination is to be successful, several problems will need to be resolved before the pandemic virus emerges. A global process for quickly registering pandemic vaccines will be necessary. A system for forecasting the demand for pandemic vaccines must be developed for each country. The information for each country must include purchase commitments and guaranteed prices and must be aggregated in such a way that vaccine companies will know how many doses of pandemic vaccines they will be called upon to

produce. Responsibility for liability for vaccine-associated adverse events must be assumed by governments, because without this, companies may be unwilling to produce pandemic vaccines. Equitably allocating limited supplies of pandemic vaccines to countries that do not have vaccine companies may prove to be the most difficult of all problems to solve, but it will be easier to solve if the global supply of pandemic vaccines is large instead of small. However, none of these problems will need to be solved if companies are unable to develop and produce effective pandemic vaccines.

The emergence of SARS and the resultant efforts to develop a SARS vaccine have presented a set of problems that will be solved only with a coordinated international approach (60,61). The challenges posed by pandemic influenza and the development of a pandemic vaccine are far greater. It is uncertain whether an international policy agenda for developing a pandemic vaccine will be implemented, but efforts to do so will provide a good indication of the world's ability to achieve "good governance" for global public health (62).

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