Pandemic Influenza and the Global Vaccine Supply

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(See the editorial commentary by Fedson on pages 1562–3)

Use of influenza vaccine is increasing, especially in developing countries. Yet most of the world’s influenza vaccine is produced by companies located in 9 developed countries. When the threat of an influenza pandemic appears, the traditional approach to providing interpandemic vaccines will not be able to meet the global demand for pandemic vaccine. Several steps must be taken to address this problem, including the use of reverse genetics to prepare seed strains for vaccine production, the undertaking of clinical studies to define the characteristics of candidate “pandemic-like” vaccines and vaccination schedules, the development of procedures for global vaccine registration, the expansion of recommendations and reimbursement for interpandemic vaccination, the country-specific reporting of vaccine use and forecasts of future vaccine needs, and the negotiation of political agreements that will ensure the adequate production and equitable distribution of pandemic vaccine throughout the world.

In early 1962 long queues attended any clinic in Birmingham offering vaccination, because three patients with smallpox were in the isolation hospital. At this time over 100 people a week were dying [of influenza] … but this caused no great public agitation.

T. H. Flewett, 1963 [1]

That we have chosen to worry more about anthrax than about the flu is hardly surprising. The novel is always scarier than the familiar, and the flu virus, as far as we know, isn’t being sent through the mails by terrorists. But it is a strange kind of public-health policy that concerns itself more with the provenance of illness than with its consequences; and the consequences of flu, year in, year out, dwarf everything but the most alarmist bioterror scenarios.

Malcolm Gladwell, 2001 [2]

The health and economic consequences of recurring epidemics of influenza are widely understood [3, 4]. The clinical effectiveness and cost-effectiveness of influenza vaccination in re-

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Ducing influenza-associated hospitalizations and deaths among older adults are also widely known [5–8]. This knowledge has led to a substantial increase in the use of influenza vaccine in many developed countries [9, 10]. Influenza also affects developing countries, and many of them have begun to use the vaccine [10]. In the event of a future influenza pandemic, however, expectations of what can be done for prevention and control of influenza may exceed the capacities of health care systems in every country. Thus, the vaccine supply during a pandemic will be a problem that affects all countries.

An influenza pandemic will present national health officials
Susceptibility to infection with a new pandemic influenza virus will depend on a person’s previous experience. If the next pandemic is caused by the reemergence of an influenza A (H2-like) virus, only persons aged >35 years (i.e., those born before 1968) will have had previous immunological experience with this virus. Currently, more than half of the world’s population is ≤35 years old [18]. All of these younger individuals will be fully susceptible to an H2-like pandemic virus. If, however, the next pandemic is caused by a novel influenza virus, such as the avian influenza A (H5N1) virus that appeared in Hong Kong in 1997 [12], everyone in the world will be susceptible to infection.

During the initial years of a pandemic cycle, a large proportion of influenza-related deaths occur in persons ≤65 years old [2, 11, 12, 15, 19]. Moreover, schoolchildren are more commonly infected than are older adults, and schoolchildren are the most responsible for the spread of influenza throughout communities. Wherever crowding and multigenerational households are common, vaccination of schoolchildren can reduce influenza-associated morbidity and mortality in older adults [20]. Currently, influenza vaccination is recommended only for elderly people and younger persons with high-risk conditions [5, 10]. When faced with the threat of a pandemic, health officials in many countries will want to vaccinate large segments, if not most, of their populations.

**EPIDEMIOLOGY OF INFLUENZA VACCINATION IN INTERPANDEMIC YEARS**

The use of influenza vaccine in developed countries varies substantially (figure 1). In 2000, all of the 21 countries shown in figure 1 had age-based recommendations for vaccination of older persons, and most provided reimbursement for influenza vaccination of recommended groups through national or social health insurance. It is interesting to note, however, that variations in levels of vaccine use were not correlated with per capita levels of health care spending in these countries.

Influenza vaccination is no longer limited to the developed countries shown in figure 1 [10]. In the year 2000, >81 million doses were used in other countries (table 1). In central and eastern Europe, 26 million doses of vaccine were distributed, more than one-half of which were distributed in Russia. Argentina, Brazil, Chile, and Uruguay accounted for 93% of the almost 25 million doses used in Latin America. In the western Pacific, 78% of the doses distributed were used in Japan and the Republic of Korea. (Japan did not begin to vaccinate older people until 1998.) Overall, the global distribution of influenza vaccine reached almost 233 million doses. Countries other than those in western Europe, those in North America, Australia, and New Zealand accounted for 35% of all doses used.

**SOURCES OF INFLUENZA VACCINE SUPPLY IN INTERPANDEMIC YEARS**

In 2000, ~85% of the world’s supply of influenza vaccine was produced by 9 vaccine companies located in 9 countries: France, Germany, Italy, The Netherlands, Switzerland, the United Kingdom, the United States, Canada, and Australia. (The company in Switzerland subsequently ceased producing its own influenza vaccine, although it still packages and distributes imported vaccine.) Not surprisingly, there was substantial international trade in influenza vaccine. For example, in 2000, a total of 6 western European companies distributed 66 million doses of vaccine to 18 western European countries (table 1). Only 42% of these doses were distributed within the countries that produced them; the remaining 58% were exported to other western European countries. For the rest of the world, ~40% of the doses used in central and eastern Europe, 60% of the doses used in the western Pacific and Southeast Asia, and virtually 100% of the doses used in Latin America, the eastern Mediterranean, and Africa were imported from 1 or more of the 9 vaccine-producing developed countries.

**MARKET FOR INFLUENZA VACCINE IN INTERPANDEMIC YEARS**

Each year, vaccine companies sell their influenza vaccines through contracts with public health authorities or directly to distributors, institutions, employers, and physicians. Companies respond to a steady increase in market demand by increasing vaccine production. Once the threat of a pandemic appears, however, this traditional approach to meeting market demand will encounter serious difficulty.

Influenza vaccines sell for low prices and are often viewed as commodities by vaccine companies and health authorities alike. In addition, unlike the market for pediatric vaccines, it is difficult to estimate the future size of the market for influenza vaccine. Moreover, influenza vaccines have a shelf life of a few months, not a few years. Consequently, vaccine companies make conservative plans for what they will produce each year.
to avoid being caught with large stocks of unsold (and unsellable) vaccine. When there is a sudden increase in demand, companies may lack the capacity to respond quickly.

**INFLUENZA VACCINE FOR A PANDEMIC**

The trivalent influenza vaccines used in interpandemic years contain 15 μg of hemagglutinin (HA) antigen for each strain (total, 45 μg of HA) [5]. By comparison, a pandemic vaccine will almost certainly be monovalent. It could be provided as 1 full-strength (15 μg of HA) dose or as 2 half-strength (7.5 μg of HA) doses (a 3-for-1 scenario). If a future pandemic is due to a reemergent influenza A (H2-like) virus, more than one-half of the world’s population will probably need 2 doses. If the pandemic virus is entirely new, everyone may need 2 doses to ensure protection. Studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong unfortunately suggest that a dose >15 μg of HA or an adjuvanted vaccine may be required [21–24].

The 3-for-1 scenario mentioned above is hypothetical, but it illustrates how national health officials should begin thinking about their future needs for pandemic vaccine. For example, if a country is currently using 100 doses of trivalent vaccine per 1000 persons, it should automatically have 300 doses of monovalent pandemic vaccine (15 μg of HA) per 1000 persons (figure 2). If at least 1 dose of pandemic vaccine (or 2 doses of 7.5-μg HA vaccine) is to be provided to each person, the country will need to increase its level of use of trivalent vaccine from 100 to 333 doses per 1000 persons to make the switch to a pandemic vaccine. This is far beyond the level ever achieved by any country except Canada in 2000.

**LIMITATIONS OF TRADITIONAL MARKETS FOR SUPPLYING PANDEMIC VACCINE**

Currently, national health officials can attempt to secure a future supply of pandemic vaccine by negotiating long-term bilateral forward contracts with 1 or more vaccine company. In
Table 1. Global distribution of influenza vaccine in 2000.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (m)</th>
<th>Provided information on vaccine distribution, %</th>
<th>Doses of vaccine distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. of doses (%)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>387,182,000</td>
<td>100</td>
<td>65,972,000</td>
</tr>
<tr>
<td>North America</td>
<td>306,148,000</td>
<td>100</td>
<td>81,260,000</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>22,981,000</td>
<td>100</td>
<td>4,163,000</td>
</tr>
<tr>
<td>Subtotal</td>
<td>716,311,000 (12)</td>
<td>100</td>
<td>151,395,000 (65)</td>
</tr>
<tr>
<td>Central and eastern Europe</td>
<td>493,062,000</td>
<td>74</td>
<td>26,064,000</td>
</tr>
<tr>
<td>Latin America</td>
<td>522,353,000</td>
<td>84</td>
<td>24,991,000</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1,696,937,000</td>
<td>95</td>
<td>26,677,000</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1,555,081,000</td>
<td>83</td>
<td>64,000</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>518,602,000</td>
<td>73</td>
<td>998,000</td>
</tr>
<tr>
<td>Africa</td>
<td>672,175,000</td>
<td>23</td>
<td>2,409,000</td>
</tr>
<tr>
<td>Subtotal</td>
<td>5,457,210,000 (88)</td>
<td>78</td>
<td>81,203,000 (35)</td>
</tr>
<tr>
<td>World total</td>
<td>6,173,521,000 (100)</td>
<td>80</td>
<td>232,598,000 (100)</td>
</tr>
</tbody>
</table>

a Regions are those defined by the World Health Organization.
b Population data were obtained from the Division of Health Situation and Trend Assessment, World Health Organization [18].
c Data on vaccine distribution by all companies were gathered by Aventis Pasteur MSD and Aventis Pasteur.
d Excludes Australia and New Zealand.

Canada, health officials have negotiated a contract with their only domestic producer to provide 5 million doses of trivalent influenza vaccine each year for the next 10 years. Under a 3-for-1 scenario, this will be equivalent to 15 million doses of pandemic vaccine (15 µg of HA), or 1 dose for approximately one-half of Canada’s population. Health officials in other countries have tried to negotiate similar contracts without success. Once the threat of a pandemic appears, health officials in a large number of countries can be expected to urgently try to negotiate contracts for vaccine supply with several vaccine companies. As a result, several hundred simultaneous negotiations (or attempts at negotiations) will be initiated within a period of a few months. These efforts will be difficult and most likely chaotic. Moreover, they will almost certainly be compromised by the extreme political vulnerability of the vaccine companies themselves.

**POLITICAL VULNERABILITY OF VACCINE COMPANIES**

The history of swine influenza vaccination in the United States in 1976 illustrates the political dimension of pandemic vaccine supply [25–27]. In the previous year, American vaccine companies produced 25 million doses of trivalent influenza vaccine. Because a half-strength (7.5 µg of HA) dose of monovalent swine influenza vaccine was found to be sufficiently immunogenic for most adults, the vaccine companies theoretically had the capacity to produce 150 million doses of a monovalent pandemic vaccine (a 6-for-1 scenario). However, this would have been enough to vaccinate only 60% of the US population. For this and other reasons, American vaccine companies were not allowed to export swine influenza vaccine to other countries. This historical experience strongly influenced the recent Canadian decision to secure a supply of pandemic vaccine from Canada’s sole domestic producer. When the next threat of an influenza pandemic appears, political leaders in many, if not all, countries where influenza vaccines are produced can be expected to respond in similar fashion. Political leaders in countries without vaccine companies will not have this option.

**THE WORLD HEALTH ORGANIZATION (WHO) AND NATIONAL INFLUENZA PANDEMIC PREPAREDNESS PLANS**

The WHO’s Influenza Pandemic Preparedness Plan mentions several points to consider for vaccine production [28]. They include (1) reducing production time by preparing vaccine seeds and test reagents beforehand, adopting new production techniques, and encouraging streamlined central registration of pandemic vaccines; (2) planning for future emergencies (i.e., a pandemic) when negotiating interpandemic vaccine procurement contracts; and (3) exploring possibilities for a clearinghouse to balance purchases and supply. In suggesting what should be done, however, the WHO plan offers no guidance on how to do it.

Several countries have prepared or are preparing national
Figure 2. Anticipating the need for pandemic influenza vaccine according to a 3-for-1 scenario

plans for pandemics. A recent report from Europe indicates that several countries have already made arrangements for obtaining supplies of pandemic vaccine and defined target groups for vaccination (table 2) [29]. However, no details were provided on how many persons would be vaccinated or on how supplies of vaccine would be obtained.

ELEMENTS OF A NEW APPROACH TO PANDEMIC VACCINE SUPPLY: WHAT VACCINE COMPANIES CAN AND CANNOT DO

A new approach must be devised that guarantees that there will be an adequate supply of pandemic vaccine to meet the global demand. To some extent, the level of preparedness will depend on the level of vaccine use in interpandemic years. If the worldwide demand for influenza vaccine continues to grow, vaccine companies will increase production to meet this demand. Nonetheless, when the threat of a pandemic appears, not knowing the characteristics of the pandemic vaccine or how it will be produced and used will create uncertainty. Inevitable shortfalls in production capacity, the limitations of traditional markets, and the inability to anticipate global demand will be major problems. The political vulnerability of vaccine companies will add to the uncertainty.

If these obstacles are to be overcome, a new approach to planning the production and distribution of pandemic vaccine must be developed. Planning must be undertaken at the international as well as the national level. The details of this complex process need to be worked out, but its basic elements are already evident (table 3).

Preparing seed strains for pandemic vaccine production. The production of influenza vaccines begins with the preparation of reassortant seed strains by WHO Collaborating Centers. For trivalent vaccines, this process takes several months, and the growth characteristics of these seed strains cannot always be predicted. Moreover, viruses such as the avian influenza A (H5N1) virus cannot be grown in embryonated eggs; it took 18 months to find a related influenza A/Duck/Singapore/97 (H5N3) virus that would grow in eggs. Unfortunately, the yields were too low for commercial vaccine production [22, 23], and today there is no seed strain that could be used to produce an influenza A (H5N1) virus vaccine. In the face of a pandemic threat, a situation such as this will be unacceptable.

The reverse genetics of influenza viruses may provide a means for solving this problem [30]. The recently developed RNA polymerase I system for cloning cDNAs encoding all 8 segments of the influenza virus genome might be suitable for preparing nonpathogenic seed strains for producing inactivated and live-attenuated influenza virus vaccines. Vaccine companies currently do not use seed strains prepared by reverse genetics, nor are there compelling reasons for doing so; the time needed to prepare seed strains by using conventional reassortant techniques is generally sufficient to allow adequate quantities of vaccine to be produced for the market. When threat of a pandemic appears, a high growth seed strain must be rapidly obtained. Several factors, however, may impede the commercial use of reverse genetics–engineered seed strains. Some concern worker safety and animal health. Others relate not so much to the technique itself but to intellectual property rights. These critical issues must be resolved as quickly as possible. Moreover, companies and regulatory authorities must become familiar with the use of seed strains prepared by means of reverse genetics in interpandemic years. Given current uncertainties about the technique, waiting until the pandemic threat appears will simply be too late.

Characteristics of a pandemic vaccine and vaccination schedule. It is impossible to predict the dose (micrograms
Table 2. Planning for pandemic influenza in Europe, November 2000.

<table>
<thead>
<tr>
<th>Region, country</th>
<th>Pandemic plan accepted</th>
<th>Domestic influenza vaccine company</th>
<th>Arrangements made for vaccine supply during pandemic</th>
<th>Priority groups for vaccination identified</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>National</td>
<td>Regional</td>
<td></td>
<td></td>
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<tr>
<td>European Union</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria(^a)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Belgium</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Denmark</td>
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<td>—</td>
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<tr>
<td>France</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>Pending</td>
</tr>
<tr>
<td>Finland(^a)</td>
<td>—</td>
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<tr>
<td>Germany</td>
<td>Pending</td>
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<td>Yes</td>
<td>Pending</td>
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<tr>
<td>Greece(^a)</td>
<td>—</td>
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<tr>
<td>Ireland</td>
<td>Pending</td>
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<td>Pending</td>
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<tr>
<td>Italy</td>
<td>Pending</td>
<td>—</td>
<td>Yes</td>
<td>Pending</td>
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<tr>
<td>Luxembourg(^a)</td>
<td>—</td>
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<tr>
<td>The Netherlands</td>
<td>Pending</td>
<td>Pending</td>
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<td>Portugal</td>
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<td>—</td>
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<td>—</td>
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<td>United Kingdom</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>Iceland(^a)</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Norway(^a)</td>
<td>—</td>
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<tr>
<td>Switzerland</td>
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<tr>
<td>Future European Union(^b)</td>
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<td></td>
<td></td>
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<tr>
<td>Czech Republic</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Slovenia</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [30]. —, No or no information provided.

\(^a\) Not included in the survey.

\(^b\) Future European Union countries not included in the survey were Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, Bulgaria, Romania, and Turkey.
One objective of the trials will be to reduce scientific uncertainty about the characteristics of a future pandemic vaccine and vaccination schedule. The other equally important objective will be to give scientists, production staff, and business leaders in vaccine companies the practical experience they will need to deal with the problems they will face in producing pandemic vaccines.

Registering pandemic vaccines. Trivalent influenza vaccines are registered (i.e., licensed) in the countries or regions where they are produced. The registration criteria, however, for the major regulatory agencies differ. In western Europe, the European Medicines Evaluation Agency requires immunogenicity and safety trials for new influenza vaccines each year. In the United States and Australia, such trials are not required. As a result, the time needed to obtain regulatory approval varies considerably. Unless these different regulatory requirements can be modified and simplified, they will seriously impede the timely distribution of pandemic vaccines and prevent them from reaching countries whose needs are immediate. A common protocol for the rapid, global registration of pandemic vaccines produced in any licensed vaccine production facility is justified and should be considered. If the idea is accepted, the protocol must be negotiated in advance of the next pandemic.

Increasing interpandemic vaccination. An essential element for ensuring the adequate production and distribution of pandemic vaccine will be to increase the use of vaccine in the interpandemic period. Target groups for influenza vaccination have expanded recently in several countries. The most dramatic change occurred in the Canadian province of Ontario in 2000, where a decision was made to provide free influenza vaccine to anyone ≥6 months old. In describing this new program, the former chief medical officer for the province wrote, “With universal immunization, we will be better prepared for an influenza pandemic. We will have in place a vaccine pro-
curement and delivery system capable of immunizing the entire population quickly. This is exactly what we need for pandemic control” [37, p. 36].

The publication of the WHO position paper on influenza vaccines will have an important impact on countries that hitherto have paid little or no attention to influenza vaccination [38]. A simple and easily accessible system for documenting and updating vaccine recommendations in all countries could accelerate these changes. In addition, new recommendations will be adopted more readily wherever there is a better understanding of the health and economic burden of the disease. The health and economic benefits of influenza vaccination for older [5, 7] and younger [39, 40] adults have been demonstrated in a few developed countries. Similar studies are needed in other countries, including those in the developing world, because they will increase awareness of the societal value of influenza vaccination. The results should be especially important for health officials who are responsible for funding large public vaccination programs.

Epidemiology of influenza vaccination. Surveys in many developed countries routinely document vaccine coverage levels, but the results can seldom be directly compared because survey methods differ. A more convenient way to compare vaccination practices is to document the number of doses of vaccine distributed per 1000 total population in individual countries each year (figure 1) [9, 10]. This information constitutes the macroepidemiology of influenza vaccination. Publication of these comparative data has led to greater awareness of the shortcomings of influenza vaccination programs in low-use countries and has sometimes been followed by new initiatives to increase vaccine use.

For many years, gathering the data needed to determine country-specific levels of vaccine distribution has depended on individual investigators in each country [9]. The process has been slow, and the availability of the results is never up-to-date. Recently, the European Scientific Working Group on Influenza gathered vaccine distribution data for European countries directly from individual vaccine companies [10]. This promising initiative should be expanded to cover all countries of the world. The survey should be conducted each year for all countries in the Northern and Southern Hemispheres, and the results should be published immediately by the WHO on its Web site and in its periodicals for all to review.

Because comparisons of previous levels of influenza vaccine use in individual countries have been useful, similar comparisons of projected future vaccine needs should also be undertaken. Health officials in each country should be asked to prepare 5-year rolling forecasts of their estimated needs for interpandemic and pandemic vaccines [17]. This exercise should become an integral part of their ongoing national pandemic preparedness planning activities. Preparing these fore-
casts will force health officials to define explicitly what their target populations and coverage levels will be. The forecasts can then be reported to the WHO and published on its Web site. In this way, the sole responsibility for determining the global demand for influenza vaccine will rest squarely on the shoulders of health officials in each country. Vaccine companies will then be able to focus on the separate but formidable task of ensuring that the forecasted demands for interpandemic and pandemic vaccines are met.

**Political dimension of pandemic vaccine supply.** The foregoing issues are understood by most members of the scientific community involved with influenza. Their understanding, however, will have little impact unless it is communicated to business leaders in vaccine companies, national political leaders, and the leaders of international organizations.

Limitations in vaccine supply have become common. Vaccine companies are finding it difficult to absorb the development costs for new, molecularly defined vaccines while at the same time having to meet the demands of regulatory agencies and respond to the charges of antivaccine groups. In this complex business environment, company executives might be forgiven for ignoring a theoretical problem like pandemic influenza when other, real problems demand their attention every day. Unfortunately, the influenza virus will take no notice of these other, more immediate concerns.

The problem of pandemic vaccine supply has yet to register as an important issue for most national political leaders, in spite of the pandemic planning efforts of health officials in many countries. This situation may be changing, as indicated by the vigorous response of political leaders to potential bioterrorism threats, such as smallpox and anthrax [14]. More direct evidence that pandemic vaccine supply is beginning to receive political attention comes for the Europe. In November 2000, the European Commission held its first meeting on pandemic preparedness. In acknowledging that member states of the European Union were not prepared, the Commission noted that, “in the event of a pandemic, millions could die, economies will be affected and [medical and civil services] … could collapse. Members of the public will not excuse authorities, who will be held responsible for not having put in place up-to-date preparedness” [41]. In issuing its preliminary recommendations, the Commission called for a thorough review of existing and new vaccine production technologies and associated issues of intellectual property, the development of a broad agenda for vaccine and vaccination research, and accelerated centralized registration of pandemic vaccine. The Commission encouraged member states to “develop five-year forecasts for vaccine demand and communicate this information to all vaccine producers” [41]. It also urged “political leaders of the Member States to develop politically acceptable alternatives to ‘national strategies’ for vaccine production [in order to] … ensure eq-

The forecasted demands for interpandemic and pandemic vaccines will then be able to focus on the separate but formidable task of ensuring that the forecasted demands for interpandemic and pandemic vaccines are met.

The WHO will play a leading role in addressing the many issues that confront supply of pandemic vaccine. For the past 50 years, the WHO has successfully coordinated a global network for influenza virus surveillance and vaccine strain selection. With its new Global Agenda on Influenza, the WHO will now begin to address the health and economic burden of influenza, especially in developing and tropical countries, and to give attention to expanding recommendations for and the use of influenza vaccine in interpandemic years [42, 43]. For vaccination during pandemics, the WHO can be expected to help define the global vaccine production capacity, encourage clinical research on pandemic-like vaccines and vaccination schedules, and ensure timely registration of pandemic vaccines. The WHO leadership will also be needed in documenting the macroepidemiology of influenza vaccine use and will be essential for coordinating national forecasts of future vaccine demand.

Integrating national demand forecasts and vaccine production capacities may require a new set of international agreements and/or institutions. If necessary, a Global Influenza Vaccine Fund might be needed to facilitate multinational vaccine purchases and distribution, especially for countries with limited resources. As a last resort, a WHO Framework Convention for Influenza Pandemic Preparedness and Vaccine Supply could be negotiated [17]. On 24 May 2003, the World Health Assembly adopted a resolution that focuses attention on these issues (K. Stohr, personal communication, 26 May 2003).

**NEED FOR A GLOBAL RESPONSE TO THE CHALLENGE OF SUPPLY OF PANDEMIC VACCINE**

Public health officials, vaccine companies, and the international community of influenza scientists recognize the need to improve the prevention and control of influenza. Advances in basic influenza virology [44–46] and the molecular pathophysiology of influenza virus infection [47, 48] will be important. Improved virological surveillance and greater understanding of
the burden of disease and the benefits of vaccination will contribute to this effort. Nonetheless, threat of a pandemic will place unprecedented demands on health officials and vaccine companies. Failure to plan in advance an effective and equitable system for the global supply of pandemic vaccine is politically and morally unacceptable. The planning effort will be more than a matter for experts in the fields of influenza virology, surveillance, and epidemiology; it must also involve experts in international politics, economics, and law. At a time when the international dimensions of bioterrorism are forcing the leaders of many nations to plan a rapid and coordinated response to a potential threat, there are far more compelling reasons for them to plan a similar response to the undeniably real threat of pandemic influenza.

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