

SYMPOSIUM

The United States Vaccine Supply: Challenges in Preparing for an Avian Influenza Pandemic

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INTRODUCTION

Since influenza may be prevented by vaccine, development and successful implementation of public health programs to prevent spread of a potential avian influenza strain relies upon vaccination as a strategic cornerstone. Although both the Department of Health and Human Services (HHS)[†] and the World Health Organization (WHO) highlight the role of influenza vaccination as the core of an effective prevention and control strategy, should there be an avian influenza pandemic there is (at the time of this symposium) currently no available vaccine with demonstrated efficacy against the H5N1 strain. Indeed, the recent focus upon preparation for an avian influenza pandemic highlights many of the weaknesses that are generalizable to the entire vaccine development and supply system. This paper will provide general background on the fragility of the current vaccine development and production infrastructure in the United States and identify specific challenges for vaccine suppliers in preparing for a potential influenza pandemic.

VACCINE DEVELOPMENT AND PRODUCTION CONSIDERATIONS

Following the seminal 19th- and early 20th-century elaboration of microorganisms as the cause of infectious diseases, the middle of the 20th century witnessed a period of tremendous scientific breakthroughs in combatting infectious disease. The discoveries of penicillin and the sulfonamides to treat bacterial infections were paralleled by major breakthroughs in vaccines. The successful campaign to develop a polio vaccine is perhaps the best known of these, but effective vaccines against influenza, measles, mumps, rubella, yellow fever, and Japanese encephalitis also were developed two to three generations ago. At the time, there was a buoyant mood in the medical community that infectious diseases could be largely vanquished. In the late 1960s, U.S. Surgeon General William Stewart confidently declared “it was time to close the book on infectious disease” and move on to controlling chronic diseases [1]. At the Yale University School of Medicine itself, there was so much optimism over the apparent

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[†]Abbreviations: HHS, Department of Health and Human Services; MDCK, Maden-Darby canine kidney; NVIC, National Childhood Vaccine Injury Compensation; WHO, World Health Organization.

conquest of infectious disease that the faculty had decided to dispense with the study of infectious disease altogether [2].

A critical weapon in the pending victory over infectious disease was vaccine production. In 1967, there were 37 companies authorized to manufacture vaccines in the United States [3, 4]. The large number of manufacturers provided excess capacity, with some of the most common vaccines produced by several suppliers. However, by 2002, this number had fallen to 11. Presently, five companies manufacture all pediatric vaccines. Three of the 13 pediatric vaccines currently recommended in the United States are produced by sole suppliers. The public health consequences of the limited contingencies for supply became apparent during 2002 and 2004, when there were shortages of vaccines targeted against eight of the diseases recommended for vaccination, including diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, and pneumococcal infections. In 2004, following persistent shortages of the conjugate pneumococcal vaccine, the Center for Disease Control (CDC) took the extraordinary step of recommending vaccine rationing, suggesting that the third and fourth dosages of the normal four-dose regimen might be eliminated, in order to provide partial vaccine coverage to twice as many children [5]. Recent experience with the influenza vaccine also underscores the consequences of the limited national vaccine reserve capacity. In October 2004, at the beginning of what would normally have been the beginning of the annual U.S. influenza vaccine campaign, international news headlines informed the public that only one-half of the planned vaccine supply would be available: "U.S. flu vaccine supply halved: health officials face record shortage as Britain shuts down supplier [6]." At the time, almost the entire U.S. influenza vaccine supply was produced by two manufacturers, one of which was found by the British regulatory authority (U.K.

Medicines and Healthcare Products Regulatory Agency) to have quality control concerns requiring that the production plant be closed during the critical months for the influenza season. As a consequence of this shortage, the CDC again recommended rationing available vaccine by targeting immunization to groups at highest risk for serious influenza infections [7]. While the 2004 influenza vaccine shortage was well publicized, perhaps because of the concurrent concern about sudden acute respiratory syndrome (SARS) and the general public health anxiety about a global influenza pandemic, influenza vaccine shortages are not extraordinary. In fact, just one year before the 2004 episode, vaccine suppliers also had been unable to meet the anticipated demand [8].

Why is it that vaccines, which are certainly among the most important public health interventions of the last century, and whose successful implementation has rendered age-old scourges such as smallpox, diphtheria, tetanus, measles, and polio largely into vague topics of passing historical interest for most Americans, have fallen on such hard times? Why are there fewer manufacturers now than 40 years ago, and why, as public health officials look with trepidation at the prospect of an influenza pandemic, is there limited capacity in influenza vaccine production?

The explanation is multifactorial. Firstly, there has been consolidation within the industry. Nine companies are currently responsible for more than 85 percent of all vaccine dosages sold in the United States and Europe, as well for the majority of vaccine sales in the rest of the world [9]. Several of the largest manufacturers have absorbed other vaccine producers into much larger corporations. For example, Sanofi-Pasteur counts as its corporate ancestors the Pasteur, Merieux, and Connaught companies, each of which had at one time been an independent vaccine manufacturer. While the pharmaceutical industry is large, it is still considered by

economists to be largely fragmented, with the largest of companies controlling no more than 10 percent of global revenues. The major vaccine producers now reside within large global pharmaceutical companies, which, as private companies, are ultimately answerable to shareholders interested in returns on their investments. Within these companies, drug-related revenue dwarfs that of vaccines. It has been estimated that annual global sales of vaccines are approximately \$6.5 billion, which represents only about 2 percent of the global market for therapeutic drugs [4]. During the 1990s, with the rise of individual drugs generating more than \$1 billion in annual revenue, it has been argued that it was difficult for vaccine research and development to secure resources to commit to vaccine development in anything like the magnitude available for new drug development. Put another way, global sales of all vaccines produced in the world are less than that of the single largest-selling drug for hyperlipemia [10].

A critical feature differentiating the vaccine from the pharmaceutical marketplace is that more than one-half of all pediatric vaccine doses are purchased directly by the United States government [11]. This type of sole purchasing arrangement, or monopsony, creates an environment in which the purchaser is able to exert much greater pressure on purchasing price than is true for a typical competitive economic market. In fact, when the Institute of Medicine issued its report evaluating the weaknesses in vaccine research and development, it highlighted the dominance of government vaccine purchases as a key disincentive [11].

An additional reason for the decline in vaccine manufacturers has been concern about financial risk due to product liability. Following a 1974 case report of paralysis in a child who had received whole cell pertussis vaccine [12] (a component of the diphtheria, tetanus, pertussis, or DTP vaccine), tort litigation lawsuits against vaccine manufacturers began to appear, brought by

plaintiff's attorneys seeking redress for presumed vaccine-related adverse events. In 1978, there was a single product liability suit brought against DTP manufacturers. No doubt fueled in part by the media, which offered up such provocatively titled features as the documentary, "DTP Vaccine Roulette" [13], there was a rapid escalation in vaccine-related litigation during the following years; 255 diphtheria vaccine-related lawsuits were filed in 1986 alone. Concerns regarding legal exposure led both to vaccine price increases and to the departure of several of the DTP manufacturers. By 1984, spokesmen for Lederle, the sole remaining DTP supplier, indicated that its DTP-related legal liability exposure was more than 200 times greater than its annual sales of this vaccine [13]. As a consequence of what had become recognized as a vaccine availability crisis, congressional hearings were initiated, leading to passage of the National Childhood Vaccine Injury Compensation (NVIC) Act of 1986. This act, funded by excise taxes on covered pediatric vaccines, provides for persons claiming vaccine-related injury to seek and obtain redress for pre-specified injuries considered (by independent experts) to be plausibly linked, biologically and temporally, to administration of the vaccine. The NVIC program provides an alternative to tort litigation: claims are handled on a no-fault basis, with damages capped per incident. While plaintiffs may continue to seek compensation from manufacturers, they cannot do so without forgoing compensation that would have been offered by the NVIC program [14]. While the program has been considered a success, by providing just compensation to injured persons while limiting the liability exposure of manufacturers, health care providers, and institutions, it should be noted that only certain vaccines qualify for coverage. Until 2005, the influenza vaccine was not covered by the NVIC program, potentially creating a disincentive for developing innovative H5N1 vaccines [15].

In the past, the U.S. government has been actively involved in vaccine research and development, much of which was driven by the recognition that prevention of infectious diseases is valuable in ensuring a healthy military. The U.S. Army was the first army in the world to be immunized against smallpox [16]. Government supported research was wholly or partly responsible for development of vaccines against yellow fever, typhoid fever, and adenovirus, as well as the meningococcus C vaccine — the latter notable for being the first subunit vaccine. During World War II, the U.S. military was actively involved in supporting clinical trials of the first (whole virus) influenza vaccine formulation. Although there continues to be global government investment in vaccines, for humanitarian as well as military use, government-supported vaccine research now accounts for a modest financial role in vaccine research and development. Precise figures are difficult to obtain, but in 2002, total global vaccine research and development investment was estimated to be \$1.51 billion. Of this, approximately 90 percent came from the large vaccine manufacturers. Only \$40 million, or less than 3 percent of global investment in research and development, came from direct government support [9].

Additionally, new vaccines have become increasingly more technically challenging to develop. The earliest vaccines were crude preparations obtained from donor animals. Vaccinia to prevent smallpox, the progenitor of all modern vaccines, was, after all, derived from the lymph of cattle that had been infected with cowpox. A century after Jenner's work, the great breakthroughs in microbiology and infectious disease by Pasteur, Koch, and others led to development of vaccines utilizing antisera obtained from livestock that had been intentionally infected with organisms such as tetanus and diphtheria bacilli. Production of antisera was unregulated, and indeed so casual that livery men in the late 19th century used to bleed their horses

to supplement their income. In contrast, current technologies to develop and produce vaccines are very sophisticated and, in some cases, are on the leading edge of immunologic research (Figure 1) [17]. One example is the ongoing effort to develop an HIV vaccine. Among the strategies to develop a successful HIV-1 vaccine are approaches involving use of replication-defective viral vectors encoding HIV-1 consensus genetic sequences, direct inoculation of HIV-1 DNA (so-called "naked DNA"), and the recently completed (though unsuccessful) trial of the recombinant subunit gp120 capsular antigen [18].

Vaccines are typically derived from pathogenic organisms that have been modified (through processes such as attenuation, inactivation or isolation of antigenic components) so that they induce immunogenic responses but do not cause disease. To date, most vaccines have been developed for pediatric use (with influenza vaccine one of the exceptions). Unlike most pharmaceutical products, which are usually given to treat disease, vaccines are usually given to healthy individuals in order to prevent disease. These factors underlie the paramount public health imperative that vaccine development and production occur with careful regulatory oversight to ensure safety and efficacy. In fact, the genesis of the Hygienic Laboratory of the Public Health and Marine Hospital Service (which is the antecedent of the National Institutes of Health) occurred (Biologics Control Act, 1902), as the direct result of the tragic deaths of 13 children who had been treated for diphtheria with antisera later discovered to have been contaminated with tetanus bacilli. In the United States, the Center for Biologics Evaluation and Research is the division of the FDA responsible for evaluating and assuring the safety and efficacy of vaccines. Paradoxically, the success of vaccines in controlling and in some cases essentially eradicating several of the most deadly or disabling infectious diseases of

tean virus causing human disease. These negative-sense RNA viruses are categorized on the basis of core proteins into three types: A, B, and C. Of these, type A naturally infects a variety of avian and mammalian species (including humans), and is responsible for most human disease, while types B and C are practically restricted to human hosts. Types A and B are defined on the basis of the neuraminidase (NA) and hemagglutinin (HA) surface glycoproteins, which induce immunologic response and provide the basis for the current influenza vaccines. HA (16 subtypes identified to date) is involved in cell receptor binding and fusion, and NA (nine subtypes identified) has several functions, including viral transit, inhibition of viral aggregation, and cleavage of daughter virus from infected cells. Two major viral characteristics are responsible for the challenges for long lasting host control of infection and development of durable influenza vaccines. Like other RNA viruses, influenza viruses are characterized by an absence of effective viral polymerase-associated proofreading, which results in a large number of transcription errors, in turn leading to progeny virus having heterogeneous amino acid substitutions within the NA and HA glycoproteins. Occasionally, progeny virus with minor changes in NA and HA have attributes favoring selection and can successfully transmit and propagate in humans. These minor changes within an existing NA or HA subtype are termed antigenic drift [21] and have important consequences for human disease because hosts previously exposed or vaccinated to the ancestral subtype may incompletely recognize the epitopes of viruses that have undergone antigenic drift. Antigenic drift is responsible for annual influenza epidemics. Due to its segmented genome, influenza viruses may also exchange entire genes with influenza viruses of different subtypes. This phenomenon may also occur within intermediary hosts such

as domestic swine. When a reassortant influenza virus, composed of the dominant virus in circulation, but which encodes a heterologous HA or NA gene, establishes an ecologic niche in humans, this creates the potential for severe disease, as most human hosts have no preexisting immunity to the new HA or NA gene. This phenomenon, “antigenic shift” [22], is thought to occur approximately every three human generations and is responsible for pandemic influenza. A very small number of HA/NA influenza virus combinations have become established in human populations during the 20th century. Avian influenza (H5N1 subtype) is of particular concern because human populations are immunologically naïve to this virus.

Due to ongoing mutations and incomplete host response to influenza viruses that have undergone genetic drift, there is ongoing global surveillance of circulating human influenza viruses. This effort, coordinated by the World Health Organization (WHO), allows for the monitoring of influenza trends by surveillance conducted more than 80 countries. Participating centers collect specimens from patients having influenza-like illness. Viral isolates from those patients found to have culture-proven influenza are then sent to one of four WHO Collaborating Centres for antigenic and genetic analyses. Approximately 175,000 specimens are collected annually, and around 2,000 influenza isolates are identified and reviewed. In the United States, the WHO data, along with data collected from other organizations such as the FDA, the National Institutes of Health, the CDC, and the Department of Defense, are reviewed by the Vaccine and Related Biological Products Advisory Committee (VRBPAC). During January through March of each year, VRBPAC makes recommendations for influenza vaccine formulation, based upon its assessment of the most important emerging viral strains likely to cause disease during the coming influenza season. Influenza vaccine is typ-

ically prepared as a trivalent vaccine, incorporating antigens from two influenza A and one influenza B strain.

Approximately nine months are required between identification of the recommended influenza virus strains and vaccine availability for distribution. This short interval presents a vaccine production challenge for addressing annual epidemic influenza and may well be grossly inadequate for a pandemic influenza strain characterized by high virulence, accompanied by large-scale vaccine demand and complex distribution. Historically, influenza pandemics have typically spread with the speed of a “flash flood” [23]. As shown (Figure 2), during the past 50 years, influenza epidemics of particular concern have required several months before large-scale production begins, and maximum vaccine production has typically fallen short of demand. In 1976, although the rate of production was ultimately rapid, an interval of more than seven months occurred before production began. Public

health officials are concerned that an avian influenza pandemic might spread more rapidly than earlier pandemics, such as the 1918 pandemic, due to increases in human population density (including an increasing proportion of older persons and persons with medical comorbidities associated with increased risk of severe influenza), which favors high mortality and rapid transmission, and improvements in transportation systems, which facilitates rapid geographic spread of disease.

All current influenza vaccine commercial production requires growing influenza virus in embryonated hens’ eggs, a technology almost 70 years old. While this approach obviously requires large-scale egg availability, technical subtleties include the need for standardized egg sizes and shells to ensure efficient automated production and recognition that an individual egg can only grow a single influenza virus type. Due to the cost of maintaining large-scale contracts with egg suppliers, and the annual variation in demand for

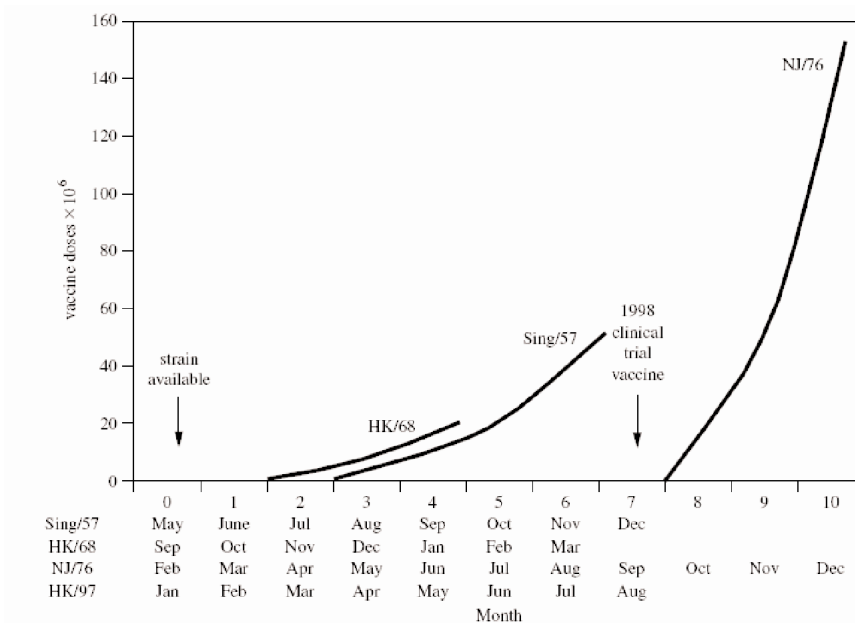


Figure 2. Influenza vaccine production during four pandemic/pandemic alert years, relative to date of strain availability. Reprinted with permission from Wood JM [24].

influenza vaccine, it has been advantageous to delay contracting with poultry farmers until as late as possible — which creates a challenge in addressing vaccine demand within the setting of a rapidly moving pandemic. Although initial influenza vaccines were formulated as whole-virus preparations, these were associated with increased reactogenicity and have been largely replaced by split or subunit vaccines, consisting of purified antigens. A live attenuated cold-adapted virus formulation (also using hens' eggs as growth substrate) recently has been approved, which, it is hoped, may offer greater immunogenicity than the inactivated formulations. It is important to note that vaccine production technology has improved substantially since the 1970s, when reassortant influenza vaccines (produced by selection of influenza strains optimized for cultivation, obtained from eggs coinfecting with target virus expressing appropriate HA and NA genes and high-yield master virus strains) were introduced. Reassortant technology was responsible for the rapid scale-up of production during the 1976 swine flu outbreak [25].

From a public health perspective, it would be ideal if manufacturers were able to provide a highly immunogenic vaccine optimally targeted against the dominant circulating H5N1 strain and for which vaccine production could be scaled up rapidly as needed (assuming vaccine was not already stockpiled). The complexity of assuring appropriate quantities of eggs currently represents a rate-limiting step in vaccine production. Use of mammalian cell culture as a viral substrate would, in principle, allow for high volume influenza vaccine production. To date, Vero cells and Maden-Darby canine kidney (MDCK) cells have been demonstrated to support growth of influenza virus, but neither is yet accepted by most regulatory authorities out of concern that the cells might contain some potentially injurious contaminant [26]. In fact, in 2003, global sur-

veillance indicated a shift in circulating influenza virus strains, and some argued to include antigen derived from the emerging Fujian (China) vaccine strain. The decision was made not to do so, precisely because the only available Fujian influenza virus strain had been grown in MDCK cell culture [27]. Several approaches have been proposed to enhance influenza vaccine immunogenicity, one of which involves “reverse genetics,” producing transfectant or recombinant influenza viruses [28]. It has been argued that this strategy would allow for rapid identification and production of codon-optimized strains that could serve as attenuated master seed strains for vaccine production. Webby et al. recently applied this approach to develop a candidate reference SARS virus (for vaccine production) within four weeks of initial virus isolation, utilizing Vero cells as substrate, and have proposed that this method could be used for production of H5N1 viruses [29]. At present, most regulatory authorities do not consider that they have sufficient information to assure the safety and efficacy of vaccines produced with the newer technologies and have not approved their use. Hence production continues to be reliant upon egg media as influenza viral growth substrate. An additional hurdle is intellectual property, as the newer technologies are typically associated with intellectual property rights, which represents another obstacle in making these technologies feasible for rapid deployment.

What preparations are being made on the federal level that affect vaccine manufacturing? In 2004, HHS issued a draft National Pandemic Influenza Preparedness Plan [30], which proposes a comprehensive public health strategy to prepare for and to control the impact of a potential influenza pandemic. This includes enhancement of surveillance capacity, stockpiling of antiviral drugs, and elaboration of a public health strategy aimed at disease control. Vaccines play a central role, and challenges in vac-

cine development, production, and distribution are explicitly discussed. From a manufacturing perspective, the plan recognizes the need to actively develop and assess candidate H5N1 strains as vaccine candidates, the potential value of tissue cultures to grow virus (and overcome the challenges with egg based media), and the promise of recombinant technologies to engineer influenza vaccine for maximal immunogenicity. It also recognizes the need for proper evaluation of these technologies before they can be utilized. Enhancing surveillance capability, particularly in countries where H5N1 has already appeared, holds the promise of earlier identification of a potentially pandemic virus strain, and hopefully, a shorter time to large-scale vaccine production. In May 2004, HHS funded two manufacturers, Sanofi-Pasteur and Chiron Corporation, to manufacture candidate H5N1 vaccines for testing [31]. Initial immunogenicity studies are ongoing, with hopes that the vaccine will both be immunogenic in low doses and require just a single dose (so that the supply can be stretched and to ease strains on the health care infrastructure). Plans are under way to stockpile millions of doses [32]. Hopefully, too, stockpiled vaccine will remain highly immunogenic against an emergent pandemic strain that may be, due to genetic drift, somewhat distinct from the H5N1 strain used to prepare the stockpiled vaccine.

The HHS plan is reassuring in that it recognizes the unprecedented need for vaccine in the event that an avian influenza pandemic appears imminent, and the efforts being made to facilitate more efficient vaccine development and production. However, the plan expects that vaccine demand will at least initially exceed supply. Challenges remain. As for the coming influenza season, which is expected to continue to be dominated by a non-pandemic H3N2 strain, the CDC has recently issued guidance on prioritization of vaccine based on the recognition that there have been vaccine shortages for three of the past five years and that it is

uncertain whether vaccine supply will be sufficient for the current year [33].

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