The Precautionary Principle and Emerging Biological Risks: Lessons from Swine Flu and HIV in Blood Products

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SYNOPSIS

Two examples—the "swine flu affair" in 1976 and the emergence of HIV in the blood supply in the early 1980s—illustrate the difficulties of decision-making in public health. Both cases illustrate trade-offs between product risks and public health benefits, especially with regard to uncertainty in estimates of product risks, public health risks, and the benefits of prevention. The cases also illustrate the tendency of public health policy makers to go all the way or do nothing at all, rather than consider intermediate options that can be adapted as new information emerges. This review suggests three lessons for public health policy makers: (1) be open and honest about scientific uncertainty; (2) communicate with the public, even when the facts are not clear; and (3) consider intermediate, adaptable policy options, such as obtaining more information, thus reducing uncertainty, and building in decision points to reconsider initial policies. Underlying all of these lessons is the need to commission studies to resolve important uncertainties and increase the information base for public communication, and to review regulations and other policy options in the light of the new data that emerge.

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As new cases and further information about anthrax cases emerged in the United States in the autumn of 2001, public health officials struggled to inform the public and to make recommendations for individuals and the general public about testing, treatment, and prevention. These decisions involved weighing risks and benefits to different people, and had to be made under considerable scientific uncertainty. But such situations are common in medicine and public health. For example, less urgent but equally difficult policy decisions are regularly made by public health agencies about the use of childhood vaccines that prevent many cases of serious diseases, but may cause some harm to a few children.

Each of these situations offers historical lessons that can guide and improve current public health policy-making under uncertainty. In this article I use two examples—the "swine flu affair" in 1976 and the emergence of HIV in the blood supply in the early 1980s—to illustrate the difficulties of decision-making in public health, and the application of the precautionary principle. Both examples involve biological products (the development and use of a new influenza vaccine in the first case, the regulation of whole blood and plasma products in the second) that are subject to oversight by the U.S. Public Health Service (PHS) and especially the interplay between the Centers for Disease Prevention and Control (CDC) and the Food and Drug Administration (FDA). They thus offer insights that illustrate current issues in vaccine safety and bioterrorism.

Both cases also illustrate trade-offs between product risks and public health benefits, especially with regard to uncertainty in estimates of product risks, public health risks, and the benefits of prevention, and the impact of that uncertainty on policy decisions. In both cases, uncertainties regarding the risk of an infectious disease were seriously understated. The cases also illustrate the tendency of public health policy makers to go all the way or do nothing at all, rather than consider intermediate options that can be adapted as new information emerges. Following the presentation of the cases, I argue that the precautionary principle offers a helpful approach to avoid both kinds of problems.

The cases are both based on published accounts that resulted from efforts by the Department of Health and Human Services (DHHS)—formerly the Department of Health Education and Welfare (HEW)—to look back and learn from what happened. The first example is based on *The Swine Flu Affair*, a report commissioned by the HEW Secretary and prepared by Richard Neustadt and Harvey Fineberg of Harvard University.[1] The second is based on *HIV and the Blood Supply*, a report from the Institute of Medicine.[2] Each case is far more complex than can be related here, so I have focused on aspects that best illustrate the use of the precautionary principle.

THE SWINE FLU AFFAIR

Influenza epidemics are common winter occurrences, but the swine flu pandemic of 1918, which was responsible for 20 million deaths worldwide including 500,000 in the United States, has never been rivaled in terms of numbers affected or severity. Information available in the winter of 1976, however, suggested that a 1918-like outbreak could occur the following year.

Part of the evidence was epidemiological. On February 13, 1976, health officials in New Jersey reported four cases, including one death, among new recruits training at Fort Dix. An investigation indicated the cause was not the Victoria strain that was predominant that season. Two additional factors heightened the concern. First, the outbreak occurred in healthy young men. Second, the subsequent antibody testing not only suggested an antigenic similarity between the responsible strain and the virus responsible for the 1918 pandemic, but also an antigenic shift in the virus—meaning that few would be immune based on past exposure.

The second part of the evidence was theoretical. On February 13, the *New York Times* published an op-ed piece by Dr. Edwin Kilbourne, a highly respected virologist, about a 10 to 11 year cycle of antigenic shifts and resulting pandemics. Since the last antigenic shift, which resulted in a major influenza outbreak, was in 1968, Kilbourne warned of an "imminent national disaster." Another theory suggested that the next pandemic would be swine flu. Since so few people would have natural immunity to the virus that caused the 1918 pandemic and the population had grown, epidemiologists estimated up to a million deaths in the U.S. if a similar strain were to reemerge.

The CDC responded promptly. On February 14, Director David Sencer called a meeting that included representatives from the FDA, the National Institute of Allergy and Infectious Diseases (NIAID), the Army, the New Jersey Department of Public Health (NJ DPH), and Dr. Kilbourne. The participants decided to set up special surveillance systems, including active surveillance and intensive retrospective antibody testing at Fort Dix; active surveillance of the surrounding area by the NJ DPH; and stepped-up national surveillance by NIAID. On February 19, fearful of leaks, the CDC called a press conference to inform the public about

these developments. The *New York Times* reported, ". . . the virus that caused the greatest world epidemic of influenza in modern history . . . may have returned."

In the following month, no new swine flu cases were found in New Jersey, the U.S., or the rest of the world. The lack of new reports could have been due to the return of warm weather in what had been an exceptionally cold winter. Tests on soldiers at Fort Dix who had been sick in January, however, identified nine additional cases of swine flu, all the result of human-to-human contact.

On March 10, there was a meeting of the federal Advisory Committee on Immunization Practices (ACIP), which advises the government and manufacturers on vaccine issues, including the composition of the vaccine for the next flu season. Since vaccine production takes many months, an immediate decision had to be made to prepare swine flu vaccine for the 1976–1977 season if it was to be useful at all. The meeting focused on two options: do nothing, or implement a national immunization campaign. The first was quickly rejected since officials felt that the public would demand action if they knew any risk existed. Since the possibility of a major outbreak could not be dismissed, several participants felt that an extraordinary federal response was required. Some recognized, on the other hand, that the epidemic may not materialize, and that public health officials would look foolish if it did not. They also knew that a decision to mount a national campaign would divert resources from other programs and could lead to possibly serious side effects.

Epidemiologist Reuel Stallones summed up the analysis as follows: "First, there was evidence of a new strain with man-to-man transmission. Second, always before when a new strain was found there was a subsequent pandemic. And third, for the first time, there was both knowledge and the time to provide for mass immunization." So, "if we believe in preventive medicine we have no choice." Or according to Dr. Kilbourne, "Better to vaccinate without an epidemic than an epidemic without a vaccine."

Immediately following the meeting, CDC Director Sencer and others recommended to HEW Secretary David Mathews, and subsequently to President Gerald Ford, that a national immunization campaign be mounted. Because it was thought necessary to "sell" the program to policy makers and the public, the presentation de-emphasized uncertainty about the course of the epidemic. It focused on the possible consequences, using the 1918 flu as a vivid metaphor, rather than the level of risk, which was hard to grasp.

On March 24, President Ford convened a group of respected scientists at the White House to advise him about the PHS plan. Drs. Jonas Salk and Albert Sabin, famous to the public as developers of rival polio vaccines and known in the scientific community as adversaries on most scientific issues, both agreed on the need for a national campaign. Ford asked if there were any dissenting voices, but heard none.

With President Ford's backing, the CDC mounted a $135 million campaign to "inoculate every man, woman, and child in the United States" for swine flu by the start of the next flu season. Shortly after vaccine administration began in the autumn of 1976, serious adverse events attributed to the new vaccine began to emerge. The immunization campaign was suspended on December 16, after more than 40 million were immunized, and since there were no cases of swine flu during that time, the program was never restarted.

One lesson of this case is the importance of probing assumptions and exploring uncertainty. When asked later by researchers, members of the ACIP gave estimates of the likelihood of a new swine flu pandemic ranging from 2% to 20%, but these estimates were not part of the decision process in 1976. If HEW Secretary Matthews and President Ford knew about these estimates they may not have felt so strongly about a national program. Similarly, the decision process conflated the risk of antigenic shift and the resulting severity. Those scientists who felt that the risk of antigenic shift was high did not necessarily believe that it would be as severe.

Writing about this case from a historical perspective, Harvard professors Richard Neustadt and Earnest May[3] have noted that at the March 10, 1976 ACIP meeting, Russell Alexander, a University of Washington epidemiologist, had raised a simple question—what information would make this committee change its mind about the need to prepare to immunize the nation against swine flu? What if every swine flu case was mild? Or that no one but the soldiers at Fort Dix got swine flu? Would the timing or where they occurred make a difference? Pursuing these questions would have led to a deeper exploration of the tradeoffs between vaccine side effects and the flu, the considerations of the virulence and contagiousness of the strain, the distinction between severity and rapidity of spread, the programming and scheduled review, and the questions about stockpiling.

The second lesson is to communicate with the public, even when the facts are not clear. The governmental decision process and the resulting national immunization campaign systematically downplayed uncertainty regarding the risk of a recurrence of a major epidemic as well as the side effects of the vaccine.

When the swine flu failed to appear, the credibility of all of the government officials, from the CDC up to President Ford, was diminished. This loss of credibility cost public health officials dearly in the autumn when problems with the vaccine emerged, and a decade later, when the CDC's first warnings about HIV in the blood supply went unheeded.

The third lesson is to consider a full-range of alternatives, including intermediate and adaptive ones. For instance, although Alexander had identified stockpiling as an option at the March 10 meeting, it was not given serious consideration. Under this option, the vaccine would have been manufactured as quickly as possible, but not deployed unless, and until, epidemiological findings demonstrated its need. This approach offered the benefits of vaccine availability if needed, while minimizing the risks associated with immunizing millions of individuals. It seems to have been rejected for three reasons: the assumption that there was not enough time to get everyone immunized after an outbreak was detected, that it was not the ACIP's role to design administrative machinery, and the perception that anything less than a national immunization campaign would appear to the public like the government did nothing if there were a pandemic.

HIV AND THE BLOOD SUPPLY

Two decades into the HIV and AIDS epidemic, so much is known about the epidemiology of the disease that it is now difficult to appreciate the debates about appropriate control measures in the first years after its emergence. However, between the first case report in 1981 and the development of the first serum test for HIV in 1985, much more was unknown than known, and policy-making was extremely difficult. Much of the policy-making at this stage concerned the safety of the blood supply, which includes both whole blood and its components and products derived from blood plasma, such as antihemophilic factor (AHF) concentrate for the treatment of hemophilia.

The first cases of unusual immune-suppressive disorders—pneumocystis pneumonia and Kaposi's sarcoma—in homosexual men were reported in the early summer of 1981. In 1982, the first cases of what would later be named acquired immunodeficiency syndrome were reported in IV drug users in June and in hemophiliac patients in July. Based on these risk groups, epidemiologists noted a similarity to the transmission patterns of hepatitis B, but this was considered speculative. The evidence became stronger, however, when the first case of AIDS, diagnosed in an infant who had received a blood transfusion, was reported in December 1982.

Convinced that the available epidemiological evidence strongly suggested that blood and blood products transmitted AIDS, the CDC called a public meeting on January 4, 1983 to identify opportunities to prevent the disease. The major Public Health Service agencies, especially the FDA, were represented as well as the Red Cross and the blood services industry. However, without a test for HIV, or even the knowledge that AIDS was caused by a virus, the possibilities were limited. Heat treatments to inactivate the virus in plasma were under development, but not yet available. CDC epidemiologists made two suggestions for immediate action: blood banks should question donors directly about their sexual behavior, and not accept blood from homosexuals; and blood collection agencies should run donated blood through a series of surrogate marker tests, including hepatitis B core antibody, a test for exposure to hepatitis B. These options were not well received.

Gay activists saw the questioning of blood donors about their sexual behavior as discriminatory. Blood banks, concerned that it might drive donors away, felt it was inappropriate. As a compromise, the plasma industry recommended donor education and self-deferral programs for high-risk groups. The PHS recommendations issued in March 1983 essentially took this approach, recommending that members of groups at increased risk for AIDS should not donate plasma and/or blood products.

The CDC's surrogate marker test recommendation was based on an 88% "correlation" between hepatitis B core antibody and AIDS in one small study. The plasma industry recommended against surrogate testing until its feasibility was assessed, and the March 1983 PHS recommendations called for studies to evaluate screening procedures, including lab tests and physical exams. Later that year, there were attempts to reformulate policies at meetings of the FDA's Blood Products Advisory Committee (BPAC). In each case, evidence about the risk of AIDS was downplayed by the blood products industry, and estimates about the substantial costs of safeguards were accepted uncritically.

In June 1983, representatives of the plasma industry stated that the risk of AIDS appeared to be one per million patients transfused, and thus concluded that donation deferral programs would not increase safety, but would seriously disrupt the nation's blood supply. No analysis was offered to support either claim (the risk of AIDS or the impact on the blood supply.)

In July, the BPAC considered the issue of contaminated plasma lots. Because plasma from many donors is pooled in the manufacturing process, there was concern that if even one donor were found to have AIDS

the entire lot in which his or her serum was mixed would be contaminated. After reviewing the issue, the BPAC decided to withdraw lots of AHF concentrate on a case-by-case basis, and only if there was good evidence that infected plasma was present in the lot. This decision reflected the concerns of the blood industry representatives on the BPAC about the supply of AHF concentrate as well as their skepticism that blood products transmitted AIDS.

In December, the BPAC reviewed the use of surrogate marker tests, such as hepatitis B core antibody, to identify donors who might be at risk for AIDS. Blood industry representatives argued that the use of an imprecise test would eliminate non-infected donors and threaten the blood supply. Moreover, they said that such a test cannot differentiate high-risk donors from other homosexual men, and would defer too many Asians and others from areas with a high prevalence of hepatitis B. As a result of these discussions, surrogate marker tests were not recommended.

Beyond public health interventions to protect the blood supply, patient groups and physicians who treated individuals with hemophilia tried to address the possibility that products used for treatment could be contaminated. AHF concentrate—derived from the pooled plasma of many individuals—was seen as particularly risky. In January 1983, in response to the CDC's recommendations, the National Hemophilia Foundation (NHF) recommended the use of cryoprecipitate (an older and less potent product, not based on pooled plasma) rather than AHF concentrate in infants, newly diagnosed hemophilia patients, and mild cases. The NHF found insufficient evidence to develop specific recommendations about blood product use in the treatment of severe hemophilia, and offered no advice regarding prophylactic use of AHF concentrate or safe sex. Moreover, their advice was given to physicians rather than patients, and few patients were made aware of the risks associated with products to treat hemophilia.

The Institute of Medicine report on AIDS in the blood supply found that this approach was driven by physicians' high regard for the efficacy of AHF concentrate for treating a devastating disease (hemophilia), as well as skepticism that AIDS was transmitted through blood products. Rather than inform patients about risks and benefits, however uncertain, physicians tended to decide what they thought was best for their patients and not burden them with difficult decisions about treatment options.

When making decisions about protecting the blood supply and in treating individual patients, physicians and public health officials, with firm knowledge about the benefits of blood and blood products for many, were quick to dismiss soft evidence that these products carried the risk of AIDS. Thus, as we now know, an opportunity to prevent thousands of HIV infections was lost.

The lessons from this case are similar to those from swine flu. First, it is important to probe assumptions and explore the consequences of uncertainty. Decisions were made on the basis of rather weak evidence—suggesting AIDS was a blood-borne disease—and the uncertain estimates of the risk per transfusion or use of blood product, the performance of available screening methods, the impact of screening on the amount of blood and blood products available, and the availability of alternatives for blood and blood products. If efforts were made in 1983 to clear up some of these uncertainties, better decisions might have been possible by the end of that year. For example, studies could have been commissioned on the risk of AIDS associated with blood product use, or on the impact of proposed control strategies on the availability of blood products.

Second, it is crucial to speak honestly about uncertainty, so that individuals can make their own informed decisions. If physicians, patient advocates, and health officials spoke openly to hemophiliacs in 1983 about the potential that AHF concentrate might cause AIDS, some patients would have reduced its use and lives would have been saved. In addition, the credibility of the public and private organizations that we rely on to serve the public interest would have been better preserved.

Third, we must consider intermediate options, such as implementing self-deferral and studying its impact on blood supply, warning people with hemophilia of the risks to themselves and sexual partners, involving patients in decisions about their own care and behavior, and stopping prophylactic use of AHF concentrate. It is impossible to know how much of a difference any of these options would have made, but they certainly would have improved the outcome at least marginally.

THE PRECAUTIONARY PRINCIPLE

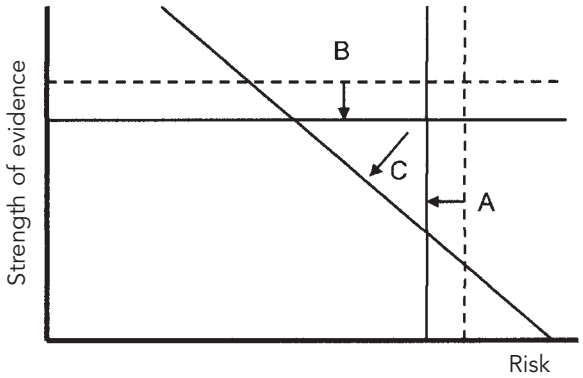
The precautionary principle has many different definitions, but most incorporate three general ideas. First, considerations of public health and the environment should have priority over economic gain. This typically involves increasing public participation in decision-making to counterbalance industry. Second, there should be consideration of the appropriate burden of proof for maintaining the status quo and for making

changes. And third, there needs to be explicit recognition of scientific uncertainty in policy-making.

The standard approach to risk management can be described schematically (see Figure). Some regulatory processes focus on quantitative estimates of the level of risk, represented in the Figure by the horizontal axis. For example, if the expected number of fatalities exceeds one per million people exposed, a product or activity is restricted.[4] Other regulatory agencies focus on the strength of the evidence (the vertical axis in the Figure) rather than the magnitude of risk, such as if a food additive is shown, according to accepted scientific standards, to cause cancer, the Delaney Cause prohibits it, regardless of the magnitude of the risk.[5]

On the other hand, the precautionary principle recognizes uncertainty in both risk estimates and the science that establishes cause and effect relationships. As illustrated in the Figure, the precautionary principle attempts to give the "benefit of the doubt" to public health concerns by lowering the thresholds for regulation. This is in recognition of the difficulty of making precise risk estimates and of establishing causal relationships. The diagonal line represents another aspect of decision-making that is sometimes incorporated into the precautionary principle: When the apparent risk is high, the standard of scientific proof should be lower.

Figure. Approaches to risk management



Standard regulatory risk management models are formulated in terms of the estimated magnitude of risk (horizontal axis) or the strength of the evidence (vertical axis). The precautionary principle can be interpreted as lowering the threshold for decision-making in terms of risk (A), strength of evidence (B), or when the apparent risk is high, the standard of scientific proof should be lower (C).

In the health and environmental issues where the precautionary principle is most commonly applied, public health concerns are usually clear and often in opposition to the concerns of industry. However, in the emerging infections examples examined in this article, there are public health concerns on both sides of the decision. In the swine flu affair, the trade-off was between the risk of a pandemic and the risk of side effects (among other costs) of a national immunization campaign. In the HIV case, the blood products industry had legitimate (although uncritically examined) concerns about the availability of essential blood and blood products.

The European Union (EU) has recently published guidelines for application of the precautionary principle that aid in its interpretation.[6] One guideline is that regulatory actions should be "proportional to the chosen level of protection." For instance, zero risk is generally not thought to be achievable, so decision makers are urged to adopt the least restrictive option that meets public health needs. For example, with regard to HIV and the blood supply, the precautionary principle would favor warning hemophiliacs of risks to themselves and sexual partners, and involving patients in decision-making about their own care and behavior.

Another EU guideline is that regulatory actions should be "based on examination of the potential benefits and costs of action or lack of action." This includes the use of economic cost-benefit analysis where appropriate and feasible, and consideration of social concerns such as distributional effects (consideration of who bears the costs and gains the benefits, as they are often different), ethical obligations, and institutional credibility. With respect to HIV and the blood supply, this might mean balancing a potential reduction in the risk of AIDS against a potential problem with the availability of blood products. The guidelines also state that considerations of public health should have priority over economic gain.

The EU also recommends that regulations be "subject to review in the light of new data" and "capable of assigning responsibility for producing the scientific evidence for risk assessment." Russell Alexander's option for swine flu—stockpiling the vaccine for use when and if necessary—illustrates these guidelines. In the case of HIV and the blood supply, these guidelines would call for reconsideration of the risk of AIDS associated with various products, their uses, and the impact of screening alternatives on that risk and the availability of blood and blood products.

CONCLUSION

The two cases considered in this article and the precautionary principle suggest important lessons for public health policy makers dealing with biological risks:

- Be open and honest about scientific uncertainty in both risk estimates and the science that establishes cost and effect relationship on which policy is based. In particular, do not allow firm knowledge of a small cost or drawback to overwhelm soft evidence of a major risk.
- Communicate with the public. Policy makers sometimes are uncomfortable doing this when the facts are not clear, but it is precisely in this situation when good communication is most necessary. Such communication, especially if coupled with an honest representation of the uncertainty, is important for maintaining credibility.
- Consider intermediate, adaptable policy options. Adaptable policy options include a process for obtaining more information, thus reducing uncertainty, and building in decision points to reconsider initial policies.

Underlying all of these lessons is the need to commission studies to resolve the important uncertainties, and review regulations and other policy options in light of new data that emerges.

The Institute of Medicine, a component of the National Academy of Sciences, is moving in this direction in its current Immunization Safety Review project.[7] In contrast to a series of congressionally mandated studies—which reviewed only the evidence of adverse effects of immunizations—in the early 1990s, the current committee is explicitly charged with examining "the significance of the issue in a broader societal context." The committee's first report, which addresses concerns about a possible relationship between measles-mumps-rubella (MMR) vaccine and autism, found the available evidence to be lacking, and proposed specific targeted research efforts and more rigorous data-gathering procedures to give scientists a firmer understanding of MMR vaccination and any possible side effects.

Current public health debates arising from concerns about bioterrorism could also benefit from analyses incorporating the precautionary principle. Decisions regarding the post-exposure use of anthrax vaccine, prophylactic use of smallpox vaccine, and the stockpiling of both vaccines, parallel the swine flu case. In both cases, the benefits are uncertain due to the likelihood of an intentional release, as well as the concerns about efficacy and the serious concerns about side effects. During the anthrax attack in the autumn of 2001, policy makers' credibility was undermined by seemingly definitive statements, which later proved false. For example, on the day the CDC confirmed the first anthrax case, DHHS Secretary Tommy G. Thompson announced that the case appeared to be an isolated incident.[8] Much is simply not known about bioterrorist agents and methods for treatment and prevention, so confusion is to be expected during an attack. However, health officials must be honest and open about this uncertainty and engage in a public discussion about the appropriate range of options. They must also be open to plans to stockpile vaccines, identify and analyze outbreaks as early as possible, immunize population groups according to the unfolding evidence and a well defined plan, and monitor the impact of interventions and update plans.

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