

## CASTING A WIDER NET FOR COUNTERMEASURE R&D FUNDING DECISIONS

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Among potential bioweapons attacks, endemic infectious diseases (that is, those naturally occurring diseases that afflict us every year), and a potential influenza pandemic, how should we apportion funding and resources for basic research and countermeasure development? To address this question, I argue for a “combined risk assessment” that considers bioweapons attacks with natural pandemics and endemic infectious disease. At present, risk assessments for bioweapons attacks are carried out separately from the assessments long carried out for endemic infectious diseases to make public health and medical care decisions. One result of this separation is that funding decisions may be unduly influenced by an overblown fear of a big bioweapons attack and by political whim. The result of the simplified combined risk assessment presented here argues for more funding and resources for endemic infectious disease and for placing biodefense against anthrax and other bioweapons in a place lower in the risk hierarchy. Since the assessment here considers only fatalities to make the point that our priorities are skewed, the conclusions are only a “first word” on the subject, far from the last. Furthermore, the impact of other issues on priorities, such as national and international policy, is not considered. It is a call for a debate on the public stage of the policy and other rationale and the quantitative risk assessment arguments that now place bioweapons attacks at the top of our risk ranking.

LET’S DIVIDE the infectious disease world into three arbitrary categories: (1) potential bioweapons attacks; (2) a potential influenza pandemic; and (3) endemic infectious diseases, which comprise a very long list, including the common flu for which many of us receive yearly vaccinations, HIV/AIDS, tuberculosis, and staph infections. Bioweapons attacks and pandemics are potential threats, ones that we don’t expect to occur in most years. Pandemics and endemic infectious diseases as defined here result from natural causes and are a focus of traditional medicine and public health.

Among bioweapons attacks and natural infectious diseases and pandemics, how should we apportion funding for

research and countermeasure development? To keep the analysis simple, I consider only mortality (fatalities) and ignore completely morbidity and the myriad direct and indirect costs associated with all disease. Thus, conclusions are tentative and are meant only to elicit much needed *quantitative* risk-assessment discussion on funding and resource priorities.

### COMBINED RISK ASSESSMENT

The idea behind the analysis is to consider bioweapons attacks with natural pandemics and endemic infectious dis-

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ease, hereafter called a “combined risk assessment.” The difference between present practice and combined risk assessment is as follows: If  $a, b, c$  represent different bioweapons attacks and  $1, 2, 3, 4, 5, 6$  represent different endemic infectious diseases, and  $P$  represents pandemic influenza, present practice would generate an ordered list of relative risk for each: for example,  $b, c, a$  and  $3, 2, 6, 4, 1, 5$  with  $P$  sitting alone. When grouped together in a combined risk assessment, we end up with a single ordered ranking of risks from the greatest to the least:  $P, 3, 2, 6, b, 4, c, a, 1, 5$ . It is no accident that I placed  $P$  at the head of this fictional relative risk list (see below).

Combined risk assessment should allow us to make better funding decisions that are less dependent on political whim. The analysis is U.S.-centered because it is U.S. policy, which focuses on bioweapons attacks, that is being addressed.

## INCIDENCE AND MORTALITY OF INFECTIOUS DISEASE

In Table 1, the yearly incidence and mortality of selected naturally occurring infectious diseases are presented. For comparison, the table also includes the natural occurrence of diseases from bioweapons agents. Table 1 demonstrates that bioweapons agents are no natural public health threat in the U.S. They may become a threat only if intentionally or accidentally introduced. In contrast, the “selected other

pathogens” in the table occur with certainty each year, and they cause a significant number of deaths.

## WHAT IS THE RISK OF A BIOWEAPONS ATTACK?

A major difference between endemic infectious disease and bioweapons attacks and pandemic flu is that the former occurs with yearly probability ( $= 1.0$ ) and the latter two are only possibilities with unknown yearly probability ( $= p$ ). A complete risk assessment would include both the likelihood of an attack and its consequences and may be expressed as:

$$\text{risk} = \text{likelihood} \times \text{consequences}$$

Importantly, likelihood expressed as probability of occurrence has a directly proportional influence on risk. One way to assess the risks of bioweapons is to compare them with each other. In the simplified analysis here, the only consequence considered is fatality.

An example: For a bioweapons attack with 30,000 fatalities and a guessed-at 0.03 probability of occurrence each year, the *expected number* of fatalities in any year would be  $0.03 \times 30,000 = 900$ . These expected fatalities, weighted for probability of occurrence or likelihood, I call probability-weighted or likelihood-adjusted fatalities. In comparison, there will be about 36,000 deaths from garden-variety

Table 1. Natural incidence of and fatalities from infectious diseases caused by bioweapons agents compared with those caused by some other pathogens. The numbers are for recent years.

<i>Infectious Disease Agent</i>	<i>Average U.S. Cases per Year</i>	<i>Average U.S. Deaths per Year</i>
<b>Bioweapons agents</b>		
Tularemia	122	0
Anthrax	3	0
Plague	5	0
Glanders	0	0
Melioidosis	0	0
Brucellosis	2	0
<b>Other selected pathogens</b>		
Influenza	30,000,000	36,000
HIV/AIDS	44,108	18,000
Staph aureus (MRSA)	300,000	12,000
Tuberculosis	14,517	662
Salmonellosis	42,197	
Pertussis	25,827	
Syphilis	33,401	
Gonorrhea	330,132	
Chlamydia	929,462	

Sources: References 1–5.

flu (Table 1) each year with probability = 1.0, so the likelihood-adjusted fatalities are  $1.0 \times 36,000 = 36,000$ .

There is no way to know the yearly probability of a particular bioweapons attack, but reasonable bounds can be established as a first step toward making a crude estimate of probability—fortunately, good enough to draw qualitative conclusions. The number of fatalities in a bioweapons attack is also not known, but estimates can be made with high enough fatalities so as not to bias the conclusion that argues for substantially more funding for research and countermeasure development for natural infectious disease than for bioweapons.

To make the discussion more concrete, I assume an anthrax attack with 30,000 fatalities. Anthrax is still the number one focus of our biodefense efforts. This would be a big attack, requiring smoke-like, virulent anthrax spore particles to be dispersed over a sizable population. Such an attack would require a sophisticated bioweapons program to prepare for and launch.

Estimates of the number of fatalities in a well-executed anthrax attack vary widely, ranging from 1,440 to more than 500,000 per kilogram of anthrax used.<sup>6-9</sup> Macfarlane asserts that “Most of these estimates were made on the basis of little actual data.”<sup>6</sup>

Let’s start with a broad range of probabilities. Is the probability that a significant bioweapons attack will occur in any one year 0.1 or 0.01 or 0.001? To understand better the meaning of these three probabilities, Table 2 expresses them in a more intuitive way: the number of years that must go by to have a 50-50 chance that we will have suffered *at least one* attack. What does the table tell us? If the probability per year is 0.1, there is a 50-50 chance in 6.6 years that we will have suffered at least one anthrax attack resulting in 30,000 fatalities. Only the most fearful among us would believe this to be the seriousness of the anthrax threat today.

Let’s now look at the lowest 0.001 probability: 692 years would pass before there was a 50-50 chance that we will have suffered at least one attack. Only the blissfully optimistic among us would believe the threat is so slight. What most of us believe lies somewhere between these two ex-

trêmes, so the extremes serve as reasonable bounds on the probability of any bioweapons attack of significant size.

Let’s look at the middle 0.01 probability, where 69.9 years will have passed to reach a 50-50 chance of an attack. In my mind, this may be somewhat optimistic as well, but others may have a different opinion, since 30,000 fatalities represents a very successful attack.

For the analysis here, I take a somewhat bigger probability, which is 0.03 (approximately the average of 0.1 and 0.01 on a logarithmic scale). For this intermediate probability, 22.8 years will have passed before there is a 50-50 chance that we will have suffered at least one anthrax attack with 30,000 fatalities. Recognizing that it is arbitrary, this is the probability I will use. The likelihood-adjusted fatalities in any year are therefore  $0.03 \times 30,000 = 900$ —more fatalities than tuberculosis but significantly fewer fatalities than HIV/AIDS, staph infections, or the endemic yearly flu (see Table 1).

This illustrative combined risk assessment supports a conclusion that the U.S. should be focusing more funding and resources on a host of endemic infectious diseases ahead of bioweapons. The conclusion is quite insensitive to the fatalities and probability used in the assessment. For instance, using the higher probability,  $p = 0.1$ , and a hypothetical attack with extreme high-end fatalities (150,000) resulting in 15,000 likelihood-adjusted fatalities still leads to the same conclusion.

The exquisitely detailed risk assessments for bioweapons attacks now being conducted by the Department of Homeland Security<sup>10</sup> include wide ranges of estimates for likelihood and sizable error bars on consequences of bioweapons attacks. Furthermore, almost everyone who expresses an opinion about the need to defend against bioweapons attacks is, somewhere in their minds, intuitively and implicitly making a risk assessment calculation. For at least two reasons, it is better to go through the exercise of putting numbers on our risk assessments even if some of the numbers can only be guessed at: (1) It parses biodefense decisions into their component parts, so discussion can be focused and differences in thinking can be uncovered, and (2) it could help convince you that your intuitive opinion is correct or incorrect.

To arrive at more precise probabilities for bioweapons attacks requires good worldwide intelligence about details and plans (e.g., capabilities, agents in possession, etc.) for bioweapons use for all nations and terrorist groups. Such intelligence is not available to any of us, and it may never be. The best we can ask for is specific intelligence about the high probability of a particular attack that would instantly alert us to take evasive actions.

Despite the imprecision inherent in this type of risk assessment, assessments must nevertheless be made, because we need to plan now for countermeasures for the Strategic National Stockpile 10 to 15 years down the road. As new drug development in pharmaceutical companies has taught us, it

Table 2. Likelihood of a bioweapons attack expressed both as the yearly probability of the attack and as the number of years that must go by to have a 50-50 chance of at least one attack. The formula for calculating years is:  $\text{Years} = \log(0.5)/\log(1 - p)$ , where  $p$  is the yearly probability. This is easily derived from standard college-level probability.

<i>Probability of an Attack in Any One Year</i>	<i>Years until 50% Probability of at Least One Attack</i>
0.1	6.6
0.01	69.0
0.001	692.8

will take that long to discover, develop, and produce new countermeasures. Furthermore, intuition about probabilities of attack assumes the status quo. If, for example, the situation changes radically in the Middle East for better or worse, our intuition about probabilities could change as well.

## WHAT IS THE THREAT OF A FLU PANDEMIC?

A 1993 paper by Webster and Walker bluntly stated the worst scenario: “The world is teetering on the edge of a pandemic that could kill a large fraction of the human population.”<sup>11</sup> This is a catastrophic prediction from a highly respected virologist (Webster), but do all virologists agree? Equally respected virologists question this extreme view. Offit is skeptical: “The [avian flu] virus is clearly not highly contagious among mammals, and I just don’t think it’s going to become so.”<sup>12</sup> Offit anticipates the next pandemic will occur sometime around the year 2025.

The World Health Organization takes a conservative position:

An influenza pandemic is a rare but recurrent event. Three pandemics occurred in the previous century: “Spanish influenza” in 1918, “Asian influenza” in 1957, and “Hong Kong influenza” in 1968. The 1918 pandemic killed an estimated 40–50 million people worldwide. That pandemic, which was exceptional, is considered one of the deadliest disease events in human history. Subsequent pandemics were much milder, with an estimated 2 million deaths in 1957 and 1 million deaths in 1968.<sup>13</sup>

WHO has used a relatively conservative estimate—from 2 million to 7.4 million deaths—because it provides a useful and plausible planning target. This estimate is based on the comparatively mild 1957 pandemic. Estimates based on a more virulent virus, closer to the one seen in 1918, have been made and are much higher. However, the 1918 pandemic was considered exceptional.<sup>13</sup>

At the higher end for possible fatalities, Osterholm arrived at a figure of 180 to 360 million deaths (270 million average) worldwide from extrapolating the 40 million 1918 flu fatalities to the world’s present population.<sup>14</sup> Others believe that if the current Asian bird flu becomes contagious in humans, fatalities can be much higher even than the Osterholm estimate.

For an illustrative risk assessment for pandemic flu, I take arbitrarily the logarithmic average between a conservative estimate of 5 million deaths and a high estimate of 270 million deaths, arriving at 36 million deaths worldwide—coincidentally about the number of deaths from the 1918 pandemic influenza. The U.S. population of 300 million is

about 4.6% of the world population of 6.5 billion, so the number of estimated deaths in the U.S. is 1.7 million.

What is the probability that a pandemic flu will visit us in any one year? From recent history, the world experienced flu pandemics in 1918, 1957, 1968, and, if the next pandemic started tomorrow, in 2007. The average *minimum* number of years between pandemics then is 29.7 years. Based on this meager data, an estimate of the probability in any year is  $1/29.7 = 0.034$ .

Using these numbers for fatalities and yearly probability, the likelihood-adjusted number of fatalities is  $0.034 \times 1.7$  million = 57,300, which is more than any single infectious disease in the U.S. These likelihood-adjusted fatalities are about a third of the yearly 177,000 fatalities from all infectious disease in the U.S. (In the U.S. about 63 deaths per 100,000 people can be attributed to omnipresent infectious disease. For 300 million people in the U.S., this translates to 177,000 deaths from infections every year.)<sup>15</sup>

As with the anthrax illustrative calculation, there is a wide range of numbers that could be used; nevertheless, it is clear that pandemic influenza deserves considerable funding and resources, which the U.S. government is now providing.

Government mathematicians and economists are already carrying out detailed risk assessments for different bioweapons attacks.<sup>10</sup> These assessments should be combined together with detailed assessments for particular endemic infectious diseases and for pandemic flu. This process would reduce the “fear politics” that likely now dominates funding and resource allocation decisions. The results of a detailed combined risk assessment would place biodefense against anthrax and other bioweapons attacks in a position in the relative risk hierarchy significantly lower than the place bioweapons attacks presently hold.

## CURRENT FUNDING

BioShield 2004<sup>16</sup> and BioShield 2006<sup>17</sup> address countermeasure development and procurement for bioweapons. BioShield 2004 authorizes \$5.6 billion over several years for chemical, biological, radiological, and nuclear weapons (CBRN) countermeasure development and procurement for the Strategic National Stockpile, with most funding likely to be spent on bioweapons countermeasures. BioShield 2006 authorizes (but Congress has not yet funded) about \$1 billion over each of two years for countermeasures to CBRN and natural diseases considered to be a security threat (e.g., pandemic flu; it is unlikely that endemic infectious diseases, even HIV/AIDS, will ever be considered security threats, so they are ineligible for BioShield funding). The National Strategy for Pandemic Influenza provides over \$6.1 billion for R&D over several years for stockpiling and manufacturing influenza vaccines and antivirals,<sup>18</sup> with some possible additional funding from BioShield 2006.

Unfortunately, direct comparisons between BioShield and endemic infectious disease spending are difficult to make as BioShield covers development and manufacturing. But there is one comparison we can make that may be meaningful: NIH spent \$3.1 billion in 2006 on infectious disease research and \$1.77 billion on biodefense research.<sup>19</sup> The infectious disease category includes research on endemic infectious diseases, and it may include research on some bioweapons agents. From these two numbers, it appears that nearly half of NIH infectious disease research was for biodefense in 2006. Given that the total yearly U.S. fatalities for endemic infectious diseases is about 177,000, and that likelihood-adjusted risk assessments for all bioweapons attacks is unlikely to exceed a few thousand (900 in our illustrative anthrax example), our spending is heavily lopsided toward biodefense. Looking at particular diseases, the funding is still lopsided: NIH spent \$0.21 billion for influenza, \$0.15 billion for tuberculosis, and \$0.15 billion for anthrax in 2006. (An exception is HIV/AIDS where \$2.9 billion was spent by NIH; this amount presumably includes nonresearch items.)

Considering only fatalities, we would need to suffer bioweapons attacks with 177,000 fatalities *each year* to equal the fatalities from all infectious diseases and, more specifically, 18,000 fatalities *each year* to equal the fatalities from a single disease, AIDS. Bioweapons attacks with these fatalities are quite unlikely in any year, and for such an attack to happen every year is unimaginable.

## CONCLUSIONS

This simplified combined risk assessment is sufficient to alert us to a likely real imbalance in funding and effort between biodefense and endemic infectious disease, and it invites those who support our massive biodefense spending for countermeasure R&D to justify these expenditures. So, I tentatively conclude that our biggest need is for an increase in funding for research and countermeasure development for endemic infectious diseases. This new funding should be used mainly to support extramural academic and commercial infectious disease research and development and intramural NIH research in the programs mostly in place at NIH before 9/11. Funding should include international public health threats as well. I do not recommend yet another round of BioShield funding. Both the analysis and conclusions pertain to countermeasure R&D only, not other important aspects of biodefense and public health, such as infrastructure to deal with an infectious disease event.

The Department of Health and Human Services recently published a long-range countermeasure plan for chemical, biological, and nuclear threats.<sup>20</sup> While the main focus of the plan is clearly bioweapons agents, the approach is encouraging:

[The plan takes an] holistic, end-to-end approach that considers multiple aspects of the medical countermeasures mission including research, development, acquisition, storage, maintenance, deployment, and guidance for utilization. . . . A fixed defense or “one-bug, one-drug” approach for medical countermeasure development is determined to be effective and viable for some of the highest priority threats such as smallpox and anthrax. As the list of material threats increases, and technology advances, HHS will be focusing its medical countermeasure research, development and acquisition efforts on broad spectrum and platform approaches.<sup>20</sup>

In less detail, a recent Presidential Directive says the same.<sup>21</sup>

At present, endemic infectious disease research and countermeasure development (R&D) benefits biodefense more than biodefense R&D benefits infectious diseases. For example, the present “one bug, one drug” biodefense strategy—an anthrax drug would be effective only against *Bacillus anthracis*; a plague drug would be effective only against *Yersinia pestis*; and so on—does little for endemic infectious diseases. We should focus instead on endemic disease by developing broad-spectrum countermeasures targeting new, common metabolic pathways in model bacteria, and we should develop new strategies for viruses. This research focus would equally benefit biodefense.

There are many factors not addressed in this illustrative combined risk assessment. These include cost of treatment; long-term costs for the chronically ill; psychological, economic, and environmental impacts; and availability of countermeasures to reduce morbidity, among other factors. The cost of widespread unwarranted fear is one factor—likely a much greater concern for a bioweapons attack but not entirely absent from endemic infectious disease—which must be considered as well. Gilbert provides an excellent discussion of the elements involved in understanding the risk of a bioweapons attack.<sup>22</sup> Despite the omissions here, this simplified risk assessment argues strongly for reapportioning our funding and resources more toward natural disease.

Could other factors propel bioweapons agents to the top of the relative risk list in a combined risk assessment? For instance, would the cost of loss of use and decontamination of buildings after an anthrax attack be big enough to propel anthrax to the top of the list? It's doubtful. A publicly available combined risk assessment considering the many factors other than expected fatalities should answer these kinds of questions. Secrecy here, where public health is at risk, is not justified. We all need to be part of the discussion.

It is a political reality that we spend a staggering amount on defense, and that mindset is reflected in our biodefense spending. Some argue that a bioweapons attack is a direct threat to our national security justifying massive biodefense funding. Furthermore, our relative allocation of funding

accurately reflects the relative values that policymakers attribute to biodefense and endemic infectious disease.

In my opinion, policymakers are not responding rationally to the threat of bioweapons attacks. Also, our focus should not be defined so narrowly as to encompass only the explicit direct threat of a bioweapons attack; it should include indirect threats such as the cost of deflection of any new funding from traditional public health where new funding is needed. If one adopts this broader focus, then traditional public health is relevant. Furthermore, the broader consequences of our massive biodefense program, such as the perceptions of other nations about the meaning of our biodefense activities that could unintentionally trigger an arms race in bioweapons, must be considered as well. The resources available to the federal government are limited, so we must use them optimally. This dictates that we base our decisions on the best combined risk assessments we can muster.

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