

# Protecting Public Health in the Age of Emerging Infections

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**ABSTRACT:** Emerging and re-emerging infections cause huge concern among public health workers and international and national bodies such as the World Health Organization (WHO) and the U.S. National Institutes of Health (NIH). Indeed, scientists around the world express the view that despite the danger, research on these emerging virulent pathogens is crucial and must continue. While most of the studies underway are targeted at improving and protecting public health, some studies bear potentially serious risks resulting from misuse. These studies are defined as dual-use research of concern (DURC), where it is not evident that the benefits outweigh the risks. The H5N1 controversy has pushed various governments to institute new policies to govern such research. We describe the regulations that govern this emerging field of research in the United States and Israel, two countries that have taken leading stands on these issues. We suggest that the existing policies are able to mitigate many of the risks that this research encapsulates, yet more work is required – especially on the global level.

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The last two decades have seen troubling developments in the fight against infectious diseases as novel pathogens emerge and old ones re-emerge, some with pandemic potential. A good example is the emergence of the avian H5N1 and H7N9 influenza viruses in human populations. We are currently witnessing an emerging novel coronavirus (MERS-CoV) that causes Middle East respiratory syndrome (MERS), and the Ebola virus is hitting again. It is suspected that animal reservoirs are the sources of these viruses [1-4]. These developments cause great concern among public health workers and international and national bodies such as the World Health Organization (WHO) and the United States National Institutes of Health (NIH). Indeed, scientists around the world express

## Novel pathogens present serious public health risks

the view that in spite of its danger, research on these emerging virulent pathogens is crucial and must continue [5-8].

Obviously, most of the studies that are being conducted and the methods they employ are targeted at improving and protecting public health. Synthetic biology, genetic sequencing, advanced drug screening and other emerging biotechnologies enable scientists to pursue these research goals in a very effective way. Nonetheless, at the same time, some studies, examples of which we provide below, bear potentially serious risks. The U.S. government has defined these studies as dual-use research of concern (DURC): namely “life sciences research which, on the basis of current understandings, could be reasonably anticipated to provide knowledge, information, products, or technology that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security” [9].

Clearly, almost any scientific research can be used for both beneficial and malevolent purposes, but some pose more significant and immediate risks and are referred to as DURC [10]. Specifically, DURC is research that appears to have a high risk of misuse with potentially substantial harm resulting from such misuse. In other words, DURC is characterized as research in which it is not evident that the benefits outweigh the risks. A few publications are commonly referred to as exemplifying DURC, such as the chemical synthesis of the polio virus\* [11], the reconstruction of the extinct 1918 influenza virus [12], the re-engineering of the mouse pox virus to overcome the vaccine [13], to name a few.

More recent research created novel pathogens using advanced biological methods: one study created a novel influenza virus from segments of an avian influenza virus very similar to the 1918 pandemic influenza and other amino acids from currently circulating influenza viruses [14]. Two studies of the highly pathogenic avian influenza (HPAI) H5N1

\*Researchers artificially synthesized a “live” polio virus from scratch, following the map of the polio virus DNA genome published on the internet. They stitched together corresponding strands of DNA they had purchased by mail order, and added protein, which resulted in the creation of a virus that paralyzed and killed mice. The researchers had created the virus “to send a warning that terrorists might be able to make biological weapons without obtaining a natural virus” and similar techniques might enable the production of smallpox or Ebola.

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viruses generated novel viruses that are transmissible via the air between ferrets, the best animal model for human influenza infection [15,16]. These studies have important health-related benefits; for example, they could provide information essential for epidemiological surveillance as well as for developing vaccines. Accordingly, these studies could assist in mitigating and perhaps even averting the next pandemic. Yet these studies also raise serious ethical concerns that relate to biosafety and biosecurity [6,17]. For example, such studies might provide information on how to create dangerous pathogens, information that might be misused to cause harm. In addition, lab accidents (if they occur) could cause serious harm [18,19]. This kind of research raises important questions; in particular, whether this research is desirable, and if so under what conditions it should be conducted.

Before discussing these questions, we describe the H5N1 studies since they provide a stark illustration of the various risks that DURC embodies. The H5N1 controversy pushed various governments to institute new policies to govern such research. We describe the regulations that govern this emerging field of research in the United States and Israel, two countries that have taken leading stands on these issues. We conclude by suggesting that the existing policies are able to mitigate many of the risks that this research encapsulates, yet more work needs to be done – especially on the global level.

#### THE H5N1 CONTROVERSY

Influenza is a recurring global health problem that takes the lives of more than half a million people every year [20]. Influenza viruses have animal reservoirs, such as birds and swine, and are known for their high rate of mutability, jumping from one species to another and resulting in a virus to which humans are highly vulnerable. The potential for a global pandemic is huge, as demonstrated in the 1918 “Spanish flu” outbreak that killed between 50 and 100 million people worldwide and resulted in enormous social and economic disruption [21]. Three other global influenza pandemics occurred in the twentieth century, in 1957, 1968 and 2009; none of them, however, was as devastating as the 1918 event.

In the last decade, a highly pathogenic strain of avian influenza – H5N1 – emerged among fowl [22] and infected approximately 600 humans who had been heavily exposed to chickens. Almost 400 of those infections resulted in death, making the mortality rate higher than 50% [23]. Given the threat that H5N1 could evolve and become transmissible via the air among mammals and result in a catastrophic pandemic, the WHO and similar bodies urged governments to promote research into this dangerous virus. The U.S. government decided to fund such research through its National Institute of Allergy and Infectious Diseases (NIAID). The goals were to study how the virus might evolve in the wild into a phenotype pathogenic to humans, to

improve disease surveillance, and to create more effective countermeasures against it – in other words, to stay as many steps ahead of potential pandemics as possible. NIAID has supported such research, including developing countermeasures such as a universal “influenza vaccine.” Within this context, two NIAID-funded studies on the H5N1virus attracted worldwide attention; they were conducted in two different laboratories, using two different methodologies. The studies employed advanced methods such as site-directed mutagenesis, genetic sequencing, as well as serial passage in ferrets, resulting in the H5N1virus becoming transmissible via air droplets among ferrets [15,16]. If this proved true in humans, the new strain could create a pandemic with a mortality rate far higher than that of the 1918 influenza outbreak.

The studies were submitted to *Science* and to *Nature*, and the articles describing this research raised unprecedented controversy [24]. They described the methodologies used to create the airborne virus as well as the mutational data that makes the virus transmissible via air. Many misgivings were raised about these studies.

The first is a biosecurity concern that stems from openly published information. Those who might seek to harm others have access to scientific journals from which they can glean methodologies as well as specific data that can be used to cause harm. This informational risk is multiplied as the biotechnological methods needed to cause harm are becoming cheaper and easier to acquire. Research describing how to enhance the harmful consequences of a pathogen is one example. The H5N1 case illustrates this point forcefully. Some have suggested that the articles provided a “blueprint” for those seeking to do harm and should not be published in full.

A second biosecurity risk stems from the biological material created in labs; dangerous pathogens can be stolen for the purpose of either releasing them or studying them. Furthermore, individual scientists might join labs in order to gain the knowledge needed to create harmful agents. The 2001 U.S. anthrax attacks that were allegedly undertaken by a scientist and resulted in 5 deaths and 17 injuries is a case in point [25]. With regard to the H5N1 case, the concern that malevolent individuals might try to steal the enhanced virus and release it was raised in various scientific meetings.

In addition to the biosecurity risks, DURC in general and the H5N1 studies in particular bear biosafety risks. These include the accidental release into the environment of pathogens that have been enhanced, conceivably through unauthorized access to dangerous pathogens, inappropriate working conditions, and other types of laboratory accidents. Given such biosafety risks, some have called for research on the highly pathogenic H5N1 to be carried out in biosafety level 4 (BSL-4) laboratories [26].

A related risk is that DURC might be carried out in places without appropriate biosafety safeguards. For example, in the

#### Research on these pathogens is crucial despite the biosecurity and biosafety risks

developing world, labs that sometimes lack proper biosafety conditions might attempt to conduct research that requires safer conditions [18,19]. This concern was especially relevant in the H5N1 case: developing countries such as Indonesia have a strong interest in promoting research on this pathogen as it poses a serious public health risk. Yet, these countries lack the biosafety conditions to conduct this research safely.

As suggested, the H5N1 case exemplifies the various risks associated with DURC. These risks notwithstanding, the H5N1 studies also offered considerable potential benefits. As said, the research would allow better surveillance of nature, as the mutational data provided by the studies could help detect changes in the wild. Moreover, the knowledge gained is crucial for developing countermeasures. These benefits, some have claimed, outweigh the risks.

Realizing the potential risks as well as the benefits, the editors of *Nature* and *Science* asked that the manuscripts be reviewed by the National Science Advisory Board for Biosecurity (NSABB), which had been established by the U.S. government in 2004 to provide counsel on the management of dual-use research. The NSABB comprises experts from many fields, including virology and synthetic biology as well as biosecurity and biosafety [10]. Crucially, the NSABB can only provide advice since it has no statutory authority. Nonetheless, the Board's recommendations carry significant moral weight since their work is perceived as responsible and balanced. In an unprecedented step, the NSABB recommended that specific details of the methodologies and mutational data be censored and that only the general conclusions be published. These recommendations elicited a major crisis in the scientific community; they created a divide between those who believe in open science that allows for replication of work and those who contend that security concerns should at times trump scientific values [27]. Interestingly, both sides argued that public health would benefit if their approach would be chosen.

In contrast to the NSABB recommendation, an expert international panel convened by the WHO concluded that the research was important for public health and should be published in full, but only after public awareness and understanding had increased and the issues of biosafety and biosecurity had been reviewed [28]. The NSABB later received revised manuscripts, conducted a new risk-benefit analysis, and concluded that the manuscripts could appear in full and, indeed, both journals ultimately published them [15,16].

The review and re-review of the H5N1 avian influenza publications by the NSABB, the complexity of the issue, and the controversy surrounding publication of the manuscripts made DURC a focus of interest, illustrating the difficulties inherent in addressing the risks of DURC and the dilemmas of regulating research aimed at benefiting public health while avoiding potential harm or misuse. Also brought to the forefront was the

question of the proper role of government in regulating science [29]. As noted, both H5N1 studies received federal funding from the NIH. Given the governmental role in funding such research, many have called for new regulations to help mitigate the risks such studies present. Heeding these calls, various governments instituted specific policies that govern this research (USA, Netherlands, Israel) while other governments are considering new policies (Germany, Australia, Britain). We will briefly describe the regulations that govern this emerging field of research in the USA and Israel, two countries that have taken leading stands on these issues. We suggest that these regulations mitigate many of the risks DURC embodies, yet because science is globalized national policies can only take us so far. Accordingly, regulations at the global level need to be considered.

#### **REGULATING DUAL-USE RESEARCH OF CONCERN IN THE USA**

Since the 2001 anthrax attacks, the U.S. federal government has established several laws to safeguard national security. These include the USA Patriot Act of 2001 and, a year later, the Public Health Security and Bioterrorism Preparedness Response Act (PHSBPRA), providing for additional requirements for listing potentially dangerous biological agents and preventing unauthor-

ful access to such agents during transfers [30]. Both laws mandate and oversee work with dangerous microorganisms and include a spe-

cific list of "select agents" first addressed in Section 817 of the Patriot Act.

These policies dealt with biosecurity but not necessarily in the context of DURC; this changed dramatically with the H5N1 case, which generated a new oversight policy. The policy is labeled "United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern" [9] and was announced on 29 March 2012 during the meeting at which the NSABB recommended publication of the two manuscripts. The policy applies to all federally funded research that uses one or more agents appearing on a list of 15 high-consequence agents and that aim to perform any one of seven specific experiments [Table 1].

If federally funded research meets these criteria, it is subject to stricter oversight, including frequent progress reports in which the risks and benefits are described and measures to lower the risks are taken. Moreover, the policy provides the government with a variety of policy tools that it lacked during the H5N1 crisis. For instance, under the new policy the government can require that investigators implement specific biosafety conditions and other measures to minimize the risks of intentional and accidental release. The new policy also provides the government with the authority to restrict funds and publication of research that is deemed overly risky.

This policy covers only partly the types of risks we have highlighted in the previous section. The policy does not cover

**Table 1.** United States Government policy for oversight of life sciences dual-use research of concern

This policy applies to all federally funded research that uses one or more of the 15 agents currently listed as high-consequence agents [A] and that aims to conduct one of the seven types of experiments noted below [B].

**A. High-consequence agents and toxins**

1. Avian influenza virus (highly pathogenic)
2. *Bacillus anthracis*
3. Botulinum neurotoxin
4. *Burkholderia mallei*
5. *Burkholderia pseudomallei*
6. Ebola virus
7. Foot-and-mouth disease virus
8. *Francisella tularensis*
9. Marburg virus
10. Reconstructed 1918 Influenza virus
11. Rinderpest virus
12. Toxin-producing strains of *Clostridium botulinum*
13. Variola major virus
14. Variola minor virus
15. *Yersinia pestis*

**B. List of experiments**

1. To enhance the harmful consequences of the agent or toxin
2. To disrupt immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification
3. To confer to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate their ability to evade detection methodologies
4. To increase the stability, transmissibility, or ability to disseminate the agent or toxin
5. To alter the host range or tropism of the agent or toxin
6. To enhance the susceptibility of a host population to the agent or toxin
7. To generate or reconstitute an eradicated or extinct agent or toxin that is listed in the 15 agents covered by the policy

the risks associated with DURC research conducted in countries that lack appropriate biosafety and biosecurity infrastructure. This is understandable as federal policies only govern research conducted in the U.S. (and in other counties if funded with federal funds). However, the U.S. and other developed countries must take steps to ensure that research done anywhere in the globe is conducted under safe conditions since the risks posed by research on highly virulent pathogens are global. Measures may include scientific treaties as well as political pressure on countries that might try to ignore the threats posed by such research. In other words, since science is global so should its regulation be.

This point also applies to the first biosecurity risk we mentioned; namely, risks that stem from the publication of research. Scientists not subject to the U.S. policy might try to publish DURC studies in journals that ignore U.S. regulation. Scientific journals are not subject to the U.S. policy, yet most major journals are likely to abide by U.S. federal standards and refrain from publishing studies that are deemed too risky [31]. This might not be true of journals located in developing countries. This issue also requires coordinated global action.

A second policy that the U.S. government instituted is a special review of H5N1 funding decisions. This mechanism is devoted to one specific kind of research: gain-of-function research involving H5N1 viruses. Studies that aim to create a virus with enhanced transmissibility among mammals are subject to a special review conducted by the Department of Health and Human Services [32].

A third policy was released on 24 September 2014. The policy, labeled the “United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern,” will become effective on 25 September 2015 [33]. As its title indicates, this policy aims to create local oversight mechanisms. Individual universities and other scientific institutions would themselves be responsible for conducting ongoing assessment of their research portfolio and establishing risk-mitigation strategies. The policy provides tools for assessing risk and raising awareness about dual-use research.

As shown, these three policies would not completely resolve the biosecurity and biosafety concerns raised by research such as the H5N1 studies, but they begin a process of mitigating such risks and gaining the public trust that the scientific community is behaving responsibly.

## REGULATION OF RESEARCH INTO BIOLOGICAL DISEASE AGENTS IN ISRAEL

From its founding, Israel has been threatened by conventional and unconventional terrorism aimed at the civilian population as well as the military sector. In response, Israel is constantly engaged in perfecting effective biosafety, biosecurity and bio-containment measures. Because of Israel's unstable geopolitical situation, a much more sensitized approach to the threats of unconventional attack, including biowarfare, has made the Israeli government's efforts a model for much larger and better-financed countries. From the end of the 1990s, when bioterror threats became a reality, Israel began to modify its existing biodefense measures while increasing its emphasis on prevention. Nevertheless, until 2008, regulation of life science research in Israel was largely concerned with biosafety.

In 2005, in the wake of renewed bioterrorism threats and the rapid pace of emerging biotechnologies facilitating development of new bioweapons, the Israel Academy of Sciences and Humanities and the National Security Council appointed the Committee for Biotechnological Research in an Age of Terrorism. The committee's mandate was to study the status of Israel's biosecurity and to draft recommendations for a national biosecurity policy [Table 2] [34]. Those recommendations were submitted to the president of the Israel Academy of Sciences and Humanities and to the head of the National Security Council, who jointly appointed the members.

As a result of the committee's recommendations, the Israeli legislature passed the Regulation of Research into Biological Disease Agents Law, 2008, which provides a

**Table 2.** Israel's Committee for Biotechnological Research in an Age of Terrorism

The Israeli Committee for Biotechnological Research in an Age of Terrorism was established in 2005, charged with addressing the following points:

- Requisite changes in Israel's existing legislative infrastructure
- Compilation of an adaptable list of biological agents and research topics requiring inspection and supervision
- Establishing a regimen to track, supervise and enforce all areas of biosecurity
- Examining the need for a national inter-ministerial body or professional committee to guide, monitor and maintain biosecurity

**Table 3.** Israeli Council for Monitoring Biological Disease Agents Research

In 2008, Israel's legislature established the Council for Regulating and Monitoring Infectious Disease Agents Research. Its duties are:

- To advise the Minister of Health in formulating regulations for maintaining disease agents and conducting research into them, in relation to research in general, and in relation to changes in the list in the Supplement to the law
- To advise the Director General of the Ministry of Health on accreditation of institutions
- To advise the Director General of the Ministry of Health on the investigation of an objection submitted
- To promote dissemination of information to the public on subjects within its field of activity, programs of advanced study, and instructions for researchers on topics connected with the conduct of research into disease agents and other forms of research
- To approve the operating rules and regulations for the proceedings of the institutional committees
- To supervise implementation of the provisions of the law and compliance with the operating rules and regulations for proceedings of the institutional committees

legislative framework for the conduct of research into biological disease agents [35]. The law provides the Israeli government with the tools to address the dual-use concern as well as other biosecurity and biosafety concerns. The Israeli law is the first legislated statute in the world that attempts to directly address the dual-use challenge. It calls for the establishment of the Council for Regulating and Monitoring Infectious Disease Agents Research to regulate and oversee research of infectious disease agents. The 15 member council comprises 6 experts from microbiology, infectious diseases or biotechnology; representatives from the Ministries of Health, Science, Environmental Protection, Agriculture and Rural Development, Industry, Trade and Employment, and Defense; as well as from the Israel Police, the National Security Council, and the Manufacturers Association. The duties of the Council are listed in Table 3.

The law requires that every academic institution receive the council's approval to conduct research on the biological agents listed by the law. It also requires that institutions review research proposals for their biosecurity and biosafety

implications, after which they must articulate risk management strategies as well as biosafety requirements. Academic institutions should then report to the council about their studies and the measures taken to manage the risks. The Israeli law is to some extent a combination of the regulations that exist in the U.S., specifically, the Select Agent rules and the DURC policies.

As discussed regarding the U.S. regulation, the Israeli regulations are a step in the right direction but they would not, obviously, resolve the global challenge posed by DURC. This underscores the need to encourage more countries to develop their own regulations as well as construct a global mechanism that could be used to address this issue worldwide.

## SUMMARY AND CONCLUSIONS

Dangerous pathogens are evolving in the wild, creating risks of epidemics and pandemics. It is incumbent on us to pursue research that could help protect the public from these pathogens. Yet such research is not without risks. In this paper we discussed some of those risks and the policies that aim to address them. We classified the risks of such research into two types: biosecurity and biosafety. In each category there are two distinct types of risks. Biosecurity risks include informational risks and risks that stem from theft of materiel. Biosafety risks comprise risks of accidental release and risks that stem from inappropriate biosafety level conditions. To illustrate these risks we used the H5N1 research controversy.

In view of the importance of this research as well as the risks it encapsulates, Israel and the United States instituted various policies that aim to manage this kind of research. The policies provide each government with tools that would enable it to track the risks of such research. Moreover, these policies provide new measures that could be implemented to mitigate the risks of a particular study to the point that the benefits of the research outweigh its risks. The policies are thus able to promote public health while protecting the public from overly risky research. Although the policies seem to be working, they are limited in reach. Since science is global so are the risks that such studies pose. Developed countries must promote a more global approach to address the risks posed by such studies.

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