Health Security
Volume 13, Number 2, 2015 © Mary Ann Liebert, Inc.
DOI: 10.1089/hs.2015.0002

Point of View

Health Security Preparedness and Industry Trends

Stanley T. Crooke

Given the number and diversity of risks in today's complex society, it is essential to focus on global risks that can be reduced through affordable, feasible approaches. Thus, the risks that should command the greatest focus are emergent infectious diseases. Fortunately, preparing responses to such threats can be entirely agnostic as to source or intent of the threat. This article considers the emergent infectious clinical threats, characterizes the steps that are essential to take to prepare for such threats, and discusses the roles that the biomedical industry should play in both the preparation for and response to such threats. The author assesses the readiness of the industry to play its role and suggests steps to consider to enable a more robust response.

The biomedical industry has played a critical role in advancing human health, prolonging and enhancing life, and reducing the financial impact of disease. It has also been instrumental in the response to emergent health trends. The industry is likely to play an even more important role in responding to future threats to the health and well-being of humankind. However, significant trends suggest that the industry will be less able to play its important role in response to threats to health in the coming decades, especially in areas critical to emergent risks to the US and the world. Thus, despite the progress in developing the resources necessary for a coordinated and effective response to acute risks to health made in response to the Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006, there is a growing risk that a key element of any response to future threats, the biomedical industry, will not be up to the challenge.

This article considers the risks to health security likely to be encountered in the future, the ability of the biomedical industry to contribute to a coordinated public-private sector response, and the trends that are likely to affect the industry's ability to respond to future threats.

The Key Problem

Although there are numerous types of risks, including chemical and radiological intoxication, the critical (manageable) risks of the future are biological—largely infectious diseases. That chemical intoxication is certainly a risk has been amply demonstrated by a number of environmental catastrophes. However, such risks are typically quite localized and do not constitute a threat to the national or global population. Moreover, the diversity of chemical agents that might be risks is such that protecting the population against any but the most obvious, such as cyanide, is prohibitively expensive. Similarly, radiation poisoning is likely to be limited to a small geographic region unless a full-scale nuclear conflict develops.

So, the principal focus for preparedness exercises must be the development of responses to emergent infectious diseases. Fortunately, preparing responses to emergent infectious diseases is largely independent of whether the emergent infectious agent is natural or man-made or whether the agent was introduced by evolutionary processes

Stanley T. Crooke, MD, PhD, is founder, chairman, and chief executive officer of Isis Pharmaceuticals, Carlsbad, California.

or by terrorist activity or as a result of a containment accident. Here again, substantial progress has been made in preparedness in response to PAHPA. Nevertheless, even now there is much to do to enhance our ability to survive emergent biological threats.

Steps in Responding to Threats

Recognizing an Emergent Threat

The obligate first step in responding to an emergent infectious disease threat is to recognize that there is a problem. For acute infectious diseases, this is typically straightforward, and there are a substantial number of epidemiologic databases and systems to assure relatively rapid recognition that there is a problem. For more chronic infections, the challenge is much greater, as clearly exemplified by the HIV epidemic. Again, the essential resource is an aggressive infectious disease epidemiologic surveillance effort. Fortunately, although the identification of an emerging chronic infectious problem takes longer, by definition there is more time to develop a response. Whether the emergent threat is acute or chronic, the key challenges are to have systematic approaches to environmental sampling, reporting of cases of novel clinical presentations, solid communication processes, and effective coordination between the various countries and agencies involved.

Identifying the Causative Agent

Thanks to advances in diagnostics, high throughput transcriptome sequencing, and other methods, rapid identification of emergent organisms is now a reality. Equally important, it is possible to rapidly position the organism taxonomically; define how, where, and when it emerged; and identify genetic markers of virulence and resistance and its relationships to other strains of the organism that may have been encountered previously.

Characterizing the Causative Organism

Although identifying the causative agent and defining its genotype are critical, it is obviously essential to understand its phenotype. To understand the phenotype requires numerous steps and skills, including growing the organism in the lab, understanding its transcriptome and proteome, and understanding its interactions with various hosts, methods of transmission, and the nature of the immune responses to it, some of which may exacerbate the virulence while others may be protective.

Once an emergent threat is identified, quarantines of various sorts may be employed to retard the spread of the threat, but the public health response is not the focus of this review. I do, however, focus on steps to take to make quarantining more effective.

Discovery of Countermeasures

The process that leads to the discovery of treatments begins with a detailed understanding of the molecular biology of the pathogen. Skills required to perform this work are lumped together under terms like molecular biology, microbiology, biochemistry, immunology, virology, and parasitology, but each of these categories encompasses groups of scientists with hyper-specialized skills that require years of training and decades of experience. This means that even for the simplest organisms, teams of specialists led by scientists with sufficient breadth of knowledge and experience are required.

Next comes the more arduous and time-consuming process of discovering an initial candidate countermeasure or "lead" agent. The optimization of the lead to a developable drug can be enormously complex and time consuming. New drug discovery technologies may reduce the time and cost of lead discovery and optimization. The skills necessary to discover a lead vaccine are entirely different from those needed to discover an antiviral or antimicrobial. The types of scientist and physician are also quite different.

Developing a New Therapeutic

Once a lead is optimized (which under normal circumstances may take years), development of the therapeutic agent begins and typically takes more than a decade, beginning in animal trials and eventually moving to clinical trials. Each step is complex, risky, costly, and highly regulated. Although approaches to limiting regulatory delays are helpful, in fact, prudent management of risk dictates that the process is time consuming. While the development process for vaccines may seem superficially similar to the development of therapeutics, it is quite different and requires different skills and types of preclinical and clinical trials.

Manufacturing the Therapeutic Agent

Small molecular and nucleic acid–based drugs are manufactured chemically and require chemical synthesis plants. In contrast, vaccines, monoclonal antibodies, and antibiotics are natural products requiring fermentation and protein or natural product purification.

Distribution

In an emergency, distribution of the therapeutic agent would likely be coordinated by the federal government. Nevertheless, storage requirements, stability, formulation, and methods of administration must be defined, and this work would likely take place in an industrial setting.

Platforms for Discovery of New Agents

Fortunately, today, thanks to discovery efforts in the biochemistry industry and large pharmaceutical companies, a

broader array of platforms that can yield new agents is available. Each has unique characteristics and requires specialized skills.

Vaccine Discovery

Arguably the first true platform for the identification of therapeutic and prophylactic agents, vaccines have been shown to be uniquely effective and have essentially eradicated many infectious diseases. Moreover, the technology has advanced so that most vaccines today are produced as recombinant proteins, thereby reducing the side effects that derive from the administration of undefined mixtures. Vaccine discovery requires very specialized training, skills, laboratory equipment, and methods. The central challenge in creating vaccines begins with the organism. Many organisms have evolved to avoid a host response, which is in essence a vaccinelike response. So, many organisms may not be amenable to the rapid identification of vaccines. Further, many likely emergent threats are intracellular agents—that is, they enter the host cells and usurp normal host processes to grow and multiply. Consequently, those organisms, which include viruses and other agents, may not be amenable to vaccine development. Nevertheless, vaccine discovery and development should be considered an essential elementary response, because it has the potential to produce curative agents, and for some organisms generating vaccines may be relatively rapid.[1]

Small Molecule Drug Discovery

Small molecule drug discovery is now more than 100 years old and requires that specific chemicals be synthesized and adapted to interact with specific targets. In the case of an emergent infectious threat, the targets are most likely located in the organism. Although small molecule drug discovery is versatile, as has been demonstrated by the numerous therapeutics created based on the technology, it has substantial limits. A large fraction of molecular targets are not "druggable" with small molecules for a variety of reasons. For infectious agents, targets in the infectious agent that may be closely related to human homologues may result in drugs with unacceptable toxicities. Many organisms go through like cycle phases during which the organism is impermeable to essentially all agents. Others present real delivery of drug issues because of cell walls and the use of immunological and pharmacological hideouts. Further, intracellular pathogens employ host systems to multiply and infect, so finding agents that can kill such organisms safely is challenging.

However, even if all the problems and limitations are surmounted, one characteristic of small molecule drug discovery severely limits its utility in an emergent threat: time. Small molecule drug discovery is costly, slow, and inefficient. Thus, long before a small molecule program identifies a potential therapeutic agent from scratch, the pandemic will have run its course.

Monoclonal Antibody Technology

Monoclonal antibodies are protein therapeutics that are more specific than small molecules and can be identified more rapidly in many cases than small molecules.[2] However, they have substantial limitations. They typically do not work on intracellular targets and are most effective for targets in the vascular system or in areas in which the integrity of the vascular system is compromised, such as cancer or inflammation. Further, many organisms are virulent precisely because they have effected strategies to circumvent immune surveillance either by not displaying immune epitopes on their surface or exploiting immunologic hideouts. Nevertheless, the efficiency and rapidity of monoclonal antibody technology make it an important platform to consider in an emergent threat.

Oligonucleotide Therapeutics

Though developed more recently and thus less fully validated than the other platforms, oligonucleotide therapeutics have the advantages of being able to be derived directly from genomic information and have almost genetic information quality specificity. The extremely rapid and efficient drug discovery and development and broad applicability of this platform mean that it should be considered an essential element of any response to an emergent threat.

Trends Affecting the Biomedical Industry

Clearly the biomedical industry must play a role in every stage of the process that leads to an effective response to an emergent threat. Perhaps less understood is the importance of the collaboration among the biomedical industry, academic scientists, and research physicians. These communities are intimately coupled and mutually dependent. Neither can succeed without the other. A strong productive partnership among all the relevant communities, the industry, regulatory bodies, and the government is an essential requirement to mount an effective response to an emergent threat. Trends that adversely affect one member of this coalition often affect the others.

The Decline in the Biomedical Industry

The decline in the productivity of the drug discovery and development industry (including vaccines) has been well documented and is the factor underlying all of the other trends. As late as 1965, it is estimated that for every billion dollars invested in R&D, 35 or so new drugs reached the market. Today a billion dollar investment might yield 0.2

to 0.4 new drugs.[3] Many factors have contributed to this decline. The virtual eradication of infectious diseases as a cause of mortality in the developed world and the more effective management of other acute or semi-chronic illnesses, while great triumphs for modern medicine, have meant that the low-hanging fruit has largely been harvested, and the chronic degenerative diseases that are the main foci of the current industry are intrinsically more challenging. They are all typically multifactorial, with complex patterns of transcriptome and proteome changes, some of which are primary while others are secondary. Animal models of chronic diseases are far less comparable to human diseases, and a positive result in animal models of chronic disease is far less predictive of success than for an acute illness. Clinical trials for chronic diseases, by definition, are much longer, much larger, much more costly, and much more likely to fail because of unforeseen flaws in the design of the trials than acute trials. Regulatory requirements, which have grown more stringent across the board, are dramatically more demanding for drugs to treat chronic diseases. The trend toward requiring ever more data culminating in the demand for studies on clinical outcomes and comparative effectiveness has increased the cost of development for some indications to such an extent that some companies are no longer pursuing some major disease areas.

While it could be argued that many of the factors contributing to the decline of the productivity of the industry are products of success or imposed by regulators, a central cause, the failure of the industry to invest effectively in disruptive but more efficient technologies for drug discovery and development, is the central failure of the industry. Again, there are many mitigating factors, but no industry prospers if it does not create and embrace new technologies that enhance productivity enough to be considered disruptive. Although monoclonal antibody technology and genetically engineered proteins (biologics) initially developed by biotechnology companies have dramatically improved therapy for a number of diseases, small molecule drug discovery remains the main engine for drug discovery. Despite improvements in many elements of small molecule drug discovery and development, the adage "change a methyl, change the drug" remains as true today as ever. This stems from the fact that small molecule drugs are relatively "low information" content molecules compared to proteins or nucleic acids, and the biochemical interactions that may affect drug behavior are numerous and still poorly understood. The net effect of this is that there is relatively little opportunity to apply learning from one small molecule drug to another—in effect, little opportunity to learn from our mistakes.

For planning purposes then, it is important to accept that the decline in productivity is likely to continue. Consequently, the industry is no longer the vibrant industry it once was, despite the emergence of biotechnology. This has led to price increases, mergers, the exporting offshore of control of many US companies, and progressively less risk tolerance. Equally important, fewer and fewer companies have the financial wherewithal to pursue a broad therapeutic agenda. Thus, many companies have exited hugely important therapeutic areas, such as diabetes and cardiovascular disease, and most of these companies exited infectious disease some time ago. Today, this means that the bandwidth to respond to surprise events is simply not there. Collectively, these trends, reinforced by the short-term horizons of Wall Street, have created a risk-averse industry that is dominated by timid incrementalism rather than bold pursuit of disruptive technologies and innovative new therapeutic strategies.

Loss of Infectious Disease Expertise and R&D Investment

As most bacterial infections were controlled with anti-infective therapies, most traditional antibacterial programs in the industry were abandoned. Since many of these efforts focused on the identification of antibiotics (natural products), fermentation and screening experience and skills were lost as were expertise in the purification and manufacturing of antibiotics. The loss has been exacerbated by an equally substantial reduction in anti-infectives research. This means that even if an organism responsible for a threat is identified, there is insufficient expertise to characterize it phenotypically and limited ability to discover, develop, and manufacture a therapeutic agent to treat it. Although in recent years NIH has enhanced funding of anti-infective research and some companies may have reentered this space, most are focused on antiviral drug discovery, and the infrastructure required for an immediate and effective response is simply no longer available.

Historically, in both the biomedical industry and academia in the United States there has been little interest in the development of therapeutics for fungal or parasitic diseases, many of which are still endemic in the underdeveloped parts of the world. With the exception of some military programs, essentially none of the infrastructure necessary to respond to threats posed by these types of agents exists. In contrast there are a number programs focused on the discovery of antivirals in industry and academia. Although most programs are focused on a few viral infections, such as hepatitis B and C and HIV, the skills needed are readily transferable to new viral threats.

Vaccine Programs Have Declined

The ideal solution to the emergence of a new infectious disease threat is to prevent its spread by developing a vaccine. The success of vaccination programs is, in fact, one of the great achievements of modern medicine. However, in common with the development of therapeutic agents, every step in the process of discovering, developing, and producing a vaccine requires very specialized skills and experience and unique facilities that are expensive to build and maintain.

For many reasons, focus on the creation of vaccines in academic medicine and in the biomedical industry has

declined even more precipitously than has been the case in other therapeutic efforts. Today, virtually no young scientist enters this field, and there are very few industry programs in which they can be trained to discover and develop new vaccines. It is no exaggeration to suggest that vaccine discoverers and developers are approaching extinction, although there are academic centers that recently have been funded to develop vaccines to some agents.

The loss of expertise in vaccine science is worldwide, but it is more pronounced in the United States as many companies have discontinued their programs and others have relocated their programs outside the US. Thus, there is a glaring absence of necessary expertise and the specialized facilities needed to discover and develop vaccines. Additionally, manufacturing facilities for vaccines are virtually not available in the US. Simply investing in new facilities, however, will be insufficient without parallel investment in the intellectual infrastructure.

Advances in RNA Targeted Therapeutics

Over the past 2 plus decades, a third platform for drug discovery, oligonucleotide therapeutics, has been developed. This technology uses a new class of chemicals, chemically modified oligonucleotides (oligo: few, typically 14-20 nucleotides), to target a class of molecules, RNA, that have not been the focus of prior drug discovery efforts, to decrease or increase targeted RNAs that affect cell function via a variety of mechanisms, such as RNase H1, siRNA, altering splicing, nonsense mediated.[4]

Oligonucleotide technology is relevant to a response to a biological threat for several reasons. It is the only direct route from the genome to the patient. In an emergent threat, the information that is most likely to emerge first is the genotype of the organism. Thus, oligonucleotide approaches can be initiated earlier than traditional drug discovery approaches and are one of the most effective means to validate targets for new therapeutics. The discovery and development of antisense oligonucleotides as therapeutics are orders of magnitude faster and less expensive than traditional approaches to drug discovery. Further, as antisense drugs of the same chemical class behave very similarly, in an emergency setting greater reassurance can be offered regarding safety, thus accelerating rapid development and clinical trials. In addition, antisense technology can be used to specifically alter host responses to infectious organisms.

Understanding and Exploiting the Innate Immune Response

The innate immune response is an ancient system designed to protect cells from invading nucleic acids.[5] It uses a large set of pattern recognition receptors, some of which are on the cell surface and others inside the cell, to identify potential threats. These receptors are coupled to intracellular response systems that may induce interferon or cytokine or chemokine releases. This very primitive system is generically responsive particularly to bacterial and viral nucleic acids that often have modifications and sequence motifs different from human nucleic acids. In recent years, significant strides in understanding the structures that activate the human innate immune system make it possible to rapidly determine if certain oligonucleotides (eg, CG motifs and G-Quartets) could ameliorate the virulence and spread of infectious agents.[6]

Transcriptomics and RNA Sequence and Structure Analysis

Extraordinary advances in transcriptomics and methods to rapidly understand shifts in RNA populations within cells have recently been reported. These tools could be invaluable in rapidly understanding the host response to infectious diseases. This could lead directly to rapid identification of factors in the host that could contribute to resistance and greater virulence. These then would provide immediate targets for antisense drugs or other approaches that could reduce the susceptibility to the emergent infectious threat.

Host Immune Responses

A key determinant of the level of virulence displayed by infectious agents is influenced by the host immune response. Despite the fact that the immune system has evolved to protect humans from infections, often immune responses result in enhancing the virulence of organisms and trigger cytokine storms that can be life-threatening.

Host immune responses are managed throughout the body but are adapted to be on a high state of alert at portals of entry for infectious agents (eg, mouth, nose, gut, skin) and in blood. The responses integrate production of antibodies, cell-based responses to the organism, and the production of signaling molecules called cytokines, chemokines, and acute phase reactants.

Today, a great deal is known about the immune system, and numerous assays to evaluate immune responses are available. At the minimum, subcategorization of humans into those likely to survive or be less affected from those most susceptible should be possible, and as the immune response is characterized, important host factors that might be altered with drug treatment to reduce the impact and spread of the disease should emerge.

Points to Consider

Emergent Organism Identification, Communication, and Response

Although this topic has been a subject of considerable attention and progress, it is vital and the progress to date is

inadequate. Initial recognition that there may be an emergent threat must be as rapid as possible. To that end, establishing emergent threat identification processes in high risk areas such as Africa and at major transportation hubs is essential. At the international level, this should be a topic on which most legitimate governments will cooperate. At the national level, it is imperative that the various local, state, and national agencies be integrated effectively. Numerous barriers to early identification of emergent organisms and communication of that information, as well as coordinating a response, exist, including the poor quality of many state and local public health laboratories. Nevertheless, new technologies exist that could dramatically enhance the ability to identify and respond rapidly. So, a systematic, thoughtful investment using modern technologies and communication processes is necessary.

Stockpiling Broad Spectrum Anti-infectives

One strategy for pathogen preparedness is to stockpile chemicals originally invented for purposes of combating certain infectious agents or chemicals that might be "repurposed" for neutralizing infectious agents by virtue of their cross-reactivity with pathogen targets. Libraries of molecules with broad spectrum antimicrobial activities exist, and many of them have undergone some clinical development. Additionally, numerous molecules discovered in anticancer programs have very broad spectrum antimicrobial and, in some cases, antiviral properties. Broad spectrum anti-infective agents that have reached the market or have undergone meaningful development could be an element of the initial response to some threats.

Given that the most likely emergent threat will be an organism that is resistant to broadly used anti-infectives, the focus should be principally on broad spectrum anti-infectives that have experienced limited clinical use. In most cases, the limitations in use are due to side effects that the more broadly used agents do not have. For example, aminoglycosides are oto- and nephrotoxic, so they are not widely used. Nevertheless, they are broad spectrum, the side effects could be minimized by effective hydration, and they would be acceptable in patients with a lethal infection for which no other agents work. Similarly, dihydrofolate reductase inhibitors, used in cancer treatments, are broad spectrum anti-infectives that could be given at doses lower than used in cancer chemotherapy. Cyclophosphamide, a DNA damaging athylating agent, which is oral and relatively easy to use might be another option.

The point is that criteria for stockpiling agents to be used in an emergent pandemic should be developed, and they are likely quite different from the criteria for more routine use. Certainly, safe and easily used anti-infectives may be stockpiled, but some of the less attractive broad spectrum agents should be also considered, and developing an inventory of the drugs with broad spectrum anti-infective activity and stockpiling the broadest spectrum agents would seem an immediate response that could delay the spread of an infectious threat. At the minimum, a number of broad spectrum agents for each major class of infectious disease should be stockpiled. Of course, there is always a concern about overuse or misuse of anti-infectives causing resistance, but in an emergent threat, the first and most important step is to control the infectious threat.

Curating Natural Product and Small Molecule Libraries

Enormous libraries of antibiotics, antivirals, and anticancer agents with anti-infective properties exist. These are located in the NIH and NCI and in industry. Curating the key libraries for molecules with broad spectrum anti-infective activities could provide useful reagents. At the minimum, the libraries might provide lead structures that could be optimized to respond.

Funding Antibiotic Discovery Efforts

Certainly one of the great achievements of the biomedical industry is the eradication of most infectious diseases as causes of death in the western world. The funding to initiate the antibiotic segment of the industry was initially provided by the government in response to the need to produce penicillin. It is important to continue to fund some antibiotic discovery efforts so that at least a minimum level of expertise and facilities is maintained. This would probably be most efficiently done in academia or the NIH. This should also encourage new scientists to enter the area, but there may be a need to earmark doctoral and postdoctoral training grants as well. To be effective, the approach must be systemic. This means that the program should focus on training new scientists, funding grants to support research in academia and industry, and establishing approved, effective incentives for the industry.

Maintaining a Vaccine Infrastructure

During an infectious threat, the capability to discover, develop, and manufacture vaccines could be a strategic resource. The US cannot be entirely dependent on facilities controlled by other governments. Some form of federal government intervention is required to maintain the remaining industry programs in the US, perhaps through tax incentives or other approaches. In the longer term, plans must be developed to encourage new generations of scientists to enter this field. This too could be accomplished cost-effectively by earmarking doctoral and postdoctoral training grants for this area. Although the Biomedical Advanced Research and Development Agency (BARDA) is already involved, a broader, more strategic integrated effort is probably needed.

Transmission of Infectious Agents

The key event in establishing an epidemic is the transmission of pathogens from one host to the next. Transmission pathways are complex and often involve nonhuman vectors or nonhuman hosts. Today, the only approach to reducing transmission is quarantine, which is simply ineffective. Support for research on how various infections are transmitted may lead to agents that could block specific generally employed processes. A panel of such agents might provide a tool to limit transmission that, when coupled with quarantine, could prevent a pandemic.

Understanding the molecular mechanisms of herd immunity is another area of research that should be supported. Historically, herd immunity derived from genetic variants that altered the life cycle of the pathogen and were often associated with a survival disadvantage in the absence of the pathogen, as in the case of malaria and thalassemia. Research here could lead to genotyping of populations to more quickly pinpoint genetic loci associated with resistance.

Evaluation of Host Response

In every epidemic to date, there have been humans who were entirely or partially resistant to the emergent organism. This has led to the establishment of herd immunity, which ultimately limited the pandemic. The key difference today is that we have the tools to rapidly identify host factors that contribute to resistance or particularly virulent responses, and they include transcriptomics, proteomics, and rapid profiling of immunologic responses.

Transcriptomics

Thanks to advances in RNA sequencing and genomics, today it is possible to rapidly understand the molecular responses to infectious disease. At the minimum, such research could rapidly subcategorize patients into genotypes likely to be severely or less severely affected or resistant, which could greatly aid quarantine efforts. It is equally likely that the research could identify molecular targets that could be manipulated with drugs to alter the course of the infection in an individual and the course of an epidemic. Host transcriptomic approaches should be integrated into any strategic plan to respond to an emergent infectious disease threat. Today, there are several major academic centers that have pioneered transcriptomics and numerous approaches and companies that are available to focus on RNA sequence and structure analysis and could be knitted into plans for a response.

Host Immunological Response

This is an area that has also experienced logarithmic growth in new knowledge. Immediately upon identification of an infectious threat, efforts to understand the molecular immunological responses should be initiated. Many of the assays necessary can be performed on blood and other accessible body fluids and are available as routine assays in clinical laboratories (eg, cytokines, chemokines, acute phase reactants).

Rapid identification of host immune responses that protect from and/or exacerbate the virulence of an infectious agent would provide additional parameters to categorize humans with regard to the likely severity of the infection and guide public health containment efforts. Further, there are numerous drugs available today that alter these immune responses, and newly created monoclonal antibodies, antisense drugs, or plasma components could be administered to reduce the virulence and spread of infectious agents.

Here again, an integrated systematic approach is required because in practice this is quite complex. It would, for example, be essential to know when in the ontogeny of an infection samples were obtained. It would be necessary to know if there were intercurrent or antecedent factors that might influence response to the agents (eg, sickle cell anemia, malaria). Further, concurrent drug use and standard of care would need to be documented. Nevertheless, this is critical. It would enhance quarantine efforts, help deal with public panic, and act as a springboard to broad solutions.

Oligonucleotide Therapeutics

As discussed earlier, antisense technology (including siRNA) has been created and validated. It is a potentially vital tool to be used to understand the infectious agent and host responses to the emergent agent as well as rapid development of new therapeutic agents. Additionally, CG and G-Quartet oligonucleotides could be important as tools to stimulate the innate immune response to the emergent organism. A focused investment in accessing this set of technologies should be considered.

Acknowledgments

Thanks to David Ecker and Emilio Emini for asking me to consider these issues and prepare a presentation for the National Preparedness Response Board, from which this commentary is derived. Also thanks to David Ecker, PhD, DVP and Carlsbad Site General Manager, Ibis Biosciences, Inc., an Abbott Company; Emilio A. Emini, PhD, FAAM, Senior Vice President, Vaccine Research and Development, Pfizer, Inc.; Richard DiMarchi, PhD, Cox Professor of Chemistry & Gill Chair in Biomolecular Sciences, Department of Chemistry, Indiana University; George Poste, PhD, DVM, CEO, Chief Scientist & Regent's Professor, Arizona State University; John C. Reed, MD, PhD, Head of Pharma Research & Early Development and member of the Enlarged Roche Corporate Executive Committee, F. Hoffmann-La Roche, Ltd.; and Dr. Moncef Slaoui, Chairman R&D, GlaxoSmithKline, for critical review and comments.

References

1. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov* 2012;11(3):191-200.
2. Stern AM, Markel H. The history of vaccines and immunization: familiar patterns, new challenges. *Health Aff (Millwood)* 2005;24(3):611-621.
3. Foltz IN, Karow M, Wasserman SM. Evolution and emergence of therapeutic monoclonal antibodies: what cardiologists need to know. *Circulation* 2013;127(22): 2222-2230.
4. Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies, and Applications.* 2nd ed. Boca Raton, FL: CRC Press; 2007.
5. Vercammen E, Staal J, Beyaert R. Sensing of viral infection and activation of innate immunity by toll-like receptor 3. *Clin Microbiol Rev* 2008;21(1):13-25.
6. Vollmer J, Krieg AM. Mechanisms and therapeutic applications of immune modulatory oligodeoxynucleotide and oligoribonucleotide ligands for toll-like receptors. In: Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies, and Applications*. 2nd ed. Boca Raton, FL: CRC Press; 2008:747-772.

Address correspondence to:
Stanley T. Crooke, MD, PhD
Isis Pharmaceuticals, Inc.
2855 Gazelle Ct.
Carlsbad, CA 92010

E-mail: scrooke@isisph.com