PEER-REVIEWED MINI REVIEW

Countering Bioterrorism: Current Status and Challenges - A Focus on Pharmaceutical Products and Vaccines -

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Abstract

Countermeasures against bioterrorism have increased since September 11 and anthrax attacks in the United States of America in 2001. The "Strategy to Make Japan the Safest Country in the World" was approved by the Cabinet in 2013. Strengthening countermeasures against naturally-occurring infectious disease outbreaks implies strengthening countermeasures against bioterrorism; however, the latter bears particular challenges. One of these challenges is the approval of counter-terrorism therapeutic or prophylactic agents, since the use of these agents is rare. To move up the market for innovative drug candidates, the "SAKIGAKE" designation scheme was introduced on a pilot basis by the Ministry of Health, Labour and Welfare in 2015. It is hoped that this scheme will be also applicable for counter-terrorism agents.

Keywords: Bioterrorism, Countermeasures, Infectious Diseases, Therapeutic or Prophylactic Agent

Introduction

With the upcoming 2020 Tokyo Olympics and Paralympic Games, the "Strategy to Make Japan the Safest Country in the World" was approved by the Cabinet in 2013[1]. Countermeasures against bioterrorism were expanded especially after the September 11 terrorist and anthrax attacks in the US in 2001. Preceding the anthrax attacks in the US, Japan also experienced bioterrorism attempts by the cult Aum in the 1990's. In 1993, an aerosolized *Bacillus anthracis* was disseminated from the roof of a building in Kameido, Tokyo[2]. This incident elicited complaints of foul odors in the neighborhood; however, at that time, it was recognized only as a nuisance posed by the odor. It was only during 1999-2001 that *Bacillus anthracis* was detected in environmental samples by microbiological tests. Since then, more than 20 years have passed. Bioterrorist attacks rarely happen; however, once they break out, their impacts on society are enormous. Thus, preparedness during peaceful times for emergency cases is indispensable. Implementing improved measures for infectious diseases control can strengthening countermeasures against bioterrorism. Nevertheless, challenges specific to counter-bioterrorism should be adequately addressed. We will describe the principle and implementation of countermeasures against bioterrorism and discuss the challenges in Japan, focusing on pharmaceutical products and vaccines.

Features of bioterrorism

Bioterrorism is defined as terrorism caused by intentional dissemination of biological agents, including virus, bacteria, fungi, and toxins. The features of bioterrorism can be described as follows[3,4]: (1) contamination caused by a single exposure to biological agents can be recognized in different areas at different times because of the latency period; (2) development of diseases could differ among individuals according to their health status, including agent-specific immunity; (3) the number of patients can increase by a secondary infection; (4) distinguishing bioterrorism from naturally occurring infectious diseases could be difficult, especially in covert cases; (5) preliminarily prevention against the biological agents of terror by a prophylactic drug or vaccine is possible (this can be an advantage for terrorists); and (6) the potential risk of generating novel agents with enhanced virulence, for example, enhanced drug resistance or infectivity to humans, by means of recent advanced technologies such as those in genetics. To implement countermeasures against bioterrorism, these features should be considered.

Outline for countermeasures against bioterrorism

The Centers for Disease Control (CDC) in the United States classified critical biological agents into three categories, from A-C[5]. Category A is the highest priority, because of the ease of dissemination and transmission from person to person, high mortality rate, potential for major public health impact, potential for public panic and social disruption, and thus the requirement of special action for public health preparedness. Category A includes anthrax (*Bacillus anthracis*); plague (*Yersinia pestis*); tularemia (*Francisella tularensis*); smallpox (variola major); viral hemorrhagic fevers, including filoviruses (Ebola and Marburg) and arenaviruses (Lassa and Machupo), and botulism (*Clostridium botulinum* toxin).

In 2001, anthrax attacks targeting senators or mass media occurred in the United States. After this incident, the Japanese government developed several countermeasures against terrorism and demonstrated a practical model to strengthen cooperation and coordination between related entities, agencies, and local governments for countermeasures

against nuclear, biological, and chemical (NBC) terrorism[6]. The Japanese governmental basic policy presented in that year for countermeasures against biological and chemical terrorism included the following issues: (I) improvement of medical preparedness such as through countermeasures against infectious diseases and preparation of vaccines; (II) strengthening the cooperation between counterterrorism-related entities including medical institutions; (III) strict management of possible biological or chemical agents for prevention of terrorism; (IV) improvement of response capacity of counterterrorism-related entities, including the police department, Japan Self-Defense Forces, fire and ambulance service, and Japan Coast Guard; and (V) proper and timely risk communication to the public[7].

Response and Preparedness

Countermeasures consist of preparedness and response. Countermeasures against bioterrorism implies an extension of countermeasures against natural outbreaks. The basic principle of infectious disease control is based on the mechanism of infection[4]. From the perspective of risk management, countermeasures are based on the principle of risk analysis, including risk assessment, risk management, and risk communications[3]. Surveillance and epidemiological investigations in bioterror incidents in comparison with natural outbreaks were described in detail as follows[4].

To respond to an incident, detection of the event is the first step[4]. Abnormal increase in the number of patients can be detected in comparison with the normal baseline of patients. Thus, understanding the baseline number of patients for each disease in the community is essential. In Japan, surveillance of infectious diseases of categories I to V is defined by the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. Patients with these diseases are reported to a public health center by medical practitioners. When an outbreak is anticipated, local government, mainly the public health center and public health laboratory, would take action toward public health response, including epidemiological investigation and identification of causative agents. Prompt identification of causative agents plays a critical role, as it enables to take prompt and adequate clinical and public health measures consequently. Recently. advanced technologies in diagnostic microbiology provide comprehensive microbiological identification. These include meta-genome sequencing using a next-generation sequencer and time-of-flight mass spectrometer (TOF-MS) analysis, which are shown to be powerful tools for field genome surveillance for Ebola outbreak[8] or in clinical settings, including the detection of Carbapenemase[9,10]. They are also expected to be effective for bioterrorism investigation, as these methods do not require agent-specific tools for identification (e.g., specific antibody or PCR primer), and the causative agents would probably be unknown.

Further responses include vaccination, prophylactic administration of antibacterial or anti-viral drugs, isolation of patients, school closure, and risk communications.

Preparedness during the non-emerging period includes a stockpile of drugs, adequate necessities and equipment for microbial tests, and training of health-care professionals. A possible scenario is that the first responders are healthcare professionals or fire and ambulance service personnel in the case of bioterror attacks[3]. Subsequently, patients' samples could be tested to identify the causative agent in the clinical or public health laboratory. Given this possible situation, training of healthcare professionals to improve diagnosis, establishing networks to share information on abnormal increase in the number of patients in different areas at different times, and building a stockpile of clinical and laboratory materials for diseases that are rarely occur are essential.

The most important difference between a bioterrorism incident and a natural outbreak is that the former rarely occurs, but occur with criminal intentions[4]. In a bioterrorism incident, the diagnosis could be uncertain or drugs could be insufficient. To protect the community, including first responders under these critical circumstances and to allay public fears, it is always important to plan public health preparedness.

Challenges for Countering Bioterrorism

Counter-terrorism therapeutic or prophylactic drugs have been developed in several countries. Among the biological agents considered to be used by terrorists, the anti-smallpox vaccine LC16m8 was licensed in Japan[11]; however, production and stockpiles for most of NBC terrorism countermeasures are not sufficient. As clinical cases caused by bioterrorism agents are rare, the safety and efficacy of counter-terrorism drugs can not be evaluated in clinical trials in the same way as those of other general drugs. The US Food and Drug Administration (FDA) approved raxibacumab, an antibody preparation against anthrax, by using rabbit and monkey animal data for efficacy evaluation, while conducting clinical tests on healthy volunteers for safety evaluation to avoid human exposure to anthrax[12].

To accelerate the time to market for innovative drug candidates, the "SAKIGAKE" designation scheme was introduced in a pilot basis by the Ministry of Health, Labour and Welfare in 2015 (Fig. 1)[13]. It is hoped that this scheme will be also applicable for counter-terrorism agents.

Conclusions

While the 2020 Tokyo Olympics and Paralympic Games attract public attentions, the concern for bioterrorism increases. Mass-gathering events could be a target of terrorists. Once bioterrorism occurs, it would evoke enormous social impact and disorder. Strengthening countermeasures for infectious diseases outbreak would minimize human damage caused by bio-terrorism. This includes enhancement of public health surveillance, improvement of diagnostic accuracy, and development of the capacity to conduct laboratory microbial tests. Challenges exist in conducting clinical trials for the approval of counter-terrorism vaccines or drugs. Thus, a novel framework for safety and efficacy evaluation is needed.

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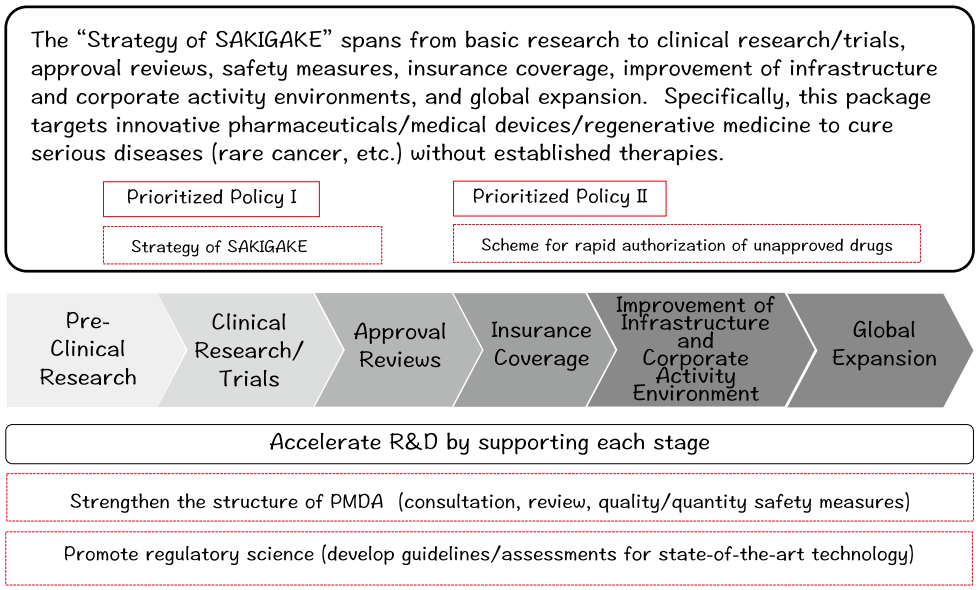

Fig. 1. Strategy of SAKIGAKE by MHLW
Lead the world in the practical application of innovative medical products.

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