Chapter

Nurturing Responsible Future Generation of Scientists: Focus on Maintaining International Health Security Competency

Aroem Naroeni and Budiman Bela

Abstract

Rapid progress of technologies does not only exclusively belong to developed countries nowadays but also spread out to developing countries including Indonesia. There are many Indonesian universities and emerging translational medicine centers that had declared themselves as research centers focusing on to bring science from bench to bedside. Since the outbreak of 2007 Avian Influenza, Indonesia had been starting to accumulate more knowledge and experiences related to biosafety and biosecurity. While Indonesian researchers were focusing on biorisk management of high pathogenic bioagents, students were also being exposed gradually to more sophisticated biological hazards through the utilization of synthetic biology and genetic modifications on their own researches. Nurturing the responsible future generation of scientist whom aware of the ethical, biosafety, biosecurity concerns cannot become more important, considering the possibility of dual use research results, which could bring either prosperity or chaos to the universe.

Keywords: biosafety, biosecurity, dual use research of concern

1. Introduction

Since the outbreak of 2007 Avian Influenza, Indonesia had been starting to accumulate more knowledge and experiences related to biosafety and biosecurity. While Indonesian researchers were focusing on biorisk management of high pathogenic bioagents, students were also being exposed gradually to more sophisticated biological hazards through the utilization of synthetic biology and genetic modifications on their own researches.

Trainings and workshops on aforementioned issues had been organized regularly, and at the same time, High Containment Facilities as BSL3 had been built in some locations with supports from various International organizations such as BEP, WHO, and FAO. One of the projects is the establishment and evaluation of Biorisk Management in University of Indonesia [1].

In 2005, WHO has established International Health Regulation (IHR) to strengthen health security, which defined as "activities required to minimize the danger and impact of acute public health events that endanger the collective health and population living across geographical regions and International boundaries."

IHR has purpose to provide swift response to global threats of spread of diseases without imposing significant disturbance to international traffic and trade [2]. One of implementations of IHR was by establishment of Global Health Security Agenda (GHSA) consortium to give participant countries such as Indonesia a capacity to prevent, detect, and respond to this spread, regardless of the root causes such as natural, deliberate, or accidental occurrences.

To achieve these goals, GHSA developed concept called "Action Packages," where Biosafety and Biosecurity are important elements. This Action Packages consist of:

Prevent 1: Antimicrobial Resistance
Prevent 2: Zoonotic Disease
Prevent 3: Biosafety and Biosecurity
Prevent 4: Immunization
Detect 1: National Laboratory System
Detects 2 and 3: Real-Time Surveillance
Detect 4: Reporting
Detect 5: Workforce Development
Respond 1: Emergency Operation Centers
Respond 2: Linking Public Health with Law and Multisectoral Rapid Response
Respond 3: Medical Countermeasures and Personnel Deployment Action Package [3].

A country achievement to GHSA Active Pack implementation is assessed voluntarily by a Joint External Evaluation (JEE). Indonesia was assessed back in 2017 by JEE with several recommendations:

1. to formulate necessary regulations to allow development and integration of IHR in a country multisectoral level;

2. to define a coordination mechanism between IHR and global security task force with relevant local ministries, agents, and institution; and

3. to evaluate and simplify bureaucratic structure of decision makers to enable Indonesia to act fast to national and international issues.

The report also noted the absence of National Biosafety and Biosecurity manual and the absence of select agent list and National Inventory of Biological agent [4, 5].

One Health University Network and One Health Laboratory Network were established to promote Biorisk Management at university level, which was participated by Indonesian well-known university such as Gadjah Mada University, Airlangga University, and Syiah Kuala University with pilot project at their own medical and veterinary labs. Major outcomes from this project were the establishment of institutional biosafety committee, a certification program for professional biorisk management, and the development of laboratory assessment tools.

In National scope, Indonesian Biosafety Association was founded in 2011 with objectives to:

- build a proper capacity in biorisk management in laboratories in Indonesia (research institutions, diagnostics, industry, and hospitals);

- collaborate with government and other authorities by providing technical inputs for national strategies, policies, and guidelines on biorisk management as well as advocate for a better understanding of biorisk management itself;

- become an efficient, functional, and sustainable biosafety organization;
- build interaction and communication between scientists and nonscientist professionals in order to support the development of biorisk in Indonesia;
- provide a forum to represent the interests and needs of biorisk practitioners, as well as a source for continuous information updates; and
- conduct training to ensure the implementation of safe laboratory quality and standards that are carrying out according to principles of biorisk management [6].

In addition, Biorisk Management standard had been successfully formulated under Indonesian National standard (SNI) nos. 8340:2016 and 8434:2017, which was adopted from CWA 15793 and CWA 16393, respectively [7–10].

At this report, we are focusing on the following areas:

- select agents and risk group;
- emerging and reemerging disease researches; and
- researches that use emerging technologies in Indonesia.

2. Methods

References from National and International Biorisk Management Guidelines in health, education, veterinary, and agriculture areas in various countries were sought to provide an in-depth view on this matter. It is noted that scientific journals on biorisk management and responsible science are still limited; therefore, some sources could only be obtained from unpublished reports and webpages.

3. Defining select agents and risk group in Indonesia

Definition of select agent according to the US Centers for Disease Control and Prevention (CDC) is "biological agent and toxins determined to have the potential to pose a severe threat to public health and safety to animal and plant health or to animal or plant products."

There are 67 organisms in CDC's list agents, which developed from initial list which contained 42 agents and toxins introduced in 1997. It included some agents that could affect both humans and animals (for example, *Bacillus anthracis* and *Francisella tularensis*) but not those whom affecting animals and plants only. It was preceded by some events such as:

- international commitments not to use disease as a weapon are embodied in the Geneva Protocol, which was signed in 1925 and entered into force in 1928. This protocol prohibited the usage of chemical and biological as weapons; however, it did not band the production, storage, or transfer of those materials and
- the Biological and Toxin Weapons Convention (BWC), which was signed in 1972 and entered into force in 1975 as well as Chemical Weapons Convention in 1993. This closed the gap, which was not covered by Geneva Protocol previously.

Article I of the BWC states that "Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

1. Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

2. Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict."

Group	**WHO [18]**	**NIH [19]**	**EU [13]**	**China [20]**
1	Well-characterized agents are likely not cause human or animal disease.	Agents are not associated with disease in healthy adult humans.	Agents are unlikely cause human disease.	Agents do not cause human or animal disease under normal circumstances.
2	Agents cause human or animal disease but unlikely to be a serious hazard to laboratory workers, the community, the livestock, or the environment. Effective treatment and preventive measure are available.	Agents are associated with human disease, which is rarely serious. Effective treatment and preventive measure are often available.	Agents can cause human disease and might be a hazard to workers. It is unlikely to spread to the community. Effective prophylaxis or treatment is usually available.	Agents cause human or animal disease under normal circumstances but do not pose a serious hazard to people, animals, or the environment, and the risk of transmission is limited. Laboratory-associated infection rarely causes serious illness with effective treatment and prevention.
3	Agents usually cause serious human or animal disease but do not spread from one individual to another. Effective treatment and preventive measures are available.	Agents are associated with serious or lethal human disease. Preventive or therapeutic interventions may be available. Risk of spreading to individual is high but to community is low.	Agents can cause severe disease and pose a serious hazard to workers. It may spread to community, but effective prophylaxis or treatment is usually available.	Agents can cause serious human or animal disease. It is relatively easy to spread between people, animals and people, among animals, directly or indirectly.
4	Agents usually cause serious human or animal disease. They can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	Agents likely cause serious or lethal human disease. Preventive or therapeutic interventions are not usually available. Risk of spreading to individual and to community is high.	Agents cause severe human disease and pose a serious hazard to workers. Risk of spreading to community is high. Effective prophylaxis or treatment is usually not available.	Agents can cause very serious disease in humans and animals, including biological agents that have not been found in China.

Table 1.
Comparison of biological agent category criterion based on biosafety.

The BWC does not prohibit research on defenses against biological weapons where a number of countries, including the USA and its major allies, have continued to do. Indonesia signed the BWC in 1972 and signed the ratification in 1992. Currently, there are 183 countries that have ratified BWC [11].

In developed countries such as the USA, Europe, Canada, China, and Singapore, select agents have been defined well, but most of the developing countries including Indonesia do not have it yet [12–16]. Resources of biological agents in developing countries are very significant; thus with the presence of various biological agents and toxins, it can cause a real threat. Some countries can refer to the biological agent list of the US CDC, but this is not a universal list because it may contain some preferences to the US national interest. Developing countries should evaluate characteristics of each biological agent and threats faced, existing biodefense capabilities based on its specific regional conditions. The CDCs of developing country play an important role in this process and cooperate with other related departments and organizations [17]. Although some US organizations had facilitated discussion with relevant Indonesian institution and initiate list of select agents but the list could not be defined yet. Indonesian Ministry of Agriculture has "red microorganisms," where the usage and distribution must be limited to certain laboratories; however, it is not a standard practice for others. Nowadays, there is no select agent list in Indonesia. Controlling the work of using these pathogens and high pathogenic organisms has been performed by each institution individually. Most of laboratories do not have the awareness about the importance to limit the usage of select agents. Furthermore, Indonesia also does not have risk group category criterion. WHO or CDC criterions were followed, which sometimes may not be suitable with local condition (**Table 1**).

4. Emerging and reemerging infectious diseases

Other important subjects are emerging and reemerging infectious diseases, which could pose a major threat to global public health. On the other hand, these subjects also attract many scientists to obtain good publications and funding. Despite of all efforts in biorisk management, unfortunately the handling of pathogenic viruses remains a likely source of infection, and mortality, among laboratory workers [21].

Accidental infections of workers in hospitals or research laboratories are an emerging threat mainly due to the increasing amount of research with it being

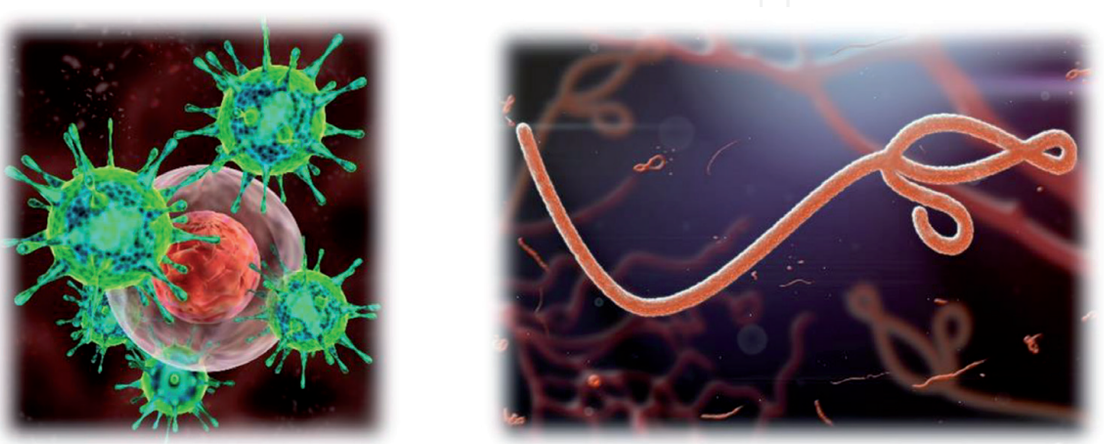

Figure 1.
Hepatitis and Ebola virus.

carried out involving the Risk Group 3 or 4 [22]. Infections due to the blood borne emerging viruses such as hepatitis C and HIV are the commonest diagnosed viral infections [23]. Laboratory-acquired infection by other emerging viruses such as SARS, Marburg, dengue, vaccinia, Crimean-Congo hemorrhagic fever, Western equine encephalitis, West Nile virus, and Zika has also been reported [24–30].

A strict biorisk assessment should be applied prior to experiments. A sufficient mitigation should be assessed by biosafety officer and Biosafety committee. Unfortunately, only some institutions in Indonesia have Institutional Biosafety Committee and do not have National Biosafety Committee yet. Currently, assessment was performed together, and decision was made based on available mitigation in the laboratory (**Figure 1**).

5. Emerging technologies

Rapid progress of technologies does not only exclusively belong to developed countries nowadays but also spread out to developing countries including Indonesia. Life sciences such a molecular biology, bioengineering, genetic engineering, bioinformatics, and synthetic biology could not be more important nowadays since it plays a pivot role in developing translational medicines and biotechnologies. There are many Indonesian universities and emerging translational medical centers that had declared themselves as research centers focusing on to bring science from bench to bedside. Also, many biotechnology centers provide sources for livestock, pharmacy, cosmetics, industry, and many more. They always try to bring experiments to applications.

On the other hand, the development in life science is no longer obtained exclusively through formal educations but could also be acquired from powerful informal sources such as Internet and social network. Without a proper guidance, biosafety, biosecurity, and dual use issues can become a major risk in human life itself. It could be said that biosafety focuses on procedures and techniques to prevent an accidental or unintentional release of bioagents, and biosecurity focuses more on accountability measurements and procedures to protect bioagents from unauthorized access, misused, thievery act of an intentional release [9, 31, 32]. Dual use according to the US Government is "a life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies 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." The US Government's oversight of DURC is aimed at preserving the benefits of life science research while minimizing the risk of misuse of the knowledge, information, products, or technologies provided by such research. Whereas WHO's definition is "life sciences research that is intended for benefit, but which might easily be misapplied to do harm."

During this time, we also met with students whom very interested in participating on International Genetically Engineered Machine (IGEM), where Indonesia is an active participant since 2013. On one of IGEM project on TBC diagnostic system called "Blue Ivy Project," it brought us to important realization regarding dealing with the amplification of risk in growing cultures and biofilm where rigorous SOPs during works were required to satisfy its biosafety and biosecurity aspect of this project (**Figure 2**) [33].

Challenges in biosafety and biosecurity became more complicated year by year such as "BaContraception Project" to design contraception by using *Bacillus subtilis 168a* and *Escherichia coli BL21* to express SboA—the spermicidal protein and

Figure 2.
IGEM project in University of Indonesia.

ndoA—the suicide protein, where researchers were exposed to risk of sterility. The lessons learnt from this project were "who create risk will be the responsible person to manage the risk" and realization of no official bodies in Indonesia handling synthetic biology domain [34].

In the next project, the Hi Vax project, we knew that Indonesia got attention from the IGEM board as we got information from FBI during its workshop in Jakarta. They would like to make us aware that technologies are progressing fast in Indonesia and urge a control going along it to not cause harm and threats. Hi Vax project is a project to make HIV DNA Vaccine. Basically, they are capable of making the HIV proteins with this system. It is why FBI emphasized this issue to all stakeholders in Indonesia to have concerns about the science progress in Indonesia and think about the risk particularly dual use research of concerns along the progress of technologies. In addition, in the recent IGEM project which working with the synthetic toxin of Diphtheria, team started to establish carefully the risk assessment, so they are capable of analyzing the possibility of dual use research and communicating it to IGEM's Biosafety and Biosecurity Board [35].

Based on our experiment, we realize the urgent of need of National Biosafety Committee or at least Institutional Biosafety Review Board. But, how many lectures or researchers have concern about this? Whereas many new emerging technologies are coming with fast progressing to arrive in the border of ethical problems and of course, the biosafety, biosecurity, and dual use research of concern. Recombinant protein, Genetically Modified Organisms, induced-Pluripotent Stem Cell (iPS), Gain of Function (GoF), and CRISPR (clusters of regularly interspaced short palindromic repeats) are now coming and become a common methods at life science laboratories. In addition, DIY-bio (Do it Your self Biology) is omnipresent at the same time of the emerging of biotechnology program and biotechnology start up. They must be equipped with a sufficient Biorisk Management. Recombinant protein is a technology to produce protein made based on DNA recombinant that has been cloned in system that supports expression of the gene. Modification of gene by using recombinant technology leads to the expression of a mutant protein, over expression or suppress expression. Gain of Function (GoF) is a research that involves experimentation that aims or is expected to (and/or, perhaps, actually does) increase the transmissibility and/or virulence of pathogens. The aim of GOF research is to improve understanding of disease causing agents, their interaction with human hosts, and/or their potential to cause pandemics. GOF research (GOFR) can pose risks regarding biosecurity and biosafety. Nowadays, new technologies that become a star are CRISPR and iPS. CRISPR or CRISPR Cas 9 system allows genetic material to be added, removed, or altered at particular locations in the genome, whereas iPS allows whatever cells in the body to be reprogram into

stem cells. These future technologies are expected to resolve many problems in disease therapies, and at the same time, we have to minimize the side effects of these technologies.

6. Responsible science

The advance of biotechnology benefits for life science research. It resulted in important biomedical products and resolved many health problems. However, advances in technology and research can unintentionally lead to techniques and/or findings that:

- increase virulence, transmission, or host range of a pathogen;
- confer antibiotic resistance so as to decrease currently effective treatments;
- enable evasion of currently existing diagnostic or detection mechanisms; and
- demonstrate weaponization of a pathogen.

WHO created guideline Responsible life science research for global health security for promoting excellent, safe, secure and responsible life science research. It consists of three pillars supporting public health:

- research excellence;
- ethics; and
- biosafety and laboratory biosecurity.

This guideline shows that the best protection against the possibility of accidents and deliberate misuse of life science can be attained by promoting culture of scientific integrity and excellence and distinguished by openness, honesty, accountability, and responsibility (**Figure 3**).

Research excellence means encouraging quality of life science activities that serve as the basis of development of new treatments and therapeutics. It supports health research system and promotes public health surveillance and response activities. These all elements are essential to protect and improve health and well-being of all people. To attain them, countries or institutions are requested to:

- support capacity development for research and
- use existing tools and frameworks, which are health research systems (HRS), the WHO strategy on research for health, and the International Health Regulations (IHR) as these can provide useful tools for contributing to responsible life science research.

Ethics are promoting responsible and good research practices. It provides tools and practices to scientists and institutions that allow them to discuss, analyze, and resolve dilemmas they may face in research including problem related to the possibility of accidents or misuse of the life sciences. Countries and institutions are requested to:

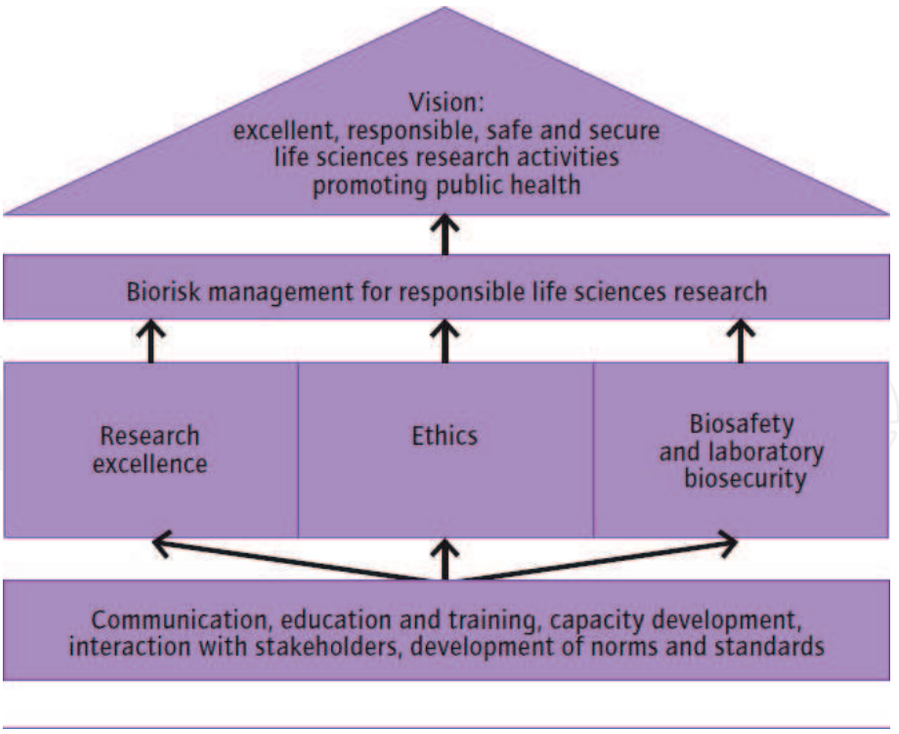

Figure 3.
Biorisk management framework for responsible life science research.

- use current ethical platforms, if appropriate;
- promote ethics education and training for students and professionals;
- encourage discussion and reflection on research practices;
- hold institutions and researchers to account and ensure they are aware of their responsibilities; and
- ensure institutions and researchers are aware of existing and new legislation, regulations not only at the country but also at the regional and international levels.

Biosafety and biosecurity are the implementation and strengthening of measures and procedures to:

- minimize the risk of worker exposure to pathogens and infections;
- protect the environment and the community; and
- protect, control, and account for valuable biological materials (VBMs).

All measures are applied in the laboratory or institution in order to prevent accidental and deliberate release of pathogens and valuable biological materials. They are aimed to ensure a safe and secure laboratory environment. Countries and institutions are requested to:

- conduct biosafety and laboratory biosecurity risk assessments and prepare mitigations to reduce the risk;

- implement a laboratory biorisk management system;
- explore the use of existing biorisk management structures (e.g., laboratory biorisk management adviser and the biosafety committee) to address issues related to the risks posed by life science research; and
- set performance objectives and work on continuous improvement [36].

7. Recommendation and lesson learned

The progress of biotechnologies in developing countries especially in Indonesia does not walk in parallel with the raising of awareness for more responsible science, which gives an alert for future development on life science research itself. Thus, a task to raise awareness for more responsible science should be done in all sectors particularly in universities and research centers. In addition, responsible science must reach young scientists and spread at all universities in Indonesia.

Although Indonesia had established national standards for biorisk management, yet they are still on voluntary basis and not implemented in all related institutions. Thus, establishment of more detail guidelines and compulsory regulations on biorisk management should be accelerated and performed by all stakeholders.

8. Conclusion

University medical research center is one of a front line to face emerging technologies and emerging diseases. It is a place that could bring a silver lining in developing health security, but at the same time, it could pose a concern on dual use research application.

Medical research center is a good place to start applying more responsible science and nurturing the next generation of scientists whom have more awareness on biorisk issues. However, it is still long way to go at least for Indonesia to establish the biosafety committee at institutions as well as at national level. A need to define National Select Agents and Risk group microorganisms is also noted to provide guideline and better support for biorisk management itself.

Regardless all limitations above, efforts to raise awareness in young scientists should continue not only by established organizations such as Indonesian Biorisk Association and One Health Laboratories Network but also by full supports from other relevant stakeholders in order to motivate them to create a better research environment.

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