

# Chapter 3

## The Global Threats from Naturally Occurring Infectious Diseases



Alessandro Mancon, Davide Mileto, and Maria Rita Gismondo

**Abstract** Biological risk relates to a broad spectrum of possible scenarios, that can be classified in three categories: natural occurring, unintended and deliberate. The prevention and management of such events require dedicated measures at national and international level, in terms of biosafety and biosecurity: an optimized intervention can minimize the probability of occurrence, but also adverse short-term (i.e.: number of casualties, population reaction...) and long-term (i.e.: chronic illnesses, ecological changes, trades drop...) consequences. Natural scenarios include common, emerging/re-emerging and chronic infectious diseases: they are caused by biological agents, which can be normally present in the communities, as acute or chronic pathologies, or suddenly appear, causing new or uncommon syndromes. In particular, a lot of environmental and human factors can influence emerging and re-emerging diseases: for example, urbanization and people mobility facilitate microorganisms spread, while climate changes are likely to induce a relocation of pathogens vectors. Unintended events are usually due to research and diagnostic activities: laboratories are the places where biological agents are handled and a lack in Biosafety measures or negligence can result in accidental release; the so called Laboratory Acquired Infections represent the main consequence, since they cause pathologies in the laboratory workers, but could be also transmitted in the population. Deliberate use of biological agents is strictly related to terroristic activities: microorganisms are very suitable for this purpose, since they are hidden and can easily spread. The present chapter summarizes the main characteristics of biological

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Alessandro Mancon and Davide Mileto equally contributed to this work.

A. Mancon • D. Mileto

Laboratory of Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli-Sacco, "L. Sacco" – University Hospital, Milan, Italy  
e-mail: [alessandro.mancon@unimi.it](mailto:alessandro.mancon@unimi.it); [davide.mileto@unimi.it](mailto:davide.mileto@unimi.it)

M. R. Gismondo (✉)

Laboratory of Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli-Sacco, "L. Sacco" – University Hospital, Milan, Italy

University of Milan, Milan, Italy

e-mail: [mariarita.gismondo@unimi.it](mailto:mariarita.gismondo@unimi.it)

agents related events, taking in account their origin and the principal consequences on the community.

### 3.1 Introduction

Nowadays, when speaking about Biological risk we have to take in account a broad range of possible scenarios, varying from the simple exposure to a microorganism responsible for an infection to an intentional release of biological agents to cause epidemics.

Specifically, the wild spectrum of these risks can be attributable to different events with dissimilar levels of intent: natural occurring, unintended and deliberate (Fig.3.1).

The category of events naturally occurring is represented by all the naturally occurring infectious diseases of humans, animals and plants at national and/or international levels, jointly with the re-emerging ones often responsible of outbreaks that occur cyclically over time.

The unintended events represent a wild category in which it is possible identified different levels of responsibility for the involved staff. Often, the events can be the unintended consequence of a research or in other case can be the consequence of a laboratory accidents in which untrained staff is involved. Within the unintended event the lack of awareness, the underestimation of the risk as well as the negligence by the workers during the conduction of procedures for the management of biological agents represent a big source of risk for the occurrence of unintended event.

The deliberate misuse represents the last zone into the broad range of the biological risk. All the aimed actions to intentional use of pathogens for harmful purposes are include into this last part of the risk spectrum.

As a consequence of the different nature of the biological risk, its management focuses on different sectors:

- preparing for the management of the naturally occurring disease outbreaks, on a national or international scale, facing the impact of the events on the individuals and public health, national and international economies, and social systems;

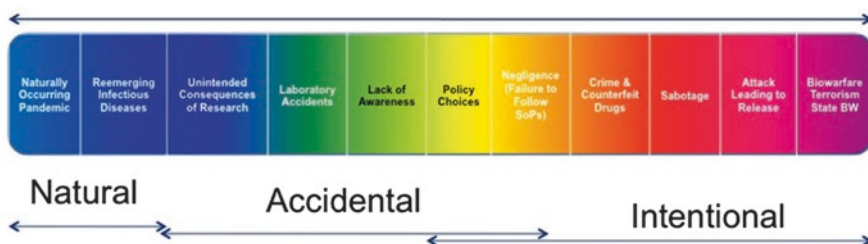


Fig. 3.1 The spectrum of Biological risk (Available on <http://iclscharter.org/>)

- *Biosafety* defined by the UN as “principles, technologies, practices and measures implemented to prevent the accidental release of, or unintentional exposure to pathogenic agents” [1];
- *Biosecurity*, which refers to the “protection, control and accountability measures implemented to prevent the loss, theft, misuse, diversion or intentional release of pathogenic agents and related resources as well as unauthorized access to, retention or transfer of such material” [1].

## 3.2 Consequences of Biological Events

The occurrence of a biological event, both on national or international scale, may have social implications with consequence in the short or in the long run.

### 3.2.1 Short-Term Consequences

Subsequently the occurrence of a biological, local and/or national institutions implement an emergency plan as first response throw specific preparedness strategies with the increasing of medical resources and infrastructures.

Naturally, the different degree of the emergency response depends on the availability of resources, know-how and the specific skills to manage the emergency of each different context in which the emergency occurs.

The consequence of a biological event in terms of number of casualties, also depends on the essential features of the biological agent involved: infectivity, virulence, incubation period, transmission, pathogenicity, lethality and stability, surely are all key features that play a crucial role in defining the severity of the outbreak. This is certainly true especially in the early moments following the emergency breakdown when not all the emergency containment and management measures are already fully active.

Within of a Bioemergency scenario, the negative psychological reactions are unpredictable and the perception of a real biological risk triggers terror and panic within the population.

It is for that reason that the communication is not just the conveyance of information but media should be seen as a partner in supporting risk communication to bridge the gap between the perception of the public and the scientific assessment of risks [2].

### **3.2.2 Long-Term Consequences**

The elements affecting the seriousness of the event are several: density of population of the affected area, geographical features of the affected area, quantity of dispersed material and health-care response efficiency [3]. Many of such parameters have a cascade effect which is reflected on the affected community by the event in terms of economic impact, geographical extension, quality of human health, etc., i.e. long-term effects.

According to WHO, effects of biological events may extend beyond their immediate target both in time and space and include: chronic illness, delayed effects, new infectious disease becoming endemic, effects mediated by ecological changes.

Considering a hypothetical scenario in which a biological event could affect plants or animals, the effects could lead to strong ecological changes that could be reason of reduction in the quality and quantity of food supply derived from plants or animals.

## **3.3 The Spectrum of Biological Events**

As mentioned above, the biological risk is linked to a wide range of occurrences, that could be natural, accidental or intentional. Every day population is exposed to common pathogens, that cause many different diseases, such as influenza or gastrointestinal syndromes, while an unintentional exposure to microorganisms more or less dangerous is usually related to research and health activities; fortunately, the deliberate misuse of biological agents has been infrequent among human history, but the low control on these agents in some countries (i.e.: scarce resources, war...) and the rising number of terroristic activities represent a dangerous scenario also from this point of view.

### **3.3.1 Naturally Occurring Events**

Infectious diseases are a stable travel companion for human kind, as demonstrated by the description of such syndromes in ancient times: antique Egyptian paintings depict people with typical poliomyelitis skeletal deformations [4], while during the fifth century BC, in Greece, Thucydides and Hippocrates described different epidemics, the Plague of Athens and the Cough of Perinthus respectively [5]. Many pathogens disappeared, other arise and some other still go with humans, animals and plants.

In order to describe contemporary infectious diseases, we can classify them into three categories: common, emerging/re-emerging and chronic.

Common infections are normally present in the community, in which they induce pathologies of variable severity, according to host and agent characteristics. A main aspect to be considered is the immune system of the affected individual: in normal conditions, it is enough to contrast pathogens action, acting through cell response and antibodies; on the contrary, in immunocompromised patients the infections are likely to evolve to worse conditions and increase to a life-threatening state [6]. In developed countries the use of drugs and public health measures succeeded in contrasting many of these diseases, which remain a big issue in low income nations: the best example are AIDS, malaria and tuberculosis, controlled in Europe, Northern America and other rich areas, while recognized as principal enemies in the other world region by World Health Organization [7].

Emerging and re-emerging infectious diseases are a main global concern, since many of them involve highly hazardous pathogens or a very large population. The US National Institute of Health defined the Emerging infectious diseases as those never occurred in humans before or occurred affecting few individuals in isolated communities or occurred throughout human history but only recent recognition of the infectious etiology. Similarly, Re-emerging infectious diseases are those that were a major health problem, declined dramatically and are now becoming again a concern in a significant population [8].

Swine Flu, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Ebola Virus Disease (EVD) are perhaps the most well-known examples of emerging diseases, due to the large spread of information through mass media.

Swine Flu emerged during 2009 in Mexico: researchers isolated in humans a H1N1 Influenza A virus, founding a history of contact with pigs in the first cases [9]; the pandemic declared by WHO in the same year resulted in a limited number of infections and deaths: European Centre for Disease Prevention and Control estimated in January 2010 approximately 14,300 deaths Worldwide, very low if we compare with Spanish Flu accounting for more than 100 millions [10].

SARS and MERS are respiratory syndromes, both caused by Coronaviruses. The first was discovered in 2003 in China, where an American business man was hospitalized for an atypical pneumonia: the Italian microbiologist Carlo Urbani, analyzing the clinical case, understood that a new infectious disease was the cause of the illness and permitted to identify a new virus; unfortunately, he contracted the infection, dying after few months [11]. MERS appeared in Middle East area in 2012: a new Coronavirus was isolated from patients in Saudi Arabia, Gulf region and Jordan, causing 34 cases as of May 2013, with a mortality rate of 60% [12]. Such high mortality decreased over time, reaching the actual estimated value of 35%, but WHO experts believe that it is an overestimated data, due to lack in cases reporting; moreover, the restricted geographical region interested suggests a hard human-to-human transmission [13].

Ebola virus belongs to *Filoviridae* family, which also includes *Marburg* virus: these pathogens are known to be highly infectious and to cause severe syndromes characterized by hemorrhages. After their discovery in 1976 and 1967, several epidemics have been reported in Central Africa: these events typically involved a small

population, owing to isolation of rural areas in which occurred, but the mortality rates ranged from 50% to 90% [14]. However, in 2014 in the Western Africa Guinea country a new epidemic started, assuming a completely new aspect: the infection spread to border nations Sierra Leone and Liberia, then to Nigeria, Senegal and Mali and it was also imported in US and Europe, with patients repatriated to be cured or, in the US, by a traveler. The epidemic was declared an international health concern and lasted 2 years, like never before, with number of cases and deaths increased up to more than 28,000 and 11,000 respectively [15].

Considering re-emerging diseases, malaria and bacterial infections are considered major concerns. Antimalarials, antibiotics, swamplands reclamation, hygiene practice and other measures reduced the incidence of these pathologies in high-income countries, but also achieved important results in low-income ones. However, some reports underline how the risk of raise of plasmodium and bacteria is increasing: in a book of Organization for Economic Co-operation and Development (OECD) on environmental changes, the authors underlined that the population exposed to the risk of malaria infection will increase up to 5.7 billions in 2050, if no action is take [16]; in the same way, O'Neil and colleagues pointed out that, if the insurgency of antibiotics resistant bacteria is not stopped, in 2050 we will see ten millions deaths ascribable to bacterial-related pathologies, a situation similar to the pre-antibiotics era [17].

Many common diseases have the potential to become an emerging or re-emerging one, certainly because biological agents evolve and adapt to new conditions, but also environment and human action play a main role in these event. Among the multiple factors influencing this process, the followings are the main actors.

- *High mobility of population*: the high number of daily flights, the availability of cars and roads, the presence of efficient railways and the use of touristic boats allow people to rapidly move inside their countries and across them. Such a high mobility helps biological agents, since they travel with people as hidden hosts.
- *Urbanization*: due to urbanization, deforestation causes the loss of natural habitat for many animals, that could be reservoirs of biological agents: since cities take place of forests, the probability of contact between humans and these animals increases, augmenting the risk of microorganisms transmission.
- *Climate change*: many world areas are experiencing a change in temperatures and climates, in particular becoming hotter and more raining. Such events favor the expansion of vectors, like mosquitoes and ticks, in places where they have been eliminated or haven't been ever present: the consequence is a higher probability of infection in populations which were exposed to such risk only in the past or have never been exposed/affected.
- *Encroachment of habitats*: high density of population means more contacts, which in turn entail higher risk of transmission.

### 3.3.2 *Accidental Release of Biological Agents*

Accidental releases of biological agents are certainly a relevant issue in Biosafety.

The risks in a health-care facilities are related to the presence of a series of danger factors, both material and procedural, such as: agents (chemical, physical and biological), equipment (high voltage equipment, centrifuges, pressure and vacuum systems, high and low temperatures, needles, sharps), space (crowding or space limitation), organizational-management aspects, lack of information, education and training of the staff (especially the external personnel).

The organization-management aspects are often underestimated: sometimes communication between workers might be difficult and the facilities are often lacking of internal procedures.

As it is often the case, the simultaneous presence of different staff in the same work space can contribute to increasing the risk of an accident: researcher or technical-scientific staff and sometimes external personnel as adjunct researchers, graduate students, fellows or guests are contemporary present in the same room.

The main accidents that may occur in a health-care facilities are: spills of materials, projection of infected liquids from a pressurized device or equipment, break of tubes in a centrifuge, projection of liquid in the eye, cut or prick when handling contaminated materials, bite by a laboratory animal, accidental injection of a contaminated solution, wound or loss of consciousness in a laboratory [18].

As a part of biological accident, surely the Laboratory-Acquired Infections (LAIs) occupy a major role. LAIs also called occupational illness or laboratory-associated infections are defined as all infection acquired through laboratory or laboratory-related activities regardless whether they are symptomatic or asymptomatic in nature [19].

The infections may happen subsequently to an exposure of the biological agent that can be through the respiratory tract, mucous membranes, oral intake, or percutaneous methods.

This is not a new phenomenon for the microbiological laboratories and different type of facilities can be involved: clinical laboratories, research laboratories, production installations.

To determine whether the micro-organism responsible of the worker's disease is present in the laboratory only or if it is present also in the community sometimes might be difficult.

LAIs are also a public health problem because the infected worker may represent a source of infection for his colleagues, relatives, family members or other citizens.

An exhaustive report on LAIs doesn't exist but only voluntary reports of cases study are available. The problem of undeclared laboratory events is widely acknowledged due to fear of reprisal and the stigma associated with such events [20].

During the years, a large number of LAIs were documented and from 2000 the most frequent acquired diseases are: brucellosis, Q fever, hepatitis, tularaemia, tuberculosis and psittacosis [19].

Among the accidental release of biological agents occurred over the years, two cases are certainly noteworthy. The first regards a case of SARS laboratory acquired infection occurred in September 2003 in a BSL-3 laboratory of Singapore when a 27 years old microbiology student got infected due to a laboratory incident: *“From the results of the epidemiologic investigation surrounding the recent case of SARS, it appears that inappropriate laboratory standards and a cross contamination of West Nile virus samples with SARS coronavirus in the laboratory led to the infection of the doctoral student. No evidence could be found of any other source of the infection. West Nile virus and SARS coronavirus were detected in the virus samples handled in the laboratory. There is no evidence of secondary transmission and this is an isolated case of SARS”* [21].

The second case regards an environment accidental release of biological agents due to an error in effluent control of laboratories in Europe regard the release of Foot-and-mouth disease virus.

Foot and mouth disease (FMD) is a highly contagious viral disease which affects all cloven-hoofed animals and it has a negative impact on livestock productivity in countries where the disease is endemic [22]: *“In the European Union (EU), at least three different FMD outbreaks were linked to virus escape from laboratories. The incidents in Tübingen (Germany) and in Maisons-Alfort (France) occurred before 1991, when systematic prophylactic vaccination of cattle against FMD was employed in the majority of countries in continental Europe. The third incident occurred in 2007 in Pirbright (United Kingdom)”* [23].

### ***3.3.3 Intentional Release of Biological Agents***

During history, many armies unknowingly used biological agents as weapons. The presence of microorganisms was unknown, but their effects were evident: transmissible diseases were killing people and soldiers could spread them to weaken enemies, by contaminating water supplies and cities by means of infected corps.

A significant example is the siege of the Crimean city Caffa, in 1346. An account by Gabriele de’ Mussi reports that Tartars hurled plague cadavers inside the town, trying to conquer it; the author also suggested that it was the origin of European Black Death in the fourteenth century, but this hypothesis has not ever been confirmed [24].

During the nineteenth century, the scientific evolution in the microbiology field allowed to understand the pathogenic mechanisms related to bacteria, virus, fungi and parasites, and to find new cures; however, it also paved the way for research on bioweapons. In particular, after the World War I until the end of Cold War, different countries implemented military programs aiming to develop such new war tools. In Japan, the general Shirō Ishii found and headed the Unit 731, which between 1936



and 1945 conducted a lot of experiments with biological agents on alive subjects. This Unit studied the effect of various agents (i.e.: *Y. pestis*, *B. anthracis*, *V. colerae*...), directly infecting the prisoners and exposing Manchurian population to these agents using bombs [25]. Similarly, in 1942 the British army started to test the effect of *B. anthracis* on the Gruinard island: aerosols containing the bacterial spores were spread in the environment, in order to infect several sheep and observe the consequences; the animals acquired infections and died, but the epidemic reached also farms on the mainland [26]. The British government first stopped the project and then quarantined the island until 1990, the year of anthrax-free declaration.

The two previous examples underlined the defects of the Geneva Protocol, the first international effort to limit these kind of highly hazardous programs: the Protocol prohibited the use of biological weapons, but not their possession or development [27]. For this reason, in 1972 the Biological Weapons Convention (BWC) was opened to signature and then it entered into force in 1975: this new document establishes that development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons are strictly forbidden [28].

Since the majority of World countries undersigned the BWC, the main concern related to bioweapons is bioterrorism. Terroristic groups aim to generate panic inside the communities and the possible arise of dangerous highly infectious diseases is one of the most frightening nightmare; fortunately, only few attempts occurred, with limited consequences. In 1984, a group of fanatic followers of the spiritual leader Osho Rajneesh used *Salmonella typhimurium* to contaminate food in some restaurants at The Dalles, Oregon: a total of 751 cases of gastroenteritis occurred, among restaurants employees and customers, but no patient died; 2 years after, the suspects were sentenced to prison [29]. A similar case took place in Japan, by the religious sect Aum Shinrikyo. This group is well-known for the Tokyo tube sarin attack in 1995, but they also implemented a bioweapon program, to get various biological agents; in particular, it succeeded in retrieving *C. botulinum* and *B. anthracis* and used them in some unsuccessful attacks: in 1990, the sect members, thinking to spread botulinum toxin, pumped an aerosol in Tokyo, Narita airport and Yokohama and Yokosuka US naval bases, but did not achieve the expected results; 3 years later, they tried twice to spray anthrax from the roof of a building in Tokyo, with the same null result [30]. Perhaps the most known case of bioterrorism is the anthrax one in 2001 in USA: letters containing *B. anthracis* spores were mailed to news media and two senators offices, causing 5 deaths and 17 infections; in 2007, FBI accused the scientist Bruce E. Ivins to be the author of the attack, declaring in 2008 that he was the only culprit, but many doubts exist about the investigations; Ivins committed suicide few days before such declaration.

The recent rising number of terroristic acts underlines the importance of implementing a biosecurity program, at both national and international levels.

### 3.4 Conclusion

Within the control of infectious diseases, indistinctly caused by natural, accidental or intentional events, the rapid detection of the biological agent and the proper management of the event itself, represent a crucial key point, since emerging, re-emerging, and novel infectious diseases are involved. In an increasingly globalized world, an active monitoring of outbreaks, as well as strategies and resources for an adequate and effective response are required to avoid the spread of such diseases. The 2013–2016 West Africa Ebola epidemic represents an example of how the lack of resources and preparedness can affect the response. The outbreak began in December, 2013, in a Guinean rural area, but the country did not have the capacity to detect it; in March, 2014, several organizations, such as Médecins Sans Frontières (MSF), responded and at the same time new cases were confirmed in the capital Conakry and in the bordering Liberia. During the two following months, the operators managing the epidemic realized that adequate diagnostic tools, protective gears, supportive cures and disease knowledge were missing, increasing healthcare workers and communities exposure; MSF warned about the severity of the problem, but both Guinea government and WHO downplayed it to avoid panic. The consequences became soon evident: the epidemic turned into an out of control scenario, resulting at the end in more than 28,000 infections and more than 11,000 deaths [31]. As positive outcome, WHO quickly reacted to the new Ebola outbreak in the Democratic Republic of Congo in May, 2017: experts, resources and training were provided for emergency management, minimizing the infection spread and increasing the preparedness [32].

The management of emergencies is usually considered only a public health issue, but it very often regards also plants and animals.

Above mentioned events highlight the different effects arising not only from lack in implementation of biosafety and biosecurity measures and adequate funding, but also the insufficient training of the health-care workers and risk awareness; moreover, the described cases emphasize the need for a national legislative basis for standardization in laboratories.

Certainly, the increase of internal protocols for laboratory practice, as well as the proper day-to-day maintenance of all high containment equipment and structures could help to contain any possible microorganism spreads. In the same way, continuous training for health-care workers plays a crucial role, in order to reduce errors during the management of the biological agents and to improve the quality of response in case of emergencies.

Also our institution is engaged in these purposes. Thanks to the availability of high level containment facilities, as national referral center, “L. Sacco” University Hospital is directly involved in the management of bioemergencies: the Emergency Room has an isolation triage room for suspect cases management; an high containment isolation unit is present at the Infectious Diseases Department for the hospitalization of confirmed patients; the Clinical Laboratory of Microbiology includes Biosafety Level 3 and 4 laboratories, for the diagnosis of highly hazardous agents.

Moreover, as centre of excellence in the field of Biosafety and Biosecurity, we periodically organize training courses on biosafety, aimed at strengthening the skills of health-care workers, and implement several international projects for biosafety culture spreading.

In conclusion, infectious diseases still represent a main concern for public health and global community; nevertheless, responsible national and international joint efforts are likely to properly face the possible coming emergencies.

## References

1. Meeting of the states parties to the convention on the prohibition of the development, production and stockpiling of Bacteriological (Biological) and toxin weapons and on their destruction. Report of the meeting of states parties. Geneva; December 1–5, 2008. BWC/MSP/2008/5. [http://www.opbw.org/new\\_process/msp2008/BWC\\_MSP\\_2008\\_5\\_E.pdf](http://www.opbw.org/new_process/msp2008/BWC_MSP_2008_5_E.pdf). Accessed 27 Oct, 2016
2. Dickmann P, Bhatiasevi A, Chaib F, Baggio O, Banluta C, Hollenweger L, Maarouf A (2016) Biological Risks to Public Health: Lessons from an International Conference to Inform the Development of National Risk Communication Strategies Report of an international conference on risk communication strategies before, during, and after public health emergencies, Rabat, Morocco, October 22–23, 2015. *Health Security* 14(6.) Mary Ann Liebert, Inc. <https://doi.org/10.1089/hs.2016.0050>
3. Cavallini S, Bisogni F, Mastroianni M (2014) Economic impact profiling of CBRN events: focusing on biological incidents. *Arch Immunol Ther Exp* 62:437–444. <https://doi.org/10.1007/s00005-014-0306-x>
4. Galassi FM et al (2017) Poliomyelitis in ancient Egypt? *Neurol Sci* 38(2):375
5. Martin PMV, Mertin-Granel E (2006) 2,500-year evolution of the term epidemic. *Emerg Infect Dis* 12(6):976–980
6. Barton FH et al (2014) Introduction to the immune system. In: Kasper D et al (eds) *Harrison's principles of internal medicine*, cap. 360, 19 edn (electronic version). McGraw-Hill, New York
7. World Health Organization – WHO (2015) Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases (HTM). WHO, Geneva. Available from: [http://apps.who.int/iris/bitstream/10665/204419/1/9789241510134\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/204419/1/9789241510134_eng.pdf?ua=1)
8. National Institutes of Health (US), Biological Sciences Curriculum Study; Understanding Emerging and Re-emerging Infectious Diseases; NIH Curriculum Supplement Series [Internet], Bethesda (MD): National Institutes of Health (US) (2007) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK20370/>
9. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, Gubareva LV, Xu X, Bridges CB, Uyeki TM (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 361. <https://doi.org/10.1056/NEJMoa0903810>
10. European Centre for Disease Prevention and Control; ECDC Daily Update – Pandemic (H1N1) 2009–18 January 2010 (PDF)
11. Ksiazek TG et al (2003) A novel coronavirus associated with severe acute respiratory syndrome. *NEJM* 348:1953–1966
12. De Groot RJ et al (2013) Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the coronavirus study group. *J Virol* 87(14):7790–7792
13. World Health Organization – WHO (2017) Middle East respiratory syndrome coronavirus (MERS-CoV) – Fact sheet (updated May 2017); World Health Organization, Media centre, Available from: <http://www.who.int/mediacentre/factsheets/mers-cov/en/>. Last access 31 May, 2017

14. Centers for Disease Control and prevention – CDC; Ebola (Ebola Virus Disease) – Outbreaks Chronology; Centers for Disease Control and prevention, Available from: <https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>, Last access 31 May, 2017
15. Centers for Disease Control and prevention – CDC; Marburg hemorrhagic fever (Marburg HF) – Outbreaks Chronology 1967–2014; Centers for Disease Control and prevention, Available from: <https://www.cdc.gov/vhf/marburg/outbreaks/chronology.html>, Last access 31 May, 2017
16. Organisation for Economic Co-operation and Development – OECD (2012) OECD Environmental Outlook to 2050. OECD publishing. <https://doi.org/10.1787/9789264122246-en>
17. O’Neill J (2014) Review on antimicrobial resistance antimicrobial resistance: tackling a crisis for the health and wealth of nations. London: Review on Antimicrobial Resistance. Available from: [https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations\\_1.pdf](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf)
18. World Health Organization (2004) Laboratory biosafety manual, 3rd edn, Available from: [http://www.who.int/csr/resources/publications/biosafety/WHO\\_CDS\\_CSR\\_LYO\\_2004\\_11/en/](http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/)
19. <http://www.biosafety.be/HomePage.html>
20. Sewell DL (1995 Jul) Laboratory-associated infections and biosafety. *Clin Microbiol Rev* 8(3):389–405
21. Review Panel on New SARS Case and Biosafety. Biosafety and SARS Incident in Singapore September 2003. Available from: [http://www.biosafety.be/CU/PDF/Report\\_SARS\\_Singapore.pdf](http://www.biosafety.be/CU/PDF/Report_SARS_Singapore.pdf)
22. Diego Viali dos Santos et al; Identification of foot and mouth disease risk areas using a multi-criteria analysis approach. *PLOS ONE* | <https://doi.org/10.1371/journal.pone.0178464> May 26, 2017
23. OVERVIEW REPORT Bio-risk management in laboratories handling live FMD virus. EUROPEAN COMMISSION HEALTH AND CONSUMERS DIRECTORATE-GENERAL. Ref. Ares (2015)854105 – 27/02/2015. Available from: [http://ec.europa.eu/food/fvo/overview\\_reports/act\\_getPDF.cfm?PDF\\_ID=335](http://ec.europa.eu/food/fvo/overview_reports/act_getPDF.cfm?PDF_ID=335)
24. Wheelis M (2002) Biological Warfare at the 1346 Siege of Caffa. *Emerg Infect Dis* 8(9):971–975
25. Sheldon H (2002) *Harris; factories of death: Japanese biological warfare, 1932–45 and the American cover-up*, 2nd edn. London, Routledge
26. Manchee RJ et al (1981) Bacillus anthracis on Gruinard Island. *Nature* 294:254–255
27. The United Nations General Assembly; Protocol for the Prohibition of the Use of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare; Geneva, 17 June 1925
28. The United Nations Office at Geneva; The biological weapons convention. Available from: [https://www.unog.ch/80256EE600585943/\(httpPages\)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument](https://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument). Last Access 18 Aug 2017
29. Török TJ et al (1997) A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. *JAMA* 278(5):389–395
30. Smithson AE (2000) Chapter 3: Rethinking the Lessons of Tokyo. In: Smithson AE, Levy L-A (eds), *Ataxia: the chemical and biological terrorism threat and the US response*. Washington, Henry L. Stimson Center, pp 77–79
31. Moon S et al (2015) Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola; *The Lancet* 385(10009):2204–2221
32. World Health Organization; Emergencies – In equatorial Congo, WHO and its partner respond to an Ebola outbreak; <http://www.who.int/emergencies/ebola-DRC-2017/articles/working-with-partners/en/>