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CRITICAL REVIEW

PATHOLOGY/BIOLOGY

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An Overview of Zoonotic Disease Outbreaks and its Forensic Management Over Time

ABSTRACT: Most emerging or re-emerging infections are vector-borne or zoonotic and can be disseminated worldwide by infected humans or animals. They are a major public health problem and cause a great impact on economy. Zoonotic outbreaks began to be characterized in the 90s, after the creation of Europol and the FBI. Such investigations are carried by forensic pathologists and other specialists to determine whether an outbreak is natural or deliberate. This review will discuss ten zoonotic outbreaks nonrelated to wars focusing on forensic management. In conclusion, some points should be highlighted in the management of a zoonotic outbreak: (i) its diagnosis and detection by forensic pathologists and the coordination of efforts between other specialists are key factors; (ii) communication guidelines and an efficient healthcare system are crucial for any emergency response; (iii) biosafety of all specialists involved must be guaranteed.

KEYWORDS: forensic science, biocrime, biosafety, biosurveillance, bioterror, communication, investigation agencies, management, zoonoses

Zoonoses are infectious diseases that affect animals (usually vertebrates) but can be naturally transmitted to humans. They can have a bacterial, parasitic, or viral origin, as observed for brucellosis, salmonellosis, listeriosis, campylobacteriosis, trichinellosis, and hepatitis A or E (1). Transmission occurs through the exposure of a susceptible population to the pathogenic microorganism (2), and zoonotic diseases can be disseminated worldwide by infected humans or animals during transport or migration. Many zoonotic diseases are major public and animal health problem and can impair the efficient production of food originated from affected animals and also the international commerce of related products, causing a great impact in economy (1). They are also responsible for decreased consumption of animal products and losses in tourism (3), as they may be considered a biological threat (4).

Problems arise when zoonotic disease becomes an outbreak. According to the World Health Organization (WHO), a disease outbreak is “the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season” and may be circumscribed to a certain geographical area or be disseminated to numerous countries, lasting from few days to several years (5). The following circumstances are also considered to be outbreaks: (i) emergence of a transmissible disease which had been long absent from a population; (ii) occurrence of a previously unknown disease; and (iii) occurrence of a disease not previously recognized in that population or geographical area (5).

Zoonotic outbreaks may be natural or deliberately caused and should be reported to competent authorities (5). When deliberately caused, they constitute an act of bioterror or biocrime. Bioterror is defined as the deliberate release of biological agents, like zoonotic microorganisms, or of other agents, aiming at causing illness or death in humans, animals, or plants. Biocrime implies the use of a biological agent to cause illness or death of a single individual or small group of individuals. Bioterror is motivated by political, ideological, or religious beliefs, whereas biocrime is motivated by revenge or monetary extortion (6).

Europol (European Union’s Criminal Intelligence Agency) was formed in 1998 in Europe to deal with bioterror and biocrime (7). In 2016, Europol created the European Counter Terrorism Centre (ECTC) to reinforce response to terror after the mortal bombings that occurred in Madrid in 2004, in London in 2005, in Minsk in 2011, and the attacks that occurred in Norway in 2011 and in Ile-de-France and Paris in 2015. ECTC aids to coordinate response following terrorist attacks and provide investigational support to all Member States. France and the United Kingdom also have individual legislation against terrorism (8).

In the United States, Federal Bureau of Investigation’s (FBI) Hazardous Materials Response Unit (HMRU) was created earlier in the 1990s (9). The Microbial Forensics field was further developed after the anthrax outbreak (10), and around 1400 bacterial species or strains that represent major threats to human health were identified since then (11,12).

The decades before 90s were characterized by World Wars and other events, which prompted the development of biological warfare programs and bioweapons by different countries. In 1972, the Biological and Toxic Weapons Convention limited the action of these warfare programs, but it did not stop them.

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During wars, destruction of sanitary facilities and hospitals along with increased poverty may lead to natural zoonotic outbreaks. On the other hand, opponent forces may deliberately cause zoonotic outbreaks to disturb the enemy. So, during wars it is difficult to determine whether an infection is natural or deliberate (2,9,13–15).

The management of zoonotic outbreaks has changed over time. Most of the cases began to be characterized in the 90s, when police investigation agencies started to develop research teams specific for infectious outbreaks. The anthrax outbreak in 2001 was a milestone in the management of zoonotic outbreaks, after which these agencies become more dynamic (16). Since then, the public and governments awareness of how easy it is to promote bioterror increased. Cases of nondeliberate infections affecting animals and humans like the bovine spongiform encephalopathy outbreak, a prion disease in cows that occurred in the United Kingdom (U.K.) that peaked in 1993 (and which spread to humans results in Creutzfeldt–Jakob disease), West Nile Virus outbreak that occurred in the United States of America (U.S.A.) in 1999, along with cases of intentional outbreaks, such as the salmonellosis outbreak that occurred in Oregon, U.S.A., in 1984 or the hemolytic-uremic syndrome outbreak that occurred in Germany in 2011, increased the available means for biosurveillance. Biosurveillance is the most powerful tool to monitor and limit natural or intentional outbreaks and to minimize associated morbidity and mortality (2,9,11).

This review will discuss the management of zoonotic outbreaks not related to wars, considering that nondeliberate zoonotic infections have been more frequent than deliberate ones. In perspective will be how the outbreak occurred, what was done to identify its source and to control it, and what may have failed during investigation.

Zoonotic Outbreaks not Related to Wars

Several indicators may raise the suspicion that a disease outbreak was caused with criminal intentions. According to Dembek et al. (17), those indicators are as follows: (i) highly unusual event with large numbers of victims; (ii) higher morbidity or mortality than expected; (iii) uncommon disease in that specific geographical area, where the disease vector is not usually present; (iv) point-source outbreak, where all cases appear to occur simultaneously after a similar incubation period, suggesting that there was not human-to-human transmission; the epidemiological curve from these outbreaks presents a quick rise, a brief plateau, followed by a fast decrease in case numbers; (v) multiple epidemics, in which several perpetrators could together release a single or several biological agents at different locations; (vi) low attack rates in protected individuals, for example, military populations; (vii) detection of a large population of dead animals; (viii) reverse spread, with human disease preceding animal disease or human and animal disease occurring simultaneously; (xi) unusual disease manifestation, such as *Bacillus anthracis* spread by inhalation as most cases are cutaneous; (x) downwind plume pattern, that points out for an aerosol release; or (xi) direct evidence left by the criminal, as observed in anthrax letters (17).

In the presence of such indicators, a suspicion of biocrime/bioterror should be raised and pathogen characterization along with other type of evidence will be part of the criminal case (9,18).

Below, the investigation process of several natural or intentional zoonotic outbreaks will be described. Table 1 synthesizes potential epidemiological clues related to deliberate outbreaks.

TABLE 1—*Description of potential epidemiological clues to a deliberate outbreak.*

Outbreaks	Epidemiological Clues
Anthrax in the former Soviet Union, 1979	A highly unusual event with large numbers of victims Higher morbidity or mortality than expected Uncommon disease Point-source outbreak Dead animals (sheep) Unusual disease manifestation Downwind plume pattern
Salmonella gastroenteritis in Oregon, 1984	A highly unusual event with large numbers of victims Point-source outbreak Multiple epidemics Direct evidence
Hantavirus pulmonary syndrome in the U.S.A., 1993	Higher morbidity or mortality than expected Uncommon disease; Unusual disease manifestation
West Nile Virus in New York City, 1999	A highly unusual event with large numbers of victims Higher morbidity or mortality than expected Uncommon disease Dead animals
Tularemia in Kosovo, 2000	A highly unusual event with large numbers of victims; Uncommon disease; Multiple epidemics; Unusual disease manifestation
Tularemia on Martha's Vineyard (U.S.A.), 2000	Unusual disease manifestation
Foot-and-mouth disease in the U.K., 2001	Point-source outbreak Dead animals
Anthrax in the U.S.A., 2001	Uncommon disease Multiple epidemics Unusual disease manifestation Direct evidence
Shiga-toxin-producing *Escherichia coli* O104:H4 in Germany, 2011	A highly unusual event with large numbers of victims Higher morbidity or mortality than expected Uncommon disease Direct evidence (contaminated food)
Ebola disease in West Africa, 2013–2016	A highly unusual event with large numbers of victims Dead animals (wild animals)

Based on: (17).

Anthrax Outbreak in Soviet Union, 1979

In April and May 1979, an accidental release of *B. anthracis* occurred in the former Soviet Union and was the largest documented outbreak of human inhalational anthrax, associated with 66 deaths (19). According to the Centers for Disease Control and Prevention (CDC), this bacterium is classified in category A of biological agents, which includes the most dangerous agents representing a security threat to human and animal health (20,21).

Initially, Soviet authorities claimed that the outbreak was prompt by a gastrointestinal anthrax strain transmitted through contaminated food, not revealing the facts about the outbreak origin. Public health response measures were soon implemented and included a voluntary anthrax immunization program for healthy individuals (17).

Soviet authorities confiscated patient records and autopsy reports, and concealed evidences that would have aided victims' diagnosis and effective treatment (17). Fortunately, two pathologists kept notes regarding a series of 42 autopsies in persons affected by this epidemic. Necropsies demonstrated the full range of effects of anthrax bacteremia, toxemia (edema and pleural effusions), and hematogenous dissemination (hemorrhagic meningitis in 21 cases and multiple gastrointestinal submucosal hemorrhagic lesions in 39 cases) (22).

Years later, a joint team formed by Soviet and Western physicians and scientists re-examined the case and showed that the outbreak was caused by inhalation of anthrax spores and that the point of origin was Sverdlovsk-19, a military research facility, where a clogged air filter was removed and not replaced. It is known that the former Soviet Union had a massive bioweapons program (14,17), pointing out for the possibility of victims being exposed to different *B. anthracis* strains (23) due to aerosol release of anthrax formulation from the military research facility (17).

Salmonella Gastroenteritis Outbreak in Oregon (U.S.A.), 1984

Sometimes natural and intentional cases are difficult to discern, as observed in the *Salmonella* gastroenteritis outbreak that occurred in Dalles, U.S.A., in 1984 (2,24).

After the Rajneeshee cult arrived in Dalles, an increasing hostility between cult members, the county, and Dalles population arose. Problems started with strict land use laws that allowed the cult members to get premises for many of their activities. They proposed a favorable candidate to run for county elections, but after not having enough signatures to support their proposal they tried to disable voters from participate in a local election by spreading *Salmonella* Typhimurium at salad bars on at least one occasion. More than 750 individuals developed *Salmonella* gastroenteritis and ten restaurants with contaminated salad bars were identified as the infection sources (2,24,25).

Atypical events associated with this outbreak led to its classification as deliberate: (i) outbreak occurred in two separate periods, from 9 to 18 September and from 19 September to October 10, 1984; (ii) *S.* Typhimurium was more frequently isolated from patients, in comparison with the last 4 years (388 vs 8); (iii) none of the associated restaurants was found to have contaminated food, nor a common supplier was identified; and (iv) epidemiological analysis revealed multiple suspect food items as the cause of the illness, which is consistent with deliberate contamination (17).

However, more than a year after this outbreak was classified as an act of bioterrorism, when authorities found in the Rajneeshee clinic laboratory a vial containing a culture of *S.* Typhimurium similar to the outbreak strain (17,25). Interestingly, the Rajneeshee community had legally purchased it from a medical supply company because they had a certified clinical laboratory (25). Nowadays, this bacterium is classified in category B of biological agents, which includes potentially dangerous microorganisms (20,21).

Hantavirus Pulmonary Syndrome in Southwestern U.S.A., 1993

Hantavirus pulmonary syndrome (HPS) is a rapidly progressive acute respiratory disease caused by a new hantavirus that spread in southwestern U.S.A. (Arizona, New Mexico, Colorado, and Utah) in 1993. From May to December, 53 HPS cases occurred, including 32 (60%) deaths. Since then, sporadic cases have been identified in a wide geographic area of the U.S.A. (26).

Hantavirus pulmonary syndrome is characterized by a unique pattern of pulmonary, hematological, and reticuloendothelial pathological features (27). Nolte et al. (27) suggested the presence of a capillary leak syndrome restricted to the pulmonary circulation in HPS, and the specificity of this hematological feature may be valuable for the rapid identification of further HPS cases. The rapid onset of respiratory failure and shock hamper HPS diagnostic and therapeutic, leading to a high mortality rate (28,29).

This HPS outbreak presented some unusual features: there was no previously documented hantavirus disease in the patient's geographical area, the syndrome was not previously associated with hantavirus and the serological reactivity pattern was not typical of any hantaviruses. Patient specimens were initially negative for bacterial, viral and toxicological agents, being sent to the CDC for further studies (28).

Researchers also tried to trap as many different species of rodents from the southwestern region as possible, to find the animal that carried the virus. There was a close cooperation of all the agencies. In November 1993, the HPS-associated hantavirus was isolated from a deer mouse (*Peromyscus maniculatus*) trapped in New Mexico near the house of a patient with confirmed HPS (26). Deer mouse is the natural reservoir and vector of this new zoonotic virus, which is transmitted to humans by direct contact through inhalation of rodent excrement associated aerosols (28). The new virus was first designated as Muerto Canyon virus, later as Sin Nombre virus, and finally as hantavirus pulmonary syndrome. Early cases of HPS were also discovered, indicating that the disease existed before this outbreak, showing that the related virus was re-emerging (26).

It was suggested that environmental and ecological changes were primarily responsible for the HPS outbreak. After a drought period in southwestern U.S.A., the number of mice increased. In fact, there were ten times more mice in May 1993 than in May 1992, leading to an increase in HPS transmission (26,28).

West Nile Virus in New York City, 1999

West Nile Virus (WNV) was first isolated in 1937 in Uganda, and it widely spread throughout Africa, Europe, Middle East, West Asia, and Australia (1), via mosquito vectors from the family Culicidae (particularly *Culex* species) (30). The virus also reached North America, becoming endemic in the continent (17). Since 1999, WNV has settled in the U.S.A. and Canada, infecting animals and then humans (2,30,31).

Detection of a WNV outbreak in humans was achieved by a practitioner who related the patient's symptoms (encephalitis with severe muscle weakness) to WNV disease, and promptly notified authorities (32). Nearly one month after the human outbreak, there was an increase in bird's mortality, first affecting crow populations and then zoo birds. Bird deaths are expected to occur during bird's migration, and therefore, the etiology of deaths was not promptly ascertained. Only after the human outbreak in September, local veterinarians investigated and found a common encephalitis diagnosis, relating bird deaths to the human outbreak (32,33). Then, brain tissue samples from several dead crows and zoo birds were studied at the National Veterinary Services Laboratory and CDC, with RT-PCR and viral genomic sequencing revealing the presence of WNV (32).

Initially, the human outbreak was thought to be St. Louis encephalitis, due to its frequent occurrence in New York City and the high serological cross-reactivity between both virus in ELISA and IgM capture test. Only after its detection in birds, WNV was identified in human samples by using serological and immunohistochemical tests and RT-PCR (30,34,35). It is recommended to confirm all suspected WNV deaths through autopsy evaluation (36).

From 1999 to 2012, the outbreak was responsible for 292 cases of WNV infection among New York City residents, including 35 deaths (37). There was a delay on outbreak detection, resulting from an inefficient collaboration between human and animal health services (2,32). Therefore, it is recommended to promote a stronger cooperation between animal health services, agriculture agencies, and human health services, to ensure a rapid response to future outbreak or bioterrorism cases (32).

Tularemia in Kosovo, 2000

Tularemia is a zoonotic disease caused by *Francisella tularensis*. This bacterium is included in category A of biological agents (20,21), and it may be found in contaminated water or soil, animals and decaying animal carcasses. Human-to-human transmission has not yet been documented (38).

From October 1999 to May 2000, a large tularemia outbreak occurred in Kosovo, which was free of the disease since 1974. The peak of confirmed cases was observed in January 2000. A total of 327 confirmed cases of tularemia pharyngitis and cervical lymphadenitis were identified, affecting 21 of 29 Kosovo municipalities (38). Ethnic Albanians with limited economic resources in rural farming villages were the most affected (17).

The head epidemiologist at the Kosovo Institute of Public Health gave declarations concerning unidentified powders found near various wells, which led investigators to consider the hypothesis of intentional spread of tularemia by Serbian forces. However, those suspicions were not confirmed (38).

WHO intensively collaborated with Kosovo health authorities, assisting in epidemiological, environmental, and microbiological investigations (38). Through initial field investigations, researchers determined that the tularemia epizootic spread was a natural event which probably resulted due to populations poverty, lack of knowledge regarding infection symptoms, and deprived sanitation seen in Kosovo after war. Rural villagers reported an increase in the number of rodents before the outbreak, and the outbreak ended after a natural decrease of rodent populations during winter (17,38). The case–control study pointed out for foodborne transmission.

Primary Pneumonic Tularemia on Martha's Vineyard (U.S.A.), 2000

Tularemia is endemic throughout most of the Northern Hemisphere. Approximately 200 cases of tularemia are reported annually in the U.S.A. Endemic inhalational tularemia cases in this country are related to the more virulent *F. tularensis* biovar tularensis (type A) and are often characterized by acute disease with prominent pneumonitis (39). Although uncommon, it is the most severe clinical form, with a mortality rate around 60 percent in the absence of treatment (40).

The first reported outbreak of primary pneumonic tularemia, also known as "rabbit fever," in the U.S.A. occurred on Martha's Vineyard Island in 1978. It was characterized by seven cases among residents of a single cottage, which were probably infected by aerosolized *F. tularensis* aerosols (41). The first local cases of tularemia occurred after Cottontail rabbits were introduced on the island in the late 30s (42). In 2000, occurred the second major outbreak of pneumonic tularemia. At that time, 15 cases were reported, 11 of which of primary pneumonic tularemia, responsible for one death (40).

Epidemiological, environmental, and microbiological investigations concluded that the last outbreak was naturally caused by aerosol release of *F. tularensis* originated from lawn mowing and brush cutting, a usual practice of the island habitants (40).

Foot-and-Mouth Disease in the United Kingdom, 2001

Foot-and-mouth disease (FMD) virus, discovered by Loeffler and Frosch in 1898, is a member of *Aphthovirus* genus, Picornaviridae family. The virus replicates within cloven-hoofed animals such as sheep, pigs and cattle (43). It has high spreading rates and disease symptoms include weakness and blisters development in or around the mouth and in hooves (44).

In 2001, a FMD outbreak caused by the Pan Asia O strain occurred in the U.K., which affected particularly sheep populations (45,46). Disease was rapidly disseminated throughout the country and lasted almost 1 year, with overall costs reaching approximately £2 billion (44).

The first FMD case occurred on February 2001, with pigs from an abattoir in Essex being identified as the outbreak source (47). The FMD virus was probably disseminated through catering industry by contaminated meat, which had been illegally imported to the U.K. (44), most likely from the Far East (48). Catering waste was not properly heat-sterilized, and consequently, pigs were contaminated (48). Only after nearly a month, it was possible to confirm the outbreak source, but at that time the virus had already spread to several countries. After September 2001, no more outbreaks were detected, and on January 2002, the U.K. status as "FMD-free without vaccination" was reestablished (47).

Emergency vaccination to control disease spreading was considered, but due to international trade implications, it was not applied. Following the outbreak, U.K. law was changed to allow emergency vaccination and to avoid culling (44).

Disease spread to other European countries leading to high economical losses (49,50). Genetic analysis of FMD viruses isolated from outbreaks in the U.K., Ireland, Netherlands, and France during 2001, suggested the involvement of the same Pan Asia O strain (48).

From 1967 to 2001, there were four FMD outbreaks in the U.K. During that period, the number of government-employed veterinarians decreased nearly 30% (44), which was the main reason for the slow response during the last outbreak. This case illustrates the relevant role of veterinary experts in microbial forensics investigation.

Anthrax Outbreak in U.S.A., 2001

The anthrax case in the U.S.A. in 2001 was one of the most recognizable deliberate zoonotic infections in humans studied. *B. anthracis* is the etiologic agent of anthrax, a common disease of livestock that occasionally affects humans. In October 2001, *B. anthracis* spores were disseminated throughout the U.S.A. through letters posted by mail. This incident resulted in at least 23 infected humans, 11 of which via inhalation and 12 by cutaneous contamination (from which eight cases were confirmed), including five deaths, mostly among postal workers and individuals handling mail (51,52). Direct exposure to contaminated letters or postal equipment was likely to be responsible for the first nine inhalation anthrax patients (53).

Infection by inhalational anthrax can mimic other diseases: congestive heart failure, influenza, and community-acquired pneumonia (54). The 11th fatal case was a 94-year-old woman with subtle clinical manifestations, which was probably exposed to mail cross-contaminated with *B. anthracis* spores. Diagnosis was achieved through blood cultures obtained prior to antibiotics administration, emphasizing the importance of this diagnostic test (53). When patients die, an autopsy evaluation aiming at recognizing gross features like hemorrhagic mediastinitis should be performed for diagnosis confirmation. Then, organ smears and lymph nodes or pleural fluid cultures must be performed to identify the causing bacteria (54).

National response to these events was massive: unprecedented public health and law enforcement investigations succeeded, involving thousands of investigators from federal, state and local agencies (17). On January 2002, as a direct result of the anthrax dissemination by mail, federal government made available $1.1 billion in funding to states for anti-bioterrorism measures (55). In 2011, the National Academy of Sciences concluded that was "impossible to reach any definitive conclusion about the origins of the anthrax in the letters, based solely on the available scientific evidence" (56). The report also challenged the FBI and U.S.A. Justice Department's conclusion that a single-spore batch of anthrax maintained by Ivins, a top biodefense researcher in the government's biodefense laboratories, was the source of the spores found in the anthrax letters (56).

Hemolytic-Uremic Syndrome Outbreak Caused by Shiga-Toxin-Producing Escherichia Coli *O104:H4 in Germany, 2011*

One of the largest outbreaks of enterohemorrhagic *Escherichia coli* (EHEC) serotype O104:H4 transmitted via contaminated food occurred in Germany, in 2011. It was caused by a highly antibiotic resistant, hybrid enteroaggregative, Shiga toxin producer *E. coli* strain. Infection was characterized by increased bloody diarrhea and hemolytic-uremic syndrome (HUS) (25%) and high mortality rate (57). From May to September, a total of 3842 EHEC cases were registered and related to 18 deaths (0.6 percent). From the EHEC patients, 855 developed HUS, responsible for 35 further deaths (4.1 percent) (58).

The outbreak disseminated to other European countries and the U.S.A., being observed that most of these patients visited northern Germany during the outbreak peak (59).

The epidemiological curve onset was in the first of May, and its peak in May 22, after which the reported number of EHEC and HUS decreased. The last reported case was on July 4, and on July 26, the Robert Koch Institute (RKI) declared the outbreak end. The Hamburg health authority notified the RKI only 18 days after the beginning of the outbreak, which constitutes a relevant notification delay. The following day, RKI sent a team of experts to Hamburg to initiate case–control and cohort studies and explorative and online interviews. Two days after RKI notification, it was determined that vegetables were the infection source. On May 25, the pathogen present in patient samples was identified as EHEC O104:H4, but only in June federal authorities found that the epidemic originated from a fenugreek seeds (*Trigonella foenum-graecum*) sprouts lot imported from Egypt (59,60).

This serotype is rare and was not previously described in animals, being rarely identified in humans. Interestingly, the EHEC O104:H4 outbreak strain presents a combination of genomic features from enteroaggregative and enterohemorrhagic *E. coli* strains, representing a new pathotype with high virulence and resistance profile (59,61).

Curiously, there were no data on similar outbreaks in Egypt caused by the same strain and on the suspected seeds origin. Also, nor the fenugreek seeds or the suspected sprout lots distributed in Germany were positive for EHEC O104:H4 (62). So, it was not possible to determine whether this was an intentional or a deliberate outbreak. Two epidemiological assessments were performed to differentiate between a natural/accidental and a deliberate outbreak: one based on scoring models (63) and another based on potential clues to a deliberate outbreak without a numerical ponderation (17). Analysis showed that neither one of the possibilities (food contamination by the EHEC O104:H4 strain being deliberate or accidental) could be discarded (61).

Ebola Hemorrhagic Fever Outbreak in West Africa, 2013–2016

In 1976, two simultaneous outbreaks of hemorrhagic fever caused by Ebola virus occurred in South Sudan and in the neighbor Democratic Republic of the Congo. Since then, multiple outbreaks were described in central and eastern Africa. The 2013–2016 outbreak in West Africa caused by the *Zaire* strain was the largest one, with 28,646 reported cases and 11,323 reported deaths. It started in Guinea and spread to other countries in and out of Africa, being associated with high mortality rates ranging from 50% to 90% (64,65).

In the early phase of the outbreak, Lassa fever was considered as the more probable cause, because no sporadic human cases or outbreaks of Ebola had been previously reported in West Africa. The widespread of the West African outbreak is related to, among other causes, the densely and highly mobile populations, fragile states due to recent civil wars, poverty, traditional burial rituals and dependence on healers, delayed identification, lack of communication and a weak health system (65).

The virus is transmitted to humans through direct contact with blood or body fluids of ill or dead wild animals (like chimpanzees, gorillas and fruit bats, which is the probably the natural host), and through contaminated surfaces and materials (e.g., bathroom surfaces and medical equipment) and is easily transmitted between humans through direct contact with blood or body fluids of an ill or dead person. The virus can enter a person's body through damaged skin or unprotected mucous membranes including the eyes, nose, or mouth (66,67). Due to its high transmissibility, CDC established guidelines to protect healthcare workers and other patients at facilities (68), including to protect them against Ebola's postmortem spread (69). For example, direct contact with any dead bodies from patients which suspected cause of death was Ebola must be avoided. All management protocols recommend that healthcare workers and all providers should be trained and frequently evaluated to ensure biosafety.

This virus is classified in category A of biological agents (20,21). The fear that Ebola could be turned into a bio-weapon lead to an increase in research funding (70), resulting in the development of over 23 different vaccines against this virus, 15 of which are at a preclinical stage (71). However, it is unlikely that Ebola virus could become airborne and weaponized, especially since it spreads easily through a population and considering the intrinsic differences of Ebola's infection in different animal species (70).

Discussion

Nowadays, we are facing nontraditional biological threats that may be responsible for zoonosis outbreaks, for which effective vaccines or treatments are not available (4). Furthermore, bacteria and virus can be genetically changed to evade human immune system, aiming at its use in bioterror events.

Different collaborations are being established for biosurveillance and terrorism preparedness and response. Local, state and federal public health institutes as well as veterinary, food and environmental laboratories and other agencies are involved. Medical examiners and coroners (ME/Cs), public health officials and animal health specialists are part of this multidisciplinary network. A critical issue in multidisciplinary teams is the fulfillment of designated functions and the respect for each entity functions and obligations (72). To improve future investigations, adequate training and funding should be made available (72) and specific roles and responsibilities should be assigned to each entity (and further redefined if necessary). These probably may imply the reformulation of related laws.

ME/Cs have the legal authority to investigate human deaths that are sudden, suspicious or violent (72). For example, if a person dies at home from inhalational anthrax, it would be up to the ME/Cs to perform diagnosis (54). ME/Cs and public health authorities are familiar with biologic terrorism-related investigation procedures including operative, jurisdictive and evidence issues. Their role in terrorism surveillance is vital and requires reliable standards for collecting, analyzing and disseminating data. Nolte et al. (72) discussed the roles and responsibilities of ME/Cs and associated personnel and made several recommendations aiming at improving the response to potential biologic terrorism, including that U.S.A. laws should be changed to enable ME/Cs to assume jurisdiction and investigate deaths that might represent a public health threat.

Animal health specialists can be the first sentinels to detect a natural or intentional outbreak with animal origin. Unfortunately, they are not familiar with biologic terrorism-related investigations, which limit their contribution. For them to assume a key role in terrorism surveillance, preliminary forensic training and certification are required, including on dealing with legal requirements associated with evidence handling, ensuring the chain-of-custody, performing the follow-up of evidence items, the accreditation of related processes and quality assurance (2,13). As suggested by Anderson (44), in an inquiry on the foot-and-mouth disease outbreak that occurred in the U.K., a task force of veterinary “paramedics” with forensic expertise capable of responding to an alert should be created.

Terrorism management can be expensive and most health specialists’ facilities do not have the capacity to perform autopsies at Biosafety Level 3. So, funding is needed and some strategies were suggested to overcome this situation (72).

Outbreaks may arise suddenly, demanding a prompt action by the healthcare system and its personnel and may result in a catastrophe (73). Communication standards are crucial for any emergency response (72). To provide a reliable outbreak management, authorities should: (i) ensure communication between and within countries; (ii) provide the public with timely and truthful information about the outbreak magnitude, risks and protection measures; (iii) conduct surveillance and report results; (iv) provide quality care and essential medicines; and (v) develop organizational infrastructures, allowing an effective emergency response (74,75).

Finally, biosafety should be guaranteed to all specialists who might be in contact with category A, B, and C agents that can potentially be used in bioterrorism (20,21). With that purpose, Nolte et al. (76) created a model surveillance system (Med-X) designed to enable ME/Cs and their public health partners to identify fatal infections and deaths due to bioterrorism.

Biosafety is especially critical for autopsy personnel, such as ME/Cs, who might contact bodies, remains and surfaces contaminated with biologic terrorism agents (72). Therefore, basic protective measures should be maintained during autopsy, written biosafety protocols should be available at autopsy facilities and autopsy personnel should be trained and evaluated in all protocols. Protective measures include (i) the use of PPE—personal protective equipment (e.g., surgical scrub suit, eye protection, shoe covers and double surgical gloves), (ii) standard safety practices to prevent injury due to sharp items, (iii) appropriate engineering strategies and facility design (appropriate autopsy room with adequate air circulation, biosafety cabinets available for examination of smaller specimens), (iv) vaccination and post-exposure prophylaxis (e.g., vaccines against diseases like anthrax, plague and tularemia are available), (v) decontamination of body-surface contaminants, (vi) waste disposal (solid waste should be appropriately contained and then incinerated in a medical waste incinerator), (vii) storage and disposition of corpses (e.g., bodies contaminated with highly infectious such as smallpox, hemorrhagic fever viruses and spores-producing agents like *B. anthracis* should be cremated) (72,77).

This review discusses the management of ten zoonotic outbreaks out of war. Only two of the described cases were proven to be deliberate outbreaks (*Salmonella* gastroenteritis in Oregon, 1984, and the anthrax outbreak in the U.S.A., 2001) and one was suspected to be so (hemolytic-uremic syndrome outbreak in Germany, 2011). Questions on how the outbreak happened, what was done and what may have failed during investigations were addressed, being observed different problems in each case.

In the anthrax outbreak that occurred in the Soviet Union in 1979, Soviet military hides the real outbreak source and affected patients were disregarded. Therefore, there was an enormous delay between outbreak occurrence and its investigation by a trustworthy group of scientists (17,19,22).

In the *Salmonella* gastroenteritis outbreak that occurred in Oregon, U.S.A., in 1984, there was a one-year delay between the outbreak onset and its identification as an act of bioterrorism, because the proof, a vial containing a *S.* Typhimurium culture from the Rajneeshee clinic laboratory, was found much later. Although a deliberate outbreak was considered possible, authorities were not expecting it to be an act of bioterrorism, as the 80s mindset was different (17,25).

In the Hantavirus pulmonary syndrome outbreak in southwestern U.S.A., 1993, virus was isolated from a deer mouse in a matter of months. The rapid result was remarkable and was achieved due to the collaboration between different research agencies. Previous studies on hantaviruses done by several laboratories were also vital. It was possible to determine that HPS outbreak was naturally caused by an increase in the transmission vector and zoonotic reservoir populations (26–28).

In the West Nile virus outbreak that occurred in New York City, U.S.A., in 1999, cooperation between animal and human health services failed. Veterinarians performed the correct diagnosis of bird deaths but faced challenges in communication with human health counterparts. The outcome would be different if animal health specialists had a more active involvement in local, state, and federal surveillance programs against bioterrorism (32).

In the tularemia outbreak that occurred in Kosovo in 2000, destruction caused by war provided ideal conditions for the re-emergence of this disease 25 years after the establishment of Kosovo status as tularemia-free. War also potentiated the concealed use of biological agents by governments, rendering investigations difficult (17,38). International cooperation in outbreaks investigation during wars is of major importance and should be reinforced.

In the Martha's Vineyard case, the outbreak natural origin was easily established due to the habits shared by victims, namely brush cutting and lawn mowing. Because the bioterrorism threat continues, clinicians should remain attentive. Although tularemia is endemic throughout much of the Northern Hemisphere, primary pneumonic tularemia is an uncommon manifestation of the disease and may lead to a possible suspicion of biocrime (39,40).

In the foot-and-mouth disease outbreak that occurred in the U.K. in 2001, authorities took a long time to solve the problem, mostly due to the lack of veterinarians to act as sentinels to detect natural or intentional zoonotic outbreaks. As emergency vaccination was not applied, disease spread faster and a large number of animals were culled. After the outbreak, laws were changed to allow emergency vaccination and avoid culling (44).

There are still some missing links regarding the identification of the responsible for the anthrax outbreak that occurred in the U.S.A. in 2001. Soon it was shown to be a novel method for disseminating terror by using mail post, as the letters represented a direct evidence of a deliberate attack with a biological agent. The exposure source of two patients infected by inhalation anthrax is still unknown (53). All resources were used to accelerate the perpetrator capture and to prevent future outbreaks (17). This case highlighted the importance of blood culture prior to antibiotics administration and of autopsy in the diagnostic of inhalation anthrax (53,54).

In the hemolytic-uremic syndrome outbreak caused by Shigatoxin-producing *E. coli* O104:H4 that occurred in Germany in 2011, there was an 18-day delay between the outbreak onset and disease notification, mainly due to a poor communication system and inadequate separation of responsibilities between state and federal ministries. There was no agreement between food communications groups related to public health. In fact, a local food agency from Hamburg first claimed that the O104 strain originated from cucumbers imported from Spain, causing major economic losses in this and other European countries (78). The possibility that the pathogen was introduced intentionally in the food chain is still under evaluation (61). This case highlighted the importance of an adequate communication between all entities involved and of the proper distribution of functions and responsibilities.

In the Ebola hemorrhagic fever outbreak in West Africa, 2013-2016, there was an initial delay on the diagnosis because no human cases of Ebola had previously been reported in this region, and Lassa fever was considered as the most probably cause (65). Also, the combination of extreme poverty and illiteracy still observed in several African countries lead to devastating consequences: the healthcare system and communication resources are insufficient or absent, dependence on healers, traditional burial rituals and migrations to other countries searching for resources contributed for the exponential increase in disease transmission. Ebola is highly transmissible, so the need to rapidly establish guidelines to ensure biosafety to healthcare providers, forensic specialists and populations was a major challenge.

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