Consequences of Failure to Apply International Standards for Laboratory Biosafety and Biosecurity: The 2007 Foot-and-Mouth Disease Outbreak in the UK

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Abstract

International standards have been elaborated for laboratory biosafety and biosecurity in relation to work on both human and animal pathogens. Comparing the findings from the two official reports (HSE, 2007; Spratt, 2007) regarding the 2007 Foot-and-Mouth Disease outbreak in the United Kingdom (UK) with these international standards highlights several areas of deficiency in biosafety and biosecurity standards in laboratory facilities and in national guidance and procedures, suggesting that had the international standards been fully applied, the outbreak would not have occurred.

Introduction

In August and September 2007, eight farms in Surrey and Berkshire (southern England) were affected by an outbreak of Foot-and-Mouth Disease (FMD). Two official investigations that rapidly took place established a very high likelihood that the outbreak was caused by inadvertent release of FMD virus from the nearby Pirbright laboratory site, where three groups were working with similar strains of the virus.

The World Health Organization (WHO) and the Office International des Epizooties/World Organization for Animal Health (OIE) publish standards for laboratory biosafety and biosecurity. This article examines whether the outbreak would have occurred had these standards been appropriately applied. International standards are important in this area because of the transboundary nature of infectious disease and related control efforts. One of the groups at the Pirbright site—the Institute for Animal Health—is an OIE World Reference Laboratory for FMD; therefore, consideration of OIE standards is particularly relevant to this case.

Background

Foot-and-Mouth Disease

FMD is highly contagious among cloven-hoofed animals, infecting up to 100% of livestock exposed to it. It is potentially massively economically damaging as measures to contain its spread affect both domestic and export markets. The UK National Audit Office estimates that a 2001 FMD outbreak cost the UK £8 billion (2007, p. 1). FMD is an OIE “listed disease”—“a transmissible disease with high potential for international spread”—for which it advises particular control measures. Due to its virulence and economic significance, OIE classifies FMD as a Category or Group 4 animal pathogen, which should be worked on only within maximum containment/biosafety level 4 laboratory conditions. “OIE guidelines for the containment level for Group 4 pathogens are generally equal to the USDA’s biosafety level 3Ag guidelines” (OIE, 2008, Chapter I.1.02).

Outbreak and Response

On 3 August 2007, FMD was confirmed in cattle on a farm in Surrey. Given the stage of infection and the incubation period of the virus (14 days), the most likely period of exposure was identified as 14–26 July (HSE, 2007, para. 28). The UK government acted rapidly to contain the outbreak with reasonable success (although it did spread to several sites nearby) and fulfilled its international reporting requirements (OIE, 2007, Chapter 1.2.2).

The FMD strain was identified as OIBFS67, responsible for an FMD epidemic in the UK in 1967. The strain is no longer naturally occurring but was worked on at the nearby Pirbright laboratory site during the infection window. Investigators concentrated on examining this site as the likely source of the outbreak.

Biosafety and Biosecurity

As used internationally in relation to laboratory facilities, biosafety and biosecurity are distinct terms. Biosafety aims to prevent accidental/unintentional exposure to or release of pathogens within or from the laboratory environment. Biosecurity aims to prevent deliberate release or theft of pathogens from laboratory facilities.

Sources

The reports of the two official investigations into the cause of the outbreak—the Health and Safety Executive’s Final Report on Potential Breaches of Biosecurity at the Pirbright Site and the Independent (Spratt) Review of the Safety of UK Facilities Handling Foot-and-Mouth Disease Virus—are used as sources of information about conditions at the Pirbright site that may have contributed to the outbreak. Two further reviews (the Callaghan Review and the Anderson Review) were also consulted, but do not directly relate to conditions at the site.
The international standards/guidelines consulted include OIE’s *Terrestrial Animal Health Code* (TAHC) and the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (Terrestrial Manual); and the WHO’s *Laboratory Biosafety Manual and Biorisk Management: Laboratory Biosecurity Guidance*. The 2007 edition of the Terrestrial Code and 5th edition of the Terrestrial Manual are used in this article because they were the versions available at the time of the outbreak. 2008 versions of both have since been published, with some changes to both structure and content.

**Deficiencies in Biosafety and Biosecurity**

Comparing conditions at the Pirbright site with the international standards is used to draw insights in three main areas:

1. Errors in biosafety and biosecurity at the site that may have led to the release, and points at which the standards were not met
2. Possible deficiencies in national governance, particularly points at which national rules, policies, and procedures did not meet international standards (These have been reviewed since the outbreak and changes are in progress.)
3. Lessons in terms of new issues/areas for inclusion in the international standards

**Main Findings of the Official Investigations**

The two main investigations found that there was a very high likelihood that the Pirbright site was the source of the outbreak: “There is very little doubt that the FMD outbreak was caused by Foot-and-Mouth Disease virus (FMDV) from one of the two facilities at Pirbright” (Spratt, 2007, p. 5). Three groups at the site—the Institute of Animal Health (IAH), Merial Animal Health Ltd., and Stabilitech—were working on closely related strains of the virus.

The most likely route of transmission from the site to livestock identified in the reports was the passage of vehicles associated with construction work at the site, through infected soil or water around the area of an exposed and broken effluent pipe, carrying infected material off-site and past nearby farms. The reports were confident that the release was inadvertent because it did not follow patterns of a deliberate release; however, both reports noted deficiencies that could have provided determined individuals an opportunity to access the virus (Spratt, 2007, para. 11, 28; HSE, 2007, para. 13, 46, 200). They also identified a range of biosafety deficiencies at the site. In several instances these did not breach national rules and procedures, despite clearly falling below international standards.

**Comparison of Conditions at Pirbright with International Standards for Biosafety and Biosecurity**

*Use of a decontamination process that did not guarantee virus deactivation and subsequent discharge of effluent that potentially contained live virus*

International standards relating to biosafety level 4 containment require complete virus deactivation prior to release of effluent. The Terrestrial Code summarizes laboratory requirements for different containment groups. It specifies that liquid effluent must be sterilized and monitored (Chapter 1.4.5). By definition, sterilization requires that all living organisms are killed. Chapter I.1.6 of the Terrestrial Manual lists as an “essential requirement for all work” that “no infectious material should be discarded down laboratory sinks or any other drain.” Likewise, the WHO *Laboratory Biosafety Manual* states that “the overriding principle is that all infectious material should be decontaminated, autoclaved or incinerated within the laboratory” (p. 17).

The Pirbright laboratories used a system of chemical decontamination (HSE, 2007, para. 139-152). The system falls short of international guidance, with the HSE Report raising “concerns as to whether a system of chemical treatments could ever be considered to sterilise liquid waste” (para. 137) and stating that the chemical system “does not achieve complete inactivation” (para. 8).

**Damaged and leaking drainage system and poor maintenance and inspection regimes for effluent drains**

It appears to have been recognized that live virus might enter the site’s effluent drainage system. The Department for Environment, Farming, and Rural Affairs (Defra) considered that the drainage system was part of Pirbright’s Category 4 containment zone. At the time of the outbreak, Defra was the licensor, regulator, and inspector for the laboratories. The HSE reported:

- Weaknesses were identified in the containment standard of the effluent drains across the Pirbright site. These included displaced joints, cracks, debris-build up and tree root ingress...recordkeeping, maintenance and inspection regimes were considered inadequate” (paragraph 153) and that the drainage system was not “demonstrably leakproof”; “airtight or negatively pressured”; “proofed against ingress or egress of insects”; or “isolated from flooding. (Annex, p. 57)

The international standards do not expect live virus to be present in the drainage system and do not address the issue of their condition. The standards do state, for example, that “production facilities have to be designed in such a way that contamination of the external environment is prevented” (TAHC, Chapter 1.1.7). Thus, it is clear that the failure of containment in the site’s drainage system falls short of international standards.
**Poor recordkeeping of human and vehicle movements into and around site and no proper control of access to site or into its restricted areas**

Controlled access to restricted areas is important for biosafety and biosecurity reasons. Only appropriately trained and authorized personnel should be able to access restricted areas, and access should be properly documented so that all materials and movements can be traced if problems subsequently arise. Recommendations on these issues can be found in the international guidance. The Laboratory Biosecurity Guidance’s program of accountability involves “identification and selection of personnel with access” to dangerous pathogens (WHO, 2008, p. 8); the Laboratory Biosafety Manual advises that “only authorized persons should be allowed to enter the laboratory working areas” (p. 10); and limited personnel access is part of the TAHC’s level 4 requirements (Chapter 1.4.5.5).

The HSE Report found that “not all human and vehicle movements via the IAH gatehouse to the site were recorded”; “evidence of poor monitoring and control of access to restricted areas”; and “vehicles involved [in construction] were likely to have unrestricted access to the site” (para. 12, 13, 15). Additionally, the report noted that:

- Access to the main restricted area is through a single self-closing door, which is protected by digital lock entry. The digital code has not been changed in years... No log is kept on a day-to-day basis of who has entered the high containment facility. (para. 200)

**Poor siting of HEPA filters, meaning that tests could not be conducted to standard**

HEPA (high energy particulate air) filters play an important role in containment, ensuring that only air from which all pathogens have been removed leaves the laboratory. At level 4 the Laboratory Biosafety Manual instructs that “both supply and exhaust air must be HEPA-filtered” (p. 26). Specific requirements depend on whether positive pressure suits or biosafety cabinets are used for primary containment. The Pirbright laboratories used cabinets. For these, supply air must be HEPA-filtered and “exhaust air...must pass through two HEPA filters prior to release outdoors” (p. 26). The filters “need to be tested and certified annually” (p. 27).

The HSE Report indicates that the main laboratory may not have met these standards. “We have concerns about the filter arrangements throughout the main laboratory...it does not allow both filters to be tested independently; therefore, it cannot be guaranteed that both filters are working at any one time” (para. 108).

**Potential for positive pressurization of laboratories**

Biosafety level 4 requires maintenance of negative air pressure so that air will be drawn into the laboratory from areas of higher pressure—rather than travelling outwards—contributing to containment by preventing the release of unfiltered air. The Laboratory Biosafety Manual includes advice that “the building ventilation system must be so constructed that air from the containment laboratory...is not recirculated to other areas of the building” (p. 21); “laboratory doors should be kept closed” (p. 10); and in level 4 laboratories using bio-safety cabinets, entry should be through two doors to maintain separation from the rest of the facility (p. 25).

Two main issues at the Pirbright laboratories had potential to cause positive pressurization. First, laboratory doors were left open. “When lab doors were left open (as we observed when laboratory work was in progress), the pressure in the labs would effectively become the same as in the corridor” (HSE, 2007, para. 102). Second, in some of the laboratory spaces, air leaked between rooms. “Our investigations revealed that some individual laboratories could become positively pressurized when the doors were closed and there was leakage of air between laboratories through unsealed pipe ducting” (HSE, 2007, para. 102). The HSE Report also noted problems of air leakage due to the condition of the building. “The fabric of the building was poor, with visible cracks in the walls and ceilings, and leak points around some windows” (para. 104).

**Lack of vehicle decontamination**

Given that the likely route of transmission involved transfer on vehicle tires, it is significant that “there was no evidence of wheel washes or basic cleaning of vehicles” (HSE, 2007, para. 222). The Terrestrial Code Appendix 3.6.1.1 (OIE, 2007) recommends “washing and disinfecting the outside of vehicles”.

**Comparison of National Rules and Procedures with International Standards for Biosafety and Biosecurity**

Unclear distinction between laboratory biosafety and biosecurity

Defra and the HSE Report were unclear on the distinction between laboratory biosafety and biosecurity. This may well result in laboratories’ uncertainty about what standards they ought to apply. The terms are clearly defined and distinguished in the international standards. While they can be mutually supportive, they have different aims, and the distinction is important.

The HSE Report states:

- There is no accepted definition of “biosecurity.” For the purposes of this report, the term will cover the implementation of a combination of containment measures and working practices, supplemented by management controls, to prevent inadvertent exposure of susceptible species to biological agents. (para. 37)

The focus on unintentional exposure or accidental release, according to the international standards, falls under the definition of biosafety not biosecurity:
Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release.

Laboratory biosecurity describes the protection, control and accountability for valuable biological materials...within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release.” (WHO, 2006, *Biorisk management: Laboratory biosecurity guidance*, para. iv)

For example, the HSE states (para, 5):

We looked at biosecurity controls in four areas where we judged it possible for the virus to escape containment arrangements at Pirbright, namely solid waste disposal, airborne routes through the fabric of site buildings or faults in filtration systems, liquid waste disposal, and human movements.

In this case, they were looking at routes of accidental release and were considering biosafety controls. The Spratt Review distinguished the terms in the same way as the international standards.

**Confusion over requirements for work with animal pathogens and standards of containment**

There appears to have been confusion about what standards apply to laboratory work on animal pathogens and whether these differ from those on human pathogens. This is outlined in the following paragraphs from the HSE Report:

45. The guidance states that the containment requirements are based on those published by the Advisory Committee on Dangerous Pathogens (ACDP) as being suitable for work with ACDP Category 4 human pathogens.... This is then qualified by the following statement: “However, it should be noted that the Defra categorisation of pathogens and conditions of containment differ in points of detail from those published by ACDP. The reason for this is that ACDP is concerned with protection of workers in the workplace, whereas Defra is concerned with protection of livestock and the environment. Laboratories must meet Defra containment requirements to be considered for licensing under the Specified Animal Pathogens Order 1998 (SAPO). In addition the relevant ACDP requirements apply.”

46. It is our opinion that this statement can cause confusion as to the standards required. And: “Although the guidance states that the containment is based on ACDP Level 4, the practical reality is quite different. This may be because the organisms being used are exclusively animal pathogens, and controlling worker exposure is not considered a priority. ...At IAH Pirbright, the culture is quite different from that observed in ACDP Containment Level 3 or 4 laboratories.... The practical application of physical and procedural approaches to containment varied considerably between the Defra (SAPO) and ACDP standards.” (para. 46)

According to the international standards, both animal and human exposure should be considered when categorizing pathogens for laboratory work, in case either requires additional measures to be taken. As FMD does not affect humans (although they can carry the virus), “the principal purpose of containment is to prevent the escape of the pathogen from the laboratory into the national animal population” (TAHC, Chapter 1.4,5.5).

This may appear to leave some uncertainty as to whether standards for containment of human and animal pathogens should generally be the same. At biosafety level 4 the international requirements are equally stringent. The *Laboratory Biosafety Manual* includes in Risk Group 4 any pathogen “that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly” (p. 1). Its requirements at each biosafety level make no distinction between work on human or animal pathogens.

Under the international standards, all work on FMD must take place under maximum containment conditions, regardless of whether the primary aim is prevention of human exposure or prevention of release into the animal population—with maximum containment conditions no less stringent for animal pathogens than for human ones.

**Rules unable to identify some key points as biosafety breaches**

Some of the areas in which the Pirbright facilities fell short of international standards do not appear to have been identifiable as biosafety breaches under the national rules. For example, in regard to inactivation processes used at Pirbright, the HSE Report found these “fully in compliance with their SAPO [Specified Animal Pathogen Order] requirements” with the presence of live virus in effluent “in accordance with Defra’s requirements” and the conclusion that “this act of discharge was permitted by Defra, hence...there was no breach of biosecurity at this juncture” (para. 16, 8, 9).

**Inspection and licensing procedures allowed site to continue operating despite deficiencies**

Defra was the licensor for the site under the Specified Animal Pathogens Order 1998 (SAPO). Licenses are renewed on a 5-year basis, thorough inspections take place before they are issued, and there are subsequent annual inspections (HSE, 2007, para. 40, 41).

The *Laboratory Biosafety Manual* expects regular inspection and licensing activities to involve “systematic examination of all safety features and processes within the laboratory” (p. 36), including procedures for decon-
tamination of waste, and that “certification of the laboratory should not be completed...until deficiencies have been adequately addressed” (p. 37). Similar points are made in the Terrestrial Code:

A laboratory should be allowed to possess and handle animal pathogens in group 3 or 4 only if it can satisfy the relevant authority that it can provide containment facilities appropriate to the group. (Article 1.4.5.6)

Concern over standards used for licensing is raised given that Defra had licensed both Merial and IAH work at the site (Stabilitech was operating under the IAH license), particularly since the reports pointed to many of the problems at the site not being new but related to the age and condition of the buildings and lack of maintenance and testing of key aspects of the site. “The category 4 laboratories at IAH are very old and are well short of the standards expected of an internationally important laboratory handling such livestock-threatening pathogens as FMDV” (HSE, 2007, para. 13).

Insufficient financing for maintenance

Problems in the condition of buildings and in drainage at IAH had been recognized but, due to a shortage of and disputes over funding, the necessary maintenance work had not taken place:

Adequate funding has not been available to ensure the highest standards of safety for work on FMDV carried out at this aging facility.

There had been concern for several years that the effluent pipes were old and needed replacing but, after much discussion between IAH, Merial and Defra, money had not been made available. (Spratt, 2007, para. 6, 33)

SuggestedAreasforAmendmentofand/or
AdditiontotheInternationalStandards
Adviceonsitingoflaboratoriesandusageofsentinelunits

No particular advice was presented in the international standards on siting of laboratories working on Category 4 animal pathogens. Such advice may have questioned the appropriateness of siting such a laboratory within a few miles of farms on which livestock is kept. The 2008 version of the Terrestrial Manual advises that facilities be “in an isolated location” (Chapter 1.1.2.k.a), but further details would be helpful. This may include suggestions on the use of sentinel units to warn of releases. A general suggestion regarding the use of sentinels for animal health surveillance is included in the Terrestrial Code, and involves “the identification and regular testing of one or more animals of known health/immune status in a specified geographical location to detect the occurrence of disease” (Appendix 3.8.1). Placing sentinels between a laboratory site and surrounding farms may allow early identification and containment of disease releases before they reach the general animal population.

Guidance on shared facilities, conflicts of interest, and use of contractors

Communication and ownership issues can arise in shared facilities, hindering biosafety efforts—something noted in the Spratt Review (p. 8). The reports identified access between different areas of the site as a potential problem. The Spratt Review also highlighted potential conflicts of interest—Merial’s Director being its biosafety officer, and IAH’s main customer (Defra) being its regulator (pp. 5, 8). Guidance on these issues would be helpful. Additionally, guidance on use of contractors could be provided, advising, for example, on access controls and restrictions, recordkeeping, biosafety training, and disinfection procedures.

Standards for licensing and inspection

The Laboratory Biosafety Manual provides useful checklists for inspection, and the international standards recommend regular inspection and licensing of laboratories. Additional guidance may be useful—for example, specification of particular breaches for which licenses should be suspended or withdrawn.

Standards for status as a World Reference Laboratory

IAH Pirbright is designated as the OIE/Food and Agriculture Organization World Reference Laboratory for FMD and nine other animal diseases. The Terrestrial Manual states that these laboratories “have considerable experience in the operation of safe working practices and provision of appropriate facilities” (Chapter I.1.6). Questions arise about whether, particularly in regard to “appropriate facilities,” this description applied to IAH at the time of the outbreak, and what the standards were for assigning this status. The OIE’s Internal Rules for Reference Laboratories (OIE, 2006) shows that the experts at the laboratories and their competence are the basis for the approval of the designation. The achievement of core laboratory biosafety standards should also be considered, given that these laboratories are set out as examples of international excellence.

Conclusion

The analysis in this article strongly suggests that, had international laboratory biosafety and biosecurity standards been appropriately applied, the 2007 FMD outbreak in the UK would not have occurred. Application of international standards was lacking in several significant areas, which made the Pirbright site unsuitable for maximum containment work. Problems with national rules, procedures, and financing failed to identify and/or address these issues. Applying international standards may have been sufficient to prevent the outbreak, but there are some areas that could be dealt with more clearly in those standards.
References


EPA Green Lights First Antimicrobial Pesticide against Anthrax (News Release) (Washington, DC—May 28, 2009)

The Environmental Protection Agency has approved the first registration, or license, of an antimicrobial pesticide product to deactivate anthrax spores on hard surfaces. “Peridox with the Electrostatic Decontamination System” can decontaminate buildings, structures, vehicles, ships, aircraft, personal protective equipment, and other items infected with anthrax spores. Its use is limited to dry, precleaned, hard, nonporous surfaces.

EPA reviewed extensive data provided by the manufacturer, Clean Earth Technologies, to be sure that the product will be effective and not cause unreasonable adverse effects. EPA also reviewed the labeling of Peridox and associated training materials to ensure that they are consistent with EPA’s Pesticide Registration Notice 2008-2, which specifies the terms and conditions that would apply to anti-anthrax products.

The notice provides guidance to prospective applicants of antimicrobial products that claim to deactivate anthrax spores. The availability of such products will better prepare the United States to respond to anthrax incidents. The guidance assures that anthrax-related products are registered, bear appropriate labeling, and are effective when applied as directed. The use of anthrax-related products will be limited to federal on-scene coordinators, the U.S. military, and persons trained and certified competent by the manufacturer.

Peridox is the first pesticide registered to deactivate anthrax spores. EPA previously issued crisis exemptions allowing use of unregistered antimicrobial chemicals to clean buildings and any contents contaminated with anthrax spores.

Anthrax is a disease caused by Bacillus anthracis. Both humans and animals are susceptible. Anthrax, if untreated, can cause acute illness or death.

More information about the registration notice: www.epa.gov/pesticides/factsheets/chemicals/peridox-eds.html