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Commentary

Biosecurity 101: Pirbright's Lessons in Laboratory Security

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Foot and mouth disease (FMD) ceased to be endemic—continually present—in Britain in 1889. It is reasonable to suppose that all subsequent outbreaks have had the importation of virus as their starting point. So when on 3 August this year two cases were confirmed in cattle on a farm in Surrey the origin of the virus was an immediate question. Surrey is commuter belt country. Its farms are small. They are dotted between medium-sized towns and large villages and so are not the loci of the kinds of intensive agriculture thought to be particularly at risk from exotic and imported animal diseases. But a potential source was close by, at Pirbright, only about 6 kilometres from the farm.

Public health professionals are keenly aware that when outbreaks start at a weekend the associated communication difficulties may make their tasks harder. Some even maintain that onsets with this timing are commoner than stochastic initiation times would predict. August 3rd was indeed a Friday, and confirmation of the diagnosis was made at 9 p.m. But there was no delay in raising an epidemiological hypothesis about the source of the virus. The only laboratories in Britain that hold and handle infectious foot and mouth virus are at located on a single site at Pirbright: the Institute for Animal Health (IAH, the government diagnostic, research and international reference laboratory) and Merial Animal Health Ltd, a vaccine manufacturing factory. The issue was settled beyond reasonable doubt by gene sequencing. The outbreak strain was of type O1 BFS67, the strain recovered from the 1967 FMD epidemic in England and Wales. 'O' indicates the immunologically distinct serotype, '1' an antigenic variant of this type, and 'BFS' stands for 'British field strain'. This strain has not circulated anywhere in the world for many years. It only exists in FMD reference laboratories and vaccine plants and was being handled in both Pirbright establishments just before the outbreak.

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The only comfort factor for the present Pirbright managers is that they join a long list of other workers on the virus who have let it escape. The first was Friedrich Loeffler, Director of the Hygiene Institute at the University of Greifswald. In research funded by the Prussian Kultusministerium he showed in 1898 that the foot and mouth virus was a filterable (in operational terms also meaning invisible by light microscopy) but particulate replicating agent. This was the first time these properties had been shown for an animal pathogen. In textbooks Loeffler is named as one of the founding fathers of virology. But his foot and mouth virus activities were associated with repeated outbreaks of the disease at Greifswald. He came under pressure to relocate, and in 1910 set up a new laboratory not far away, on the Baltic Island of Riems. It was the first single-purpose virus research laboratory in the world. But even an island location does not seem to guarantee safety. An accident at Riems and subsequent airborne transmission was blamed for starting FMD outbreaks in Denmark in 1982 and 1983.

There have been problems much closer to home as well. In 1960 an outbreak occurred on a Surrey farm only 1.5 kilometres from Pirbright. The virus was of a South African type being worked on there. Its escape was blamed on a breach in the ventilation system which allowed the virus to get into fields near the laboratory, with onward transmission by wildlife. High efficiency particle abstraction (HEPA) filtration was installed in consequence. It broke down in 1967 but only cattle and sheep within the perimeter fence got infected. There was a similar outbreak in 1970, again without any distant spread.

Vaccine problems have also caused outbreaks. They were responsible for 13 of the 23 'home bred' cases in Western Europe that occurred between 1978 and 1988. The British example is the Isle of Wight outbreak in March 1981. Cattle in Brittany had developed disease after vaccination with a product that still contained live virulent virus. Infection spread to pigs and the virus from them blew across the English Channel, infecting animals in Jersey on the way. The significance of this event is not as a vaccine breakdown, even taking account of its human parallel—the Cutter incident, when in 1955 improperly inactivated Salk polio vaccine made by the Cutter Laboratories caused 94 cases (59 paralytic) with contact spread to another 266 (133 paralytic) and 10 deaths—and even bearing in mind the molecular similarity (but not disease-causing potential) of poliovirus and foot and mouth virus. The importance of the Isle of Wight is its dramatic demonstration of the foot and mouth virus' transmissibility—its ability to travel as far as 300 kilometres on the wind—and as an equally impressive example of the predictive ability of FMD scientists: a mathematical model of aerial transmission developed by Pirbright and the UK Meteorological Office accurately predicted the location of virus landfall in 1981. An important stimulus for this work was the very big 1967 epidemic, in which about 300 outbreaks occurred downwind, and few upwind, from the initial outbreak.

Veterinarians interested in infectious disease have the big advantage over those who study humans in that they can experimentally infect the species they need to study under controlled conditions. In part, this explains why the spread of foot and mouth virus is better understood than that of most human pathogens. Thus it is known that in general pigs are by far the most dangerous spreaders of infection, because in 24 hours they breathe out 10,000 times more virus than a heifer. However, unlike cows, they are very resistant to infection, needing to be exposed to more than 80 times as much virus for disease to develop. In contrast, cows are very susceptible. Exposing one to ten virus particles over a 24-hour period

will establish a clinically apparent infection more often than not; this has been calculated to mean that the threshold concentration for infection is less than 0.1 virus particle/cubic metre of inspired air. In another way, sheep are even more dangerous than pigs, because they can suffer from a silent infection in which they excrete virus without having any signs of infection at all.

All this information is very useful to policy-makers. Nevertheless, it has to be used with caution. Different strains of virus behave in different ways. At present it is not possible to use the genome sequence of an outbreak isolate to predict how good it will be at spreading on the wind. More often than not the wind itself is too capricious to be forecast accurately, even when the most powerful computers are called into play. And the virus evolves in real time; on average, annual sequence changes change about 1 per cent of its genome. Such uncertainties are usual in biological systems. Policy-makers compensate for them by putting much weight on recent events as guides for the future. FMD is as good an example of this as any. The title of the most recent look back at an epidemic in Britain says it all: *Foot and mouth disease 2001: Lessons to be learned inquiry*. Its report had many precursors. Nineteenth-century Select Committees were succeeded by Departmental Inquiries; one in 1912, two chaired by Captain the Right Hon. E.G. Pretyman (1922 and 1924), one chaired by Sir Ernest Gowers (1954), and one chaired by the Duke of Northumberland (1968).

It could be said that the existence of so many inquiries supports the view that their purpose is to assuage public opinion rather than to stimulate action to prevent further outbreaks, and that support for this view comes from the detailed attention they paid to outbreak control. There is truth in this assertion. But policy-makers face a particularly slippery adversary. Its transmissibility makes it so. And each of the four outbreaks that have occurred in the UK in the last 40 years has been very different from its immediate predecessor. The 1967 outbreak had been preceded by a large number of small outbreaks from imported virus (179 between 1954 and 1967). More than half had never spread to cause secondary cases. So the explosive expansion after a week of a few cases in October 1967 took official veterinarians by surprise. The epidemic went on for 222 days. There were 2,364 cases and 434,000 cattle, pigs and sheep were slaughtered. Spread on the wind across the Cheshire plain, the home of probably the highest-density of dairy cattle anywhere in the world, helped the virus to spread. Better import controls aided by immunization programmes in South America and Europe then led to a long period of freedom from the virus. The Isle of Wight outbreak in 1981 was very small. So 2001 came as another surprise. There was a Contingency Plan. Not unreasonably, its working assumptions were based on European experience over the previous decade. They were designed to deal with an outbreak of ten cases. But by the time the first case was confirmed the virus had infected animals on at least 57 farms in 16 counties. Its dissemination had been speedy because the first case had been in pigs; silent, because they had gone on to infect sheep; and widespread, because the sheep were then moving long distances to market.

The 2007 Surrey outbreak also failed to follow precedent. Although small, it went on much longer than expected: examining cattle on smallholdings was difficult due to poor handling facilities and the disease festered on. But the response of the government at the start of the outbreak could not have been faster. And the epidemiology reports issued by the Department for Environment, Food and Rural Affairs (DEFRA) were of the highest

scientific quality. They were published in full without delay. Memories of 2001—221 days of disease when control measures caused the slaughter of 4,163,000 animals and cost the government £2,790,000—were still fresh. The media played a part too. FMD was the lead item on the BBC Six O'clock News for four days running.

As a biosecurity problem FMD is special. Its ability to leave the confines of a laboratory is unmatched by any other microbe. There have been laboratory escapes of Q fever and smallpox but they never directly infected individuals outside the building. However, there are no FMD 'microbiology martyrs'—scientists killed by an infection contracted in the laboratory. Biosecurity policies and technical developments have been driven by infections like plague, glanders, tularaemia, brucellosis, typhus, herpes B and yellow fever. More recent policy drivers have been the occupational risk to scientists from HIV, tuberculosis and E.coli O157. But foot and mouth virus does not infect humans. Neither in general does it cause much mortality in the animals it infects. It is very different, for example, from high pathogenicity avian influenza strains like H5N1. It is primarily an economic disease. Animals recover from it but have lower value because they are below par. Milk yields are suboptimal. Many countries will not accept imports of meat and animals from regions where the disease is active. For more than a century, British policy has been based on the calculation that the cost of stamping it out (mainly compensating farmers for losses caused by compulsory culling of infected animals and their contacts) has been worth the economic benefit. The aim has been to emulate New Zealand (FMD never introduced), Australia (last outbreak 1870), and the USA (last outbreak 1929). But for much of the twentieth century there were frequent importations of the virus. They owed much to the nature of British–Argentine trade relations. British industrial exports to Argentina were linked politically to British imports of Argentine beef and beef products. But the Argentinian *estancieros* called FMD *aftosa*. To them it was a mild disease of little importance. From 1928, British veterinary inspectors were stationed in Buenos Aires to prevent the export of diseased carcasses. Success was finally achieved 40 years later.

Three reports were published on 7 September: the Health and Safety Executive's *Final report on potential breaches of biosecurity at the Pirbright site 2007*, an *Independent Review of the safety of UK facilities handling foot-and-mouth disease virus*, chaired by Professor Brian Spratt, and an epidemiological report by the DEFRA National Emergency Epidemiology Group. The government response was published on the same day. All concluded that, on the balance of probabilities, liquid waste containing live virus on its way from the vaccine plant to final disinfection at the IAH had escaped from 40-year-old drains on the Pirbright site. Flooding played a role. The virus was then carried to the farm where the outbreak started on the wheels of trucks being used by workmen engaged in site upgrading, work that included drain renewal.

These reports are of high technical excellence. In seeking evidence and in considering how the virus escaped they left no stone unturned. The government has accepted their recommendations. Pirbright will be rectified. The regulatory framework for animal pathogens and the position of DEFRA as regulator, licensor and inspector of Category 4 (the most dangerous) animal pathogens will be reviewed. The Spratt report concluded that: 'the fact that animal viruses like FMDV [foot and mouth virus] do not infect humans, and that there had not been any previous problems with infections of animals around Pirbright for nearly 50 years, may have led to some complacency about safety'. Far from being

Category 4, the drains did not even meet the British Standards for workmanship (BS 8000–14:1989) for foul drainage. Many of the 1,000 vehicle visits to the site between 14 and 26 July went unrecorded.

It is certain that the outbreak will lead to even more emphasis on laboratory biosecurity—already of concern because of bioterrorism. But its significance is wider. It is yet another example of a disaster caused by a leaking pipe. Cadbury was fined £1,000,000 on 16 July (the week before the foot and mouth virus escape) for selling chocolate contaminated with *Salmonella* Montevideo. A leaking waste pipe had dripped faecal bacteria into the crumb used to make bars. The product recall cost the company another £20,000,000. And on 28 August 2007 ICL Plastics and ICL Technical Plastics of Glasgow were fined £400,000 for health and safety breaches: an explosion on 11 May 2005 caused by a leak of liquid petroleum gas from a pipe installed in 1969 destroyed their factory, killing nine and injuring 33.

In *Man-Made Disasters*, Barry Turner proposed that disasters have an incubation period. The foot and mouth virus escape from Pirbright fits his analysis so well that it will enter the textbooks. Incubation began long ago, when poor drains were installed. Letters were written about them, but nothing happened. There were information difficulties: the IAH biosecurity officer did not know that the drain from Merial might contain live virus. 'Strangers' were present: workmen were coming and going. In Turner's analysis an incubation period ends with a precipitating event; at Pirbright the DEFRA epidemiologists consider it to be a notable surge of rainfall on 20 July and heavy falls on 21–22 and 23–24 July.

That the outbreak had its roots in past financial stringency and administrative complacency, and was initiated by bad luck with the weather and the wheels of lorries engaged in the £121 million Pirbright rebuilding programme, will bring no comfort to the farmers, auctioneers, cattle float operators and organizers of agricultural shows whose activities came to a sudden and uncompensated halt throughout Britain at the beginning of August. The outbreak was very small but its consequences very great. Was the Thomas theorem 'If men define situations as real, they are real in their consequences' in operation? Were the government's actions proportionate? A very British solution to these questions is in hand. Iain Anderson, author of the 2001 *Lessons to be learned inquiry* has been called in.

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