# Agriculture shock

Fears about terrorism usually centre on nuclear or biological weapons. But attackers could cause huge economic damage by spreading plant or animal diseases. Virginia Gewin asks how this threat is being confronted.

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The statistics on the 2001 outbreak of foot-and-mouth disease (FMD) in Britain make for disturbing reading. Four million cattle were culled to contain the disease, and estimates of the cost to the British economy — primarily to the agriculture and tourism industries — run as high as £30 billion (US$48 billion).

The outbreak was unintentional, probably the result of illegal imports of infected meat being fed to pigs. But it can also be seen as an expensive warning. Although smallpox and anthrax receive the bulk of government and media attention when it comes to assessing the risk of bioterrorism, a deliberate attack on agriculture could disrupt trade and cripple agricultural industries. The risk of human fatalities or a serious food shortage is low, but few events would cause more economic damage than attacking the food supply. "The British FMD epidemic has given a blueprint to any terrorist," says Martin Hugh-Jones, a veterinary epidemiologist at Louisiana State University in Baton Rouge.

If such an attack seems unlikely, it is worth noting that agricultural bioweapons have been used before. During the First World War, German agents infected Allied horses with the bacterium *Burkholderia mallei*, which causes glanders — a disease that can kill horses and can also infect humans. And Simon Whitby, a peace-studies researcher at the University of Bradford, UK, says that any country that has studied biological weapons, including the United States and Russia, will have looked at plant and animal diseases. Iraq, for example, is known to have weaponized wheat pathogens.

The main effects of any new attack are likely to be economic. The World Trade Organization lists few reasons for refusing to import crops and animals, but the presence of disease is one of them. Such bans can have rapid and severe consequences. When karnal bunt, a fungal disease of wheat, was found in northern Texas in 2001, over 25 countries banned wheat imports from the four infected counties within a single day. The estimated loss of revenue was $27 million.

Agriculture is also now more open to attack, as a result of large-scale methods such

**Close combat: could intensive factory farms become another battleground in the war on bioterrorism?**

as the use of factory farms and monoculture cropping systems. "There is a vulnerability. It isn't anyone's fault, it's just how agriculture has evolved," says Jim Cook, a plant pathologist at Washington State University in Pullman. And although the ease with which a pathogen could be introduced is the root of the problem, weaknesses in the systems used to detect an outbreak could exacerbate any damage.

## On the alert

Thankfully, the threat is now receiving attention. Funding in the United States has increased since the attacks on 11 September 2001 — President George W. Bush's proposed budget for the 2003 financial year includes an extra $146 million to protect agriculture and the food supply, including money for monitoring animal health and for setting up a coordinated system to respond to disease outbreaks. And last September, the US National Academy of Sciences released *Countering Agricultural Bioterrorism*, a report detailing the problems that it says need to be addressed, from better diagnosis to improved communication between those who monitor potential outbreaks.

In Europe, defences are being boosted in response to an increase in the number of diseases that the continent's agriculture is expected to be exposed to, whether through increased trade or the possibility of climate change. "We have to be prepared to fight diseases that we didn't have to fight before," says Alex Thiermann of the Paris-based World Organization for Animal Health (OIE). Britain's FMD epidemic has also given a new urgency to research on diagnostic tools and vaccines, as well as encouraging countries to coordinate their plans for responding to future outbreaks.

Of all the lines of defence, rapid detection is considered most important. In many agricultural settings, surveillance systems usually rely on a farmer or local-government agent noticing something unusual. But the clinical symptoms of some diseases appear days after infection. With animals kept so closely confined, entire farms can rapidly become infected before anyone is aware of the problem. "Animals are kept in perfect environmental conditions for spread," says Larry Madden, a plant pathologist at Ohio State University in Columbus. It is not uncommon, for instance, to find 5,000 animals on 20 hectares of land in a typical US dairy operation. Rapid and extensive movement of animals between farms, slaughterhouses and markets also accentuates the problem. FMD, for example, had spread across Britain before it was detected.

The backbone of the global disease-detection system is the chain of 156 reference laboratories and collaborating centres run by the OIE, which analyse samples taken from animals that are thought to be infected. In the United States, the laboratory responsible for diagnosing exotic diseases is the Plum Island Animal Disease Center in New York, run by the US Department of Agriculture (USDA). It currently conducts fewer than 1,000 tests every year for FMD, each of which is sent in to the lab. But an outbreak of FMD would require it to run tens of thousands of tests. And the quicker it could deliver the results, the sooner vets working in the field could decide what action to take.

'Pen-side' tests could help to speed up the process. Researchers at Britain's Institute for Animal Health in Pirbright, Surrey, for example, have adapted the laboratory procedure used to check for the presence of the FMD virus so that fieldworkers can perform the test by applying a treated paper to a tissue sample from a live animal. By monitoring the change in colour of the paper, the researcher can determine whether the antigens are present in about 10 minutes. The test has its drawbacks: false negatives can occur at rates of 10–20% when only small amounts of the FMD virus are present, and a cell-culture test is needed to confirm results that prove negative for the virus. But it could yet be a useful aid when time is short, and it is expected to undergo field trials in the next few months. "Those kits are extremely valuable if we have to make quick decisions," says Thiermann.


**Devastating diseases: accidental outbreaks of karnal bunt (above) and foot-and-mouth (left) have wreaked havoc on farming economies.**

C. RIEDEL/AP

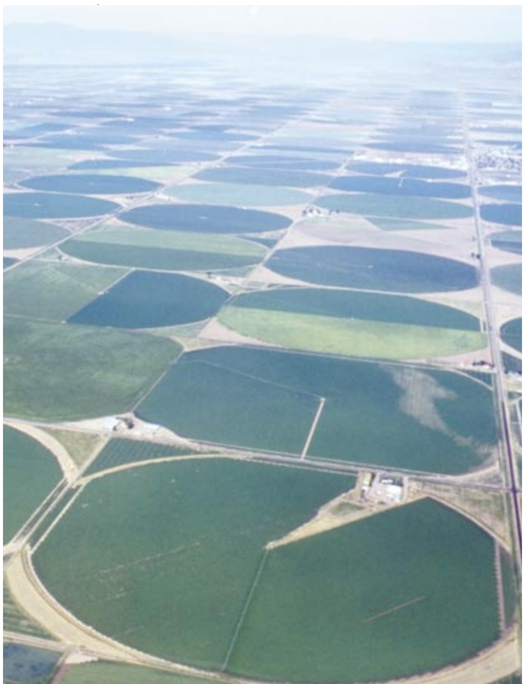
S. FRASER/SPL

Another quick, but more sensitive, approach to FMD testing is being explored at Plum Island and Pirbright. Researchers have been evaluating field versions of a method for detecting viral RNA using the polymerase chain reaction (PCR), a common tool used to copy lengths of genetic material. Pirbright officials say they have a fully automated version of the test that could readily be established in a mobile lab should the need arise.

## Below the radar

Early detection of crop pathogens is also vital. The United States has more than four million square kilometres of farmland, much of it in remote areas where surveillance is virtually non-existent. Crop diseases can go unnoticed for a long time, during which they are continually spreading. It is estimated that the plum pox virus, discovered in Pennsylvania fields three years ago, was present for six to eight years before it was detected. In the past, a disease sample might have awaited identification until it eventually found its way to the often solitary plant clinician in the agricultural department of the local university.

The USDA is now attempting to improve this situation. Training modules are being developed for 'first responders', such as the farmers and crop consultants who are likely to be the first to notice a problem. And of the $43 million allocated to agricultural-bioterrorism preparedness in the 2002 budget, $20 million is earmarked to establish a network of diagnostic labs for plant and animal pathogens.



J. GIPE/AGSTOCK/SPL

**Wide open: extensive monocultures such as maize can leave farms vulnerable to infections.**

Five new regional centres are currently being set up at universities around the country, with the goal of providing rapid and accurate diagnosis of disease threats. Many existing labs will also get much-needed improvements. For example, the Great Plains Diagnostic Network at Kansas State University in Manhattan couldn't even run tests involving PCR until the recent funding arrived.

Once diagnoses have been made at the regional centres, all of the relevant information will be transferred to the National Agricultural Pest Information System, a database maintained at Purdue University in West Lafayette, Indiana.

To treat an infection once it has been detected, better knowledge of the pathogen involved is often required. Gaps in our understanding are being filled by new genomic sequences of animal and plant pathogens. In September 2002, for example, scientists at The Institute for Genomic Research (TIGR) in Rockville, Maryland, sequenced the genome of *Brucella suis* (V. G. DelVecchio *et al. Proc. Natl Acad. Sci. USA* **99,** 443–448; 2002), a pathogen that is considered a likely bioterrorism agent — the US military itself weaponized the bug in the 1950s. *B. suis* primarily affects animals, but can cause a debilitating disease in humans that can be lethal to people with weakened immune systems.

Surprisingly, the genome of this bacterium suggests that animal and plant pathogens are not as different as was once thought (see I. T. Paulsen *et al. Proc. Natl Acad. Sci. USA* **99,** 13148–13153; 2002). Many of the genes that control the metabolism of *B. suis* are also found in the plant pathogen *Agrobacterium tumefaciens*, as well as in *Mesorhizobium loti*, a soil bacterium that forms a symbiotic relationship with plants. By investigating these links, TIGR researchers hope to reveal how *B. suis* survives outside its host, and thus generate new leads for tackling the pathogen.

Progress with plant diseases has been less impressive. As of September 2002, less than 6% of microbial genomes that had been sequenced and made publicly available belonged to plant-associated microbes. Animal pathogens are generally viruses or bacteria, but over three-quarters of plant pathogens are fungi, which have much larger genomes. "Compared to human and animal pathogens, plant pathogens are definitely behind," says Jacqueline Fletcher, president of the American Phytopathological Society.

Things are set to improve, albeit slowly. The US Department of Energy's Joint Genome Initiative announced in October that it will sequence two species of *Phytophthora*, a genus of fungus that is responsible for diseases as varied as sudden oak death syndrome and potato blight. What's more, a joint USDA and National Science Foundation programme has funded the sequencing of *Fusarium graminearum*, a fungus that causes disease in wheat and barley.

Forensic studies of deliberately caused outbreaks could also benefit from sequence data. Take the investigation of the US anthrax attacks, for example. Scientists had already sequenced the type of anthrax used — the Ames strain — and so were able to whittle down the number of possible places from which the bug could have been obtained. If sequences of different strains of other pathogens were available, investigators could eliminate many dead ends, as well as gaining incriminating evidence. "One of the differences is to be able to trace back and be able to get enough evidence to bring a case against the perpetrator," says Cook.

## Take the strain

But realizing these ambitions will take hard work. Fourteen more strains of anthrax are being sequenced, and for other pathogens, many strains will also have to be sequenced if genomic databases are to be of any forensic use. Several researchers have called for the creation of a database of pathogen genomes, which could be used to investigate outbreaks of animal diseases, but it will take many years to gather enough information to respond to the range of possible bioterrorism agents.

More immediate improvements to our defences could come from new vaccines that are currently under development. Vaccines are an important means for dealing with animal disease, but existing versions are plagued with problems. FMD vaccines, for example, struggle to cope with different strains of the pathogen. "No single vaccine can bring immunity to more than a few of strains," says Mark Wheelis, a bioterrorism expert at the University of California, Davis. Immunity is also often short-lived, and vaccinated animals cannot be distinguished from infected ones — and so are impossible to sell — because a weakened version of the live virus is used in the vaccine.

A new class of vaccines could counter some of these problems. Rather than using a version of the live virus, researchers are creating deleted, or 'subunit', vaccines, in which some genes have been removed. Proteins that are not crucial for antibody production, for example, can be removed from the vaccine. The treatment still prompts the production of the antibodies that protect against the virus, but vaccinated animals do not produce antibodies against the missing protein, and so can be distinguished from infected animals. Subunit vaccines have already been developed for Aujeszky's disease in pigs and bovine respiratory disease in cattle, and several groups are working on one for FMD.

## Prepare for the worst

Like most recent developments, the vaccine work is driven by the need to contain an accidental outbreak of disease. But should countries be preparing specifically for a deliberate pathogen release? An intentional release could cause even more damage than an accident. The perpetrator could choose to release several highly virulent pathogens simultaneously in remote areas, for example. Authorities in the United States and Europe say that they are considering specific anti-terrorism measures, but many of the steps taken so far, such as the development of better diagnostic networks, tie in with conventional strategies for tackling plant and animal disease.

Given the scale of damage that a deliberate pathogen release could cause, some researchers say that stronger measures are needed. But others question this argument. In the bag of terrorist tricks, agricultural bioterrorism is the wild card, and some experts feel that it is unlikely to appeal to terrorists. "People attracted to terrorism wouldn't be as attracted to this," says Rocco Casagrande, who studies biological-agent detectors at Surface Logix in Brighton, Massachusetts. "Most terrorists are urban. They want a big bang. Killing cows or pigs is not a big bang," agrees Hugh-Jones.

But others warn that different approaches are likely to be used in future terrorist attacks. Whitby, for example, says that he and his colleagues consider an attack on agriculture to be the most likely form of biological terrorism that we're going to see. Predicting the behaviour of terrorists is, of course, notoriously difficult. But if economic damage is the aim, agricultural bioterrorism is certainly a viable threat. The size of that threat may be hard to define, but the financial scars left by Britain's FMD outbreak show just how serious it could be. ■

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