

**PCR Tests to enable early diagnosis
in a range of infectious animal diseases -
with particular reference to Foot and Mouth Disease**

**Letter from Dr Roger Breeze to Mary Critchley, www.warmwell.com.
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www.warmwell.com

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Dear Mary:

Thanks for [your note](#). I thought I should reply at some length over the Holidays. I will mostly reply in terms of the US since I am not familiar enough with the EU or UK to make comments on specifics of your situation.

When I became Director of the Plum Island Animal Disease Center in 1987, I went to visit the APHIS leadership in Washington to ask what our only customer required from our research program (I was Director of the Center and of the ARS research program: APHIS' diagnostic lab was a tenant and I had no role in their program). To my surprise, APHIS said, "Nothing. In the event of an FMD outbreak we will diagnose the disease by cell culture at Plum Island as we have always done, and we will slaughter without vaccination, as we have always done. We don't want new tests and we don't want new vaccines." I asked, "What then is the function of the ARS research program?" And I was told, "Public relations, to make it look like USDA is doing something new."

My belief is that the generation of young men who halted the 1946 to 1952 Foot and Mouth epidemic in Mexico carved US policy in stone during their professional careers over the next 30 years and then fossilized the policy after they retired and had lots of free time to attend USAHA conferences for the last 25 years. The slow opening to new ideas now is connected to this generation fading from the stage.

APHIS was resolute in sticking to its old ways throughout my time in USDA - until I left in 2004. Of course, I did not see things the APHIS way. It was crystal clear to many people that mass slaughter in the US would be a debacle in modern agricultural markets and that new tools that allowed for vaccination and rapid response to limit the scale of the problem would be needed when the US policy eventually changed. Our hope was that the policy would be changed in advance of any FMD epidemic here, not in the middle of a disaster. So that is why the ARS group headed by Fred Brown devised the differential test

for FMD vaccination and previous infection in 1994 (ironically, the lead on this was Juan Lubroth, an APHIS scientist and the work was also supported by Alex Thiermann when he was head of APHIS International Programs). We also developed the portable real time PCR tests for FMD and other infections in 2000 and started to look at safer vaccines that could be made in the US. Several viable vaccine candidates have been on the shelf for years - the problems are that the US does not buy significant amounts of FMD vaccine and thus has no influence on the manufacturing interests (why would companies manufacture a vaccine designed for use under North American, EU and Australasian constraints when these nations don't use vaccines?) and the fact that the pharmacopoeia standards for FMD vaccine efficacy are designed for vaccines that will be used in countries where the disease is endemic, not absent or very rare. Does the US really need a vaccine that lasts the life of the animal or one that works immediately and vanishes after 6 months? The known potential vaccines are probably good enough for our use.

With regard to the real time PCR tests, an analogy I often use is that of the word processor and the IBM Selectric typewriter. If one had held a meeting with Executive Secretaries in 1983 and proposed to replace the IBM Selectric typewriter (with its two fonts) on their desks with a keyboard, a bulky screen like a television, a big box under the desk, and a bulky printer in another room to which they would walk to collect the written paper, they would have said the new system was useless. To persuade them, one might have said, "The computer has 100 fonts (but we only ever use two), corrections are easy (but we rarely make mistakes), your boss will also have one and type his own documents (are you totally crazy!!), and by the way it costs three times as much as an IBM and requires novel technical support (you just proved why it will never catch on)". The point is that the PC was not just a replacement for the IBM Selectric - it was a transforming technology that totally changed what was possible and opened up completely unforeseen ways of doing business. As a result, as happens with all transforming technologies, the IBM all but disappeared.

FMD diagnostic technology of the late 20th century depended upon tests that involved live virus or reagents to perform the tests that were derived from live virus and thus were confined to biological safety level 3 (BSL 3) diagnostic laboratories for biological safety reasons to prevent accidental escape of live virus contaminating the reagents (no one bothered to safety test the reagents to show there was no live virus contaminant so they could be moved out of biological containment). These tests could have been moved out of BSL3 labs like Pirbright or Plum Island but there was no incentive: APHIS were the only ones who would use them in the US, they had them in BSL3 at Plum and did not want to move them out to the mainland. In the 1990s, when ARS tried to move reagent components to the mainland, APHIS would not grant a permit. When the new Plum Island buildings were dedicated in 1995, I wanted to have the Deputy Secretary of Agriculture detect (dead) FMD virus in a sample during his boat ride to the island. APHIS would not let us set up this demonstration - the fear was that this might indicate that the APHIS lab was not necessary anymore. In the 1990s, FMD seemed a remote threat in the US, EU and Australia/NZ. The world of diagnostics was a small and traditional club in which people talked only to each other in a circle of mutual assurance and mutual congratulation. There was certainly an element of job protection in this internationally in that these were labs

that governments could not easily privatize - nor could governments transfer the test reagents to private companies outside the physical limits of the BSL 3 labs. Reviews of one country's capability were performed by club members from other countries. The idea that these labs might all use the same tests and reagents prepared for the group was unthinkable.

The PCR tests completely changed this cozy arrangement. But development and testing of PCR tests would not have been possible without people knowledgeable of FMD etc and with access to viruses in BSL 3 - there is clearly a continuing vital need for BSL 3 national facilities and skilled foreign animal disease scientists, it's just that the diagnostic role of central government labs has changed from test performance to quality control and quality assurance of a distributed system of laboratories that can respond very quickly. Many FMD viruses representative of all 7 serotypes were genetically sequenced by Dan Rock's team at Plum Island and the sequence information was transmitted electronically to Tetracore in Maryland. Rock and Tetracore worked together to compare the complete sequences of many different viruses simultaneously to find regions of the sequence that were identical between all the different viruses - these common regions would be targets for PCR tests. Tetracore have some proprietary software that eases this comparison. Having identified likely targets, Tetracore made reagents to these targets and Rock tested these with real viruses at Plum Island. From this, the ARS Tetracore FMD PCR test was developed, and this did not require any materials that had ever been in contact with live viruses. The key factor was that electronic information was sent to Tetracore from Plum Island - this information did not require an APHIS permit. The reagents were made without BSL 3 containment off Plum Island and sent back for testing. Certainly, had it been necessary to send any piece of the virus or any reagent derived from virus to Tetracore, APHIS would have denied a permit to do this and this generation of tests would not be available today. But the computer technology of sequence and transmission over the Internet overcame the longstanding APHIS barrier.

APHIS was totally uninterested in new tests for FMD - particularly PCR. There was no interest when the tests were being developed and none immediately after (ARS developed these tests for national security purposes as part of a wider government activity). When ARS told APHIS in 2000 about the new FMD PCR test, the response was an angry enquiry from the Head of APHIS Veterinary Services as to how FMD components had been taken off Plum island without an APHIS permit and why ARS had done something to overturn the APHIS policy of testing being done only by APHIS at Plum, particularly something that might enable the states to assume an APHIS function. In January 2001, Dave Huxsoll, Plum Director, and I arranged to meet with the Vet Services Head in his office in DC to bring him up to date on new technology but despite long advance notice he never turned up! When the FMD PCR test was demonstrated in the USDA HQ in DC in February 2001, after the UK FMD outbreak started, the Head of Vet Services complained that APHIS would now have to buy a PCR machine for each of 50 states. (By the way, I kept copies of all these USDA memos when I left and have them available if this record is challenged). At this same meeting, APHIS declared that the ARS PCR test could not be used because it had not been validated by APHIS. I had taken the precaution of calling the APHIS Biological Licensing group in Ames Iowa the day before this

meeting to ask for advice on how to demonstrate validation and obtain an APHIS license for a PCR test to be used in the US. I was told that APHIS had no validation protocol for any PCR test and had never licensed any PCR test for diagnosis of any animal or plant disease in the US, nor was any application in the pipeline. APHIS was at that time diagnosing FMD and other diseases in its own labs using APHIS-derived PCR tests - none of these PCR tests had been validated, they were developed with far less stringency than the ARS tests, there was no validation protocol, and the Head of Veterinary Service stated that his agency was exempt from APHIS licensing rules and did not need to do any validation. Ironically, USDA Secretary Veneman was being advised by the California State Veterinarian, who was also opposed to providing the new FMD test and equipment to the states: of course, a year or so later, California was using its own Newcastle disease real time PCR test (not validated by APHIS) to control a disease outbreak there. California did not need to invent an inferior real time PCR test for Newcastle disease in an emergency - the ARS Newcastle PCR test, which is far superior to the California test (as proven by trials later), was already sitting on the APHIS shelf where it had been since 2001 as a result of USDA and Secretary Veneman's policy.

I am not arguing in any way that diagnostic tests should not go through an independent validation process to validate the claims of their makers. Indeed, I was astonished to discover that APHIS actually did not have such a process. What happened with the FMD and other PCR tests is that "validation" became a smokescreen to preserve monopoly and jobs. And as was demonstrated by California, all the waffle from those insisting on "further validation" and federal not state responsibility disappears out the window when the fire starts in their own homes.

Currently, I understand that the ARS Tetracore FMD PCR test is very close to approval by USDA and OIE, a matter of months I hear. I hope there is a clear regulatory process after that so that future test manufacturers will know what standards they need to meet for validation, so we don't have APHIS and others moving the goalposts. The Department of Homeland Security deserves some credit for forcing APHIS to enter the 20th century of laboratory diagnosis (that is not a typo for 21st century by the way).

It is clear that until about 2003 APHIS was in a job preservation mode, unwilling to allow states to perform FMD PCR tests. This was always a silly policy that was bound to change once technology allowed it and need arose. California as a state has an economy that is in the top 10 of all countries - it makes no sense that this state does not have the human resources or need to diagnose diseases itself rather than send samples 3000 miles away. (The role of APHIS should be to ensure through quality control and assurance processes that a diagnosis of FMD is absolutely the same in all 50 states, APHIS should not be the sole performer of diagnosis.) So USDA, prompted by Homeland Security, is grudgingly setting up a network of foreign animal disease diagnostic capabilities using PCR in certain state labs. I used to work in the State of Washington's animal disease diagnostic lab, which is in Pullman, WA, on the Idaho border in the southeast corner of the state. The dairy industry in Washington is strong and located about 350 miles away, in the northwest corner of the state north of Seattle. So putting a PCR machine in Pullman to protect the Washington dairy industry is like putting one in Paris to protect England. The

state of Oregon, for example, is about the size of the UK, so providing a PCR machine at the Oregon diagnostic lab in Corvallis is certainly an improvement over sending samples to Plum Island. But don't forget that this means that Oregon is now in the same boat as UK so the problem of rapid, timely diagnosis is still there!

I will accept the proposal that samples from a cow that has FMD in the northeast corner of Washington State could be rushed to the nearest small airport and immediately carried on a chartered plane to get to Pullman in 4 hours or less so that a diagnosis could be made in 6 hours or so. But I don't think this is what will happen in practice. I was assured that this would be the case in UK when I met in 2004 with the DEFRA science advisor - he told me that PCR capability at Pirbright could serve all the UK with samples being taken at all speed to Pirbright from all corners of UK. But this did not happen in Ireland or Penrith, and probably elsewhere. High speed air transport is always available - in theory.

The question that should be uppermost is: "What will you do with a rapid PCR test giving results in 45 minutes that you can't do now with cell culture?" I don't see any serious policy attempts to answer this question and the distributed US lab network will likely have minimal impact on the speed of diagnosis and no impact at all on what happens after. The US still does not have vaccine stocks to protect any significant number of animals, and neither does the UK. So there will still be mass slaughter based on geographical proximity to the initial infected herd. I don't believe there will be any attempt to test herds for FMD with PCR before deciding to slaughter them (it will be interesting to find out whether the US will be able to sustain a slaughter policy in the courts when immediate testing is available but unused.). As you know from my papers, I believe the PCR offers a transforming moment for FMD control by which one can monitor all the herds in an area continuously and only slaughter those where there is infection (and I believe in vaccination immediately also).

Let me just touch on the differential test for FMD vaccination and infection, such as that developed by UBI on Long Island, New York. This arose from the work done by Fred and Juan Lubroth. In 1998, I asked APHIS how they would produce tests kits for the US should the need ever arise - I was told they would be made by APHIS itself in its own labs and no further APHIS test validation was required. Plainly, this was preposterous - APHIS has no facilities or equipment for such mass production. UBI tried very hard to get APHIS validation assistance in the late 1990s for their differential test and peptide vaccine - they got little assistance and many roadblocks, principally because these were not APHIS priorities since the US did not intend to vaccinate and would need neither a vaccine nor a differential test with this policy. This was the same in the UK. I had to laugh when I heard British vet authorities stating that they could not use the differential test because it had not been validated for UK! Whose job exactly is it to protect British agriculture against foreign disease threats with the very best technology? Why would a US company go to the expense of getting regulatory approval in the US and UK for products that the only customers in those countries opposed and had no intention of buying? Can British veterinary authorities claim today that they are constantly scrutinizing the world of science for better means to protect UK agriculture? If not, why not?

Between the Spanish Armada in 1588 and Jutland in 1916, naval warfare consisted of two lines of opposing warships sailing parallel to each other and firing their guns at close, visual range. By 1943, at Midway, this was all over and has never been seen again. The technology totally changed. I actually believe the battle for PCR diagnosis of FMD and foreign animal diseases outside a handful of specialist labs belonging to a select club is over, and the new technology won. People are kicking and screaming, and keeping the blocks in place with their fingernails, but it's all over. However, the true battle was never over tools - it was always about outcomes. And this battle remains to be fought.

I am not bound to real time PCR - technologies change all the time and there are new and better ones already - not in terms of what they do but in how they allow you to achieve your desired outcome - but if your outcome is not clear, it's not clear how technology helps.

I believe it is a serious mistake for public interest groups to focus on tests and technologies for FMD control in the US or UK. They will get mired in trivia and scientific details. Public interest is all about outcomes. If the US and UK policy were that mass slaughter would not be adopted and financial costs were minimized, we could judge government plans and preparations on how well they can assure us that these outcomes will be met. If a government does not have vaccine stocks to protect over 50% of susceptible livestock against all the potential virus types, it is not credible that mass slaughter can be avoided. If there were a series of time goals for all the key steps in detection and control, we could examine their credibility - if the government can plan and achieve transport of samples from anywhere in UK to Pirbright within 4 hours of report, I will accept that timeline (it won't solve other problems) - but the plans to achieve outcomes are vague and not quantifiable, so they are not really plans at all. Currently, in the field of FMD control, never have so many spent so much to do so little for so few, as Winston Churchill might have said. The need for new science and technology policy has never been greater because the threats have never been greater. The amount of money devoted to agricultural defense is now astonishing, but the scientific talent pool and ideas have never been as shallow. I have no confidence that the US or UK is any better prepared for FMD today than in 2001. So sad given what might have been.

If you wish to post this for a wider audience, that's fine.

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—— Original Message ——

From: [maryatwarmwell](#)

To: [Roger Breeze](#)

Sent: 12/21/2005 7:07:21 AM

Subject: Plum Island and the GAO

Dear Dr Breeze

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I do apologise for troubling you but I amÊpuzzled by the apparent wilful neglect of rapid diagnostic on-site tests in both our countries and the EU.Ê I remember listening to Fred Brown trying to get the then Chair of the EFRA Committee back in 2001 to understand its elegance and efficacyÊ .Ê Why - after four years and more - does RT-PCR not figure at the head of any UK or US Contingency Plan?Ê What on earth is going on?

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I see from the latest [GAO report](#), in which your name is at the top as one of the experts consulted, thatÊ APHIS and DHS are both “researching” diagnostics.Ê But why the duplication that fails to overlap? Why Êis there still no validation for use with FMD?

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On the website that I have felt compelled to update ever since the FMD horrors here, I have often referred to on-site diagnosis.Ê I feel increasingly that something wrong and unethical must be blocking this tool against the disease rather than mere inefficiency and lack of funding - but I may be wrong.Ê Are you able to help me understand this?Ê It seems pretty evident to me that no one in the UK Government has a clue.

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With best wishes

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Mary CritchleyÊ <http://www.warmwell.com>

