

Foot-and-Mouth Disease

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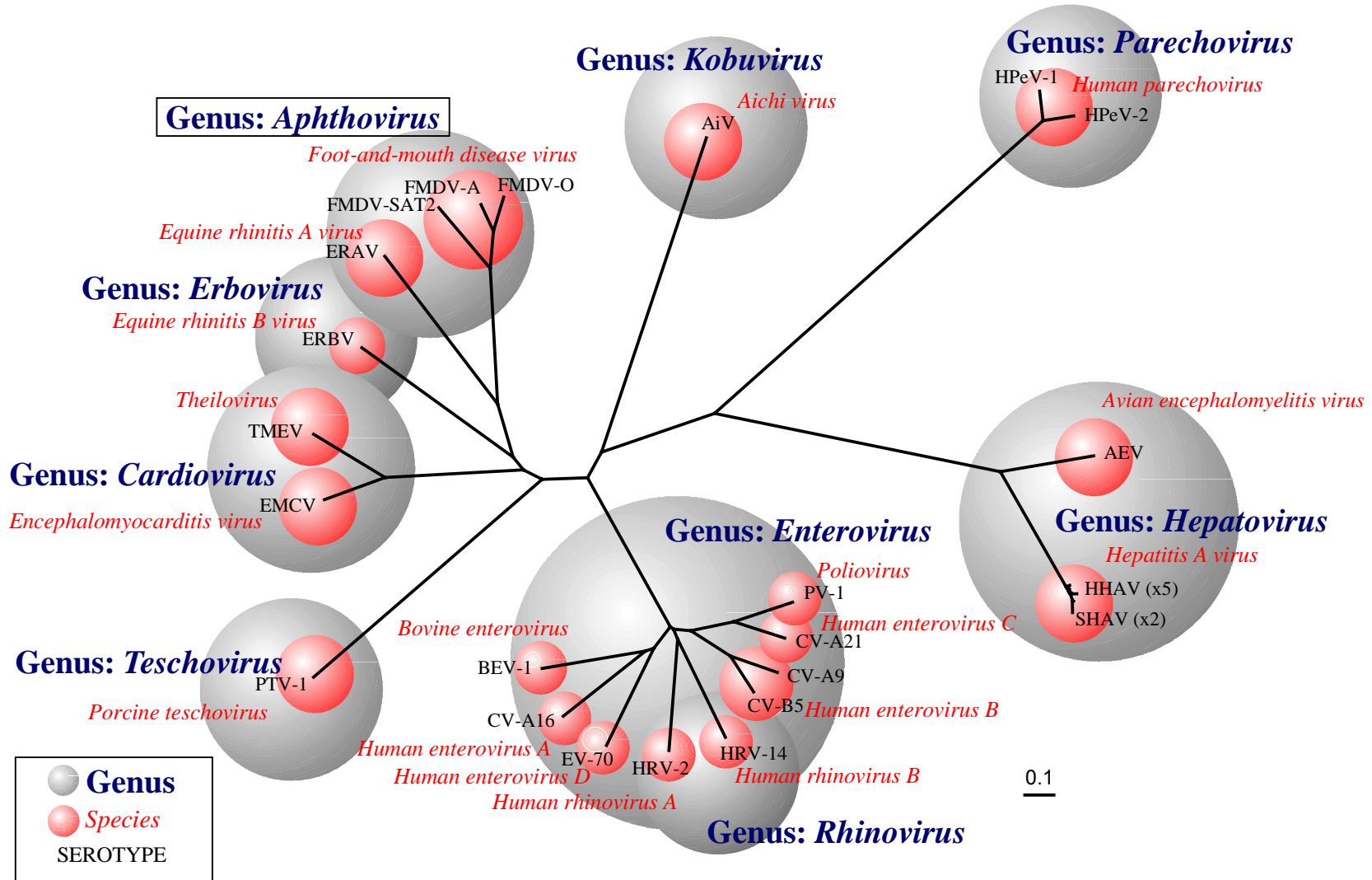
Good science, useful science

Foot-and-mouth Disease Virus.

- FMDV is the causative agent of foot-and-mouth disease, an economically important and highly contagious disease of many domestic livestock, such as pigs, sheep, goats and cattle.
- The primary route of infection by FMDV is through the upper respiratory tract.
- FMDV has a strong predisposition for epithelial cells. The initial sites of virus replication are thought to be epithelial cells of the oropharynx and associated lymphoid tissues
- During the development of disease, virus is widely disseminated throughout the body with secondary sites of replication in many epithelial tissues.
- Epithelial cells of the soft palate and pharynx are most likely the sites of virus replication in persistently infected animals.

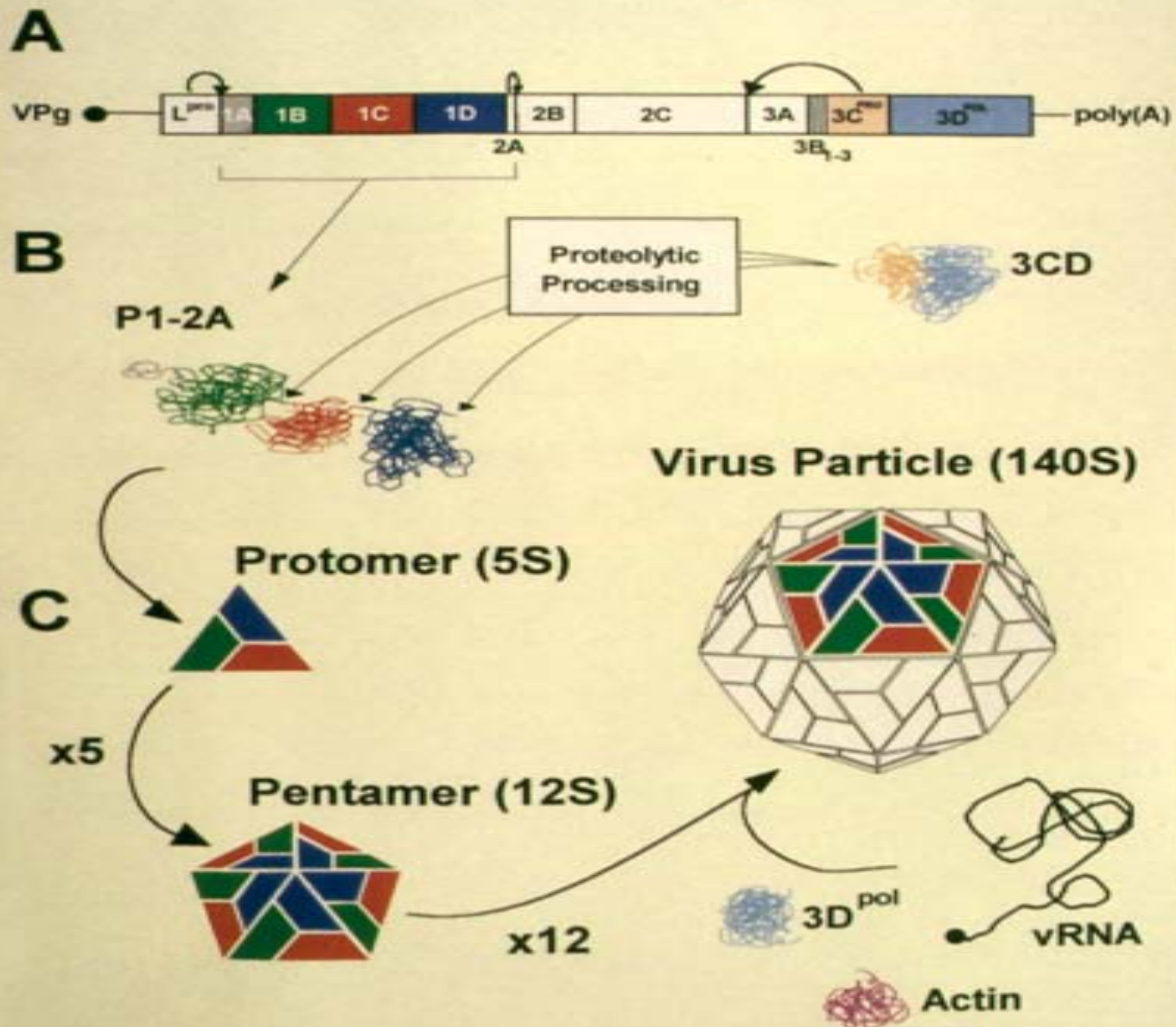


The nine genera that comprise the *Picornaviridae*



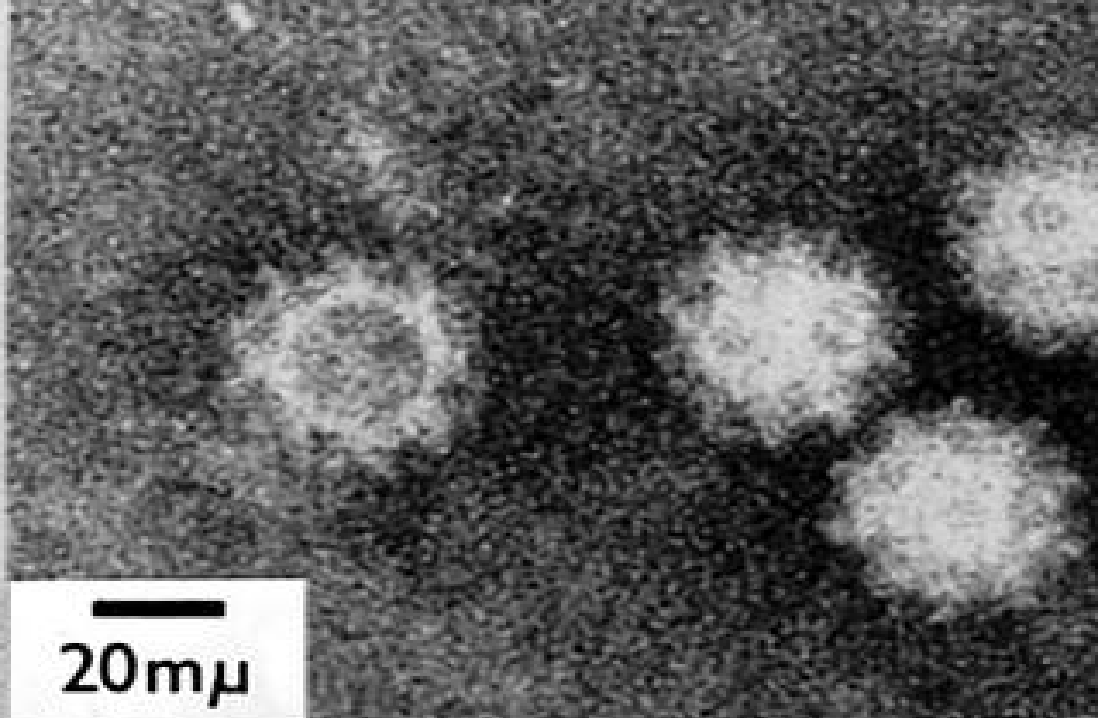
Neighbor-joining tree based on a comparison of amino acid similarities of P1 (capsid)

Foot-and-Mouth Disease Virus Capsid Morphogenesis

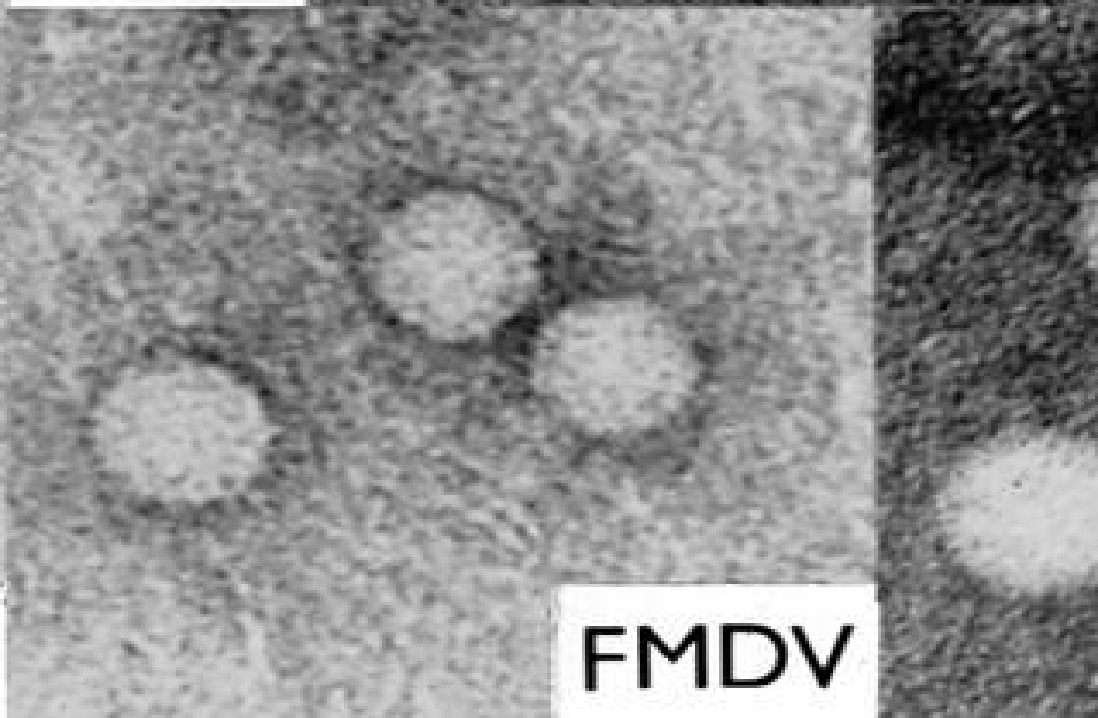




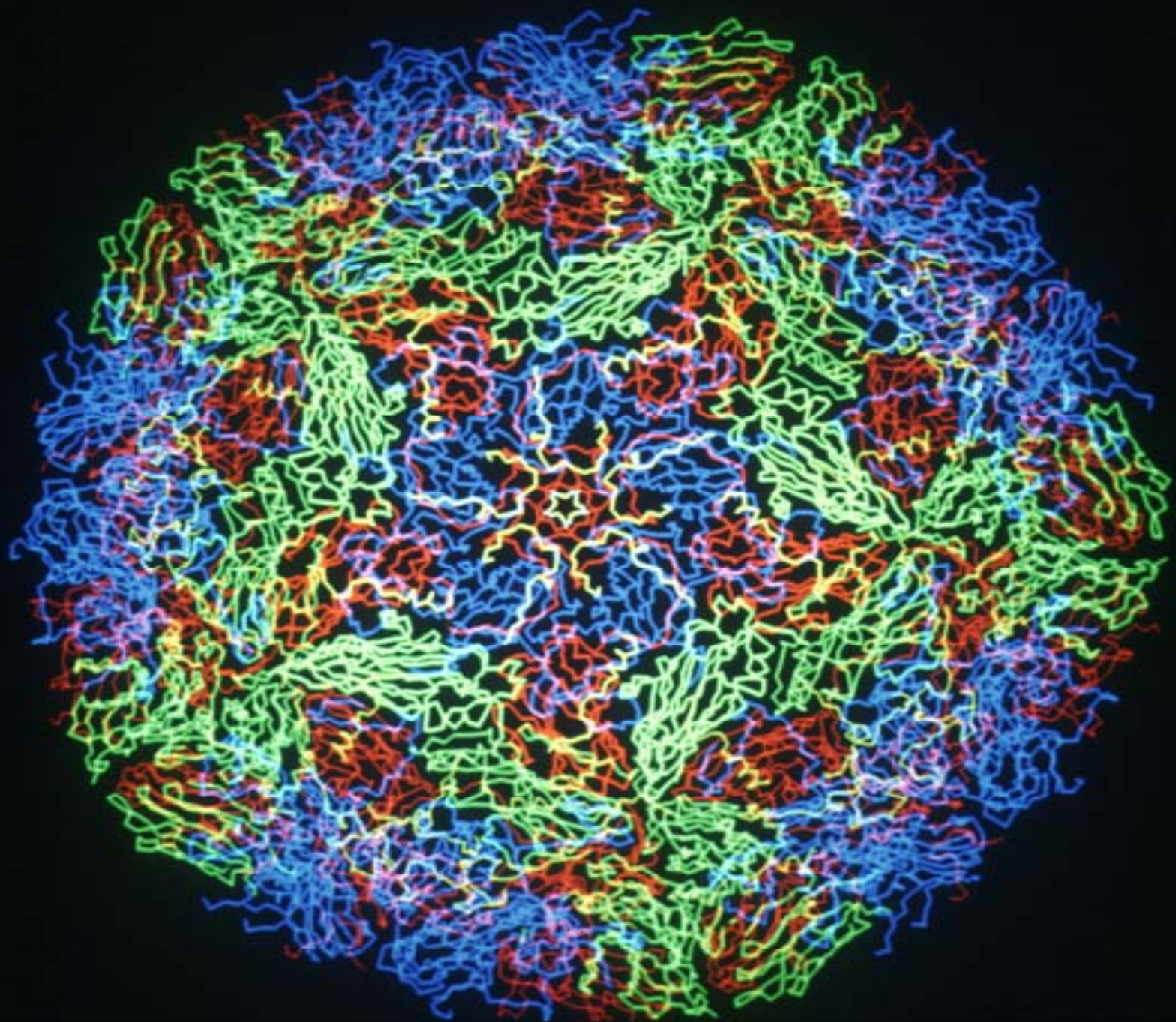
VSV

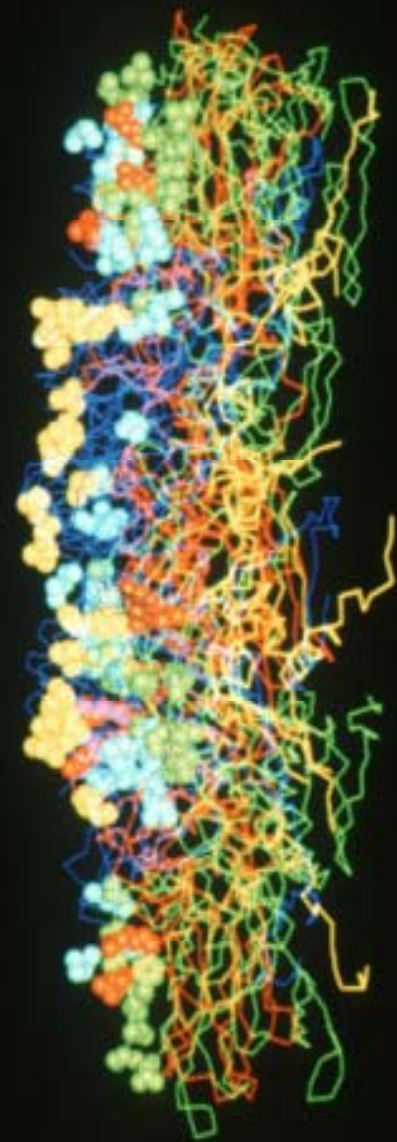
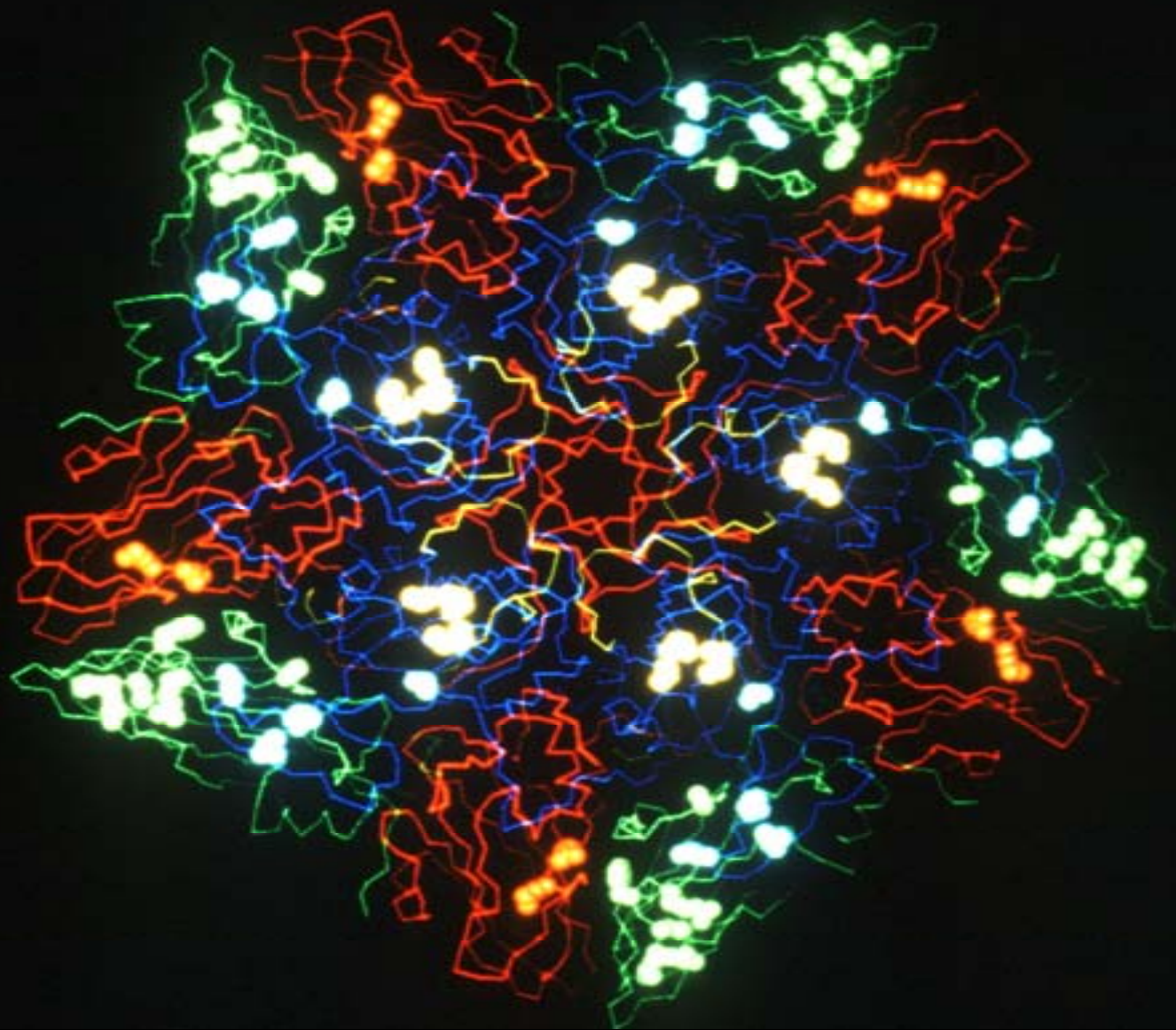


20mμ



FMDV



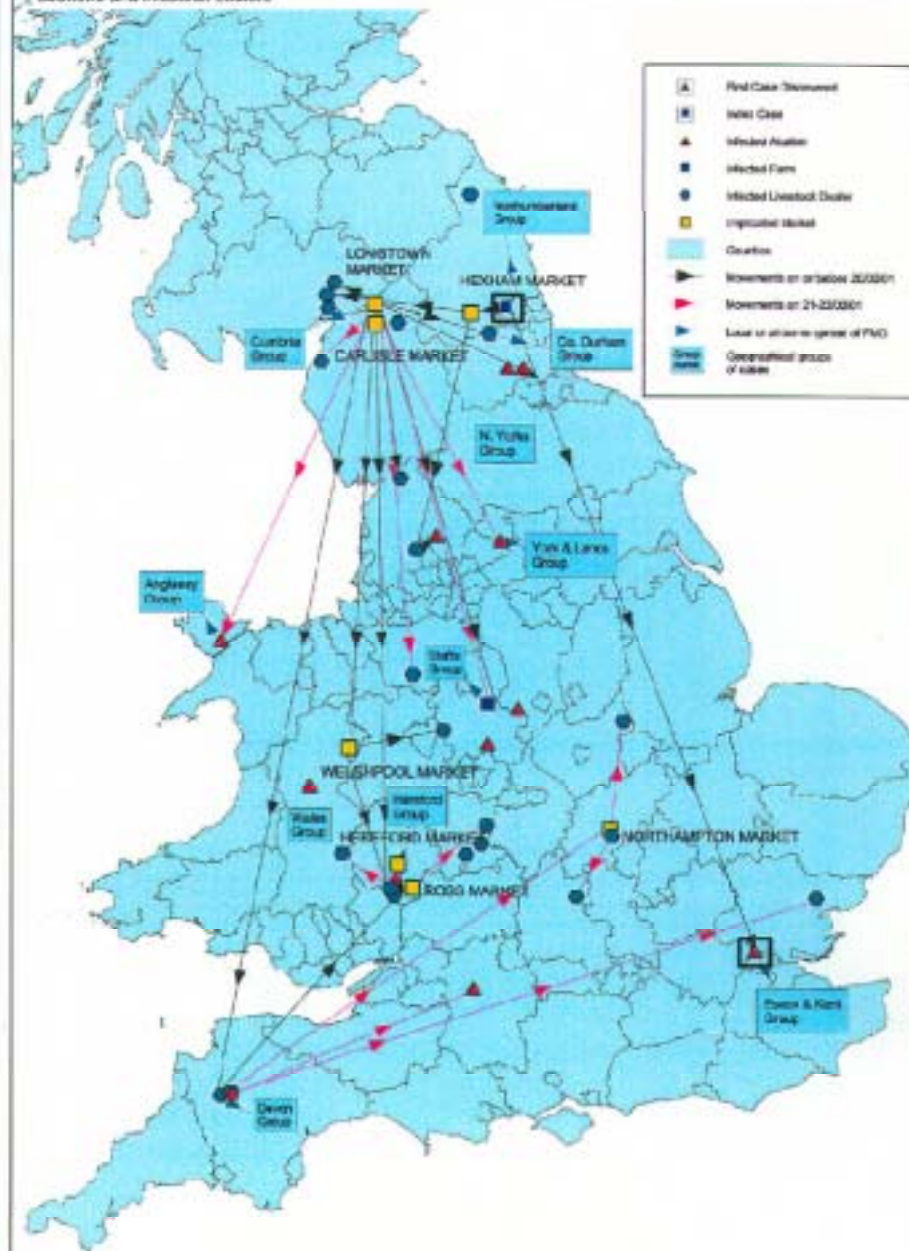


The UK FMD outbreak 2001

IMPORTANT EVENTS IN THE SPREAD AND CONTROL OF FMD IN THE UK

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- 15 March - Sheep, goats & pigs within 3 km of an IP in Lockerbie, Carlisle and Solway targeted for culling.
- 23 March - Contiguous premises (CPs) were included in the cull.
- 26 March - Epidemic reached its maximum with 54 outbreaks in one day.
- 27 March - 3 km cull started in Penrith valley, Cumbria
- 29 March - 24/48 hour cull policy began, IPs slaughtered within 24 hours CPs culled within 48 hours
- 26 April - cattle in farms with high biosecurity exempted from culls

Figure 1: Known movements of FMD-infected animals before 23 February 2001 and location of affected markets, abattoirs and livestock dealers



Stamping out involves:

- identification of infected animals
- culling of infected herds and flocks
- movement restrictions
- tracing of dangerous contacts
- culling of contiguous premises
- safe disposal of culled animals







Photograph Courtesy: AUSTVET

01 06 2001



Photograph Courtesy: MAFF, Leeds, May 2001



Photograph Courtesy: MAFF, Leeds, May 2001



Photograph Courtesy: MAFF, Leeds, May 2001

Foot and mouth crisis

Cattle low mightily, then the thuds begin

Killing fields Cumbria fears disease is now uncontrollable

John Vidal

The three slaughtermen are young, cheerful and clear-eyed. Killing is their business and they have never known trade like this. In the spring morning light they were on a farm near Wigton, Cumbria, shooting more than 100 cows and 500 sheep. Now the Ministry of Agriculture has told them to go to Jim Hutcheson's scale End farm near Penrith.

Our mobile death squad rattles through the lowlands south of Carlisle. We carry, in the back of a 16-year-old white van, cartridges, stun guns, decontamination suits, blue overalls, rubber gloves, sprays, wellington boots, forms and all the paraphernalia of modern slaughter.

The landscape is flat and desolate. Most farms here have been condemned and there are no animals in the field.



The white smoke of incineration pyres drifts into the van. We pass decomposing sheep carcasses piled high in the corner of fields where they have been waiting days to be picked up. The sickly stench of death hangs over some farms; in others the cattle and sheep lie sweetly together, their limbs spreadeagled, bellies swelling, tongues rigid and out.

Scale End was condemned on Sunday, but in the watery

sunlight it seems normal. At the end of a long closed road is a tangle of ancient and modern buildings. Seven lambs play in a small paddock behind the farm. A bull stalks the yard. The cattle low quietly in the barns and the sheep are penned in a field beyond. This is spring; there are daffodils on the roadside, birds in the hedges, and the Hutcheson family is waiting expectantly, as if for a relative.

But we bring only death. The three slaughtermen change into their overalls and white suits. They smoke a cigarette and share a joke. They don't like this, they say. It is messy and too human. Yesterday a farmer cracked up.

We cross the straw border that separates the clean from the unclean, and dip our feet in disinfectants. There are handshakes and nods. Mr Hutcheson is almost too emo-

tional to speak, but a toothless old cowherd shows them round. "There are plenty sheep and cattle," he says.

The slaughtermen reckon several hundred cows and 400 sheep. It will take four hours, they say, and start moving machinery around the barn to prevent the animals trying to bolt. Now the cattle squeal and low and the sheep bleat hard. The legs of a cow give way and it drops to the ground. Five heads strain out of the barn.

passed through them. It has not been spotted, they say, because the authorities have not had the resources, or perhaps the will, to check.

But in the past few days it has ominously spread deeper into the Scottish borders, with four cases, and, significantly,

farmers could vaccinate everything in a day. They are crying

Slaughtered sheep awaiting burial in a massive trench at Great Orton outside Carlisle where the army also plans a pyre for 15,000 cattle. Photograph: Colin McPherson

31st March 2001

had not and yet again he was frustrated. He still does not

The Guardian

Chief constable's daughter
Putting the record straight



Inside Goya's mind
Adrian Searle on an artistic treat



England go down grumbling
Umpires in the firing line



Foreign mission
Recruiting in South Africa

In Q2

In Q2

In Sport

In Education

The making of an epidemic

John Vidal, Paul Brown, Peter Hetherington, and Kate Connolly in Berlin

The epidemic began with which Ministry of Agriculture staff began to suspect last week how extensive these animal species. Five countries and many British counties at first and mouth disease carried by British sheep themselves to spread through Europe and into further afield.

But in mainland Europe, government officials try to identify and quarantine all those animals which they suspect may have come into contact with infected British sheep. It was becoming clear that the "contaminated" stock trade is so complex that a sheep farm in Aberdeenshire could be tracked 1,600 miles before being diagnosed as far away as Berlin.

The defective story starts for the moment, when 40 sheep were sent from the Williams's Prestwick Hill farm at Prestwick near Newcastle airport to Berlin market on February 23. It is known that more than 3,500 animals were sold that day and all the buyers and sellers have to be traced and their animals monitored. The ministry hopes to complete tracing them in the next 24 hours.

More than a week later, first and mouth disease was confirmed in cattle at Prestwick Hill farm shortly after Burns Hall farm at Strathclyde. The virus was carried from Burns Hall - heavily from within - was transported by the Ministry of Agriculture as the likely source of the outbreak. This, however, the virus was carried from infected pigs by wind to Prestwick Hill farm, and then to a

neighbouring farm at Westerhope, near Newcastle - introduced yesterday as the fifth outbreak.

They believe that the 40 sheep from Prestwick were sold to Willy Clove, a Devon dealer who has 11 farms in the west country where he keeps sheep before sending them on to British abattoirs or for export. The 40 were then shipped on February 23 to Longtown market, Carlisle, which is one of the largest sheep markets in Europe and also acts as a holding centre. However, the ministry still does not know for certain whether those sheep were the infected ones.

What is known is that the Longtown 40 were collected shortly afterwards and taken to Mr Clove's Highampton farm in Devon. Cattle there developed foot and mouth but it was not known at the time that they had caught it from sheep.

On February 25, some sheep from Highampton were trucked to Brunham slaughterhouse in Wiltshire, where they developed foot and mouth. The next day sheep from Clove's farm were sent to Northampton and sold at the local auction. Nearly about 80% of the 1,000 sheep sold that day would go for export but because the export route had been closed on February 22, those sheep would have been sold by dealers. All are now being traced.

Separately, Mr Clove had, on February 22, trucked 348 sheep from Devon to Germany via Dover to the Cap Atrique, Britain's only dedicated livestock export ferry. Since then, according to the ministry, he has sold other batches of sheep to British dealers intended for export. All those are also being searched for.

The last sheep export from Britain to the continent was on 24th February 17. The Cap Atrique left Dover for Dunkirk loaded with hundreds of animals. From 7 PM, the ferryway which carries it, said it had exported about 30,000 sheep in the two weeks before the ban. The ministry is having to trace all sheep exported on the Cap Atrique in the past three weeks.

Yesterday, the German authorities traced the 248 sheep sent directly by Mr Clove to



How foot and mouth spread

- 1** Foot and mouth outbreak at Burns Hall farm, Heddon-on-the-wall, Northumberland
- 2** Animals at nearby Prestwick Hill farm, Ponteland, are infected, probably as the virus is carried on the wind
- 3** 40 sheep from Prestwick Hill are among 3,500 animals sold at Hexham
- 4** The sheep are shipped to Longtown market, Carlisle, which acts as a holding centre
- 5** The sheep are taken to Mr Clove's Burdon farm, Highampton in Devon
- 6** Sheep from Highampton are taken to Bromham slaughterhouse in

Wiltshire where they develop foot and mouth. Other sheep were sold to Hill farm in Liancloud, Herefordshire, and another batch were sold at auction in Northampton

7 348 sheep sent before the foot and mouth outbreak were exported from Devon to Germany via Dover. Yesterday they were destroyed as a precautionary measure



Main points

- Number of confirmed cases rose to 12, with one outbreak in Belgium (Northampton, Dorset and Northumbria)
- Countrywide Alliance (politicians) planned London march until May
- Officials are to plan to close public transport

the first confirmed outbreak, but the European authorities say it may have better to use to prevent the disease spreading through Europe.

After long discussions from at first in Scotland, Northern Ireland, Wales and the west country animals are known to be highly susceptible to disease. If any of those exported animals 1 million, there are

any one of more than 80 UK registered "holding stations" where they are kept, often with many thousands of other animals. For up to several days, British exporters' farms in Belgium and Holland.

However, according to Gillie Forgie of the British holding stations. Le Galloway and Ayrshire 1 million, there are

possibly escape the authorities' investigations.

Travelling between towns across Europe is difficult, and Mike Gooding of Farmers First, a British sheep exporter, British animals have full documentation, but sheep animals are considered healthy, owners are required to ask vets to inspect their property of origin.

From those staying pens and markets, sheep go on to the continent and many are found to be infected but it had not checked whether he had them.

"If the virus spread to the continent, the entire European Union would risk being in agriculture minister, Sir John Grieve, has received thousands of sheep and pigs from farms.

A potential danger to the European region."

Foot and mouth virus, page 6-8

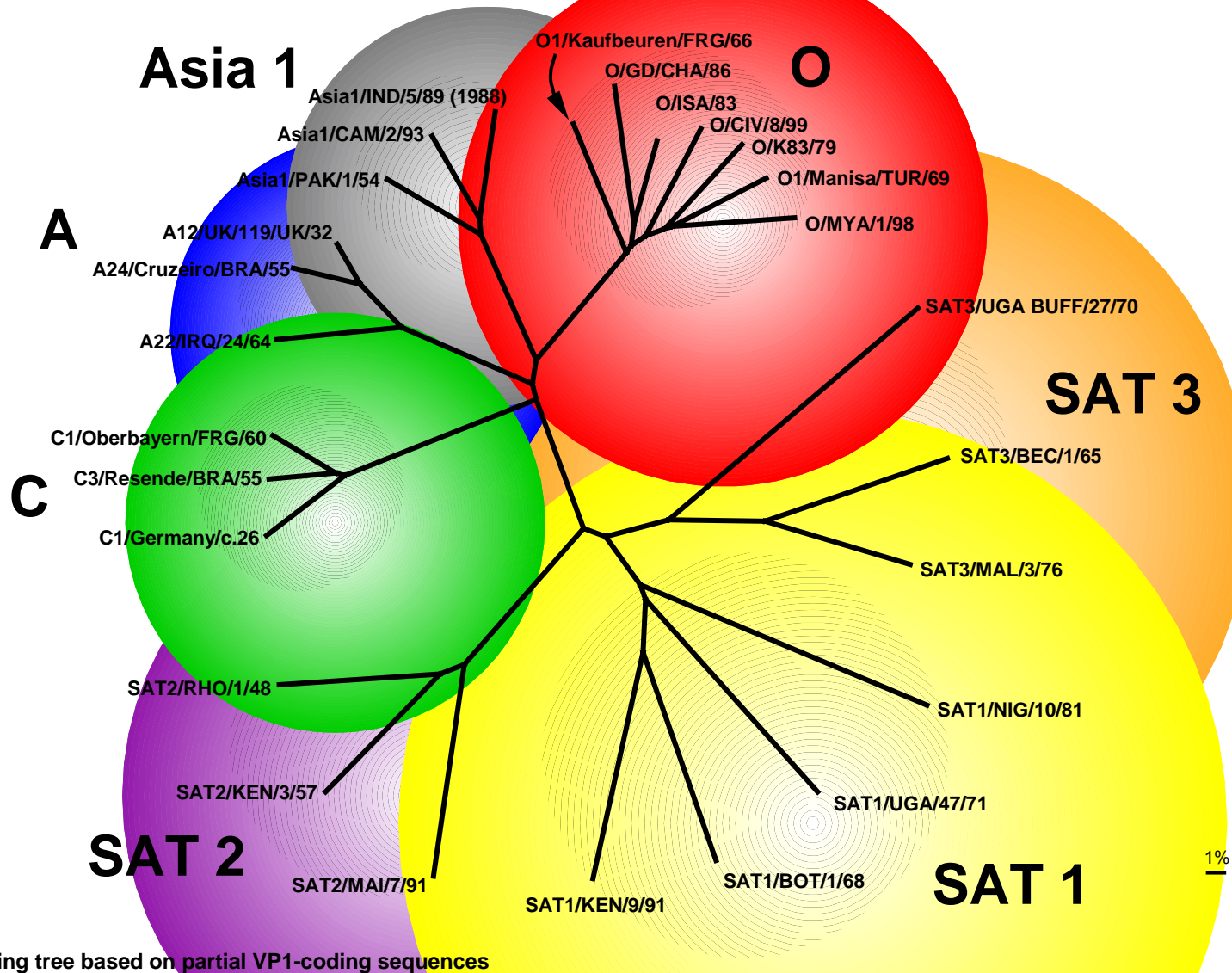
27th February 2001

What was the causative virus?

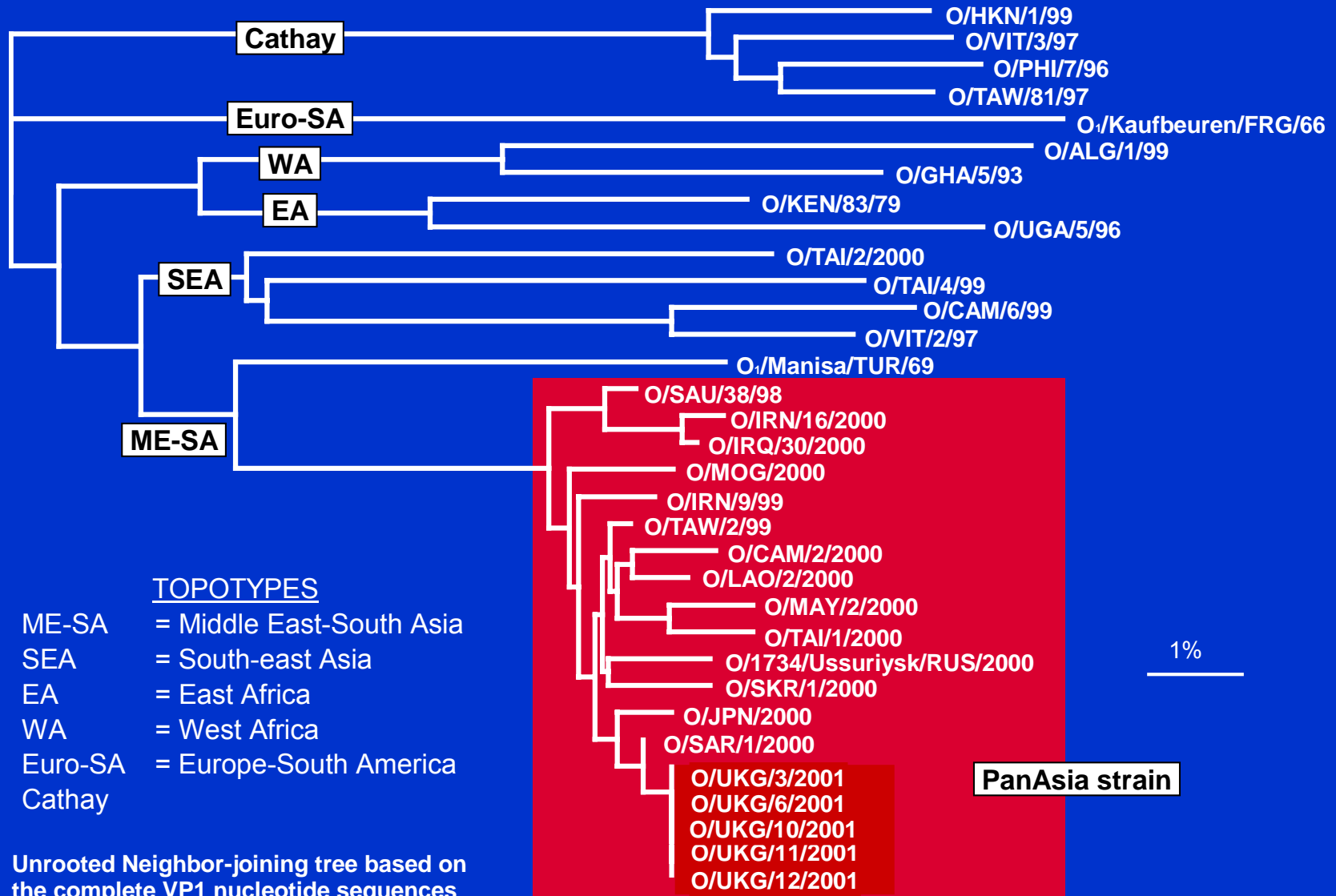
Within 24 hours nucleotide sequencing had shown it to be serotype O Pan Asia strain



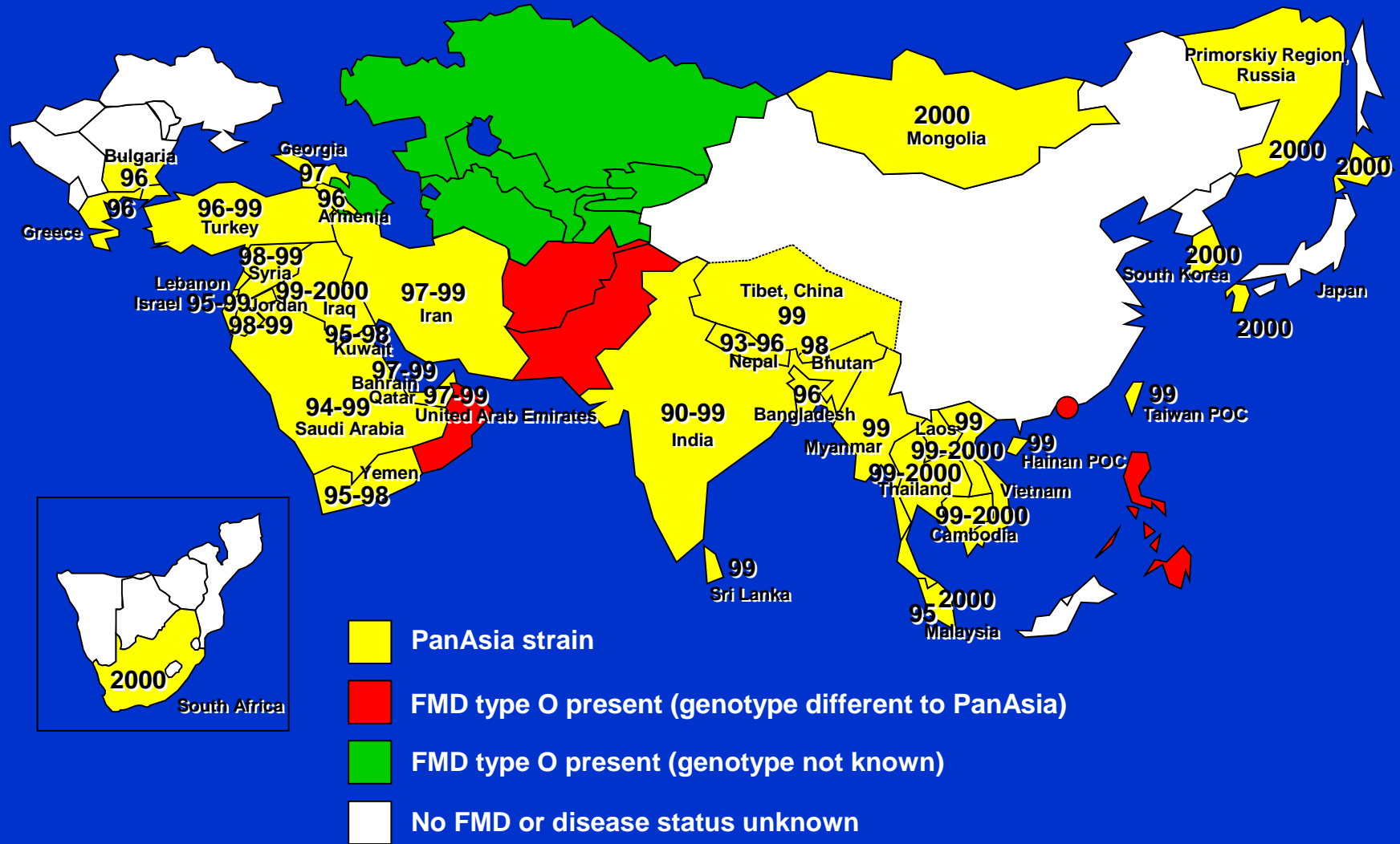
The seven FMDV serotypes

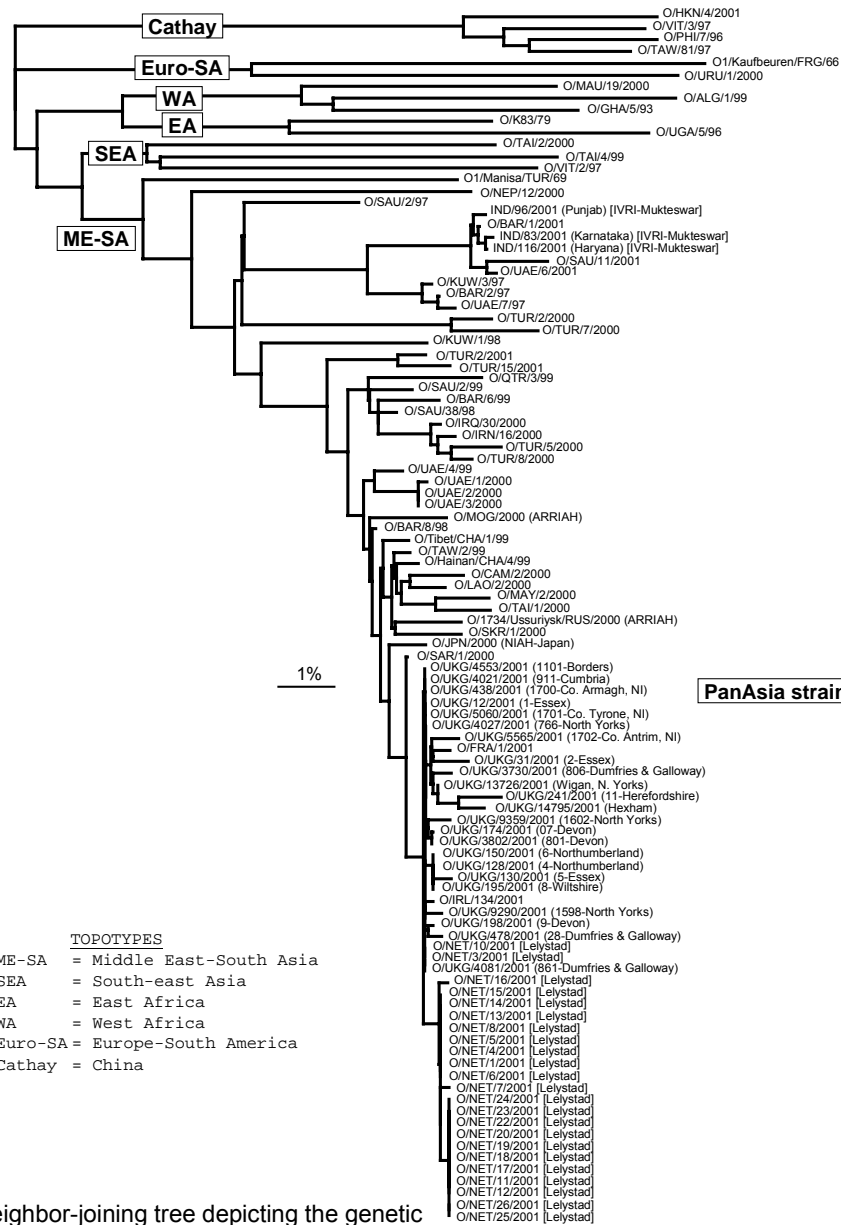


Genetic relationships between the UK outbreak virus and other FMDV type O strains



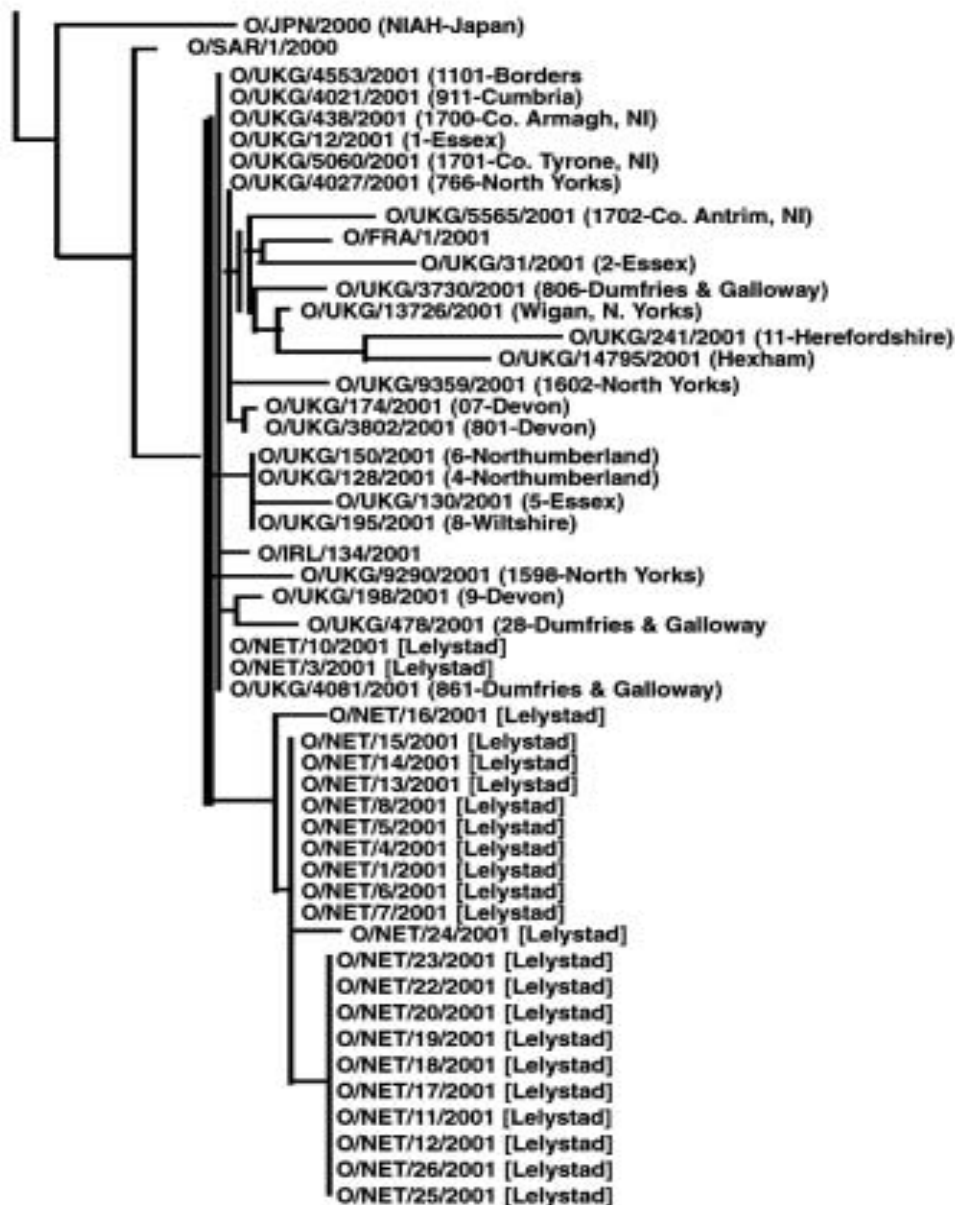
Occurrence of the PanAsia strain of FMDV-O





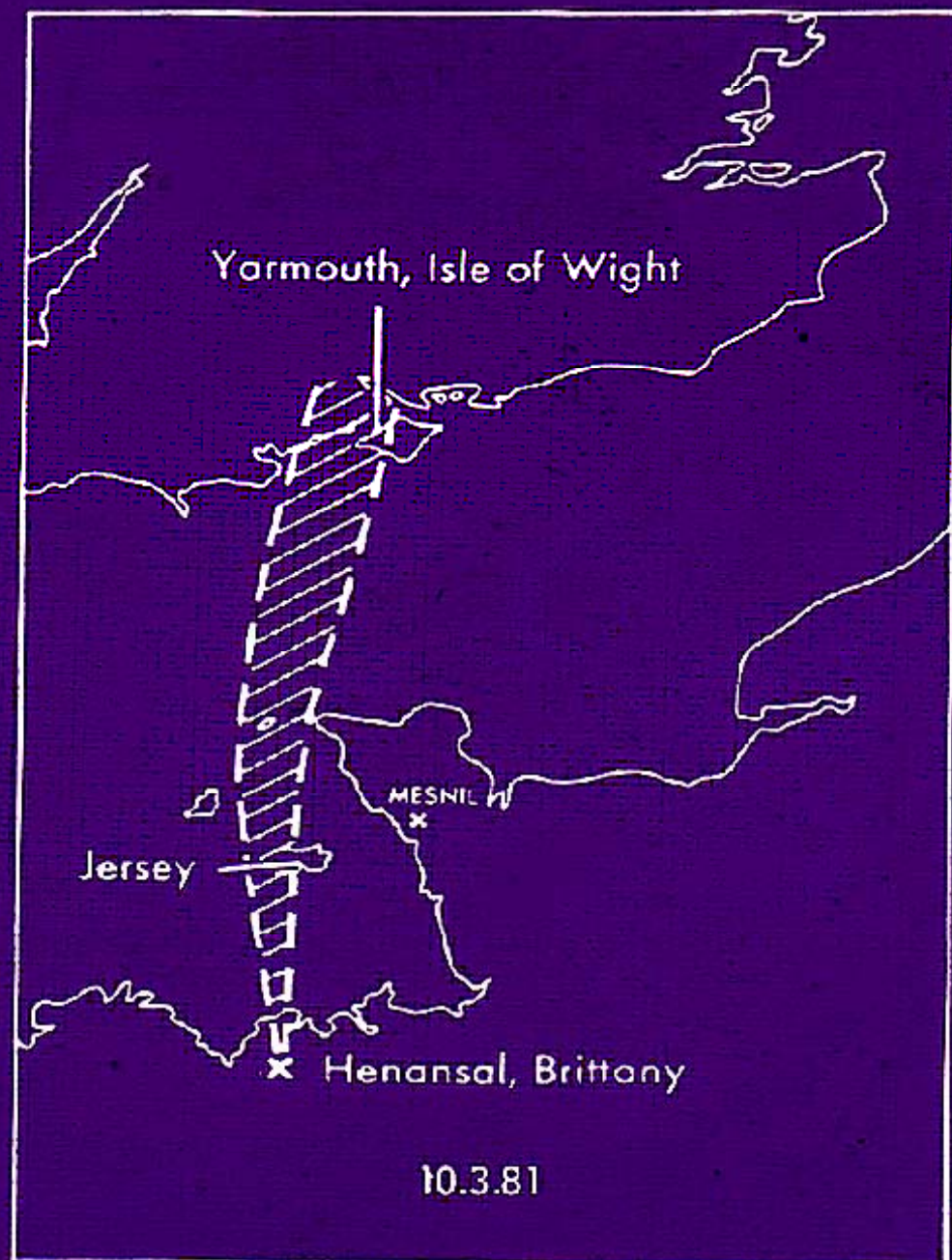
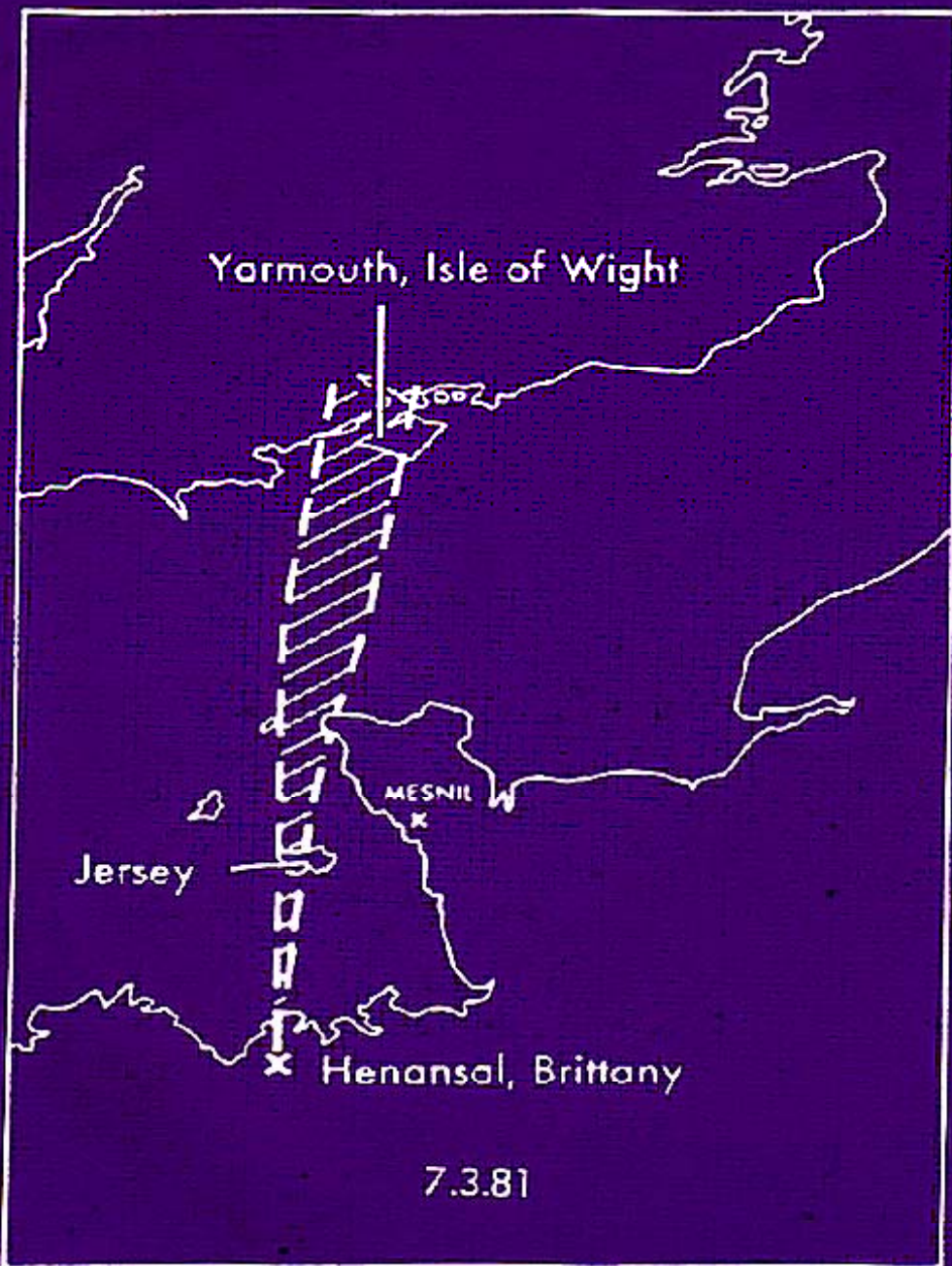
Neighbor-joining tree depicting the genetic relationships between various FMD type O viruses

PanAsia strain



MECHANISMS OF SPREAD OF FMD

- CONTROLLABLE SPREAD
 - movement of infected animals
 - movement of animal products e.g. meat, milk, offal
 - farm equipment, milking machines, vehicles, people etc
- UNCONTROLLABLE SPREAD
 - spread by the carriage of virus on the wind
 - role of wildlife and birds?



AIRBORNE SPREAD FROM HEDDON, NORTHUMBERLAND



Key:

0.01 - - - - -

0.1 —————

1.0 —————

5.0 —————

Scale 10 km

*Effect of species and number of animals excreting virus on the
PREDICTED risk for spread of FMDV O UKG 2001 downwind.*

Species excreting virus	Distance downwind at which species may be at risk		
	Cattle	Sheep	Pigs
1000 infected animals			
Pigs	6-20 km	2-6 km	<0.2 km
Cattle	0.7km	0.2 km	<0.1 km
Sheep	0.7km	0.2 km	<0.1 km
100 infected animals			
Pigs	2-6 km	< 2 km	<0.1km
Cattle	0.2 km	<0.1 km	<0.1 km
Sheep	0.2 km	<0.1 km	<0.1 km
10 infected animals			
Pigs	< 2 km	< 1 km	<0.1 km
Cattle	<0.1 km	<0.1 km	<0.1 km
Sheep	<0.1 km	<0.1 km	<0.1 km
1 infected animal			
Pig	< 0.5 km	< 0.5 km	<0.1 km
Steer	<0.1 km	<0.1 km	<0.1 km
Sheep	<0.1 km	<0.1 km	<0.1 km

PREDICTED distances at which virus concentration in a plume may be sufficient to infect.

Estimated using the airborne excretion values for UKG 2001.

Much further airborne spread may be possible for certain other strains, for example C Noville.

It should be noted that these estimates assume ideal topographical and meteorological conditions for airborne spread and that considerable variability may occur.

Most likely method of spread for cases in each geographic group and overall

Group Name	Conveyor										Percent due to local
	Airborne	Milk tanker	Infected animals	Local	Other fomite	Person	Swill (suspected)	Vehicle	Under investigation	Total	
Anglesey			1	12						13	92%
County Durham	3		5	82	1	4		1	7	103	80%
Cumbria	2	8	41	927	3	23		10	55	1069	87%
Devon	1	1	8	146	1	6		2	19	184	79%
Essex and Kent			4	5		1		1	5	16	31%
Hereford			11	118	3	12			24	168	70%
North Yorkshire	3	2		81	1	3		4	27	121	67%
Northumberland	4		2	76		7	1		11	101	75%
Sporadic			5	2	1	2		3	6	19	11%
Staffordshire			8	52		4		4	17	85	62%
Wales	3		2	44	2	10		1	18	80	53%
Yorks & Lancs			4	11					4	19	58%
Lancashire	2	2	1	31		1		3	5	45	69%
Grand Total	18	13	92	1587	12	73	1	29	198	2023	78%
Total percent	0.9%	0.6%	4.5%	78%	0.6%	3.6%	0.0%	1.4%	9.8%	100%	

Based on all cases with data to 21st October 2001

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Introduction of the 24/48 cull policy

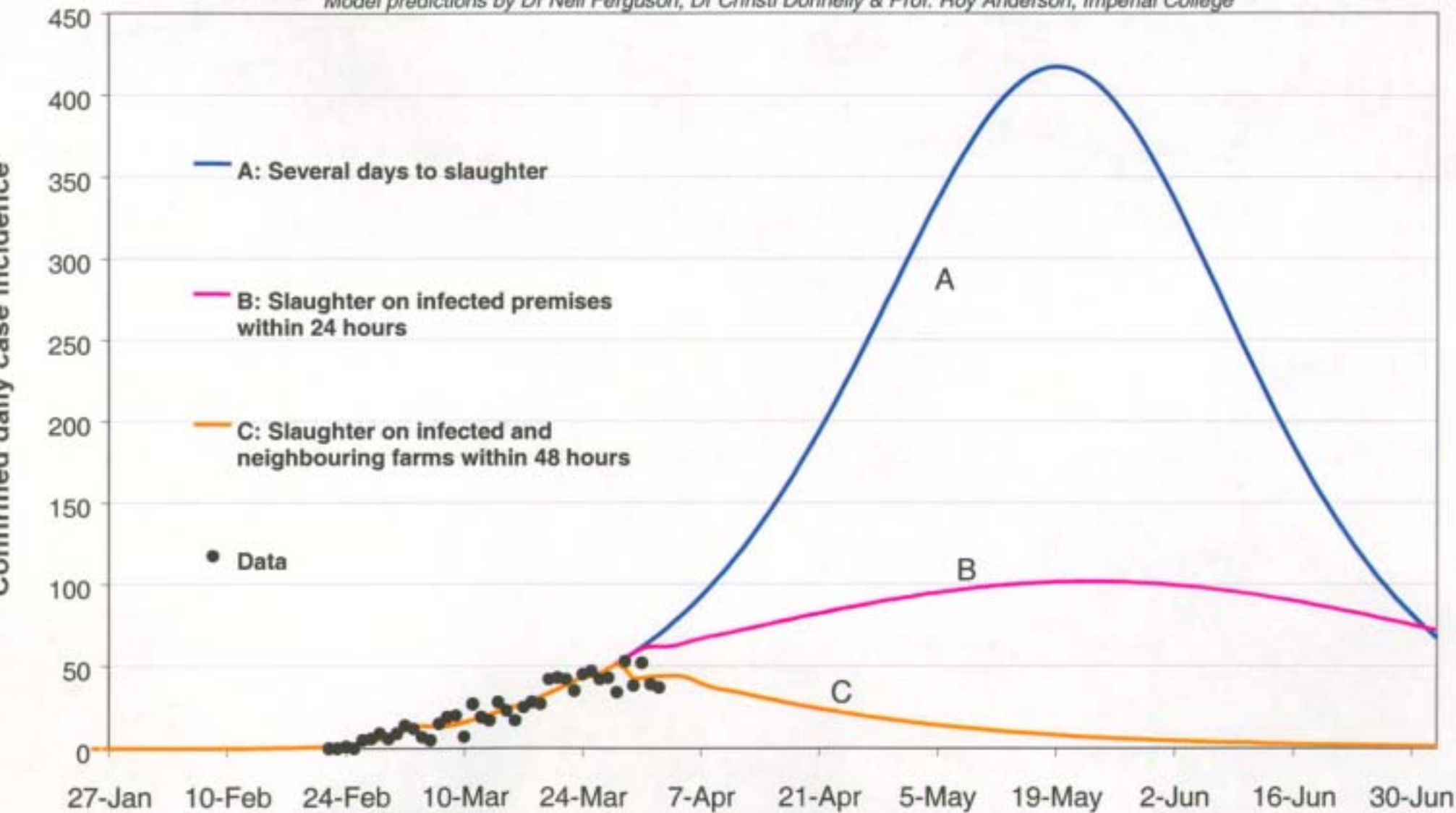


Good science, useful science

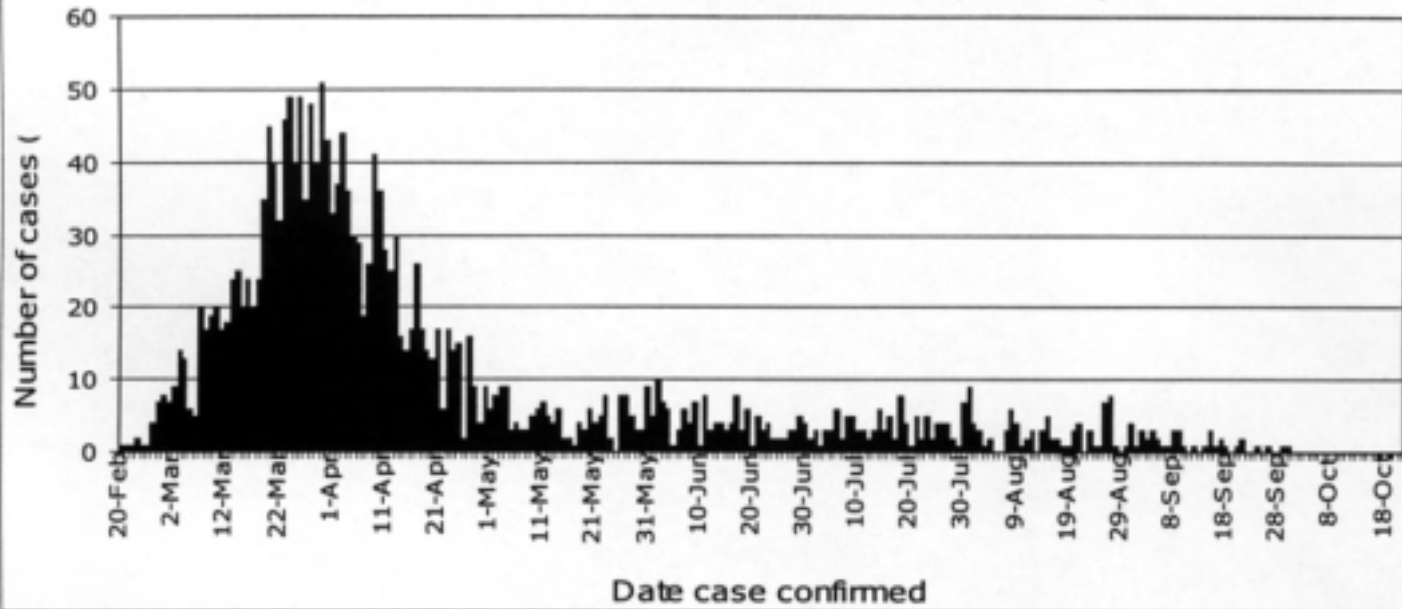
FMD in GB: control options



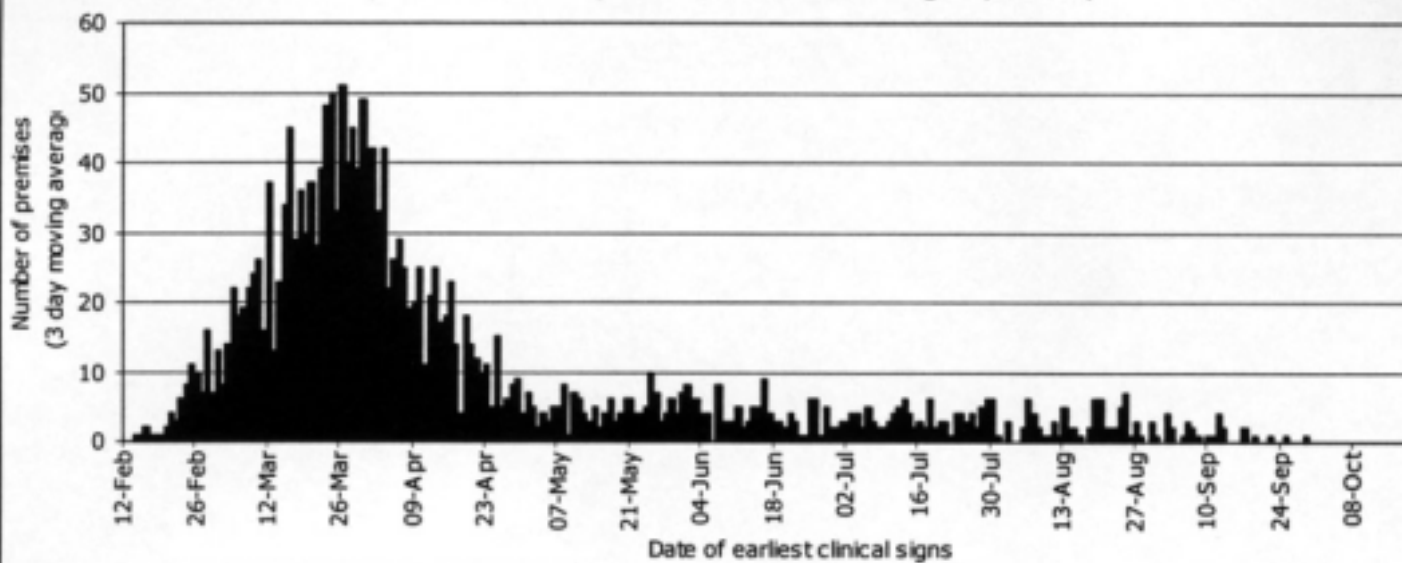
Model predictions by Dr Neil Ferguson, Dr Christl Donnelly & Prof. Roy Anderson, Imperial College



Epidemic curve by confirmation date (n = 2030)



Epidemic curve by date of first clinical signs (n=2019)



Animals slaughtered for disease control measures*.

Species	Number	Percentage
Cattle	595,884	15
Sheep	3,297,385	82
Pigs	144,931	4
Goats	2,368	<1
Deer	1,017	<1
Other	581	<1
Total	4,042,166	

* Source: DEFRA Disease Control System 09 January 2002.

Note: Figures are provisional and subject to change.

The need for rapid diagnosis



Good science, useful science

Current diagnostic tests for FMD:

- **Antigen detection by ELISA - ~4 hours**
- **Infectious virus detection through infection of bovine thyroid cells - ~4 days**

BUT

- **time is taken to get samples to the Laboratory**

Future tests may be based on:

- **PCR, both laboratory based and portable**
- **Penside strip tests**



13305



C



T

SS

13315



C



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The big debate: to vaccinate or not



FMD VACCINES

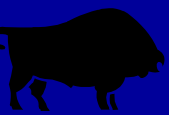
- FMD vaccines are inactivated, concentrated, purified preparations of virus mixed with an adjuvant.
- All clove-hoofed species can be immunised.
- One dose of emergency vaccine will protect for 4 to 6 months.
- Two doses of commercial vaccines are require to give protection for 6 to 9 months.
- Do not prevent establishment of carrier state.

FMD VACCINATION IN AN EMERGENCY

- Time is taken to identify protective vaccine strain and formulate vaccine.
- If incubating animals are vaccinated then disease can be expected.
- The period from vaccination to protection is 3 to 4 days with a potent emergency vaccine. (With a commercial vaccine the period is 2 to 3 weeks.)
- Re-excretion of virus and spread to animals in-contact can be expected if vaccinated animals are exposed to virus in the period before they become fully immune.

The problem of persistent infections and the carrier state





Duration of FMDV persistence **(Ruminants only - not pigs)**

- **Cattle up to 3.5 years**

(around 50% of recovered animals are carriers at 4 weeks, but can range from 0-100% depending on the strain of virus and probably the challenge dose. The % decreases over time, but may be up to 40-50% at 6 months, 20% at 8 months and up to 12% at 12 months)

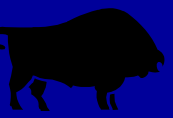
Sheep up to 9 months

(about 45-50% of recovered animals are carriers at 8 weeks, 25% are at 12 weeks)

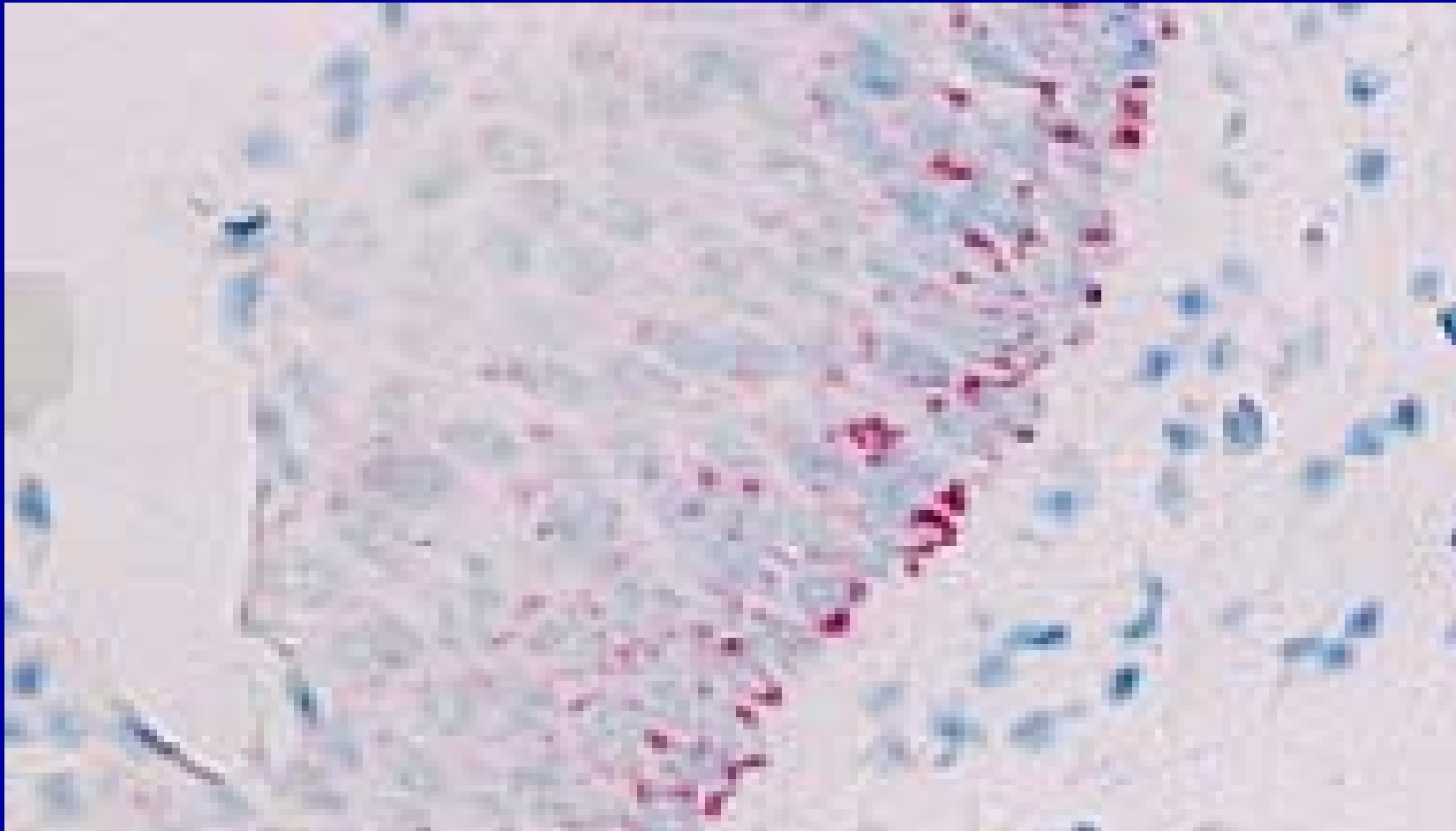
Goats up to 4 months

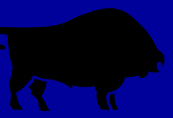
African buffalo at least 5 years - about 55-70% may be carriers under free-living conditions

- **Virus levels decline over time - final elimination of persistence ?**



ISH-TSA detection of FMDV RNA in persistently infected bovine soft palate tissues





Duration of FMDV persistence

II

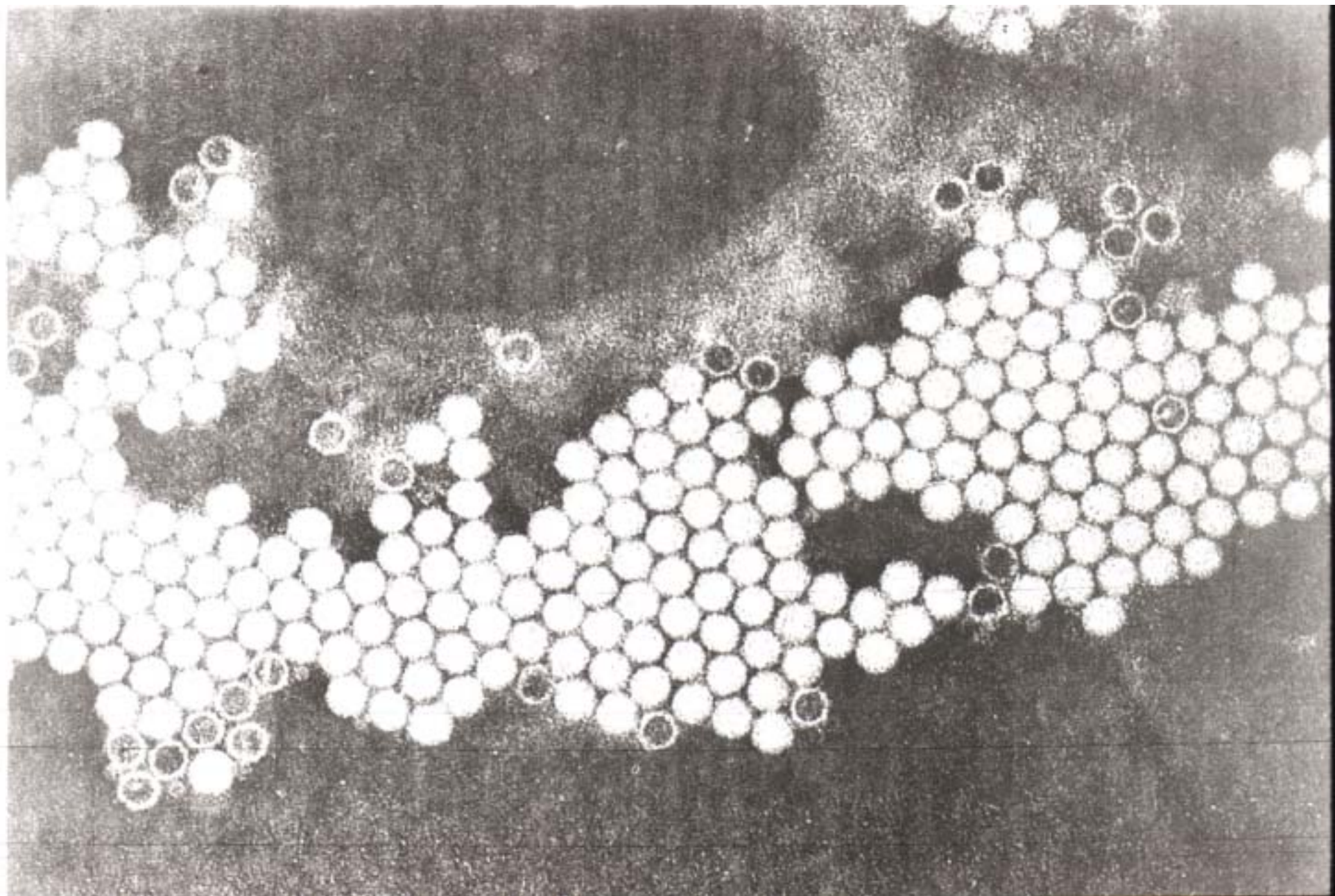
- Vaccinated animals or naturally protected animals exposed to live virus may also become infected in the pharynx and develop a subclinical infection but, in many cases, leading to persistent infection**
- The % of such animals which become carriers, the virus levels present and the duration of the carrier state have not been shown to be significantly different from non-vaccinated reconvalescent animals (up to 80% carriers have been demonstrated after experimental challenge of vaccinated cattle)**

Can vaccines be improved?

The ideal vaccine needs to:

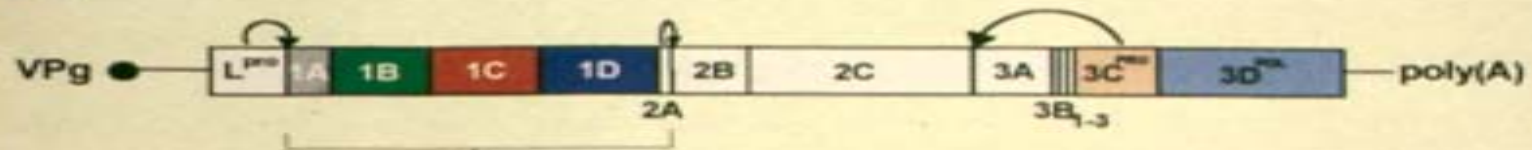
- **Have wide specificity**
- **be safe**
- **be stable**
- **be “marked” so that vaccinated animals can be distinguished from infected animals**
- **prevent persistent infections**
- **give long term immunity**



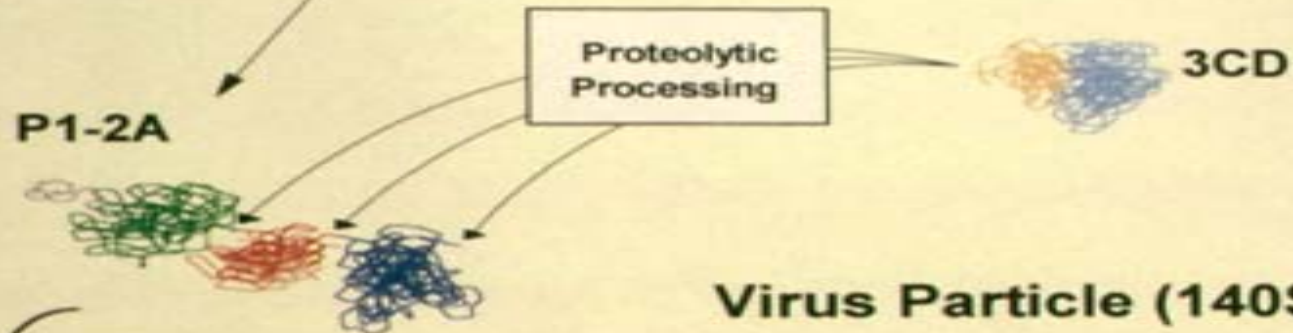


Foot-and-Mouth Disease Virus Capsid Morphogenesis

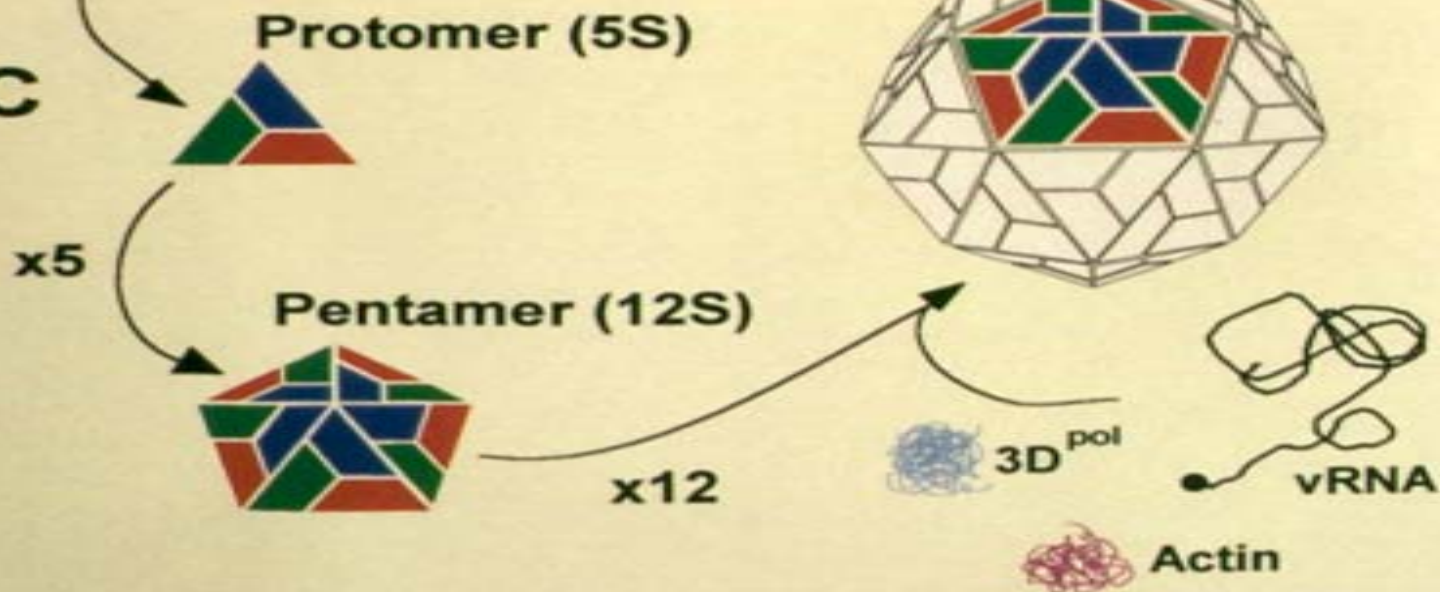
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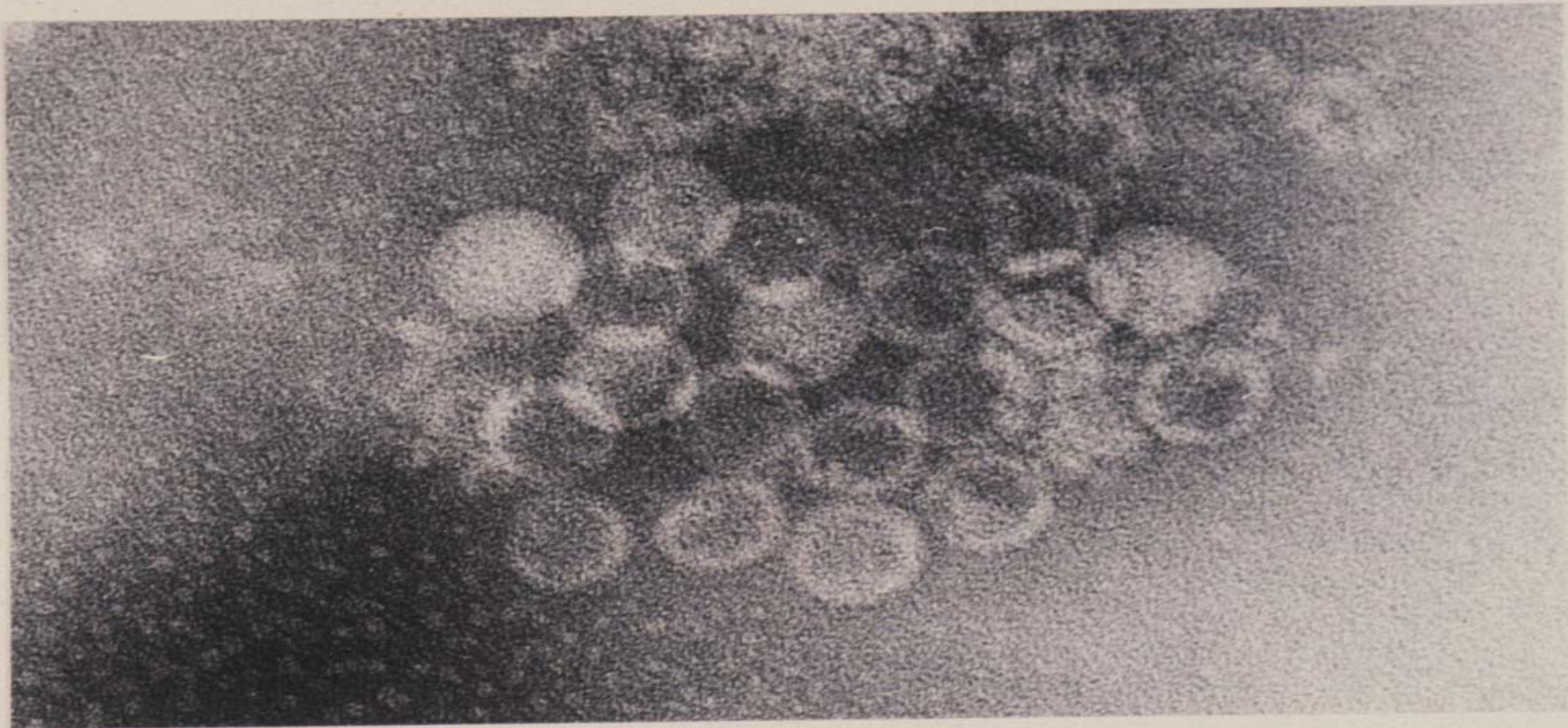


B



C





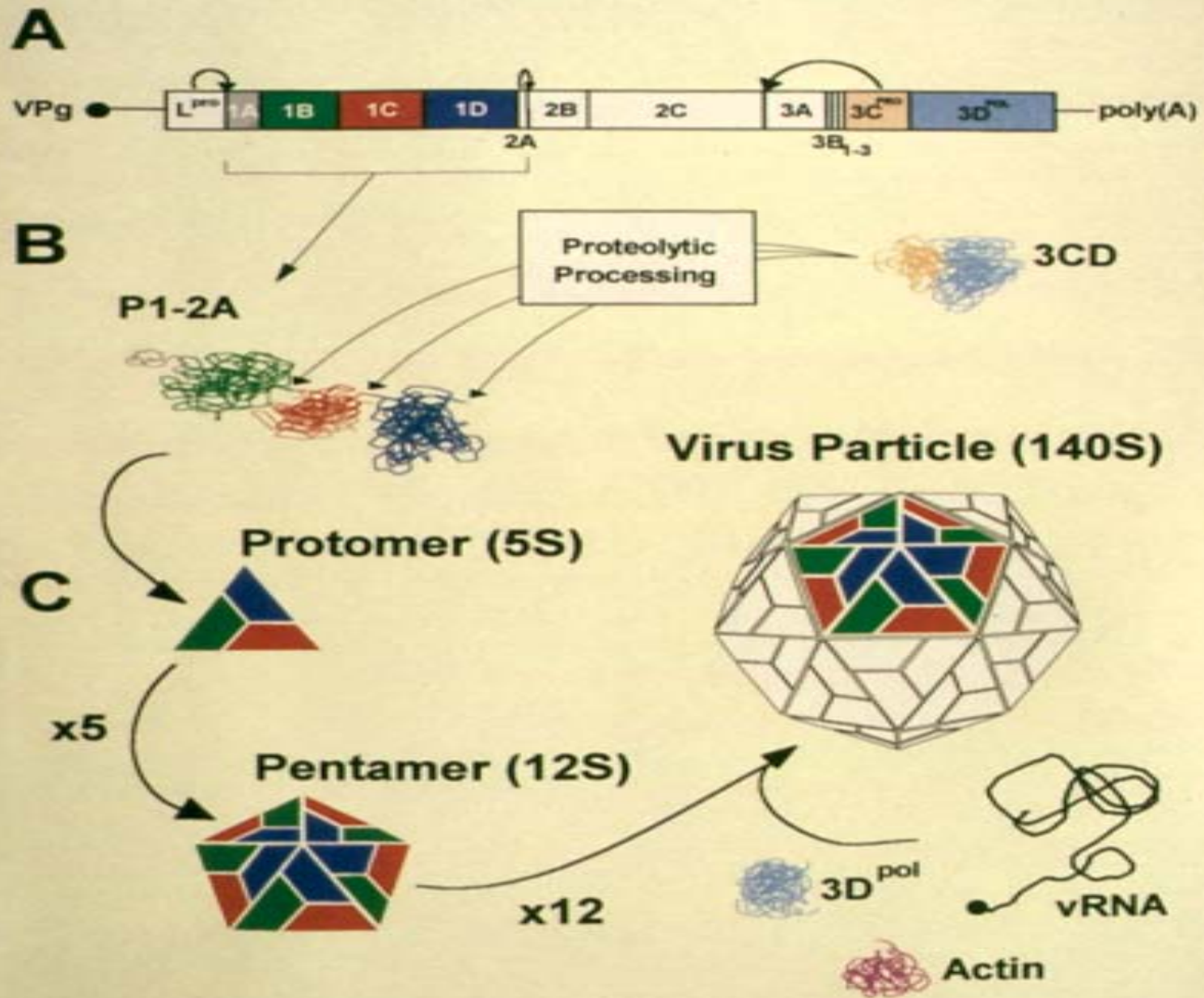
50 nm



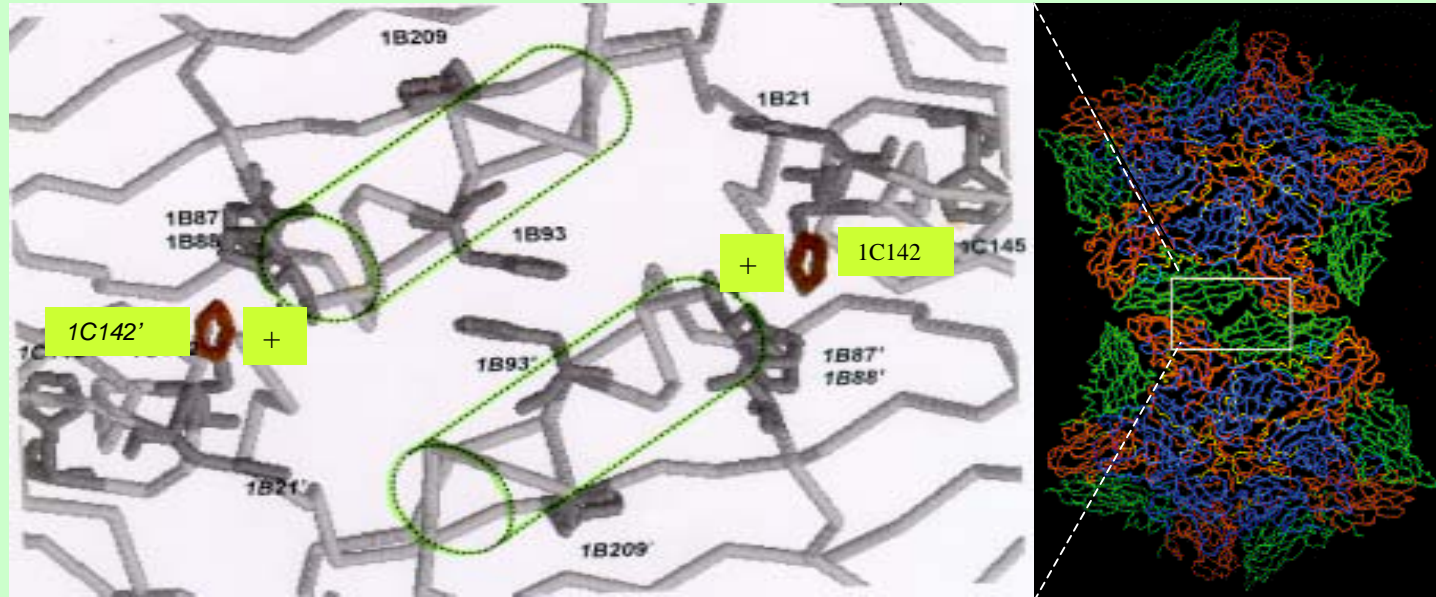
ASSEMBLY OF FMDV EMPTY CAPSIDS

IN ν T7MR1+ ν TF73 INFECTED CELLS

Foot-and-Mouth Disease Virus Capsid Morphogenesis

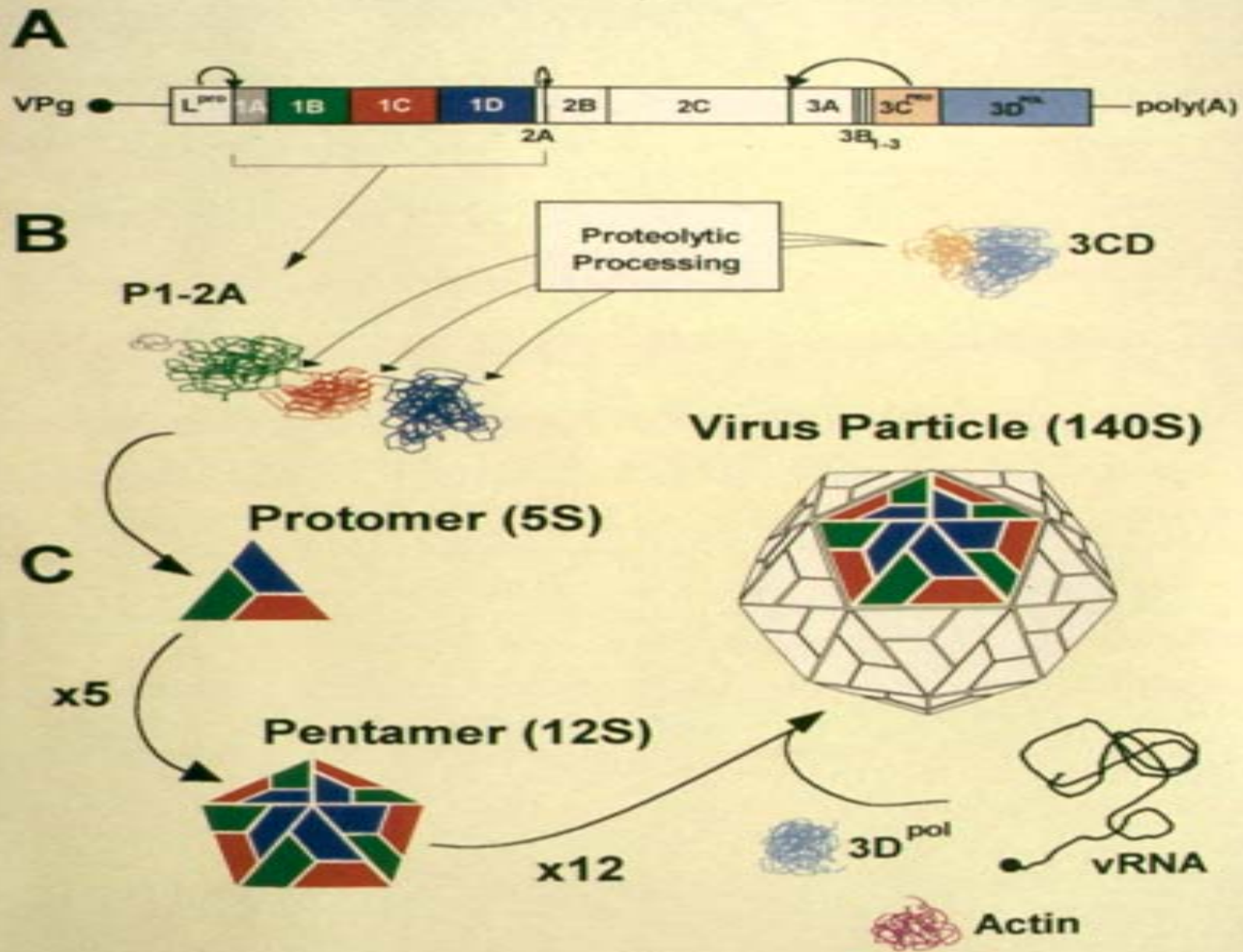


Stabilising the *Foot-and-mouth disease virus* capsid

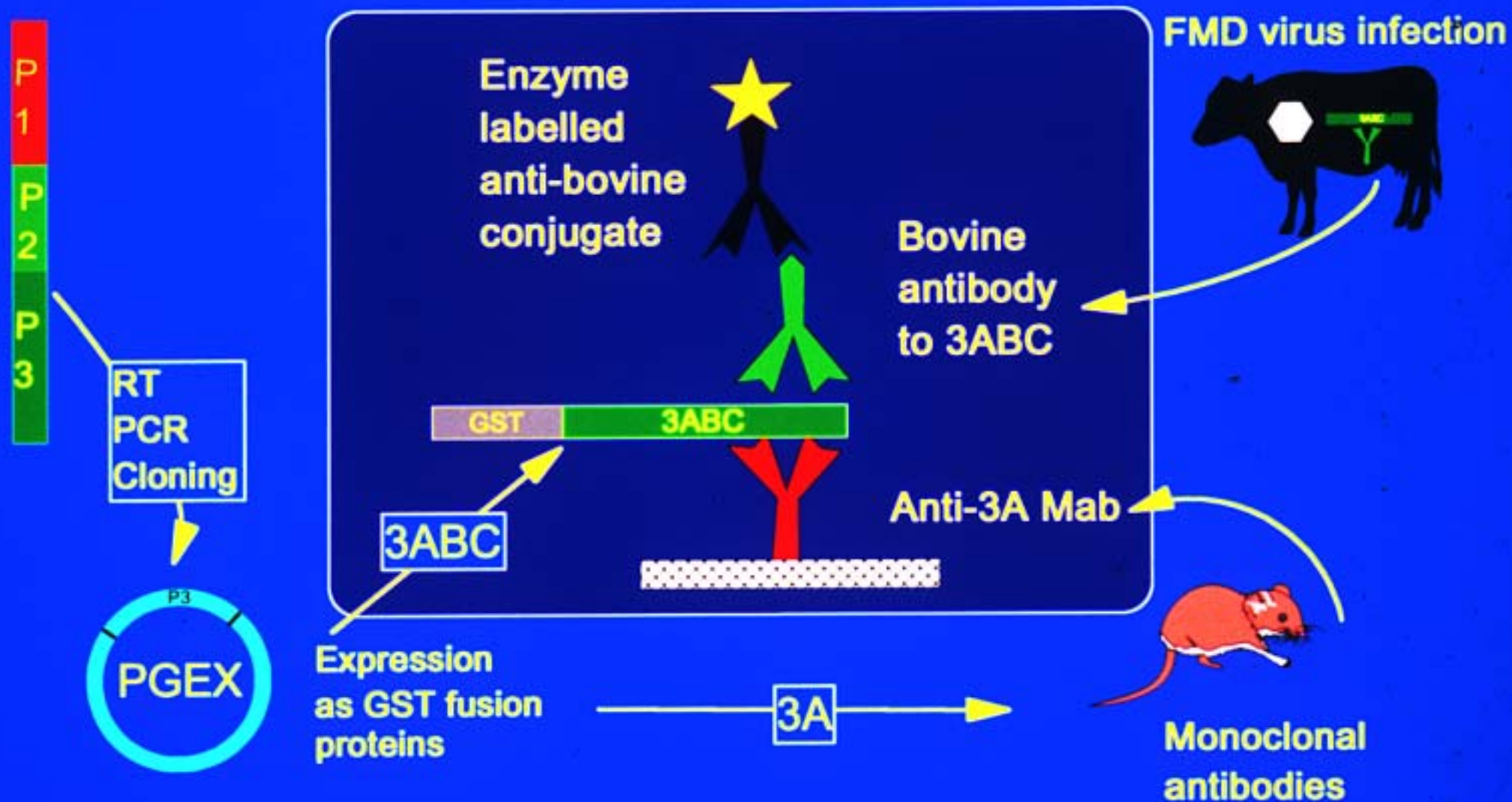


The disassembly of FMDV that occurs in very mild acid is controlled by one amino acid: a highly polarised histidine at position 142 in protein 1C. The virus particle is stabilised by replacing it with a negatively charged amino acid.

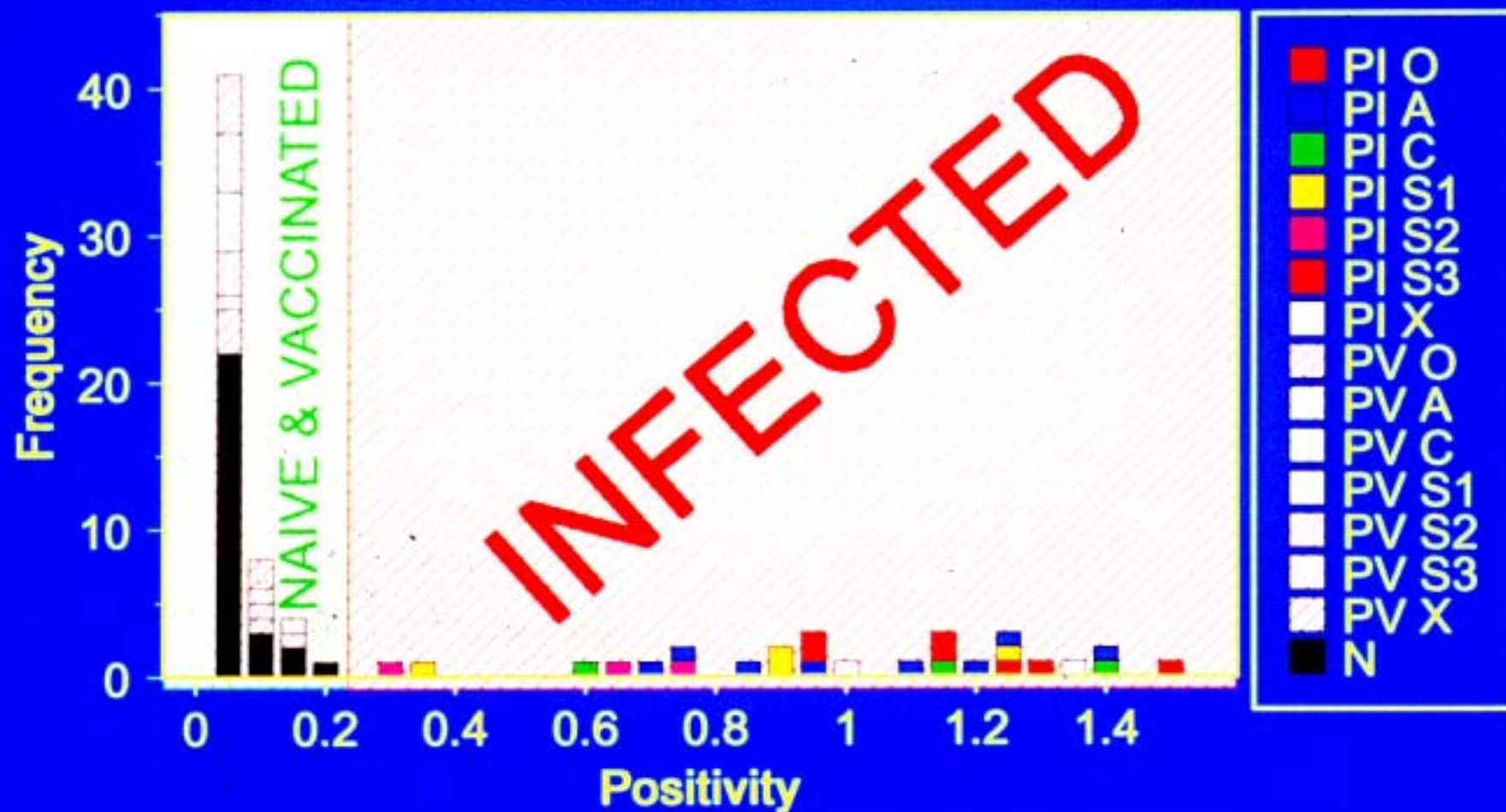
Foot-and-Mouth Disease Virus Capsid Morphogenesis



Molecular techniques in the identification of FMD virus infected animals



Differentiation of infection from vaccination using the 3ABC MAT-ELISA



**Can alternatives to
emergency vaccination
against FMD be
considered?**

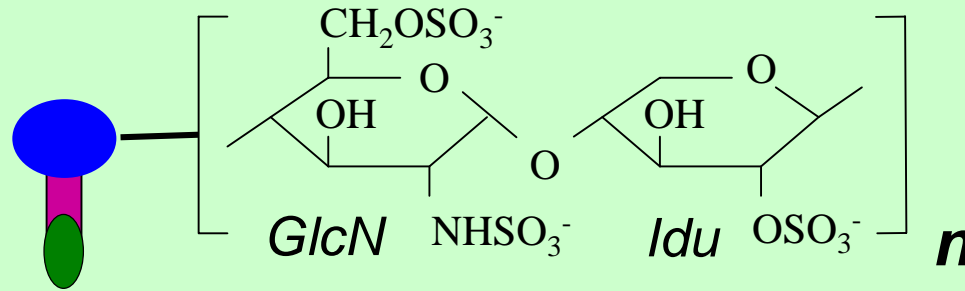


Good science, useful science

Cellular receptors for FMDV

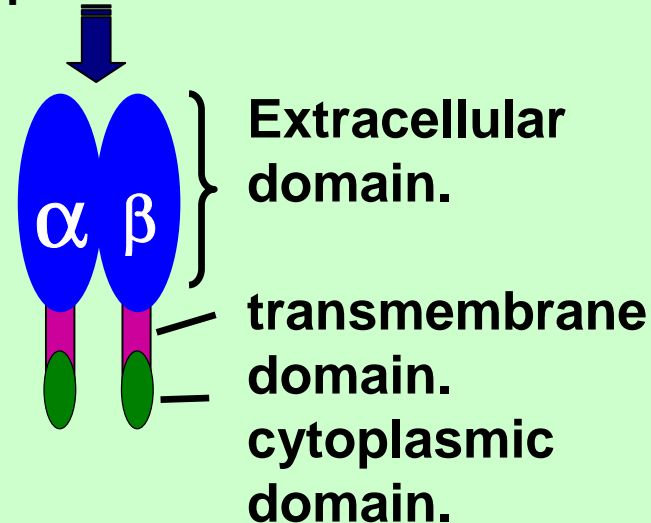
2 types:

heparan sulphate proteoglycans



integrins

Ligand binding
pocket



'RGD' binding
integrins

$\alpha v \beta 1$

$\alpha v \beta 3$

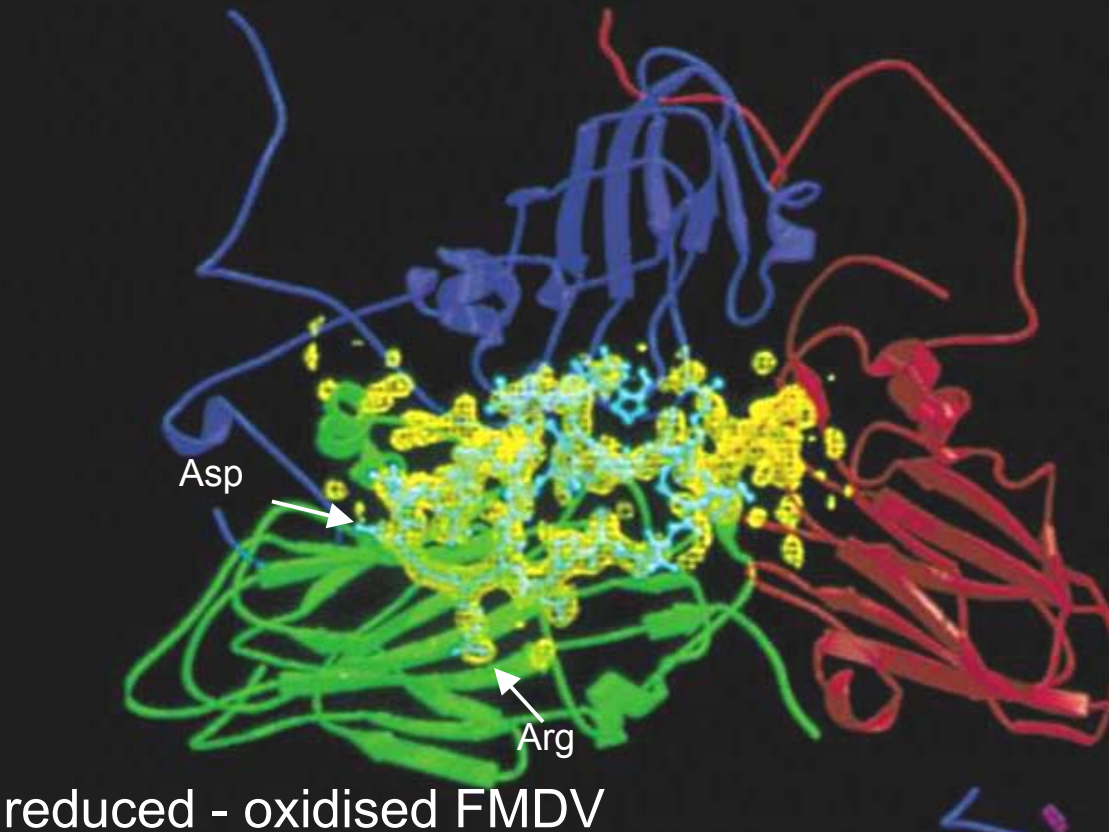
$\alpha v \beta 5$

$\alpha v \beta 6$

$\alpha 5 \beta 1$

**structural basis of integrin recognition;
the RGD-containing loop ('G-H loop') of VP1**

FMDV
electron density difference maps
showing receptor binding loop



VP1_{C134S} - wild type

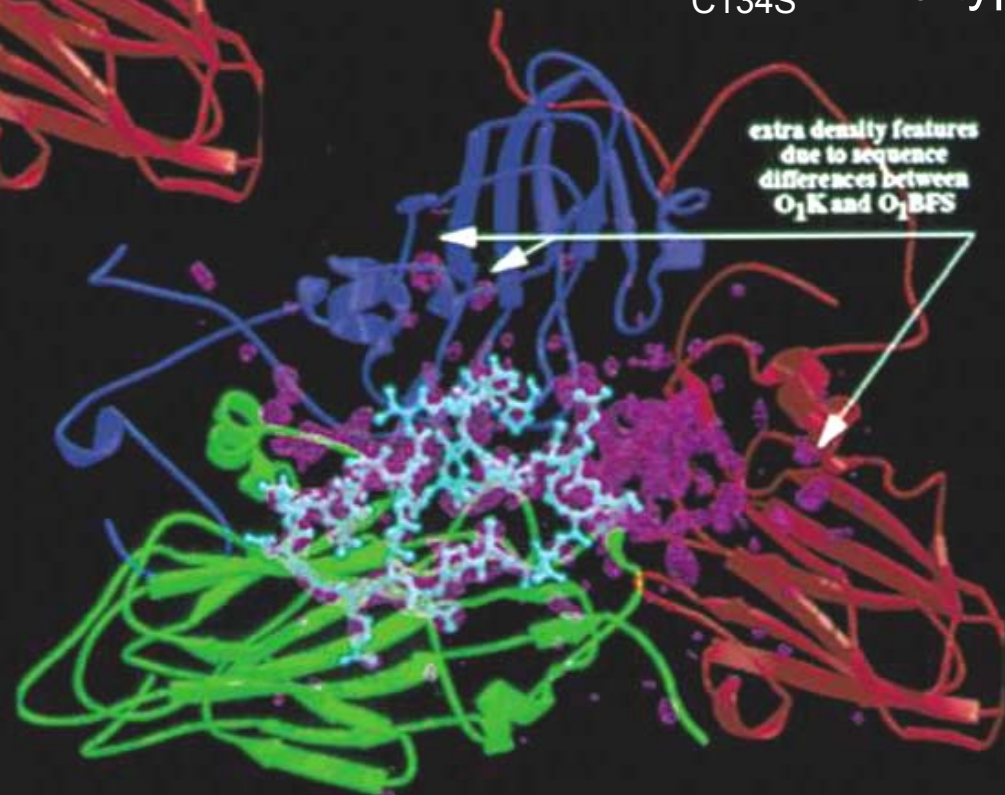


Table1: FMDV specificity for integrin receptors

<u>integrin species</u>	<u>binds:</u>		<u>mediates infection:</u>	
	<u><i>in vitro</i></u>	<u>on cells</u>	<u>in culture</u>	<u>in host</u>
$\alpha v \beta 1$	nd ^a	Y	Y	nd
$\alpha v \beta 3$	Y	N/Y ^b	N/Y	N ^c
$\alpha v \beta 5$	nd	N	N	nd
$\alpha v \beta 6$	nd	Y	Y	Y ^c
$\alpha 5 \beta 1$	Y	N	N	nd

^and = not determined ^bN/Y = poorly detectable ^cpreliminary observation

significance of $\alpha v \beta 6$ as receptor for FMDV

- exclusively epithelial
- normally expressed at low or moderate levels
- upregulated in inflammatory conditions/wound healing
- specific
- bidirectional signalling molecule (activates TGF- β)
- nonessential

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