From: R.A.M. Fouchier
Sent: Sat, 8 Feb 2020 19:52:33 +0000
To: Garry, Robert F; Fauci, Anthony (NIH/NIAID) [E]; Jeremy Farrar; Vallance, Patrick (GO-Science); Edward Holmes; (b)(6) Andrew Rambaut
Cc: Collins, Francis (NIH/OD) [E]; Josie Golding; M.P.G. Koopmans; (b)(6) Mike Ferguson; Government Chief Scientific Adviser (GO-Science)
Subject: Re: 2019 N-CoV

In addition to the animal component (no. of species, inbred/outbred, no. of individuals,variation in inoculation routes and doses, etc) environmental factors may also vary more in nature, providing more opportunity for generating divergence.
Nevertheless, we see substantial convergent evolution for flu in pandemics, (inbred) lab animals and pigs and (outbred) marine mammals.
Ron

From: Garry, Robert F (b)(6)
Sent: Saturday, February 8, 2020 1:01 PM
To: Fauci, Anthony (NIH/NIAID) [E]; Jeremy Farrar; Vallance, Patrick (GO-Science); Edward Holmes; (b)(6) Andrew Rambaut
Cc: (b)(6) Collins, Francis (NIH/OD) [E]; Josie Golding; (b)(6) (b)(6) Mike Ferguson; Government Chief Scientific Adviser (GO-Science)
Subject: Re: 2019 N-CoV

Very good question.

In the wild you will be dealing with passage in outbred animals and no selection for mortality.

In the lab you could do it differently by using inbred animals and more intense transfer. This is also essentially why highly pathogenic flu viruses arise in commercial inbred chicken flocks, a situation different than nature.

Another example: For our Lassa studies (https://www.sciencedirect.com/science/article/pii/S0166354216303515#bib13) we use a strain of LASV Josiah, which had been passaged from terminally-ill outbred guinea pigs into healthy animals, four times (https://www.nature.com/articles/srep14775). The resultant isolate demonstrates a uniformly lethal phenotype at challenge doses of 10^4 $TCID_{50}$ or greater (LD_{50} = 10^3 $TCID_{50}$). The original isolate only kills about 30% of outbred animals. It's possible to fairly rapidly select for more pathogenic variants in the laboratory.

From: "Fauci, Anthony (NIH/NIAID) [E]" (b)(6)
Date: Saturday, February 8, 2020 at 11:36 AM
To: Jeremy Farrar (b)(6) "Vallance, Patrick (GO-Science)" (b)(6) Edward Holmes (b)(6), Kristian Andersen (b)(6) Andrew Rambaut (b)(6) Robert Garry (b)(6)
Cc: (b)(6) "Collins, Francis (NIH/OD) [E]" (b)(6) Josie Golding (b)(6), (b)(6) (b)(6) Mike Ferguson (b)(6) "Government Chief Scientific Adviser (GO-Science)" (b)(6)
Subject: RE: 2019 N-CoV

External Sender. Be aware of links, attachments and requests.

Would serial passage in an animal in the laboratory give the same result as prolonged adaptation in animals in the wild? Or is there something fundamentally different in what happens when you serially passage versus natural animal adaption? This is not my specific area of expertise and so I do not know.

From: Jeremy Farrar (b)(6)
Sent: Saturday, February 8, 2020 10:13 AM
To: Vallance, Patrick (GO-Science) (b)(6) Edward Holmes (b)(6) (b)(6) Andrew Rambaut (b)(6) (b)(6)
Cc: (b)(6) Collins, Francis (NIH/OD) [E] (b)(6) Fauci, Anthony (NIH/NIAID) [E] (b)(6) Josie Golding (b)(6) (b)(6) Mike Ferguson (b)(6) Government Chief Scientific Adviser (GO-Science) (b)(6) (b)(6)
Subject: Re: 2019 N-CoV

Bob – Andrew shared your thoughts on the glycans:

"I'd say the existence of the glycans is pretty strong evidence of evolution in the presence of an immune system. I don't think it is random chance since the glycans appear in other betacoronaviruses that "evolve" a furin site, eg MHV and HKU1. MHV and HKU1 also simultaneously evolve a variable and sometimes large patch of O-linked glycans at the top of the prefusion (virion) form of the spike. Seems pretty clear this is immune based selection all around to me.

Yes serial passage in animals would do the same thing. There are a couple passage of H5N1 in chicken papers - the furin site appears in steps."