To: [redacted] [redacted]@rivm.nl]
From: [redacted])
Sent: Tue 1/5/2021 7:12:08 AM
Subject: FW: Spike mutants
Received: Tue 1/5/2021 7:12:16 AM

Hoi [redacted]

Hier wat mail wisseling met background info over variant virus en links naar papers die laten van zien dat de mutaties in variant virus een rol kunnen spelen in antibody escape.

Groeten, [redacted]

From: [redacted]) <[redacted]@uu.nl>
Sent: dinsdag 29 december 2020 16:04
To: [redacted]) <[redacted]@uu.nl>
Subject: Re: Spike mutants

Zeker, denk wel dat DARPin effectiviteit afneemt als 1 poot het niet meer doet..

De schatting is dat de nieuwe UK variant 56% meer besmettelijk, wat de R0 enorm verhoogt. Verlichting van lockdown is voorlopig nog niet aan de orde vrees ik..

Van: [redacted]) <[redacted]@uu.nl>
Datum: dinsdag, 29 december 2020 om 15:33
Aan: [redacted]) <[redacted]@uu.nl>
Onderwerp: FW: Spike mutants

Zou mooi zijn als de DARPins hier tegen beschermen vanwege hun multi-mode of inhibition!!!

From: [redacted])
Sent: dinsdag 29 december 2020 15:31
To: [redacted]) <[redacted]@uu.nl>
Subject: RE: Spike mutants

Hoi [redacted]
Ik zie je punt, en idd goed om snel te testen en de uitslagen dan de wereld in te gooien!
Groeten, [redacted]

From: [redacted]) <[redacted]@uu.nl>
Sent: dinsdag 29 december 2020 15:21
To: [redacted]) <[redacted]@uu.nl>
Subject: FW: Spike mutants

Ha [redacted]
Ik maak me best zorgen over de variant in Zuid Afrika. Deze variant is mogelijk ontstaan agv intrahost evolutie in een immunocompromised host en ik ben bang dat die variant best veel consequenties kan hebben op vaccine efficacy... (zie hieronder).
Fijne dagen verder!
Groet, [redacted]

Van: [redacted]) <[redacted]@uu.nl>
Datum: dinsdag, 29 december 2020 om 15:11
Aan: [redacted] <[redacted]@uu.nl>
Onderwerp: Re: Spike mutants

Hi 5.1.2e

I am particularly worried about the three mutations found in the spike in the South African lineage (501Y.V2) that is spreading across the world. The mutations have been found in *in vitro* studies to correlate with evasion from polyclonal and monoclonal antibodies.

Here are the considerations with hyperlinks to papers:

- New SARS-CoV-2 lineage (501Y.V2) characterised by eight lineage-defining mutations in the spike protein, including three at important residues in the receptor-binding domain (K417N, E484K and N501Y)
- This new variant (as well as the UK version is of concern), it is transmitting better, severity of disease is not changed, but if more people get infected, then number of hospitalizations will also rise.
- Mutations that increase receptor binding (e.g. N439K, N501Y) may allow Ab escape mutations (e.g. K417N) at other positions that weaken receptor binding
- Based on high-throughput experiments, all three spike receptor binding site mutations (K417N, E484K and N501Y) were shown to mildly increase receptor binding.
- N501Y and E484K also found in immunocompromised patient
- E484K also found in in vitro mutants that escape neutralization by polyclonal antibodies
- K417N allows escape from mAbs
- E484K allows escape from mAbs
- E484 substitutions associated with resistance for bamlanivimab (=LY-CoV555, https://www.fda.gov/media/143603/download) and to some extent for LY-CoV016 and REGN10933 antibodies
- K417 substitutions associated with resistance to LY-CoV016 and REGN10933 antibodies
- E484 substitutions associated with resistance to broad panel of antibodies AND polyclonal seral (the latter suggesting that high titer neutralizing antibodies may be directed toward a narrow repertoire of epitopes following natural infection)

We already generated the E484K and are making the N501Y substitution. I think we should generate also the K417N mutation to see whether the IMI, benchmarking antibodies as well as 47D11, lead DARPins and HCAbs are affected by those mutations. Are you ok with that?

Cheers, 5.1.2e

From: 5.1.2e) < 5.1.2e @uu.nl>
Sent: zondag 20 december 2020 10:38
To: 5.1.2e < 5.1.2e @uu.nl>
Subject: Re: Spike mutants

https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563

Van: 5.1.2e) < 5.1.2e @uu.nl>
Datum: dinsdag, 15 december 2020 om 08:42
Aan: 5.1.2e < 5.1.2e @uu.nl>
Onderwerp: Spike mutants

Hi 5.1.2e
Yesterday there was in the news that is variants have been popping up in England that could affect vaccine/antibody efficacy. These variants have mutations in H69/V70 and N501 residues. H69/V70 was speculated to have an effect on RBD conformation. See twitter threads:
https://twitter.com/GuptaR_lab/status/1338610098663526402
https://twitter.com/firefoxx66/status/1338534500935012355

Would be interesting to test H69/V70 deletion on binding/neutralization by our benchmarking REGN/S309/CR3022 antibodies. The

N501Y substitution we did not make yet, but might be interesting to make that one also, if time allows (not a high priority).

cheers, 5.1.2e