Agility Program Biweekly Progress

CEPI

Agility Program: To enable the rapid assessment of the biological impacts of new variants of SARS-CoV-2

Partners:
Public Health England (PHE)
National Institute for Biological Standards and Control (NIBSC)

Slideset provided on a biweekly basis to update latest in vitro neutralization activity and in vivo pathogenesis and cross protection data against SARS-CoV-2 virus variants

Find this slide set posted at:

https://epi.tghn.org/covax-overview/enabling-sciences/agility_epi/#ref1

WHO Variants of Concern and Interest Monitored by the Agility Project

WHO Variants of Interest	Status*		WHO Variants of Concern	Status*
†Epsilon - B.1.427/B.1.429	Sourced		Alpha - B.1.1.7	Assessed
†Zeta – P.2	Assessed		Beta - B.1.351	Assessed
Eta – B.1.525	Seeking		Gamma - P.1	Assessed
†Theta – P.3	Deselected		Delta - B.1.617.2	Assessed
Iota – B.1.526+E484K or S477N	Seeking			
Kappa – B.1.617.1	Sourced			
Lambda – C.37	Sourced			
ID pending - B.1.621	Sourced			

Link to the WHO weekly Epi report website:
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

*From; Not selected/Seeking/Sourced/Assessed
†No longer a WHO VUI

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Table updated as of Aug 23, 2021

Agility Project: Variant Growth/Testing for Neutralization Phenotype

	Variant	Sourcing or Propagation Seeking/In progress/Complete	Characterisation In progress/Complete/No longer required	In vitro (neutralisation) In progress/Complete/No longer required	In vivo Not selected/Planning/In progress/In-life complete
WHO VOCs	**Alpha (B.1.1.7)**	Complete	Complete	Complete	In-life complete
	Beta (B.1.351)	Complete	Complete	Complete	
	Gamma (P.1)	Complete	Complete	Complete	
	Delta (B.1.617.2)	Complete	Complete	Complete	In-life complete –reporting underway
WHO VOIs	**Eta (B.1.525)**	Seeking			
	†Epsilon (B.1.427/B.1.429)	In progress	No longer required		
	†Zeta (P.2)	Complete	In progress	Complete	
	†Theta (P.3)	Deselected	No longer required		
	Iota (B.1.526+E484K)	Seeking			
	Kappa (B.1.617.1)	Complete	In progress	In progress	
	Lambda (C.37)	In progress			
UK	**Alpha + E484K**	Complete	In progress	In progress	
Others	**B.1.621**	Complete	In progress		
n/a	**Cluster V (Denmark) and N439K**	Complete	No longer required	No longer required	*n/a*

†No longer a WHO VUI

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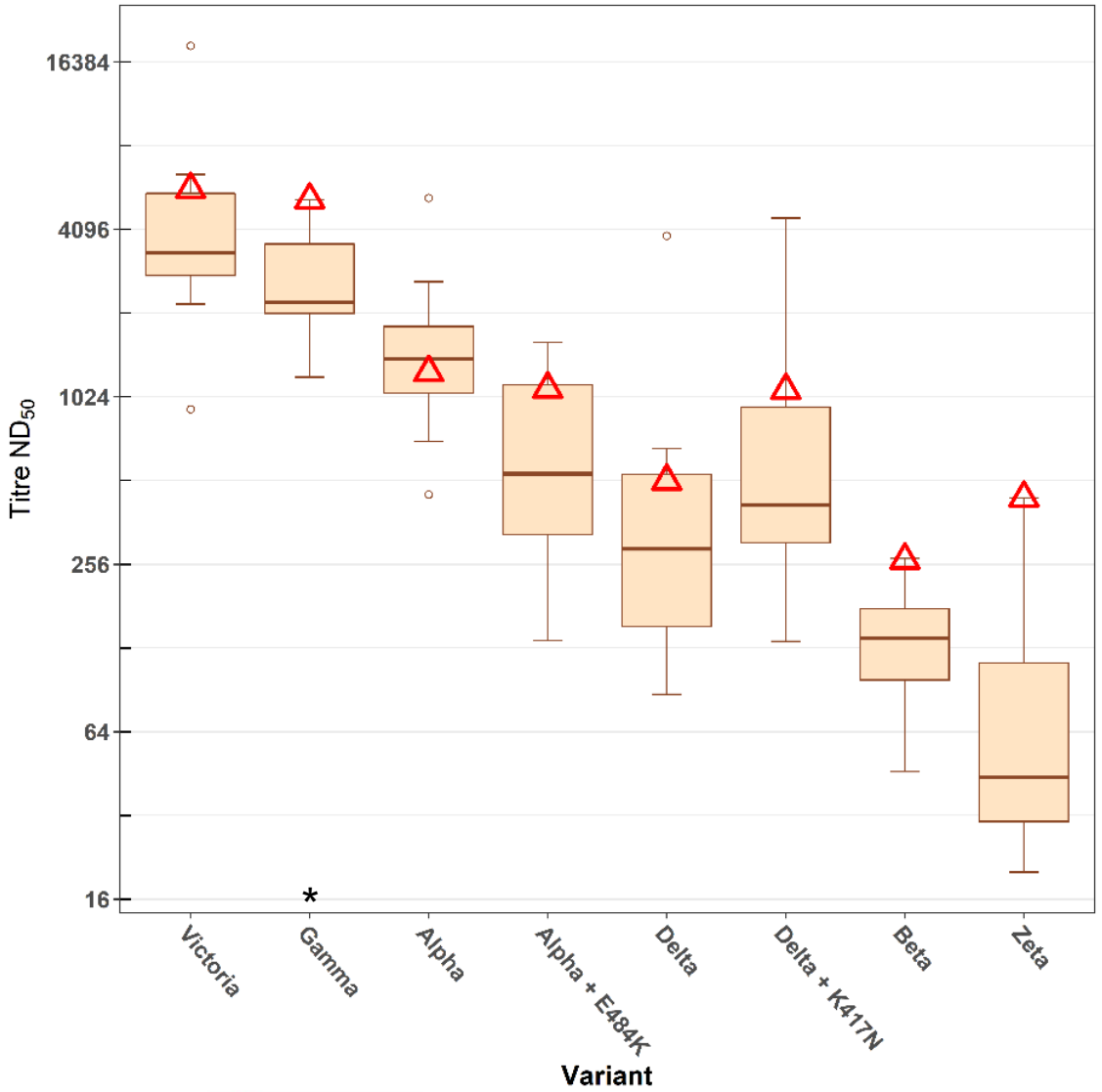
Live-virus *in vitro* antibody neutralization assay progress



- Variants assessed in neutralisation assay to date against a "pre-Alpha" serum panel
- WHO International Standard shown as red triangles
- Most serum in panel neutralise all tested variants
- Lowest neutralisation has been seen for Beta and Zeta
- Delta resistance is similar to Alpha plus E484K
  - Delta-plus (eg. AY.1) does not appear to be substantially more resistant to neutralisation

* Refinement of previous estimate based on additional data from two sites

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In vitro susceptibility of variants

Table 1 – Variants tested with expanded Agility Serum Panel

	Variant ID							
sample ID	Victoria (B)	Alpha	Alpha + E484K	Beta	Gamma	Delta	Delta + K417N (AY.1)	Zeta
NIBSC 7	18703	5308	1360	269	2944	3883	4500	266
NIBSC 24	3496	2656	869	129	3493	161	339	85
NIBSC 31	2733	1507	450	53	2055	263	266	32
NIBSC 32/33	5447	945	189	166	2113	632	544	278
NIBSC 47	924	456	136	46	1205	87	135	20
NIBSC 61	2819	707	351	111	4608	167	484	40
NIBSC 78	6444	1380	603	215	4049	668	1280	38
NIBSC 80	3776	1659	1604	150	2099	102	360	20
NIBSC 82	3177	1092	486	139	1576	321	898	48
NIBSC 83	3256	2485	1247	139	2386	346	319	78
NIBSC 86	2208	1429	265	68	2010	131	271	26
WHO IS 20/136	5706	1253	1092	265	5231	510	1081	443
GMT	**3762**	**1428**	**553**	**127**	**2571**	**309**	**536**	**65**
Fold-change relative to Victoria	**1**	**2.6**	**6.8**	**29.6**	**1.5**	**12.2**	**7**	**57.9**

** NIBSC 32/33 are two aliquots from the same individual on the same date*

Notes:

- All sera are convalescent donations from early pandemic period; prior to emergence of Alpha
- These *in vitro* assessments are based on humoral responses only and it may be the case that cell-mediated immunity would tell a different story

The broader scientific community is currently collecting biological infection data to understand disease severity and immune reponse to variants of concern in the following ways, plus many others:

- Human clinical studies assessing vaccine effectiveness against variant infections
- Animal studies in various laboratory model species to evaluate effectiveness of original vaccines against variants, and new vaccines, need for boosters, etc.

The Agility Program is leveraging CEPI Preclinical Laboratory Network Partners to perform hamster modeling studies under high ethical standards

- CEPI Network of Partners was established in 2019 via a call for proposals to engage laboratories with high animal ethics standards, biocontainment laboratory capabilities and high-quality research methods that meet regulatory requirements
- All animal studies are performed in accordance with UK NC3Rs guidelines (https://www.nc3rs.org.uk/the-3rs)
- All research is done in compliance with CEPI's Animals in Research Policy

Primary infection studies confirmed typical coronavirus disease; and Re-Infection Studies showed solid protection from disease in hamsters, even across variants

Initial infection	*Re-infection*	*Clinical signs after re-infection?*	*Weight loss after re-infection?*	*Protection against re-infection?*
Alpha	Delta	No	No	Yes
Victoria	Delta	No	No	Yes
Beta	Gamma	No	No	Yes
Beta	Beta	No	No	Yes
Gamma	Beta	No	No	Yes
Gamma	Gamma	No	No	Yes

- ✓ **For all VOCs tested, prior infection was able to protect against secondary infection 28 days later.**
- ✓ **None of the combinations of VOCs tested showed escape from immunity.**
- ✓ **Preliminary pathology data has not identified any difference between VOCs.**

All studies were conducted in compliance to all UK government regulatory requirements. In-life phase complete: full data analysis is underway, with ELISA, microneutralization and pathology data pending.

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Important considerations for laboratory methods

- Serial propagation of SARS-CoV-2 variants in Vero E6 or other cell types may lead to furin cleavage site mutations that affect how the virus grows and behaves in vitro or in vivo. Propagation of unwanted mutations can be mitigated by growth in cells such as Vero/hSLAM and by frequent sequence confirmation (deep sequence methods preferred). link
- WHO International Antibody Standard should be used for neutralization assays, but it performs differently for each variant. Any data presented comparing the WHO IS should always identify the variant under test.

Recent relevant publications

- Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays Nature Protocols **16**, 3114-3140 (2021)
- A cautionary perspective regarding the isolation and serial propagation of SARS-CoV-2 in Vero cells NPJ Vaccines **6**:83 (2021)

Recent online conference presentations

- 19 August 2021: WHO SARS-CoV-2 Animal Modeling Working Group
- 19 May 2021: WHO SARS-CoV-2 Assays Working Group
- 19 April 2021 ECDC/WHO Euro laboratory network