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	Seeking			
ID pending - B.1.621	Seeking			

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 2, 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	In progress	In progress	In progress
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		
	Lambda (C.37)	Seeking			
UK	**Alpha + E484K**	Complete	In progress		
Others	**B.1.621**	Seeking			
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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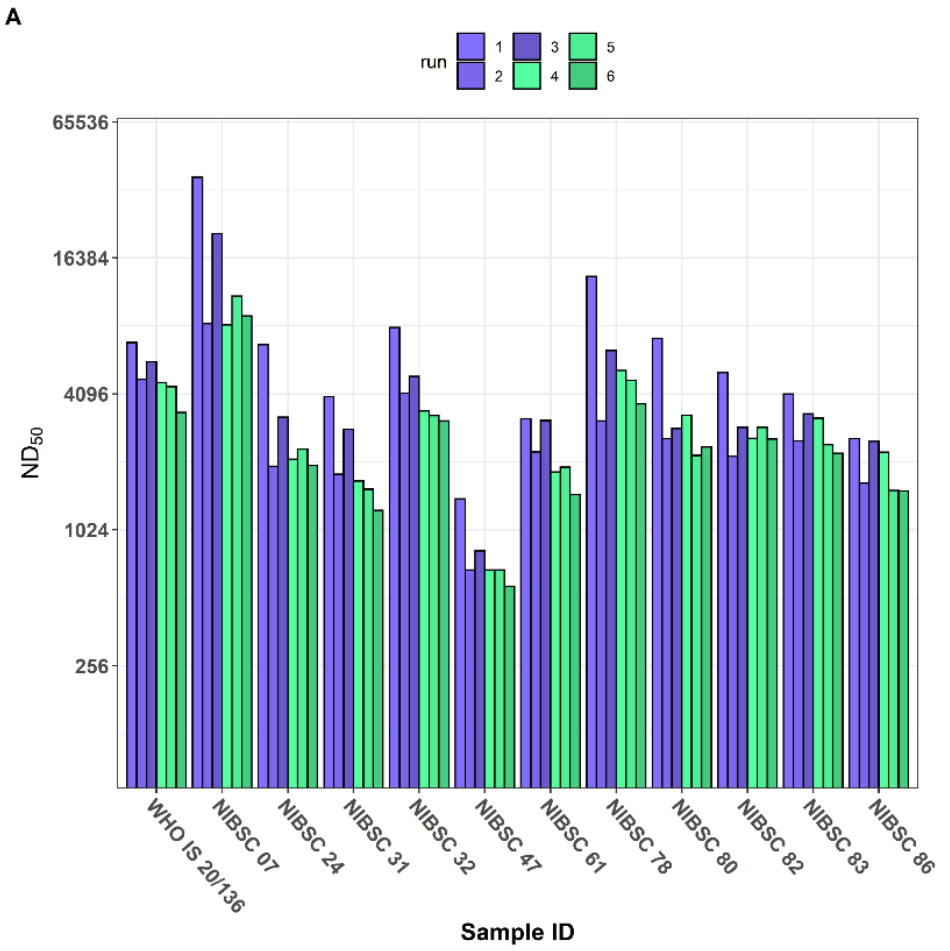
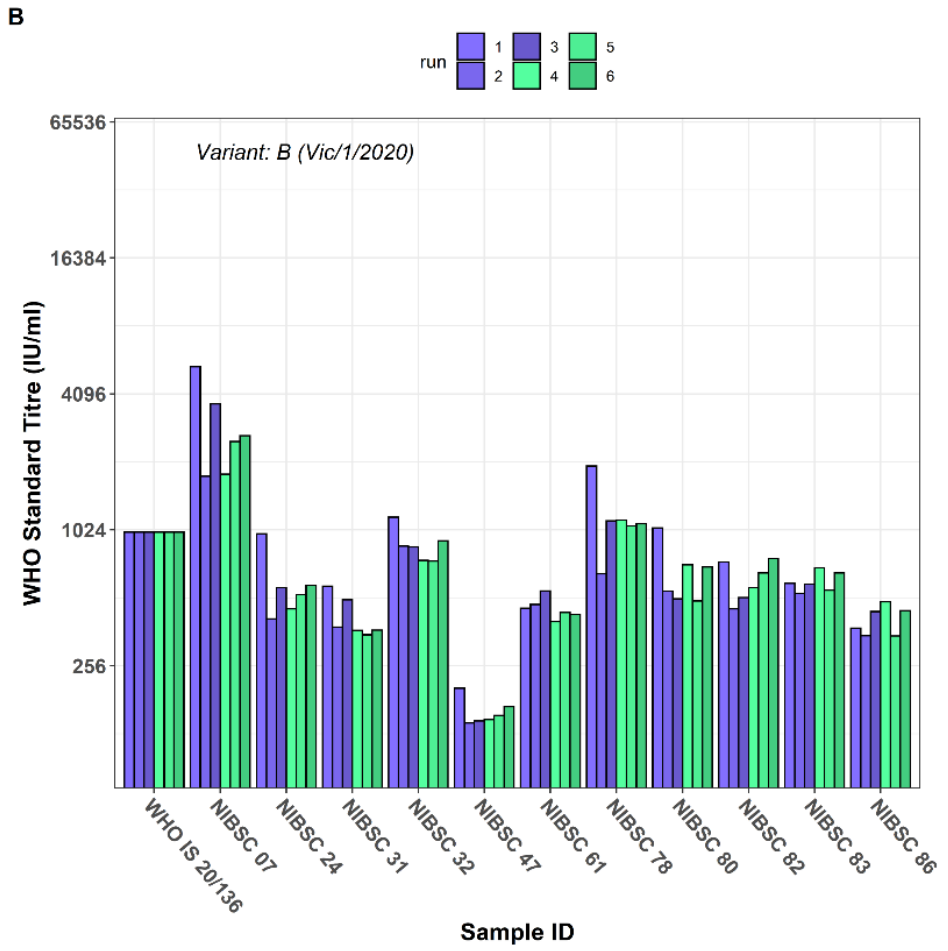
Table updated as of Aug 2, 2021

Agility project: Inter-lab assay agreement (Virus: Clade B/Victoria/1/2020)





Runs 1-3 – PHE lab
Runs 4-6 – NIBSC lab

ND50 = 40.4 %GCV
IU/ml = 22.5 %GCV

Improvement 17.9%; P <0.001

- Intra-lab variation in ND_{50} good; comparable with qualified assay variation of 50%
- Conversion to IU/ml significantly improves variation

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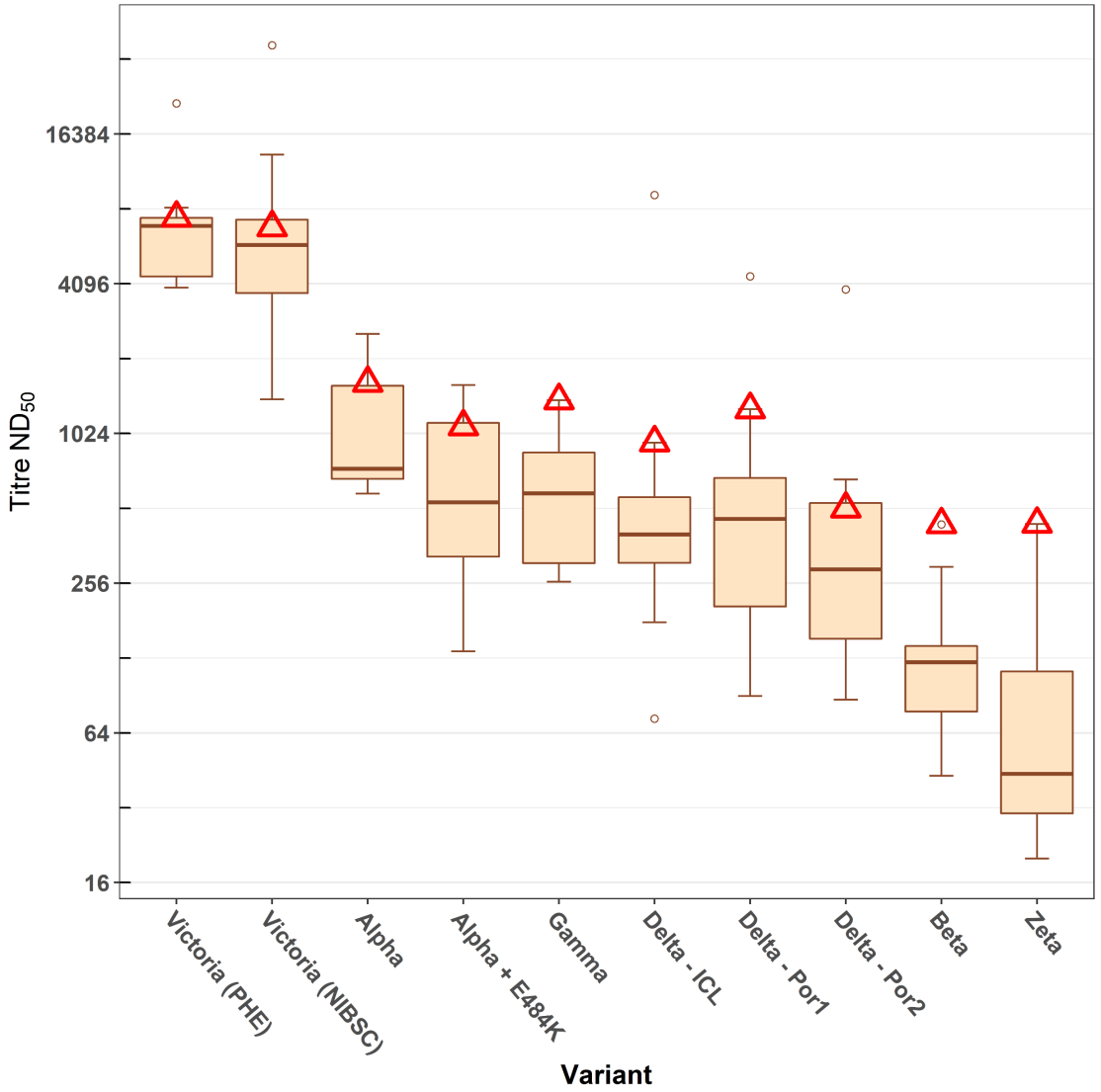
Agility project: Inter-lab assay agreement (Virus: Clade B/Victoria/1/2020)

ND_{50}	PHE		NIBSC	
	GMT	%GCV	GMT	%GCV
NIBSC 07	18703	87.3	9398	15.1
NIBSC 24	3496	69.2	2128	8.3
NIBSC 31	2733	41.3	1481	15.6
NIBSC 32	5447	35.8	3271	5.2
NIBSC 47	924	39	643	9.8
NIBSC 61	2819	19.1	1738	15.1
NIBSC 78	6444	84.9	4481	17.8
NIBSC 80	3776	61	2578	21.9
NIBSC 82	3177	45.3	2693	6.5
NIBSC 83	3256	24.5	2590	18.8
NIBSC 86	2208	25.8	1738	22.8
WHO IS 20/136	5706	18.9	4093	16.6
Average	**3762.2**	**48.5**	**2508.4**	**14.3**

IU/ml	PHE		NIBSC	
	GMT	%GCV	GMT	%GCV
NIBSC 07	3278	61.7	2296	21.5
NIBSC 24	613	46	520	12.1
NIBSC 31	479	21.4	362	2.7
NIBSC 32	955	17.3	800	11.8
NIBSC 47	162	20.1	157	6.8
NIBSC 61	494	9.3	424	4.8
NIBSC 78	1129	59.4	1095	3.1
NIBSC 80	662	41.3	630	20.9
NIBSC 82	557	25.2	658	14.9
NIBSC 83	571	5.8	633	11.9
NIBSC 86	387	12.7	425	18.2
WHO IS 20/136	1000	0	1000	0
Average	**659.5**	**29.1**	**612.9**	**11.7**

- ND_{50} results between labs have a difference in average GMT of the panel of 1254; P = 0.025 (significant)
- When converted into IU/ml using WHO IS, the difference is 47 IU/ml (PHE > NIBSC); P = 0.22 (not significant)

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 Gamma
  - Three distinct Delta isolates with different spike mutations assessed
    (Delta - Por2 is lineage defining set)

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Updated as of Aug 2, 2021

In vitro susceptibility of variants

Table 1 – Variants tested with initial Agility Serum Panel

	Variant ID			
SampleID	Victoria (B) Batch A	Alpha	Gamma	Beta
NIBSC 7	21789	2571	1043	298
NIBSC 24	5386	1277	665	123
NIBSC 31	3952	739	259	43
NIBSC 32/33*	7618	695	304	83
NIBSC 61	4258	627	308	78
NIBSC 78	7333	1593	588	131
NIBSC 82	4374	587	355	143
WHO IS 20/136	7545	1634	1391	441
GMT	**6609**	**1062**	**514**	**131**
Fold-change relative to Victoria	**1.0**	**6.2**	**12.9**	**50.5**

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

Table 2 – Variants tested with expanded Agility Serum Panel

	Variant ID				
SampleID	Victoria (B) Batch B	Alpha + E484K	Delta	Delta + K417N	Beta
NIBSC 7	18703	1360	3883	4500	269
NIBSC 24	3496	869	161	339	129
NIBSC 31	2733	450	263	266	53
NIBSC 32/33*	5447	189	632	544	166
NIBSC 47	924	136	87	135	46
NIBSC 61	2819	351	167	484	111
NIBSC 78	6444	603	668	1280	215
NIBSC 80	3776	1604	102	360	150
NIBSC 82	3177	486	321	898	139
NIBSC 83	3256	1247	346	319	139
NIBSC 86	2208	265	131	271	68
WHO IS 20/136	5706	1092	510	1081	265
GMT	**3762**	**553**	**309**	**536**	**127**
Fold-change relative to Victoria	**1.0**	**6.8**	**12.2**	**7.0**	**29.6**

Notes:

- All sera are convalescent donations from early pandemic period; prior to emergence of Alpha
- Expanded Agility serum panel used to generate data in Table 2 contains additional sera identified as lower titre
- 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

1st Infection Variant virus	Weight loss over 7 days after infection	Clinical signs over 7 days after infection	2nd Infection Variant virus	Weight loss over 7 days after 2nd infection	Clinical signs over 7 days after 2nd infection
Gamma (Brazil P.1.)	>10%	+++	None	-	-
Beta (South Africa B.1.351)	>10%	+++	None	-	-
Gamma (Brazil P.1.)	>10%	+++	Gamma (Brazil P.1.)	None	None
Beta (South Africa B.1.351)	>10%	+++	Beta (South Africa B.1.351)	None	None
Gamma (Brazil P.1.)	>10%	+++	Beta (South Africa B.1.351)	None	None
Beta (South Africa B.1.351)	>10%	+++	Gamma (Brazil P.1.)	None	None

All studies were conducted in compliance to all UK government regulatory requirements. Study complete: full data analysis is underway. Alpha and Delta variant studies are ongoing.

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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 May 2021: WHO SARS-CoV-2 Assays Working Group
- 19 April 2021 ECDC/WHO Euro laboratory network
- 16 April 2021 COVAX ES-SWAT Workshop 'Global and Local Efforts to Detect and Interpret SARS-CoV-2 Variant'