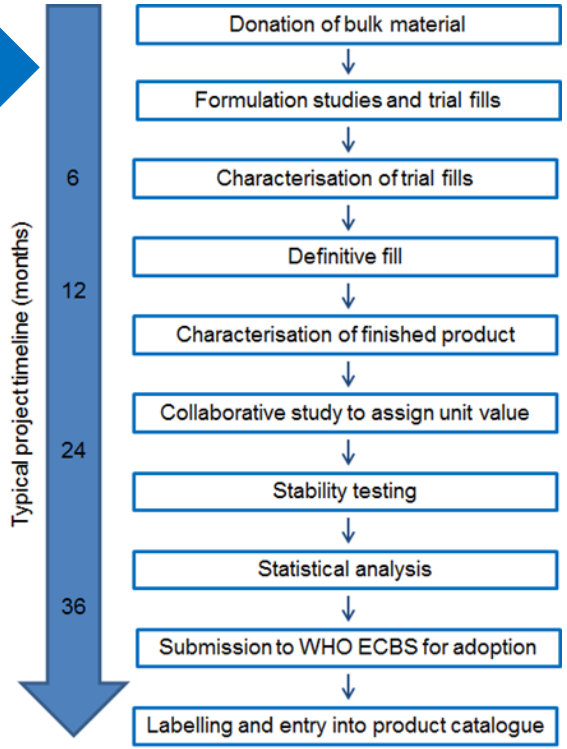
Medicines & Healthcare products Regulatory Agency

NIBSC

NIBSC serology reference materials, reagents & assays

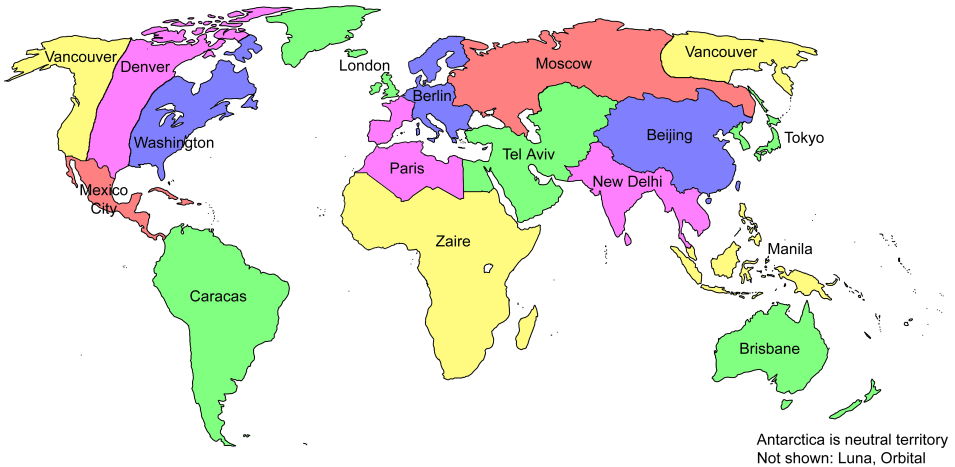
Standards projects - overview

Project endorsement
- NIBSC
- WHO ECBS



Collaborative study Participants

- Number depends on the study/assays
- Typically between 5-25 participants
- Representative of end users (eg product manufacturers, national control laboratories, public health laboratories, diagnostic kit manufacturers in HIC and LMICs)
- For a WHO standard include all WHO regions where appropriate and possible



Source materials

- Pool of convalescent plasma/serum
  - Commutability
  - Average (broad) antibody repertoire

Other samples

panels of high, medium and low titre

mabs

negative controls

cross reactive plasma/sera

animal sera

Antibody Characterisation

- Wild type virus neutralisation assay (CL3)
  - CPE/PRNT/microneut
- Pseudovirus neutralisation (CL2)
  - VSV core

	20/130	20/120	20/122	20/124	20/126	20/128
Live virus (CPE)	1280	200	70	40	35	<20
VSV-PV	2240	267	90	20	<20	<20
$PRNT_{50}$	853	107	33	13	<20	<20

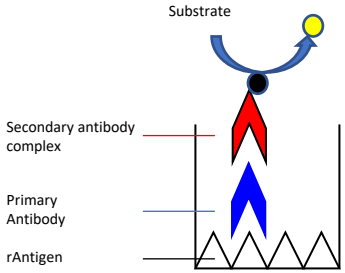
- ELISA
  - S1, S2
  - Spike trimer
  - NP

	20/130	20/120	20/122	20/124	20/126	20/128
EuroImmun IgG	**Pos (7.77)**	**Pos (8.59)**	**Pos (3.47)**	**Pos (1.62)**	**Neg (0.64)**	**Neg (0.21)**
EuroImmun IgM	**Pos (9.74)**	**Pos (10.1)**	**Pos (1.1)**	**Pos (1.84)**	**Pos (1.63)**	**Neg (0.02)**
IgG S1	**5388**	**5580**	**3202**	**1636**	**1181**	**<50**
IgG N	**17197**	**3417**	**2425**	**3296**	**995**	**<50**
IgG sSpike	**2707**	**2693**	**1488**	**118**	**8**	**<50**

Provided in datasheet for information

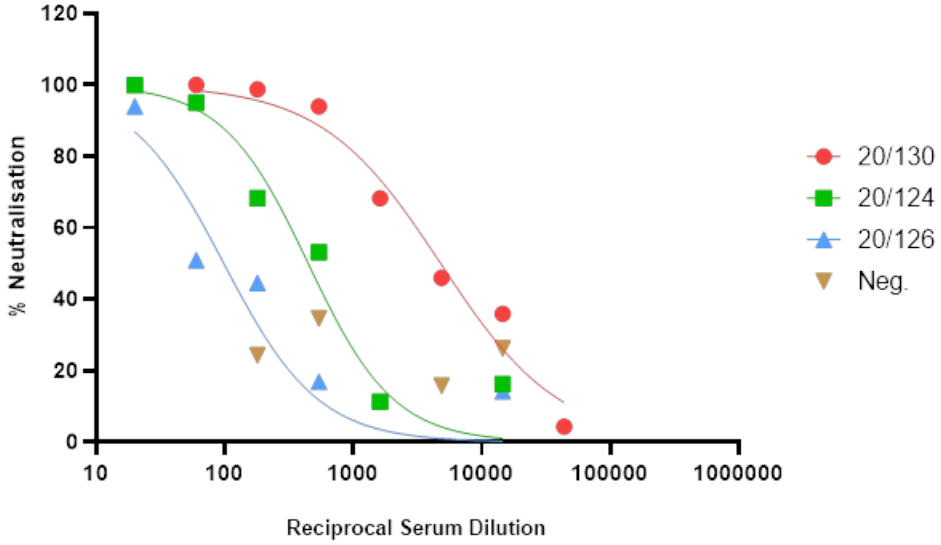
SARS-CoV2 ELISA

- Direct binding ELISA with recombinant SARS-CoV2 proteins
  - S1
  - RBD
  - Trimer
  - S2
  - Np



- Using for screening convalescent samples for IgG/IgM developing IgA
- Can be used for screening other species antibodies

PV neutralization



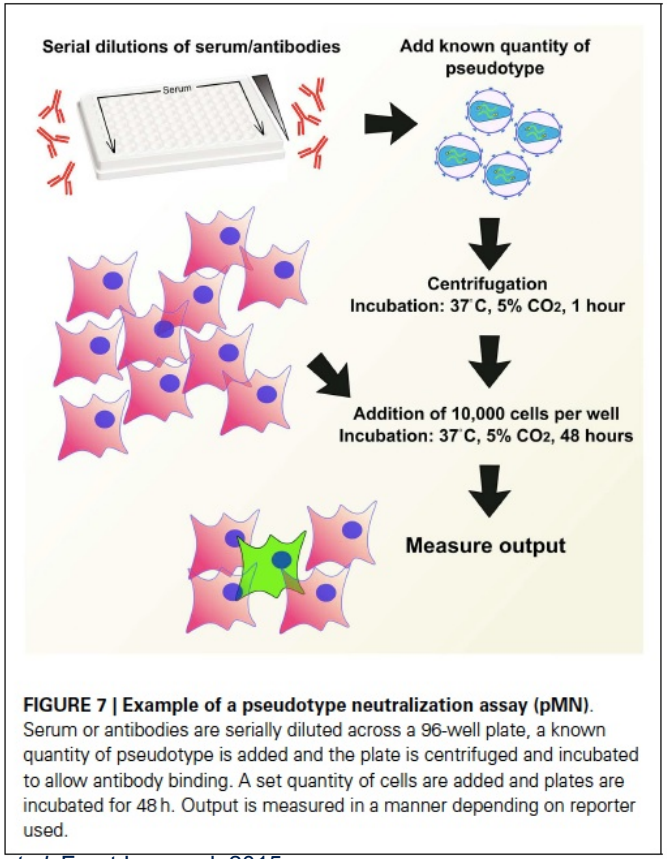
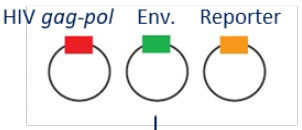


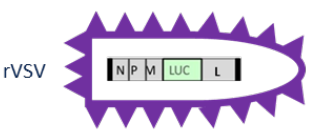
FIGURE 7 | Example of a pseudotype neutralization assay (pMN). Serum or antibodies are serially diluted across a 96-well plate, a known quantity of pseudotype is added and the plate is centrifuged and incubated to allow antibody binding. A set quantity of cells are added and plates are incubated for 48 h. Output is measured in a manner depending on reporter used.

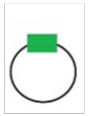
Carnell *et al*. Front Immunol, 2015

Pseudotyped-based neutralisation assays

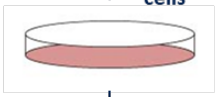


1. Expression plasmid containing envelope sequence

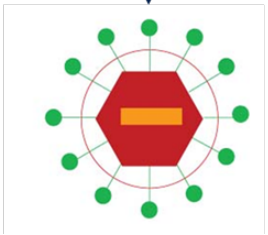




Plasmid co-transfection of producer cells

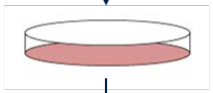


Harvest lentiviral pseudotype

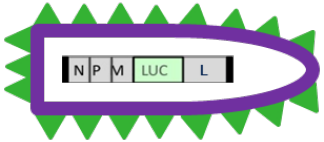


2. Optimise transfection

Inoculate rVSV onto cells expressing foreign envelope glycoprotein

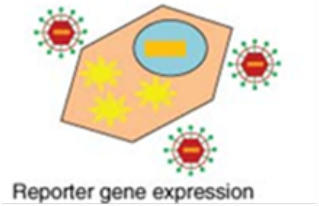


Harvest pseudotyped rVSV

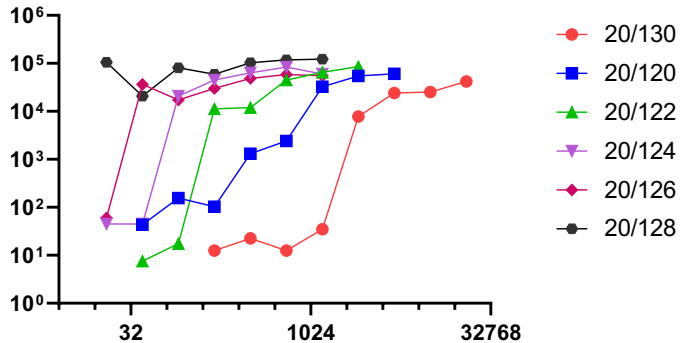


3. Identify permissive target cells

Titration on permissive target cells

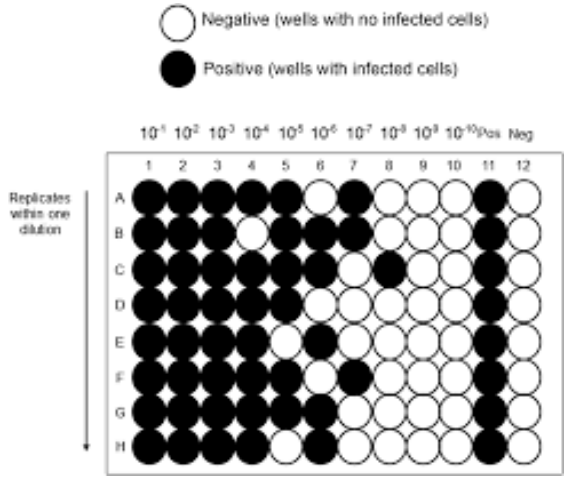


Whitt, (2010) Journal of Virological Methods, 169 [2]



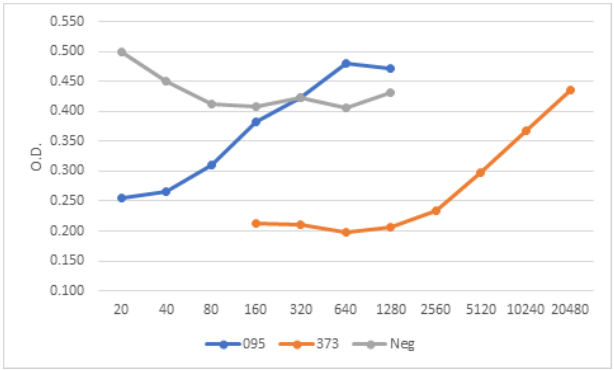
Live SARS-CoV-2 neutralisation assays

1) Detection by CPE



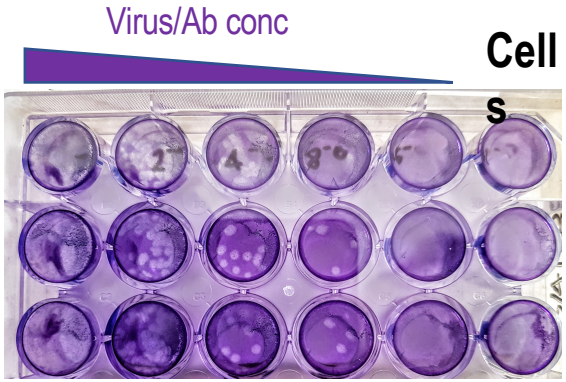
5 days

2) Immunostaining



3 days

3) Infectivity



4 days

Collaborative study samples

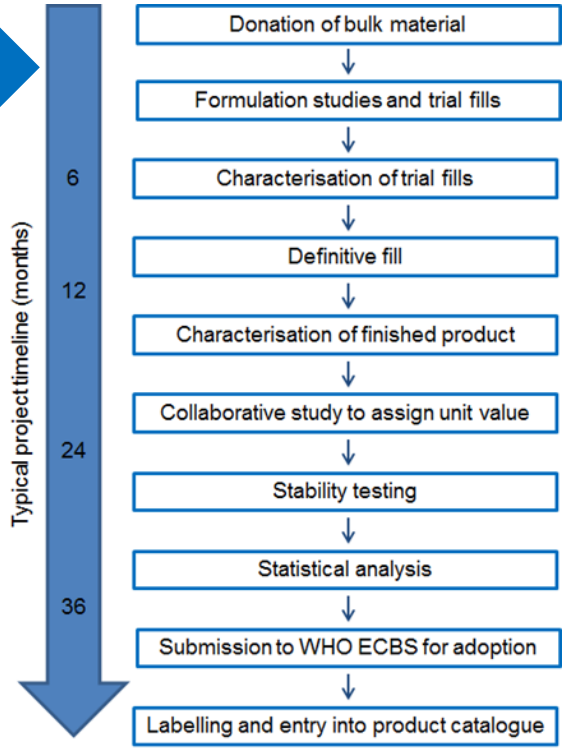
Table 1. Collaborative study samples shipped under NIBSC dispatch reference CS570.

EBOV Ab Collaborative Study Sample Code	NIBSC Product Code	Sample Name and description	Preparation
79*	15/220	WHO 1st IRR for Ebola antibodies ARC convalescent plasma 1unit/mL	100 µL frozen plasma
38	15/284	Candidate Panel Member 3: NOR Anti-EBOV Convalescent Plasma	0.25 mL plasma Freeze-dried
39	15/288	Candidate panel Member Negative Human Plasma (anti-EBOV)	0.25 mL plasma Freeze-dried
66	15/282	Candidate Panel Member 2: NHSBT Anti-EBOV Convalescent Plasma	0.25 mL plasma Freeze-dried
85	15/286	Candidate Panel Member 4: INMI Anti-EBOV Convalescent Plasma	0.25 mL plasma Freeze-dried
92	15/262	Candidate WHO 1st International Standard Anti-EBOV Convalescent Plasma Pool Sierra Leone	0.5 mL plasma Freeze-dried
93	NA	Mab 1-P6 in buffer#	100 µL Liquid
94	Not Applicable	Mab 1-2-66-4-C12 in buffer#	100 µL Liquid
95	15/280	Candidate Panel Member 1: ARC Anti-EBOV Convalescent Plasma	0.25 mL plasma Freeze-dried

Abbreviations: * Sample Code 79 was established as the WHO 1st International Reference Reagent for Ebola antibodies (NIBSC 15/220) by ECBS in 2015 [1]. IRR = International Reference Reagent; ARC = American Red Cross; NOR = Norway; NHSBT= National Health Service Blood and Transplant; INMI = National Institute for Infectious Diseases Lazzaro Spallanzani; NA = Not Applicable; MAb = monoclonal antibody.

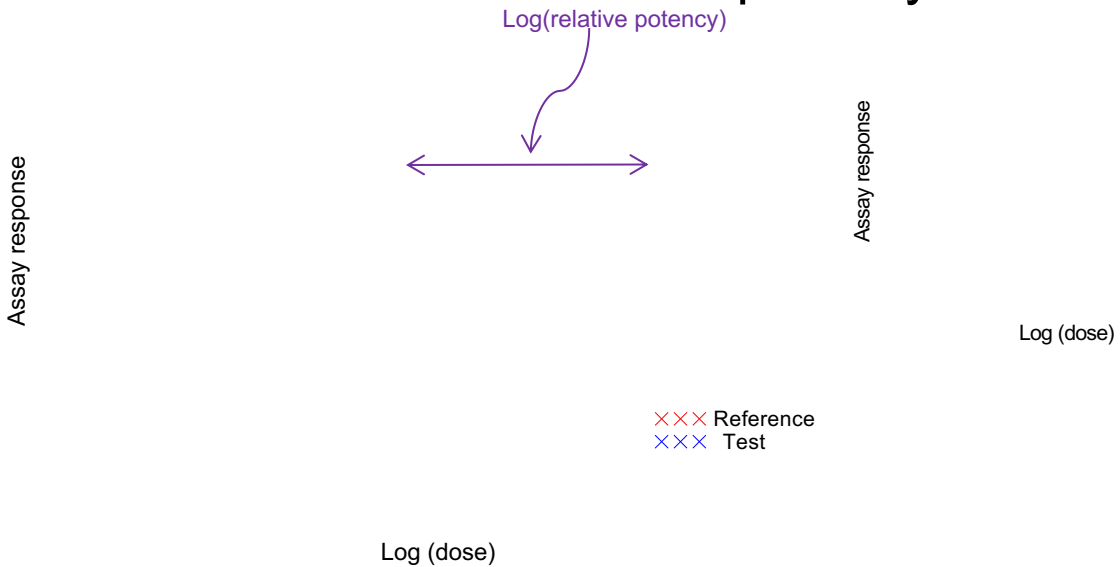
Standards projects - overview

Project endorsement
- NIBSC
- WHO ECBS



Statistical models

- Commonly used example: parallel-line model, “parallel” sigmoid curves - used to determine relative potency



Reduction in inter-lab variability

Neutralisation Method	Lab code	Median Neut/PsN titres RNT50 unless stated otherwise					
		15/220	38	66	85	92	95
Neut, Whole virus Makona isolate C05	15b	160	n/a	28	20	80	80
Neut, Whole virus, Mayinga	16a	304	27	64	27	512	256
LVV-PsN, EBOV	2	610	349	178	217	436	290
LVV-PsN, Makona	4	187	76	65	123	365	311
LVV-PsN, Makona	9	220	63	153	108	186	171
LVV-PsN, Makona isolate C15	11	226	20#	7241#	226	905	n/a#
VSV-PsN, EBOV	10b	5230	1331	1619	1101	5845	3953
rcVSV-PsN, EBOV	12	426	n/a	n/a	n/a	198	279
nrVSV-PsN, EBOV	13	1978	240	782	371	2572	1843
	Overall GM	474	116	271	139	529	399
	Overall GCV	228%	348%	558%	275%	282%	258%

Neutralisation Method	Lab code	Potencies relative to sample 92					
		15/220	38	66	85	92	95
Neut, Whole virus Makona isolate C05	15b	2.00	n/a	0.35	0.25	1.00	1.00
Neut, Whole virus, Mayinga	16a	0.59	0.05	0.13	0.05	1.00	0.50
LVV-PsN, EBOV	2	1.40	0.80	0.41	0.50	1.00	0.67
LVV-PsN, Makona	4	0.51	0.21	0.18	0.34	1.00	0.85
LVV-PsN, Makona	9*	n/a	n/a	n/a	n/a	1.00	0.92
LVV-PsN, Makona isolate C15	11	0.25	0.02#	8.00#	0.25	1.00	n/a#
VSV-PsN, EBOV	10b	0.89	0.23	0.28	0.19	1.00	0.68
rcVSV-PsN, EBOV	12	2.15	n/a	n/a	n/a	1.00	1.41
nrVSV-PsN, EBOV	13	0.77	0.09	0.30	0.14	1.00	0.72
	Overall GM	0.87	0.13	0.42	0.20	1.00	0.81
	Overall GCV	108%	251%	292%	105%	0%	37%

Collaborative study

World Health Organization

WHO/BS/2017.2316
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17-20 October 2017

WHO collaborative study to assess the suitability of the 1st International Standard and the 1st International Reference Panel for antibodies to Ebola virus

Dianna E. Wilkinson[1,#], Mark Hassall[1], Giada Mattiuzzo[1], Lindsay Stone[1], Eleanor Atkinson[2], Jason Hockley[2], Peter Rigsby[2], Antonino Di Caro[3], Sheila MacLennan[4], Richard W. Olaussen[5], Pramila Rijal[6], Susan Stramer[7], Calum Semple[8], Mark Page[1], Philip D. Minor[1], the Collaborative Study Group* and the Ebola CP Consortium**

Product Number	20/130
Product Description	Research Reagent for Anti-SARS-CoV-2 Ab
Type of Standard	Non WHO Reference Material
Category	Vaccines > Emerging VirusesVaccines
Instructions for Use	20-130.pdf
Keywords	COVID-19, SARS-CoV-2, Antibody, Serology, plasma
Related Products	19/304, 20/118,
Customer Notes	
Minimum Quantity	0
Unit Price	£0.00

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	Influenza	Tetanus
		Tuberculosis
		Vaccinia
		Yellow Fever
		Livestock diseases
		Hepatitis A Virus
		Rabies

WHO International Standard Timeline

Milestone	Date
Sourcing material	May 2020
Definitive fill and post-fill characterisation	May-June 2020
Collaborative study	June-Sept 2020
Analysis and report	Oct-Nov 2020
Submission to ECBS	December 2020

Acknowledgements

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Sam Richardson

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