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Genome-based surveillance of resistance to COVID-19 therapeutics in the UK

Hassan Hartman, senior bioinformatician

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UKHSA's COVID-19 therapeutics programme

Workstream	1	2	3	4	5	6
Activity	Knowledge and evidence build	Structural modelling University of Oxford (Structural Biology)	Laboratory testing	Genomic surveillance	Epidemiological surveillance	Antimicrobial stewardship
Objective	Work with academic partners and clinical triallists to synthesise evidence on resistance risk, mechanism and antimicrobial stewardship	Provide structural modelling evidence on the likely impact of different variants and mutations on priority treatment agents	Provide laboratory evidence on the likely impact of different variants and mutations on priority treatment agents Establish procedures for routine testing capabilities	Provide genomic surveillance data and analysis for mutations and variants identified in WS1,2 and 3	Provide epidemiological surveillance on the use and outcomes of treatment (where appropriate given trials)	Support and monitor appropriate use of therapies to minimise the development of resistance
Partners	AGILE Trial PANORAMIC Trial RECOVERY Trial	University of Oxford	Genotype to Phenotype Consortium		University of Edinburgh University of Oxford	NHS England and Improvement

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Sampling strategy

- All patients receiving treatment with neutralising monoclonal antibodies or antivirals, in either hospital or community settings.
- Therapeutic samples prioritised for sequencing.
- Treatments:
  - (Casirivimab/imdevimab – discontinued)
  - Sotrovimab
  - Remdesivir
  - Molnupiravir
  - Nirmatrelvir plus ritonavir (Paxlovid)

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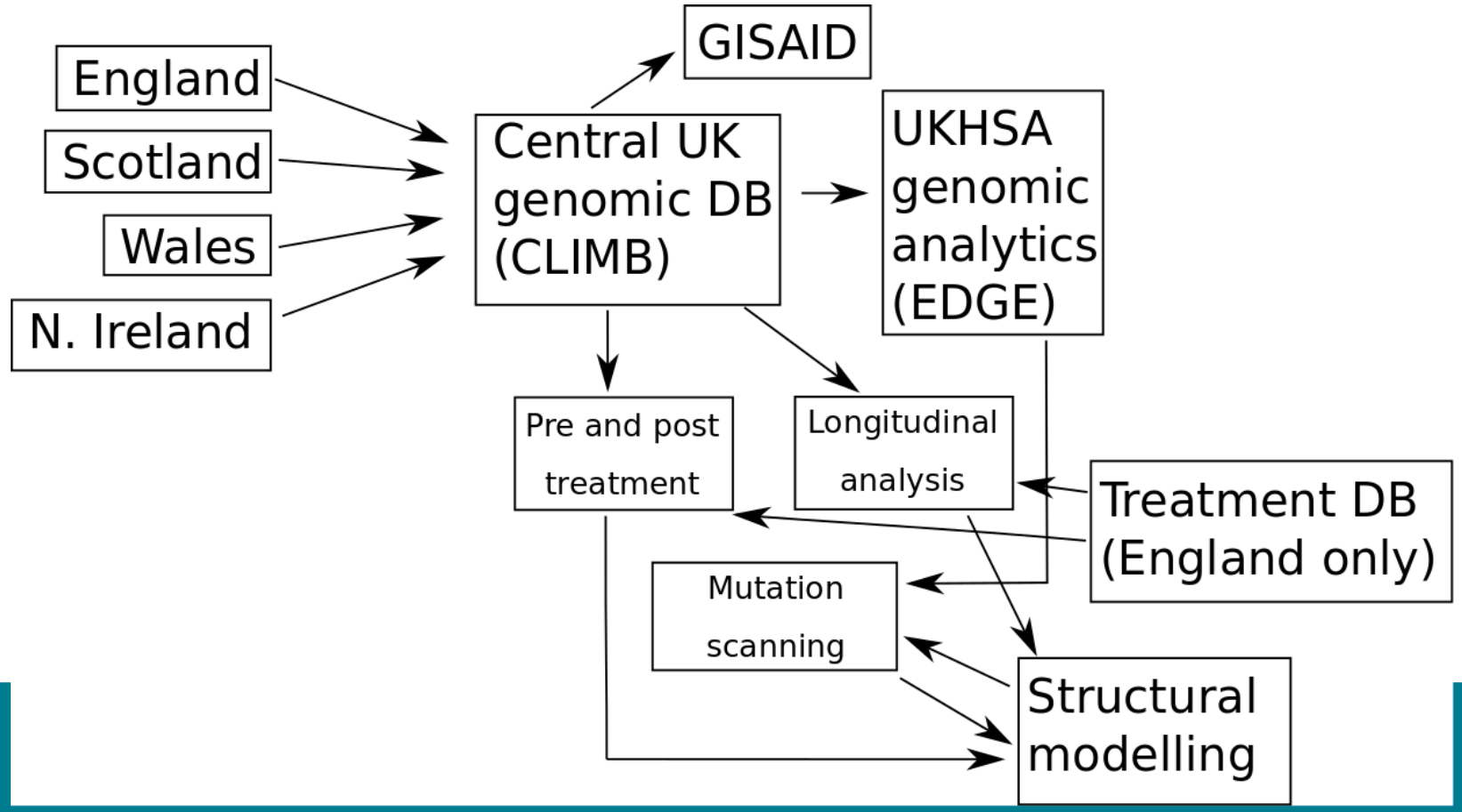
Genomic surveillance infrastructure for COVID-19 therapeutics



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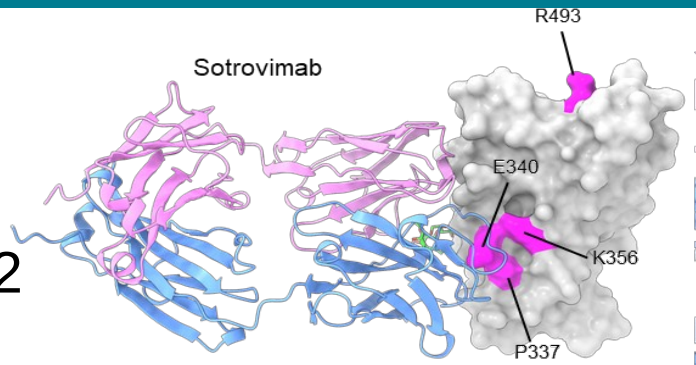
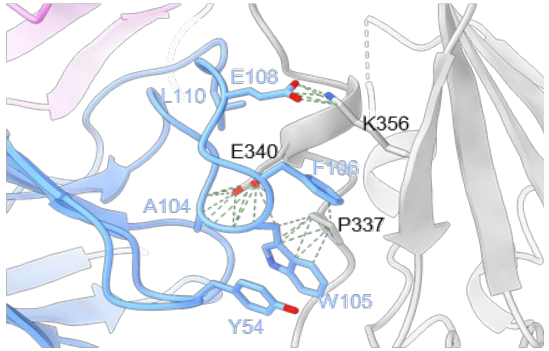
Structural modelling: Identification of potential resistance-conferring mutations

- Carried out by academic partners in Structural Biology Division, University of Oxford.
- Modelling based on published SARS-CoV-2 protein – drug complexes.
- Exhaustive *in silico* search for nonsynonymous mutations with potential to destabilise complexes.
- Mutation severity scoring.
- Structural assessment of novel mutations.





aa Mutation	346 R	439 N	440 N	441 L	443 S	444 K	445 V	446 G	447 G	448 N	449 Y	450 N	498 Q	499 P	500 T	501 N
	2	2.5	5	5	10	7	5.5	9	8	7	4	2	2	5.5	6	2
A	12	15	30	30	50	42	33	18	16	42	24	12	12	27.5	30	12
C	12	15	30	30	30	42	33	54	48	42	24	12	12	33	36	12
D	12	5	10	30	60	42	33	54	48	14	24	4	10	33	36	4
E	12	12.5	25	30	60	42	33	54	48	35	24	10	4	33	36	10
F	12	15	30	15	60	42	27.5	54	48	42	8	12	12	33	36	12
G	12	15	30	30	60	42	33	0	0	42	24	12	12	33	36	12
H	12	12.5	25	30	60	42	33	54	48	35	12	10	6	33	36	10
I	12	15	30	10	60	42	16.5	54	48	42	20	12	12	33	30	12
K	4	15	30	30	60	7	33	54	48	42	24	12	10	33	36	12
L	12	15	30	5	60	42	27.5	54	48	42	20	12	12	27.5	36	12
M	12	15	30	10	60	42	27.5	54	48	42	20	12	12	33	36	12
N	12	2.5	5	30	50	42	33	54	48	7	24	2	6	33	30	2
P	12	15	30	25	60	42	27.5	54	48	42	24	12	12	5.5	30	12
Q	12	7.5	15	30	60	35	33	54	48	21	24	6	2	33	36	6
R	0	15	30	30	60	14	33	54	48	42	24	12	12	33	36	12
S	12	12.5	25	30	10	42	33	54	48	35	24	10	10	33	12	10
T	12	12.5	25	30	20	42	33	54	48	35	24	10	12	27.5	6	10
V	12	15	30	25	60	42	5.5	54	48	42	24	12	12	27.5	36	12
W	12	15	30	25	60	42	33	54	48	42	12	12	12	33	36	12
Y	12	15	30	25	60	42	33	54	48	42	0	12	12	33	36	12

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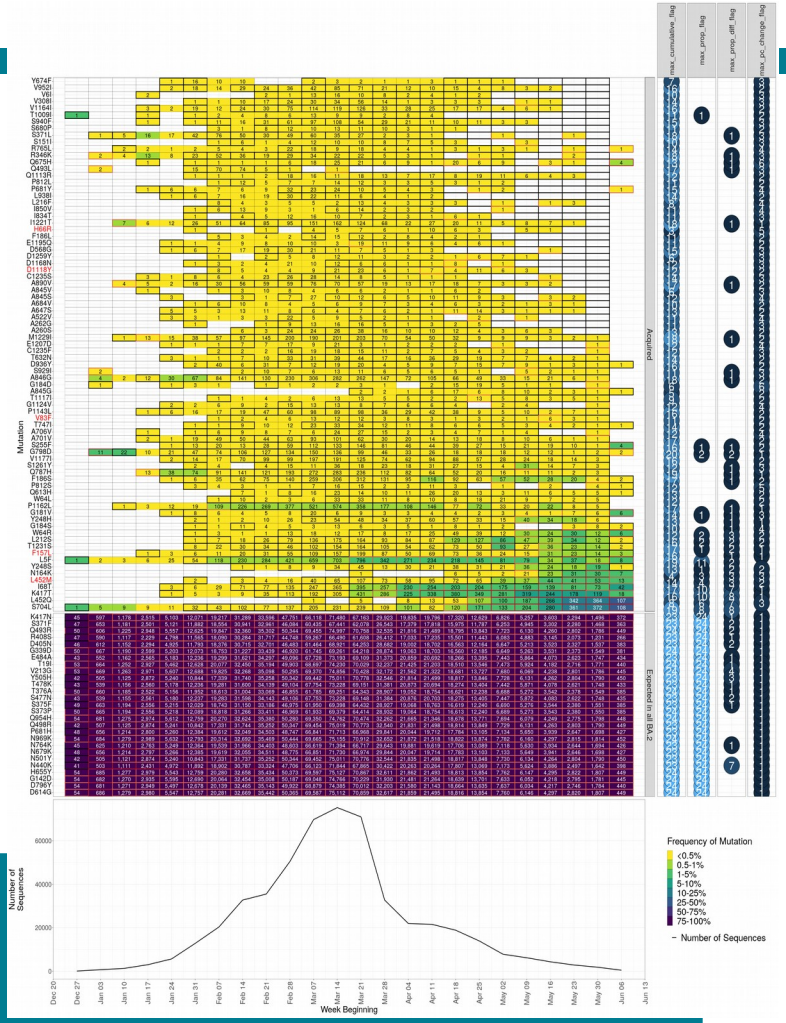
Mutation scanning: Monitoring and identification of potential resistance markers

- Acquired mutations – nonsynonymous and not part of lineage definition.
- Identification of acquired mutation (2 or more thresholds, weekly basis):
  - ≥50 samples in total
  - ≥5% weekly increase
  - ≥1% prevalence
  - ≥2.5% increase in proportional representation
- Recent data indicates increase in prevalence of mutations in BA.2 and BA.4 that are predicted to interfere with sotrovimab binding.



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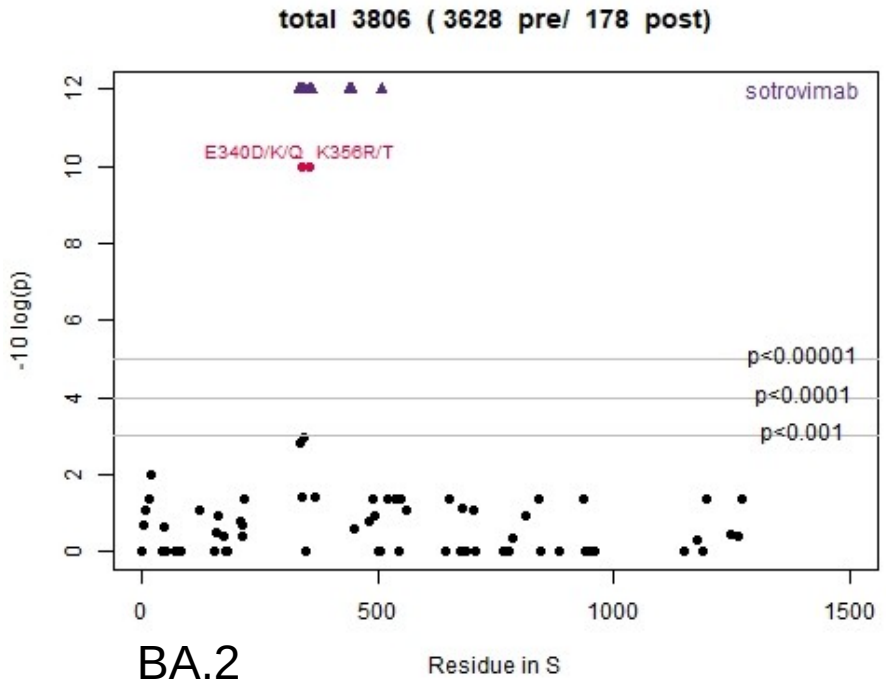
Pre and post treatment analysis: Detection of treatment-emergent mutations

- Identification of mutations with significantly increased frequencies after treatment, as compared to before treatment (up to a week before first dose).
- Recent analysis identified 14 treatment-emergent amino acid residue changes:
  - S:G446V, Y453F, L455F/S (Delta, casirivimab and imdevimab)
  - S:P337L/R/S plus S:E340A/D/G/K/Q/V, S:K356T, S:L455S/W, R493L/Q (BA.1, sotrovimab)
  - S:E340D/K/Q plus K356R/T (BA.2, sotrovimab)
  - NSP12:E136A/D, V166A/L, V792I, F694Y, NSP14:I42V (mostly Alpha, remdesivir)



BA.2

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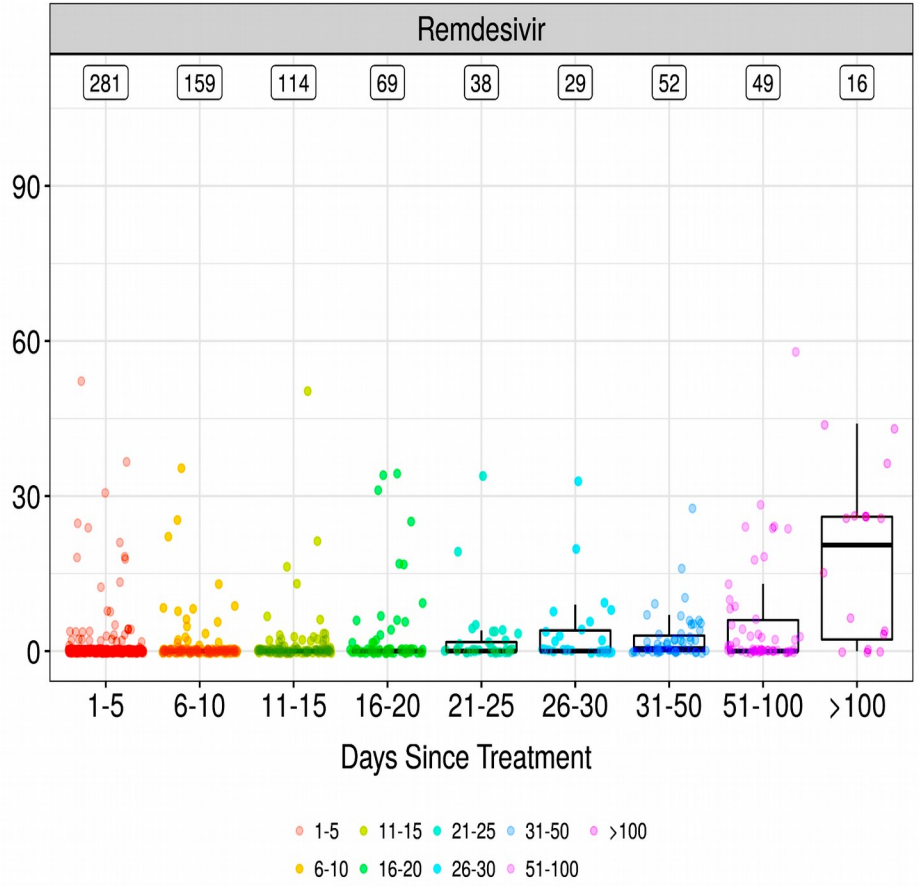
Longitudinal analysis: Serial sampling of persistent infections

- Identification of all mutations accumulated in samples from patients with persistent infections, stratified by treatment.
- Most recent analysis supports hypothesis that variant selection is unlikely to be driven by patients cleared of infection by day 10.



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Challenges and future directions

- Challenging to assess role of community transmission with reduced testing.
- Difficult to predict impact of multiple mutations on resistance to therapeutics.
- Integration of genomic and epidemiological data.
- Improved methods for predicting resistance profile from genomic data.
- Development of experimental and computational methods for assessing impact of mutations on resistance to small antiviral compounds.