We’ve created calculator that aggregates deep mutational scanning data to estimate how mutations to #SARSCoV2 RBD affect recognition by human polyclonal antibodies. The calculator emphasizes extensive antigenic change in #Omicron variant. URL (1/n)

Calculator uses experimental measurements of how all mutations to #SARSCoV2 RBD affect binding by 33 neutralizing antibodies (<https://twitter.com/jbloom_lab/status/1377100608688156681>) to calculate antigenic effects of mutating arbitrary combinations of RBD sites. (2/n)

Below is video of toy example with just 3 antibodies to explain principle. As mutations ablate individual antibodies, that reduces binding of polyclonal mix at their epitope sites. Explore this toy example at <https://jbloomlab.github.io/SARS2_RBD_Ab_escape_maps/mini-example-escape-calc/> (3/n)

Actual calculator uses 33 antibodies. As video below shows, it calculates net effect of mutating sites. Experimental data define importance of sites & how mutating one site affects binding at others. Explore using interactive calculator at <https://jbloomlab.github.io/SARS2_RBD_Ab_escape_maps/escape-calc/> (4/n)

This approach is \*not\* a complex black-box computational algorithm: it’s just simple aggregation of direct experimental data to define polyclonal antibody binding map, and then intuitive calculation of how it’s affected by mutations. (5/n)

Calculations correlate well w neutralization assays by various groups (@VirusesImmunity, @SystemsVirology, David Ho) on #SARSCoV2 variants & mutants. See <https://jbloomlab.github.io/RBD_escape_calculator_paper/neut_studies.html> for interactive plot enabling mouseovers to see details for points. (6/n)

What about Omicron? Here’s how all 15 mutations in Omicron RBD affect antibody binding. Seems dire: all biggest peaks are gone. If you explore interactively at <https://jbloomlab.github.io/SARS2_RBD_Ab_escape_maps/escape-calc/> you’ll see mutations at sites 417, 446, & 484 biggest culprits, but others contribute too. (7/n)

Plot above also shows sites of possible future Omicron escape (eg, 346, 378, 444, 504). @richardneher notes there is already Omicron subvariant w R346K, including sequences from Seattle by @pavitrarc. R346K subvariant should be monitored. <https://nextstrain.org/groups/neherlab/ncov/21K-diversity/unmasked?c=gt-S_346> (8/n)

Here’s total calculated RBD antibody binding to Omicron (w/o R346K) & #SARSCoV2 variants (see <https://jbloomlab.github.io/RBD_escape_calculator_paper/variants.html> for mouseover-enabled version). Omicron has much less binding than other variants; is close to artificial spike polymutant PMS20 of @PaulBieniasz @theodora\_nyc (9/n)

For reference, polymutant PMS20 spike (<https://www.nature.com/articles/s41586-021-04005-0>) has avg ~20 to 80-fold reduction in neutralization for various human cohorts. This is similar to ~25 to 60-fold reduction predicted for Omicron by extrapolating correlation in Tweet 6 of this thread. (10/n)

Some caveats of escape calculator: only considers RBD antibodies, assumes antibodies w data represent polyclonal neutralization, treats all mutations at site equivalently, & assumes people immunized w RBD similar to Wuhan-Hu-1 (currently mostly true, but becoming less so). (11/n)

Despite these caveats, calculator works pretty well on current data. More generally, #SARSCoV2 is going to continue to evolve new variants, so we need prospective approaches in addition to reactively running neutralization assays on new variants. (12/n)

When a new SARS-CoV-2 variant arises, there are three main questions: (1) How transmissible? (2) How virulent? (3) How much antigenic change? Third question important as it’s the most actionable: we can update vaccines & develop new antibodies. (13/n)

The first two questions (transmissibility and virulence) can only be answered by waiting for epidemiology and clinical data, as transmissibility and virulence are \*so complicated\* we can’t even begin to predict them from sequence. (14/n)

But while direct neutralization assays will always be gold standard for antigenic change, we can interpret a lot about antigenicity from sequence. Antibody neutralization has complexity, but not mind-boggling complexity like transmissibility and virulence… (15/n)

Ultimately, antibody neutralization involves binding of antibodies to spike, which we can understand. Scientific community has now run many 1000s of neutralization assays on variants, solved ~100 X-ray/cryoEM structures, plus deep mutational scanning: <https://covdb.stanford.edu/page/susceptibility-data/> (16/n)

It’s imperative to keep generating such data for new variants, but we also need to put the current data into coherent frameworks to synthesize the knowledge accumulated so far. (17/n)

Escape calculator takes step in that direction by aggregating data to intuitively visualize what is known about antigenic effects of RBD mutations to promote understanding & interpretation. So go to <https://jbloomlab.github.io/SARS2_RBD_Ab_escape_maps/escape-calc/> & try it out. (18/n)

Thanks @AllieGreaney & @tylernstarr for key role in this work. @Tuliodna et al for first sharing Omicron mutations. Escape calculator uses <https://altair-viz.github.io/>, thanks @jakevdp for creating that software. (19/n)