



Original antigenic sin in severe COVID-19

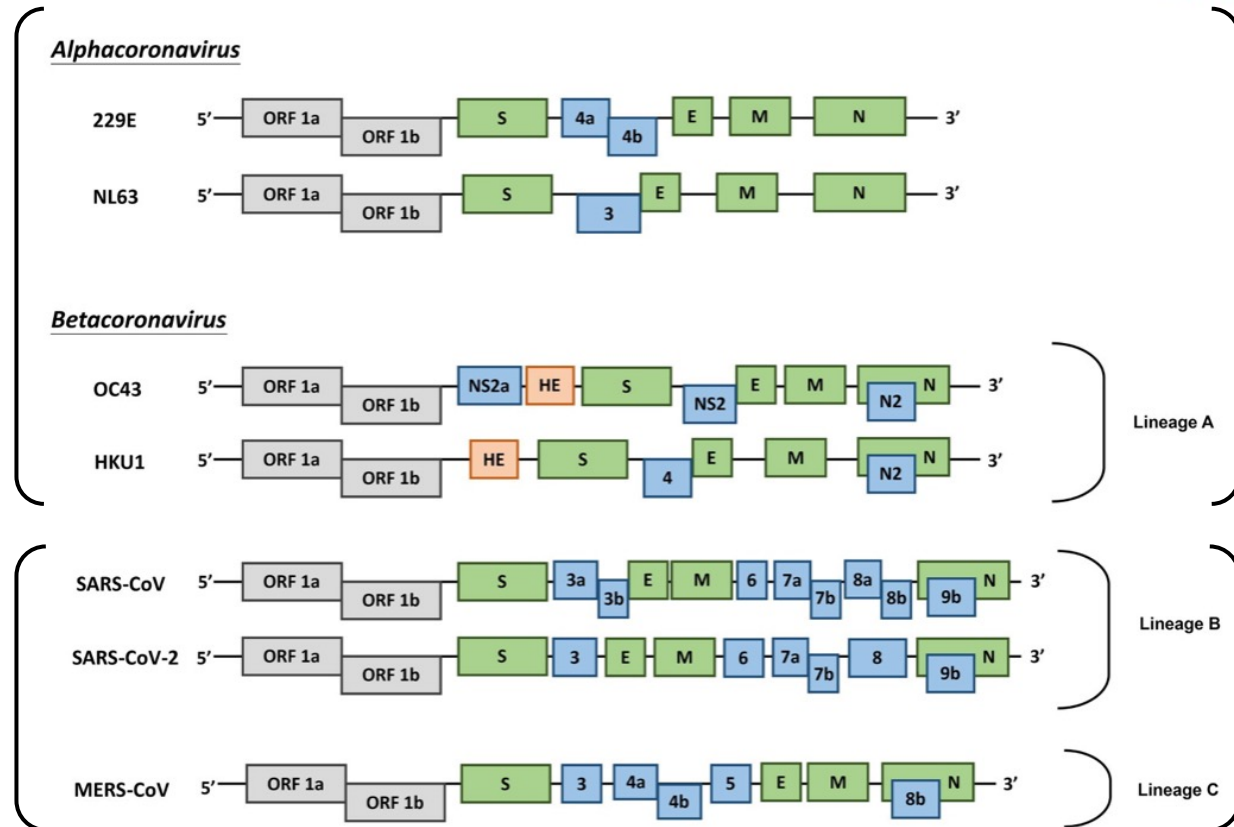
Muriel Aguilar-Bretones, Brenda M. Westerhuis, Matthijs P. Raadsen, Erwin de Bruin, Felicity D. Chandler, Nisreen M.A. Okba, Bart L. Haagmans, Thomas Langerak, Henrik Endeman, Johannes P.C. van den Akker, Diederik A.M.P.J. Gommers, Eric C.M. van Gorp, Corine H. GeurtsvanKessel, Rory D. de Vries, Ron A.M. Fouchier, Barry H.G. Rockx, Marion P.G. Koopmans, [Gijsbert P. van Nierop](#)

SARS-CoV-2: New virus, old tricks



Common-cold
human coronaviruses (hCoV)

pandemic/epidemic strains (pCoV)



Fung et al., Emerg Microd and Infections 2020



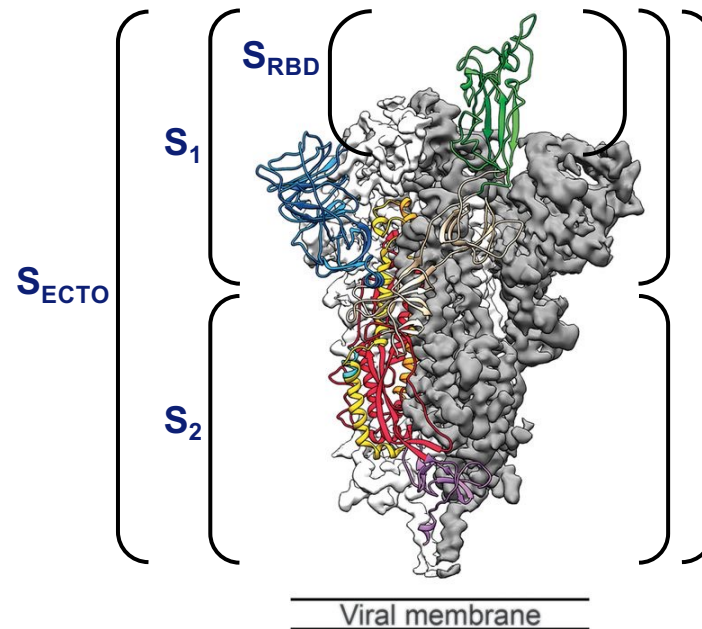
Pre-existing immunity to SARS-CoV-2?

Sequence & structural homology between SARS-CoV-2 and common-cold human coronaviruses (hCoV)

Research questions:

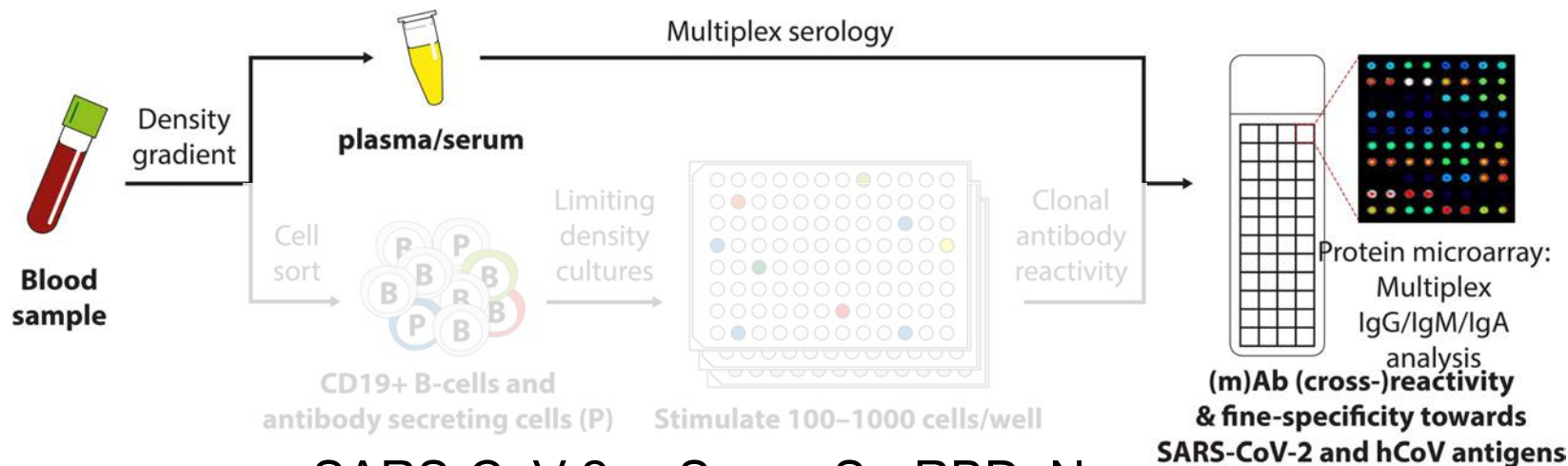
- How does pre-existing hCoV immunity influence the SARS-CoV-2 IgG response and the outcome of infection?
- What hCoV strains, antigens and domains cross-react?
- Do pre-existing hCoV IgG aid in viral clearance?

SARS-CoV-2 spike; the dominant target for virus neutralising antibodies



Wrapp et al., Science 2020

Protein microarray: In-depth analysis of serum IgG response



SARS-CoV-2: S_{ECTO}, S₁, RBD, N

hCoV: 229E: S_{ECTO}, S₁, N

NL63: S_{ECTO}, S₁, N

HKU1: S_{ECTO}, S₁, N

OC43: S_{ECTO}, S₁, N

pCoV: SARS: S_{ECTO}, S₁, N

MERS: S_{ECTO}, S₁, N

Patient cohort



Patient group

Disease control
n=6



SARS-CoV-2 RT-PCR negative
Similar symptoms as mild COVID-19 patients

Mild COVID-19
n=12



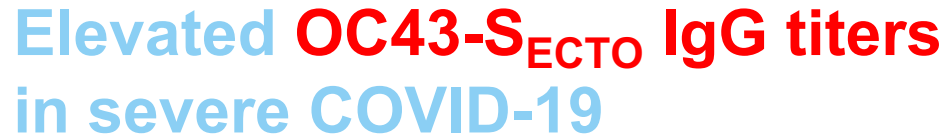
SARS-CoV-2 RT-PCR positive
Mild respiratory illness

Severe COVID-19
n=20

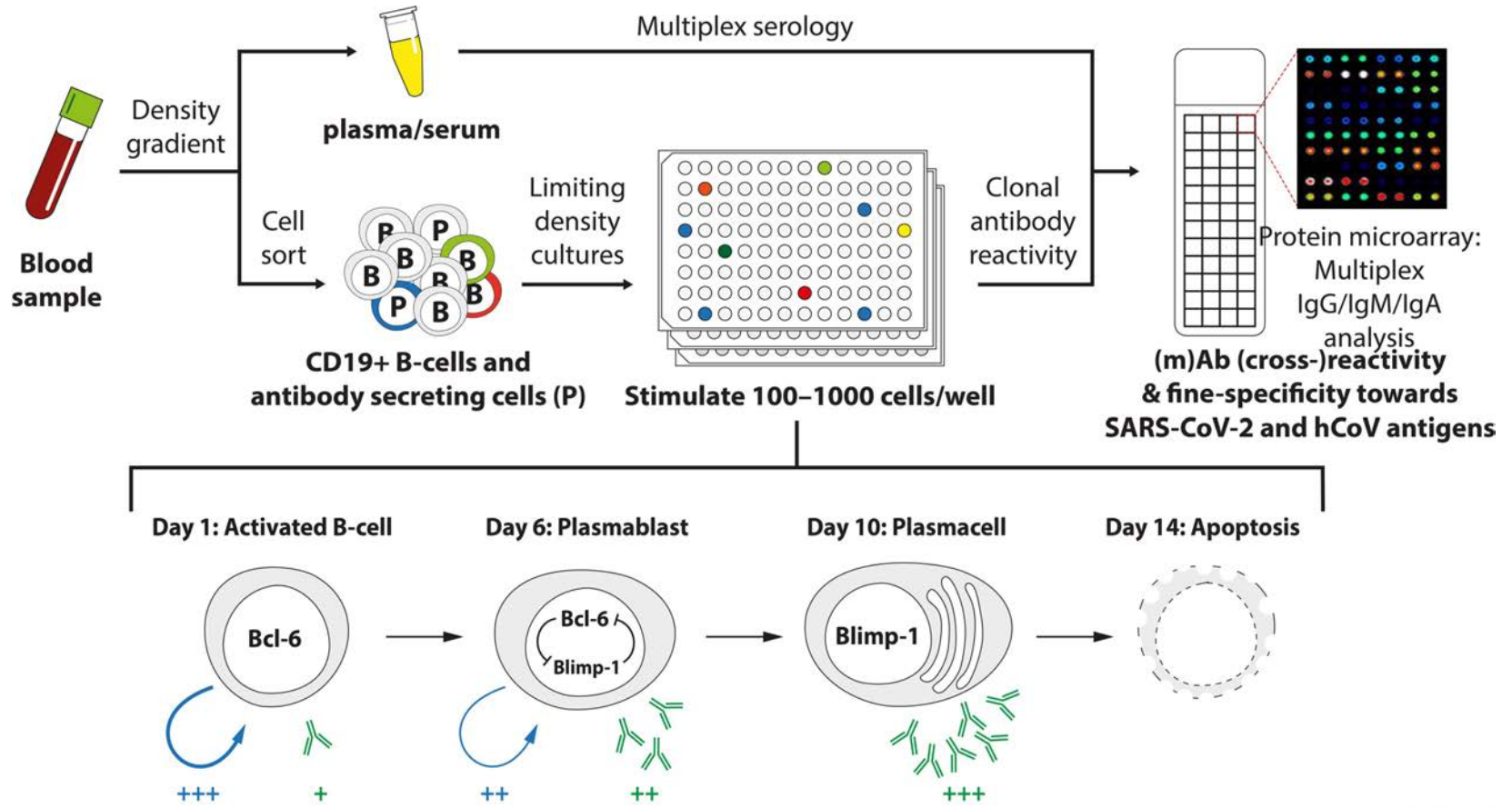


SARS-CoV-2 RT-PCR positive
ARDS, admitted at ICU





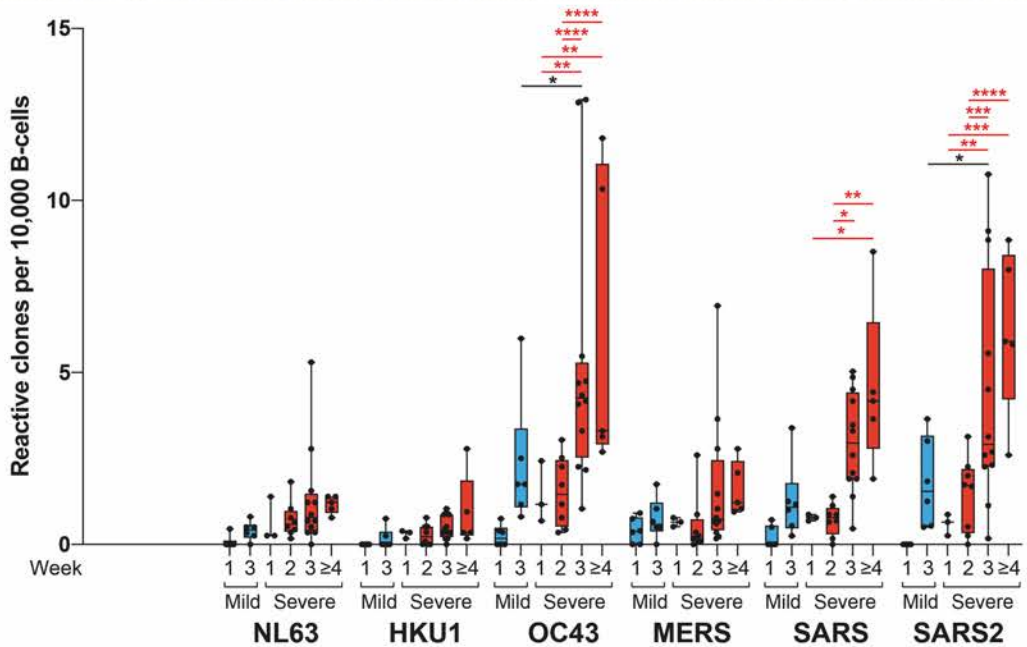
In-depth analysis of IgG clones: B-cell profiling



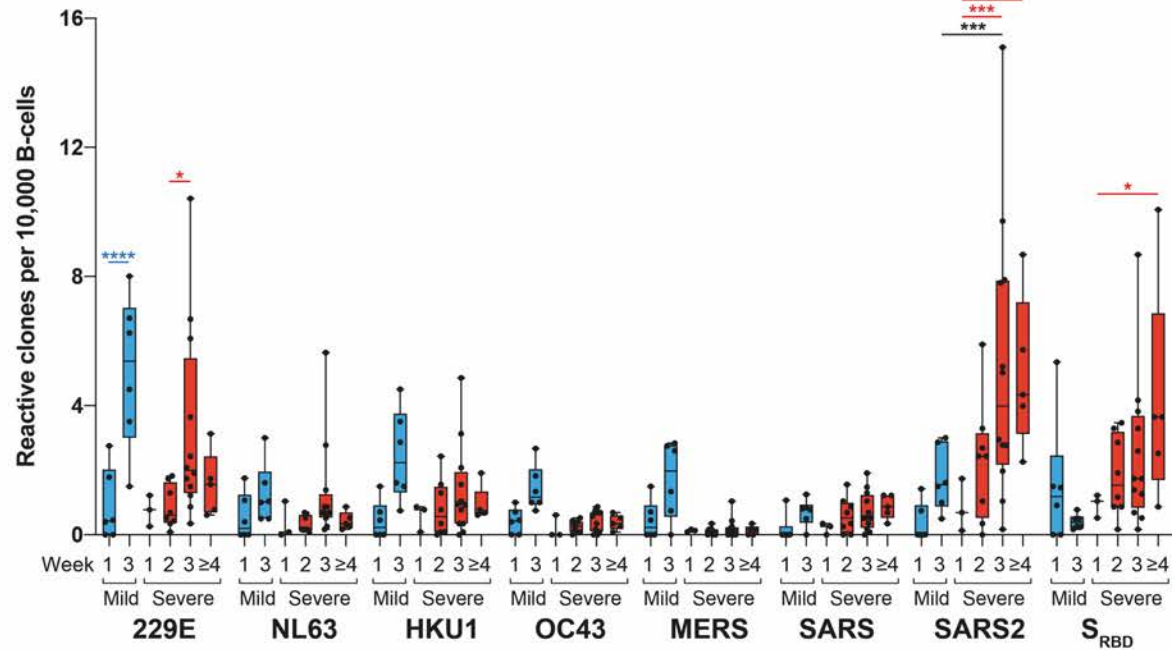
B-cell clone counts

- Normalized B-cell clone count shows similar trends to serum IgG titers

S_{ECTO}



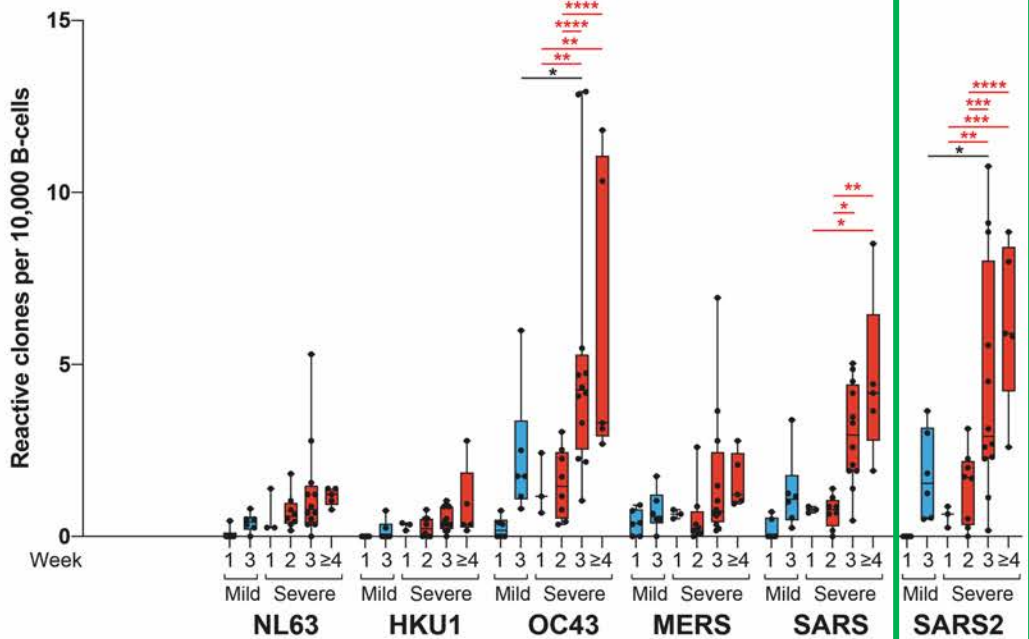
S_1



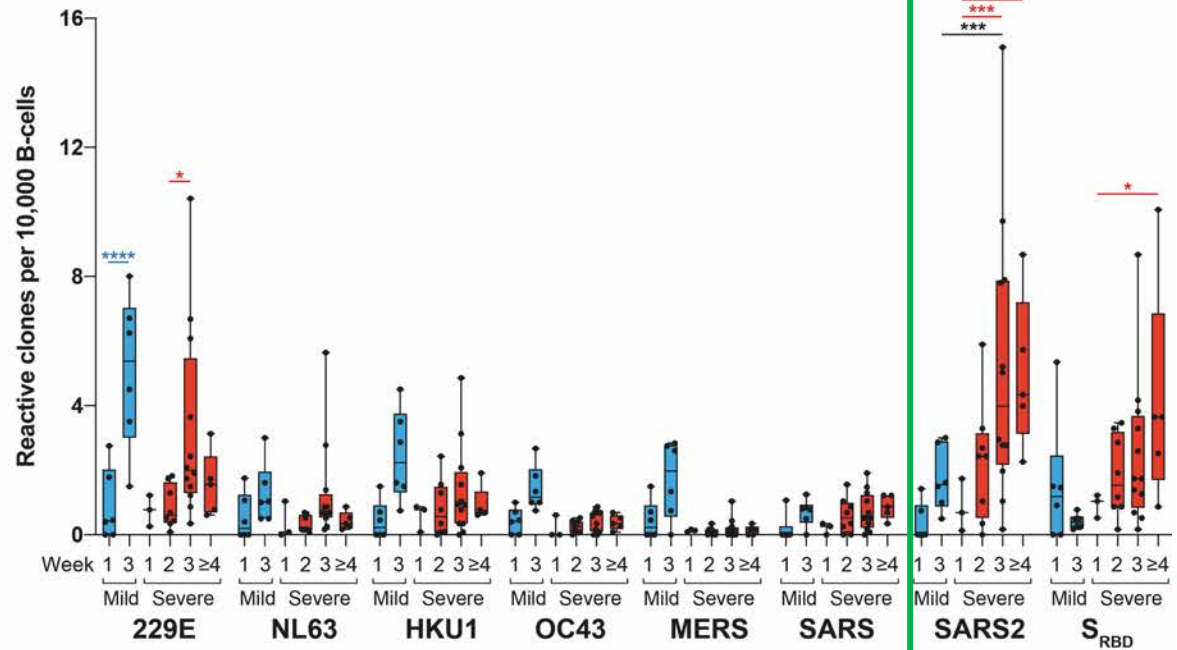
B-cell clone counts

- Normalized B-cell clone count shows similar trends to serum IgG titers
- Stronger SARS-CoV-2 B-cell response in severe COVID-19

S_{ECTO}



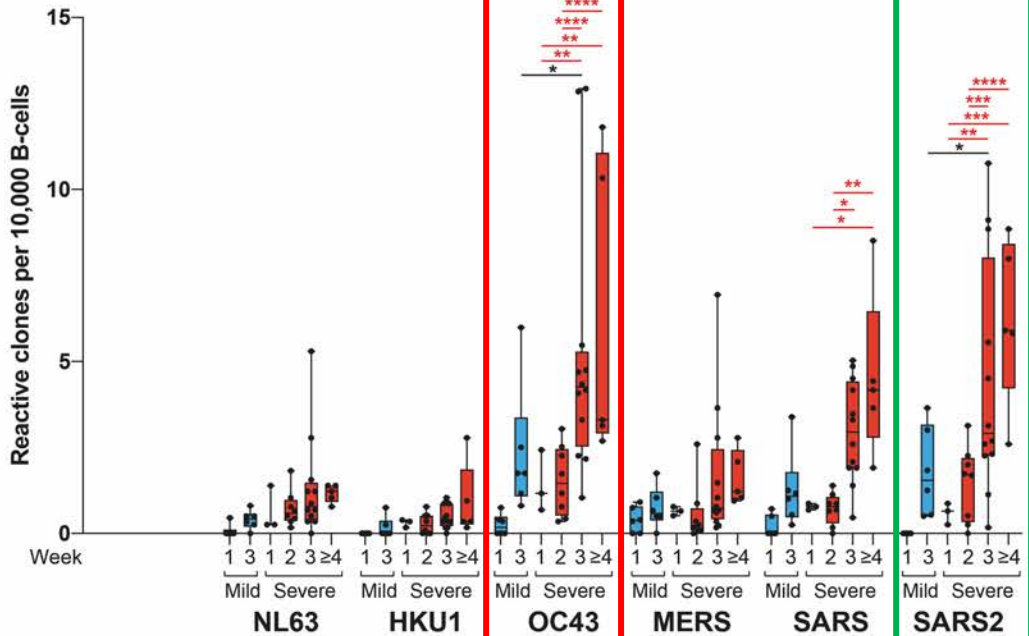
S_1



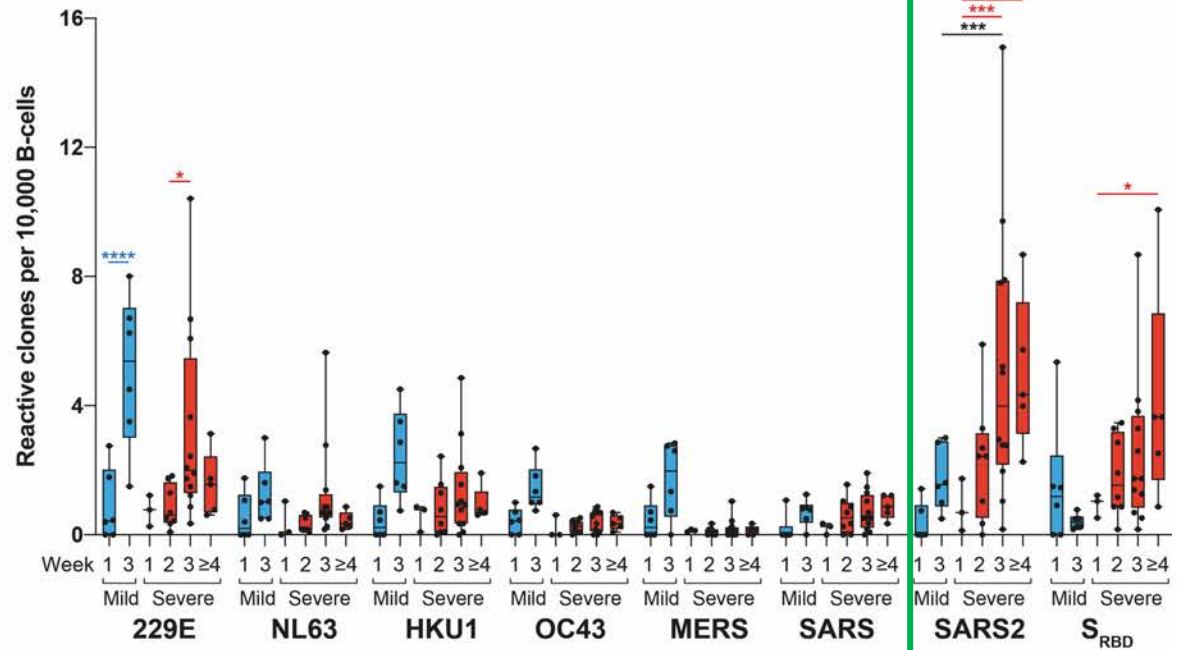
B-cell clone counts

- Normalized B-cell clone count shows similar trends to serum IgG titers
- Stronger SARS-CoV-2 B-cell response in severe COVID-19
- Strong increase in OC43- S_{ECTO} B-cells in severe COVID-19

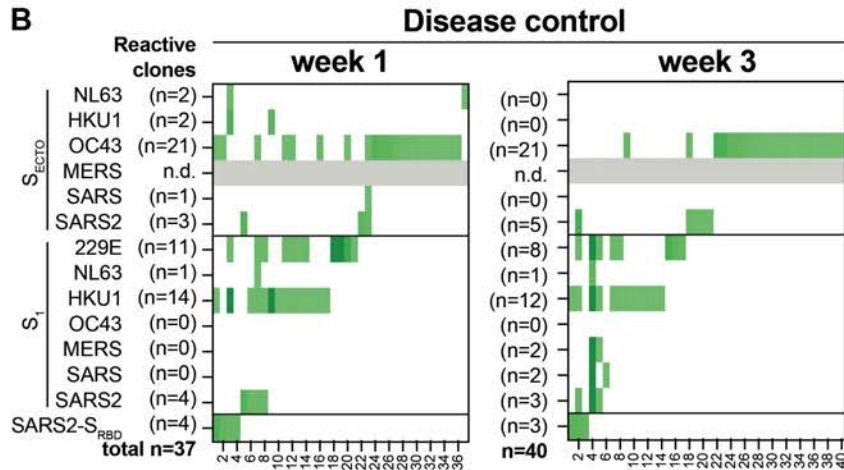
S_{ECTO}



S_1

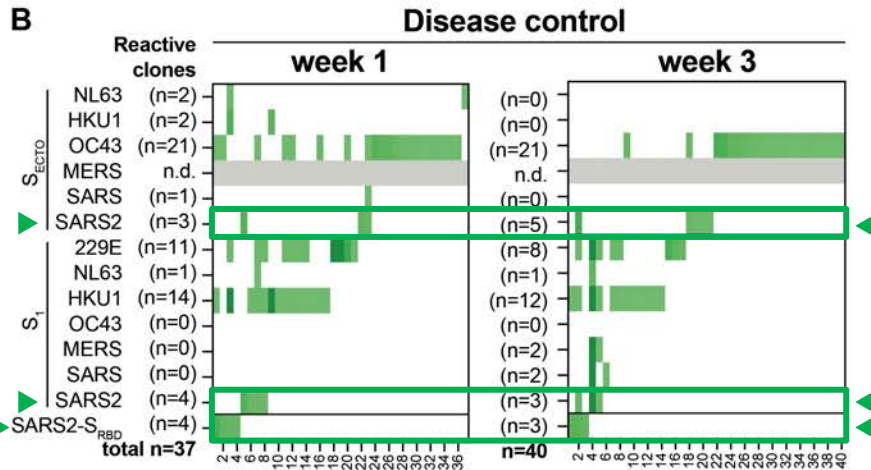


S-reactive IgG B-cell clones in disease control



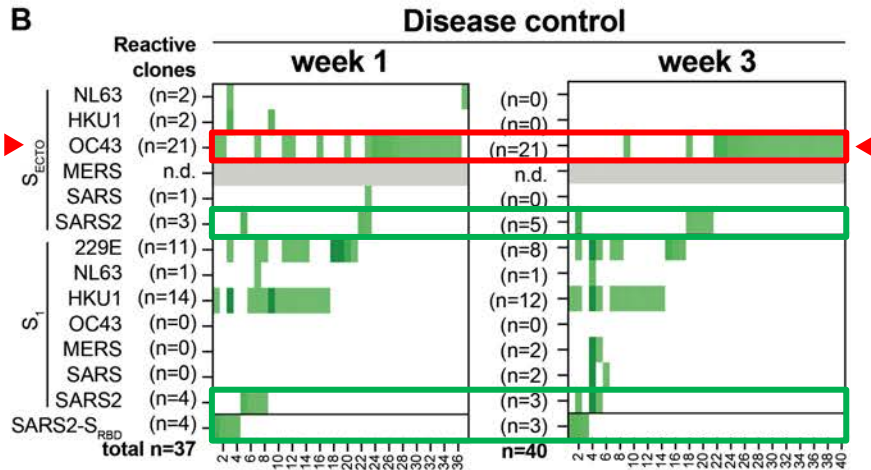
- Pattern is stable over time

S-reactive IgG B-cell clones in disease control



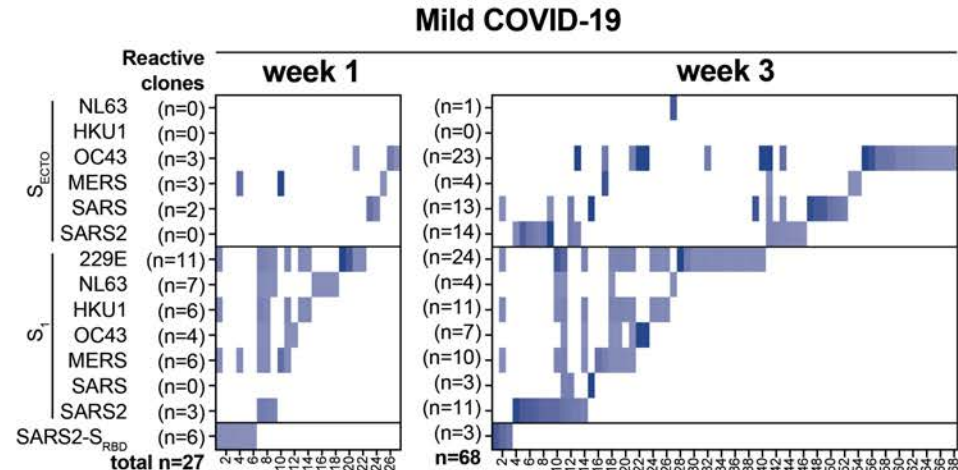
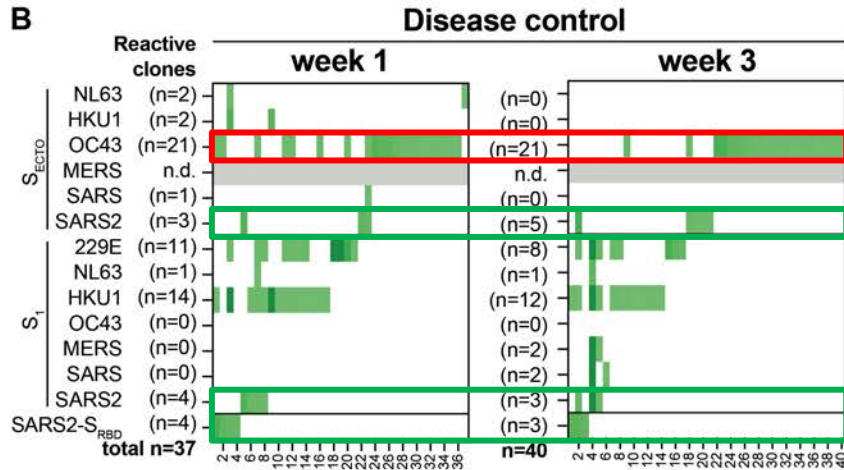
- Pattern is stable over time
- Some cross-reactive SARS-CoV-2 clones detected

S-reactive IgG B-cell clones in disease control



- Pattern is stable over time
- Some cross-reactive SARS-CoV-2 clones detected
- OC43-S_{ECTO} is immunodominant

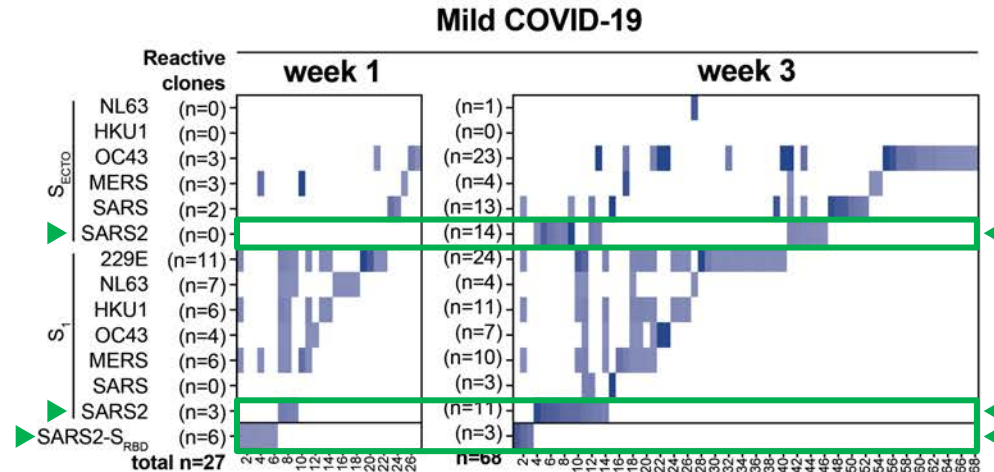
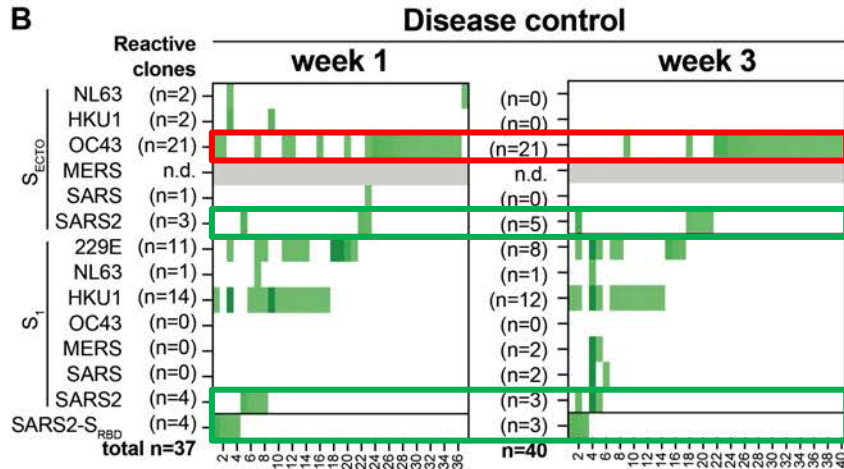
S-reactive IgG B-cell clones in mild COVID-19 case



- Pattern is stable over time
- Some cross-reactive SARS2 clones detected
- OC43- S_{ECTO} is immunodominant

- Most clones remain stable over time

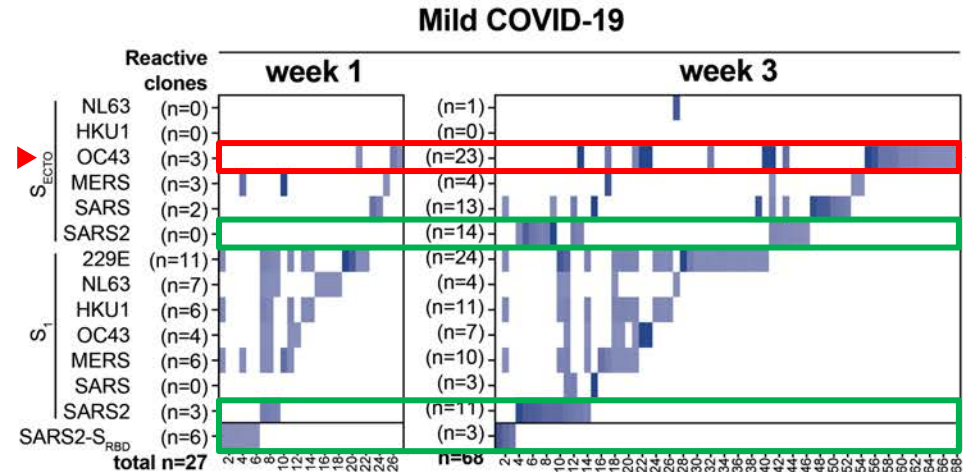
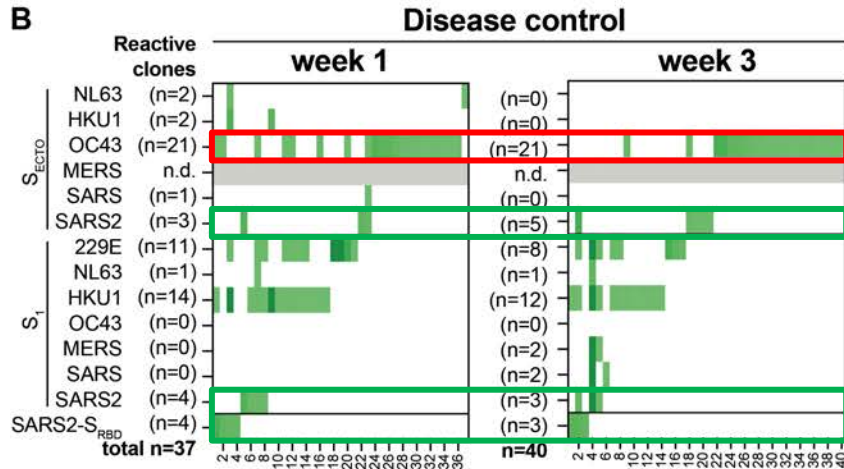
S-reactive IgG B-cell clones in mild COVID-19 case



- Pattern is stable over time
- Some cross-reactive SARS2 clones detected
- OC43- S_{ECTO} is immunodominant

- Most clones remain stable over time
- Increasing type-specific SARS-CoV-2 response

S-reactive IgG B-cell clones in mild COVID-19 case

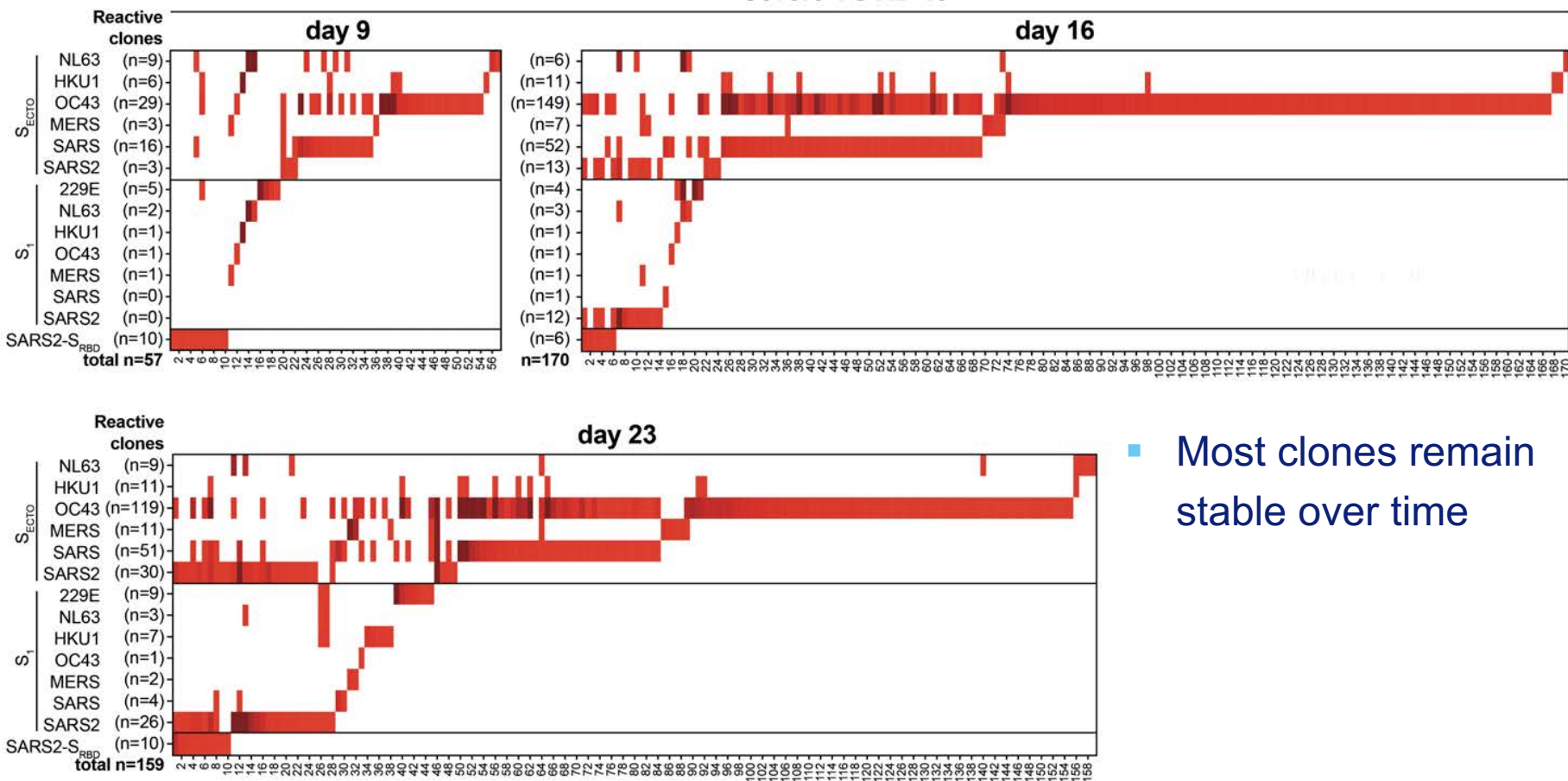


- Pattern is stable over time
- Some cross-reactive SARS2 clones detected
- OC43-S_{ECTO} is immunodominant

- Most clones remain stable over time
- Increasing type-specific SARS-CoV-2 response
- Slight increase in OC43-S_{ECTO} clones

S-reactive IgG B-cell clones in severe COVID-19 case

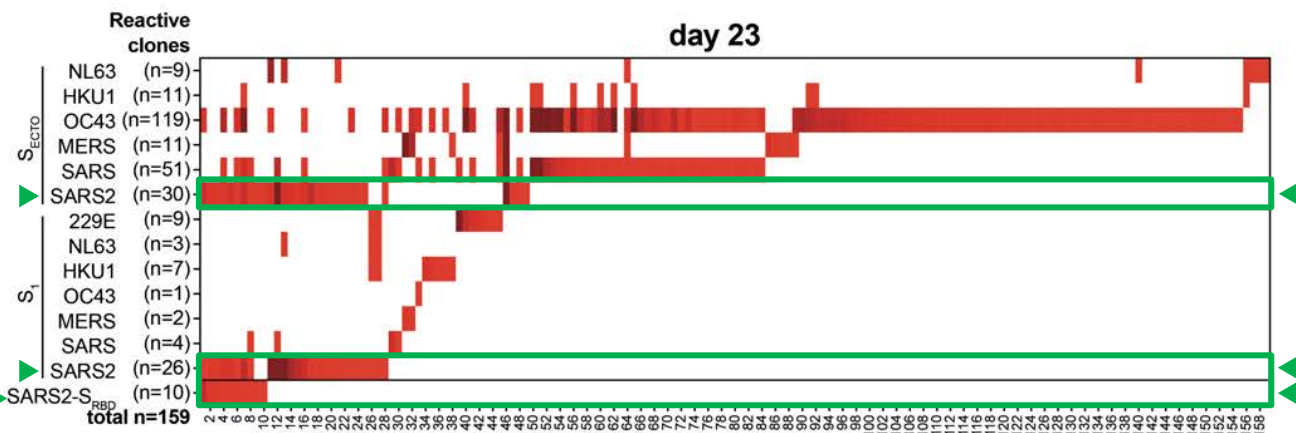
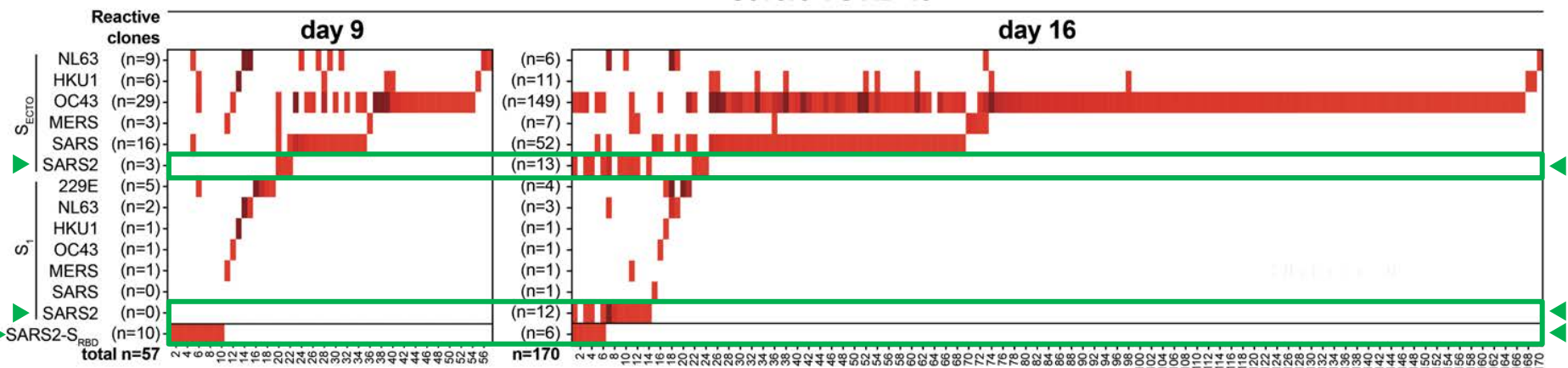
Severe COVID-19



- Most clones remain stable over time

S-reactive IgG B-cell clones in severe COVID-19 case

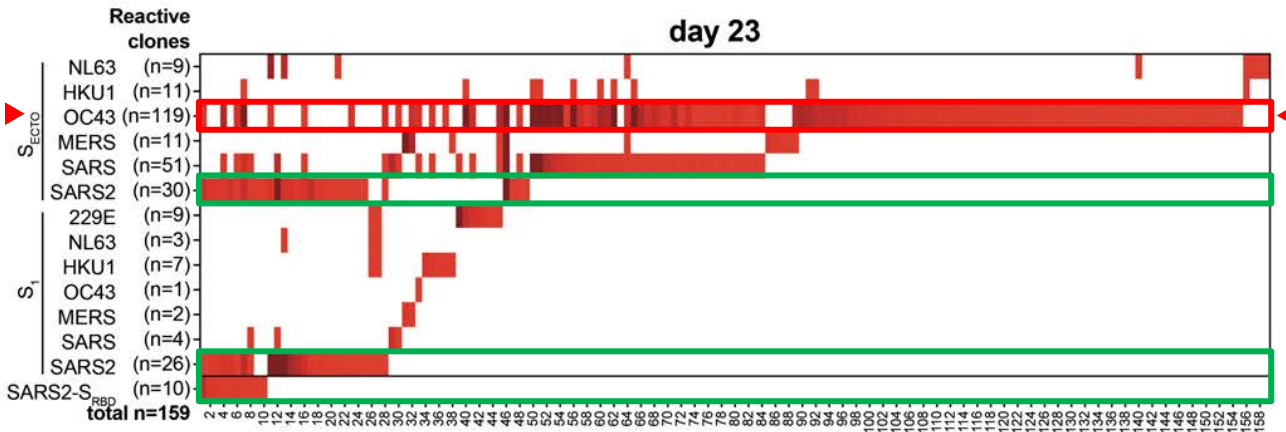
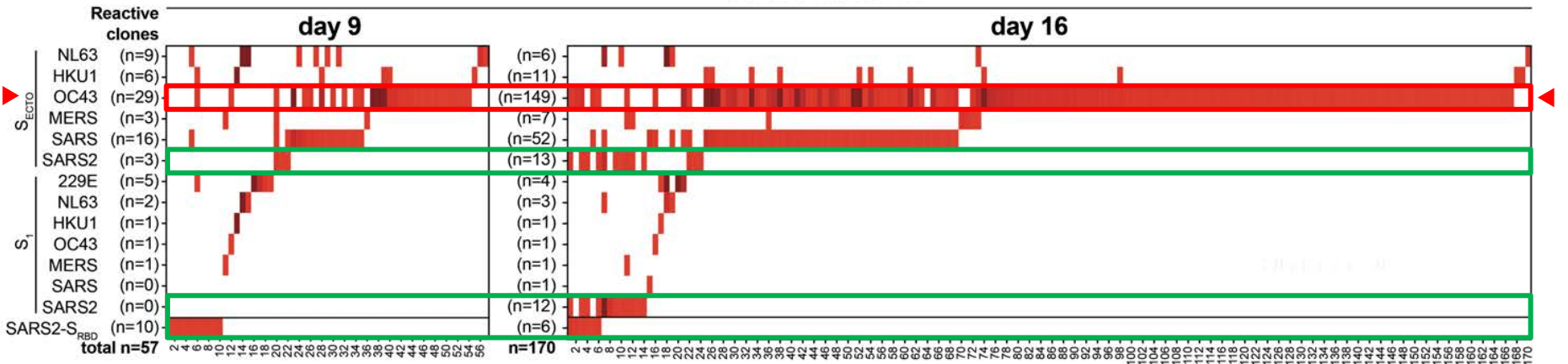
Severe COVID-19



- Most clones remain stable over time
- Emerging SARS-CoV-2 IgG mostly type specific

S-reactive IgG B-cell clones in severe COVID-19 case

Severe COVID-19

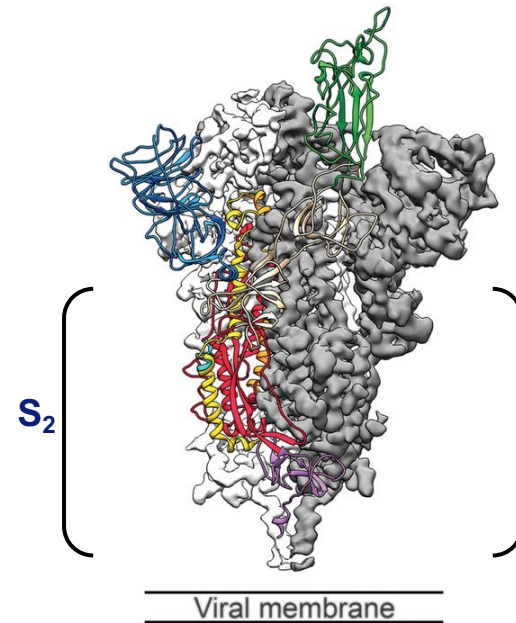
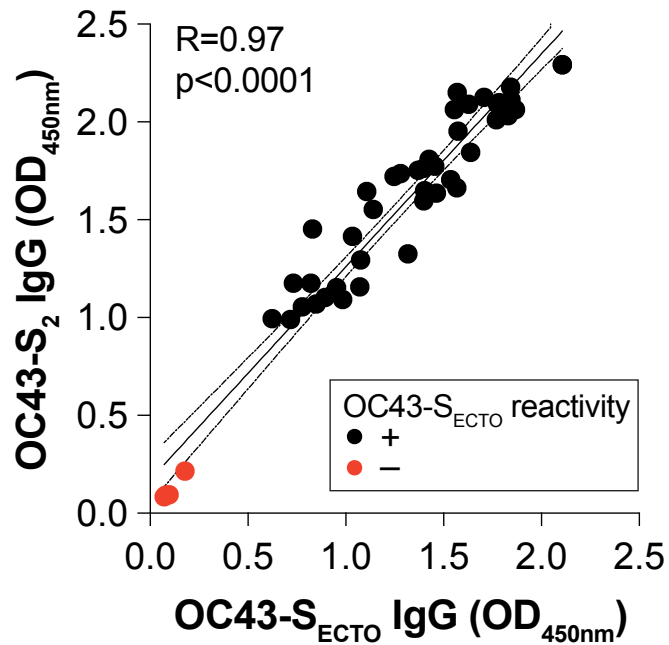


- Most clones remain stable over time
- Emerging SARS-CoV-2 IgG mostly type specific
- Dominant boost of OC43-S_{ECTO} clones with little S₁ or SARS-CoV-2 cross-reactivity

Boosted OC43-S_{ECTO}-specific IgG clones recognize S₂



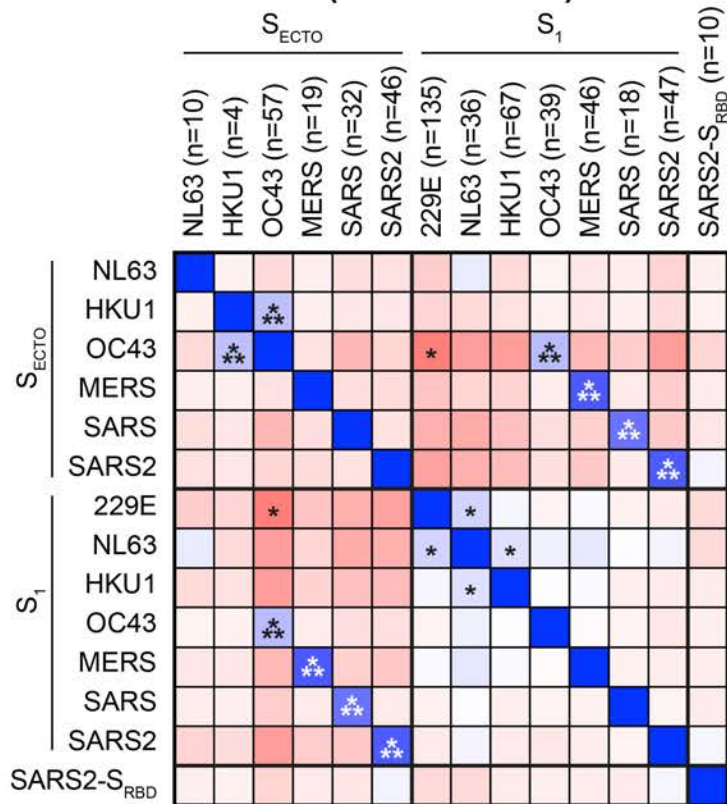
OC43-Secto reactive clones



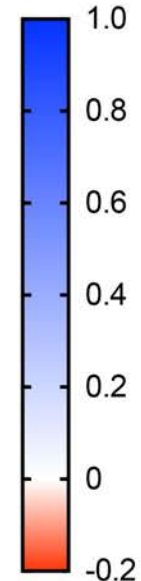
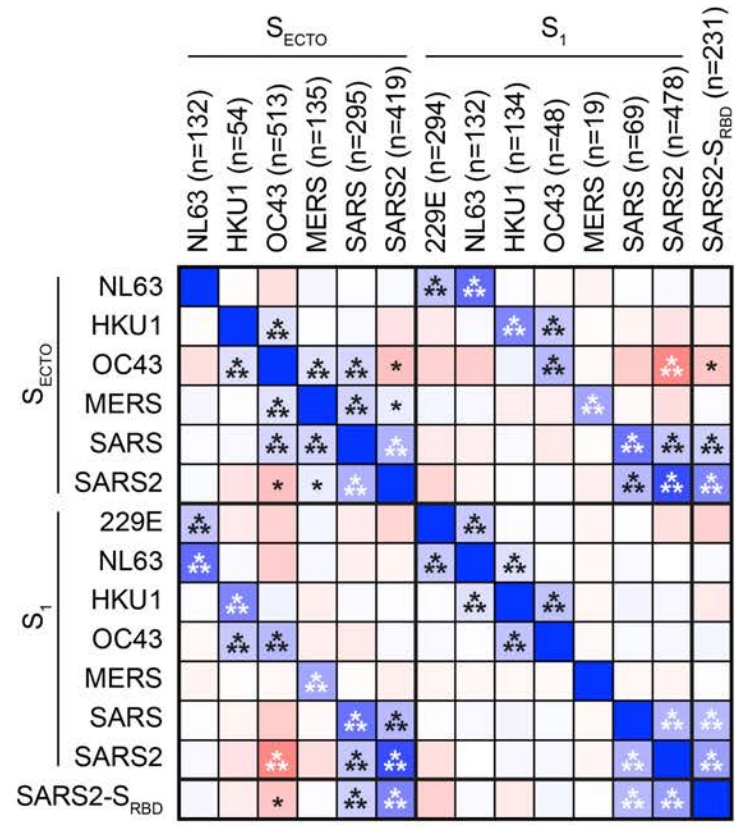
Wrapp et al., Science 2020

Correlation of clonal IgG responses

**Mild week 3
(n=283 clones)**

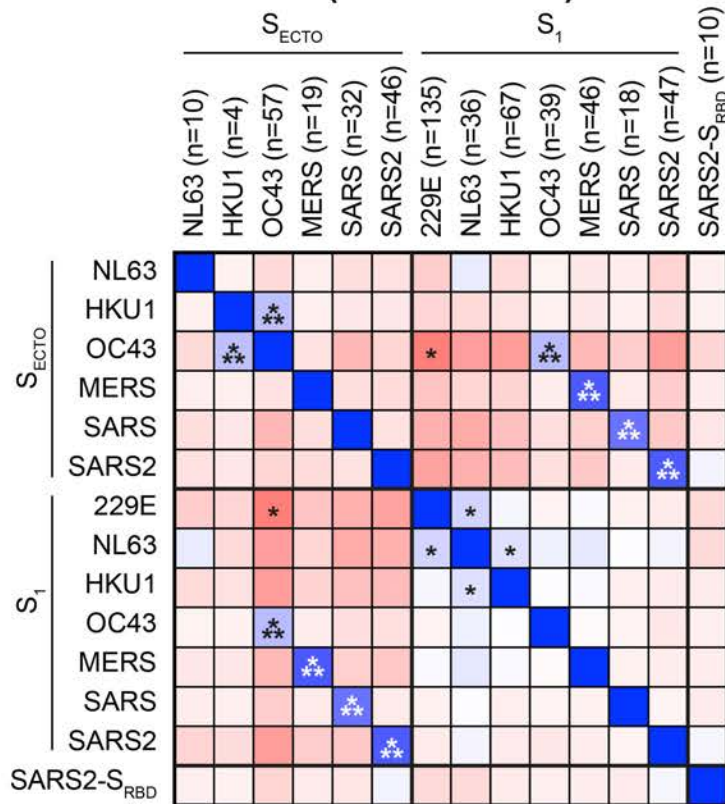


**Severe week 3
(n=1375 clones)**

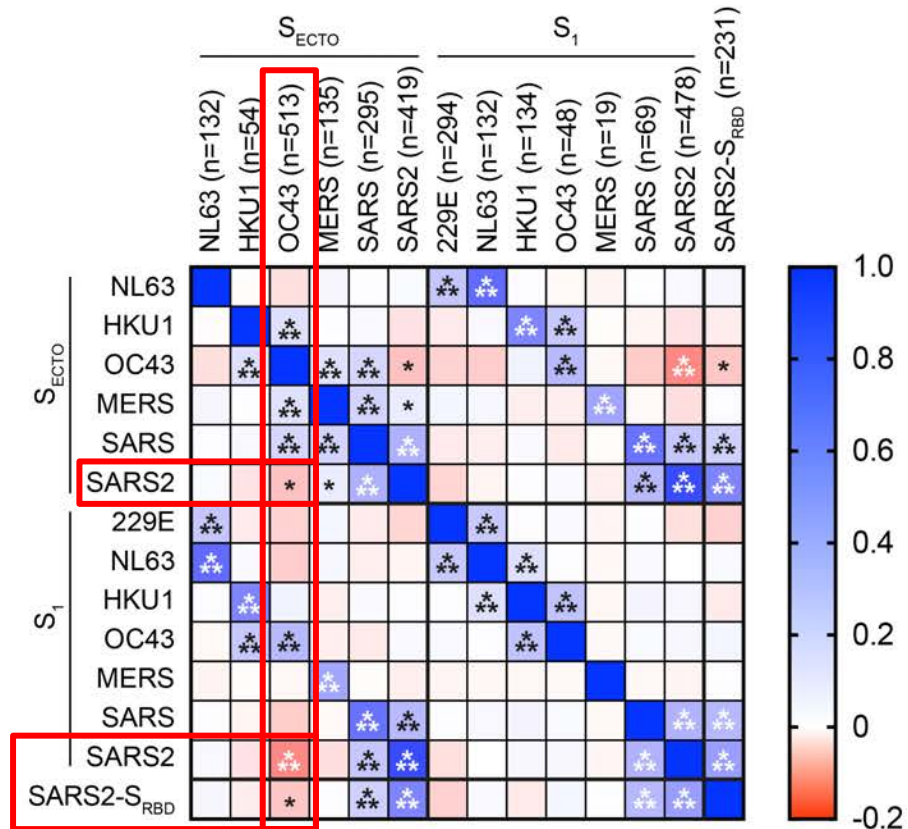


Correlation of clonal IgG responses

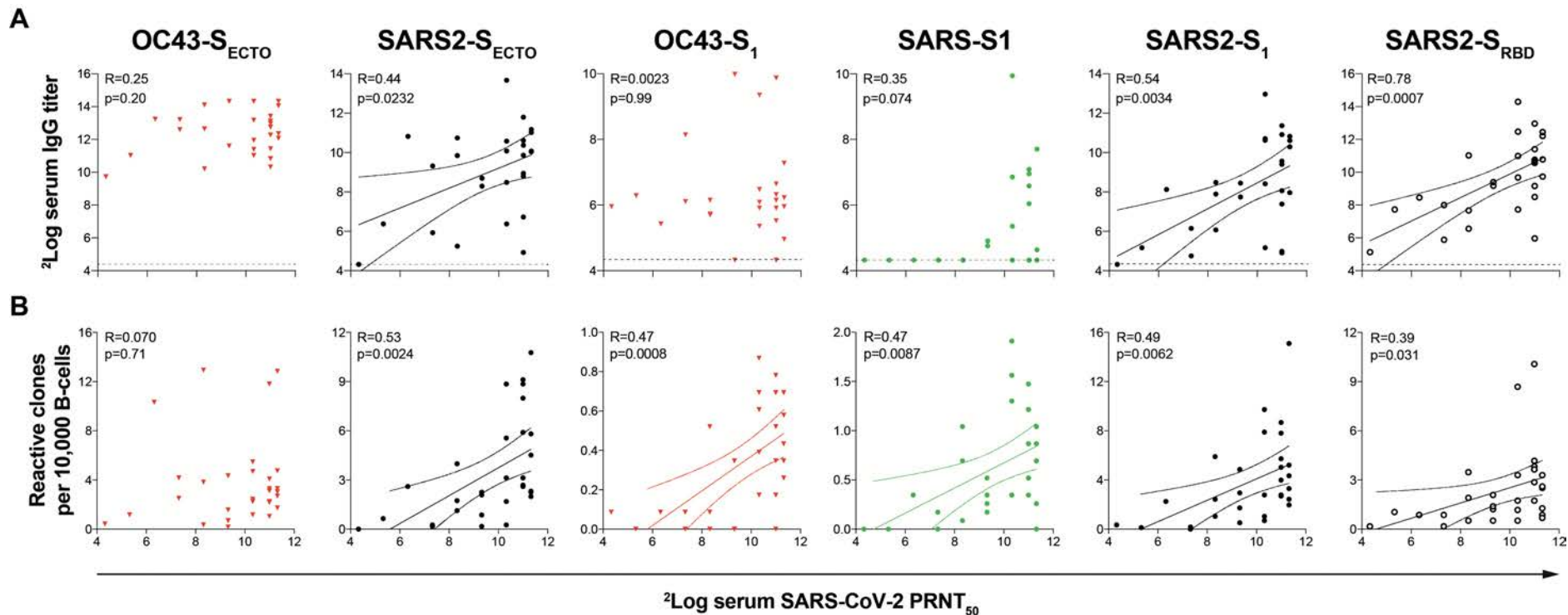
**Mild week 3
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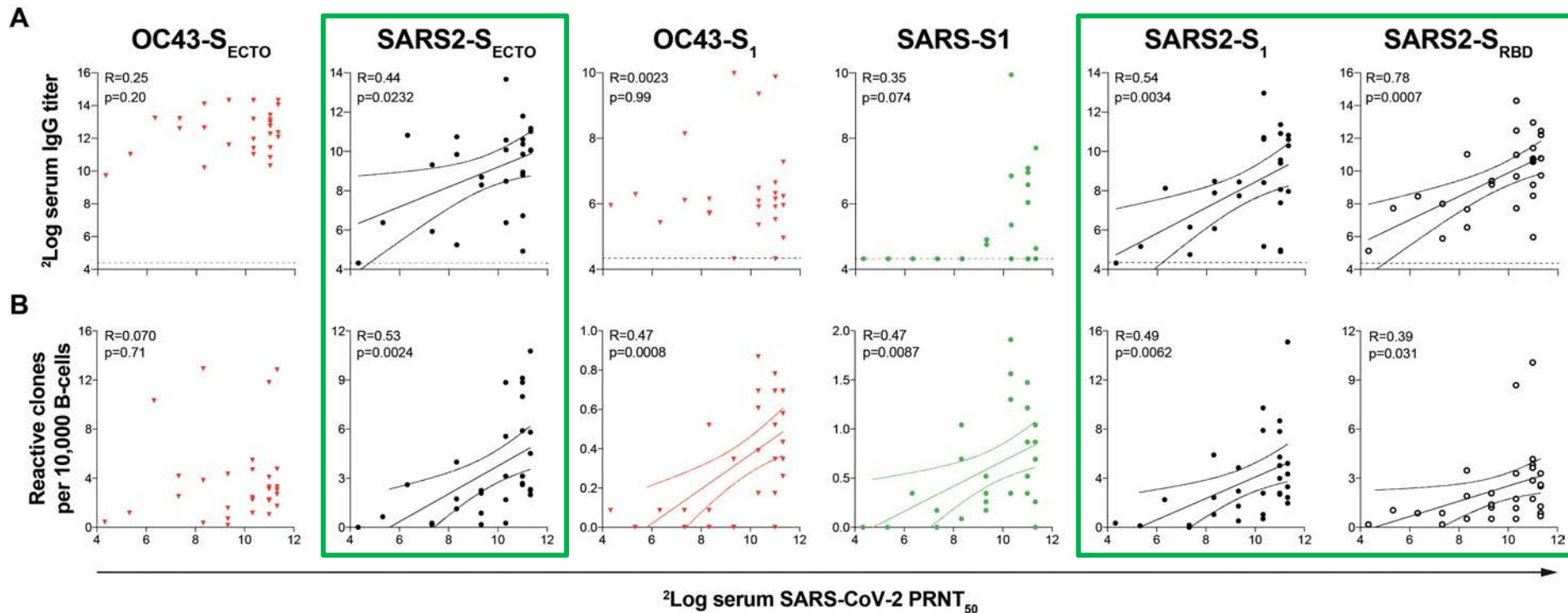
**Severe week 3
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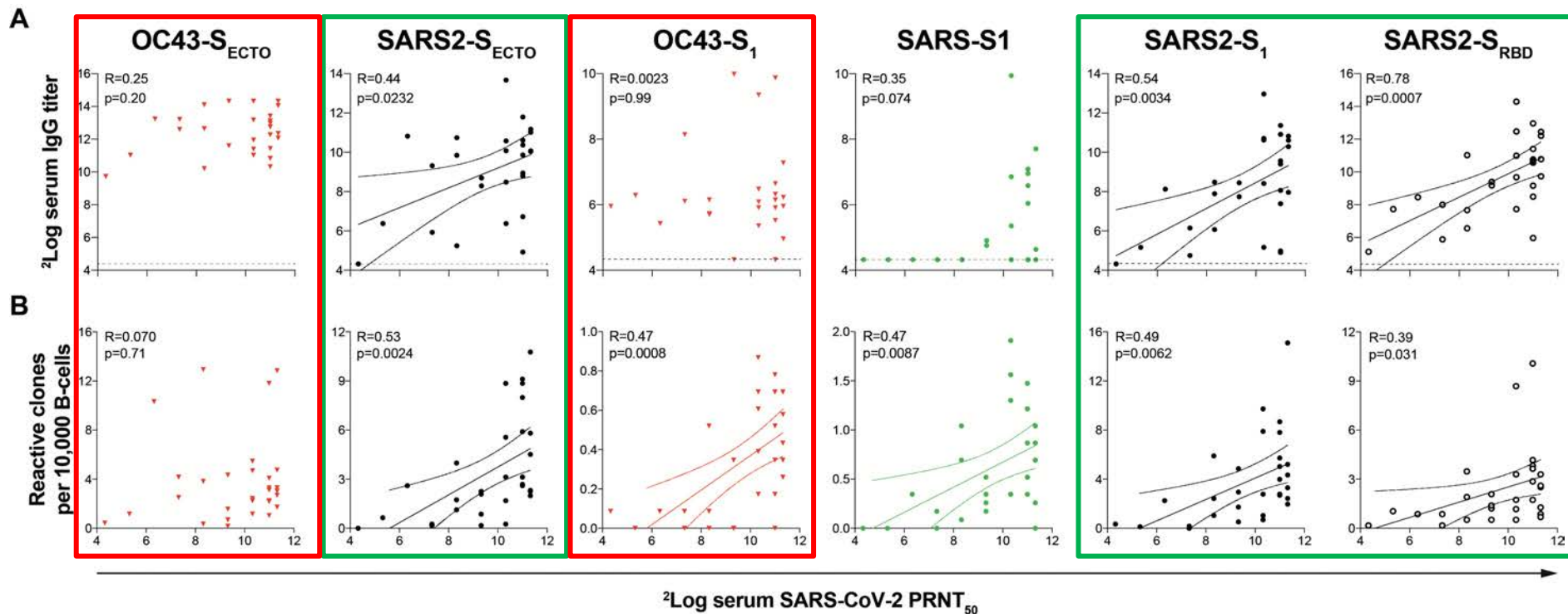
Correlation of serum IgG & B-cell clone counts with SARS-CoV-2 virus neutralization titers



SARS-CoV-2-specific IgG & B-cells correlate with serum SARS-CoV-2 neutralization



OC43-S_{ECTO}-specific IgG & B-cells do not correlate with serum SARS-CoV-2 neutralization





Conclusions

- COVID-19 patients mount a mostly type-specific SARS-CoV-2 IgG response: Severe > Mild COVID-19
 - Immunodominant boost of OC43-S₂ IgG in patients with severe COVID-19
 - Cross-reactivity of OC43-S₂ IgG with SARS-CoV-2 is limited
 - No evidence for contribution of OC43-S₂ IgG to viral clearance
-
- Immunodominant boost of pre-existing, poorly protective IgG in patients with severe COVID-19
 - Original antigenic sin in severe COVID-19



Conclusions B-cell profiling

Multiplex serology:

- Generated antibody landscapes towards array antigenically related viruses
- Allows analysis of potential immune interactions

B-cell profiling:

- Unbiased and broadly applicable tool for host exposure assessment
- Clonal screening of mAbs that are representative of immunological breadth
- Detailed cross-reactivity patterns of antibody clones
- Identifying type-specific memory clones aids in defining infection history

Acknowledgements



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