Viral replication kinetics and antibody responses

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Viral dynamics and infectiousness of SARS-CoV-2

Peiris et al., Lancet 2003

"- - pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza"

"- - require strategies different from those required for the control of SARS-CoV. “

Zou et al NEJM Feb 18 2020

SARS

COVID -19; Flu
Infectiousness profile of SARS-CoV-2

Estimated that about 44% of infectiousness occurred in pre-symptomatic stage

He et al Nature Medicine 2020
Duration of SARS-CoV-2 RNA detection

**Factors affecting duration of RNA detection:**

- **Type of specimen:** sputum > NPS; Peak Temperature; hydrocortisone Rx


- **Asymptomatic vs. matched mild cases:** 19 (IQR 15-26) days vs. 14 (IQR 15-26) days (p=0.03)


Relevant to differentiating persistence from “re-infection” - CDC 3 months


Median ranges 14 – 24.5 days
Maximum ranges from 25 to 47 days
SARS-CoV-2 viral load in different clinical specimens of severe (n=12) and mild (n=11) cases over time

Median age 56 yrs (range 24-82 yrs)
Severe cases: viral RNA up to 30-40 days; Mild cases: viral RNA ≤15 days
Duration of infectiousness? (Mild COVID-19)

Viral RNA load, virus culture vs. days illness.

Culture positive  X  Culture negative

\[ \log_{10} N \text{ gene copies / mL} \]

Day Illness

Virus culture vs. subgenomic RNA vs. viral RNA load

sgRNA correlates with culture

Perera et al Emerging Infectious Diseases 2020
Severe cases / immunocompromised shed infectious virus for longer.
Even in severe cases, 88% culture negative by day 10, 95% negative by day 15
Van Kampen et al medRxiv
Infectiousness, test “sensitivity” and testing strategy

Modified from Mina et al NEJM Oct 2020
**Serology**

SARS-CoV-2 spike protein

![SARS-CoV-2 spike protein diagram](Image)

<table>
<thead>
<tr>
<th>Genus</th>
<th>Virus</th>
<th>Spike protein</th>
<th>N</th>
<th>RBD</th>
<th>NTD</th>
<th>S2</th>
<th>Whole S</th>
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<td>Beta CoV</td>
<td>SARS-CoV</td>
<td>73%</td>
<td>90%</td>
<td>53%</td>
<td>90%</td>
<td>77%</td>
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<td>BatCoV RaTG13</td>
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<td>MERS-CoV</td>
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</table>

*NS: No statistically significant sequence alignment can be observed


Figure independently created by GSK based on concepts from the references. Data first published in Amanat et al. Nat Med 2020. DOI: 10.1038/s41591-020-0913-5
• Cohort of 24 patients followed up with multiple serum samples
• First 4 days → no detectable antibody
• >28 days 100% have antibody
• 200 blood donors: No cross reactions
• RBD IgG ELISA ideal screening assay for large scale population sero-epi

Perera et al Eurosurveillance 2020
Duration of 50% plaque reduction neutralization test (PRNT) antibodies in COVID-19 convalescence (192 patients; 293 sera)

- Asymptomatic – 31; mild – 151; severe – 13
- Day >90 after onset (n=61); 98% remains PRNT50 pos
- Severe patients: Higher peak, peaks later
- Estimates 372, 416 and 133 days to fall to undetectable in severe, mild and asymptomatic infections
- Age >60 trend to higher antibody titres, adjusted for severity, corticosteroid use
Surrogate virus neutralization test (sVNT)

- With PRNT90 as gold standard, sVNT has sensitivity of 98.9%, specificity 98.7%, PPV 97.8%, NPV 99.4%
- Overall concordance 98.4%
- Species independent; validated on human, dog, cat, hamster sera.

Human sera: 205 COVID-19 and 196 controls

- COVID-19 ≤10 days after onset
- COVID-19 >10 days after onset

Tan et al Nature Biotechnol 2020

Peiris - unpublished
Landscape of antibody responses to 15 SARS-CoV-2 proteins using luciferase immuno-precipitation

- Immuno-dominance N>ORF8>ORF3b
- ORF8: Not found in seasonal HCoV

Hachem et al Nature Immunol 2020
Virus epitope profiling of COVID-19

Peptide scan of SARS-CoV-2 proteome
Immuno-dominance: N>S>>ORF1>>>>others
ORF1 is cross reactive with seasonal CoVs, non-discriminative

COVID-19 sera: Increased peptide hits to seasonal CoVs. Anamnestic booster responses to prior seasonal CoV memory

Shrock et al Science Sept 2020
Cross-reactive antibody B cell responses to SARS-CoV-2 spike

- Weak evidence of pre-existing SARS-CoV-2 cross reactive antibody in pre-pandemic sera
- Stronger evidence of pre-existing cross-reactive memory B cells activated following SARS-CoV-2 infection
- Mabs with varying degree of cross reactivity with beta-CoV. These have higher binding constants (KDs) to HKU1 rather than SARS-CoV-2 \( \rightarrow \) suggests initially elicited by HKU1

Memory B cells detected in COVID-19 donors

HCoV spike reactivity of MAbs from COVID-19 donors in cell-ELISA

Song et al bioRExiv Sept 2020
Summary

• Viral load kinetics of SARS-CoV-2 more like flu than SARS-CoV-1 → explains early transmission from pre/asymptomatic infections → challenge for control
• Viral shedding may be prolonged but infectiousness does not correlate with positive RT-PCR. In mild infections, virus can be isolated in culture in first 8-9 days after onset of illness and correlates with viral load $>10^6$/mL and sub-genomic RNA rather than RNA detection per-se.
• Robust neutralizing antibody responses which are long lasted, likely similar to SARS-CoV-2. Older people make at least as good antibody responses as younger adults.
• SARS-CoV-2 infection boosts some memory cross-reactive B-cell epitopes acquired from prior infections with seasonal HCoV.
Acknowledgements

• Leo LM Poon, Sophie Valkenburg, Daniel Chu, Mahen Perera, Niloufar Kavian, Asmaa Hachem, Eric Lau, Ben Cowling, Kathy Leung, Joe Wu, School of Public Health / Pasteur Research Pole, University of Hong Kong
• Clinical collaboration: Dr Owen Tsang & Dr Mike Kwan Princess Margaret Hospital, Prof David Hui, Prince of Wales Hospital, Dr Susan Chiu, Queen Mary Hospital, Dr Wai-Hung Chan, Queen Elizabeth Hospital, Hong Kong
• Prof Jincun Zhao, State Key Laboratory for Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangdong
• Dr Jie Wu, Guangdong Provincial Centre for Disease Control and Prevention
• Research Funding: CEIRS Program, US NIAID Contract (contract no. HHSN272201400006C); Health and Medical Research Fund - Commissioned Research on the Novel Coronavirus Disease (COVID-19) (reference nos. COVID190126)