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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* 2020; published online Oct 27. https://doi.org/10.1016/S1473-3099(20)30773-8.

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Proposed severity grading scores for SARS-CoV-2 disease

- WHO Severity Grading(1)
- US FDA criteria(2)
- NEWS2 Score(3)
- Seven-point ordinal scale(4)
- China CDC Severity Score(5)
- NICE COVID-19 Rapid Guideline(6)
- Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment(7)
- APACHE II Score, SOFA Score, CURB65(8)

Key clinical outcomes for determining vaccine efficacy against COVID-19 disease(9)

- Rates of virologically confirmed COVID-19 disease meeting pre-specified symptoms and signs
- Rates and duration of hospitalisation
- Rates and duration of time off work
- Incidence of severe disease

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- Numbers of patients requiring supplemental oxygenation
- Numbers of patients requiring invasive ventilatory support
- Incidence of multi-organ dysfunction syndrome
- Mortality

Obstacles to the use of SARS-CoV-2 CHIM studies to assess vaccine efficacy(10)

- Lack of challenge agent manufactured to Good Manufacturing Practices.
- Appropriate infecting dose is unknown.
- Potential for severe disease (including death), even in young individuals, with no reliable 'rescue treatment' yet identified.
- High transmissibility of SARS-CoV-2 and risk of onward community transmission of challenge strain.
- Limited generalisability of findings to high-risk populations (e.g. elderly, immunocompromised).
- Long term sequelae of disease in survivors is unknown.

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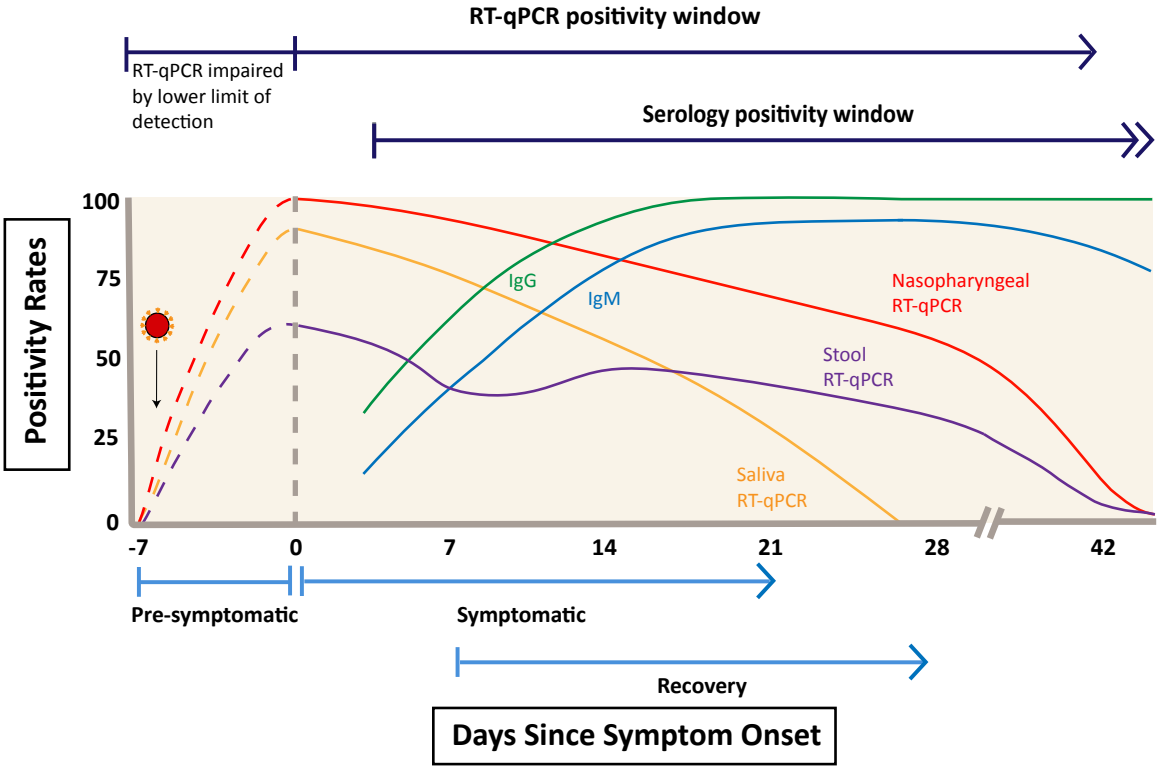

Figure: Relationship between SARS-CoV-2 exposure, symptom onset and diagnostic windows for RT-qPCR and serology.

RT-qPCR positivity curves based on data presented by Zheng et al.(11) and To et al.(12) Serology data for individuals with acquired infection adapted from Long et al.(13) and Seow et al.(14) Dashed lines represent estimates of rising qRT-PCR positivity rates in the pre-symptomatic period of infected individuals.

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