

# A Hierarchical Framework for Assessing Transmission Causality of Respiratory Viruses: Focus on SARS-CoV-2

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## BACKGROUND

- Understanding the modes of transmission (MOT) and influencing circumstances of SARS-CoV-2 has been hampered by a lack of high-quality evidence (HQE).<sup>1-6</sup>
- The lack of HQE has highlighted the need for a contemporary conceptual framework to assess causality in the transmission of human respiratory viruses (HRVs), especially SARS-CoV-2.

## OBJECTIVE

- To review the history of causality assessment related to HRV transmission
- To systematically review studies which have assessed the MOT of SARS-CoV-2 in this context.

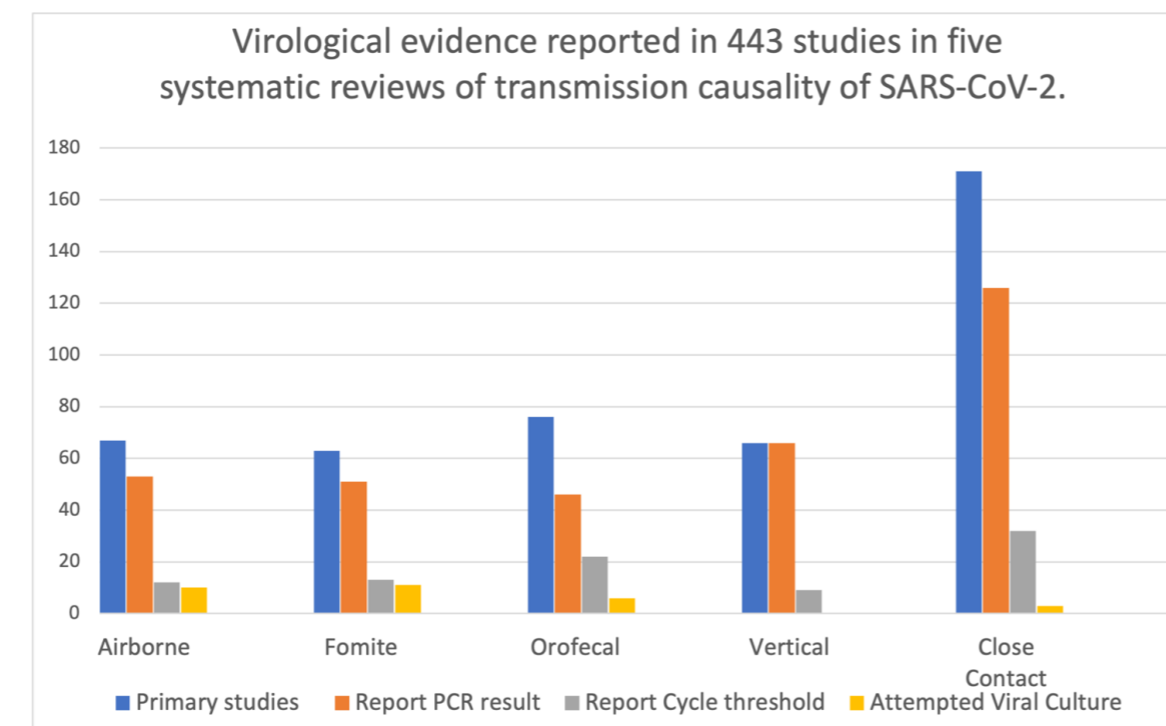
## METHODS

- We sought to review the history of causality assessments with a focus on HRVs and through a series of systematic searches of primary studies (03/2020-05/2022) to systematically review and synthesize them assessing transmission by mode, population, setting and isolation of replication- and infection-competent virus.
- A series of systematic reviews funded by the WHO on MOT of SARS-CoV-2 served as the background for this current study.
- Primary studies were evaluated for the rigour applied to transmission causality with a focus on laboratory confirmation..
- The results were assessed to see if any existing methods could be readily applied or whether a new framework should be established.

## RESULTS

- The historic searches identified the classic works of Koch's postulates, Rivers adaptations of Koch's postulates, Hubener's Bill of Rights, Evan's reformulation, Hill's criteria, the Gwaltney-Hendley viral postulates and the Fredricks- Relmans' genomic postulates.
- Of 534 primary studies identified to date from the SRs, 443 were suitable to assess for MOT.
- Only 17 (3.8%) attempted viral culture whereas 77% of the included studies reported qualitative PCR results (Figure 1).
- We found no standardised methods for extraction and primer sets for specific genes to determine the Ct/Cq using RT-PCR.
- Overall, the studies revealed significant methodological shortcomings and bias with a lack of standardization in the design, conduct, testing and reporting of SARS-CoV-2 transmission.
- The shortcomings limited the capacity to draw inferences, leading to data loss and heterogeneity of the results.
- However, despite differences in platforms and reagents, the likelihood of finding a positive viral culture for SARS-CoV-2 was very infrequent above a Ct/Cq >30.

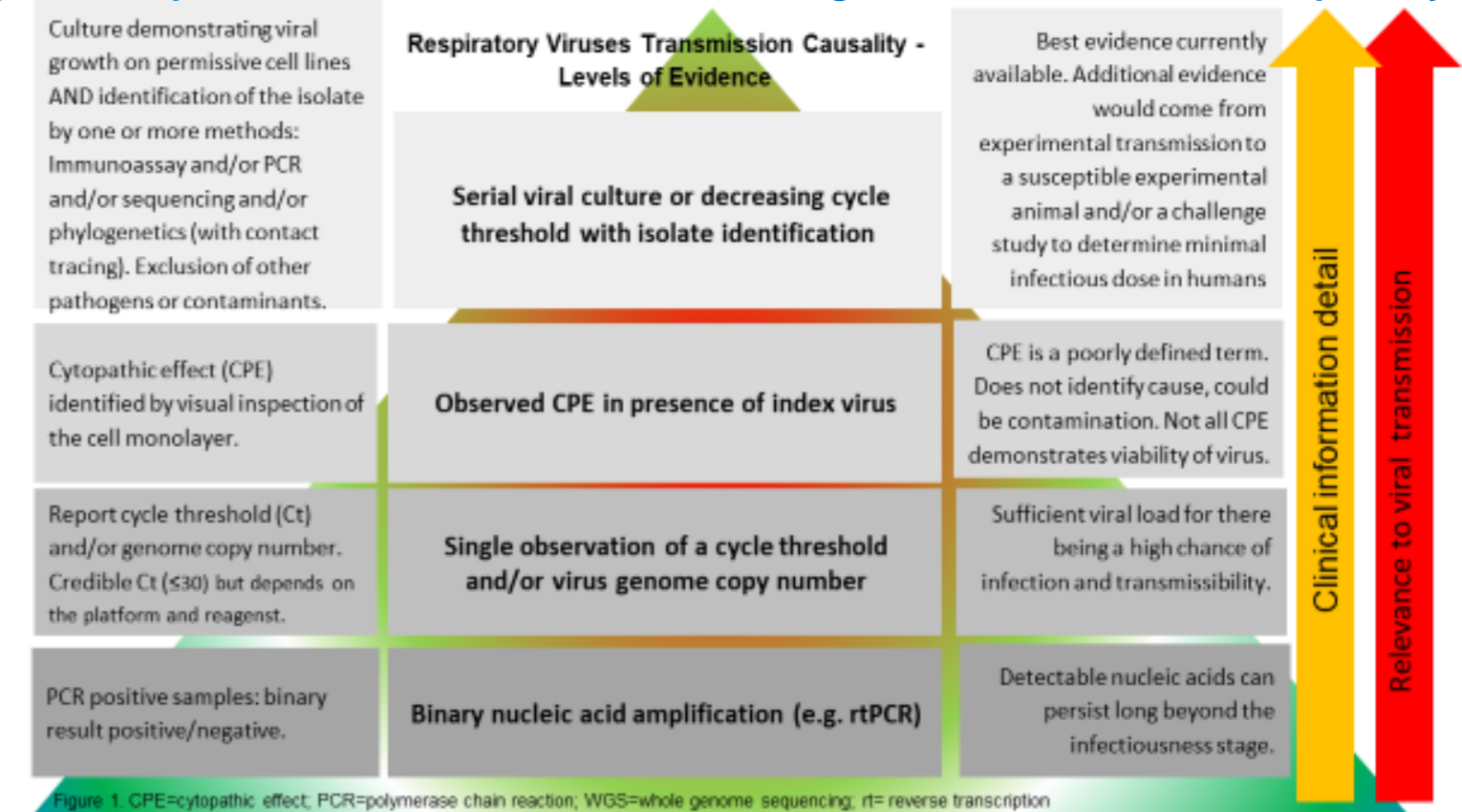
**Figure 1. Only 17 of 443 (3.8%) studies attempted viral culture whereas 342 (77.4%) of the included studies report qualitative PCR results only**



## CONCLUSION

- Our findings suggest high quality studies are required using robust causality assessment.
- These findings led to a hierarchy of evidence proposal to integrate clinical, epidemiologic, molecular and laboratory perspectives on transmission (Figure 2), incorporating the principles of evidence-based medicine.
- Evidence that follows Bradford Hill's principles for assessing causation: strength, temporality and experimentation (Gwaltney's fifth postulate) with independent replication and the hierarchy of transmission outcome events provides a coherent framework for assessing causation for the transmission of HRVs.
- if applied to future studies, it should narrow the uncertainty over the twin concepts of causality and transmission of HRVs.
- Application of the proposed framework to three systematic reviews have facilitated identification of better quality evidence and expedited synthesis.<sup>7-9</sup>

**Figure 2. Proposed levels of evidence in ascertaining transmission of human respiratory viruses**



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