Effective real-time transmission estimations incorporating population viral load distributions amid SARS-CoV-2 variants and pre-existing immunity

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Background

Tracking community transmission is critical in monitoring the epidemic dynamics but suffers delays due to the unavoidable right-censoring (i.e., incubation period and delay in case identification). Previous study established a novel temporal association between epidemic dynamics and population cycle threshold values (Ct values) from reverse transcription quantitative polymerase chain reaction (RT-qPCR). We have since developed a simplified method to incorporate the temporal population Ct distribution into real-time Rt estimates in the waves of ancestral strains without vaccines in Hong Kong. Therefore, the generalizability of the model to epidemics caused by subsequent SARS-CoV-2 variants and vaccinations remained under-investigated.

Objectives

This study aimed to examine the impact of the evolving SARS-CoV-2 variants and population immunity on the application of *Rt* estimation using population viral load distribution of laboratory-confirmed COVID-19 cases from July 2020 to January 2023 in Hong Kong.

Methods

- **Study settings:** we collected the first Ct values of local cases in Hong Kong, and the whole observed period was split into five sub-periods, i.e., 1 July to 31 August 2020 (wave 3) and 1 November 2020 to 31 March 2021 (wave 4), which were dominated by ancestral strains, 1 January 2022 to 22 May 2022 (wave 5), 23 May 2022 to 30 September 2022 (wave 6a) and 1 October 2022 to 29 January 2023 (wave 6b), which were dominated by Omicron variants.
- ***Rt* estimation based on case counts (incidence-based *Rt*):** we applied robust incidence deconvolution estimator with delay from infection to reporting, to reconstruct the epidemic curve by infection time. Then we estimate the local incidence-based *Rt* based on Cori's method.
- **Incorporating Ct distribution into *Rt* estimates (Ct-based *Rt*):** we fitted a linear regression model of the daily mean and skewness of Ct on log-transformed incidence-based *Rt,* using training data from the third wave, and applied it to predict *Rt* in the waves 4 to 6b. We included a 31-day period in the training set, consisting of 10 days before and 20 days after the day when local cases peaked in that wave (rolling average), as suggested by previous study.
- **Cross-validation between epidemic waves:** we trained the model on data from 31-day training periods in wave 4, 5, 6a and 6b, separately. With each training set, the other waves as well as wave 3 were used as test sets.
- **Stratified analysis of two symptom severity groups:** Omicron waves tended to report more severe cases. Thus, we fitted the established model from Ct data from either mild to moderate or severe group only in 5 waves, respectively, and then used model and date from corresponding severity group to estimate the scenarios in wave 5, 6a and 6b.

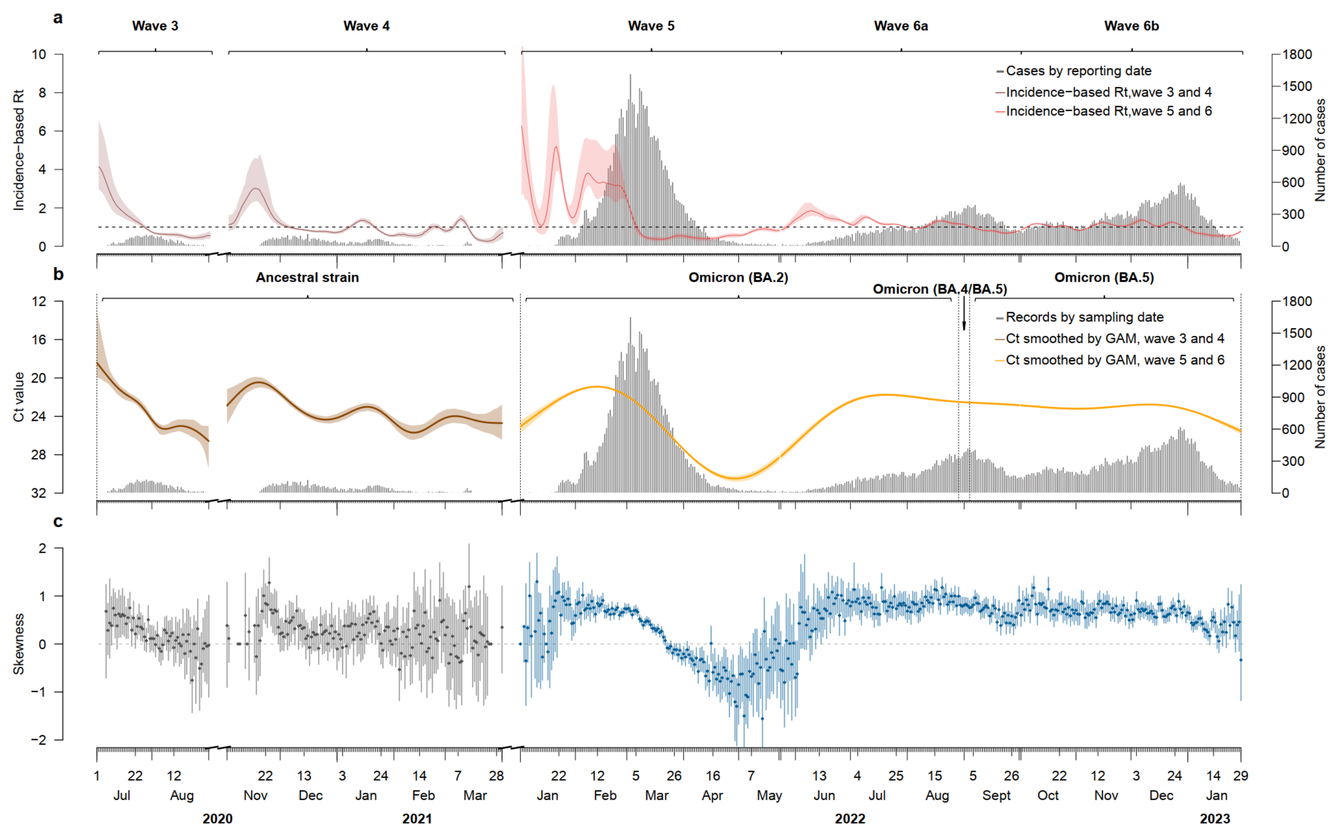

Figure 1. Temporal distribution of incidence-based Rt and population-level Ct values

With 114,714 local cases with available Ct values included, higher incidence-based Rt were observed with lower average Ct values and as Ct skewed towards lower values, although such relationships were not significant for wave 6a.

Results

The main model trained on wave 3 accurately predicted Rt for waves 4, 5 and 6b. Cross-validation between epidemic waves showed that high accuracy still held for wave 3 and 5 as test sets derived from the rest four training sets.

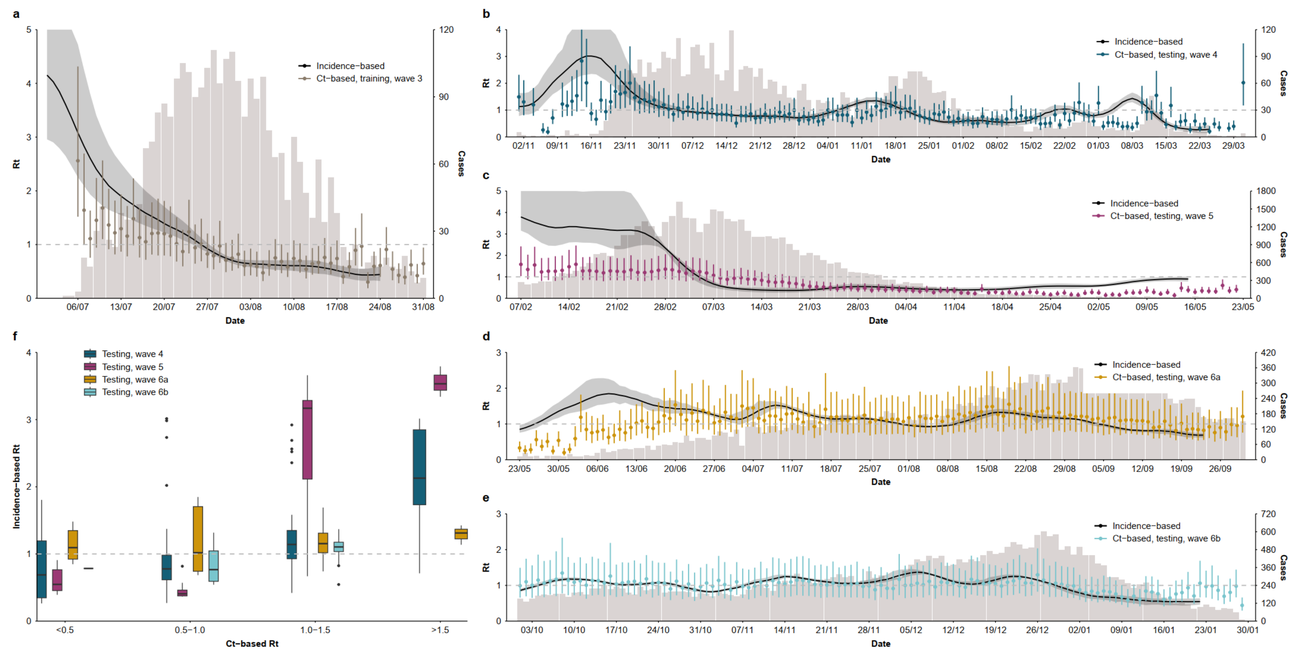

Figure 2. Nowcast Ct-based Rt during wave 4, 5, 6a and 6b in Hong Kong.

Table 1. Area under the ROC Curve: cross-validation for *Rt* prediction in Hong Kong's COVID-19 waves.

	Training period: wave 3* (19 Jul-18 Aug 2020)	Training period: wave 4 (24 Nov - 24 Dec 2020)	Training period: wave 5 (21 Feb -23 Mar 2022)	Training period: wave 6a (23 Aug-22 Sep 2022)	Training period: wave 6b (19 Dec 2022-18 Jan 2023)
Wave 3	0.94 (0.86,1)	0.93 (0.84,1)	0.8 (0.7,0.89)	0.91 (0.82,0.99)	0.92 (0.83,0.99)
Wave 4	0.68 (0.61,0.76)	0.69 (0.61,0.76)	0.67 (0.6,0.74)	0.7 (0.62,0.77)	0.71 (0.64,0.78)
Wave 5	0.98 (0.96,1)	0.98 (0.96,1)	0.96 (0.91,0.99)	0.99 (0.97,1)	0.98 (0.96,1)
Wave 6a	0.62 (0.53,0.71)	0.62 (0.53,0.7)	0.53 (0.49,0.57)	0.66 (0.59,0.74)	0.66 (0.56,0.74)
Wave 6b	0.8 (0.73,0.87)	0.81 (0.73,0.87)	0.49 (0.45,0.52)	0.53 (0.51,0.57)	0.67 (0.6,0.75)
Overall [a]	0.78 (0.75,0.82)	0.83 (0.79,0.87)	0.53 (0.49,0.57)	0.69 (0.65,0.72)	0.8 (0.76,0.84)

Incidence-based Rt was natural log-transformed. * The main model used to estimate Ct-based Rt
a Overall: combined all test sets into one to calculate corresponding AUC

Omicron waves intended to report more severe cases. Results for the effect of severity profile suggested that using Ct values from mild to moderate or severe group only yielded decreased AUCs when ancestral strains dominating waves was set as training sets. However, utilizing Ct from one group yield increased AUCs when Omicron waves were set as training sets.

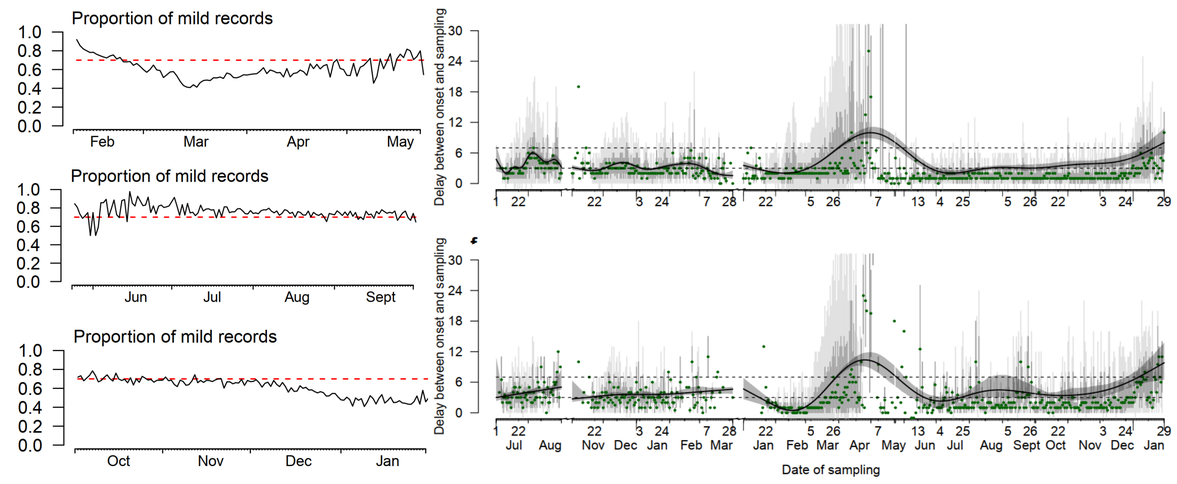

Figure 3. Proportion of mild cases and delay between onset and sampling among different severity groups.

Conclusion

Our study provides valuable insights into the potential of population-level Ct distribution as a predictive tool for timely assessing Rt during waves characterized by variants dominating and population immunity shifting. These findings suggest the potential generalizability of this simplified framework across various settings and situations. However, it is important to exercise caution when interpreting the results due to the fluctuation of sampling delay and severity proportion. Further research is required to validate these findings and improve sensitivity of estimating Rt when community transmission was stable and consistent.

References

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[2] Lin, Y. et al. Incorporating temporal distribution of population-level viral load enables real-time estimation of COVID-19 transmission. Nat Commun 13, 1155 (2022).

Acknowledgements

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