SARS-CoV-2 in Malaysia: A surge of reinfection during the predominantly Omicron period

Su Lan Yang,[a,1]* Hoon Shien Teh,[a,1] Jing Lian Suah,[b] Masliyana Husin,[b] and Wen Yea Hwong [a,c]

[a]Centre for Clinical Epidemiology, Institute for Clinical Research, National Institute of Health, No. 1, Jalan Setia Murni U13/52, Seksyen U13, Setia Alam, 40170 Shah Alam, Selangor, Ministry of Health Malaysia, Malaysia
[b]Centre for Clinical Outcome Research, Institute for Clinical Research, National Institute of Health, No. 1, Jalan Setia Murni U13/52, Seksyen U13, Setia Alam, 40170 Shah Alam, Selangor, Ministry of Health Malaysia, Malaysia
[c]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, 3584 CG Utrecht, the Netherlands

The Lancet Regional Health - Western Pacific 2022;26: 100572
Published online xxx
https://doi.org/10.1016/j.lanwpc.2022.100572

Throughout the COVID-19 pandemic, SARS-CoV-2 evolved rapidly from the original strain.[1] While COVID-19 control measures are relaxed with country's transition to endemicity, it is imperative to be mindful that as SARS-CoV-2 continues to mutate and circulate. Reinfection has also become increasingly common due to the dominance of the highly transmissible variants, immunity evasion, and inadequate preventive strategies from the public because of pandemic fatigue.[2] Case surveillance is underpinned by the National Testing Strategy, and comprehensive data of the COVID-19 situation is open access, but the reinfection rate during the Omicron period warrants deeper analysis due to Malaysia's socio-economic, demographic, and vaccine platform compositions that are more comparable to regional countries. This clarifies the general assumption that COVID-19 infection protects against future infection, despite limited evidence on who is at higher risk and the extent to which booster vaccination protects against reinfection. In this study, we aim to investigate the risk and rate of COVID-19 reinfection across different age group, exposure level, vaccination status and vaccine type. Our findings are expected to inform public health messaging policies by alluding to the differential risk of reinfection across targeted risk groups and proposing ways to mitigate these risks.

We used consolidated national administrative data in Malaysia from April 1, 2021 to March 31, 2022 to calculate the incidence rate of SARS-CoV-2 reinfection before and during the predominant-Omicron periods. This is a retrospective cohort of individuals who had at least one SARS-CoV-2 infection throughout the study period. We followed the reinfection definition by Centres for Disease Control and Prevention to enumerate an individual as case when the reverse transcription-polymerase chain reaction (RT-PCR) or rapid antigen test (RTK-Ag) confirmed infection occurred 90 days after the prior infection.[3] Reinfection rates were stratified by period, age group, exposure level, vaccination status and vaccine type. Person-time at risk for reinfection was calculated by subtracting the date of study entry (date of first infection) from date of event (date of reinfection). Individuals with only one infection throughout the study period were censored at the end of study period. Genomic sequencing of COVID-19 sample is highly targeted in Malaysia. According to GISAID database, Omicron began dominating in January 2022[4] but the sequenced samples were from entry point travellers from high-risk countries with known Omicron outbreaks, hence were not representative of variants circulating in the community. To overcome this, a Malaysian study used Bai-Perron sequential breakpoint test on Malaysia's COVID-19 data to estimate the start of Omicron-dominant period in Malaysia, which was likely in early February 2022.[5] Therefore, we determined February 1, 2022 as the breakpoint for the pre-Omicron and Omicron periods. We excluded individuals with single-dose regime and defined individuals to be fully vaccinated with two or three doses at 14 days after the last vaccine date, allowing immunogenicity to develop. We categorized one's exposure risk based on the frequency that one was tagged as "casual contact" to a SARS-CoV-2 positive case by the Malaysia COVID-19 mobile application contact tracing system (MySejahtera). The automated "casual contact" tracing system in MySejahtera measures exposure because (i) the tagging of contacts is location- and time-specific, with tracing windows calibrated to best predict post-exposure transmission at the location-level and (ii) the positivity rate of "casual contact" is about 10–15% according to surveillance. One becomes a "casual contact" when present in the same premise and time window as another individual who tested positive by the end of the day, hence potentially exposed to SARS-CoV-2. Low exposure is defined if a person was not flagged as "casual contact" throughout the follow-up period; moderate exposure if flagged 1–5 times; and high exposure if flagged more than 5 times. All analysis

*Corresponding author.
E-mail address: slyang@moh.gov.my (S.L. Yang).

[1] Contributed equally.

were performed in R version 4.2.1 and Stata version 13 (Statacorp LP).

We included 3,432,651 COVID-19 positive cases that were recorded throughout the study period. Among these, 62,522 (1.8%) had at least one episode of reinfection. There was a drastic increase in reinfection case during the Omicron period relative to pre-Omicron period. (Supplementary Figure 1) In overall, the reinfection incidence rate was 6.6 times higher during the Omicron period compared to the pre-Omicron period (0.69 [95% CI 0.67 – 0.71] vs 4.55 [95% CI 4.51 – 4.58] per 100-person years [PY]) regardless of age group and exposure risk. (Supplementary Table 1) High exposure individuals in the 18–59 age group had a

Subgroups	Case	Population	PY at risk	Forest plot	Incidence rate per 100 PY (95% CI)	P value[a]
Low exposure						
Age Group <18						
noVax	5,443	632,087	292,693		1·86 (1·81 - 1·91)	0·019
oneDose	89	28,465	4,393		2·03 (1·65 - 2·49)	0·033
twoDose	106	51,750	7,125		1·49 (1·23 - 1·80)	ref
Age Group 18-59						
noVax	3,262	240,181	150,057		2·17 (2·10 - 2·25)	<0·001
oneDose	979	59,078	35,211		2·78 (2·61 - 2·96)	0·179
twoDose	2,199	243,059	84,079		2·62 (2·51 - 2·73)	0·025
threeDose	216	84,852	7,019		3·08 (2·69 - 3·52)	ref
Age Group ≥ 60						
noVax	590	57,102	35,738		1·65 (1·52 - 1·79)	0·215
oneDose	264	17,320	11,112		2·38 (2·11 - 2·68)	0·104
twoDose	842	112,196	44,831		1·88 (1·76 - 2·01)	0·827
threeDose	75	43,551	3,897		1·92 (1·53 - 2·41)	ref
Moderate exposure						
Age Group <18						
noVax	736	33,006	21,305		3·45 (3·21 - 3·71)	0·030
oneDose	60	2,808	1,150		5·22 (4·05 - 6·72)	<0·001
twoDose	82	22,338	3,038		2·7 (2·17 - 3·35)	ref
Age Group 18-59						
noVax	10,754	261,951	191,035		5·63 (5·52 - 5·74)	<0·001
oneDose	5,039	130,617	81,112		6·21 (6·04 - 6·39)	<0·001
twoDose	10,293	554,032	190,667		5·4 (5·30 - 5·50)	<0·001
threeDose	1,439	341,405	29,660		4·85 (4·61 - 5·11)	ref
Age Group ≥ 60						
noVax	269	11,031	8,763		3·07 (2·72 - 3·46)	0·007
oneDose	142	6,451	4,359		3·26 (2·76 - 3·84)	0·004
twoDose	440	39,001	16,698		2·64 (2·40 - 2·89)	0·109
threeDose	63	32,663	2,958		2·13 (1·66 - 2·73)	ref
High exposure						
Age Group <18						
noVax	70	999	664		10·55 (8·35 - 13·33)	0·115
oneDose	1	63	27		3·77 (0·53 - 26·75)	0·756
twoDose	7	944	121		5·77 (2·75 - 12·10)	ref
Age Group 18-59						
noVax	7,066	72,721	54,183		13·04 (12·74 - 13·35)	<0·001
oneDose	3,784	38,687	24,345		15·54 (15·06 - 16·05)	<0·001
twoDose	6,871	153,042	49,948		13·76 (13·43 - 14·09)	<0·001
threeDose	1,117	144,989	13,600		8·21 (7·75 - 8·71)	ref
Age Group ≥ 60						
noVax	59	1,368	1,122		5·26 (4·08 - 6·79)	0·046
oneDose	40	745	507		7·88 (5·78 - 10·75)	<0·001
twoDose	110	3,962	1,659		6·63 (5·50 - 7·99)	0·002
threeDose	15	5,216	499		3·01 (1·81 - 4·99)	ref
				0.0 4.0 8.0 12.0 16.0		

***Table 1*: Reinfection incidence rate up to Omicron period, stratified by age group, exposure risk and vaccination status.**

PY, Person-years; noVax, not vaccinated; oneDose, received 1 dose of vaccine; twoDose, received 2 doses of vaccine; threeDose, received third dose of vaccine as booster dose. Low exposure means the individual was not flagged as "casual contact" throughout follow up period; moderate exposure means the individual was flagged 1–5 times; high exposure means the individual was flagged more than 5 times.

[a] *P* value is calculated based on the incidence rate ratio of the unvaccinated, one dose or two doses against the reference group booster dose in each subgroup. For age group <18 subgroups, the reference group is those who had fully vaccinated with two doses.

Vaccine platforms[a]	Case	Population	PY at risk	Incidence rate per 100 PY (95% CI)	*P* value[b]
Overall	2,914	650,100	57,397	5.08 (4.90–5.26)	-
PPP	910	251,271	22,153	4.11 (3.85–4.38)	ref
SSS	165	45,435	4,016	4.11 (3.53–4.79)	0.99
AAA	215	55,429	4,859	4.42 (3.87–5.06)	0.33
Heterologous with P booster	1,441	270,900	24,092	5.98 (5.68–6.30)	<0.001
Heterologous with A booster	183	27,065	2,278	8.03 (6.95–9.29)	<0.001

***Table 2*: Reinfection incidence rate of people who received booster vaccination, stratified by vaccine platforms.**

[a] PPP, three doses of Pfizer-BioNTech mRNA vaccine; SSS, three doses of Sinovac inactivated virus vaccine; AAA, three doses of AstraZeneca viral vector vaccine; Heterologous with A booster includes Pfizer-Pfizer-AstraZeneca (PPA) combination and Sinovac-Sinovac-Astrazeneca (SSA) combination; Heterologous with P booster includes AstraZeneca-AstraZeneca-Pfizer (AAP) combination and Sinovac-Sinovac-Pfizer (SSP) combination.

[b] *P* value is calculated based on the incidence rate ratio of the corresponding vaccine combination with PPP as the reference group.

remarkably higher incidence rate and the rates were significantly different in two periods (13.26 [95% CI 13.07–13.45] during Omicron vs 1.34 [95% CI 1.27 –1.42] during pre-Omicron per 100-PY). (Supplementary Table 1).

Booster vaccination was highly advocated in Malaysia's national vaccination campaign and is eligible from October 2021 onwards for those aged 18 years and above. The different regimes of vaccine combinations are shown in Supplement Figure 2. Briefly, Pfizer-BioNTech mRNA vaccine and AstraZeneca viral vector vaccine were the main recommendations by Ministry of Health for booster vaccination, whereas Sinovac inactivated virus vaccine were only offered for homologous boosting or to those who cannot tolerate the former.[6] We found that the third dose vaccination reduced the reinfection rate for all adults with moderate and high exposure risk (Table 1). The reinfection rate was significantly lower among the high exposure, 18–59 years old, boosted adults than the unvaccinated and two-dose group (8.21 [95% CI 7.75 – 8.71] vs 13.04 [95% CI 12.75 – 13.35] and 13·76 [95% CI 13.43 – 14.09] per 100 PY) (Table 1). Among those who received booster dose, homologous regimes and heterologous regime with Pfizer vaccine have significantly lower reinfection rates than heterologous regimes with AstraZeneca (Table 2). For individuals with low exposure risk, reinfection incidence rate was not significantly different by vaccination status (Table 1).

We have three main messages. First, reinfection has become more common in Malaysia during the Omicron period. This trend is consistent with other countries,[7,8] some with evidence of multiple reinfections.[9] The mutated and highly transmissible strain circulating in the community leads to higher infection rate and hence higher chance for reinfection to occur. Second, reinfection rates were higher among adults 18–59 years of age and those with high exposure. People naturally have increased exposure when they regain pre-pandemic mobility and start frequenting public places as the society reopened. It is important to raise this awareness and maintain persistent efforts to remind the public to remain vigilant because the risk of reinfection still lurks if cautionary steps are not followed. Up to the point of analysis, homologous regimes and heterologous booster with Pfizer conferred better protection against reinfection for this risk group and should be encouraged. Lastly, booster vaccine, however, does not further reduce the reinfection rate in low exposure group. This poses the questions whether a second booster will be of additional benefit to those with low exposure. There may be residual confounding factors that are masking the benefit of vaccination among this group, such as underlying comorbidities (people with comorbidities and the elderly tend to stay home to avoid exposure) and more relaxed preventive measures among household members. Members living in the same household as COVID-19 case are susceptible to infection, even if not tagged as "casual contact" by MySejahtera, because of close proximity and caring duties for infected member.

In conclusion, the surge in reinfection rate was consistent with the emergence of the Omicron variant and the reinfection risk was higher among high exposure, 18–59 years old and unboosted group. As more economic sectors reopen, the SAR-CoV-2 viruses are expected to continue mutating and circulating. The existing COVID-19 surveillance system may need to be appropriately adapted to detect the epidemiological signals of (re)infection cases and immunity evasion by newer variants for any alarming surge. Apart from booster vaccination, public health messaging should convey the reinfection risk to the general public and advocate for risk mitigation measures supported by the social and behavioural sciences.

Contributors

All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization and design: SLY, HST, WYH. Data acquisition: JLS, MH. Data cleaning and analysis: SLY, HST, WYH. Data interpretation: All authors. Drafting of manuscript:

HST, SLY. Critical revision and approval of the manuscript for important intellectual content: All authors. Supervision: WYH.

Data sharing statement

The dataset analysed for the current study are available from corresponding author upon reasonable request.

Declaration of interests

All authors declare no conflict of interest.

Acknowledgements

We thank the Director General of Health Malaysia for his permission to publish this manuscript. We are grateful to the Real-World Evaluation of COVID-19 Vaccines under the Malaysia National COVID-19 Immunisation Programme (RECoVaM) study team for their support in data acquisition and provision.

Ethics Approval

The study was approved by the Medical Research and Ethics Committee (MREC) Ministry of Health Malaysia and registered (NMRR-21-1660-60697).

Funding

This study receives no funding.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100572.

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