

Oral antiviral utilisation among older adults with COVID-19 in primary care: A population-wide study during successive Omicron waves in Singapore

Dear Editor,

Studies have repeatedly demonstrated the real-world effectiveness of oral antivirals (OAVs) in preventing hospitalisation and death in patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 when initiated within 5 days of symptom onset, even during waves of Omicron transmission.¹ However, there is a need to determine if OAVs are reaching recommended groups, particularly among older adults and socioeconomically disadvantaged groups at higher risk of severe COVID-19. Disparities in access to OAVs based on area-level socioeconomic status (SES) have been documented in the US, UK and Australia,²⁻⁴ with substantially lower dispensing rates reported from more deprived areas. However, to the best of our knowledge, no studies have evaluated disparities in OAV access among urbanised Asian populations, including Singapore.

We therefore aimed to evaluate disparities in OAV access, including SES, among older Singaporean adults aged ≥ 60 years with COVID-19 presenting to primary care during successive Omicron waves over a 5-month period from 1 July 2022 to 31 December 2022, using a retrospective cross-sectional study design. We hypothesised that despite free SARS-CoV-2 testing (polymerase-chain-reaction [PCR]/rapid-antigen-test [RAT]) at all healthcare providers and full coverage of OAVs' cost,⁵ primary care characteristics and SES, such as housing type, may still influence OAV uptake. In Singapore, housing type is a key indicator of SES.⁶ The majority of Singaporeans ($\geq 90\%$) stay in owner-occupied public housing under a tiered subsidy scheme; there are also heavily subsidised rental flats for those who cannot afford home ownership.⁷ Over the study period, testing for SARS-CoV-2 was compulsory for all individuals who presented with acute respiratory illness to any healthcare provider; all COVID-19 cases were recorded in the Ministry of Health's national registry.⁵ Omicron BA.4/5 predominated community transmission ($\geq 90\%$ of sequenced isolates on national genomic surveillance) in July 2022; subsequently, Omicron XBB emerged as the dominant strain from September 2022 onwards.⁸ OAVs received interim authorisation in February 2022 and were made available at selected polyclinics and Public Health Preparedness Clinics (PHPCs)—the latter comprising a network of

over 1000 private general practitioner (GP) clinics providing subsidised testing during public health emergencies.¹ Age ≥ 60 years was considered a risk factor for progression to severe COVID-19 and a criterion for early treatment with OAVs in the national COVID-19 treatment guidelines. Receipt of OAVs was defined as any prescription for either nirmatrelvir/ritonavir or molnupiravir, within 5 days of a positive SARS-CoV-2 result (PCR/RAT).

Anonymised data, including demographic variables, such as age, sex, ethnic group (Chinese, Malay, Indian or others), comorbidities (Charlson Comorbidity Index), immunocompromised status and indicators of SES (housing type) were extracted from official Ministry of Health databases. This study was done as part of national public health research under the Infectious Diseases Act and hence, a separate Institutional Review Board approval was not required. Given the absence of information on individual-level employment/education in the electronic-health-record data, average housing value based on individuals' place of residence (postal codes) was additionally included. Prediction of average housing value for all residential properties in Singapore listed by postal code was performed using a machine-learning algorithm and results were classified by quintiles, as per previously published methodology.⁹ Multivariable logistic regression was utilised to identify clinical and sociodemographic variables independently associated with receipt of OAVs. The cluster option was used to control for potential correlation within residential districts (as defined by group representation constituencies, a type of electoral division in Singapore). Analysis was performed using STATA version 17.0 (StataCorp, College Station, TX, US).

During the study period, a total of 112,215 older adults were diagnosed with COVID-19 at primary care. After excluding those with missing sociodemographic information ($n=474$), a total of 111,741 older adults were included (median age 68 years, interquartile range 63–74). There were 4.71% (5,266/111,741) who received OAVs; the majority ($\geq 95\%$) were prescribed nirmatrelvir-ritonavir. On multivariable analysis, after adjusting for other sociodemographic and clinical factors (sex, age, ethnicity, comorbidities, immunocompromised status and pandemic phase), primary care characteristics and indicators of SES were independently associated with receipt of OAVs at primary care (Table 1). Odds of receiving OAVs were lower among

patients diagnosed at private GP clinics, including PHPCs (adjusted odds ratio [aOR] 0.18, 95% CI 0.09–0.37) and those not part of the PHPC network (aOR 0.20, 95% CI 0.01–0.06), compared with public primary care clinics (polyclinics). This is likely reflective of more limited access to OAVs among private GPs. Odds of receiving OAVs were higher (aOR 2.32, 95% CI 1.26–4.35) among patients

diagnosed at clinics offering telemedicine services for COVID-19. SES indicators, including staying in private housing (aOR 1.76, 95% CI 1.43–2.17) and living in an area with higher average housing value (aOR 1.38, 95% CI 1.93–1.86) were independently associated with higher odds of receiving OAVs (Table 1).

Table 1. Sociodemographic and clinical factors associated on multivariable analysis with receipt of oral antivirals for COVID-19 among Singaporean adults aged≥60 years who presented to primary care.

Sociodemographic and clinical factors	Received oral antivirals, no. (%)	Multivariable logistic regression of factors associated with receipt of oral antivirals (n=111,741)	
		Adjusted odds ratio [95% CI] ^a	<i>P</i> value
Demographic factors			
Sex			
Female	2714/61,270 (4.4)	1.00 (ref)	
Male	2552/50,471 (5.1)	1.09 [1.03–1.16]	0.004
Age, years			
60–70	2313/63,955 (3.6)	1.00 (ref)	
71–80	1937/33,401 (5.8)	1.58 [1.45–1.72]	<0.001
≥81	1016/14,385 (7.1)	1.92 [1.73–2.13]	<0.001
Ethnicity			
Chinese	4359/92,262 (4.7)	1.00 (ref)	
Malay	417/10,840 (3.9)	1.00 [0.86–1.17]	0.979
Indian	392/7038 (5.6)	1.26 [1.09–1.47]	0.002
Others ^b	98/1601 (6.1)	1.49 [1.24–1.77]	<0.001
Socioeconomic factors			
Housing type			
5-room/executive condominium-type public housing	1088/28,235 (3.9)	1.00 (ref)	
1–2 room public housing	237/5245 (4.5)	0.95 [0.74–1.23]	0.693
3–4 room public housing	2376/58,811 (4.0)	1.00 [0.90–1.11]	0.992
Private housing	1565/19,450 (8.1)	1.76 [1.43–2.17]	<0.001
Area-level housing value (quintiles)			
First quintile (lowest value)	826/22,086 (3.74)	1.00 (ref)	
Second quintile	806/22,527 (3.58)	0.93 [0.73–1.18]	0.559
Third quintile	876/22,395 (3.91)	0.99 [0.69–1.41}	0.940
Fourth quintile	1112/22,682 (4.90)	1.13 [0.81–1.56]	0.472
Fifth quintile (highest value)	1645/22,041 (7.46)	1.38 [1.93–1.86]	0.030

Table 1. Sociodemographic and clinical factors associated on multivariable analysis with receipt of oral antivirals for COVID-19 among Singaporean adults aged ≥60 years who presented to primary care. (Cont'd)

Sociodemographic and clinical factors	Received oral antivirals, no. (%)	Multivariable logistic regression of factors associated with receipt of oral antivirals (n=111,741)	
		Adjusted odds ratio [95% CI] ^a	P value
Primary care characteristics			
Primary care provider			
Public polyclinic	1872/19,998 (9.4)	1.00 (ref)	
Private general practitioner clinic part of the PHPC network ^c	3376/88,392 (3.8)	0.18 [0.09–0.37]	<0.001
Private general practitioner clinic not part of the PHPC network ^c	18/3351 (0.5)	0.20 [0.01–0.06]	<0.001
Clinic offers telemedicine services for COVID-19 ^d			
No	3286/85,266 (3.9)	1.00 (ref)	
Yes	1980/26,475 (7.5)	2.32 [1.26–4.35]	0.007
Phase of pandemic			
Omicron BA.4/5 phase, earlier phase	1936/60,647 (3.2)	1.00 (ref)	
Omicron XBB phase, later phase	3330/51,094 (6.5)	2.04 [1.81–2.29]	<0.001
Clinical factors			
Patient is immunocompromised			
No	4580/100,424 (4.6)	1.00 (ref)	
Yes	686/11,317 (6.1)	1.20 [1.09–1.32]	<0.001
Comorbidity burden (Charlson Comorbidity Index, CCI)			
No comorbidities, CCI 0	2807/65,493 (4.3)	1.00 (ref)	
Mild comorbidities, CCI 1–3	1628/30,955 (5.3)	1.09 [1.03–1.16]	0.002
Moderate comorbidity burden, CCI 3–4	559/10,276 (5.4)	1.05 [0.96–1.15]	0.285
Severe comorbidity burden, CCI ≥5	272/5017 (5.4)	1.00 [0.87–1.15]	0.986

^a Adjusted for sex, age, ethnicity, housing type, area-level housing value, primary care provider and characteristics, comorbidity burden, immunocompromised status in multivariable logistic regression model, controlling for clustering within residential districts (as defined by Singapore's group representation constituencies).

^b Includes individuals of other ethnicities or mixed ethnicities.

^c Among those diagnosed at private general practitioner (GP) clinics, differences in proportions of patients receiving oral antivirals (OAVs) between those diagnosed at single-operator GP clinics versus those diagnosed at GP clinics belonging to a chain were compared using chi-square test. Those diagnosed at single-operator clinics had higher odds of receiving OAVs—single-operator: 4.2% (1971/47404), chain: 3.3% (1415/43449), odds ratio 1.28, 95% CI 1.19–1.37, $P<0.001$. Numbers do not add up to the total number of COVID-19 cases originally diagnosed at all GPs (N=91,743) because sufficient information to distinguish single-operator versus chains was not available in all cases.

^d Information on telemedicine services provided was obtained by cross-checking the list of GPs/clinics providing telemedicine services for either the Home Recovery Programme for COVID-19 patients, or GPs/clinics providing teleconsultation for acute respiratory illness, including tele-antigen rapid testing services.

Oral COVID-19 antivirals represent a key component of public health strategies as COVID-19 moves towards endemicity. As such, ensuring equitable access is crucial. Both individual-level and area-level SES disparities were independently

associated with OAV uptake, despite widespread availability and free provision. Reduced uptake of OAVs among lower SES strata—even with subsidised treatment and testing—is of concern. Although free SARS-CoV-2 treatment and testing was available at

healthcare providers, disparities in OAV uptake may persist due to individuals' past experiences with the healthcare system influencing their present care-seeking behaviour. Pre-pandemic, only a minority of lower-income Singaporean residents expressed a preference, when ill, to approach a primary care practitioner as their first choice for consultation, largely due to cost concerns.⁷ Targeted efforts are needed to overcome potential barriers in a contextually sensitive manner in order to improve OAV uptake among lower SES strata.

Characteristics of primary care, specifically, being diagnosed at a public primary care clinic and being diagnosed at a clinic offering telemedicine services for COVID-19, were positively associated with higher odds of receiving OAVs. However, a potential limitation was that information on whether specific patients were diagnosed via face-to-face consultation or teleconsultation was unavailable. Telemedicine has been increasingly deployed in lieu of face-to-face consultations during the COVID-19 pandemic. By leveraging telemedicine, Singapore's healthcare system navigated successive COVID-19 waves without impacting severity/mortality rates and hospital capacity.¹⁰ Going forward, primary care physicians have a significant role in facilitating OAV uptake in at-risk population groups during COVID-19 endemicity. Indications for OAVs can be disseminated more widely among primary care doctors, including private GPs. Telemedicine can potentially be leveraged upon to augment this capability.

Disclosure

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Data sharing

The databases with individual-level information used for this study are not publicly available due to personal data protection. Deidentified data can be made available for research, subject to approval by the Ministry of Health of Singapore. All inquiries should be sent to the corresponding author.

Keywords: COVID-19, nirmatrelvir, oral antiviral treatment uptake, primary care, SARS-CoV-2, socioeconomic status

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Ren Ying Tan¹, Borame Dickens² PhD,
Joyce Tan¹ BSc, Ching Li Lee¹ PhD,
Betty Wong¹ MPA, Ruth Lim¹ MMed (FM),
Kelvin Bryan Tan^{1,2,3,4} PhD, Liang En Wee^{3,4,5} MPH

¹ Ministry of Health, Singapore

² Saw Swee Hock School of Public Health, National University of Singapore, Singapore

³ National Centre for Infectious Diseases, Singapore

⁴ Duke-NUS Graduate Medical School, National University of Singapore, Singapore

⁵ Department of Infectious Diseases, Singapore General Hospital, Singapore

Correspondence: Dr Liang En Wee, Department of Infectious Diseases, Singapore General Hospital, 16 College Road, Block 6 Level 7, Singapore 169854.
Email: ian.wee.l.e@singhealth.com.sg