Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Antibiotic use among COVID-19 patients in Hong Kong, January 2018 to March 2021

Dear Editor,

We read with interest the paper by Seaton and colleagues who reported 38.3% of SARS-CoV-2 hospitalized patients were prescribed antibiotics based on a one-day prevalence survey during the peak of the initial COVID-19 epidemic Scotland.[1] Compared with literatures which reported high rates of antibiotic prescribing among COVID-19 patients (74.6%[2], 74.0%[3]), the authors attributed their low prevalence of antibiotic use to their national antimicrobial stewardship initiatives. However, caution should be exercised when interpreting such reported rates of antibiotic use because they are dependent on the types of SARS-CoV-2 patients who were hospitalized. In addition, to further unravel the impact of the COVID-19 pandemic on antibiotic prescribing, it is useful to compare the antibiotic use in the community in the pre-pandemic period and that in the peri-pandemic period. To this end, we report the dispensing pattern of antibiotics in public hospitals for managing COVID-19 cases and compare the change of antibiotic use by such cases in general outpatient settings unrelated to COVID-19 from 2018 to 2020 in Hong Kong.

In this study, inpatient records of COVID-19 cases admitted to hospitals affiliated with the Hospital Authority were retrieved up to 3 March 2021. Pharmacy dispensing records of general outpatient settings for this cohort was available from 2018 onwards. Inpatient antibiotic use was expressed as defined daily doses (DDD)/days of therapy (DOT) per 1000 bed-days. Outpatient antibiotic use was expressed as DDD per 100,000 person-days, where each case's person-day contribution was assumed as 365 days in 2018 and 2019, and as the number of days prior to their diagnosis of COVID-19 in 2020. Co-infections alongside COVID-19, based on ICD-9 discharge diagnoses and empiric classification of physicians, were grouped into bacterial or others. More methodological details is in Appendix I.

As of 3 March 2021, there were 11,047 laboratory-confirmed COVID-19 cases in Hong Kong, of which 11,004 were hospitalized and were included in the analysis. The mean (SD) age at hospital admission was 44.7 (19.9) years, with 8.2% of cases aged <18 years. Patient characteristics are summarized in Table S1. Antibiotic use was 251.0 DOT per 1000 bed-days and 289.7 DDD per 1000 bed-days among 10,106 adult cases. There were 29.1% of cases treated with antibiotics, but only 1.84% had confirmed bacterial co-infections. Of the overall antibiotic use, 6.1% was prescribed to cases with bacterial co-infections (confirmed: 9.6 DDD per 1000

Table 1
Antibiotic use by co-infections among adult COVID-19 cases treated with antibiotics.

Antibiotic class	ATC code	Co-infections						
		Bacterial only		Other viral/fungal	Indeterminate/unknown	Multiple types	None	Total
		Confirmed	Presumed					
Tetracyclines	J01AA	0.94	0.74	0.82	4.34	2.16	20.5	29.5
Penicillins with extended spectrum	J01CA	0.00	0.00	0.08	0.10	0.03	0.53	0.73
Beta-lactamase resistant penicillins	J01CF	0.98	0.00	0.04	0.16	1.13	1.55	3.86
Combinations of penicillins	J01CR	2.88	4.23	2.90	18.6	10.9	115.6	155.1
Cephalosporins, 1st generation	J01DB	0.00	0.05	0.00	0.00	0.00	0.12	0.16
Cephalosporins, 2nd generation	J01DC	0.05	0.08	0.00	0.25	0.31	0.95	1.63
Cephalosporins, 3rd generation	J01DD	1.43	0.85	0.96	6.07	5.64	31.1	46.0
Cephalosporins, 4th generation	J01DE	0.14	0.00	0.00	0.27	1.90	0.72	3.03
Carbapenems	J01DH	0.63	0.67	0.24	2.62	3.18	5.09	12.4
Other cephalosporins and penems	J01DI	0.00	0.00	0.00	0.00	0.40	0.00	0.40
Combinations of sulfonamides and trimethoprim, including derivatives	J01EE	0.03	0.39	0.02	0.65	1.97	1.40	4.47
Macrolides	J01FA	0.43	0.00	0.32	1.19	1.17	3.67	6.78
Lincosamides	J01FF	0.00	0.00	0.00	0.04	0.00	0.00	0.04
Aminoglycosides	J01GB	0.17	0.00	0.00	0.00	0.30	0.08	0.55
Fluoroquinolones	J01MA	1.21	0.59	0.48	3.45	2.82	7.53	16.1
Glycopeptides	J01XA	0.50	0.25	0.04	1.28	1.44	1.07	4.59
Polymixins	J01XB	0.00	0.00	0.00	0.00	0.24	0.16	0.40
Imidazole derivatives	J01XD	0.10	0.05	0.14	0.35	0.32	0.62	1.58
Nitrofuran derivatives	J01XE	0.00	0.18	0.00	0.08	0.06	0.26	0.57
Other antibacterials[†]	J01XX	0.15	0.03	0.02	0.36	0.69	0.51	1.75
Total		**9.63**	**8.10**	**6.05**	**39.8**	**34.7**	**191.4**	**289.7**

Numbers in table are defined daily doses per 1000 bed-days. [†] Fosfomycin, linezolid, daptomycin. ATC: Anatomical therapeutic chemical.

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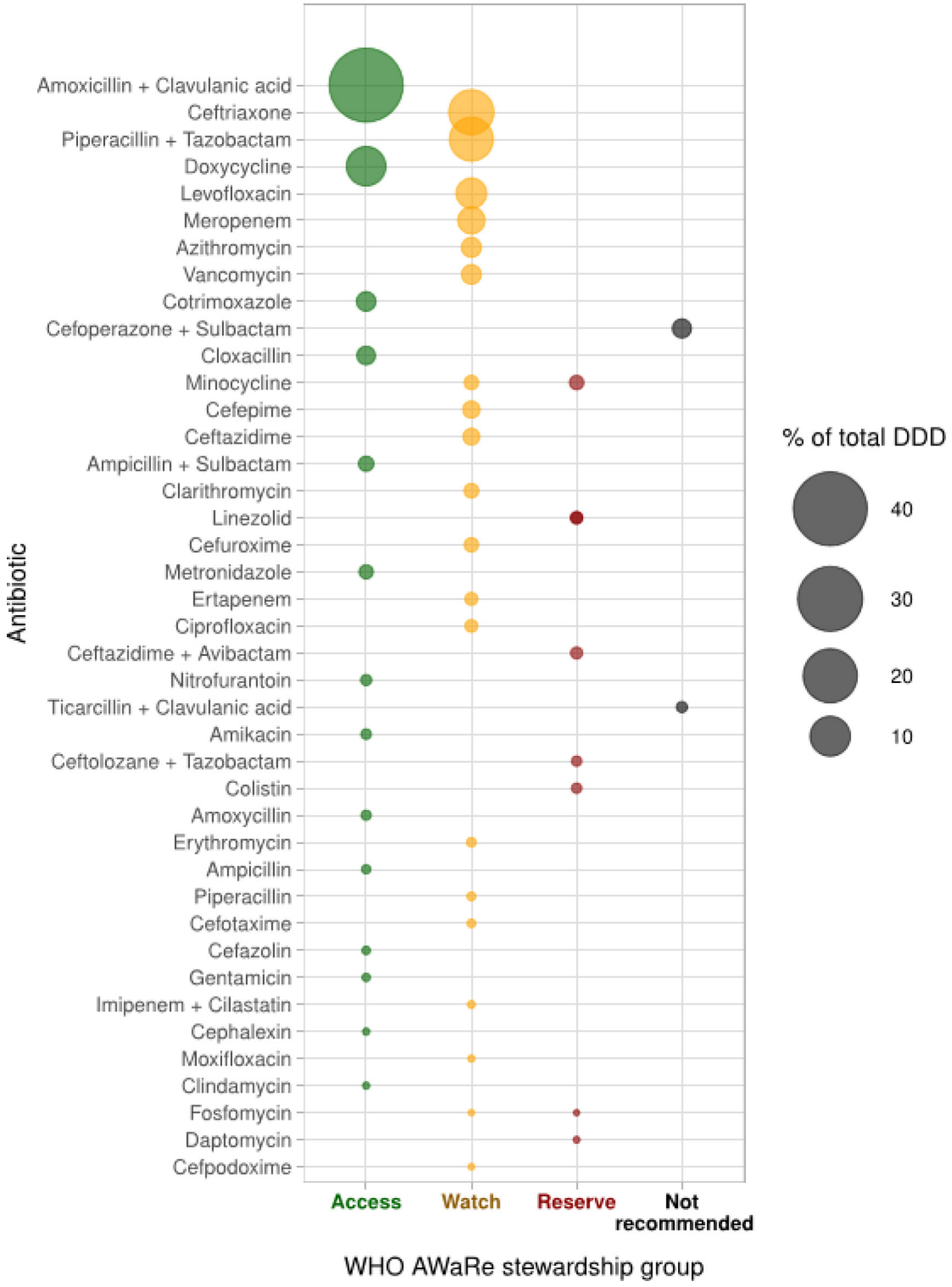

Fig. 1. Inpatient antibiotic use for the management of COVID-19 stratified by the WHO AWaRe classification.

bed-days; presumed: 8.1 DDD per 1000 bed-days) (Table 1). Antibiotic use was common in cases without any co-infections (66.1%, 191.4 DDD per 1000 bed-days) or when the co-condition was uncertain (13.7%, 39.8 DDD per 1000 bed-days). Almost all inpatient antibiotic use fell into the WHO's AWaRe classification list (access: 54.6%; watch: 42.0%; reserve: 1.16%) (**Fig. 1**). Cefoperazone/sulbactam, and ticarcillin/tazobactam, which are not recommended by WHO for clinical use, were also prescribed. In general outpatient settings from 2018 to 2020, community antibiotic use dropped from 52.8 to 45.9 DDD per 100,000 person-days (**Table S2**). This decreasing trend was also observed for individual antibiotics, except for amoxicillin/clavulanic acid, the

use of which increased from 25.9 to 29.3 DDD per 100,000 person-days.

With data from the same individuals prior to and amid the pandemic, we draw inferences based on a self-controlled case series method that eliminates all time-invariant confounding.[4] Our results have three public health implications.

First, this study adds to the literature with the rate of antibiotic use in a complete cohort of cases, which is more adaptable to regions with a low prevalence of COVID-19. In Hong Kong, the number of cases was low such that hospitalization can be used as an isolation strategy (i.e. all cases were hospitalized). With the inclusion of mild and asymptomatic cases, it is not surprising that our reported rate is lower than that of other countries (74.6%[2]) where cases were abundant and only severe cases could be hospitalized. Therefore, caution should be exercised when generalizing our reported rate of antibiotic use among COVID-19 patents (29.1%) to countries with overwhelming numbers of cases.

Second, our results indicate that antibiotic overuse is high among hospitalized COVID-19 cases, highlighting the importance of safeguarding antibiotic stewardship during a pandemic. Although our rate of antibiotic use (29.1%) is lower than that of other countries (74.6%[2]), in line with a systematic review,[2] it was much higher than that of bacterial co-infections (1.8% in our cohort). While it is understandable that the lack of specific therapy for COVID-19 and uncertainty in clinical manifestation can trigger a high rate of empiric antibiotic prescriptions, the scarcity of bacterial co-infections, which was evidenced in many studies,[5,6] suggests restrictive guidelines of antibiotic use are needed. Empiric antibiotic use might be withheld in cases with mild symptoms. In addition, the prescription of antibiotics in the "Watch" (42%), "Reserve" (1.7%) and "Not recommended" (2.3%) groups of the WHO's AWaRe classification system during this pandemic pushed the antibiotic pipeline closer to collapse.

Third, stewardship with monitoring of selected antibiotics should be implemented in outpatient settings. Consistent with significant decline in the community antibiotic use in Canada during the pandemic,[7] such decline was also observed in Hong Kong, indicating a slowdown of emergence of antimicrobial resistance in the community. However, caution should be taken when extrapolating such a decline globally because the epidemic size and intervention policies vary by region. In Hong Kong, the government adopted a suppress-and-lift strategy[8] such that the antibiotic use in outpatient settings were less driven by COVID-19 itself. However, in regions where the health system was on the brink of collapse, antibiotic use in the community may skyrocket. In addition, caution should be taken when assuming declining use of individual antibiotics. In our cohort, the increasing use of amoxicillin/clavulanic acid probably evidences the treatment of infections in the community, once present, to evade hospitalization in the peri-pandemic period. In fact, an ecological study in England also found that certain broad-spectrum antibiotics were taking up a larger proportion despite an overall decrease in antibiotic use in the community.[9]

This study has two limitations. *First,* we assumed that antibiotics prescribed in the public outpatient settings were unrelated to COVID-19. Though cases, before diagnosis, might have obtained antibiotics for COVID-19 from public outpatient settings, this possibility was minimal because of the intense contact-tracing (and the following quarantine) in place and that hospitalization was the isolation strategy such that treatment of COVID-19 should predominantly take place in hospitals. *Second,* we only had data from the public healthcare sector such that a complete description of antibiotic use in the community is limited by the lack of data from the private healthcare sector.

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Kin On Kwok: Conceptualization, Formal analysis, Data interpretation, Writing original draft. **Wan In Wei:** Conceptualization, Formal analysis, Data interpretation, Writing original draft. **Bosco Hon Ming Ma:** Formal analysis, Data interpretation, Writing review & editing. **Margaret Ip:** Data interpretation, Writing review & editing. **Heidi Cheung:** Data interpretation, Writing review & editing. **Elsie Hui:** Data interpretation, Writing review & editing. **Arthur Tang:** Data interpretation, Writing review & editing. **Edward Mcneil:** Formal analysis, Data interpretation, Writing review & editing. **Samuel Yeung Shan Wong:** Conceptualization, Data interpretation, Writing review & editing. **Eng Kiong Yeoh:** Conceptualization, Data curation, Data interpretation, Writing review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.02.014.

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