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ORIGINAL RESEARCH

Rebound of Antibiotic Use and Respiratory Infections After Resumption of Normalcy From COVID-19 in Hong Kong

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Purpose: During COVID-19 pandemic, use of antimicrobial has been shown to be reduced coupled with various respiratory infections. We investigated whether this effect on reduction of antibiotic prescription can be sustained after resumption of normalcy and lifting of public health measures.

Methods: We compared the wholesale supply of antimicrobials using mean annual Daily Defined Dose/1000 inhabitants (DID) in different sectors in pre-COVID-19 (2014–2019), COVID-19 (2020–2022) and post-COVID-19 (2023) periods. We grouped the data according to AWaRe categorisation namely Access, Watch and Reserve defined by WHO, and analysed the trends of the top 10 antibiotics and broad-spectrum antimicrobials. The trends in statutory notifiable diseases including scarlet fever, pneumococcal infections, chickenpox, tuberculosis, and pertussis and influenza-like-illness detected by sentinel surveillance system was analysed by negative-binominal regression.

Results: Compared to baseline level, an overall reduction of 27.2% of antimicrobial utilization was observed during the pandemic years, with a rebound recorded in 2023, up to 89.5% of the pre-pandemic level. The access group of antimicrobials accounted for 57.9% in 2014 gradually increased to 60.2% in 2023 across the pandemic years. Concurrently, reduction in incidence of scarlet fever, pneumococcal infections, chickenpox, tuberculosis, pertussis and influenza-like-illness was observed during COVID-19 pandemic with statistical decreasing trend, $p<0.05$ for scarlet fever, pneumococcal infections and chickenpox. Rebound in all these infections was reported in 2023, except for chickenpox which showed continued decrease in incidence.

Conclusion: We demonstrated a substantial reduction of antibiotic use during the COVID-19 pandemic, which rebounded in 2023, likely due to increased incidence of respiratory diseases after lifting of public health and social measures. We urged for close monitoring of the antimicrobial resistance pattern of different bacteria due to the inter-connectiveness and global impact of these two pandemics.

Keywords: antimicrobial resistance, antimicrobial utilization, antibiotics, COVID-19, surveillance

Introduction

The effect of Coronavirus Disease 2019 (COVID-19) pandemic on antimicrobial utilization has been examined since extensive use of antimicrobial may result in worsening of the antimicrobial resistance (AMR) situation. The possible reciprocity between the two contemporaneous pandemics of COVID-19 and AMR is complex and the syndemic of these two conditions has tremendous implications on global health.[1–4] On one hand, the overuse of antibiotics in COVID-19 patients without secondary bacterial infections, in particular the early phase of the pandemic may adverse the AMR situation. An early systematic review involving over 30,000 COVID-19 patients has shown that the prevalence of antibiotic prescribing was 74.6% with estimated bacterial co-infection rate of 8.6% only.[5] This situation does not improve much in

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2023 from a meta-analysis involving 29 studies with 157,623 participants in 11 countries, which reported that antibiotics were prescribed to 67% of COVID-19 patients of which 80% of prescriptions were provided without confirmed bacterial coinfections.[6] On the other hand, it has been shown that the respiratory infections including scarlet fever, pneumococcal infections, *Haemophilus influenza* infection, *Neisseria meningitis* were reduced during the COVID-19 pandemic in many parts of the world including Hong Kong.[7–9] The reduction in these diseases is probably due to public health interventions such as mask wearing, hand hygiene, social distancing, environmental hygiene and disinfection. Coupled with the reduction in these respiratory infections, it has been further studied that antimicrobial utilization was reduced in the same period.[10,11]

However, previous study only examined the effect in 2020 and 2021, but not in 2022 when Omicron subvariant BA.2 and Delta variant of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged leaving to a much larger scale of community outbreaks.[9] Moreover, it is also uncertain whether the effect on reduction of antibiotic prescription can be sustained after the resumption of normalcy and lifting of public health measures. This variation in antimicrobial utilization has far reaching implications on AMR control, and it has been stressed the importance of surveillance of antimicrobial utilization and AMR in the peri-pandemic period.[12] In Hong Kong, public health and social measures have been widely implemented during the pandemic from 2021 to 2023 including universal masking, frequent hand hygiene, enhanced environmental cleaning and disinfection, social distancing and intermittent school closures in the community. With the availability of antiviral treatment and gradual climbing up of herd immunity by both vaccination and natural infection, the aforementioned non-pharmacological interventions have gradually been adjusted in the mitigation phase in 2023. The Government of Hong Kong Special Administrative Region has announced to lift all mandatory mask-wearing requirements to enable the society to resume normalcy in full with effect from 1 March 2023.[13] It is crucial to closely monitor the surveillance data of antimicrobial utilization and assess whether there is any rebound of the respiratory infections and antimicrobial utilization in both hospitals and the community. The aim of the present study is to examine any change in antimicrobial utilization and the respiratory infections during COVID-19 and in the post-COVID-19 period. This would provide useful insight on implications on tackling AMR.

Methods

Study Design

This was a time-series study of the data on antimicrobial use and the selected respiratory infections recorded by the Centre for Health Protection (CHP), Department of Health (DH) in Hong Kong. We compared these data in the pre-COVID-19, COVID-19 and post-COVID-19 periods. The baseline (pre-COVID-19) period was defined from 2014 to 2019 in which 2014 was the earliest year that the wholesale data of antimicrobial supply were available. For simplicity, the pandemic period was defined from 2020 to 2022 and post-COVID-19 period in 2023.

Data on Antimicrobial Use and Respiratory Infections

We collected the annual wholesale supply data from all registered drug wholesalers in Hong Kong. This served as good proxy of antimicrobial consumption for the whole territory of 7.3 million population. The supply data were analysed according to different sectors, namely DH, Hospital Authority (HA), private hospitals, private doctors (mutually exclusive with private hospitals), community pharmacies and dentists. Supply to non-human sector (veterinary surgeons and farmers) was excluded from this analysis, and they accounted for only about 1% of the total wholesale supply. We followed the recommendation of the World Health Organisation (WHO) on surveillance of antimicrobial consumption in calculation of amount of antimicrobial as Daily Defined Dose (DDD), adopt the following core set of antimicrobials under WHO's Anatomical Therapeutic Chemical (ATC) classification system, using version 2022 for calculations.[14,15] The ATC Groups included "antibacterials for systemic use", "nitroimidazole derivatives, agents against amoebiasis and other protozoal diseases", as well as "antibiotics, intestinal anti-infectives". Antimicrobials for systemic use were included while topical antimicrobials were excluded as recommended by WHO.

We grouped the wholesale supply data of antimicrobials according to WHO AWaRe categorisation namely Access, Watch and Reserve in 2023 and those not listed under WHO AWaRe were grouped as 'Others'.[16] We reported the top 10 antibiotics sold in the baseline, pandemic and post-pandemic periods. Wholesale supply figures for a top 10 broad-

spectrum antimicrobials were examined separately for their importance in the treatment of resistant bacterial infections. The surveillance period was defined by calendar year. Results were analysed and presented as DDD and DID (DDD per 1000 inhabitants per day) as the units adopted by the WHO. Version 2023 of the DDD values were adopted for calculations.

We examined the trends of statutory notifiable diseases (required by law for doctors in Hong Kong to report them to Department of Health) which were transmitted through respiratory route including scarlet fever, pneumococcal infections, chickenpox, tuberculosis, and pertussis in the three peri-pandemic periods. The annual number of cases reported to the CHP, DH was divided by the mid-year population reported by Census and Statistics Department in the corresponding years. In addition, trends of influenza-like illnesses (ILI) in the community were monitoring through sentinel surveillance system among private medical practitioners. ILI was defined as fever >38 degree Celsius and having cough or sore throat. The sentinel surveillance system collected data from disease syndrome reported among some 50 general practitioners who were distributed territory-wide in Hong Kong. Details on operation of the sentinel surveillance system can be found in previous publication.[17] The surveillance system has been shown to be a geographically representative system to monitor different infections.[17] The present research is a retrospective study with secondary analysis of routinely collected surveillance data under the DH, Hong Kong Special Administrative Region, including the surveillance data of antimicrobial utilization, statutory notifiable diseases and sentinel surveillance data for ILI. The study was exempted from ethics approval as it contained no identifiable data.

Statistical Analysis

The annual DID and percentage distribution by sector was computed from 2014 to 2023. The distribution of DID according to the AWaRe category in the peri-pandemic periods was examined. For each of the three periods, the mean wholesale supply of antimicrobial is calculated. The mean value in the pre-COVID-19 period was considered as baseline and compared with that of during COVID-19 and post-COVID-19 period. The change in percentage of DID for total antimicrobial utilization and for each sector was calculated. The trends of the 10 top antibiotics and 10 top broad spectrum antibiotics supply from 2014 to 2023 were examined. For ILI, the area under the curve was compared. The mean value of incidence of selected notifiable diseases was estimated and compared in the three periods using negative binomial regression. Statistical significance was considered if $p<0.05$ and SPSS version 27, Chicago was used.

Results

Change in Antimicrobial Utilization

In the pre-COVID-19 years, the mean DID was 19.09, ranged from 18.41 to 20.37 (Table 1). Private doctors accounted for about half of the antimicrobial utilisation ranging from 52.6% to 57.5% (Figure 1) during the baseline period. Public hospitals under HA accounted for 19.7% to 23.6% while private hospitals accounted for 4.9% to 7.5%. There was

Table 1 Antimicrobial Utilization by Different Sector in Peri-COVID Periods

Sector		Hospital Authority	Private Hospitals	Private GP	Community Pharmacies	Department of Health	Dentists	Total
Pre-COVID-19 (2014–2019)	**Mean (range) DID during the period**	4.11 (3.80–4.47)	1.18 (0.93–1.38)	10.40 (9.69–10.91)	2.76 (1.46–3.82)	0.19 (0.17–0.21)	0.45 (0.27–0.64)	19.09 (18.41–20.37)
During COVID-19 (2020–2022)	**Mean (range) DID during the period**	4.14 (4.01–4.29)	0.87 (0.81–0.93)	7.12 (6.79–7.71)	0.91 (0.78–1.05)	0.18 (0.16–0.19)	0.67 (0.61 −0.71)	13.89 (13.59–14.39)
	Change in DID (%)	0.7%	−26.6%	−31.5%	−66.9%	−6.5%	49.8%	−27.2%
Post-COVID-19 (2023)	**Mean DID during the period**	4.84	1.06	9.76	0.71	0.19	0.53	17.08
	Change in DID (%)	17.7%	−10.8%	−6.2%	−74.3%	−2.1%	18.5%	−10.5%

Note: Antimicrobials supplied to veterinarians and non-human use antimicrobials were not included.
Abbreviations: DID, Defined Daily Dose per 1000 inhabitant.

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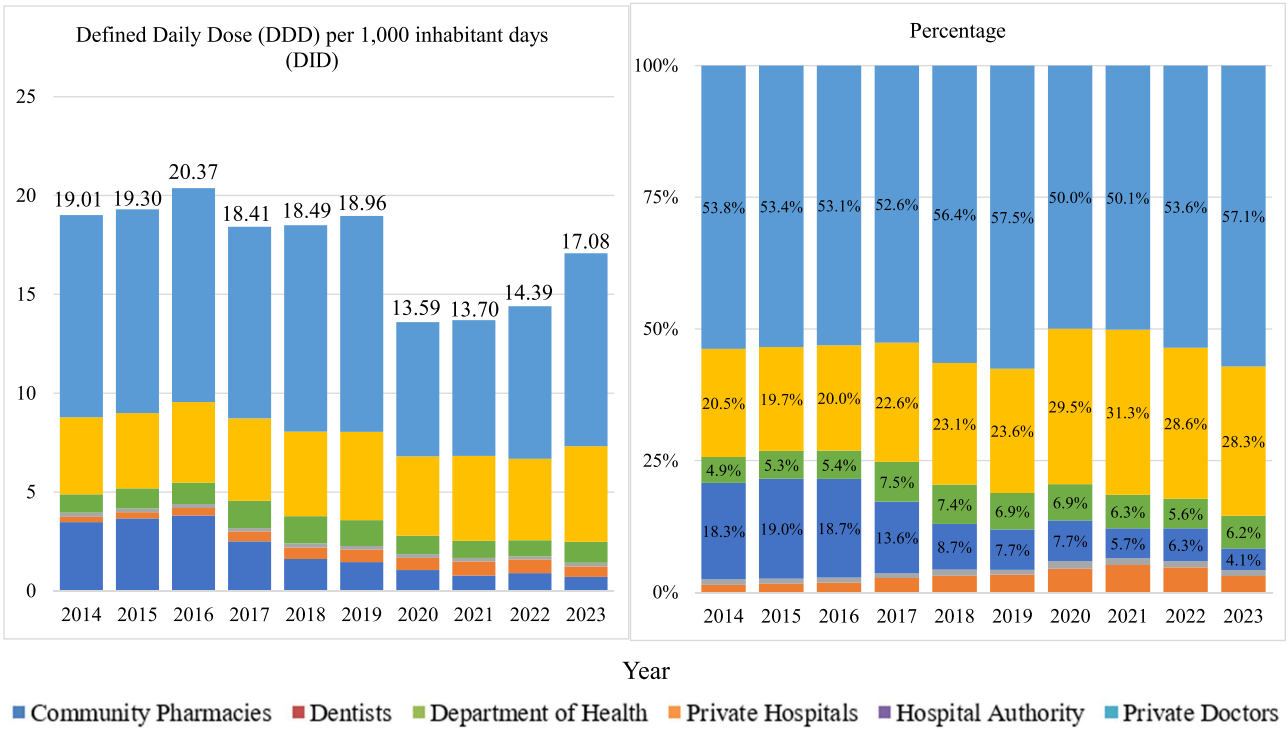

Figure 1 Distribution of antimicrobial utilization by sector, 2014–2023.

a decreasing trend of antimicrobial supply to community pharmacies from 18.3% in 2014 to 7.7% in 2019. During the three years of COVID-19 from 2020 to 2022, there was an overall drop of antimicrobial utilization by 27.2% from 19.09 to 13.89 DID when compared with the baseline period. The drop was most significantly seen in community pharmacies (from 2.76 to 0.91 DID, −66.9%), followed by private practitioners (10.40 to 7.12 DID, −31.5%) and private hospitals (1.18 to 0.87 DID, −26.6%). While the DID for public hospitals was almost the same as that in baseline period, a rise in DID was seen among dentists (0.45 to 0.67, +49.8%). In 2023, we recorded a rebound of antimibrobial use but the total supply has reached only up to 89.5% of the pre-COVID-19 period. The trends in private doctors and private hospitals followed this slightly rebound observation while the DID of public hospital has exceeded that of the baseline (4.84 in 2023 vs 4.11 in baseline). A continuous decrease was seen in antimicrobial supply in community pharmacies (0.71 in 2023 vs 0.91 DID during COVID-19 vs 2.76 in baseline).

In 2014, the Access group of antimicrobial supply accounted for 57.9% according to the AWaRe category. It gradually increased to the peak of 64.2% in 2021 and has met the WHO target of 60% since 2020 (Figure 2). On the contrary, the Watch group gradually decreased from 40.3% in 2016 to 31.8% in 2021. The Reserve group remained at a low level, ranging from 0.1% to 0.2% in the past decade.

Change in Top 10 Antimicrobials and Broad Spectrum Antibiotics Supply

From 2014 to 2023, the 10 antimicrobials contributed to more than 82% of all antimicrobials supplied in the corresponding year (Supplementary Information 1). In 2023, amoxicillin and beta-lactamase inhibitor (J01CR02) continued to be the most supplied antimicrobial, accounting for 29.2% of all antimicrobials in wholesale supply, followed by amoxicillin (J01CA04) (11.8%) and doxycycline (J01AA02) (9.0%). The trends of the top 10 antimicrobials supply are shown in Figure 3. Except for doxycycline and metronidazole, all antibiotics showed notable drop in utilization during the pandemic period of 2020 to 2022 compared to the baseline. Rebound in utilization of these antibiotics, in particular amoxicillin and beta-lactamase inhibitor was observed in 2023.

In 2023, piperacillin/tazobactam (J01CR05) continued to be the most supplied (42.5%) broad-spectrum antimicrobial, followed by meropenem (J01DH02) (22.9%) and vancomycin (J01XA01) (13.7%) (Supplementary Information 2). These

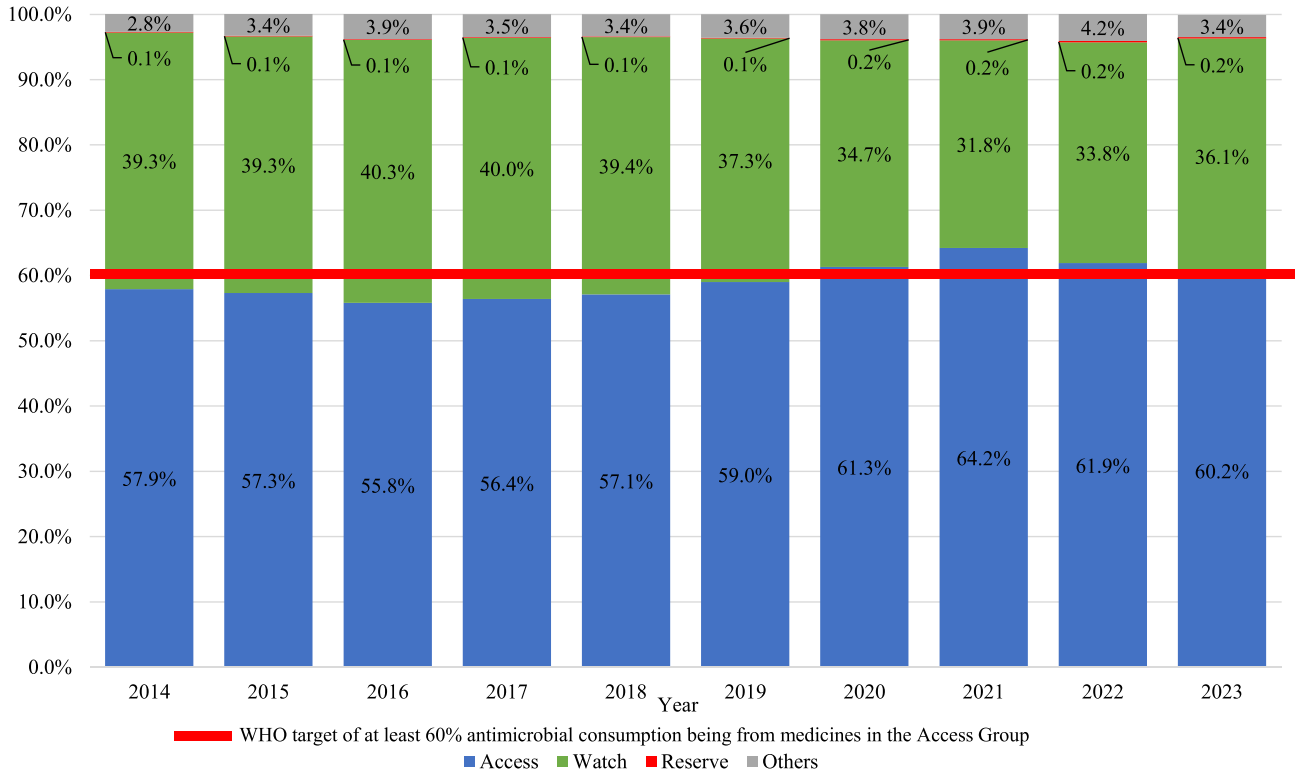

Figure 2 Distribution of antimicrobial utilization by AWaRe category, 2014–2023.

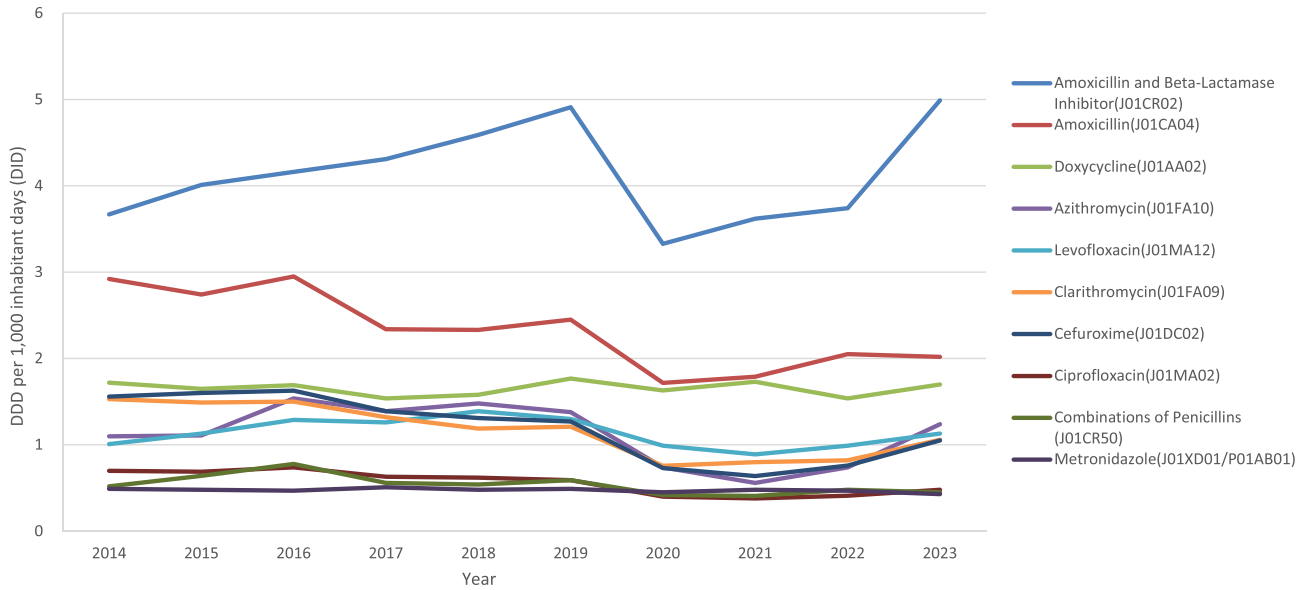

Figure 3 Trend of top 10 prescriptions in peri-COVID-19 period (2014–2023).

three broad-spectrum antimicrobials accounted for about 79.1% of all broad-spectrum antimicrobials supplied in 2023. Except for cefoperazone and beta-lactamase inhibitor, and ceftaroline fosamil, all broad spectrum antibiotics showed an increasing trend from 2014 to 2023 across the pandemic years (Figure 4).

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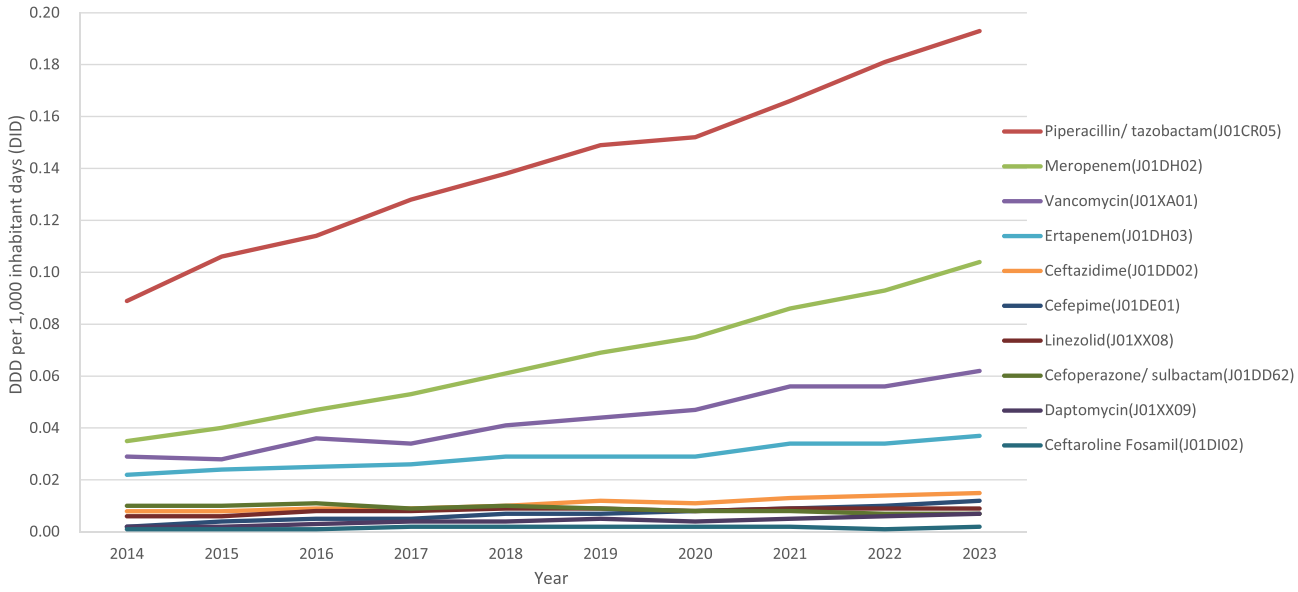

Figure 4 Trend of broad spectrum antibiotics in peri-COVID-19 period (2014–2023).

Change in Incidence of Notifiable Diseases and Respiratory Illness Detected by Sentinel Surveillance

The incidence of the selected notifiable diseases is shown in Table 2 and Figure 5. Compared to the baseline period, there was a reduction of incidence in all of these respiratory diseases including scarlet fever, pneumococcal infections, chickenpox, tuberculosis, and pertussis during COVID-19, ranging from a reduction of 19.2% to 92.2%. A rebound in incidence rates of scarlet fever, pneumococcal infections, and pertussis was noted in 2023, yet the rates were still 9.9.0% to 50.6% lower compared to the pre-COVID levels. For tuberculosis and chickenpox, a further decrease in notifications was reported after the pandemic period. Negative binomial regression showed a statistical decreasing trend for chickenpox, pneumococcal infection and scarlet fever, with all p-values <0.05 (Table 3). Unlike chickenpox, the reduction in 2023 for pneumococcal infections and scarlet fever became non-significant when compared with the baseline incidence. Similarly, a reduction of 62.1% in ILI was also reported through the sentinel surveillance system during pandemic years, and the rates rebound in 2023. The area under the curve in 2023 was 85.0% of the pre-pandemic years (Figure 6 and Table 4).

Discussion

We reported the effect of COVID-19 on antimicrobial utilization and tracked its trends after resumption of normalcy. We have demonstrated a rebound in antimicrobial utilization, especially among general practitioners after its reduction in the three years of COVID-19 from 2020 to 2022. This is likely due to rebound of respiratory infections as reflected in sentinel surveillance for ILI and other respiratory notifiable diseases such as scarlet fever and invasive pneumococcal infections. The rebounds in respiratory diseases may result in both appropriate use of antibiotics to treat bacterial infections and inappropriate use for viral diseases due to diagnostic uncertainty. It is noted that the magnitude of rebound in antimicrobial utilization has not returned to the level in the pre-COVID-19 period. It only accounts for about less than half of the difference between the baseline level and that recorded during the pandemic years. It may be due to the sustained effect of personal and environmental hygiene such as mask wearing, cough etiquette and hand hygiene, environmental cleaning and disinfection. Non-pharmacological public health interventions have been shown to reduce various infections.[18] Yet, it needs more time to observe whether such new norm can be sustained in a longer term. Rebound in consumption of antibacterials was also seen for systemic use (ATC J01) in the community sector in the European Union/European Economic Area in 2022, which has been brought back at pre-pandemic levels after

Table 2 Change in Incidence of Respiratory Diseases in Peri-COVID-19 Period

Notifiable Infectious Disease	Streptococcus pyogenes			Streptococcus pneumoniae (invasive)*			Tuberculosis			Pertussis			Chickenpox		
	Total notifications	Mean annual notifications (range)	Mean annual notifications per 100000 inhabitants (% change compared to baseline)	Total notifications	Mean annual notifications (range)	Mean annual notifications per 100000 inhabitants (% change compared to baseline)	Total notifications	Mean annual notifications (range)	Mean annual notifications per 100000 inhabitants (% change compared to baseline)	Total notifications	Mean annual notifications (range)	Mean annual notifications per 100000 inhabitants (% change compared to baseline)	Total notifications	Mean annual notifications (range)	Mean annual notifications per 100000 inhabitants (% change compared to baseline)
Pre-COVID-19 (2014–2019)	9967	1661.2 (1210–2353)	22.50	915	183.0 (162–189)	2.47	25,990	4331.7 (4003–4705)	58.83	386	64.3 (30–110)	0.87	49,261	8210.2 (6898–9347)	111.50
During COVID-19 (2020–2022)	391	130.3 (41–262)	1.75 (−92.2%)	100	33.3 (25–47)	0.45 (−81.8%)	10,572	3524.0 (3200–3716)	47.52 (−19.2%)	27	9.0 (2–22)	0.12 (−86.2%)	4578	1526.0 (1002–1987)	20.55 (−81.6%)
Post-COVID-19 (2023)	167	167.0 (167–167)	2.22 (−90.1%)	94	94.0 (94–94)	1.25 (−49.4%)	3260	3260.0 (3260–3260)	43.26 (−26.5%)	15	15.0 (15–15)	0.20 (−77.0%)	1396	1396.0 (1396–1396)	18.52 (−83.4%)

Note: *'Streptococcus pneumoniae (invasive)' has been listed as a notifiable infectious disease since 9 January 2015.

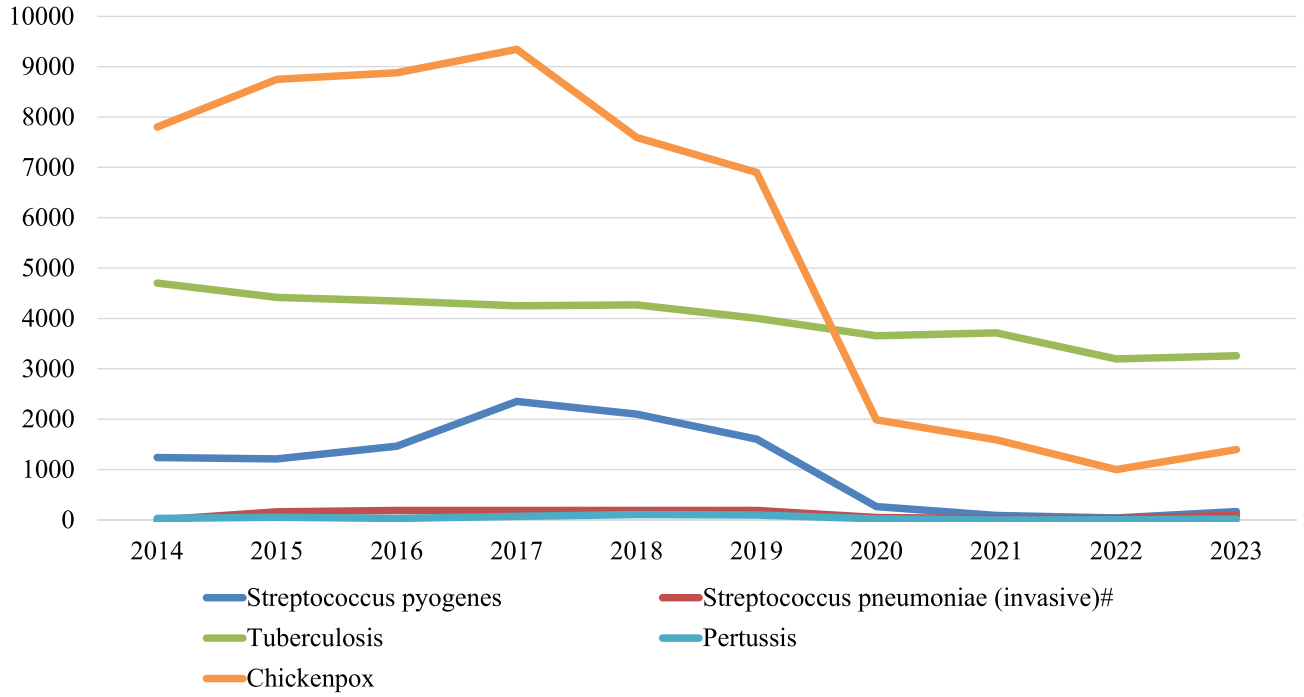

Figure 5 Number of statutory notifications for selected respiratory diseases in peri-COVID-19 period (2014–2023). #'Streptococcus pneumoniae (invasive)' has been listed as a notifiable infectious disease since 9 January 2015.

a significant decrease in antibiotic consumption.[19] It can be explained by early resumption of normalcy in the European countries than in Hong Kong.

The effect of COVID-19 on antimicrobial utilization varies in different phase of the pandemic. In early phase in 2020, over-prescription of antibiotics was commonly seen in COVID-19 patients probably due to lack of diagnostic uncertainty and lack of availability of the antivirals. In a systematic review done in early pandemic period (up to April 2020), it has been shown that antibiotics were prescribed in 71.9% of COVID-19 patients and yet, only 6.9% were confirmed to have bacterial infections.[20] In the first year of the pandemic in Switzerland, total overall inpatient antibiotic consumption measured in defined daily doses (DDD) per 100 bed-days remained stable (+1.7%), with a slight increase in ICUs of +4.2%.[21] However, the study has shown the increase in consumption of broad-spectrum antibiotics was +12.3% overall and 17.3% in ICUs. In other part of Europe, similar increase in hospital antimicrobial utililisation with a shift towards broad-spectrum antimicrobials was also reported.[22] Compared with the baseline, we reported a very similar finding of 1%

Table 3 Negative-Binomial Regression on Annual Incidence of Respiratory Diseases in Peri-COVID-19 Period (2014–2023)

Variable	Streptococcus pyogenes		Streptococcus pneumoniae (invasive)#		Tuberculosis		Pertussis		Chickenpox	
	Incidence Rate Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value
Year	0.99 (0.71–1.39)	>0.9	0.98 (0.86–1.12)	0.8	0.97 (0.95–0.99)	<0.001	1.14 (0.54–2.38)	0.7	0.94 (0.86–1.03)	0.2
Time Period										
Pre-COVID-19 (2014–2019)	—	—	—	—	—	—	—	—	—	—
COVID-19 (2020–2022)	0.06 (0.01–0.41)	0.004	0.19 (0.10–0.36)	<0.001	0.93 (0.85–1.03)	0.2	0.05 (0.00–2.86)	0.15	0.24 (0.15–0.38)	<0.001
Post-COVID-19 (2023)	0.11 (0.01–1.69)	0.11	0.57 (0.22–1.49)	0.3	0.92 (0.80–1.06)	0.2	0.11 (0.00–43.9)	0.5	0.25 (0.13–0.51)	<0.001

Note: #'Streptococcus pneumoniae (invasive)' has been listed as a notifiable infectious disease since 9 January 2015.

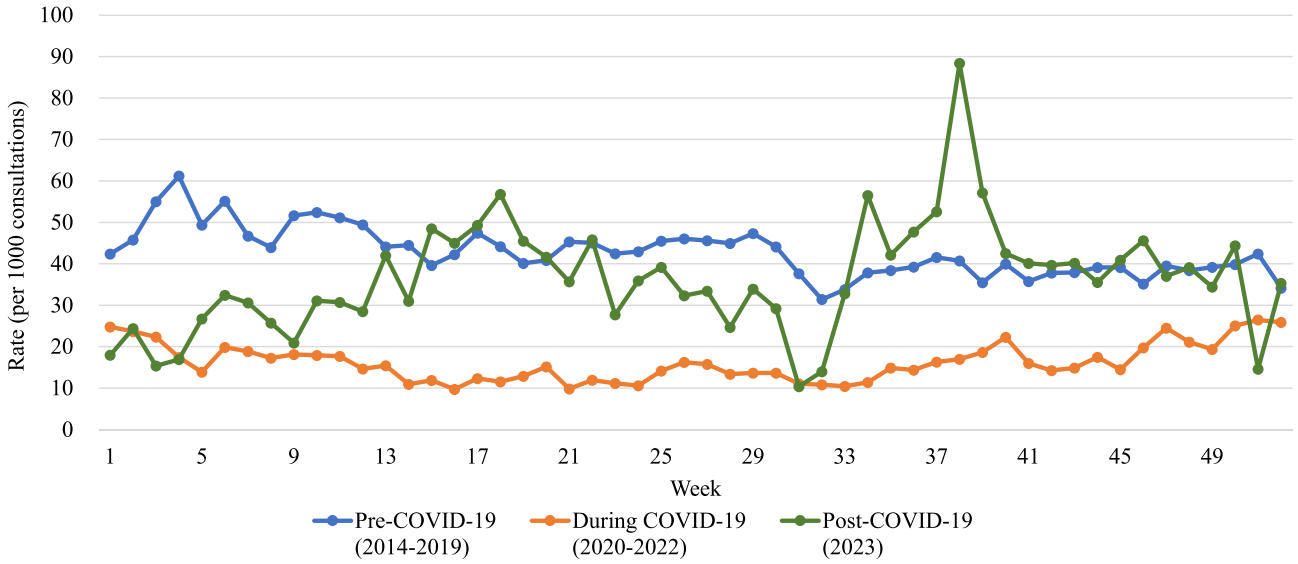

Figure 6 Consultation rate of influenza-like-illness in peri-COVID-19 period (2014–2023).

increase in antimicrobial utililisation in HA during pandemic period. However, in the private hospital, there was a 27% decrease in antimicrobial utilisation, probably due to fear of attending healthcare facilities by public to avoid contracting COVID-19. In Hong Kong, vast majority of the COVID-19 patients were admitted to public hospitals for treatment or isolation. We also recorded a rise in consumption of some broad spectrum antibiotics, partially explained by increased number of severe infections in the 5th wave with exponential increase in COVID-19 infections in the community.

In contrast, there is a drastic drop in antibiotic consumption in the community in EU countries,[23] and Canada.[24,25] From April to August 2020, antimicrobial consumption decreased worldwide by 18.7% ($P < 0.001$) compared with the previous year.[26] In an Ireland study, it was found increase in antimicrobial consumption in hospitals while a decrease in antimicrobial consumption in primary care setting.[27] The drop is probably due to reduction in respiratory illnesses as a result of non-pharmacological public health measures such as mask wearing, hand hygiene, social distancing, environmental hygiene and disinfection. Besides, this might be accounted by reduced medical attendance for mild illness due to fear of getting infection, and disruption of health services due to sick medical workforce.[28] We also reported a differential change of antimicrobial utilisation in public hospitals and community setting, with a substantial drop in general practitioners (27%) while antimicrobial utilisation in public hospitals was basically maintained compared with baseline level. Our findings in reduction of antimicrobial utilization (27%) are very similar to that (18.5%) reported in the EU countries.[19] This is also reflected in the trends of the top 10 antibiotics, many of which are used for treating community acquired respiratory infections such as ampicillin with or without beta-lactamase inhibitor, amoxicillin, doxycycline, levofloxacin and azithromycin.

Table 4 Consultation Rate of Influenza-Like-Illness in Peri-COVID-19 Period (2014–2023)

Consultation rate of influenza-like-illness (Rate per 1000 consultation)	**Weekly Mean (Range) (% change)**	**Area under the curve for Figure 6 (% change)**
Pre-COVID-19 (2014–2019)	42.2 (5.9–61.2) (reference)	22.13 (reference)
During COVID-19 (2020–2022)	16.0 (3.3–26.5) (−62.1%)	8.33 (37.6%)
Post-COVID-19 (2023)	36.3 (10.4–88.4) (−14.0%)	18.81 (85.0%)

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We have demonstrated the close link between the trends in antimicrobial utilisation and the respiratory infections including scarlet fever, pneumococcal infections, chickenpox, tuberculosis, and pertussis. Similar reductions in viral and bacterial respiratory diseases were also reported during the COVID-19 pandemic.[8,29–31] The number of cases decreased mainly among respiratory diseases (from −86% for measles, to −12% for tuberculosis).[32] The rebound in infections is most likely due to lifting of public health and social measures. It has been critically debated on the role of immunity debt on the disease epidemiology.[33–37] The lack of immune stimulation due to the reduced circulation of microbial agents and the reduced vaccine uptake may contribute to the immunity debt. This results in a growing proportion of susceptible people and a declined herd immunity in the population, which may possibly explain a higher rate of different infectious diseases. It is too early to conclude the rebound in infections observed was due to the immunity debt, and more scientific evidence are required to understand the transmission dynamics (how diseases are spread from one person to another) within the population.

Unlikely the antimicrobial utilization in private doctors and HA, we reported a reduction in antimicrobial utilization in community pharmacies after resumption of normalcy. This may be attributed to enhanced public education and enforcement actions to tackle illegal sales without prescription. One of the key measures in the "Hong Kong Strategy and Action Plan on AMR 2023 to 2027" is to strengthen the public health actions against illegal sales of antibiotics in the community pharmacies.[38] Stepped up actions have been implemented to conduct more test purchase and special inspections by the Department of Health on suspicious pharmacies with large volume of antimicrobial sales. On the other hand, there was a sustained increase in antimicrobial utilization among dentists over the pandemic and beyond. The exact underlying reason is not known and worth further exploring.

To our best of knowledge, this is the most comprehensive time-series analysis examining the antimicrobial utilization and disease pattern in the peri-pandemic period. Data from wholesale supply of antimicrobials for the whole territory and statutory notifications reported to the Department of Health were used for analysis. The breakdown of wholesale antimicrobial supply data allows subgroup analysis to compare any change in the public and private sectors. Our study has several limitations. The wholesale supply data is not equal to antimicrobial consumption. Yet, it is a very good proxy and since the same method has been adopted to examine the trends, any bias should not affect the direction of trends of antimicrobial use. Second, there may be under-reporting of the statutory notifications to the DH. Disruption of healthcare services among general practitioners during the COVID-19 period may increase the number of under-reporting. Lastly, the ILI pattern detected by sentinel surveillance system may vary after introduction of COVID-19 compared with pre-COVID-19 era.

In this study, we have shown the reverse trend in both respiratory illnesses and antimicrobial utilization in the first year after resumption of normalcy from the COVID-19 pandemic. It is recommended to continue monitor the disease epidemiology and antimicrobial surveillance to assess whether there is sustained beneficial effect of the public health measures to reduce infections and antimicrobial utilization in a longer term. In addition, more research should be conducted to study the effect of reduction and rebound of antimicrobial utilization in antimicrobial resistance pattern of different bacteria. The available evidence published so far seems not conclusive.[39–47] In one systematic review which included 38 studies up to July 2022, there is an increase in the rate of multidrug resistant gram positive eg methicillin-resistant *Staphylococcus aureus* (MRSA), and gram-negative bacteria like vancomycin-resistant enterococci (VRE), while the rate of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) has decrease during the pandemic.[48] In another systematic review up to almost the same period (June 2022), 22 studies are included in the meta-analysis.[49] In contrast, this meta-analysis revealed that COVID-19 pandemic was not associated with a change in the incidence density or proportion of MRSA or VRE cases, while a non-statistically significant increase was noted for resistant Gram-negative organisms such as ESBL, carbapenem-resistant Enterobacterales, carbapenem or multi-drug resistant or CRPA or *Acinetobacter baumannii*. We recommend conducting further research to examine the change in utilization of antimicrobial on resistance pattern of various bacteria in both community and hospital settings.

Conclusion

The COVID-19 pandemic has changed the disease epidemiology of many respiratory infections, disrupted the delivery of medical services, and altered the antimicrobial utilisation pattern. We have demonstrated a substantial reduction of antibiotic use during the pandemic in 2020 to 2022, which was followed by a rebound in use in 2023. The rebound is likely due to rebound of respiratory diseases in the community after lifting of non-pharmacological public health measures. We urge for close monitoring of the antimicrobial resistance pattern of different bacteria due to the inter-connectiveness and global impact of COVID-19 and AMR pandemics.

Ethics Approval

Not required since the current study is a secondary analysis not involving human subjects.

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