Impact of COVID-19 on antimicrobial resistance in Taiwan

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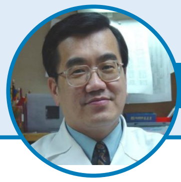

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Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) at the end of 2019, its associated disease, coronavirus disease 2019 (COVID-19), has affected more than 144 million people and resulted in more than 3 million deaths across 223 countries[1]. During the COVID-19 pandemic, overuse of antibiotics has occurred due to the following reasons:

1. Both SARS CoV-2 infection and community-acquired bacterial pneumonia share similar presentations, such as cough, fever, and radiological infiltrates.
2. The lack of effective anti-SARS CoV-2 treatments.
3. Potential bacterial coinfection, fungal, or other secondary infection along with COVID-19, but the incidence of this is low[2].

Therefore, the issue of increasing antimicrobial resistance (AMR) following the high rate of antibiotic utilisation for patients with COVID-19, particularly in severe cases, should be seriously considered[2].

In contrast to many other countries with an intense impact of COVID-19, Taiwan is relatively safe, wherein only 1,100 patients have been confirmed with SARS CoV-2 infection as of April 27, 2021 and 12 of them have succumbed to the disease[3]. The successful control of COVID-19 in Taiwan could be attributed to the aggressive efforts and preemptive deployment of response actions preventing rapid disease spread[4]. Even in such a scenario, a recent study reported a high consumption of antibiotics in the National Taiwan University Hospital, a 2500-bed medical center that provides primary and tertiary care in northern Taiwan in January–September 2020 compared with January–September 20192. These included ß-lactam / ß-lactamase inhibitor combinations, quinolones, carbapenems, colistin, tigecycline, fosfomycin, glycopeptides, linezolid, and daptomycin Moreover, increased levofloxacin resistance in *Streptococcus pyogenes*, ciprofloxacin resistance in non-Typhi *Salmonella* species, ampicillin-sulbactam, imipenem, and levofloxacin resistance in *Acinetobacter baumannii* complex isolates has been observed in the National Taiwan University Hospital[2]. However, we wondered whether the situation in a single hospital could be generalised to all other hospitals in Taiwan. Therefore, we conducted the analysis using the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) database and database from Taiwan Healthcare-associated Infection and Antimicrobial Resistance Surveillance System (THAS) established by the Taiwan Centers for Disease Control.

SMART

SMART has been used to monitor the *in vitro* AMR of non-duplicate clinically important bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Salmonella* spp., *Shigella* spp., *Neisseria gonorrhea, A. baumannii* complex*, Pseudomonas aeruginosa, Campylobacter* spp., and *Haemophilus influenzae*, which have been isolated from hospitals throughout Taiwan since 2017[5,6]. In this study, we analysed data on antimicrobial susceptibility and major resistance mechanisms, especially those underlying carbapenemase resistance, of clinically important bacteria isolated from 18 hospitals in Taiwan in 2019 and 2020.

Increasing proportions of methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium*, ertapenem-nonsusceptible *K. pneumoniae*, imipenem-nonsusceptible *P. aeruginosa* and imipenem-nonsusceptible *A. baumannii* complex were observed (**Figure 1**). In contrast, decreasing proportions of ertapenem-nonsusceptible *E. coli*, colistin-non-wild-type (NWT) *E. coli*, colistin-NWT *K. pneumoniae* and colistin-NWT non-typhoid *Salmonella* spp. were observed (**Figure 1**). Decreasing rates of carbapenem resistance from 2019 to 2020 were observed for both *E. coli* (1.4% [6/421] to 0.9% [3/335]) and *K. pneumoniae* (12.2% [45/370] to 11.1% [35/316]). Among the carbapenem-resistant *E. coli* isolates, only one was found to carry the carbapenemase-encoding gene *bla*$_{KPC-17}$ in 2019. Among the carbapenem-resistant *K. pneumoniae* isolates, 19 and 17 isolates in 2019 and 2020, respectively, were found to carry carbapenemase-encoding genes. *bla*$_{KPC}$ was the most common carbapenemase-encoding gene, and in particular, *bla*$_{KPC-2}$ was the most common KPC gene.

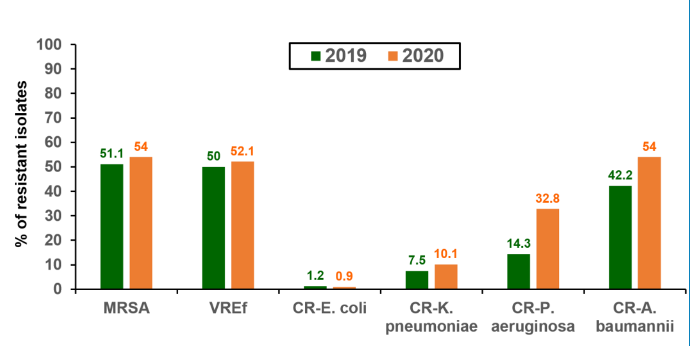

Figure 1. The proportions of clinically important multidrug-resistant organisms associated with bloodstream infection, as recorded in the SMART database, in 2019 and 2020. MRSA. Methicillin-resistant *S. aureus*; VREf, vancomycin-resistant *E. faecium*; CR, carbapenem-resistant.

THAS

In addition to applying SMART, we also assessed the change in AMR before and after the COVID-19 outbreak using an open access database, Taiwan Nosocomial Infection Surveillance System (TNIS), which was launched by the Taiwan Centers for

Disease Control in 2007 and renamed to THAS on 4 February 2020[7]. This system aims to monitor the occurrence of healthcare-associated infections (HAIs) and assess the epidemiologic trends of HAIs. Moreover, this system also provides antimicrobial susceptibility data from the reporting hospitals, including medical centers (n = 22) and regional hospitals (n = 84), across different regions in Taiwan. This study used the recent report of THAS[7], which presents the surveillance data of HAIs and associated AMR until September 2020, for analysis.

First, the summary of AMR in the clinical isolates causing HAIs in intensive care units (ICUs) collected between January and September 2020 showed that the carbapenem resistance rates of clinical isolates of *A. baumannii, Enterobacterales, E. coli, K. pneumoniae, and P. aeruginosa* were 75.3%, 26.1%, 1.9%, 44.4%, and 22.6%, respectively. The vancomycin resistance rates of *Enterococcus* species and *E. faecium* were 45.0% and 68.1%, respectively. The methicillin resistance rate of *S. aureus* was 56.9% (**Figure 2**). Second, the findings in regional hospitals' ICUs showed that the carbapenem resistance rates of clinical isolates of *A. baumannii, Enterobacterales, E. coli, K. pneumoniae, and P. aeruginosa* were 78.1%, 20.3%, 4.5%, 34.3%, and 20.3%, respectively. The vancomycin-resistance rates of *Enterococcus* species and *E. faecium* were 40.8% and 60.8%, respectively. The methicillin resistance rate of *S. aureus* was 65.1% (**Figure 2**). Third, evaluation of the changes in the AMR rate between 2019 and three-fourths of the year 2020 showed that the carbapenem resistance rates of *A. baumannii, Enterobacterales* and *K. pneumoniae* had increased in the medical centers from 2019 to 2020. In contrast, the AMR rate decreased from 2019 to 2020 (**Figure 2**). Finally, a similar trend was observed with the regional hospitals. The carbapenem resistance rates of *A. baumannii*, *Enterobacterales*, *K. pneumoniae* and *P. aeruginosa* increased, but their rate of resistance to other antibiotics decreased (**Figure 2**).

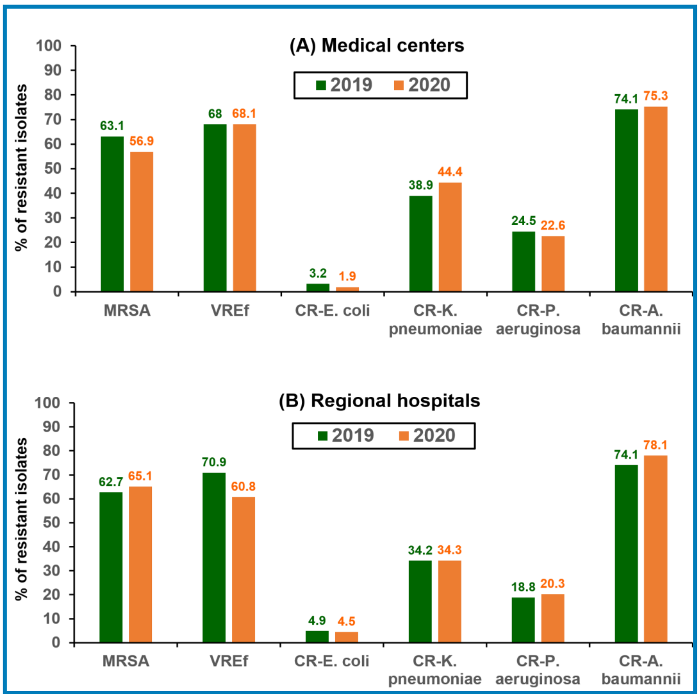

Figure 2. The rates of incidence of common multidrug-resistant organisms in intensive care units of (A) medical centers (n = 22) and (B) regional hospitals (n = 84), as reported in the Taiwan Healthcare-Associated Infection and Antimicrobial Resistance Surveillance System (THAS) in 2019 and 2020. MRSA. Methicillin-resistant *S. aureus*; VREf, vancomycin-resistant *E. faecium*; CR, carbapenem-resistant.

Overall, the increase in the carbapenem resistance rate in the THAS report was much lower than that obtained with SMART. These differences could be due to the different clinical settings considered for compiling these two databases. THAS included 22 medical centers and 84 regional hospitals, focusing on ICUs including medical, surgical, and mixed ICUs, and cardiac care units. Moreover, most hospitals in THAS did not care for patients with COVID-19; hence, the impact of the COVID-19 pandemic on the changes in AMR rate could be diluted in the THAS report and was not as large as that observed with SMART, wherein all the 18 hospitals were involved in caring for patients with COVID-19, especially the critical cases.

Conclusions

Based on our analysis using SMART and THAS, we found that the carbapenem resistance rate of clinical bacterial isolates increased from 2019 to 2020, especially using SMART. The cause was multifactorial, specifically because of the high rate of antimicrobial agent utilisation with a relatively low rate of coinfection or secondary infection in patients with COVID-19. Appropriate prescription and optimised use of antimicrobials according to the principles of antimicrobial stewardship (AMS) programmes, together with quality diagnosis and aggressive infection control measures, may prevent the occurrence of infections of multidrug-resistant organisms during COVID-19. Clinicians should continue following appropriate antibiotic prescription practices according to the AMS programmes, especially with the use of carbapenem in Taiwan. In addition, regular monitoring of AMR data in every hospital would help establish an epidemiologic database for clinicians' reference for prescribing antimicrobial agents. Our findings were based on only a short-term surveillance. Therefore, further long-term assessment of the impact of COVID-19 on AMR is warranted.

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