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# Increased antimicrobial resistance during the COVID-19 pandemic

Chih-Cheng Lai [a], Shey-Ying Chen [b,c], Wen-Chien Ko [d], Po-Ren Hsueh [e,f,*]

[a] Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan
[b] Department of Emergency Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[c] Center for Quality Management, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan
[d] Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[e] Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[f] Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

## ARTICLE INFO

## ABSTRACT

In addition to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection itself, an increase in the incidence of antimicrobial resistance poses collateral damage to the current status of the COVID-19 (coronavirus disease 2019) pandemic. There has been a rapid increase in multidrug-resistant organisms (MDROs), including extended-spectrum $\beta$-lactamase (ESBL)-producing *Klebsiella pneumoniae*, carbapenem-resistant New Delhi metallo-$\beta$-lactamase (NDM)-producing Enterobacterales, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA), pan-echinocandin-resistant *Candida glabrata* and multi-triazole-resistant *Aspergillus fumigatus*. The cause is multifactorial and is particularly related to high rates of antimicrobial agent utilisation in COVID-19 patients with a relatively low rate of co- or secondary infection. Appropriate prescription and optimised use of antimicrobials according to the principles of antimicrobial stewardship as well as quality diagnosis and aggressive infection control measures may help prevent the occurrence of MDROs during this pandemic.

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## 1. Introduction

Since the first case of COVID-19 (coronavirus disease 2019), initially named 2019 novel coronavirus (2019-nCoV) pneumonia, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, China, the disease has affected more than 32.7 million people, with over 1 million fatalities worldwide [1,2]. To combat this global health crisis, every health authority developed and implemented numerous infection control and prevention measures, including mask wearing, practicing good hand hygiene, social distancing, avoiding crowded areas, active identification and quarantine of close contacts, and rapid set up of shelter hospitals and lockdown strategies [3–7]. These aggressive management measures in response to COVID-19 brought additional benefits in terms of reducing other infections. Many studies have reported a decreased incidence of several infectious respiratory diseases, such as seasonal influenza, invasive pneumococcal disease and tuberculosis during the COVID-19 pandemic compared with the same period in previous years [8–11]. However, we cannot neglect the increased incidence of antimicrobial resistance, which may be attributed to the excess use of antimicrobial agents during the COVID-19 pandemic [12].

## 2. Increasing incidence of antimicrobial resistance

Several recent reports have described an increase in multidrug-resistant organisms (MDROs) during the COVID-19 pandemic [13–23]. A retrospective study found that the incidence of carbapenem-resistant Enterobacterales colonisation increased from 6.7% in 2019 to 50% in March–April 2020 [13]. The underlying reasons included the high intensity of care required for patients, the susceptibility of 4–5 healthcare workers (HCWs) with prolonged contact with the patient, and the presence of 32 new HCWs lacking work experience in an intensive care unit (ICU) setting [13]. In Wuhan, China, Li et al. demonstrated that among 159 strains of bacteria isolated form 102 hospitalised COVID-19 patients with acquired secondary bacterial infections, *Acinetobacter baumannii* was the most common pathogen (35.8%; $n = 57$), followed by *Klebsiella pneumoniae* (30.8%; $n = 49$) and *Stenotrophomonas maltophilia* (6.3%; $n = 10$) [14]. Moreover, the carbapenem resistance rate for *A. baumannii* and *K. pneumoniae* was 91.2% and 75.5%, respectively [14]. Another retrospective study in a French ICU found that 26 COVID-19 patients who were admitted to the ICU for acute respiratory

* Corresponding author: Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.
*E-mail address:* hsporen@ntu.edu.tw (P.-R. Hsueh).

failure were considered to be co-infected with a pathogenic bacterium, and two and five isolates were resistant to third-generation cephalosporins and amoxicillin/clavulanate, respectively [15]. Similarly, a cohort of 19 COVID-19 patients who required ICU admission had secondary infection due to 17 multidrug-resistant *A. baumannii* and 1 methicillin-resistant *Staphylococcus aureus* (MRSA) [16]. Fu et al. observed five cases of critical COVID-19 patients with secondary infections, in which extended-spectrum $\beta$-lactamase (ESBL)-producing *K. pneumoniae, S. maltophilia, Burkholderia cepacia* and *Pseudomonas aeruginosa* were considered the causative pathogens [17]. Nori et al. reported five COVID-19 patients from New York (USA) who were co-infected with New Delhi metallo-$\beta$-lactamase (NDM)-producing *Enterobacter cloacae* [18]. Farfour et al. reported an outbreak of NDM-5-producing *Escherichia coli* involving six COVID-19 patients in a 12-bed ICU in France [19].

Fungal co-infections in COVID-19 patients pose a common challenge for clinical treatment. Posteraro et al. reported a complicated 53-day clinical course of a COVID-19 patient with type 2 diabetes mellitus who developed three episodes of secondary bloodstream infection by MRSA, *Morganella morganii* and potentially fatal *Candida glabrata* [20]. The development of *FKS*-associated pan-echinocandin resistance was detected in *C. glabrata* isolated after 13 days of caspofungin treatment [20]. In New Delhi (India), candidaemia affected 15 critical COVID-19 patients during April–July 2020 and multidrug-resistant *Candida auris* accounted for 10 cases and 6 deaths [21]. Mohamed et al. reported on an Irish patient with severe COVID-19 pneumonia that was complicated by a fatal co-infection with a multi-triazole-resistant strain of *Aspergillus fumigatus* [22].

## 3. High rate of antibiotic utilisation

In light of the COVID-19 pandemic, it has been reported that the necessity for the use of antimicrobial agents has increased compared with previous years. In an early report of 99 cases in China, more than 70% of patients with COVID-19 had received antibiotic treatment, approximately 15% of whom received antifungal agents [24]. Another study including 138 hospitalised patients showed that moxifloxacin, ceftriaxone and azithromycin were prescribed in 89 (64.5%), 34 (24.6%) and 25 (18.1%) patients, respectively [25]. A large-scale study showed that 58% of 1099 patients received intravenous (i.v.) antibiotics [26], whereas in a smaller Brazilian cohort of 72 hospitalised patients 84.7% had received i.v. antibiotic therapy [27]. Additionally, a recent review showed that 72.1% (1450/2010) of hospitalised COVID-19 patients received antibiotics [28]. Overall, more than one-half of COVID-19 patients may receive an i.v. antibiotic, and this number can be higher in patients with severe disease.

This high rate of antibiotic utilisation for patients infected with SARS-CoV-2, particularly in severe COVID-19 cases, could be due to the following: (i) as the prevalent presentations of SARS-CoV-2 infection (cough, fever and radiological infiltrates) are also hallmarks of community-acquired bacterial pneumonia, clinicians empirically add a broad-spectrum antibiotic despite the suspicion of a viral origin; (ii) the anxiety and uncertainty regarding the COVID-19 outbreak as well as the absence of effective anti-SARS-CoV-2 treatments are potential drivers of widespread and excessive prescription of antibiotics; and (iii) co-bacterial, fungal or secondary infection with COVID-19 is possible; however, it is difficult to differentiate between sole SARS-CoV-2 infection and co- or secondary infections.

## 4. Variable rate of co-infection

Patients with COVID-19 could be vulnerable to other infections owing to multiple co-morbidities in patients with severe COVID-19,

prolonged hospitalisation and SARS-CoV-2-associated immune dysfunction [29,30]. However, the prevalence of co-infection among COVID-19 patients is considerably lower due to the frequency of antibiotic use for patients with SARS-CoV-2 infection. In the UK, a retrospective study involving 836 patients with SARS-CoV-2 infection showed 3.2% of patients (*n* = 27) to have confirmed bacterial infection within the first 5 days after admission, the incidence of which rose to 6.1% (*n* = 55) for the duration of admission [16]. Li et al. showed that 6.8% (*n* = 102) of 1495 patients hospitalised with COVID-19 in Wuhan, China, had acquired secondary bacterial infection during hospitalisation [14]. A review by Rawson et al. noted that only 8% (*n* = 62) of 806 COVID-19 patients had superimposed bacterial or fungal co-infections [28]. Another review indicated that the prevalence of co-infection among COVID-19 patients varied; however, it could be up to 50% among non-survivors [31]. At present, many micro-organisms have been reported as the co-pathogens, including *Streptococcus pneumoniae, S. aureus, K. pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila, E. coli, P. aeruginosa, S. maltophilia, A. baumannii, Mycobacterium tuberculosis, Candida* spp., *Aspergillus* spp. and viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza virus, metapneumovirus, influenza B virus and human immunodeficiency virus (HIV) [15,28,31–34]. However, the majority of MDROs developed in patients with severe or critical COVID-19 and the incidence of co- or secondary infection may increase, resulting in prolonged hospitalisation [16,18,20,25,28,31].

## 5. The scenario in Taiwan

The increase in the incidence of antimicrobial resistance was reported in sites with a high burden of severe or critical COVID-19 cases [14–19], including New York (USA), Wuhan (China), France, Iran and Brazil during the earlier pandemic period. In Taiwan, as of 10 October 2020, a total of 527 laboratory-confirmed COVID-19 cases, including 55 indigenous cases and 7 deaths, were reported (Taiwan Centers for Diseases Control and Prevention; https://www.cdc.gov.tw/En). The low incidence (2.2 per 100 000 population) of COVID-19 in Taiwan could be due to the implementation of many infection control and prevention measures [35]. Since the end of 2019, the healthcare authority made a quick response, including surveillance, laboratory diagnosis, border control, control of community transmission, medical system response and preparedness, stockpile and allocation of personal protective equipment and other medical supplies, health education and disinformation management. Furthermore, the government rapidly established a Central Epidemic Command Center (CECC) to co-ordinate inter-ministerial responses, to mobilise resources and to conduct daily press briefings. By the effort of the CECC, people can obtain enough masks to use and adequate antiseptics for hand hygiene, which can effectively prevent droplet and contact transmission [35].

The National Taiwan University Hospital (NTUH) is a 2500-bed, academically-affiliated medical centre that provides primary and tertiary care in northern Taiwan. As of 10 October 2020, only 18 patients with COVID-19 were treated at the hospital, of whom 11 (61.1%) had pneumonia and 4 (22.2%) were admitted to the ICU. No HCWs at the hospital were reported to be infected with SARS-CoV-2. Fig. 1 shows the monthly number of confirmed cases of COVID-19 in Taiwan (*n* = 515; 12 were diagnosed between 1 July 2020 and 10 October 2020) and those treated at NTUH (*n* = 17; 1 was diagnosed in August 2020) during January–June 2020. The patient census between January–June 2019 and January–June 2020 was 1 271 140 and 1 157 262 for outpatient clinics, respectively, and 58 007 and 46 096 for the emergency department, respectively (Fig. 1). The numbers of inpatient-days at the hospital between these periods were 377 790 and 360 409, respectively. Over-
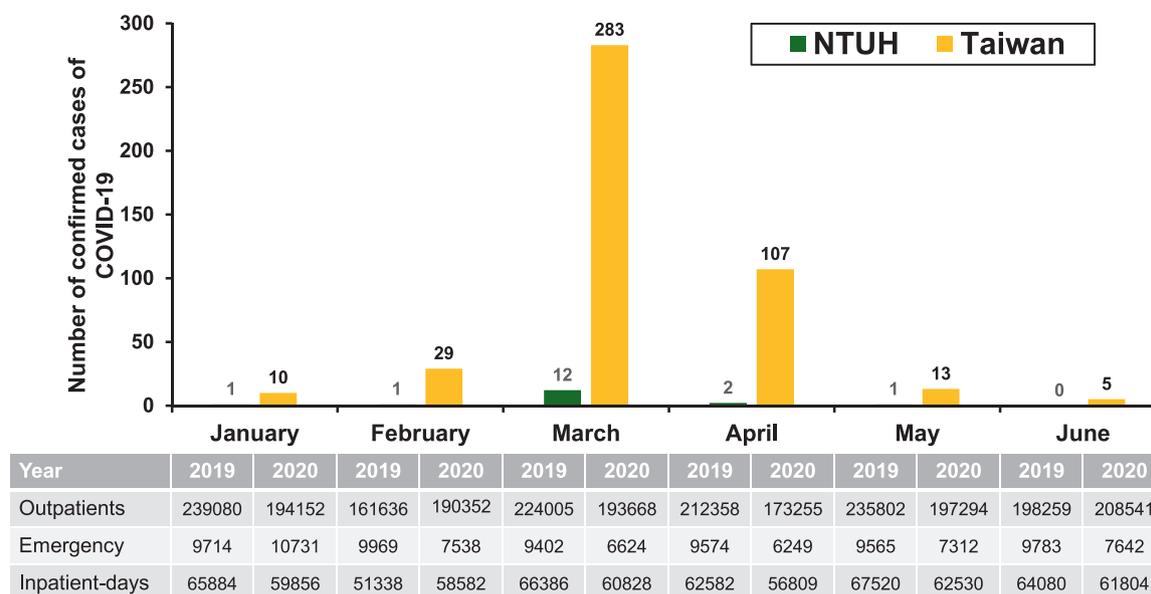
**Fig. 1.** Monthly number of confirmed cases of COVID-19 in Taiwan ($n = 447$) and those treated at National Taiwan University Hospital (NTUH) ($n = 17$) during January–June 2020. The patient census of outpatient clinics, emergency department and inpatient-days of hospitalisation of NTUH during January–June 2019 and January–June 2020.

**Table 1**
Consumptions of broad-spectrum antimicrobial agents at National Taiwan University Hospital during two time periods: January–June 2019 and January–June 2020

| Antibiotic | Antibiotic consumption (DDDs/1000 patient-days) by indicated time period | | % change |
|---|---|---|---|
| | January–June 2019 | January–June 2020 | |
| $\beta$-Lactam/$\beta$-lactamase inhibitor combinations [a] | 372.3 | 387.6 | 4.1 |
| Extended-spectrum cephalosporins [b] | 763.5 | 763.7 | 0.0 |
| Quinolones [c] | 182.3 | 201.8 | 10.7 |
| Carbapenems [d] | 330.4 | 376 | 13.8 |
| Aminoglycosides [e] | 237 | 221.3 | –6.6 |
| Colistin | 63.3 | 78.4 | 23.9 |
| Tigecycline | 56.3 | 89.7 | 59.3 |
| Fosfomycin | 23.7 | 41.4 | 74.7 |
| Glycopeptides [f] | 340.1 | 384 | 12.9 |
| Linezolid | 12.1 | 15.4 | 27.3 |
| Daptomycin | 77.3 | 95.1 | 23.0 |

DDD, defined daily doses.
[a] Including cefoperazone/sulbactam, piperacillin/tazobactam and ceftazidime/avibactam.
[b] Including cefotaxime, cefoperazone, flomoxef, ceftazidime, ceftriaxone and cefepime.
[c] Including ciprofloxacin, moxifloxacin and levofloxacin.
[d] Including imipenem, meropenem, doripenem and ertapenem.
[e] Including gentamicin, amikacin and streptomycin.
[f] Including vancomycin and teicoplanin.

all, the number of patients hospitalised between these periods was similar. However, higher consumption of antibiotics, including $\beta$-lactam/$\beta$-lactamase inhibitor combinations, quinolones, carbapenems, colistin, tigecycline, fosfomycin, glycopeptides, linezolid and daptomycin, was observed during January–June 2020 compared with January–June 2019 (Table 1).

Fig. 2 illustrates the number and rate of antimicrobial-resistant infections of clinically important bacterial species recovered from patients who visited NTUH during the period January–June in 2019 and 2020. The number of isolates of *S. pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* and non-Typhi *Salmonella* spp. notably decreased during these periods (Fig. 2A). These findings were partly consistent with those of other studies [9,11]. However, the number of isolates of *S. aureus*, *Enterococcus* spp., *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* complex remained stable (Fig. 2B). In general, the resistance rates of the se-

lected antibiotics remained constant between the two time periods ($\leq 5\%$ difference), with the exception of a decline in ampicillin and trimethoprim/sulfamethoxazole resistance of *H. influenzae* (15% and 9% difference, respectively) and an increase in levofloxacin resistance of *S. pyogenes* (15% difference), ciprofloxacin resistance of non-Typhi *Salmonella* spp. (7% difference), and ampicillin/sulbactam, imipenem and levofloxacin resistance of *A. baumannii* complex isolates (9%, 7% and 8% difference, respectively). The rate (per 10 000 inpatient-days) of ampicillin/sulbactam-, imipenem- and levofloxacin-resistant *A. baumannii* complex infection was 43.7, 59.5 and 49.0, respectively, during January–June 2019 and was 71.4, 86.1 and 75.6, respectively, during January–June 2020. An increase in the incidence of antimicrobial resistance during the COVID-19 pandemic was observed for *A. baumannii* complex isolates at NTUH despite strict implementation of infection control measures and an antibiotic stewardship programme. How-

**(A)**



| R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PCN | 18 | 14 | TC | 57 | 52 | AMP | **72** | **57** | CTX | 19 | 16 |
| EM | 94 | 91 | EM | 53 | 54 | AMC | 3 | 4 | CIP | **16** | **23** |
| LVX | 1 | 3 | LVX | **8** | **23** | SXT | **64** | **56** | SXT | 36 | 35 |

**(B)**



| R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 | R | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| OX | 37 | 38 | VAN | 20 | 21 | CTX | 33 | 31 | CTX | 25 | 27 | CAZ | 13 | 12 | SAM | **25** | **34** |
| - | - | - | - | - | - | IMP | 1 | 1 | IMP | 7 | 8 | IMP | 14 | 13 | IMP | **34** | **41** |
| - | - | - | - | - | - | LVX | 34 | 35 | LVX | 15 | 16 | LVX | 14 | 11 | LVX | **28** | **36** |
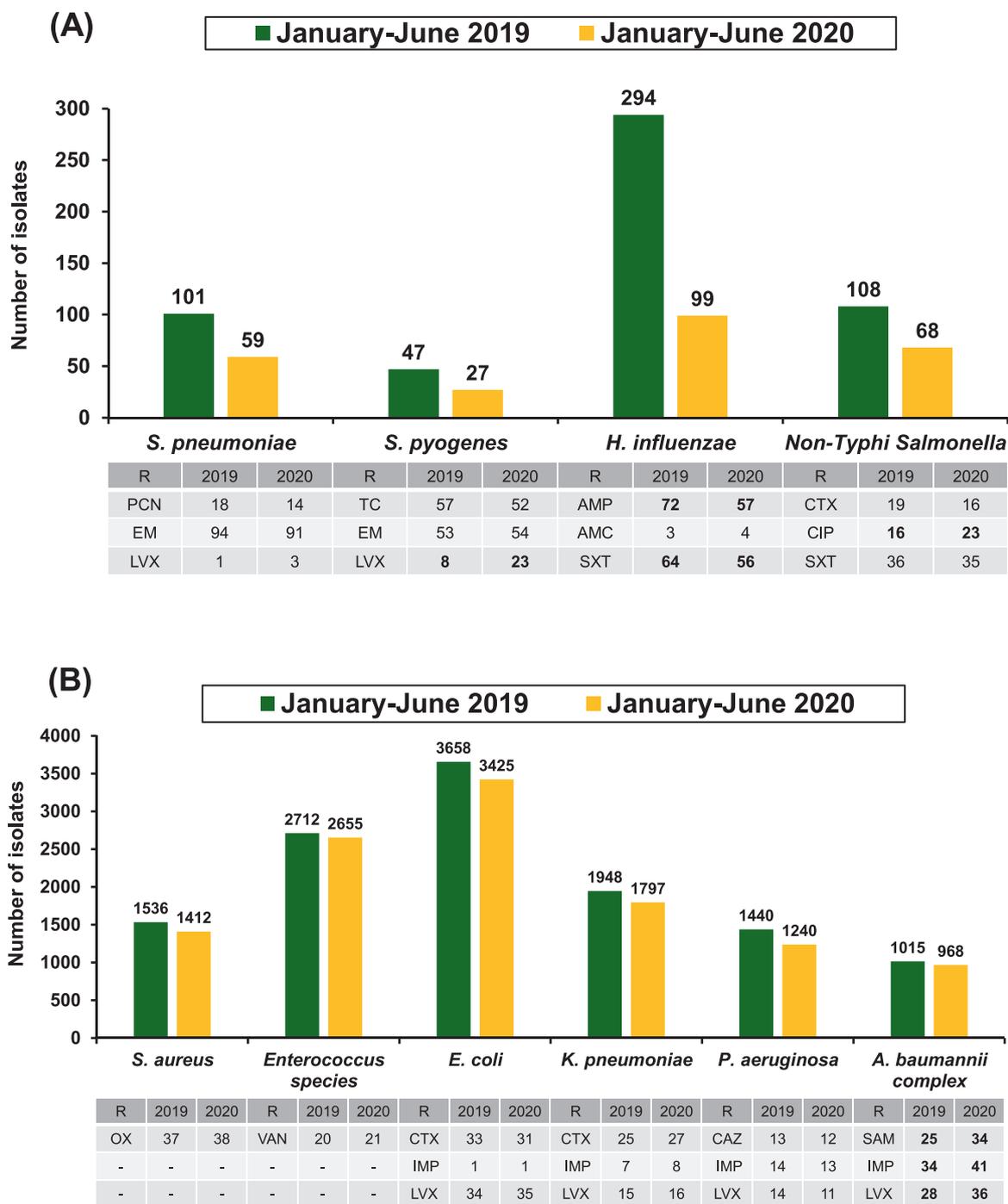
**Fig. 2.** Comparison of the number and rate of antimicrobial-resistant infections of clinically important bacterial species recovered from various clinical sources of patients treated at National Taiwan University Hospital (NTUH) between January–June 2019 and January–June 2020: (A) *Streptococcus pneumoniae*, *Streptococcus pyogenes, Haemophilus influenzae* and non-Typhi *Salmonella* spp. (predominantly associated with community-acquired infections); and (B) *Staphylococcus aureus, Enterococcus* spp., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex (causing community- and hospital-acquired infections). R, resistant to the indicated antibiotic; PCN, penicillin; EM, erythromycin; LVX, levofloxacin; TC, tetracycline; AMP, ampicillin; AMC, amoxicillin/clavulanate; SXT, trimethoprim/sulfamethoxazole; CTX, cefotaxime; CIP, ciprofloxacin; OX, oxacillin; VAN, vancomycin; IMP, imipenem; CAZ, ceftazidime; SAM, ampicillin/sulbactam. Differences in rates of resistance >5% between two time periods are indicated in boldface.

ever, further long-term study is warranted to investigate the association between the use of antibiotics and antimicrobial resistance in COVID-19 cases.

Of the 18 patients with COVID-19 treated at NTUH, 3 exhibited co-infections. Two patients with COVID-19 suffered complications with pneumonia and co-infection with a multidrug-resistant *A. baumannii* complex isolate (resistant to ampicillin/sulbactam, levofloxacin, amikacin, cefepime and imipenem but susceptible to col-

istin) and *Streptococcus dysgalactiae*, respectively, while the other patient was co-infected with influenza virus B.

## 6. The resolution

Combating an increase in the incidence of antimicrobial resistance during the COVID-19 pandemic remains a great challenge. First, reducing inappropriate antibiotic prescription remains the

**Table 2**
The resolution for high rates of antimicrobial resistance and utilisation and unresolved issues during the COVID-19 pandemic

| Issue | Resolution | Unresolved |
|---|---|---|
| High antimicrobial resistance | • Infection control measures: mask wearing and good hand hygiene practice<br>• Implementation of infection prevention bundle care within hospital<br>• Increased awareness of HCWs<br>• Consistent monitoring of antibiotic resistance patterns | • Immense COVID-19 burden on HCWs<br>• Lack of appropriate kit for early detection of antimicrobial resistance |
| High antibiotic utilisation | • Appropriate use of antibiotics according to antibiotic stewardship<br>• Avoid unnecessary use of antibiotics for mild COVID-19 patients | • Lack of biomarker to differentiate bacterial and SARS-CoV-2 infection<br>• Lack of laboratory method for early detection of co-pathogen in severe COVID-19 patients |

COVID-19, coronavirus disease 2019; HCW, healthcare worker; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

most effective way to tackle antimicrobial resistance, and international or local guidelines always advise restrictive antibiotic prescribing for respiratory tract infections. However, non-adherence to or poor uptake of local and international guidelines was commonly reported in previous studies [36–39]. Moreover, unnecessary use of antimicrobial agents would be associated with a significant economic burden on healthcare systems, which could be directly caused by the drug itself and indirectly caused by healthcare costs for the management of drug-related adverse events. Although the ongoing pandemic is stretching the limits of optimal antibiotic stewardship, continuing this intervention to curb inappropriate antibiotic usage and surveying the reasons for guideline non-adherence should be conducted within hospitals [40]. Second, early detection of possible respiratory pathogens using newly developed syndromic multiplex panels that incorporate SARS-CoV-2 is fundamental [41]. However, diagnosis of other respiratory pathogens through old syndromic multiplex panels cannot definitively rule out COVID-19 at this stage of the pandemic. Third, due to most MDROs developing in critical COVID-19 patients with prolonged ICU admission or hospitalisation, every hospital should continue implementing bundle care for prevention of device-associated infections within the hospital, including ventilator-associated pneumonia, catheter-associated bloodstream infection and catheter-associated urinary tract infection. Fourth, infection prevention initiatives fostered among HCWs could increase awareness of effective hand washing, cleaning equipment after use and appropriate use of personal protective equipment, which could subsequently reduce healthcare-acquired infections with MDROs [42,43]. Finally, healthcare authorities and hospital administrators should be responsible for providing adequate personal protective equipment, particularly masks and gloves, and hand sanitiser and disinfection to prevent nosocomial transmission of MDROs. Concurrently, the infection control department should continue monitoring the prevalence of antibiotic-resistant bacteria and the possible outbreak of MDROs (Table 2).

## 7. Unresolved issues

The greatest barrier to appropriate use of antimicrobial agents is that clinicians cannot definitively diagnose a co-pathogen with a SARS-CoV-2 infection, or easily identify the precise co-pathogen in a severe COVID-19 patient (Table 1). Although we can use the newly developed SARS-CoV-2 incorporated syndromic multiplex panels to detect SARS-CoV-2 and other common respiratory pathogens in a short time, these kits are not available in most conventional laboratories. Additionally, although procalcitonin (PCT) has been proposed as one of the promising biomarkers for differentiating bacteria and other pathogens, the usefulness of PCT in

COVID-19 patients remains unclear [44]. Among patients with severe COVID-19, an elevated level of PCT was common and could be associated with adverse outcomes [44–46]. However, a previous meta-analysis of 32 randomised controlled trials showed that the use of PCT to guide initiation and duration of antibiotic treatment in patients with acute respiratory tract infection could result in a lower risk of death, antibiotic utilisation and antibiotic-associated adverse events [47,48]. Therefore, the use of PCT in the context of antibiotic stewardship may be applied when caring for severe COVID-19 patients. Based on the experience of influenza patients, PCT has a high sensitivity, particularly in ICU patients. However, it has a low specificity for identifying secondary bacterial infections and may not be sufficient as a stand-alone marker for discontinuing antibiotics [49,50]. Thus far, there is little associated research regarding the use of PCT in COVID-19 patients [48,51]. Further study is warranted to define the role of PCT in COVID-19 patients.

## 8. Conclusions

The emergence of antimicrobial resistance is an unforeseen and unavoidable consequence of the COVID-19 pandemic. The cause is multifactorial, particularly a high rate of antimicrobial agent utilisation in COVID-19 patients with relatively low rates of co- or secondary infections. Appropriate prescription and optimised use of antimicrobials according to the principles of antimicrobial stewardship, together with quality diagnosis and aggressive infection control measures, may prevent the occurrence of MDROs during this pandemic.

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