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Viewpoint

Detection of Bacterial Coinfection in COVID-19 Patients Is a Missing Piece of the Puzzle in the COVID-19 Management in Indonesia

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ABSTRACT: Bacterial coinfection in COVID-19 patients has the potential to complicate treatments and accelerate the development of antibiotic resistance in the clinic due to the widespread use of broad-spectrum antibiotics, including in Indonesia. The surge of COVID-19 patients may worsen antibiotic overuse; therefore, information on the actual extent of bacterial coinfection in COVID-19 patients in Indonesia is crucial to inform appropriate treatment. This Viewpoint elaborates on a nascent research project focused on sequencing of swab samples to detect bacterial coinfection in COVID-19 patients in Indonesia. Supported by a L'Oréal-UNESCO For Women in Science National Fellowship, it is designed to inform better clinical management of COVID-19 in Indonesia.

The COVID-19 pandemic has affected many countries, including Indonesia. As of December 28, 2020, there have been over 713 000 confirmed cases and over 21 000 deaths reported nationwide,[1] in spite of interventions to limit its spread. As a consequence, the objectives of many research projects were shifted to those that can alleviate the burden of the pandemic and aid in its management. Government funding for research was already limited and extremely competitive, so availability of other funding schemes from private organizations is indispensable, including the L'Oréal-UNESCO For Women in Science (FWIS) national fellowship.

A collaboration between L'Oréal, Paris and UNESCO, the L'Oréal-UNESCO FWIS national fellowship aims to inspire the next generation of female scientists and acknowledge their scientific contribution, as depicted in the slogan "*the world needs science, and science needs women*". Initiated in Indonesia in 2004, it has since awarded research fellowships to 57 Indonesian young female scientists. This fellowship offers funding to conduct any research project of interest and opens up opportunities for collaboration at national and international levels. As a female early career researcher in a low- and middle-income country (LMIC), this prospect for international collaboration is invaluable to expand my scientific network and enhance exposure to the international scientific community through joint publications in high impact journals, which would otherwise be quite difficult to achieve.

In light of the pandemic, the FWIS fellowship called for proposals that offer solutions to mitigate the COVID-19 pandemic. Focusing on my interest in antimicrobial resistance (AMR), I proposed to tackle what I perceive as a critical issue in COVID-19 management in Indonesia, which is the lack of information on the incidence and prevalence of bacterial coinfection in COVID-19 patients. High antibiotic use[2] and a high level of antibiotic resistance in clinical isolates[3] have been reported in some Indonesian hospitals, highlighting the urgency of minimizing the impact of COVID-19 pandemic on AMR in Indonesia and better implementation of antibiotic stewardship programs (ASP) in Indonesian hospitals. The earlier severe acute respiratory syndrome (SARS) pandemic was shown to cause rising numbers of multidrug resistant bacteria due to high antibiotic use.[4] Similarly, this current situation could exacerbate the global threat of AMR. This issue is especially important in Indonesia, where ASP implementation still faces many obstacles, which include a lack of antibiotic use guidelines and suboptimal functioning of antimicrobial resistance control programs (ARCP).[5]

Coinfection with bacteria, other respiratory viruses, and fungi in COVID-19 patients has been reported to occur,[6−8] with bacteria being a major causative agent of coinfection.[4] Bacterial coinfection in particular is a worrying problem as it complicates treatment in COVID-19 patients and may worsen the prognosis and increase the likelihood of fatality.[8,9] However, inappropriate prescribing of antibiotics *when not needed* can amplify the increasing antibiotic resistance problem, especially as the prescribed antibiotics tend to be broad-spectrum.[6]

The reported prevalence of bacterial coinfection in COVID-19 patients varies in different studies. Relatively low percentages were reported from retrospective observational studies in New York and Barcelona, where bacterial coinfection was documented in 3.6% (152/4267)[10] and 7.2% (72/989)[11] of COVID-19 patients, respectively. Interestingly, a retrospective study in a French hospital reported 28% (26/92) of severely ill COVID-19 patients were coinfected with pathogenic bacteria upon intensive care admission.[12] Regardless of this variation in

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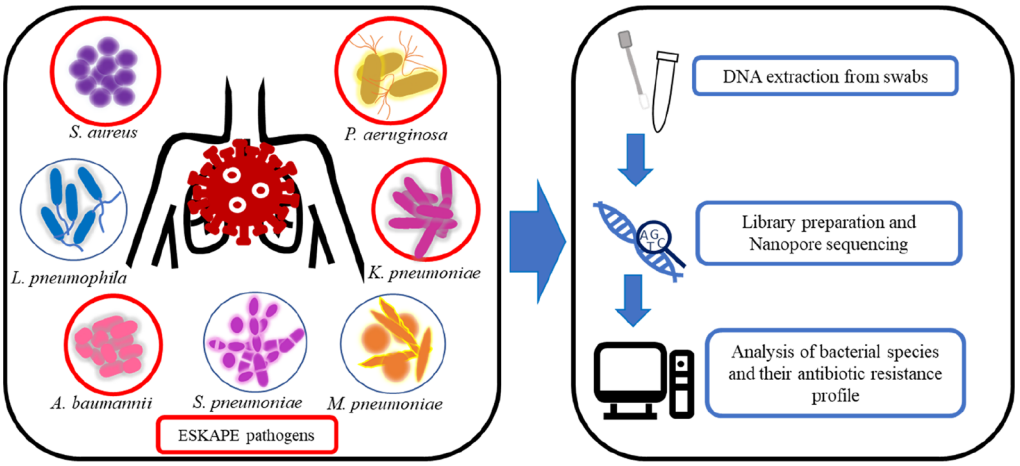

Figure 1. Proposed workflow for detection of bacterial coinfection from swabs of COVID-19 positive patients.

numbers, it is particularly important to note that the bacterial strains that have been found to coinfect COVID-19 patients include *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophila*, *Haemophilus influenzae*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Chlamydia* spp., *Streptococcus pneumoniae*, and *Acinetobacter baumannii*.[7,13] Some of those bacteria are ESKAPE pathogens that could harbor multidrug resistance, and this is exemplified by respiratory bacterial cultures from COVID-19 patients of which 15% (17/112) were multidrug resistant Gram-negative bacteria.[10]

The most recent clinical management interim guideline for COVID-19 from the WHO discourages the use of antibiotics in mild COVID-19 cases to prevent exacerbation of antibiotic resistance.[14] In moderate cases, antibiotic prescribing is also not recommended unless a bacterial infection is suspected.[14] However, ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium) encompassing data from 95 966 patients from 42 countries reported that 81.9% of COVID-19 patients received antibiotic treatment without clear indications of the necessity of antibiotic prescription.[15] Additionally, studies have reported >90% of COVID-19 patients received antibiotics despite a much lower incidence of bacterial coinfection in those patients.[9,16] Subsequently, this puts an immense strain on ASP in hospitals due to increased antibiotic prescribing in a bid to save COVID-19 patients' lives, even without confirmation of a bacterial coinfection.[17]

It is evident that a fast and accurate method to detect bacterial coinfection in COVID-19 patients in Indonesia is needed. Detection using a culture-based method is not ideal due to the long turnaround time of several days. My fellowship proposed a sequencing-based approach using the Nanopore platform to detect bacterial coinfection in COVID-19 patients using swab samples (Figure 1) in an international collaboration with Australian experts in Nanopore sequencing. Metagenomic sequencing using the Nanopore platform has been successfully used to detect influenza virus infection directly from clinical throat swab samples, including a coinfection with a coronavirus[18] and for fast diagnosis of severe pneumonia[19] as well as a bacterial lower respiratory infection.[20] Nanopore sequencing also allowed for a fast detection of infection with coronavirus and other respiratory viruses in 6−10 h.[21] This evidence supports the use of Nanopore sequencing for enhanced detection of different pathogens from one sample type and its suitability for detection of bacterial coinfection during viral infection. Caveats in this study include the unavailability of bacterial culture samples for comparison; however, this study was designed to optimize the readily available swab samples, thus eliminating the need to take additional samples.

This research project is expected to generate beneficial outcomes and offer solutions to a number of critical problems posed by the COVID-19 pandemic. First, we anticipate to obtain data on the incidence of bacterial coinfection in COVID-19 patients in some Indonesian hospitals, the types of bacterial species, if present, and their antibiotic resistance profiles. This crucial information could inform clinicians to improve management of COVID-19 patients with different degrees of severity. Informed decisions on antibiotic prescribing for COVID-19 patients would also help to improve the implementation of ASP during the pandemic. This is especially important as comprehensive data regarding AMR burden and ASP implementation in Indonesia are currently limited, and these conditions are likely to worsen during the pandemic. Second, this research will also assess the feasibility of detecting bacterial coinfection from swab samples using Nanopore sequencing, which could be adaptable for detection of other pathogens directly from clinical samples and more generally useful for other bacterial−viral coinfections. Last but not least, another benefit is the exciting prospect of a long-term international collaboration on Nanopore sequencing that may extend to other sequencing-based projects. The transfer of skills and knowledge initiated by this research could offer long-term benefits in enhancing the capabilities of human resources, which is especially needed by researchers in LMICs such as Indonesia.

To summarize, the management of COVID-19 in Indonesia would benefit from information regarding the extent of bacterial coinfection in COVID-19 patients. In addition to informing better care for COVID-19 patients, results from this research program could help alleviate the existing AMR problem in Indonesia and therefore provide long-term benefits beyond the pandemic.

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Notes

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■ ABBREVIATIONS

AMR, antimicrobial resistance; ARCP, antimicrobial resistance control program; ASP, antibiotic stewardship program; COVID-19, Coronavirus Disease 2019; FWIS, For Women in Science; ISARIC, International Severe Acute Respiratory and Emerging Infections Consortium; LMICs, low- and middle-income countries; SARS, Severe Acute Respiratory Syndrome; UNESCO, United Nations Educational, Scientific and Cultural Organization

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