

Title

The Outlook for the Emergence of Nanosilver-resistant tuberculosis and Its Consequences to Rural Communities in Indonesia

Name

Elizabeth Valentin

Supervisors' name

Dr. Cindy Gunawan, Prof. Liz Harry, Dr. Amy Bottomley

Email

elizabeth.valentin@student.uts.edu.au

Summary

The prevalence of multi-drug resistant pathogens has fuelled the incorporation of silver nanoparticles into medical care. Nanosilvers are heavily engineered to exert powerful antimicrobial activities. It has been shown to improve the efficacy of tuberculosis (TBC) treatments and potentially reduces the treatments cost. This is particularly attractive since TBC is almost always associated with poverty. The recent discovery of bacterial resistance to nanosilver is an alert for the use of nanosilver in the treatment of TBC or in any of the now increasing use in medical devices, urging for immediate elucidation of the emergence and molecular basis of resistance in clinical bacteria. The generated knowledge will form a base template for the design of new nanosilver generation with fewer tendencies for resistance.

Research work

Antimicrobial-resistant (AMR) infection has been a global health crisis, forecasted to cause 10 million deaths in 2050 worldwide, with the current casualties sitting at approximately 700,000 deaths.¹ Hopelessly, the administration of multiple antibiotics to treat these antimicrobial-resistant infections is ineffective; toxic to the patients and costly.² Silver nanoparticle or nanosilver, as a potent alternative antimicrobial,³ has been incorporated in medical devices to prevent or even counteract the issues of multi-drug resistant infections in patients. An important example, it was clinically studied that nanosilver showed antimicrobial effect to clinical isolates of tuberculosis (TBC),⁴ currently still a major health issue affecting the rural areas of Indonesia. The efficacy improvements leads to potential treatment cost reduction.⁵ A threat to this seemingly mutualistic medical treatment, the recent discovery of bacteria adapting to nanosilver naturally raises concerns on the applicability of nanosilver on the long run. Bacteria were found to be capable of developing resistance mechanisms that manifest under prolonged exposure to nanosilver.³ Since nanosilver is really powerful, it has been reported that healthcare providers tend to incorporate nanosilver more than it is needed, potentially facilitating resistance development.⁶ This research aims to study the nanosilver emergence for the first time and to discover the molecular basis for nanosilver resistance in clinical bacteria. Prolonged exposures of clinical bacteria to lethal and sub-lethal nanosilver concentration will be conducted, emulating the treatment course in patients and resulting in a

resistant strain for subsequent studies. The molecular basis of nanosilver resistance will be then identified by comparing the genome and gene expression profile for non-resistant and resistant strains.

Target

The societies living in rural area of Indonesia are the main target of this research finding. In Indonesia, rural areas are closely related to poverty, amounting approximately to 10% of the Indonesia total population in the late 2015.⁷ The Indonesian Central Bureau of Statistics stated that the member of society living under poverty earn only 600,000 IDR (~60 AUD) per month without any liquid saving and most likely uneducated (elementary school or under).⁷ World Health Organization (WHO) reported that, due to low sanitation and malnutrition, poverty has always been associated to TBC,⁸ currently sitting as one of top 5 death causes in Indonesia.⁹ Poor societies diagnosed with TBC might also see themselves in a downward poverty spiral because the disease weakens them and affects their productivity heavily. While unable to work, a significant portion of earning, if not all, needs to be allocated for medical treatment and access to healthcare facilities.¹⁰ A study showed that in Central Java, where health service is relatively more accessible than that of Borneo, Celebes or Maluku Islands, average cost of cured TBC would be approximately 340 AUD.¹¹ A huge gap between their average earning and treatments cost is obviously an economic burden. Should they be infected with multi-drug-resistant (mdr) TBC, the cost was approximately 42 times higher than for normal TBC.¹¹ It is important to note that successfully cured TBC needs to be treated for at least 6 months, even longer for mdr-TBC.¹² The administration of nanosilver treatment may plausibly reduce the TBC treatments cost,⁵ however, prolonged exposure without acknowledging the possibility of resistances may create worse conditions for patients, physically and financially. Patients infected with nanosilver-resistant TBC will go through the same downward poverty spiral, or may be even worse than TBC or mdr-TBC, since neither resistant to nanosilver is yet made aware nor cure is discovered.

Benefit

The profound knowledge and understanding obtained from this research could, firstly, create awareness for government, health institutions and healthcare providers regarding the emergence of nanosilver resistance. Guidance to the development of a judicial review in the form of health regulations to control and limit the amount of nanosilver incorporated in drug administration and/or medical care products could also be based on the results obtained in this study. The establishment of proper prevention regulation and mechanism will subsequently reduce the chance of resistance development significantly; hence reducing the number of nanosilver-resistant infected patients. However, as cure for nanosilver-resistant bacteria have not yet been found, prevention of this phenomenon should be the major action to perform and a huge benefit for the society to receive. As an example, off-target expenses such as ineffective multi-drug administration for nanosilver-resistant TBC patients will be eliminated. In addition to that, global and local casualties are refrained, in agreement with sustainable development goals (SDG) of United Nations (UN) by 2030.¹³ Nevertheless, if nanosilver resistance still emerges in the society, clinical researchers in research institution and/or university could harness the molecular basis of nanosilver resistance to conduct a relevant and suited research in discovering and developing new drug to cure nanosilver-resistant TBC patients. It is in such a way that the mechanism bacteria developed to resist nanosilver could be the target of this new drug treatment. Discovery of new engineered nanosilver will also be enabled,

aiming for reducing the resistance tendency. In conclusion, should both prevention and treatment be conducted, nanosilver-resistant TBC infection could be completely avoided as well as its affiliation with poverty.

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