Original Article

Antimicrobial stewardship and oxazolidinones use, a consideration for a Zambian health system

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Abstract: Antimicrobial stewardship is the organized and systematic way of educating and enforcing evidence-based prescribing of antimicrobial agents to control misuse and overuse of antibiotics with the aim of curbing antimicrobial resistance. There is need to initiate antimicrobial stewardship program at various levels in the health sector such as health facilities or hospitals in order to safeguard and sustain the current antimicrobial agents in use. In addition, oxazolidinones are potent drugs in management of multidrug resistance (MDR) related infections and linezolid is already on the market and being considered as a drug of 'last resort' for the treatment of MDR bacterial infections. Therefore, to avert the development and rapid spread of drug resistance against linezolid and other oxazolidinone drugs, antimicrobial stewardship program needs to be established for critical monitoring and regulation of their use at all critical levels in the health system hierarchy, especially in resource limited countries.

INTRODUCTION

The rising global burden of infectious diseases is worrisome. This had prompted the implementation of disease surveillance programs among World Health Organization (WHO) Regional Office for Africa (AFRO) member states, with the effort to improve on the detection, communication to the next level of authority, management/treatment and control of disease dissemination[1]. Surveillance is defined as the 'ongoing systematic collection, collation, analysis and interpretation of data and the dissemination of information to those who need to know in order that action may be taken'[1,2]. Surveillance is an important system to use when planning, implementing and/or evaluating public health practices. Therefore, in 1998 WHO/AFRO began to promote the Integrated Disease Surveillance and Response (IDSR) to strengthen national disease surveillance system[1]. Through this surveillance program, diseases such as cholera, viral hemorrhagic fevers, malaria, severe acute respiratory illness, diarrheal diseases, HIV/AIDS and tuberculosis were classified as public health priorities[2]. The effective monitoring of disease trends at any level of health system and effective communication within the health level hierarchy system is cardinal for proper management and prevention of infectious outbreak. Hence, the adoption and utilization of IDSR system may aid in mounting a rapid detection and response structure to any disease outbreaks besides the above cited ones.

Zambia adopted the IDSR in the year 2000 to monitor, prevent and control priority notifiable infectious diseases in the country, and Zambia public health system through the Ministry of Health developed and operationalised the IDSR implementation structure which starts from the community level up to the national level[3]. To

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improve the detection of notifiable infectious diseases such as Acute Flaccid Paralysis (AFP), Measles, Neonatal Tetanus, Dysentery, Cholera, Plague, Rabies, Typhoid Fever, Yellow Fever, Tuberculosis (TB) and Human Influenza, the IDSR complements the Health Management Information System in immediately communicating detected/ suspected and/or confirmed reports of any notifiable infectious disease to the next level in the reporting chain[4]. However, the rate of laboratory integration is quite low in Zambia as observed from the summary report of priority diseases, condition and events for weeks 1 – 50, 2018 (Table 1; [5]).

Table 1: Extracted summary report of priority diseases for weeks 1 – 50, 2018[5]

	Cases suspected	Cases tested	Cases confirmed	Number of deaths	Case testing rate %
Cholera	5 945	2 087	944	113	35.1
Meningitis (Neisseria)	188	0	0	0	0
Measles	543	298	19	5	54.8
Dysentery	45 277	3 379	309	0	7.5
Typhoid fever	692	363	57	0	52.5
Yellow fever	7	0	0	0	0
Anthrax	10	0	0	0	0
Non-bloody diarrhoea	262 912	924	101	0	0.4
Schistosomiasis (Bilharzia)	16 903	2 580	843	0	15.3

Since IDSR system aims mostly at strengthening district level surveillance and response for priority diseases, integrating laboratory with laboratory support, reducing duplication in reporting, sharing resources among disease control programs, and translating surveillance and laboratory data into specific and timely public health actions[2]; the laboratory work in this whole process is so valuable in confirming the disease etiological agents and possible antimicrobial susceptibility. The latter is so fundamental in supporting the choice of potent antimicrobial agents and to avoid irrational antimicrobial use, and minimize resistance development. All these can be achieved once antimicrobial stewardship programs are established and integrated in surveillance programs at a hospital level. Therefore, this review discusses antimicrobial stewardship in relation with antimicrobial resistance, and its benefits in averting oxazolidinone resistance in resource limited countries like Zambia.

Antimicrobial Stewardship

The evolutionary rate of antimicrobial resistance (AMR) to commonly used antimicrobial agents in health systems is alarming. Research scientists in association with various stakeholders are working tirelessly in finding the undying solution to this problem. As the search for effective antimicrobial agents is ongoing, various levels in the health sector such as health facilities or hospitals, need to be actively involved in safeguarding and sustaining the current antimicrobial agents in use. This can be achieved through initiating an antimicrobial stewardship program (ASP). As IDSR system is being implemented, ASP can also work concurrently by monitoring and regulating the correct/confirmed use of antimicrobial agents. According to the Infectious Disease Society of America, antimicrobial stewardship is defined as the rational, systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes[6]. ASP is a promising program to curb irrational use of antimicrobial agents and to safeguard the community from AMR outbreaks. For instance, Gaffin (2015) reported the abuse of ceftriaxone and how this problem was curbed through the formidable ASP team[7]. This report further stated the challenges faced in implementing a radical decision of reducing the use ceftriaxone especially in *Clostridium difficile*

infections. Therefore. It is imperative that hospitals should establish and adhere to the ASP for effective curtailing of AMR[8]. The formed ASP team in various hospitals will have an enormous role to play and may receive a lot of objections from prescribing clinicians but ASP teams may provide guidelines for antimicrobial use, educate clinicians regarding preferred antimicrobial therapy and provide reports on the trends of antimicrobial use versus patient management or resistance[9]. Lessons on developing an ASP can be drawn from countries that are using the program. Skodvin *et al.* studied factors that influenced doctors' antimicrobial prescribing practices in Norwegian hospitals[10]. The authors revealed contextual factors such as a common work practice for seeking collegial advice, logistics of microbiology test results, and formal leadership and systematic training on prudence, that should be considered when developing antimicrobial stewardship programs in Norway[10]. These factors are also applicable to the Zambian health system. For instance, a cordial consultational relationship between junior/intern doctors and senior/ specialized doctors when prescribing drugs must be encouraged at all levels in the health sector. Further evidence based antibiotic prescription among clinicians should be encouraged when treating bacterial infections and microbiology laboratory testing logistics should be supported by hospital managements. Restoring microbiology laboratory operation may promote evidence based treatment and management of microbial infections. Thus, hospital laboratories being the custodian of antibiotic resistance profile data for instance, should periodically update clinicians on the status of AMR and the potency of currently utilized empiric antimicrobial therapy through antibiogram study reports.

Oxazolidinones

Over decades ago, infections due to Gram positive pathogens were hit with widespread resistance to commonly prescribed antibiotics. By then vancomycin was a last therapeutic option for infection due to methicillin resistant *Staphylococcus aureus* but vancomycin resistant *Enterococci* had no known alternatives while penicillin resistant pneumococci were on the rise[11]. Fortunately, oxazolidinones were efficacious against Gram positive pathogens and two Food and Drug Administration (FDA)-approved oxazolidinones were linezolid (released in 2000) and tedizolid (released in 2014) .[12]

Oxazolidinones are novel synthetic bacteriostatic class of antibiotics that inhibit protein synthesis by preventing formation of the ribosomal-N-formylmethionyl-tRNA initiation complex through binding to the P site of the 50S ribosome . They are effective against a wide range of Gram-positive bacteria, including methicillin resistance Staphylococci, vancomycin resistant *Staphylococci*, vancomycin resistant *Enterococci,* penicillin resistant pneumococci and anaerobes; and the use of linezolid, has already been effected in hospitals for treatment of Gram positive infections and multidrug resistance tuberculosis complex[12, 13].

Among the *Staphylococcus* species, *S. aureus, S. epidermidis* and *S. saprophiticus* are associated with hospital acquired nosocomial infections, indwelling medical device linked infections and urinary tract infections especially in girls, respectively[14]. Moreover, only *S. aureus* and *S. intermedius* are coagulase positive bacteria while all other *Staphylococcus* species are coagulase negative bacteria[14]. *S. aureus* can cause various forms of human infections such as osteomyelitis, meningitis, septic arthritis, food borne gastroenteritis, brain abscesses, cellulitis and toxic shock syndrome[14,15]. Moreover, *S. aureus* is a Gram positive normal microbiota that colonizes the nasal cavity and axillae[15,16]. However, the bacterium is able to express several virulence factors that aid in colonizing host tissues, inhibiting phagocytosis and secreting of

toxins leading to host tissue damage[14,15]. Also, the bacterium has the ability to develop resistance to several antimicrobial agents which causes management of its infections of greater concern. Multiple drug resistance (MDR) keeps on rising in *S. aureus*, where methicillin resistance indicates multiple resistance and methicillin resistance *Staphylococcus aureus* (MRSA) is the common cause of infection outbreak in hospital settings[14,17]. Vancomycin has been an alternative therapeutic drug for MRSA infections[11], but due to the development of resistance, co-trimoxazole (trimethoprim/sulfamethoxazole) was revealed as an alternative drug to vancomycin in MRSA infections[18,19]. In addition, a plethora of information reveals that linezolid and tendizolid are effective against MRSA and other Gram positive pathogens. For instance, a randomized study by Harbarth *et al.,*[20] compared a 5-day combination therapy of co-trimoxazole (160mg trimethoprim and 800mg Sulfamethoxazole) thrice a day with 600mg rifampicin once daily versus a 7-day therapy of 600mg linezolid twice daily on MRSA infections. They found comparable results between the two groups and suggested that a combination of co-trimoxazole and rifampicin to offer substantial cost advantages over linezolid. In addition, a meta-analysis that compared the activities of vancomycin versus linezolid in MRSA infection showed linezolid to be more efficacious than vancomycin[21]. Tedizolid, another FDA approved drug is effective against Gram positive pathogens. A randomized study conducted in japan by Mikamo *et al*, evaluated the efficacy, safety and pharmacokinetics of tedizolid versus linezolid in patients with skin and soft tissue infections[22]. The study suggested tedizolid phosphate as a better option than linezolid even though both drug were well tolerated. In addition, Hall *et al*.[23] also pointed out shorter duration therapy and increased tolerability of tedizolid as being advantageous over linezolid in MRSA infections. In spite of some differences between linezolid and tedizolid, the studies reveal that oxazolidinone drugs are still effective and may be used as drugs of last resort in MRSA and other Gram positive infections. Due to the efficacious results of oxazolidinones on skin infections, pneumonia, central nervous system and osteoarticular infection in adults and pediatrics[24,26], protecting these drugs from abuse to avoid or minimize resistance acquisition is of paramount importance.

Besides the widely studied methicillin and vancomycin resistance genes, *S. aureus* has acquired the *cfr* (chloramphenicol/florfenicol resistance) gene which confers resistance to the phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A, and *S. epidermidis* had been reported as the reservoir of *cfr* gene[17, 27]. Therefore, with overwhelming reports on the presence of *cfr* gene in clinical, environmental and livestock bacteria species[16, 17, 18], the repercussion of having *cfr* gene in clinical isolates should be of great concern because the gene is easily transferable between strains and species.

Antimicrobial Stewardship and Oxazolidinone use

Due to the current key changes to the MDR and rifampicin resistance (RR) tuberculosis complex treatment regimen, linezolid is among the newly introduced drug for management of these infections[29]. So, what does this mean for HIV/TB endemic countries like Zambiafl

First the information about the prevalence of drug resistance among *Staphylococci,* prevalence of *S. epidermidis* amongst clinical isolates, and the prevalence of *cfr* gene among clinical *Staphylococcus* species isolates is poorly documented. Until we understand the status quo on these issues, we cannot be certain that Zambia is not affected.

Zambia has been experiencing an increase in the number of MDR/RR-tuberculosis complex in various regions and there are unconfirmed presence of pre-extended drug resistance (XDR) strains[30]. According to the recent global tuberculosis report by WHO (2018), there are high prevalence of MDR-TB and XDR-TB cases in the southern region of Africa (Table 2,[30]). These case strains may possibly spread to Zambia due to its land linked status and cause an escalation in the level of MDR/RR-TB cases. This entails that the utilization rate of linezolid may rapidly increase once introduced in treatment regimen following WHO rapid communication guidelines[29]. Even though an increased prescription of a drug does not necessarily translate into resistance acquisition, proper regulation of linezolid in this case will be required in our country. Owing to the fact that the oxazolidinone drugs are considered the last option in the management of penicillin-, methicillin- and vancomycin-resistant Gram positive bacteria[12, 13, 17], strong emphasis on its proper use (restricting it to MDR/RR-TB and XDR-TB) will be needed to prevent early development of resistance. While Wasserman *et al*.'s findings detected linezolid resistance in some studied South African MDR-TB patients[30], proper stewardship of the drug needs to be adhered to. Otherwise, infections due to MDR-TB and other MDR-Gram positive infectious agents may become incurable. Thus, ASP if properly established and welcomed by all, can help in achieving this purpose.

Table 2: Prevalence of MDR/RR-TB and XDR-TB cases in Southern part of Africa[30]

	MDR/RR-TB CASES	INCIDENCE RATE [a]	XDR-TB CASES
ANGOLA	534	13	0
NAMIBIA	409	37	14
DR CONGO	893	9.2	19
CONGO	58	12	0
MOZAMBIQUE	861	30	31
TANZANIA	200	2.9	0
SOUTH AFRICA	15986	25	747
LESOTHO	351	50	
ZIMBABWE	474	14	4
ZAMBIA	546	11	0

[a]Incidence rate per 100 000 population; MDR: Multi-drug resistance; RR: Rifampicin resistance; XDR: extended drug resistance; TB: Tuberculosis

Conclusion and future prospective

Oxazolidinones are powerful drugs in management of MDR infections and linezolid is already on the market for that effect. To avoid development and rapid spread of drug resistance against linezolid and other oxazolidinone drugs, it is cardinal to constitute an ASP team to spearhead infection prevention/ control and antibiotic use programs at a hospital. The team should fortify antimicrobial stewardship program for critical monitoring and regulation of oxazolidinone use. This can be achieved by obtaining guidance from the ASP team or an infectious disease consulting physician coupling with microbiological documentation before prescribing the drug[25, 32] as this strategy has been tested in other hospitals and found to be helpful. Secondly, studies to ascertain the prevalence levels of *cfr* gene amongst *Staphylococcus* strains will help in projecting the resistance levels that may be associated with linezolid and/or other oxazolidinone drugs in Zambia. Therefore, to avoid drug resistance development to oxazolidonine and of course any other drug, antimicrobial stewardship is a promising program to curb the scourge of antimicrobial resistance and its support and implementation should begin from the point of care up to the ministerial level. Thus, a multisectoral approach is required to curb drug resistance in Zambia and other resource limited countries in order to have and sustain an effective low cost health system.

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