

Research Article



Potential threat of New Delhi Metallo-Beta-Lactamase-1 Enzyme, Multi Drug Resistant and Extensive Drug Resistant (XDR) to achieve the Millennium Development Goals (MGD's) in South East Asian Countries

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ABSTRACT

The rational treatment and standard clinical care have key value in public health. That helps the health care professionals assure successful treatment and minimize the resistant against antibiotics. Whereas, the drug compliance, therapeutical monitoring and pharmacovigilance are main factors to determine the quality of health care system. Hence; the developing parts of the world especially need attention to establish the standards to achieve the Millennium Development Goals (MDG's) of World Health Organization (WHO). Although, the unnecessary use of drugs, irrational pharmacotherapy and wrong medication continuously generating resistance strains Indian subcontinent. However, the identification and characterization of resistant superbugs of New Delhi Metallo-beta-lactamase-1 (NDM-1) enzyme resistant, Multi Drug Resistant (MDR) and Extensive Drug Resistant (XDR), Carbapenem-Resistant Enterobacteriaceae (CRE), Methicillin Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant Enterococcus (VRE) strains have posed a potential threats for public health. Moreover, these resistant superbugs may be harbored to other parts of the world. Thus, we need an effective strategy to enforce the health standards and promulgated the drug jurisprudence to improve the overall pharmacotherapy practice. That may potentially assure the standard clinical and pharmaceutical care to achieve the Millennium Development Goals (MDGs). Additionally, an appropriate intervention of Drug Regulatory Authorities, Provincial Health Departments and professional bodies needed to improve the public health care system. Especially, the pharmacy professional and drug experts are needed to deliver their exact scientific and professional role of prescription reviewing, patient counseling, therapeutically drug monitoring, biosafety, clinical services and pharmaceutical care instead of current irrelevant, non-technical, administrative and clerical work. That will definitely help to minimize the chances of development of resistance against antibiotics and potential health hazards.

Keywords: Superbugs, drug resistance, NMD-1, MDR, XDR, MGD's, Pharmaceutical care, clinical pharmacy, Millennium Development Goals.

INTRODUCTION

The South East Asian (SEA) Countries have been a major component of different dynasties throughout the history. The varieties of culture, fashion, life style and believes has key role to determine the health condition of every individual region of Indian subcontinent.³ moreover, the current health standards need special attention to control the irrational medication, substandard clinical care and unnecessary drug usage¹ that have potentially contributed to generate the resistant superbugs of New Delhi Metallo-beta-lactamase-1 (NDM-1) enzyme resistant, Multi Drug Resistant (MDR) and Extensive Drug Resistant (XDR), Methicillin Resistant *Staphylococcus Aureus* (MRSA), Carbapenem-Resistant Enterobacteriaceae (CRE) and Vancomycin-Resistant Enterococcus (VRE). In addition of that the political instability and a variety of disputes on the boundary lines have constantly thrown into destabilization the health care system. Whereas, the "war on terror" started after 9/11 incidence have driven a massive population to move around from the conflicted partis of SEA part of the world. Thus, ≥ 2000'000 people

have been displaced, consequentially 234.589 individuals moved into the emergency shelters and 2.087.160 people forced to live outside the refugee camps in rented accommodations or with host families. Particularly the children and women made up a large share of Internal Displaced People (IDPs). In addition of that North West part of Indian subcontinent was hitten by natural disasters in 2005 and 2010. A severe earthquake with ≥80,000 deaths has displaced millions of the families. Moreover, the heavy floods with a dead toll of over 2000 people has indirectly victim 20 million individuals.

Hence; the development of dangerous resistant strains of NDM-1 enzyme, MDR, XDR, MRSA, VRE and CRE organisms have posed potential health hazard in Indian subcontinent. Therefore; we aimed this study to illustrate the issues of drug resistance and how it is being facilitated to prevent disease, prolong life and promote health standards.⁴

RESEARCH AND OUTCOMES

We designed this project to elaborate the potential threat



of New Delhi Metallo-Beta-Lactamase-1 Enzyme (NDM-1), Multi Drug Resistant (MDR), Extensive Drug Resistant (XDR), Methicillin Resistant Staphylococcus Aureus (MRSA), Carbapenem-Resistant Enterobacteriaceae (CRE) and Vancomycin-Resistant Enterococcus (VRE) to achieve the Millennium Development Goals (MDG's) in South East Asian (SEA) Countries.

Identification and Selection

The research manuscripts were selected Medline, Embase, PubMed, Cochrane Central Register of Controlled Trials, International Pharmaceutical abstracts, Cumulative Index to Nursing, and Allied Health Literature and Latin American /and Caribbean Literature on Health Sciences databases. These research article and databases were searched from inception. We also have used the combination of search terms including drug resistance, MDG's, NDM-1, MDR, XDR, MRSA, CRE, VRE and SEA Countries health care system. The duplications were removed, the titles and full texts screened to obtain the exact scientific information from selected articles. The lists reference citation of each research article was also reviewed for any additional studies. We also contact the authors to collect any possible missing information or clarification.

Data Extraction

The authors have collected data independently from research studies. The outcome information including drug resistance, infectious diseases, MDG's, NDM-1, MDR, XDR, MRSA, CRE, VRE and SEA Countries were collected. All information analyzed using Statistical Package for Social Sciences (SPSS), MS Excel and Review Manager 5.3 (Cochrane Collaboration, Copenhagen, DK). The authors do not need the Ethical Approval for this study.

Health Care System

Today, no doubt, the official regulatory authorities and government institutions have recognized the needs of public health and designing programs to reduce the incidences, disabilities and health conditions caused by poor pharmaceutical care. Currently, the incredible stride of public health care programs has potentially helped to promote the health including the control of contagious infections diseases of polio, smallpox, cholera, tuberculosis, diphtheria that plagued humanity for thousands of years. But; unluckily, we have not yet successfully controlled these fatal contagious diseases. Public health workers and health organizations still having problems because of certain bizarre supernatural believes, unfavorable political situation and communal

vulnerabilities. Moreover; the current pharmaceutical health facilities aggravated because of poverty, ignorance and recent invasion of UN (United Nations) and NATO (North Atlantic Treaty Organization) Forces in north east part of Indian subcontinent. The World Health Organization (WHO) has helped to identify the core issues¹² to provide the leadership, engaging them into partnerships where joint action is needed; design the research to generate, translate and disseminate the valuable information's; establish the standards to promote and monitor the implementation of projects; articulate the evidence based policy options; and monitor the health situation to assess the health trends.¹³

Millennium Development Goals of World Health Organization

There are eight major MDG's goals designed by the United Nations (UN). The UN members were agreed to attain these objectives by the year 2015. In September 2000, the United Nations Millennium Declaration was signed. Whereas, the leaders of the world were convinced to fight against poverty, hunger, environmental degradation, disease, discrimination against women and illiteracy^{7,8}. The MDGs were derived from declaration and having indicators and targets. The eight goals were as under;

1. To eliminate excessive hunger and poverty
2. To attain the worldwide prime education
3. To encourage equality of gender and women empowerment
4. To control the mortality of children
5. To develop the maternal health care system
6. To contest against AIDS/HIV, polio, cholera, malaria and other mortal diseases
7. To make sure the sustainability of the environment
8. To expand a worldwide partnership to establish the health care system.

These MDGs are directly related to the public health indicators including better health that enable children to study and adults to work. The equality of gender is also necessary to achieve the better health. Hence, all these factors influence and support each other to eliminate and control the poverty, hunger and environmental degradation positively; but also depend on, better health.



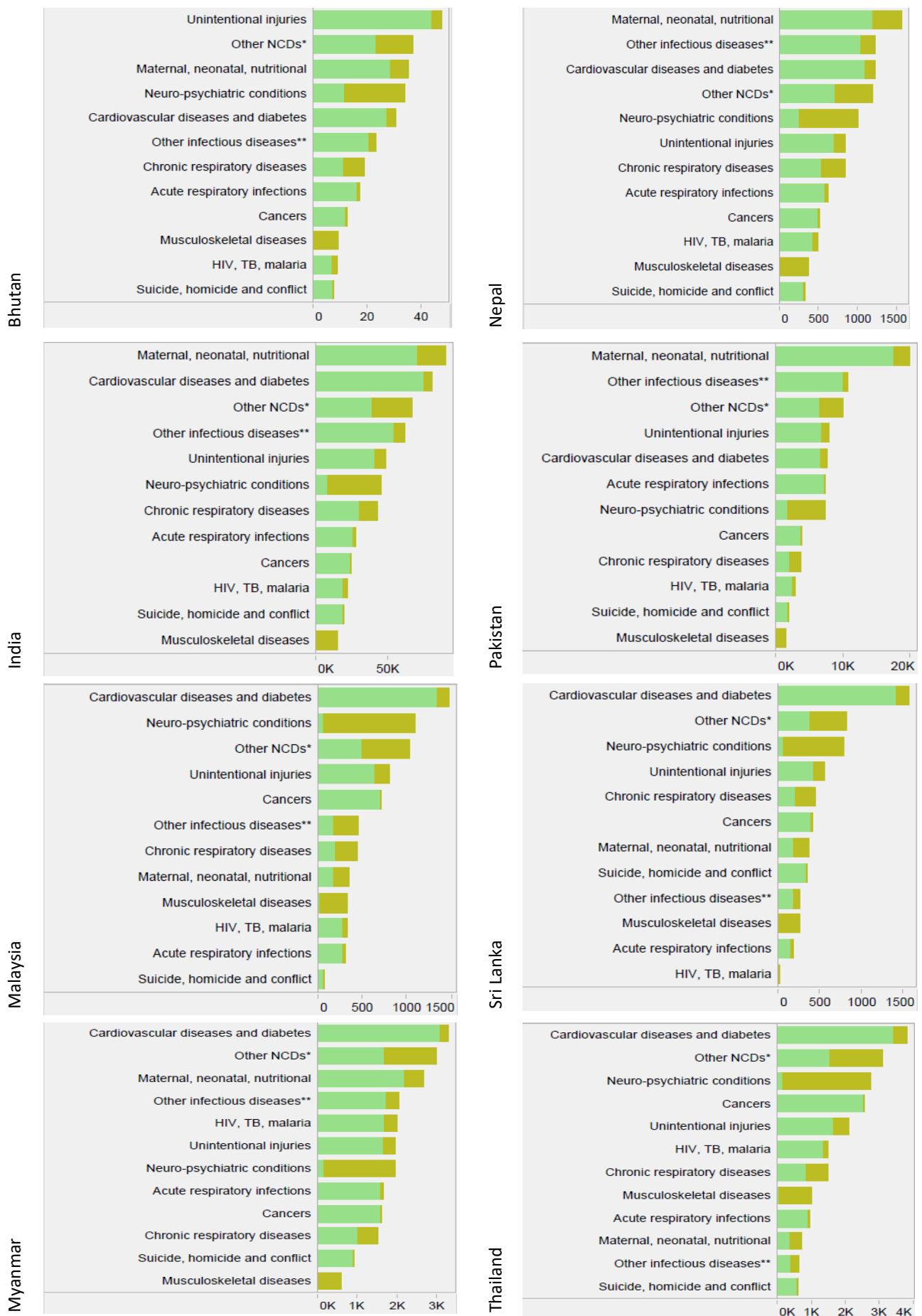


Figure 1: Burden of diseases in South East Asian countries during 2012. (Disability adjusted life years are the sum of years of life lost due to premature mortality and years of healthy life lost due to disability).



*Other no communicable diseases (NCD's) including non-malignant neoplasm's; endocrine, blood and immune disorders; sense organ, digestive, genitourinary and skin diseases; oral condition; and congenital anomalies.

** Infection diseases other than acute respiratory diseases, HIV, TB and malaria.

■ YLL (Years Life Lost)

■ YLD (Years of healthy Life lost due to Disability)

The clinical care has been impeded by geopolitical conditions and the low population density in most of the Indian subcontinent regions. Whereas, the major part of the population has limited access to basic health facilities in rural areas with almost substandard pharmaceutical care.¹³ Thus; the achievement of the MDGs may help to improve the overall health facilities. Moreover, the accomplishment of pharmacist population ratio 1:20 targeted by 2020 will support to improve the overall provincial health services by reducing the poverty, combating diseases and ensuring equitable availability of health care facilities. Different governments initiated certain projects including; Country Cooperation Strategy (CCS) 2005- 2010, National Health Policy - 2001, 10 Years' Prospective Plan 2001-11, Provincial Human Development Centers, the Poverty Reduction Strategy Plan, Narcotics Control Division, the Medium Term Development Framework 2005-10, GOP - WHO Joint Collaborative Programs and District Human Development Centers to achieve the MDG targets by 2020.

Common Infectious diseases

Acute Respiratory Infection (ARI) is the most vulnerable among immunocompromised and malnutrition children. National ARI Control Programme was started in 1990, to minimize the mortalities because of pneumonia, acute other respiratory infectious diseases. Moreover, the viral Hepatitis (particularly types B and C) are major epidemics infected. The major undermined reasons are including poor pharmaceutical care, uncontrolled medication and massive overuse of therapeutic agents. Whereas, the cholera is controllable disease, but the floods, natural disasters, warm humid weather and inappropriate clinical care enhance the transmission and ultimate mortalities of this disease. In addition of that Several deaths occurred because of the outbreak of dengue fever. The late treatment, misdiagnosis and lack of awareness in the local population has enhances the mortalities. But overall, steps were taken to kill vectors for the fever and the disease was controlled later, with minimal casualties. Furthermore, the Measles and Meningococcal meningitis has also posed potential threat for public health.

Hence; the improvement in the applicants in pharmacy programs has been remarked in all over the world.²⁵ Particularly the economically growing countries of Indian subcontinent have changed the purpose and scope of pharmacy discipline.²⁷ Similarly; the pharmaceutical institutions are increasing rapidly and providing more relevant and profession course outlines to maintain pharmaceutical care more supportive in the health care system. The situation took a spectacular revolutionized in the last decade.²⁸ Currently there are so many pharmacy

institutions offering pharmacy under graduation and graduating degree programs. There are also some other parties interested to invest in this growing field of pharmaceutical business. That has increased the interest of profession linked to the official vision for national development. Additionally; the health ministries anticipate attaining the World Health Organization's definition pharmacist to population ratio' of 1:2000 by the year 2020.^{29,30,31} The statistics of different countries has shown the ratio of pharmacist-to-population would be surprisingly exceeded, as most public and private institutions are showing interest in offering the pharmacy program.²⁰

Potential threat of Drug Resistant

There are $\geq 2'000'000$ people get resistance against antibiotics every year in United State. Centre of Drug Control (CDC) has graded bacterial resistance as worst reason that toll the deaths and hospitalizations in US. Moreover, the resistant 'superbugs' include MDR/ XDR, MRSA, CRE, NDM-1, C-Diff, *Neisseria gonorrhoea*, CRE (*Carbapenem resistant Enterobacteriaceae*) and VRE (*Vancomycin-resistant Enterococcus*) are most common threats for successful control of infectious diseases. Antimicrobial resistance is a potential risk for successful treatment and prevention of infectious diseases. Antimicrobial resistance is a serious threat for public health. That has induced new resistance mechanics, emerged and spread throughout the world. Whereas, approximately 450 000 new MDR-TB cases were identified during 2012. While the Extensively Drug Resistant tuberculosis (XDR-TB) strains were identified in 92 different countries. However, most of the resistance noticed in pneumonia, urinary tract infections and bloodstream infections in all over the world. The resistance against preliminary forms of antimalarial drugs is prevalent in most malaria endemic regions. Thus, the emergence and transmission of artemisinin resistant strains of malaria may enhance to pose potential health hazard.³²

Antimicrobial resistance

The drug resistance is the competency of microorganism to prevent antimicrobial efficacy of antibiotics. Hence; the standard medication may become unsuccessful; infections continue and may transmitted to other individuals and areas.

Drug resistance; a global problem

The expansion of worldwide travel and trade has prompted the transmission of resistant superbug strains.



Causes of drug resistance

The resistance against drugs is a evolutionary and natural phenomenon. That may be activated when susceptible exposed to antibiotics. This resistant trait can be transmitted to next generation.

Inappropriate medication induces resistance

Inappropriate use (overuse, underuse or misuse) of antimicrobials drives the development of resistance. Thus, the right dosage of right drug should be ensure through physician prescribers, pharmacy professionals, dispensers, pharmaceutical manufacturers, public health workers and intellectual policy makers. Moreover, the poor-quality control, exposing the patients to sub-optimal concentrations and poor access creates the conditions for drug resistance to develop.

Animal husbandry; a source of resistance

The sub-therapeutic regimens in veterinary practice may potential the resistant, which can be transmitted to humans.

Poor infection prevention amplifies resistance

The substandard clinical practice and poor infection control may produce resistant superbugs. The patient admitted in clinical setting are good reservoirs, carriers and source of infection transmission.

Weak surveillance induce resistance

Currently only few established networks, regularly collecting and reporting the relevant data. This may augment the competency to identify the emergence of resistance, development of superbugs and prompt action in controlling the infections.

New tools to combat resistance

The current antibiotics are losing their efficacy against resistant superbugs. Moreover, a declined trend to investigate for new antibiotics, insufficient research to collect the informations of resistant strains and unavailability of vaccines may posed potential threats.

WHO calls to combat resistance

The hazards from resistance superbugs are increasing and demanded an urgent action. The multifarious problem of resistance superbugs need a collective effort. Thus, WHO is calling for prompt action to stope the transmission of antibiotic resistance by introducing a 6 point policy package.

Table 1. Chronological review of antibiotic deployment and resistance observed

1941	Penicillin was given to its first patient
1942	Penicillin resistance reported.
1956	Vancomycin introduced
1960	Methicillin introduce

1961	Methicillin resistance reported
1992	Vancomycin resistance gene was reported in staphylococcus aureus from Enterococci bacteria
1997	Partial Vancomycin resistance reported
1999	Quinupristin/ Dalfopristin introduce
2000	Quinopristin/ Dalfopristin resistance reported
2000	Lincolid was introduced
2001	Lincolid resistance was reported
2002	Full Vancomycin resistance was reported
2003	Daptomycin introduced
2005	Daptomycin resistance reported
2005	Tigecycline introduced
????	Tigecycline resistance reported

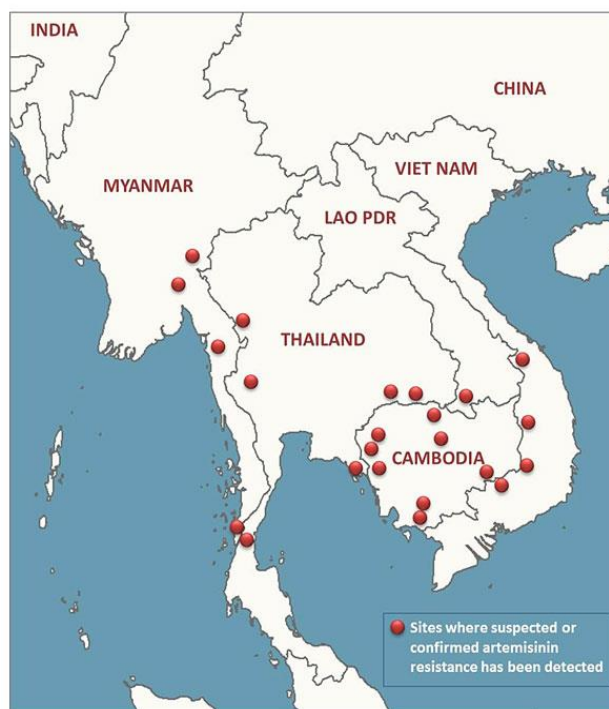


Figure 2: Locations of Greater Mekong Subregion with confirmed or suspected artemisinin resistance 2006-2013.

The key facto of MDR and XDR tuberculosis are as under;

1. Misused/ mismanaged of 1st line drugs produce MDR-TB
2. Misused/ mismanaged 2nd line drugs produce XDR-TB
3. One in three people in the world is infected with dormant TB.
4. Immuno-compromised people (HIV, old age, medical conditions) get ill with TB

The resistance against tuberculosis can be controlled by;

1. Better hygiene
2. Access to clean water and sanitation
3. Infection control in healthcare facilities
4. Vaccination
5. Ensure compliance
6. Rational antibiotic usage
7. Use antibiotics prescribed by a qualified physician
8. Complete the prescribed medication, even if you start feeling better
9. Never share your drugs or use leftover medication
10. Without an urgent effect we are moving toward the post antibiotic age, when minor injuries and ordinary infectious disease can kill again.

In addition of that a high percentage of nosocomial infections are based on Methicillin Resistant *Staphylococcus Aureus* (MRSA) or MDR Gram –ive strains of bacteria. The failure of treatment because of the antibiotic resistance is the last resort for gonorrhoea; 3rd generation cephalosporins have been reported in ten different countries. Thus, gonorrhoea may become untreatable with current medications and therapy plans. Whereas, we have no new drugs or vaccines in process to develop and apply in clinical practice. Therefore, the untreatable gonococcal infections may consequently increase the rate of infection along with complications i.e. adverse pregnancy outcomes, infertility and neonatal blindness etc. Whereas, the patients with resistant superbugs are generally at high risk of severe clinical complications and death. Moreover, it consumes additional financial resources and healthcare services than patients infected with the same susceptible micro-organisms. Moreover, certain clinical and biological terms are scientifically defined as under.³³

CONCLUSION

In conclusion, the designing, approval and enforcement of appropriate drug regulations may potentially help to optimize the pharmacotherapy and mitigate the emergence of antibiotic resistance in health care system of SEA countries. Moreover, a prospective jurisprudential support is necessary to assure standard pharmaceutical care. Especially, the pharmacy professional and drug experts are needed to deliver their exact scientific and professional role of prescription reviewing, patient counseling, therapeutically drug monitoring, biosafety, clinical services and pharmaceutical care instead of current irrelevant, non-technical, administrative and clerical work. That will definitely help to minimize the chances of development of resistance against antibiotics and potential health hazards. The pharmacovigilance,

ADR's, pharmacoeconomics and pharmacometrics should also be implicated to achieve the MDG's of WHO and quality health services in SEA countries.

Authors' contributions:

This work was carried out in collaboration among all authors. Taha Nazir and Nida Taha designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Saeed Ur Rashid Nazir and Azharul Islam managed the analyses of the study. Misbah Sultana and Humayun Riaz managed the literature searches. All authors read and approved the final manuscript.

Abbreviations

- ADR: Adverse Drug Reaction
 C-Diff: Clostridium difficile
 CRE: Carbapenem-resistant Enterobacteriaceae
 GAIN: Generating Antibiotic Incentives Now; U.S. passed Act in 2012
 MDG: Millennium Development Goals
 NDM-1: New Delhi Metallo Beta Lactamase-1
 MDR: Multi Drug Resistant
 MRSA: Methicillin Resistant Staphylococcus Aureus
 NDM-1: New Delhi Metallo-beta-lactamase-1 enzyme,
 PATH: Promise for Antibiotics and Therapeutics for Health; U.S. Congress considered bill (Act)
 PQCB: Provincial Quality Control Board
 VRE: Vancomycin-resistant Enterococcus
 WHO: World Health Organization
 XDR: Extensive Drug Resistant

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