# Superbugs

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## 1. Superbugs: Drug resistant microbes

Drug-resistant microbes, i.e. superbugs, symbolize one of the most dangerous threats in the history of medicine [1]. Currently, an important interest in bacterial infections is their increasing resistance to the many available antibacterial agents. Simply, the resistance may be intrinsic (bacteria carry genes that allow them to survive exposure to the antibiotics), or acquired as part of natural selection (random changes or mutations occur in the genes of individual bacterial cells), and/ or gene that carries antibiotic resistance are passed between bacteria. Thus, superbugs: the bacteria that carry resistance genes to different antibiotics are created. Antibiotic resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae, Streptococcus pneumonia, Clostridium difficile, Neisseria gonorrhoeae, Acinetobacter baumannii, Mycobacterium tuberculosis, vancomycin-resistant Enterococcus, Salmonella, Escherichia coli,* and *Pseudomonas aeruginosa* are some examples of the 'superbugs[2]. Antimicrobial resistance (AMR) including multidrug resistance (MDR), is on the rise among many microorganisms in both health-care facilities and community [3]. Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated, antimicrobial resistant bacteria[4]. The damaging results of antimicrobial resistance (AMR) are already demonstrating themselves across the world. Antimicrobial-resistant infections currently demand at least 50,000 lives each year across Europe and the US alone, with many hundreds of thousands more dying in other areas of the world. But trustworthy estimates of the true burden are insufficient. There is considerable variation globally in the patterns of AMR, yet AMR is a problem that should concern every country irrespective of its level of income. For instance, in 15 European countries more than 10% of bloodstream *Staphylococcus aureus* infections are caused by methicillin-resistant strains (MRSA), with various of these countries detecting resistance rates closer to 50%[5]. Even though in modern, well-funded healthcare systems, maintaining access to second and third-line treatments may often not be an issue, mortality rates for patients with infections caused by resistant bacteria are essentially higher, as are their costs of treatment especially in intensive care, haematology and transplant units who have pan-resistant infections, meaning there is no effective treatment available. The threat of growing drug-resistant infections is no less severe in poorer countries. Emerging resistance to treatments for other diseases, such as TB, malaria and HIV, have tremendous effects in lower-income settings. According to World Health Organization *Global Tuberculosis Report 2014* the increasing prevalence of drug-resistant strains of TB is well-documented: there were an estimated 480,000 new cases in 2013 – of which the majority went untreated [6]. The spread of resistant strains of malaria is likewise well-documented, and the development of resistance to antiretroviral therapy for HIV is closely monitored. The variation in the AMR problems of individual countries is related to extremely large differences in how heavily they use antimicrobial drugs. Global consumption of antibiotics in human medicine rose by nearly 40% between 2000 and 2010, but this figure masks patterns of declining usage in some countries and rapid growth in others [7]. Any use of antimicrobials, still appropriate and conservative, contributes to the development of resistance, but extensive unnecessary and excessive use makes it worse. Overuse and misuse of antimicrobials is preferred in many places by their availability over the counter and without prescription. Like all infectious diseases, the speed and volume of intercontinental travel today develops new opportunities for antimicrobial-resistant pathogens to spread globally. Such mixing of different microbes, especially bacteria, supplies them with opportunities to share their genetic material with each other, creating new resistant strains at an unprecedented pace. For that reason, no country can favorably endeavour AMR by acting in isolation [8].

## 2. Multidrug-resistant organisms (MDROs)

Generally, bacteria (excluding *M. tuberculosis*) that are resistant to one or more classes of antimicrobial agents usually are resistant to all but one or two commercially available antimicrobial agents (e.g., MRSA, VRE, extended spectrum beta-lactamase [ESBL]-producing or intrinsically resistant gram-negative bacilli). Multi drug resistant organisms (MDRO)s are defined as microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Even though the names of certain MDROs describe resistance to only one agent (e.g., MRSA, VRE), these pathogens are frequently resistant to most available antimicrobial agents)[9].

 

In addition to MRSA and VRE, certain Gram negative bacteria (GNB), involving those producing extended spectrum beta-lactamases (ESBLs) and others that are resistant to multiple classes of antimicrobial agents, are of particular concern. Also, additionally *Escherichia coli* and *Klebsiella pneumoniae*, these include strains of *Acinetobacter baumannii,* resistant to all antimicrobial agents, or all except imipenem and organisms such as *Stenotrophomonas maltophilia, Burkholderia cepacia* and *Ralstonia pickettii* that are intrinsically resistant to the broadest-spectrum antimicrobial agents. In some residential settings, it is important to control multidrug-resistant *S. pneumoniae* (MDRSP) that are resistant to penicillin and other broad-spectrum agents such as macrolides and fluroquinolones[10]. *S. aureus* strains that have intermediate susceptibility or are resistant to vancomycin (i.e., vancomycin-intermediate *S. aureus* [VISA], vancomycin-resistant *S. aureus* [VRSA]) have affected specific populations, such as hemodialysis patients [11].

## 3. Emergence of MDR pathogens

MDR bacteria of most concern to clinicians worldwide are *Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, A. baumannii, P. aeruginosa* and *Enterobacter* spp (ESKAPE) pathogens [12]. Currently, the use of the term ESCAPE (also involving *Clostridium difficile* and substituting Enterobacteriaceae for *Enterobacter* spp) has been advised, but since ESBL producing *E coli* are an increasing concern the acronym ESCAPE might be more suitable. A high prevalence of Gram-negative MDR pathogens (*E coli*, *K pneumoniae*, and *P aeruginosa*) was noted in Europe, particularly in southern Europe. 14 of 17 countries reported that 85–100% of isolates resistant to third-generation cephalosporins were ESBL-producing bacteria. On the contrary, MDR in Gram positive bacteria (*Streptococcus pneumoniae*, *S aureus* involving methicillin-resistant *S aureus* [MRSA], *E faecium,* and *Enterococcus faecalis*) appears to have stabilised or even decreased in some countries [5]. Conclusions are difficult to manage because most combinations of pathogens and antimicrobial drugs vary broadly between countries. The prevalence of MDR bacteria was lower in the north than in the south of Europe for several antimicrobial– pathogen combinations such as fluoroquinoloneresistant *E coli* (>20–45% in Cyprus, Italy, and Spain *vs* 7–9% in Norway and Sweden), *K pneumoniae*, *P aeruginosa*, and for MRSA [13].

### 3.1 Clinical importance of MDROs

In most instances, MDRO infections have clinical manifestations that are similar to infections caused by susceptible pathogens. However, options for treating patients with these infections are often intensely limited. For example, until recently, only vancomycin provided effective therapy for potentially life-threatening MRSA infections and during the 1990's there were virtually no antimicrobial agents to treat infections caused by VRE. Even though antimicrobials are now available for treatment of MRSA and VRE infections, resistance to each new agent has already emerged in clinical isolates [14]. Likewise, therapeutic options are limited for ESBL-producing isolates of gram-negative bacilli, strains of *A. baumannii* resistant to all antimicrobial agents except imipenem and intrinsically resistant *Stenotrophomonas* sp [15]. These limitations may influence antibiotic usage patterns. They may suppress normal flora and create a advantageous environment for development of colonization when exposed to potential MDR pathogens [16]. Increased lengths of stay, costs, and mortality are also problems related with MDROs. Two studies documented increased mortality, hospital lengths of stay, and hospital charges associated with multidrug-resistant gram-negative bacilli (MDR-GNBs), involving a newborn intensive care unit (NICU) outbreak of ESBL-producing Klebsiella pneumoniae and the emergence of third generation cephalosporin resistance in Enterobacter spp. in hospitalized adults [17]. Vancomycin resistance has been reported to be an independent predictor of death from enterococcal bacteremia [18]. Moreover, VRE was related with increased mortality, length of hospital stay, admission to the ICU, surgical procedures, and costs when VRE patients were compared with a matched hospital population. Nevertheless, MRSA may act differently from other MDROs. When patients with MRSA have been compared to patients with methicillin-susceptible *S. aureus* (MSSA), MRSA colonized patients more often develop symptomatic infections [19]. Moreover, higher case fatality rates have been observed for certain MRSA infections, including bacteremia poststernotomy mediastinitis and surgical site infections[20]. Mortality may be increased more by *S. aureus* with reduced vancomycin susceptibility (VISA) [21]. Also some studies have reported an association between MRSA infections and increased length of stay, and healthcare costs while others have not [22].

## 4. Transmission

Any disease-causing bacteria have the potential to transform into superbugs [3]. Once MDROs are introduced into a healthcare setting, transmission and persistence of the resistant strain is determined by the availability of defenseless patients, selective pressure exerted by antimicrobial use, increased potential for transmission from larger numbers of colonized or infected patients ("colonization pressure"). Patients vulnerable to colonization and infection involve those with severe disease, particularly those with compromised host defenses from underlying medical conditions; recent surgery; or indwelling medical devices (e.g., urinary catheters or endotracheal tubes[23]. Hospitalized patients,

especially intensive care unit (ICU) patients, tend to have more risk factors than non-hospitalized patients do, and have the highest infection rates. There is sufficient epidemiologic evidence to suggest that MDROs are carried from one person to another via the hands of health care personnel (HCP)[24]. Hands are easily contaminated during the process of care-giving or from contact with environmental surfaces in close proximity to the patient[25]. The latter is especially important when patients have diarrhea and the reservoir of the MDRO is the gastrointestinal tract[26]. Strategies to increase and monitor adherence are important components of MDRO control programs [27].

## 5. Antimicrobial Resistance

A study claims drug resistant infections will kill an extra 10 million people a year worldwide - more than currently die from cancer - by 2050 unless action is taken[28]. Currently, a major responsibility in bacterial infections is their increasing resistance to the many available antibacterial agents. The resistance mechanisms may be different such as; intrinsic, acquired and genetic. The result is creation of bacteria that carry resistance genes to different antibiotics, termed as superbugs[1]. Many patients receive antimicrobial drugs. Through selection and exchange of genetic resistance elements, antibiotics promote the emergence of multi-drug resistant strains of bacteria; microorganisms in the normal human flora sensitive to the given drug are suppressed, while resistant strains persist and may become endemic in the hospital. The broadly use of antimicrobials for therapy or prophylaxis is the main determinant of resistance. Antimicrobial agents are, in some cases, having lower effects because of resistance. As an antimicrobial agent becomes extensively used, bacteria resistant to this drug finally arise and may spread in the health care setting. Many strains of pneumococci, staphylococci, enterococci, and tuberculosis are now resistant to most or all antimicrobials which were in the past susceptible. Multiresistant *Klebsiella* and *Pseudomonas aeruginosa* are widespread in many hospitals. This problem is specifically important in developing countries where more expensive second-line antibiotics may not be available or affordable. Nosocomial infections are widespread. They are important subscribers to morbidity and mortality. They will become even more essential as a public health problem with increasing economic and human impact because of increasing numbers and crowding of people, more common impaired immunity, new microorganisms and increasing bacterial resistance to antibiotics[29].

### 5.1 Antimicrobial-resistant microorganisms

The expansion of multiresistant strains of *S. aureus* and VRE is mainly by transient carriage on the hands of health care workers. The following precautions are necessitated for the prevention of spread of epidemic MRSA: Staff and patients ward transportations should be minimized. Early detection of cases, specifically if admitted from another hospital should be guaranteed; screening of high risk patients may be acknowledged. Infected or colonized patients should be isolated in a single room, isolation unit or cohorting in a larger ward. Handwashing by staff after contact with infected or colonized patients should be strengthened; and also an antiseptic handwashing agent should be used. Gloves should always be used for handling MRSA-contaminated materials, or infected or colonized patients. Also, everytime gown or apron should be worn when handling contaminated materials or infected or colonized patients. Nasal carriers should be treated with mupirocin. Antiseptic detergent daily wash or bath for carriers or infected patients should be used. Careful handling and disposal of medical devices, linen, waste, etc. should be guaranteed. Guidelines should be prepared specifying when isolation measures can be discontinued[29].

## 6. How did bugs become "super?"

Probably the most commonly known reason of the development of antibiotic resistance is the so-called misuse of antibiotics. This concept involves not only to the patient's adherence to antibiotic prescription instructions, but also to the doctors that prescribe antibiotics unnecessarily. Several times problems with over prescription of antibiotics comes from the patients request. Disregarding the reason, antibiotics used for unnecessary purposes, involving non-bacterial infections and prophylaxis, boost the development and the spread of antibiotic resistance. In a study it is demonstrated that over 90% of all infections are viral, still over half the patients are taking antibiotics for these viral infections[30].

### 6.1 Superbugs create super-problems

In regards with WHO's 2014 report on global surveillance of antimicrobial resistance; treatment failure to the drug of last resort for gonorrhoea – third-generation cephalosporins – has been proven in several countries. Resistance to one of the most commonly used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* – fluoroquinolones – is very extensive. Resistance to first-line drugs to treat infections caused by *Staphlylococcus aureus* – a frequent pathogen of severe infections acquired both in health-care facilities and in the community – is also extensive. Resistance to the treatment of last alternatives for life-threatening infections caused by common intestinal bacteria – carbapenem antibiotics – has spread to all regions of the world. In 2012, there were an estimated 450 000 new cases of MDR-TB in the world. Globally, 6% of new TB cases and 20% of previously treated TB cases are estimated to

 

have MDR-TB, with substantial differences in the frequency of MDR-TB among countries[31]. Recent reports have witnessed changing susceptibility pattern and spreading trend in AMR. Development of superbug like New Delhi metallo-β-lactamase 1 (NDM-1) positive Enterobacteriaceae have further complicated the management of such infections. Thus AMR is a major point of concern as it is associated with high death rates and fear of progression to the pre antibiotic era; also has potential to hamper infectious disease control programmes; increase in health care costs and diminish in health-care gains achieved so far[3]. In regards with the Centers for Disease Control and Prevention, superbugs infect at least two million people per year in the USA alone killing at least 23 000 people as a direct result of these infection[29]. Superbugs present an important challenge to human health, specifically for developing countries where antibiotic-resistant bacteria may go unnoticed as seen in the case of metallo-beta-lactamase-1 containing Klebsiella pneumoniae bacterium generally known as New Delhi Metallo-1[32]. Even though many developed nations including UK, USA, Greece, Finland, Germany, Iceland, Japan, and The Netherlands have declined the use of antibiotics, and displayed decrease in antibiotic resistance commonness following application of antibiotic control measures, other developing countries (e.g. Pakistan, India, Bangladesh) have avoided the emerging threat and continue the deregulated use of antibiotics, i.e. approachable over the counter, without a prescription, and with no drug resistance monitoring methods in place[33]. Due to the increasing trends of infections in the society, schools and public places are being concerned. The Centers for Disease Control and Prevention estimates that 12% of MRSA infections are now community-related, which are on the rise in comparison with healthcare-associated MRSA. Usually, the World Health Organization has highlighted superbugs as the biggest threat to human health that we face today. The challenge is to cultivate new procedures of preventing, diagnosing, and treating antibiotic-resistant infections[34]. The bothering fact is that even the most robust mechanisms to destroy superbugs had limited accomplishment[35]. Presently, nearly 6% of all hospitals in the USA are fighting outbreaks with *K. pneumoniae* infection alone, let alone other superbugs such as MRSA, *S. pneumonia*, *C. difficile*, *N. gonorrhoeae, A. baumannii, M. tuberculosis*, vancomycin-resistant *Enterococcus*, *Salmonella, E. coli, and P. aeruginosa*. Similarly, nearly 8% of UK hospital patients suffer from hospital-acquired infections, while more than 37 000 people have died in the UK in the last decade alone from hospital-acquired infections caused by superbugs such as *C. difficile* and MRSA[36]. According to the Center for Disease Control and Prevention, *C. difficile* and MRSA are killing 14 000 and 19 000 people respectively annually in the USA alone[37]. Unfortunately, free from well-established guidelines and robust interventional strategies, superbugs continue to spread, as evidenced by the NIH outbreak. Additionally, there is a deficiency of effective antimicrobials. There is an urgent necessity to do more research to develop interventional strategies to eliminate superbugs, as well as analyzing how to prevent their transmission. Other than fighting antibiotic-resistant infections, the situation has become an ethical fight for hospitals, as patients coming to hospitals for common disease or surgeries may be exposed to far deadly and sometimes untreatable infections due to superbugs[38]. The US Centers for Disease Control and Prevention in the USA released a inclusive report which highlighted the significance of enforcing public health strategies such as infection control, protection of the food supply, antiinfective stewardship, and reduction of person-to-person spread through screening, treatment, and education of health-care workers and patients[39].

## 7. Misuse of antibiotics and antibacterial products

A non-resistant bug, usually improves clinical symptoms within 1 to 3 days. Patients have difficulty continuing to take the prescription when their symptoms have been lessened. The contribution of this action to antibiotic resistance is easy: initial treatment kills most of the bacteria, specificially those susceptible to the antibiotic; those with some minor susceptibility to the antibiotic survive and grow as the dosing is lessened. Fundementally this is an acceleration of "survival of the fittest." Bacteria that have been able to survive, reproduce and pass along whatever genetic variance they carry which supplies resistance. Recent reports have warned the overuse of antibiotics as prophylaxis in the food industry, even though there is some debate over the actual contribution to food animal antibiotic administration to the growing problem of global "superbug" problems. It is proposed that unnecessary use of antibiotics in food animals will contribute to resistance in the same ways as over prescribing and lack of adherence in the human population. Even though antibiotic misuse is possibly the most publicized cause of "superbug" development, various similar mechanisms advance the resistant strains as well. Many antibacterial products contain the ingredient triclosan, which works by inhibiting essential fatty acid synthesis. Surviving bacteria develop a resistance to triclosan and as a result are not affected by future triclosan based cleansing[40].The thought of "superbug" progress in your home can be annoying, but understanding where bacteria and fungi are found, where they live, and what strains they are can help educate the public about cleanliness in the home. A recent article in *Popular Mechanics* examined places in your home where microorganisms are probably thriving and identified the top five: refrigerator, dishwasher, air around the trash can and the trash can itself, washing machine, and the shower head. Presented results implied that 23.4% of the bacteria found in the refrigerator was *Klebsiella pneumoniae;* the possibly infectious bacteria *Pseudomonas aeruginosa* were found in the washing machine; bacteria samples collected from the trash and the air around the trash contained *Staphylococcus aureus,* approximately 33% of which were methicillin resistant*; Exophiala* fungi having the ability of infecting humans was found in the dishwasher; and *Mycobacterium avium*, a bacteria that is generally benign but can infect immunocompromized individuals, was found in the shower head[41]. The essential point to take from both of these

"household" examples is that any cleansing treatment must be accessed with sufficient cleanser and enough time to guarantee that maximal bacteria or fungus has been extinguished[40]. Bacterial resistance to antibiotics is increasing day by day in both community and hospital setting, also increasing mortality and morbidity. Presently, the continuous development and the spread of bacterial resistances pose some questions about their future and represent a serious threat for their clinical utility, leading to an urgent requirement for new compounds[42]. Numerous agencies and professional societies have tried to draw attention to the lack of new antibiotics, especially for MDR Gram-negative pathogens[43].

## 8. Mechanisms of resistance development in bacteria

Bacteria can develop resistance to antibiotics by several mechanisms: the production of enzymes that inactivate antibiotics (eg, β-lactamase), the activation of efflux pumps, changes in the cell wall that destroy drug penetration (eg, porin alteration), the production of proteins that protect the target site (eg, in quinolone resistance), and mutations in target genes (eg, those encoding penicillin-binding proteins)[44]. The increase in class B β-lactamases (involving metallo-β-lactamases) that confer resistance to a broad range of β-lactam antibotics in Gram-negative bacteria such as *Pseudomonas aeruginosa* and representatives of the Enterobacteriaceae has been reported in the past 10 years. Even more worrisome is the worldwide rise in β-lactamase and carbapenemase-producing bacteria, involving *Klebsiella pneumoniae* carbapenemase (KPC)2 and KPC3, verona integrin-encoded metallo-β-lactamase (VIM)-1, oxacillinase (OXA)-48, and OXA-162-producing enterobacteria (eg, *E coli*, *K pneumoniae*, *Enterobacter cloacae*, and *Serratia marcescens*) and *Acinetobacter baumannii*[45]. Gram-negative bacteria of the Enterobacteriaceae family with resistance to carbapenem antibiotics conferred by New Delhi metallo-β-lactamase-1 (NDM-1) have been explained. This mechanism of antibiotic resistance originated in India and Pakistan and is also detected in travellers returning to Europe. NDM-1 was mainly detected in *E coli* and *K pneumoniae*, which were highly resistant to all antibiotics apart from tigecycline and colistin[13].

## 9.Infection Control

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has published guidelines for the management of infection control measures to lowering transmission of MDR Gram-negative bacteria in hospital inpatients. The several types of interventions used to prevent and control the spread of MDR Gram negative bacteria are grouped into five categories: hand-hygiene measures; active screening of patients with cultures; contact barrier precautions; environmental cleaning; and anti-infective stewardship. Basically, these measures apply both MDR Gram-negative and MDR Gram-positive bacteria. Prevention and control of MDR pathogens can be achieved by the implementation of strict hand and environmental hygiene, patient isolation, and, for some pathogens (eg, MRSA), patient or staff decolonisation. Supporting cleaning procedures and surface decontamination are strongly suggested as infection control measures against MDR pathogens. The ESCMID guidelines recommend implementing the five key infection, prevention, and control measures integrated in daily practice to lessen the transmission of MDR Gram-negative bacteria (eg, ESBL-producing Enterobacteriaceae, MDR *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, KPC, and MDR *P aeruginosa*) in hospital inpatients. Any one infection control measure alone is not possible to have a large effect on the transmission of MRD pathogens. Unfavorably, the implementation of many evidence-based intervention practices together seems more likely to achieve improved outcomes than when they are implemented separately. Vancomycin-resistant *Enterococcus* spp (VRE), MRSA, and ESBL-producing Enterobacteriaceae, and MDR *P aeruginosa* and *A baumannii* are of most concern to clinicians[13]

### 9.1 Prevention of antibiotic resistance

Due to the respective mutation rate and gene transfer rates, there is absolutely a global concern over a future inability to treat bacterial infection easily and without toxic side effects. New multidrug resistance elements, in particularly, NDM-1, is concerning because of its possibility for achievement to travel between species and produce "superbugs" at rates well above the limit of natural selection. Continued responsible use of antibiotics is currently the best way to try to slow down the progress of resistant strains. Careful attention should be paid to when antibiotics are prescribed, but even more basically which antibiotics are prescribed. It is deeeply valuable to reserve new antibiotics for strains that have displayed resistance to other drugs. Additionally, attention for patient compliance is important; promising that the full course of antibiotic is taken will display maximal eradication of the bacteria, admitting no remaining cells to pass on their "hidden" of survival[40]. For outlining several steps in antimicrobial resistance the following five themes should be explored: The effect of antimicrobial resistance on the world's economy if the problem is not tackled; how we can change our use of antimicrobial drugs to reduce the rise of resistance, involving the game-changing potential of advances in genetics, genomics and computer science; how we can improve the development of new antimicrobial drugs; the potential for other therapies to break the rise in resistance and how these new ideas can be improved; the necessity for coherent international action that spans drugs regulation, and drugs use across humans, animals and the environment[8]. Various types of interventions used to control or eradicate MDROs may be grouped into seven

 

categories. These include administrative support, wisely use of antimicrobials, surveillance (routine and enhanced), Standard and Contact Precautions, environmental measures, education and decolonization[45].

### 9.2 Administrative support

One of the most substantial is the use of active surveillance cultures (ASC)[46]. Other interventions that need administrative support include: 1) starting system changes to guarantee rapid and effective communications e.g., computer alerts to identify patients earlier known to be colonized/infected with MDROs; 2) supporting the important number and appropriate installation of hand washing sinks and alcohol-containing hand rub dispensers in the facility; 3) providing staffing levels suitable to the intensity of care necessitated; and 4) achieving to recommended infection control practices (e.g., hand hygiene, Standard and Contact Precautions) for MDRO control[47]. Other measures that have been correlated with a positive effect on prevention efforts, that need administrative support, are direct observation with feedback to HCP on adherence to recommended precautions and providing HCP informed about changes in transmission rates[48].

### 9.3 Education

The focal point of the interventions was to provide a behavior change through advanced understanding of the problem MDRO that the facility was trying to control. Either the necessitated change involved hand hygiene, antimicrobial prescribing patterns, or other outcomes, improving understanding and developing a culture that supported and advanced the needed behavior, were viewed as essential to the success of the intervention. Educational campaigns to boost adherence to hand hygiene practices together with other control measures have been related temporally with decreases in MDRO transmission in healthcare settings[49].

### 9.4 Wisely use of antimicrobial agents

Only limiting antimicrobial use may be unsuccessful to control resistance due to a combination of factors; involving 1) the comperative effect of antimicrobials on providing initial selective pressure, compared to perpetuating resistance once it has emerged; 2) insufficient limits on usage; or 3) inadequate time to observe the impact of this intervention[50]. The CDC Campaign to Prevent Antimicrobial Resistance that was launched in 2002 provides evidence-based principles for judicious use of antimicrobials and tools for implementation[51]. www.cdc.gov/getsmart/healthcare/. This accomplishment aims all healthcare settings and focuses on effective antimicrobial treatment of infections, use of narrow spectrum agents, treatment of infections and not contaminants, preventing disproportionate duration of therapy, and restricting use of broad-spectrum or more effective antimicrobials to treatment of serious infections when the pathogen is not known or when other effective agents are not ready for use. Action plans for initiating antimicrobial prescribing patterns inside healthcare facilities include education; formulary restriction; prior-approval programs, including pre-approved indications; automatic stop orders; academic interventions to correct pharmaceutical influences on prescribing patterns; antimicrobial cycling, computer-assisted management programs and active efforts to remove excessive antimicrobial combinations[52]. Surveillance is a unfavorably vital constituent of any MDRO control program, admitting detection of newly emerging pathogens, monitoring epidemiologic trends, and measuring the effectiveness of interventions[45]. Some investigators have used clinical microbiology results to calculate measures of incidence of MDRO isolates in specific populations or patient care locations (e.g. new MDRO isolates/1,000 patient days, new MDRO isolates per month). Such measures may be beneficial for monitoring MDRO trends and evaluating the effect of prevention programs, even though they have limitations. Because they depend only on positive culture results without accompanying clinical information, they do not differentiate colonization from infection, and may not fully display the burden of MDRO-associated disease. In spite of these restrictions, incidence measures based on clinical culture results may be highly correlated with current MDRO transmission rates acquired from information using ASC[53]. The results imply that incidence measures based on clinical cultures alone might be beneficial possible choices for monitoring changes in MDRO transmission rates[45]. Many investigators have used molecular typing of selected isolates to confirm clonal transmission to boost understanding of MDRO transmission and the effect of interventions inside their facility[54].

### 9.5 Active surveillance cultures(ASC)

Another form of MDRO surveillance is the use of active surveillance cultures (ASC) to identify patients who are colonized with a targeted MDRO[55]. Many authors report having used ASC when new pathogens arise in order to define the epidemiology of the specific agent[56]. Additionally, the authors of various reports have concluded that ASC(active surveillance cultures), together with use of contact precautions for colonized patients, contributed directly to the decline or eradication of the target MDRO[57]. When use of ASC is combined into MDRO prevention programs, the following should be considered: The decision to use ASC as part of an infection prevention and control program necessitates extra support for successful implementation, involving: 1) personnel to collect the appropriate cultures, 2) microbiology laboratory personnel to process the cultures, 3) mechanism for communicating results to caregivers, 4)

simultaneous decisions about use of extra isolation measures triggered by a positive culture (e.g. contact precautions) and 5) mechanism for encouraging adherence to the additional isolation measure[58].

### 9.6 Rapid detection methods

Using conventional culture methods for active surveillance can result in a delay of 2-3 days before results are accessible. If the infection control precautions (e.g., contact precautions) are withheld until the results are accessible, the desired infection control measures could be delayed. Commercially ready to use media containing chromogenic enzyme substrates has been displayed to have high sensitivity and specificity for identification of MRSA and facilitate detection of MRSA colonies in screening cultures as early as 16 hours after inoculation[58]. Moreover, realtime PCR-based tests for rapid detection of MRSA directly from culture swabs (< 1-2 hours) are commercially available as well as PCR-based tests for detection of vanA and van B genes from rectal swabs[59].

## 10. Infection Control Precautions

CDC has recommended the use of standard and contact precautions for MDROs. This advice was based on general agreement. Standard precautions have an important role in preventing MDRO transmission, even in facilities that use contact precautions for patients with an identified MDRO. Colonization with MDROs is generally undetected; yet surveillance cultures may fail to identify colonized persons due to lack of sensitivity, laboratory deficiencies, or intermittent colonization due to antimicrobial therapy[60]. For that reason, standard precautions must be used in order to prevent transmission from conceivably colonized patients. Hand hygiene is an important component of standard precautions[61]. Contact precautions are aimed to prevent transmission of infectious agents, involving epidemiologically important microorganisms, which are transmitted by direct or indirect contact with the patient or the patient's environment. A single-patient room is favored for patients who need contact precautions. HCP caring for patients on contact precautions should wear a gown and gloves for all interactions that may include contact with the patient or potentially contaminated areas in the patient's environment. Wearing gown and gloves upon room entry and discarding before exiting the patient room is done to contain pathogens, particularly those that have been involved in transmission through environmental contamination[62]. The promising role of environmental reservoirs, such as surfaces and medical equipment, in the transmission of VRE and other MDROs has been the subject of various reports[63]. As long as environmental cultures are not routinely recommended, environmental cultures were used in several studies to document contamination, and led to interventions that involved the use of dedicated noncritical medical equipment assignment of dedicated cleaning personnel to the affected patient care unit and increased cleaning and disinfection of frequently-touched surfaces[64].

### 10.1 Decolonization

Decolonization results in treatment of persons colonized with a specific MDRO, generally MRSA, to eradicate transport of that organism[65]. Decolonization regimens are not adequately effective to guarantee routine use. As a result, most healthcare facilities have restricted the use of decolonization to MRSA outbreaks, or other high prevalence situations, particularly those affecting special-care units. Several factors limit the appropriateness of this control measure on a widespread basis: 1) identification of candidates for decolonization necessitates surveillance cultures; 2) candidates receiving decolonization treatment must receive follow-up cultures to guarantee eradication; and 3) recolonization with the same strain, initial colonization with a mupirocin-resistant strain, and emergence of resistance to mupirocin during treatment can occur HCP implicated in transmission of MRSA are candidates for decolonization and should be treated and culture negative before returning to direct patient care. On the contrary, HCP who are colonized with MRSA, but are asymptomatic, and have not been linked epidemiologically to transmission, do not need decolonization[66].

### 10.2 Antimicrobial Stewardship

Many studies have displayed that previous antimicrobial drug exposure is a strong risk factor for colonization and infection due to drug-resistant bacteria. Fluoroquinolones and third-generation cephalosporins have frequently been involved in advancing the spread of MDR-bacteria, even though, the direct corporation between antibiotic therapy and the achievement of antibiotic-resistant bacteria is still uncertain. The studies are frequently astonished by insufficient data on antibiotic usage and differ in regards with microorganism, dosage, drug combinations, timing of exposure and setting. A recent Cochrane systematic review proved that interventions to reduce excessive antibiotic prescribing to hospital inpatients can decrease antimicrobial resistance or hospital-acquired infections and interventions to increase active prescribing can improve clinical consequence[67]. There are different ways to the control and limiting of antibiotics consumption in hospitalized patients. Antibiotic restriction, i.e. the need for approval of the antibiotic from an infectious diseases specialist might be one of the most persuasive control methods. A sort of such use-justification approaches have been created to improve antibiotic use. These have involved telephone approval from an infectious diseases specialist, automatic stop orders, and antibiotic order forms that require justification for the prescribed drug

 

after dispensing from the pharmacy[68]. Antibiotic cycling or rotating has been described as an essential plan of action for decreasing resistance. The aim of antibiotic cycling or rotation is a continual lessening or stabilization in antimicrobial resistance through successive, potential alterations in antibiotic selection pressures that prohibit the selection of specific resistance traits and thus, organisms. Actually, cycling of antibiotics in high-risk units can favorably alter resistance patterns and the approach of cycling is apparently enforcing. Its value, still, may be not so high because of concerns about practical relevance and the endurance of resistance genes. Essential unresolved issues involve determining the advantage of site-specific versus organism-specific rotation plan of actions,optimum period of rotation periods, types of antibiotics used and in what order, and analysis of the transmissibility of resistance elements in the several clones on the units[69]. The performance of antibiotic guidelines or protocols has been demonstrated to be a formal means of accomplishing the targets of appropriate antibiotic use, limiting inessential antibiotic use and, as a result,advancing antibiotic susceptibility profiles[70]. The strategies can be incorporated into inclusive programmes, designed to optimize antimicrobial therapy, to improve patient outcomes, guarantee cost-effective therapy and decrease the adverse effects related with antimicrobial use, involving antimicrobial resistance[71].

## 11.Current and emerging therapies

Many of the existing therapies for bacterial infections function via identical mechanisms of action. In general antibiotics inhibit one of three cellular mechanisms including: protein synthesis (aminoglycosides, macrolides, tetracyclines, and others including streptomycin, chloramphenicol, linezolid, quinupristin/dalfopristin); cell wall synthesis (carbapenems, cephalosporins, glycopeptides, and penicillins); or topoisomerase activity (quinolones). There are a few selected antibiotics that have a unique mechanism of action : daptomycin, which binds to the cell membrane and causes rapid depolarization thus inhibiting synthesis of nucleic acids and proteins; trimethoprin-sulfamethoxazole, which interferes significantly with bacterial folic acid synthesis; and metronidazole, which results in breakdown of DNA helical structure[72]. Currently, there have been a few critical developments of new antibiotics. Ceftaroline, often referred to as a 5th generation cephalosporin, has shown activity against multidrug resistant gram positive bacteria. Ceftaroline fosamil is a prodrug form which is rapidly converted to the active form after administered[73]. Like other cephalosporins, it binds to penicillin binding proteins (PBP), but differs from other β-lactams in that it has a high affinity for PBP2a, which is unique to *MRSA*[74]. Ceftaroline has been favorably used for the treatment of skin and skin structure infections caused by methicillin resistant *S. aureus, S. pyogenes, S. agalactiae, E. coli, K. oxytoca,* and *K. pneumoniae*[75]. Another novel addition to approved antibiotics is telavancin. Telavancin is a lipoglycopeptide derivative of vancomycin that inhibits bacterial cell wall synthesis. When compared to vancomycin, talavancin has displayed influence in treatment of skin and skin structure infections caused by methicillin resistant *S. aureus, S. pyogenes, S. agalactiae, S. pneumoniae,* and vancomycin resist*ant E. faecalis*[76]. The drug has also been investigated for use in hospital acquired pneumonia[77]. A recent carbapenem, doripenem, has displayed a broad spectrum of antimicrobial activity against gram positive and negative bacteria including *P. aeruginosa* (included some carbapenems resistant strains)[78]. Doripenem is indicated for complicated intra-abdominal and urinary tract infections due to enterococci, anaerobes, and *P. aeruginosa* as well as hospital acquired pneumonia resulting from *Klebsiella, Enterobacter, Acinetobacter,* and *Serratia* species or in some cases *S. aureus*[79]. Retapamulin is a currently approved topical antibiotic effective for treatment of impetigo due to *S. pyogenes* and methicillin-susceptible *S. aureus* [80]. This antibiotic is acquired from fermentation of fungi and represents the first in a class of antibiotics known as pleuromutilins. Drugs from this class interfere with bacterial protein synthesis by acting on the 50S subunit of the ribosome[81]. Another drug, fidaxomicin starts a novel class of antibiotics assigned to as macrocycles. The drug proposes a narrow range of activity as it is intended particularly for *C. difficile*[82]. Another potential antibiotic is kibdelomycin, which was chosen based on screening against multiple engineered strains of *S. aureus*. The structure identified was found to function as a type II topoisomerase inhibitor and has displayed activity primarily against gram positive bacteria. Even though it functions as a topoisomerase inhibitor, it is unique in the fact that it specifically inhibits the ATPase activity of bacterial type II topoisomerases[83]. Another promising new inhibitor (GSK299423) has displayed broad spectrum activity by inhibiting DNA gyrase. The ensuring detail about this inhibitor is that crystal structures have demonstrated that the inhibitor binds to a noncatalytic site on the DNA gyrase, as compared to the binding site for most fluoroquinolones, hence representing a new class of antibiotics and making this a prime target for further development[84].

## 12. Conclusions

The advancement of new antibiotics targeting the increasing threat of multidrug resistance is an aim that remains "dangerously secret". Low returns on antibiotic investments and an unpredictable and commonly impractible authorization pathway at regulatory agencies have caused many companies to leave the antibiotics market. The bad hospital pathogens have broke away from the hospital and are following the columns of the community pathogens[43]. The need of government support through funding is essential so as to develop drugs that are arranged to enter the

"pipeline." Considering the time necessitated for drug development, the risk of global spread of resistance is alarming[40]. Favorable control of MDROs has been recorded globally using several combined interventions. These involve advancement in hand hygiene, use of Contact Precautions until patients are culture-negative for a target MDRO, active surveillance cultures (ASC), education, enhanced environmental cleaning, and improvements in communication about patients with MDROs within and between healthcare facilities[45]. This might be one of the world's greatest problems, but it does not need to be its toughest. Many issues referred to AMR are complex and inter-related. Coordinated activity among several countries is by nature more complicated to agree than individual initiatives, but it is inevitable: drug-resistant bacteria know no frontiers. We need understandable international action that spans drug regulation and antimicrobial drugs use across humans, animals and the environment. This is an appearing global crisis, but one which the world can avoid if we take action soon[8].

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