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MISAPPLICATION AND OVEREXPLOITATION OF ANTIBIOTICS FUEL THE EMERGING ANTIMICROBIAL RESISTANCE IN INDIA

INTRODUCTION

'*Use, overuse and misuse*' are the major factors that contribute to the selection and transfer of bacterial resistance determinants to human, constituting a public health concern [1, 2, 3].

Before antibiotics, a simple wound, upon sepsis, could prove fatal. Although antibiotics have played a significant role in reducing infectious disease mortality over the decades, the prolonged unnecessary overuse of antibiotics for conditions such as common cold, is a major concern [3].
Alexander Fleming, while receiving his Nobel Prize in 1945 had quoted

"*The time may come penicillin can be bought by anyone in the shop. There is the danger that the ignorant man may easily under-dose himself and by exposing his microbe to non-lethal quantities of the drug make them resistant*"[5,6].

Although AMR is a global crisis, the hotspot of this cataclysm is India [7]. Easy access to the strongest of antibiotics without prescription or a confirmed diagnosis is the main affliction of the country; not just the quacks, who advice drugs with little thought[8, 9]. Misuse of antibiotics occurs not only in a hospital setting, but also in livestock. All of this, fuelled by poor sanitation and inadequate public health policies in India, make the country an ideal breeding ground for superbugs [10].
In short, the redundant use - with the backing of pharmaceutical industry – has made antibiotics the culprit. But now, as expected, the strongest of antibiotics seem to be ineffective in many situations. Bacteria have evolved to resist the antimicrobial threat by co-evolution. The current worldwide estimate of the annual mortality caused by antibiotic resistant bacteria is 700,000. This figure is expected to reach 10 million by the year 2050 [10, 11].

Emerging crisis in India

Resistance is emerging at an alarming rate in India for both gram (+)ve & (–)ve organisms. Eighty percent of the *E. coli* strains are resistant, even to reserve antibiotics [12]. Infectious disease mortality rate in India is 416.75 per 100,000(calculations based on world bank data and global burden of disease, 1990). Over 58,000 neonatal deaths are attributable to drug resistant sepsis. 410,000 children ≤ 5 years die from pneumonia in India annually [11, 12]. This is accompanied by a steep increase in MRSA, from 29% of the strains in 2009 to 47% in 2014 as well as the in Carbapenem resistant isolates of *E. coli* & *K. pneumoniae*. Fluroquinolone resistance in *S. typhi* isolates has increased from 8% in 2008 to 28% in 2014. Finally, the incidence of NDM-1 (New Delhi Metallo-beta-lactamase-1) and *Acinetobacter spp.* Infections, is also rising rapidly [13].

Causes of antibiotic resistance in India

a. Lack of awareness

According to a WHO survey, 75% of Indians think incorrectly that cold or flu can be treated with antibiotics, and only 58% know that an antibiotic course should be completed [14]. Even the medical curriculum in India does not adequately focus on rational antibiotic prescribing. Doctors benefit from clandestine arrangements with pharmaceutical companies/pharmacists in exchange for antibiotic prescriptions. Antibiotic overuse is fuelled not only by such financial incentives, but also by patient expectations [14].

b. Overuse

In India, the sale of antibiotics is poorly regulated,

resulting in easy access and overuse of antibiotics [15]. Online pharmacies has increase access to antibiotics also in countries with strict regulation [15].

c. Slump in antibiotic discovery

Pharmaceutical companies do not adequately fund the antibiotic R&D due to its small market size. And since the proper use of antibiotics results in complete cure of the infection, pharma-companies face a downturn of profits as soon as resistance emerges to a particular drug. Reserving new antibiotics by infection control organizations limits profits [16]. And with the majority of the R&D focusing on anti-cancer drugs, even the very low proportion invested on antibiotics focuses primarily on antiviral/anti-HIV drugs [16].

d. Inappropriate prescribing

Incorrectly prescribed antibiotics is a major cause of resistance [1, 17]. The expected reasons may be many, such as cost, lack of data for formulating a rational approach (i.e. antibiogram), lack of antibiotic guidelines or lack of periodic updates on antibiotic resistance [17]. This is reflected by the response of the physicians for treatment uncertainty and their suggestions to involve culture and sensitivity tests. The fear of resistance development alone drives doctors to prescribe a broad-spectrum antibiotic in the beginning itself (when a narrow-spectrum antibiotic would have sufficed). According to a study, purulent discharge, antibiotic-resistance concern, fever, and patient satisfaction were some of the other factors influencing the physicians to prescribe an antibiotic [17].

e. Irrational fixed drug combination

118 antibiotic FDCs are currently available in Indian market[18]. Eighty (68%) are not registered with the Central Drugs Standard Control Organisation (CDSCO), the chief regulatory authority of drugs in India. In 2016, the Indian Govt. banned around 330 irrational FDCs, 63 of which were antibiotics. However, these drugs continue to be exported to African and other South Asian countries. Conversely, while WHO has approved only 350 FDCs, over 6000 continue to be available worldwide [18].

f. Pharmaceutical pollution

Pharmaceutical pollution is not a frequently discussed pathway leading to AMR in India. Microorganisms being exposed to an antibiotic cocktail – primarily from pharma wastes - develops resistance by gene transfer [18]. Analysis of effluents from a certain plant in Hyderabad contained fluroquinolone antibiotics at concentrations of 31mg/L – which is much higher than the desired therapeutic plasma level! Another example is the case of Egyptian vultures wintering in India, which were found to harbour multi drug resistant *E. coli*, acquired from feeding on cattle carcasses[19].

Misuse of reserve antibiotics in livestock – a potential yet unresolved threat _

Antibiotics are widely used in livestock. India is a large exporter of animal food products and over 160,000 livestock animals were reported to have been affected by bacterial infections in 2009 [20]. While use of antibiotics to treat infection in animals is justified, its misuse as growth promoters at sub-therapeutic levels is questionable [20, 21]. Antibiotic resistance in veterinary populations is on the rise. Resistant bacteria in animals can spread to humans in several ways, with the consumption of animal products, exposure to raw meat products and direct contact [22].

Increasing incidence of VRSA (vancomycin resistant S. aureus) in cow and goat milk and NDM-1(New Delhi metallo beta lactamase) (+)ve E. coli in milk samples from cows and the high resistance to chloramphenicol and fluroquinolones in poultry cultures are some of the evidences for the deadly consequences of overuse in livestock [23]. A multinational chain '*Venky's*' - that supplies meat to some of the leading fast food chains in the country – advertises and sells colistin to farmers as a growth promoter for chicken[24].

Despite some global progress in limiting the veterinary use of antimicrobials, inappropriate colistin use remains uncontrolled. Colistin is the last resort antibiotic which is administered when most

other antibiotics fail [21,] . However, antibiotics continue to be indiscriminately used to promote growth and prevent infections in chicken[22]. Increasing evidence has linked this to the development of resistance against colistin in humans. MCR-1(Mobilized colistin resistance) has since been detected in bacteria from animals and humans in more than 30 countries, spanning five continents. In India, at least five veterinary pharmaceutical companies advertise products containing colistin as growth promoters or to be used metaphylactically. Such practices are dangerous, especially in India[23].

As mentioned above, *Venky's* dispose colistin-containing products as growth promoters to make better "FCR [feed–conversion ratio] and weight gain [24, 25]. According to Thomas van (ETH Zurich, Switzerland), India's utilization of antimicrobials in chickens is predicted to rise five-times by 2030 compared with 2013, while globally the amount used in animals is expected to rise by 53% [26, 27].

Over prescribing of reserve antibiotics

Watch-group antibiotics (consisting of most critically important antimicrobials – eg. macrolides and quinolones) are recommended only for specific, limited indications. Reserve group antibiotics (eg. aztreonam, polymixins etc.) are employed where all alternative antibiotics have failed[28]. Global AMR Action Plan was adopted by the World Heath assembly in alignment with WHO to combat rising antimicrobial resistance, improve access and clinical outcomes, and preserve the effectiveness of last resort antibiotics[28, 29]. Another huge challenge in India is education in antibiotic use. India continues to produce large volumes of antibiotics that already resistant to many microbes[30]. Failure of Indian drug regulatory system, the sale of antibiotics without prescription, and the proliferation of unapproved fixed-dose combination (FDC) antibiotics contribute to the high sale of such antibiotics[31] . Another major concern in the context of AMR is the group of FDCs that often contain drugs with mismatched dosing regimens, with very little data on their use in low-income and middle-income counties [32, 33].

A recent analysis of antibiotic utilization reported very high sale of key access, watch group and reserve antibiotics. The study also reported an alarming increase in the sales of FDCs containing watch group or reserve group antibiotics[33].

Conclusion

The improved health outcomes achieved with antibiotics is continuously threatened by rapidly emerging AMR. This global health crisis reflects the worldwide overuse relative to limited development of new antibiotics to address the current challenge. The scenario is worse in low and middle income countries like India. The emerging AMR warrants better public health policies - adopting stewardship programs, improving prescribing practices, optimizing therapeutic regimens, improving diagnostics to address the root causes and restricting antibiotic misuse and overuse.

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