**The menace of irrational antimicrobial drug combinations in India- Doctors need to recognize the writing on the wall and act on it.**

Antimicrobial resistance (AMR) is a public health crisis that is likely to cause about 10 million deaths every year by 2050 (1), unless strong health system based actions are taken against it. Although any antimicrobial use contributes to development of resistance; overuse, misuse and irrational use remain the biggest culprit, with or without prescription. Thus, the widespread availability, use and prescription of irrational fixed dose combinations (FDCs) of antimicrobials in India is one such contributor. The Ministry of Health and Family Welfare banned 344 FDCs in 2015, which was challenged by the drug companies and later the ban was quashed in the Delhi high court on the grounds that the government did not consult statutory authorities before enforcing the ban (2). Though there are more antimicrobial FDCs in India, about 63 are present even in these 344 FDCs. While an expert committee is reviewing the issue, clear regulatory loopholes are evident as People’s Health Movement and other public health organizations (3) have pointed out- these formulations were never approved by Central Drug Standard Control Organization (CDSCO) but the drugs are available in the market by merely receiving manufacturing approvals from state drug authorities. Interestingly, state drug control authorities are not authorized to grant marketing approvals (4).

The WHO publishes a list of Critically Important Antimicrobials for Human Medicines (WHO CIA List) (5), classifying them into three categories- critically important, highly important and important. These antimicrobials are vital for treatment in human infections, and the list urges to limit its use in veterinary and agricultural sectors. The critically important antimicrobials are further prioritized into highest priority and high priority drugs. Among the highest priority CIA’s that include Cephalosporins (3rd,4th & 5th generations), Glycopeptides, Macrolides and Ketolides, Polymyxins and Quinolones; about 39 types of such FDCs are available, prescribed, and sold in India. Unfortunately, many of these are combinations of two highest priority CIAs, for instance- Cephalosporins with Macrolides (like Cefixime and Azithromycin) and Quinolones (Cefixime and Levofloxacin). All the other categories also comprise of these FDCs with combinations of critical antibiotics like Linezolid and Cefixime, each of which is reserved for serious infections! Apart from being unscientific, these FDCs unnecessarily increase the amount of antimicrobial use in humans and maybe hazardous in terms of unknown interactions with added risk of adverse effects. Most importantly, given the unregulated and privatized healthcare of the country, these broad spectrum cocktails are often misused at the cost of proper diagnosis and treatment, leading to increased selection of resistant microorganisms (6). To further strengthen the AMR agenda, the 2017 edition of the WHO Model list of Essential Medicines (7) proposes three groups of antibiotics- i) the *Access* group which include empiric narrow spectrum, lower resistance potential drugs that should be widely available; ii) the *Watch* group which include first/second choice treatment drugs with higher resistance potential and should be used for a limited number of indications; and, iii) the *Reserve* group which are last-resort options tailored to highly specific patients and settings, when other alternatives are exhausted. Unfortunately, FDCs are abundant in the Access and Watch groups and are even available for the reserve group of drugs like Linezolid.

Does mere availability mean that they are prescribed by Doctors despite the fact that they were never mentioned in any pharmacology or medicine textbooks? Unfortunately, the answer is yes. For instance, in the summers when diarrhoea is at its peak, thousands of patients are prescribed an FDC that include a quinolone with an antiprotozoal as a blanket therapy (8). Moreover, this does not include the tens of thousands that can be directly purchased over the counter (OTC) due to weak regulation of OTC sales. It is useful to reiterate that Quinolones are highest priority CIAs and also belong to the *Watch* group. In a largely unregulated and privatized health sector, blanket combinations like that of a combikit of Fluconazole, Azithromycin and Ornidazole come in handy like a sort of ‘shotgun therapy’, first warned about in an NEJM article published in 1960 (9). Instead of using the right antibiotics, a combination of broad spectrum antibiotics are prescribed, in the hope that- if a hat is big enough, some rabbit will come out of it. The sales of the FDCs with *Watch* and *Reserve* group antibiotics rose by 73% and 174%, respectively in 2011-12 when compared to 2007-08 (10). Further, of the 118 FDC formulations, 64% have no CDSCO approval and 46% include *Watch*  group antibiotics, some even including two of them like cefixime and azithromycin (10).

In a country where most of the doctors and medical students including the authors have seen antimicrobial resistance in their clinics and hospitals, such widespread use of unscientific, irrational and hazardous FDCs is terrifying. While the complete weeding out of these FDCs involve stronger regulations and improved healthcare access to reduce non-prescription sales, weeding them out from our prescriptions is straightforward. This should be our top priority in antimicrobial stewardship. There is no riddle here, no FDCs- let alone antimicrobials should be on our medial prescriptions without a credible scientific basis. Let us not unwittingly continue to commit a mistake that jeopardises the future of humanity, where the treatable infections become untreatable. While the pharma companies have exploited the regulatory loopholes to market these drugs, but very few of us acknowledge the writing on the wall in this regard- that these FDCs should have no place in our prescriptions. There is little, if any excuse for this unethical and irrational overtreatment.

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**Authors**

***Nafis Faizi (nafisfaizi@gmail.com)***

*Assistant Professor of Community Medicine at JN Medical College, AMU, Aligarh, India.*

***Hazique Jameel (***[***haziquejameel16@gmail.com)***](mailto:haziquejameel16@gmail.com))

*Medical student, JN Medical College, AMU, Aligarh*

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