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NEWS

India's antibiotic combinations thwart efforts to curb drug resistance, say researchers

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Rising sales of antibiotic combinations in India could be undermining global efforts to limit antimicrobial resistance, says a study that found dozens of unapproved and sometimes risky formulations on the market.[1]

India is the world's top consumer of antibiotics and a hotbed for drug evading bacteria,[2 3] which are exported globally by travellers. The problem is compounded by widespread use of drug combinations that mix antimicrobials and other medicines—known as fixed dose combinations (FDCs)—because one or more of the ingredients is usually unnecessary. This fuels overuse and thus resistance, needlessly exposing patients to side effects.

"We can't blame all antimicrobial resistance on India, but they are creating a problem for themselves and everybody else with these fixed dose combinations," said Kathleen Holloway, a retired World Health Organization staffer based at the University of Sussex, UK, who has studied drug resistance in Asia but was not involved in the new study. "There is absolutely no excuse for having all these things on the market."

Combination products account for almost half of the drugs on sale in India.[4] Manufacturers tout them as new medicines with extra benefits, while patients and health providers see them as an attractive approach for treating infections that have no clear aetiology.

But experts say that many of the formulations are irrational and potentially hazardous, and the Indian government, along with health activists, has opposed them for years. In December a landmark ruling by the Supreme Court cleared the way for regulators to weed out unapproved combinations, yet even some approved FCSs are considered irrational.[5]

In the new study, researchers found 118 systemic antibiotic FDCs on the Indian market on the basis of sales data from 2007-12. The formulations gave rise to some 3300 branded products, half of which contained two antimicrobials. Sales of the FDCs climbed by 38% over the period studied and accounted for a third of all antimicrobials sold (872 million units) by 2011-12.

Only 43 combinations were listed as approved by the drugs controller general of India, and only four were approved in the UK and US. According to Indian law FDCs require the drug controller's approval before they can be marketed. In practice, however, state regulators have granted manufacturing and sales licences without such approval.

Multinational companies were selling 20 of the 75 FDCs without drug controller approval—something that the Queen Mary University of London's Patricia McGettigan, who worked on the study, said was "indefensible practice from a public health point of view." She said that the drugs, like other prescription medicines in India, can be bought over the counter.

She told *The BMJ*, "It is this combination of factors running at a national level in India that is really pulling the rug from under the moves to try to control antimicrobial resistance."

Dilip G Shah, secretary general of the Indian Pharmaceutical Alliance, said in an email that his members "are fully conscious of their responsibility to patients and have offered to cooperate with the regulatory authorities to weed out medically irrational FDCs."

Abbott Laboratories, based in Chicago, USA, was the top seller of unapproved combinations among global manufacturers, with 18 formulations on the market. The company, which has a history of questionable sales practices in India,[6-9] also made five of the eight formulations that combined two drug classes designated by WHO as "highest priority critically important antimicrobials."

Some of the formulations may be dangerous. For example, one Abbott product, Ertycin L, mixes levofloxacin and azithromycin (Indian companies were also selling this combination under different brand names), and each drug has been independently linked to increased risks of cardiac arrhythmia and death.[10] Data seen by *The BMJ* show that the product was launched in November 2011 and was still registering sales in India at least through to January 2016.

Lindsy Delco, head of public affairs for Abbott's global pharmaceutical business, told *The BMJ* that the company no longer sells Ertycin L in India. She added, "The products listed in the study were medicines Abbott acquired in 2010, many of which are no longer sold in India. The medicines that are still available in India all have central government approval. Abbott follows all Indian laws and regulations."

Abbott and many other drug makers continue to market antibiotic combinations in India that are not approved in the UK or US and that pharmacologists consider irrational. These products can be priced higher than single dose formulations, meaning larger profit margins for manufacturers, wholesalers, pharmacies, and dispensing doctors.

The University of Delhi's Anita Kotwani, who is working with the government on a national action plan on antimicrobial

resistance, said that antibiotic FDCs contribute "hugely" to the problem. Yet doctors use them readily because awareness of resistance "is really poor among all stakeholders" in India, Kotwani told *The BMJ*.

Ramanan Laxminarayan, who directs the Center for Disease Dynamics, Economics and Policy, a non-profit research organisation with offices in New Delhi and Washington, DC, noted, "When you combine drugs in irrational combinations, you very efficiently are selecting for co-resistance."

"This is a direct threat to public health," added Laxminarayan, an expert on antibiotic resistance. "It's probably worse than selling cigarettes."

India's drug controller's office and the Organisation of Pharmaceutical Producers of India, which represents global drug makers, did not respond to *The BMJ*'s requests for comments.

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