

## Access, Watch, and Reserve antibiotics in India: challenges for WHO stewardship

In its most recent Model List of Essential Medicines,<sup>1</sup> WHO adopted a new classification for antibiotics. This new model comprises three categories: Key Access antibiotics (eg,  $\beta$ -lactam, aminoglycoside, and first-generation or second-generation cephalosporin antibiotics) that “should be widely available, affordable and quality-assured”;<sup>1</sup> Watch Group antibiotics (including most of the highest priority critically important antimicrobials for human medicine—eg, macrolides, quinolones, glycopeptides, penems, and third-generation cephalosporins)<sup>2</sup> recommended only for specific, limited indications; and Reserve Group antibiotics (eg, fourth-generation and fifth-generation cephalosporins, aztreonam, polymyxins) for situations when all alternative antibiotics have failed. In alignment with the WHO Global Antimicrobial Resistance Action Plan adopted by the World Health Assembly in May, 2015,<sup>3</sup> the intention of this new classification system for antibiotics is to combat rising antimicrobial resistance, improve access and clinical outcomes, and preserve the effectiveness of antibiotics that are a “last resort”.<sup>1</sup> Following this model, WHO anticipates that the use of Watch Group and Reserve Group antibiotics will be drastically reduced.

Reduction in the use of antibiotics represents a huge challenge in India, which is a major drug producer and has some of the highest sales of antibiotics globally and highest levels of antimicrobial resistance.<sup>4</sup> Contributing factors to these high sales include failures of India’s drug regulatory system (which have been identified in government reports<sup>5</sup>), the sale of antibiotics without prescription, and the proliferation of fixed-dose combination (FDC) antibiotics,

many of which are not approved in other countries or by India’s national regulator, the Central Drugs Standard Control Organization (CDSCO). FDCs are formulations comprising two or more drugs combined in a fixed ratio of doses and available in a single dosage form. FDCs that are composed of two antimicrobial drugs, especially drugs with mismatched dosing regimens, are concerning in the context of antimicrobial resistance, but few data are available on their use in low-income and middle-income countries.

We analysed<sup>6</sup> systemic antibiotic sales in India between 2007 and 2012 using previously reported methods and data sources that captured prescription and non-prescription sales and regulatory approval status. We investigated the formulations that were sold and categorised them according to whether they were FDCs or single-drug formulations (SDFs), their WHO classification, CDSCO approval status, and approval in the UK and USA. We excluded antituberculosis and primary antiviral or antifungal formulations. For FDC antibiotics, we investigated sales of formulations composed of two antimicrobial drugs. Our findings highlight serious hurdles for controlling antimicrobial resistance in India.

In India, total systemic antibiotic sales increased by 26% from 2056 million Units (where a Unit is a strip of ten tablets or capsules, or one bottle or vial of an oral liquid or injection) in 2007–08, to 2583 million in 2011–12. The increase was due to the growth in sales of FDCs, which rose by 38%, whereas sales of SDFs increased by 20%. By 2011–12, FDCs comprised 34% (872 million Units), and SDFs 66% (1711 million Units), of total sales in India.

When examined according to the new WHO categories, sales of FDC antibiotics in India in 2011–12 consisted of: 499 million Units containing Key Access antibiotics, 367 million Units containing Watch Group antibiotics, 3 million Units

containing Reserve Group antibiotics, and 3 million Units containing unclassified antibiotics. Compared with 2007–08, Key Access antibiotic sales had risen by 20%; however, sales of FDCs with Watch Group or Reserve Group antibiotics had risen more steeply, by 73% and 174%, respectively.

The FDC antibiotic sales consisted of 118 different formulations. 75 (64%) of these formulations had no record of CDSCO approval, only 43 (36%) were CDSCO approved, and five (4%) were approved by UK or USA regulators, or both (ie, ampicillin-cloxacillin, amoxicillin-clavulanate, imipenem-cilastatin, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole). 58 (49%) of the FDC formulations were composed of two antimicrobials; of these, 43 (74%) of 58 were unapproved by the CDSCO and 27 (46%) included Watch Group antibiotics—eg, ciprofloxacin-tinidazole, ceftriaxone-vancomycin, norfloxacin-metronidazole—and sometimes two Watch Group antibiotics together—eg, cefixime-azithromycin. 489 million Units of FDCs composed of two antimicrobial drugs were sold in 2011–12, but 270 million Units (55%) of these were of unapproved formulations even though the sale of unapproved new medicines is illegal in India. The sale of FDCs containing Reserve Group antibiotics consisted entirely of CDSCO-approved combinations of fourth-generation cephalosporin formulations—ie, cefixime-tazobactam or cefixime-sulbactam.

In India during 2011–12, 86 different SDF antibiotics were available. In contrast with FDC antibiotics, most SDF antibiotics were approved by the CDSCO (80 of 86), in the UK (57 of 86), and in the USA (75 of 86). Of the 2011–12 sales, 703 million (41%) of 1711 million Units of SDFs sold were Key Access antibiotics; 967 million Units (57%) were Watch Group antibiotics; 18 million Units (1%) were Reserve Group antibiotics; and 23 million Units



(1%) were uncategorised antibiotics. Compared with sales in 2007–08, sales of Key Access antibiotics had risen by 13%, Watch Group by 24%, and Reserve Group by 69%.

These data show the scale of India's task to reduce the use of Watch Group and Reserve Group antibiotics in accordance with the WHO antimicrobial resistance action plan. Not only are overall sales of antibiotics increasing, but sales of Watch Group and Reserve Group antibiotics are increasing more rapidly, driven predominantly by FDCs that contain Watch Group antibiotics. Moreover, huge quantities of the FDCs sold are unapproved formulations composed of two antimicrobial drugs.

The changes needed to achieve the WHO vision of good use and stewardship of antibiotics are feasible. Obvious practical steps are to ban the sale of unapproved FDC antibiotics and to enforce existing regulations to prevent unapproved and illegal drugs reaching the market. The Indian Government has been unsuccessful on both counts. Although it has acknowledged the problems, commissioned reports, and banned some unapproved FDCs—including antibiotics—in 2007 and 2016, the bans were challenged and remain unresolved in the courts while the FDCs in question apparently remain on the market. Aside from regulatory measures, appropriate changes in antibiotic use would be assisted by improved access to health care to reduce non-prescription sales. Additionally, research is needed to understand why doctors complicate problems by prescribing unapproved antibiotic FDCs.

I declare no competing interests.

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