



Commentary

Antibiotic overconsumption and resistance in Turkey

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The latest report of the OECD Health Policy Studies stated that in 2015 the highest rates of antimicrobial resistance (around 35% in Turkey, Korea and Greece) were seven times higher than the lowest rates among its member countries. As the OECD country with the highest rate of resistance (38.8%), despite a 15-year hospital antibiotic restriction programme, Turkey is in urgent need of revising its policies and drawing an effective action plan to reverse the current trend. In this commentary we review previous measures taken to tackle antimicrobial overuse and resistance in Turkey and discuss their effectiveness.

Antimicrobial stewardship programmes in Turkey

The Ministry of Health (MoH) is the main regulator and provider of health care in Turkey. Total health expenditure in Turkey constituted 4.2% of the GDP in 2017, the lowest rate among OECD countries [1]. On the other hand, public sources account for 78% of overall health spending, which is above the OECD average. Turkey

provides near universal health coverage to its citizens, with declining rates of out-of-pocket spending. Hospitals play a dominant role in the Turkish health system, accounting for 52% of all health spending, the highest among OECD countries. The MoH has contracts with 90% of private hospitals to provide care and emergency services as part of its social security system. In addition, the MoH assigns every citizen to a family physician (FP), although FP referrals are not mandatory.

Turkey has two main antimicrobial stewardship programmes (ASPs) established by the MoH; the first one targets the hospitals and the second the community. The first was the National Hospital Antimicrobial Restriction Programme (NARP), legislated by the MoH in 2003. This compulsory programme aimed to reduce hospital antimicrobial use by mandating preauthorization from an infectious disease specialist for the use of several broad-spectrum antibiotics (i.e., carbapenems, glycopeptides, piperacillin/tazobactam, ceftazidime and cefepime). The NARP is enforced in all public hospitals and in private hospitals that have a contract with the MoH. The programme successfully reduced the use of restricted drugs in the short term, at least in certain hospitals [2]. The hospital antimicrobial consumption levels have not been monitored universally either before or after NARP's implementation, making inferences about the programme's long-term effects difficult. Turkey's current resistance rates, however, clearly indicate that NARP has to be boosted to combat resistance.

The hospital-based ASP involves resistance surveillance of hospital pathogens. The National Antimicrobial Resistance Surveillance System—which was established in 2011 and joined WHO's Central Asian and Eastern European Surveillance of Antimicrobial Resistance (WHO-CAESAR) in 2013—presents nationwide resistance data on eight high-priority pathogens isolated from blood and cerebrospinal fluid. The average resistance

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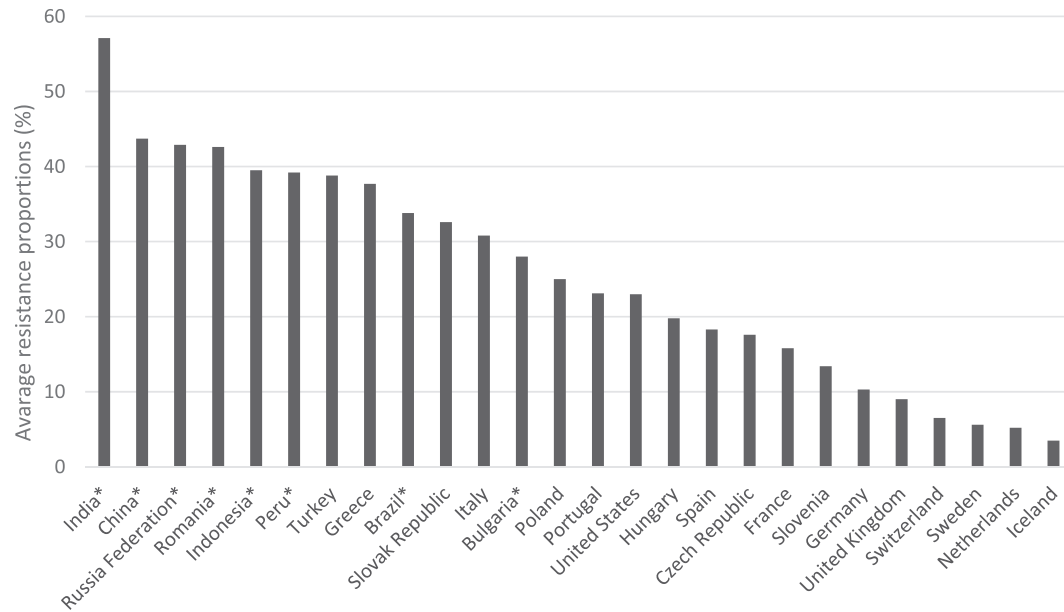


Fig. 1. Average antibiotic resistance proportions in 2015 for eight high-priority antibiotic–bacterium combinations for selected OECD and non-OECD (*) countries [3]. FREC, fluoroquinolone-resistant *Escherichia coli*; VRE, vancomycin-resistant *Enterococcus faecium* and *E. faecalis*; 3GCRC, third-generation cephalosporin-resistant *E. coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; 3GCRKP, third-generation cephalosporin-resistant *K. pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*.

proportion for eight high-priority antibiotic–bacterium combinations in Turkey was recently reported to be 38.8%, the highest level among the OECD countries (Fig. 1) [3]. Carbapenem resistance exceeded 90% in *Acinetobacter baumannii* and approached 50% among *Klebsiella pneumoniae* isolates [3,4]. Although colistin resistance data were not collected by the WHO-CAESAR, research indicates that it may reach 76% among carbapenem-resistant enterobacteria in Turkey [5].

Turkey's second ASP was initiated by the MoH upon concern expressed by the WHO regarding exceptionally high outpatient antibiotic use. This programme involved a 4-year (2014–2017) National Action Plan for Rational Drug Use, with an emphasis on community-level antimicrobials. The primary aim was to curb antimicrobial prescriptions in primary care, in particular, inappropriate prescriptions against acute respiratory tract infections. A universal prescription information system was introduced, and provincial coordinating centres covering all provinces were established to monitor and gather data on physician prescription habits. A national audit and feedback system that targeted all FP prescriptions was launched to reduce antibiotic prescriptions, which constituted 35% of FP prescriptions in 2011 (Fig. 2). Healthcare workers were trained through workshops and seminars. The Rapid Strep Test as an application of point-of-care tests was introduced into primary care as part of the same programme. A secondary aim of the programme was to raise public awareness of prudent antibiotic use. Public campaigns discouraging inappropriate antibiotic use were initiated, and over-the-counter sales of antibiotics were prohibited in 2015. Consequently, the proportion of antibiotics in FP prescriptions dropped to 25% in 2017 (unpublished MoH data). In accordance with this, nationwide antimicrobial consumption for J01 class antibiotics (β -lactams, tetracyclines, aminoglycosides, sulphonamides and trimethoprim, macrolides, aminoglycosides, quinolones) dropped from 42.2 DID in 2011 to 40.4 DID in 2014 [6] and to 35.25 DID in 2017 (unpublished MoH data). Moreover, amoxicillin became available as a substitute for amoxicillin–clavulanate for tonsillopharyngitis, indicating prudent antibiotic use, as amoxicillin without a β -lactamase inhibitor is the

first-line agent for the treatment of bacterial tonsillopharyngitis (unpublished MoH data).

Drawbacks and challenges

Despite their relative success, Turkey's two stewardship programmes at hospital and community levels need revision and improvement. Turkey's hospital stewardship programme may have alleviated antimicrobial resistance. However, restriction of broad-spectrum antibiotics resulted in an increase in the inappropriate consumption of unrestricted antibiotics. Ceftriaxone, a third-generation unrestricted parenteral cephalosporin, is widely used in Turkish hospitals. Furthermore, community cephalosporin use constituted one third of Turkey's overall outpatient antibiotic consumption in 2011 [6]. Overuse of ceftriaxone and other unrestricted antibiotics in hospitals and the community contributed to the selection of extended-spectrum β -lactamase producers and led to the development of MDR. Treatment of infections caused by MDR gram-negatives necessitated the use of restricted broad-spectrum antibiotics, e.g., carbapenems, which consequently resulted in overuse of and resistance to these last-resort antibiotics. The inadequacy of accompanying infection control measures and surveillance of antibiotic consumption are the two other drawbacks of the hospital stewardship programme. Timely detection and rapid containment of MDR bacteria is a crucial step in reducing transmission and can be achieved by effective infection prevention and control measures. However, infection control targeting MDR bacteria has not been adequately implemented in Turkey, contributing to an unprecedented increase in resistance levels [7]. Turkey's community ASP, on the other hand, helped reduce the community-level antibiotic use in the short term and is expected to further reduce resistance in the long run.

Future perspectives

The challenge is to maintain such large-scale programmes which require substantial funding for continuous monitoring. In

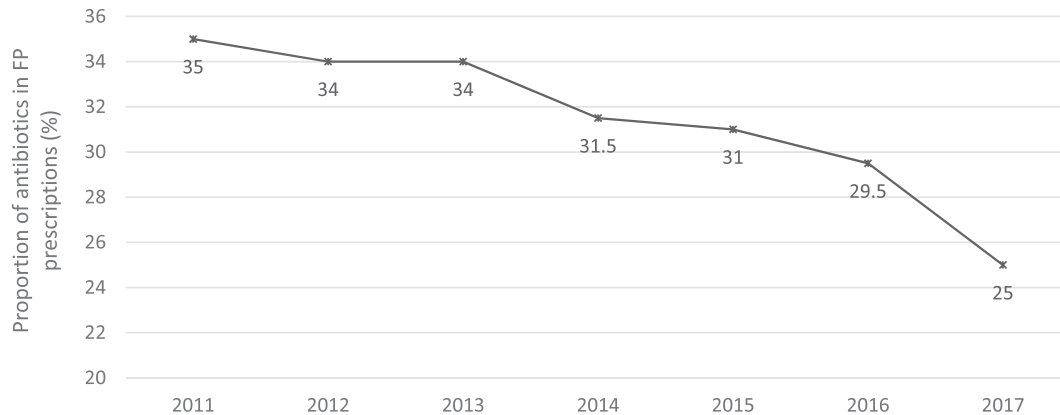


Fig. 2. Proportion of antibiotics in family physician (FP) prescriptions.

particular, resistance levels in outpatient settings are not monitored in Turkey despite surveillance being a key ASP component. Turkey should immediately start monitoring resistance rates of critical community pathogens. Similar practices have long been adopted by countries with the lowest resistance rates. For example, Sweden established a far-reaching stewardship programme in 1995 upon an increase in resistance rates (from 3.1% to 7.6%) among pneumococci [8]. Two decades later, in a setting where penicillin resistance among pneumococcal blood and CSF isolates is 50%, Turkey does not simply need the maintenance of its community stewardship programme but requires its significant improvement. In particular, surveillance of antimicrobial use and resistance needs to be extended to hospital outpatient clinics where a large proportion of antibiotic prescriptions occur [9]. Prescriptions of hospital physicians should be audited, similarly to those of FPs, and regular personal feedbacks should be provided. A follow-up programme for rational drug use for 2019–2023, which is expected to fulfil these requirements, is currently under development (unpublished MoH data).

Turkey has three urgent priorities. First, initiating an effective and binding nationwide infection prevention and control programme against primarily MDR gram-negatives is crucial, as infection control is the key strategy to deal with such public threats [10]. Second, close monitoring of hospital antibiotic use for both restricted and unrestricted antibiotics is essential. Any stewardship or infection control programme without close surveillance would risk failure. Third, resistance rates for key community pathogens should be monitored and antibiotic surveillance, which is already in place in primary care, needs to be extended to outpatient clinics of secondary and tertiary hospitals. In addition, while designing policy intervention against prescribers, key drivers of prescription behaviour (including the social, cultural, political and legal factors) need to be considered and countered.

In addition to these three priority areas, Turkey should embrace a broader approach in the fight against antimicrobial resistance. For example, there are almost no data on antibiotic consumption in husbandry and agriculture in Turkey. In the framework for national action plans, WHO encourages its member states to adopt a one-health approach as it is impossible to control antimicrobial

resistance in human health without controlling antimicrobial consumption in other sectors [10]. All of these efforts for countering resistance require dedication and long-term investment. Finally, Turkey should collaborate with other organizations and countries since “antibiotic resistance is a global risk beyond the capacity of any organization or nation to manage or mitigate alone” [10].

Transparency declaration

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References

- [1] OECD. Health spending (indicator). 2019. <https://doi.org/10.1787/8643de7e-en>. [Accessed 4 January 2019].
- [2] Altunsoy A, Aypak C, Azap A, Ergönül Ö, Balık I. The impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey. *Int J Med Sci* 2011;8:339–44.
- [3] Few JA, More D. Stemming the superbug tide [Internet]. 2018. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/stemming-the-superbug-tide_9789264307599-en.
- [4] Aydın M, Ergönül Ö, Azap A, Bilgin H, Aydın G, Çavuş SA, et al. Rapid emergence of colistin resistance and its impact on fatality among healthcare-associated infections. *J Hosp Infect* 2018;98:260–3.
- [5] Süzük Yıldız S, Kaşkatepe B, Şimşek H, Sarıgül FM. High rate of colistin and fosfomicin resistance among carbapenemase-producing Enterobacteriaceae in Turkey. *Acta Microbiol Immunol Hung* [Internet] 2018;1–10. Available from: <https://www.akademai.com/doi/10.1556/030.65.2018.042>.
- [6] WHO. Antimicrobial medicines consumption (AMC) network. AMC data 2011–2014 [Internet]. 2017. Available from: <http://www.euro.who.int/en/publications/abstracts/antimicrobial-medicines-consumption-amc-network-amc-data-20112014-2017>.
- [7] Hekimoğlu C, Batır E. 2017 national healthcare associated infections surveillance network brief report. *Repub Turkey Minist Heal Gen Dir Public Heal Dep Infect Dis* 2018.
- [8] Kamme C, Ekhdahl K, Mölsted S. Penicillin-resistant pneumococci in southern Sweden, 1993–1997. *Microb Drug Resist* 1999;5:31–6.
- [9] GÜRSOY K. An overview of Turkish healthcare system after health transformation program: main successes, performance assessment, further challenges, and policy options. *J Soc Insur (Sosyal Güvence Derg, in Turkish)* 2015: 83–112.
- [10] World Health Organization. Global action plan on antimicrobial resistance. Geneva: [Internet]. 2015. p. 1–28. Available from: http://www.who.int/drugresistance/global_action_plan/en/.