isolates are likely to be low (ie, <1 mg/L). The combination of linezolid and rifampicin was evaluated earlier, and Brown and colleagues showed that a dose of 600 mg/day would achieve the linezolid area under the concentration–time curve to minimal inhibitory concentration ratio of 99 in the presence of rifampicin in 96% of patients.[10] With an optimal dose, the remaining issue is the treatment duration. Clearly, 2–4 weeks is too short as preclinical models showed that a period of at least 6 weeks was required to ensure sterilisation.[11]

Although the trial results did not show treatment-shortening potential, it showed that the addition of linezolid for 4 weeks was well tolerated in patients with drug-susceptible tuberculosis. This study paves the way for the evaluation of new studies, increasing the duration of linezolid treatment to 4 months. Moreover, newer more potent oxazolidinone analogues might bring greater interest to this approach.[12]

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Public health burden of antimicrobial resistance in Europe


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Antimicrobial resistance is one of the greatest challenges of the 21st century. Evaluation of the public health burden of antimicrobial resistance, which is needed to drive policy interventions, is done through estimates of clinical benchmarks (mainly morbidity and crude mortality) and economic indicators (direct costs, use of resources, and drug expenditures). Most of these estimates are restricted to high-income countries and retrieve data to fit the computation models from national surveillance of clinical samples, prevalence or incidence surveys, and retrospective cohorts.[1,2] The high heterogeneity of reporting of surveillance data and the paucity of estimates of the societal effects of antimicrobial resistance (such as reduced productivity due to illness) substantially underestimate the public health burden. Global estimates are therefore limited in terms of generalisability of results and predictive values.[3]

In *The Lancet Infectious Diseases,* Alessandro Cassini and colleagues[4] measured the health burden of five types of antibiotic-resistant infection (invasive and non-invasive) caused by eight bacteria with 16 resistance patterns in the EU and European Economic Area (EAA). The estimates, presented as disability-adjusted life-years (DALYs), are shocking. The authors estimate that there were 671 689 (95% CI 583 148–763 966) cases of infections with antibiotic-resistant bacteria in 2015, of which 426 277 (63·5%) were associated with health care. These estimates correspond with an incidence of 131 (113–149) infections per 100 000 population and an attributable mortality of 6·44 (5·54–7·48) deaths

per 100 000 population. The overall DALY rate is 170 per 100 000 population, which is similar to the combined burden of HIV, influenza, and tuberculosis in the same year in the EU and EAA. The burden has doubled since 2007 and is highest in infants (aged <1 year) and older people (aged ≥65 years), and for infections caused by colistin-resistant or carbapenem-resistant bacteria. The highest health burdens (>400 DALYs per 100 000 population) were in Italy (10 762 attributable deaths) and Greece (1627 attributable deaths).

Evaluation of the burden of infectious diseases can be challenging because they occur at different time scales and are influenced by many factors (ie, demography, epidemiological setting, population ageing, and method of measurement). A comparative analysis of the burden of foodborne diseases, influenza, tuberculosis, and HIV infection in Europe showed how—by use of incidence, mortality, or DALY rates—the burden of each infection varied substantially.[5] The only resistant infection currently included by the Global Burden of Disease study, which assesses and quantifies the effects of diseases on a global level, is tuberculosis caused by resistant *Mycobacterium tuberculosis*.[6] Cassini and colleagues report the first attempt to quantify DALYs for other resistant infections.[4]

The tragic scenario depicted in the analysis demands some consideration of the method used. The model, as is typical for population-wide studies, required a high number of estimates. The European Antimicrobial Resistance Surveillance Network surveillance system is not a population-based survey and does not allow for stratification of population type and outcome; it only records invasive infections that are influenced by the propensity of sampling and country coverage. Data used in systematic reviews also have method-related limitations, heterogeneity in the definition of outcomes and duration of follow-up, and restricted analysis of confounders, which intrinsically reduce the validity of the disease models built on these data. Cassini and colleagues could not adjust their models for age-specific risks, co-infections, and appropriateness of therapy, which might affect the determination of patient outcomes. Regardless, their study adds to the evidence base on the burden of antimicrobial resistance and could have a crucial role in fighting such resistance on two major levels. First, it represents a good framework to drive improvements in data reporting in surveillance systems and contributes to the many European initiatives to homogenise surveillance systems.[7] Second, by providing for the first time DALY data for countries with a high burden of antimicrobial resistance, this study calls for increased political awareness of, and commitment to, antimicrobial resistance. Although the G7 and G20 nations pushed antimicrobial resistance up the global health agenda, in most of the EU and EEA countries, national plans still seem far from having implemented major actions.

What needs to be done in countries with the highest burden? We cannot forget that local financial resources, culture, and health-care structure (which are not accounted for in the estimates by Cassini and colleagues) have an important role in the control of antimicrobial resistance. European countries have a heterogeneous organisation of health care, in terms of the number of patients with severe infection and long hospital stays, stewardship teams, or nurse-to-patient ratios, which affect the effectiveness of infection control and antibiotic policy interventions.[8] Notably, the two countries with the highest burden have developed national plans to reduce the burden of antimicrobial resistance (in November, 2017, for Italy and in October, 2010, for Greece).[9,10] Will these plans be the answer to the alarm raised by Cassini and colleagues? Surely not. The extension and severity of the current situation cannot be solved without a more centralised global approach and decisive role of the European Parliament.

We speculate that such an approach could be achieved through different legal mechanisms, such as by clearly defining standards for antibiotic usage in hospitals and community, establishing an alert zone (eg, critical rate of resistance at which urgent actions are needed at the country level) for resistance to specific antibiotics in invasive infections, setting a minimum gold standard for infection control measures to be mandatorily applied, defining curricula for infection control and antibiotic stewardship to be compulsorily included in medical schools, and setting up appropriate indicators to monitor the implementation and effectiveness of interventions. Annual targets in national plans should be globally discussed, interconnected, and coordinated. When countries do not respect agreed targets, action should be taken.

This approach follows the example of what has been used from the European Parliament to successfully fight air pollution and reduce the related public health burden.[11] If Member States can set gold standards for air composition,

surely they can agree on gold standards for the prevention and treatment of infections due to resistant bacteria.

Economic restrictions and cultural and geographical variability cannot be accepted as explanations for the impressive difference in deaths among European citizens reported by Cassini and colleagues. The results demand increased political commitment and dedicated resources. Tackling antimicrobial resistance is not a simple task and various international stakeholders have been working for many years to reduce this public health burden. Clearly it is not enough.

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Be AWaRe: new metrics for paediatric antibiotic stewardship

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Between 2000 and 2015, global antibiotic consumption increased by 65%. Although this increase was driven by use in lower-income and middle-income countries, the rapid increase in the use of last-resort antibiotics occurred across all countries.[1] The urgent need to improve use of antibiotics throughout health care includes the prerequisite to develop appropriate stewardship metrics in the outpatient setting. Realistic standardised measurement tools and indices to monitor the effect of broad national community interventions with regards to which paediatric-specific antibiotics should be targeted have not been described before.

In *The Lancet Infectious Diseases*, Yingfen Hsia and colleagues[2] used the WHO Access, Watch, Reserve (AWaRe) antibiotic categories to present a novel, pragmatic benchmarking strategy, using three metrics to evaluate national oral consumption of child-appropriate formulations (CAFs). The metrics are based on wholesale data for antibiotics from 70 countries. The authors generated in-depth information about country-specific patterns by describing, among all CAFs sold, the percentage of Access group use, amoxicillin use (amoxicillin index), and the relative use of Access and Watch antibiotics (access-to-watch index).

Recognising the need for practical tools for antibiotic stewardship at national and international levels, and to encourage use of narrower-spectrum antibiotics, WHO updated the Model List of Essential Medicines for Children (EMLc) in 2017.[3,4] Three categories of antibiotics used for empiric treatment were established. Access (first-choice and second-choice antibiotics that are generally narrow spectrum with less resistance potential—eg, amoxicillin), Watch (antibiotic classes with broader spectrum and hence resistance potential—eg, fluoroquinolones and macrolides), and Reserve (last-resort option antibiotic classes, which should require the highest level of monitoring).

The relative proportions of each antibiotic group used forms the basis of the AWaRe index proposed previously[4] by the same authors. The intention is that stewardship programmes will prioritise the use of first and second empiric choice antibiotics—ie, those in the Access group—for the management of infection syndromes described in the EMLc. The strategy should result in fewer Watch and Reserve class antibiotics being used globally. Evidence for