

Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data



Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Summary

Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.

Methods With use of sales data for retail and hospital pharmacies from the IMS Health MIDAS database, we reviewed trends for consumption of standard units of antibiotics between 2000 and 2010 for 71 countries. We used compound annual growth rates to assess temporal differences in consumption for each country and Fourier series and regression methods to assess seasonal differences in consumption in 63 of the countries.

Findings Between 2000 and 2010, consumption of antibiotic drugs increased by 36% (from 54 083 964 813 standard units to 73 620 748 816 standard units). Brazil, Russia, India, China, and South Africa accounted for 76% of this increase. In most countries, antibiotic consumption varied significantly with season. There was increased consumption of carbapenems (45%) and polymyxins (13%), two last-resort classes of antibiotic drugs.

Interpretation The rise of antibiotic consumption and the increase in use of last-resort antibiotic drugs raises serious concerns for public health. Appropriate use of antibiotics in developing countries should be encouraged. However, to prevent a striking rise in resistance in low-income and middle-income countries with large populations and to preserve antibiotic efficacy worldwide, programmes that promote rational use through coordinated efforts by the international community should be a priority.

Funding US Department of Homeland Security, Bill & Melinda Gates Foundation, US National Institutes of Health, Princeton Grand Challenges Program.

Introduction

Antibiotic drugs have reduced the burden of common infectious diseases and become essential for many medical interventions.^{1,2} However, antibiotic-resistant pathogens have emerged and spread among human and animal populations worldwide.^{3,4} Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA)⁵ and carbapenem-resistant Enterobacteriaceae (CRE)⁶ have become a global problem. The loss of efficacy against common pathogens has not only led to a shift towards more expensive antibiotic drugs in high-income countries, but also to increased morbidity and mortality in low-income and middle-income countries, where affordability of second-line drugs restricts their use.¹

The emergence of drug-resistant bacterial strains is due to the selection pressure (an external force that reduces reproductive success of some individuals in a population) imposed by use of antibiotics. The intensity of this natural event is driven by a population's volume of consumption of antibiotic drugs, whether use is appropriate or not.^{7–11} Identification of spatial and temporal trends in antibiotic consumption is important to understand the epidemiology of antibiotic resistance. First, identification of regions in which rate of consumption of antibiotics per person is high or rising can rapidly predict where the threat of new resistant infections will be greatest¹² and can help to inform

initiatives to preserve antibiotic efficacy.^{13,14} Second, mapping of the distribution of antibiotic consumption provides a baseline for the assessment of efforts for future antibiotic drug reduction.

Although some estimates have been made, a comprehensive analysis has not been completed. In the USA, the ResistanceMap project¹² mapped the distribution of use of cephalosporins, macrolides, penicillins, fluoroquinolones, tetracyclines, and trimethoprim. Goossens and colleagues⁸ made a detailed inventory of antibiotic use in the European Union and neighbouring countries.¹⁵ In 1987, Col and colleagues¹⁶ first attempted to estimate the global use of antibiotic drugs with data for a few countries. In this report, we aim to assess antibiotic consumption patterns from 2000 to 2010 for 16 groups of antibiotic drugs in 71 countries.

Methods

We used IMS Health MIDAS (IMS Health, Danbury, CT, USA) to quantify antibiotic drug consumption. With use of national sample surveys done by pharmaceutical sales distribution channels (ie, from manufacturer to wholesaler to retailer), this database estimates antibiotic consumption from the volume of antibiotics sold in retail and hospital pharmacies. In each sector, data are collected regularly to estimate direct sales from antibiotic drug manufacturers

Lancet Infect Dis 2014

Published Online

July 10, 2014

[http://dx.doi.org/10.1016/S1473-3099\(14\)70780-7](http://dx.doi.org/10.1016/S1473-3099(14)70780-7)

See Online/Comment

[http://dx.doi.org/10.1016/S1473-3099\(14\)70809-6](http://dx.doi.org/10.1016/S1473-3099(14)70809-6)

Department of Ecology and Evolutionary Biology, Princeton University,

Princeton, NJ, USA

(T P Van Boeckel PhD,

Q Caudron PhD,

Prof B T Grenfell PhD,

Prof S A Levin PhD); Center for

Disease Dynamics, Economics,

and Policy, Washington, DC,

USA (Prof R Laxminarayan,

S Gandra MD, A Ashok MPP);

Princeton Environmental

Institute, Princeton, NJ, USA

(Prof R Laxminarayan,

Prof S A Levin, Prof B T Grenfell);

Public Health Foundation of

India, New Delhi, India

(Prof R Laxminarayan); Beijer

Institute of Ecological

Economics, Stockholm,

Sweden (Prof S A Levin); and

Fogarty International Center,

National Institutes of Health,

Bethesda, MD, USA

(Prof B T Grenfell)

Correspondence to:

Prof Ramanan Laxminarayan,

Princeton Environmental

Institute, Princeton,

NJ 08544, USA

rlaxmina@princeton.edu

and indirect sales from wholesalers. The sales estimates from this sample are projected with use of an algorithm developed by IMS Health to approximate total volumes for sales and consumption. The algorithm uses regional factors and sectorial-specific and distribution-channel-specific factors to project national estimates of antibiotic consumption. However, precise details of the algorithm are withheld for proprietary reasons (appendix). Figures for antibiotic drug consumption are given in standard units (the number of doses sold; IMS identifies a dose as a pill, capsule, or ampoule) and are available monthly for 63 countries and quarterly for eight countries. These data are broken down by sector (retail and hospital): 69 countries had records for the retail sector and 48 countries had records for hospitals (appendix). For several countries, antibiotic drug consumption reported in the database from IMS Health was underestimated because the audit did not cover the entire market; although the percentage of market coverage (percentage of sales volume) was estimated. We assumed that the sample of antibiotics sales surveyed by IMS was representative of national consumption and estimated national coverage with simple imputation. Finally, data collection procedures imposed additional limitations for a few countries (eg, sales of drugs in supermarkets were not included) that could not be accounted for (appendix).

Data analysis

To derive figures for antibiotic consumption per person over the period of 2000 to 2010, we linked consumption to population estimates from the World Bank.¹⁷

Consumption patterns were reviewed in six selected countries for years 2000 and 2010 (India, China, USA, France, UK, and Germany). To be consistent with the level of spatial reporting in the IMS dataset, we pooled population estimates for Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama into one region for Central America. Similarly, we pooled Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Mali, Senegal, and Togo into one region for French West Africa. The IMS Health MIDAS dataset comprise 16 classes of antibiotic drugs (appendix).

To derive a comparable metric of antibiotic consumption across time, we calculated the compound annual growth rate (CAGR) of total antibiotic consumption by each country:

$$\text{CAGR} = (\text{SU}_{\text{End}} / \text{SU}_{\text{Start}})^{(1/N)} - 1$$

In this equation, SU_{End} is the total number of standard units for the last reported year, SU_{Start} is the total number of standard units for the first reported year, and N is the number of years between the first and last year of reporting.

To identify seasonal peak of antibiotic consumption, we used Fourier series decomposition for each of the 63 countries with monthly reports. We defined the peak month as that corresponding to the maximum value of the annual component of the time series. Before applying Fourier decomposition, the time series of antibiotic consumption in each country were detrended for

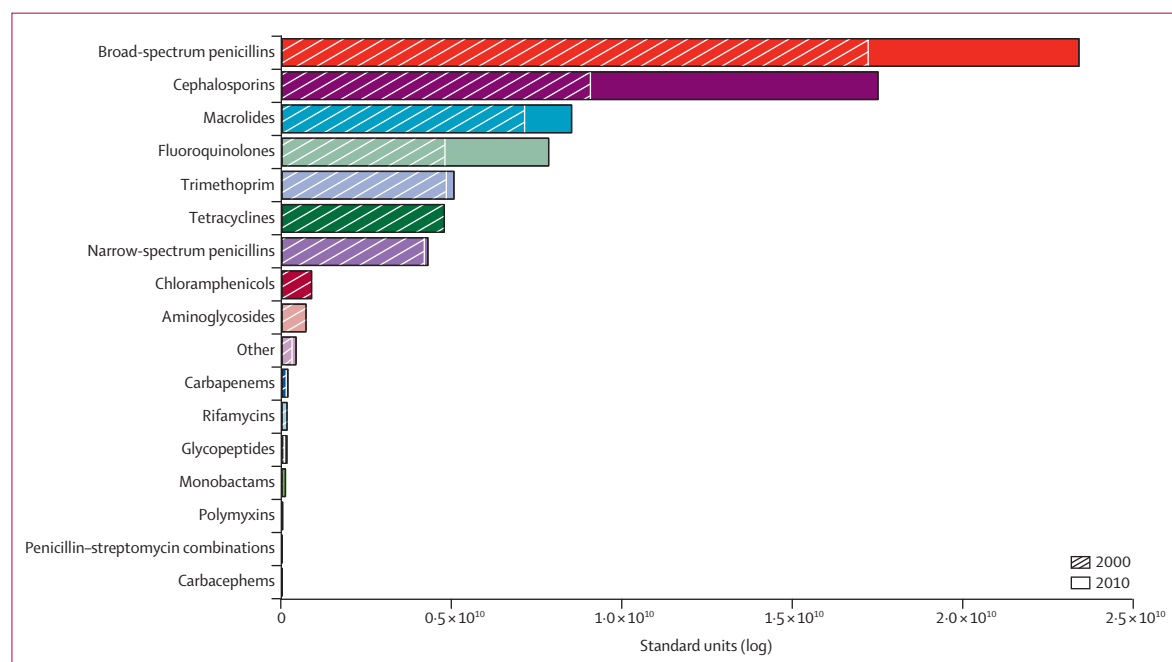


Figure 1: Global antibiotic consumption by class in 2000 and 2010

Standard units are defined as a single dose unit (ie, pill, capsule, or ampoule).

long-term changes using local polynomial smoothing with a time window of 2·75 years. We assessed robustness of the time window length through a sensitivity analysis (appendix). We decomposed the detrended signal into five harmonics—12 month, 6 month, 4 month, 3 month, and 2 month periods—using the yearly average values of the signal to compute the Fourier coefficients, thereby allowing quantification of the relative importance of these frequencies in the antibiotic consumption signal. We assessed the correlation between each harmonic and the observed signal using ordinary least squares. We mapped the Pearson correlation coefficient between the 12 month harmonic and the observed signal (appendix). To account for potential non-stationarity in the time series of antibiotic consumption for each country, we calculated the mean and the standard deviation of the monthly centre of gravity for each year that data were available (appendix).

This analysis showed that non-stationarity was negligible in regard of the temporal resolution of the antibiotic consumption time series. Finally, to check robustness, we mapped the CAGR and consumption level for 2010 from IMS Health data against defined daily dose (DDD; the assumed average maintenance dose per day for a drug used for its main indication in adults) per 1000 people, as obtained from the European Surveillance of Antimicrobial Consumption Network¹⁵ for 29 European countries between 2000 and 2010 (appendix).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

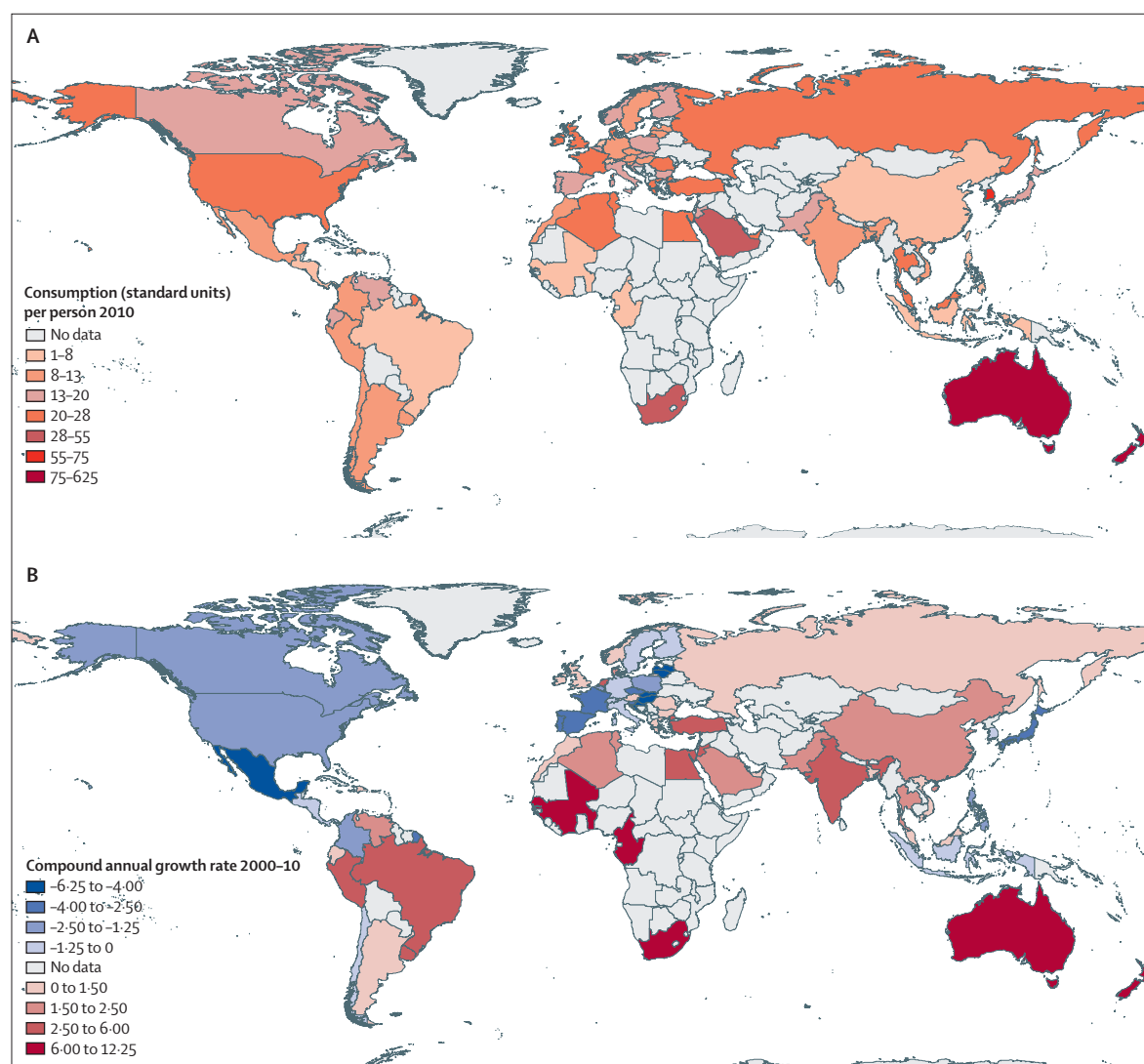


Figure 2: Consumption of antibiotics in 2010

Expressed in standard units (ie, pill, capsule, or ampoule) per person (A), and compound annual growth rate of antibiotic drug consumption between 2000 and 2010 (B)

Results

Between 2000 and 2010, consumption of antibiotic drugs increased by 36% (from 54 083 964 813 standard units in 2000 to 73 620 748 816 standard units in 2010). Cephalosporins and broad-spectrum penicillins accounted for 55% of the total standard units consumed in 2010 (figure 1). The largest absolute increases in consumption between 2000 and 2010 were observed for cephalosporins (8.4×10^9 standard units), broad-spectrum penicillins (6.1×10^9 standard units), and fluoroquinolones (3.0×10^9 standard units). The most important relative increases

from 2010 were observed for monobactams (2031%), glycopeptides (233%), cephalosporins (93%), and fluoroquinolones (64%). Significant increases in consumption rates were also noted for two last-resort classes of antibiotics: carbapenems (45%) and polymyxins (13%; appendix).

India was the largest consumer of antibiotics in 2010 with 12.9×10^9 units (10.7 units per person). China was the second largest with 10.0×10^9 units (7.5 units per person), and the USA was the third largest with 6.8×10^9 units (22.0 units per person). Antibiotic

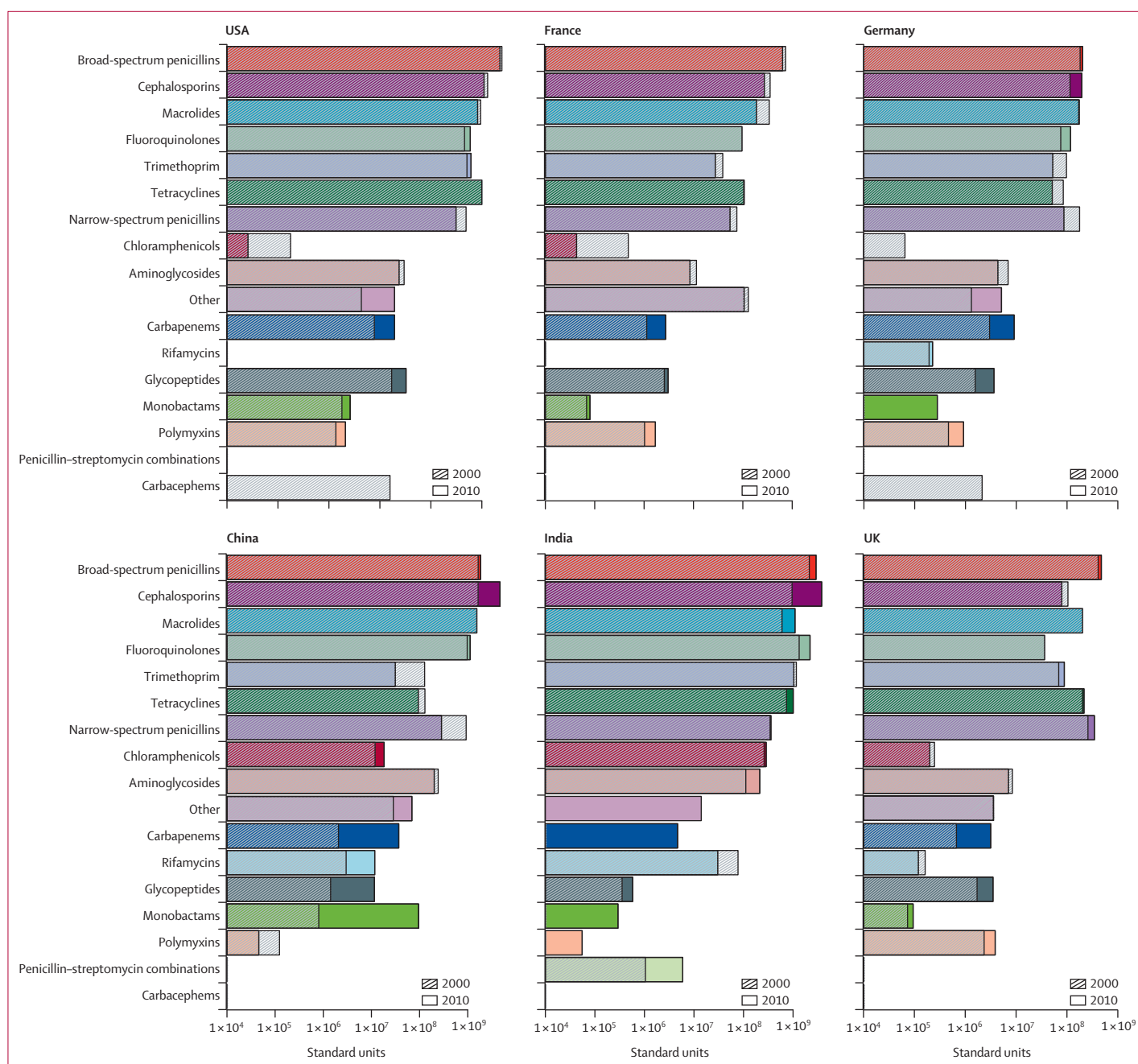


Figure 3: Antibiotic consumption by class in 2000 and 2010

consumption was stable or had moderately decreased in high-income countries between 2000 and 2010 (figure 2), with two exceptions: consumption increased substantially in Australia (from 25 in 2000 to 87 units per person in 2010) and New Zealand (from 26 in 2000 to 70 units per person in 2010) and we noted a continuous increase of antibiotic consumption. We observed very different levels of consumption per person in 2010 in other high-income countries with apparently similar rates of economic development (eg, 7.89 units per person in the Netherlands vs 23.13 units per person in France). In 2010, the high-income Asian countries and regions (Hong Kong, Malaysia, Singapore, and South Korea) all ranked within the top eight consumers of antibiotics per person. Antibiotic consumption increased substantially in developing countries, with the highest rates shown in BRICS countries (Brazil, Russia, India, China, and South Africa) and French West Africa. 76% of the overall increase in global antibiotic consumption between 2000

and 2010 was attributable to BRICS countries. Meanwhile, only 33% of the overall increase in global population occurred in BRICS countries between these years. In BRICS countries, 23% of the increase in the retail sales volume was attributable to India and up to 57% of the increase in the hospital sector was attributable to China.

Between 2000 and 2010, consumption of glycopeptides, carbapenems, and monobactams increased in all six selected countries (China, France, Germany, the UK, India, and the USA), irrespective of their income (figure 3). By contrast, we show a large increase in cephalosporin and fluoroquinolone consumption, mainly in middle-income countries (India and China), plus one high-income country (Germany). Consumption of polymyxins increased in each country apart from China.

The consumption rates for antibiotics had seasonal patterns in some countries (figure 4). In the northern

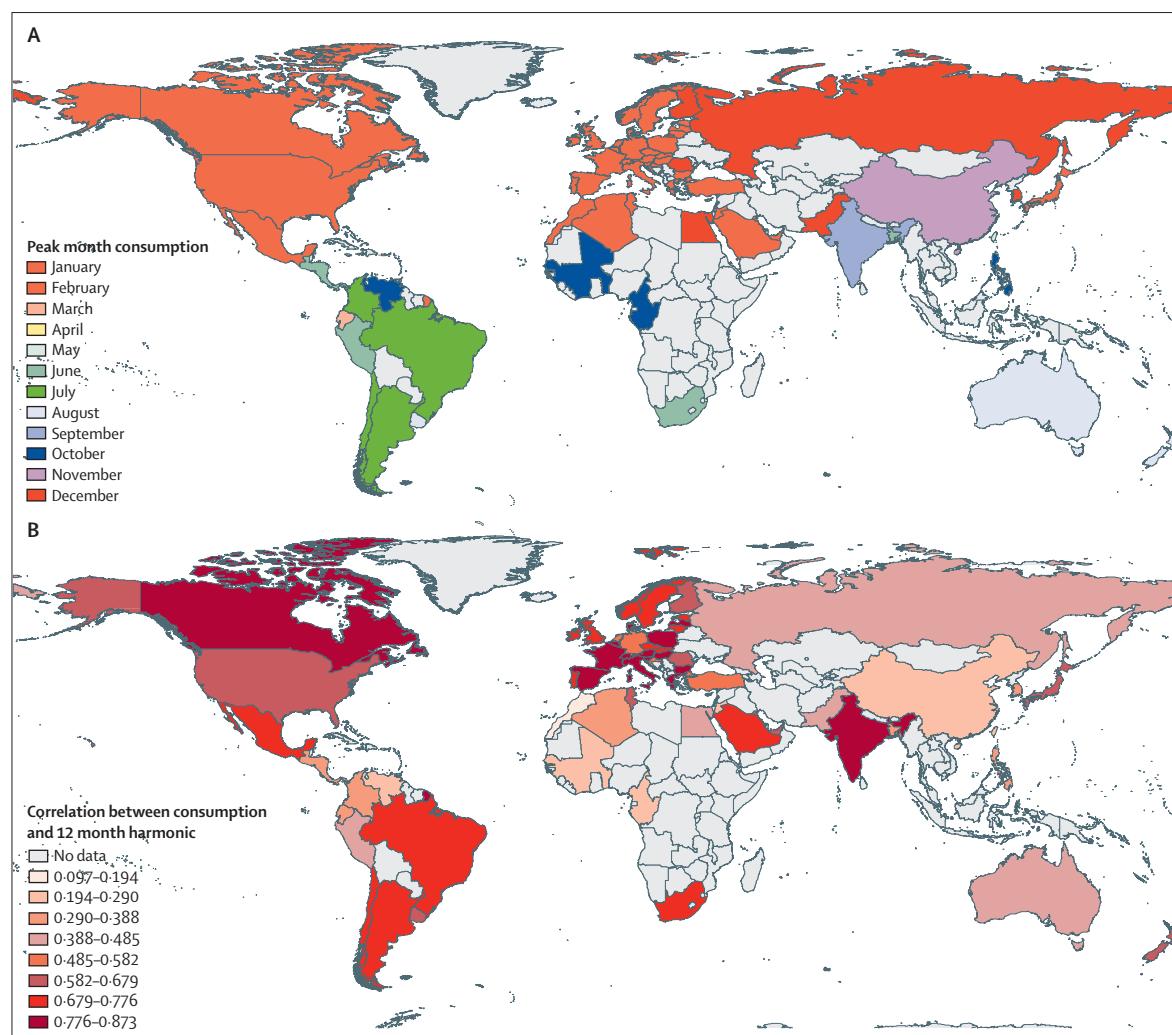


Figure 4: Peak month for antibiotic consumption (A) and correlation between consumption and its 12 month harmonic (B); darker shades show greater annual seasonality

hemisphere, consumption peaked between January and March, and in the southern hemisphere, consumption peaked between July and November. An important exception in the northern hemisphere was India, where it peaked between July and September, which is the end of the monsoon season. Countries farther from the equator generally had more important seasonal patterns in antibiotic consumption (eg, Canada vs Philippines, supplementary figure 4; appendix).

Discussion

This study, to our knowledge, is the first to attempt to map and compare the evolution of antibiotic consumption on a global scale since the previous review, 27 years ago;¹⁶ a period in which antibiotic use patterns could have changed greatly (panel).¹⁶ We showed that antibiotic consumption increased substantially (36% increase between 2000 and 2010), mainly in developing countries. Three quarters of this increase occurred in BRICS countries, whereas their share in the overall increase in global population was only 33%. This finding suggests that antibiotic consumption in BRICS countries in the past decade has been driven by factors other than simply demography (eg, economic growth, increased expenditure in the medical sector, and increased access to antibiotic drugs).^{1,18–20} We also noted very high antibiotic

consumption per person in Australia and New Zealand. This finding is consistent with surveillance data for antibiotic use in Australia. The Australian Statistics on Medicines reports annual estimates of the aggregate community use of prescription medicines, including antibiotic drugs, and the National Antimicrobial Utilisation Surveillance Program (NAUSP) reports antibiotic use in hospitals.^{21,22} Data from these two sources indicate high antibiotic consumption in community settings and in hospitals compared with some European countries.^{21,22} National campaigns have been implemented to reduce inappropriate use of antibiotics for upper respiratory tract infections. When started in 2000, these campaigns led to a decrease in number of antibiotic prescriptions for upper respiratory tract infections, and so the reason for continued high antibiotic use during 2000–10 is not clear. However, NAUSP²⁴ data for consumption in hospitals indicate decreasing use of antibiotics in 2011 and 2012. For New Zealand, a recent study investigated nationwide antibiotic use in the community for a 7 year period (2005–12).²⁵ Antibiotic consumption rate per person was high compared with many European countries and continued to rise an average of 6% per year, consistent with our study findings. We were unable to find nationwide hospital antibiotic consumption information, but one hospital study²⁶ observed lower consumption compared with many European countries. As with Australia, a national campaign in New Zealand was associated with a decrease in antibiotic prescriptions for upper respiratory tract infections among children; however, the reason for high consumption is unclear.²³ Rates of antibiotic consumption per person were high in the USA, and, on average, were greater than were those for most European countries. These differences might relate to differences in treatment guidelines, legislation for antibiotic drug advertising (prescription drugs cannot be advertised in Europe), marketing strategies, and structural differences in health-care systems that mean that in the USA, no disincentives exist for prescription of outpatient antibiotic drugs.²⁷

Across countries, we noted different trends for each class of antibiotics. Increased consumption of glycopeptides, carbapenems, polymyxins, and monobactams was observed in many countries irrespective of their income. By contrast, increased cephalosporin and fluoroquinolone consumption was observed mainly in middle-income countries such as India and China. The changing patterns correspond with changes in the global epidemiology of antibiotic resistance and to increasing occurrence of some infections that are endemic in developing countries. The increase in glycopeptides and carbapenems could be explained partly by a rise in global burden of MRSA and extended-spectrum β -lactamase-producing Gram-negative bacteria.^{5,7,28,29} Similarly, the increase in use of polymyxins, a class of last-resort drugs,^{6,30–32} could be partly due to the recent worldwide

Panel: Research in context

Systematic review

We searched PubMed for articles published up to April 17, 2014, using search terms “antibiotic” and “utilization” and “global” or “countries”. The search returned only one review, published in 1987, which attempted to estimate worldwide antibiotic usage.¹⁶ However, the authors of this review estimated antibiotic availability in only 22 countries. We could identify few studies that estimated antibiotic use in Europe^{8,15} and Latin America.¹⁶ The European studies included up to 34 countries, whereas the Latin American study included eight countries.

Interpretation

This is the largest study of antibiotic consumption in terms of the number of countries that were included and it is the first study since 1987 to map and compare evolution of antibiotic consumption on a global scale. Our results could inform policy to improve rational use of antibiotics and delay the emergence and spread of resistance. Our study highlights major differences in the levels of drug consumption per person worldwide. Although high-income countries consume more antibiotics per person, consumption rates are rising rapidly in emerging economies and represent the bulk of the increase in consumption over the decade 2000–10. Our findings point to the need for a publicly funded international surveillance initiative to provide policy makers with evidence-based information on global, regional, and national rates and trends in antibiotic consumption.

rise in the prevalence of CRE and extensively drug-resistant bacteria (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*). However, the reasons for the substantial increase in use of monobactams are not clear. Monobactams are indicated only in treatment for Gram-negative bacterial infections and in patients who are allergic to penicillin.³³ They have substantially fewer adverse effects than traditional Gram-negative antibacterial drugs such as aminoglycosides.³⁴ Monobactams might thus be preferred because of their safety profile and absence of reactivity with penicillins.

Some increases in antibiotic consumption are very likely caused by inappropriate use. Acute diarrhoeal illness and acute undifferentiated febrile illness (dengue fever, malaria, chikungunya fever, Japanese encephalitis, enteric fever, leptospirosis, and rickettsiosis) account partly for the increased use of cephalosporins and fluoroquinolones in low-income and middle-income countries, even though most of these illnesses are not bacterial in origin.^{35–43} Inappropriate consumption of antibiotics for acute self-limiting diarrhoeal infections is high in Bangladesh, China, India, and Thailand; fluoroquinolones are the most commonly prescribed, and cephalosporins the second most common.^{35–39} However, some use of cephalosporins and fluoroquinolones can be justified by rising rates of resistance in bacteria that cause diarrhoea (such as *Salmonella* spp and *Shigella* spp) to older empiric antibiotic drugs such as ampicillin, co-trimoxazole, tetracyclines, and chloramphenicol.⁴⁰ Inappropriate antibiotic consumption has also been noted for patients with viral dengue fever in India, Pakistan, and Vietnam, with cephalosporins the most frequently prescribed, and fluoroquinolones the second most frequent.^{41–43}

Our data show seasonal variations in antibiotic consumption. In the northern hemisphere, the peak of antibiotic consumption was in winter, apart from in India where the peak occurred in September. This finding is consistent with results of a study⁴⁴ from Delhi that noted high average consumption of antibiotics in September. Since 2003, incidence of dengue fever has increased—in 2010 about 33 million apparent cases of dengue fever occurred in India alone.⁴⁵ Several studies in India have noted high transmission of dengue fever in the post-monsoon season, with peak activity in September.^{46–48} In India, 51–69% of patients with dengue fever admitted to hospital were prescribed antibiotics, with most receiving third-generation cephalosporins or fluoroquinolones.⁴¹ This surge in febrile illness cases secondary to dengue infection possibly could explain why antibiotic consumption peaked in September. Antibiotic consumption in the southern hemisphere also peaked during winter months. Countries nearer the equator showed low correlation with the annual harmonics of the consumption time series, suggesting that antibiotic consumption is affected by climate variations (figure 4).

Much of the increase in antibiotic consumption occurred in countries that had rapid economic expansion

(eg, India and China). Although access to antibiotics is increasing for individuals who were previously unable to afford these life-saving drugs, many broad-spectrum antibiotic drugs (cephalosporins, fluoroquinolones, and carbapenems) are sold over the counter without presence of a documented clinical need. Carbapenems are regarded as the last resort against serious Gram-negative bacterial infections. Now carbapenem-resistant bacteria have emerged and spread widely in many developing countries.⁶

Antibiotic drugs were introduced in high-income countries after mortality rates from infectious diseases had already decreased after the effect of water treatment, improved sanitation, and immunisation,⁴⁹ whereas, in many low-income and lower-middle-income countries, antibiotics are used as a substitute for public health measures. Indeed, inadequate sanitation is thought to explain widespread CRE in India,⁵⁰ alongside financial incentives for practitioners to prescribe antibiotics,⁵¹ hospitals' financial reliance on pharmacy sales,⁵² and the effect of unregulated over-the-counter prescribing.⁵³ In view of the magnitude of the increase in antibiotic consumption and the population growth in developing countries, urgent actions are needed to prevent the systematic use of antibiotics as a short-cut to infection control. Some high-income countries such as France and the UK have reduced antibiotic consumption through better prescription practices, without measurable harm recorded.^{8,54,55} These successful experiences could provide models in Europe and developing countries. However, because of differences in economic context, policy makers need to strike the right balance between curing patients now and compromising the likelihood of curing future patients. Although antibiotic resistance is a major public health threat, far more deaths in low-income and lower-middle-income countries are attributable to poor access to antibiotics. Nearly a million children die of pneumonia every year,⁵⁶ more than half of them because of an absence of appropriate treatment.⁵⁷

Our analysis is subject to some caveats. In Europe, we saw a strong correlation between the DDD and standard units to estimate antibiotic consumption per person and CAGR. This finding means that in Europe (a region in which the trends in antibiotic use are well documented) a strong, although not perfect, agreement exists between established trends and the trends identified through the IMS database. The concordance further suggests that sales data, such as those collected by IMS Health, could potentially be regarded as a good source of information when surveillance networks are missing or weak. However, we could not establish a perfect match for these measures in European countries (appendix p 13). DDD (introduced by WHO) is generally preferred over standard units because it allows comparisons between different drugs and across different health-care environments. By contrast, standard units might vary with differences in dose and drug potency.⁵⁸ However, in the absence of

global data for DDD, the IMS Health database, defined in standard units, is the most geographically comprehensive and standardised information source for antibiotic consumption. Another limitation is non-adherence to prescribed drugs in patients, resulting in data for antibiotics sales overestimating antibiotic consumption; however, this bias is difficult to quantify without systematic information about effective drugs consumption—only a few countries (such as the UK⁵⁹) have put in place publicly funded schemes to collect expired or unwanted drugs.

The introduction of CRE from south Asia into many developed countries⁵⁰ shows the important need for concerted action to contain antibiotic resistance, to prevent a surge in resistance in developing countries, and to preserve the efficacy of existing drugs for future generations. To address the loss in antibiotic efficiency (a natural event) only through the discovery of new drugs is an unsustainable strategy because new antibiotics are increasingly difficult and expensive to discover; the easy drugs have already been found.⁶⁰ Although drug discovery should remain a priority to strengthen last-lines of defence, efforts to promote rational use of antibiotics, to put in place infection control practices, and to improve hygiene should be high on the international agenda.

Contributors

RL, TPVB, BTG, and SAL designed the study. AA and TPVB collected and cleaned the data, TPVB and QC did the data analysis, TPVB generated the figures, and TPVB, SG, and RL interpreted the results. TPVB and SG did the literature search. TPVB and RL drafted the first version of the paper, which was revised by BTG and SAL. SH cowrote the discussion. All authors contributed to the final version of the Article.

Declaration of interests

BTG, SAL, RL, QC, and TPVB were supported by the Science and Technology Directorate, Department of Homeland Security contract HSHQDC-12-C-00058. BTG and RL were supported by the Bill & Melinda Gates Foundation. BTG was supported by the RAPIDD programme of the Science and Technology Directorate, US Department of Homeland Security, and the Fogarty International Center, National Institutes of Health. SAL and RL were supported by Princeton University through its Grand Challenges Program. SG and AA were supported by the Global Antibiotic Resistance Partnership, funded by the Bill & Melinda Gates Foundation.

Acknowledgments

We thank Kelsey Walters for research assistance. The statements, findings, conclusions, views, and opinions contained and expressed in this Article are based in part on data obtained under licence from the following IMS Health information services: MIDAS (1999–2009, IMS Health). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities. The terms of our agreement with IMS Health forbid disclosure, sublicensing, and publication of data to any third party and limit access to authorised users only. Users are restricted from sharing information with third parties for re-identifying methodologies or processes used to produce information or result in the disclosure to any third party of information regarding algorithms, processes, projection or statistical methods.

References

- 1 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; **13**: 1057–98.

- 2 Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010; **74**: 417–33.
- 3 Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004; **10**: S122–29.
- 4 WHO. Antimicrobial resistance factsheet. <http://www.who.int/mediacentre/factsheets/fs194/en/> (accessed Dec 19, 2013).
- 5 Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public-health threat. *Lancet* 2006; **368**: 874–85.
- 6 Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. *Emerg Infect Dis* 2011; **17**: 1791–98.
- 7 Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. *BMJ* 2012; **344**: e1567.
- 8 Goossens H, Ferech M, Vander Stichele R, Elseviers M, for the ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579–87.
- 9 Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34–42.
- 10 Shorr AF. Epidemiology of staphylococcal resistance. *Clin Infect Dis* 2007; **45**: S171–76.
- 11 Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006; **355**: 666–74.
- 12 The Center for Disease Dynamics, Economics, and Policy. Resistance Map. <http://www.cddep.org/map> (accessed July 2, 2014).
- 13 Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis* 2005; **5**: 481–93.
- 14 Okeke IN, Klugman KP, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part II: strategies for containment. *Lancet Infect Dis* 2005; **5**: 568–80.
- 15 Ferech M, Coenen S, Malhotra-Kumar S, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *J Antimicrob Chemother* 2006; **58**: 401–07.
- 16 Col NF, O'Connor RW. Estimating worldwide current antibiotic usage: report of Task Force 1. *Rev Infect Dis* 1987; **9** (suppl 3): S232–43.
- 17 World Bank Data Catalog. Population estimates and projections. <http://data.worldbank.org/data-catalog/population-projection-tables> (accessed June 21, 2014).
- 18 Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet* 2009; **373**: 240–49.
- 19 Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med* 2003; **57**: 733–44.
- 20 Marmot M, Friel S, Bell R, Houweling TA, Taylor S, Commission on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health. *Lancet* 2008; **372**: 1661–69.
- 21 Team APW. Antimicrobial stewardship: what's it all about? Australian Prescriber. <http://www.australianprescriber.com/magazine/36/4/116/20> (accessed April 14, 2014).
- 22 Antimicrobial stewardship in Australian Hospitals 2011. 2011. http://www.sahealth.sa.gov.au/wps/wcm/connect/a8a83d00409152a8bb1bb4826472d56/national-antimicrobial-annual-report-2012_2013-phcs-ics-20131128.pdf?MOD=AJPERES&CACHEID=a8a83d00409152a8bb1bb4826472d56 (accessed June 21, 2014).
- 23 Huttner B, Goossens H, Verheij T, Harbarth S, for the CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis* 2010; **10**: 17–31.
- 24 National Antimicrobial Utilisation Surveillance Program. 2013. http://www.sahealth.sa.gov.au/wps/wcm/connect/a8a83d00409152a8bb1bb4826472d56/national-antimicrobial-annual-report-2012_2013-phcs-ics-20131128.pdf?MOD=AJPERES&CACHEID=a8a83d00409152a8bb1bb4826472d56 (accessed June 21, 2014).
- 25 Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand. *N Z Med J* 2014; **127**: 72–84.

- 26 Ticehurst R, Thomas M. Antimicrobial consumption at Auckland City Hospital: 2006–2009. *N Z Med J* 2011; **124**: 1332.
- 27 Goossens H, Ferech M, Coenen S, Stephens P. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. *Clin Infect Dis* 2007; **44**: 1091–95.
- 28 Dhillon RH-P, Clark J. ESBLs: a clear and present danger? *Crit Care Res Pract* 2012; **2012**: 625170.
- 29 Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis* 2008; **8**: 159–66.
- 30 Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clin Infect Dis* 2011; **53**: 60–67.
- 31 Higgins PG, Dammhayn C, Hackel M, Seifert H. Global spread of carbapenem-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 2010; **65**: 233–38.
- 32 Edelstein MV, Skleenova EN, Shevchenko OV, et al. Spread of extensively resistant VIM-2-positive ST235 *Pseudomonas aeruginosa* in Belarus, Kazakhstan, and Russia: a longitudinal epidemiological and clinical study. *Lancet Infect Dis* 2013; **13**: 867–76.
- 33 Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF Jr. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. *J Infect Dis* 1984; **149**: 16–22.
- 34 DeMaria A, Treadwell TL, Saunders CA, Porat R, McCabe WR. Randomized clinical trial of aztreonam and aminoglycoside antibiotics in the treatment of serious infections caused by Gram-negative bacilli. *Antimicrob Agents Chemother* 1989; **33**: 1137–43.
- 35 Fahad BM, Matin A, Shill MC, Asish KD. Antibiotic usage at a primary health care unit in Bangladesh. *Australas Med J* 2010; **3**: 414–21.
- 36 Chandy SJ, Thomas K, Mathai E, Antonisamy B, Holloway KA, Stalsby Lundborg C. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, South India. *J Antimicrob Chemother* 2013; **68**: 229–36.
- 37 Hou F-Q, Wang Y, Li J, Wang G-Q, Liu Y. Management of acute diarrhea in adults in China: a cross-sectional survey. *BMC Public Health* 2013; **13**: 41.
- 38 Kotwani A, Chaudhury RR, Holloway K. Antibiotic-prescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. *Value Health* 2012; **15**: S116–19.
- 39 Supcharassaeng S, Suankratay C. Antibiotic prescription for adults with acute diarrhea at King Chulalongkorn Memorial Hospital, Thailand. *J Med Assoc Thai* 2011; **94**: 545–50.
- 40 Diniz-Santos DR, Silva LR, Silva N. Antibiotics for the empirical treatment of acute infectious diarrhea in children. *Braz J Infect Dis* 2006; **10**: 217–27.
- 41 Bhaskar ME, Moorthy S, Kumar NS, Arthur P. Dengue haemorrhagic fever among adults—an observational study in Chennai, south India. *Indian J Med Res* 2010; **132**: 738–40.
- 42 Shoaib Khan HM, Qamar-uz-zaman, Ali Khan B, Arif M, Raza A, Anamul-Haq. Retrospective analysis of 68 cases of dengue fever. *Pak J Med Res* 2012; **51**: 18–20.
- 43 Phuong HL, de Vries PJ, Nagelkerke N, et al. Acute undifferentiated fever in Binh Thuan province, Vietnam: imprecise clinical diagnosis and irrational pharmacotherapy. *Trop Med Int Health* 2006; **11**: 869–79.
- 44 Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. *BMC Infect Dis* 2011; **11**: 99.
- 45 Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature* 2013; **496**: 504–07.
- 46 Hati AK. Dengue serosurveillance in Kolkata, facing an epidemic in West Bengal, India. *J Vector Borne Dis* 2009; **46**: 197–204.
- 47 Pramanik MK, Aditya G, Raut SK. Seasonal prevalence of *Aedes aegypti* immatures in Kolkata, India. *Southeast Asian J Trop Med Public Health* 2007; **38**: 442–47.
- 48 Sharma RS, Kaul SM, Sokhay J. Seasonal fluctuations of dengue fever vector, *Aedes aegypti* (Diptera: Culicidae) in Delhi, India. *Southeast Asian J Trop Med Public Health* 2005; **36**: 186–90.
- 49 Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA* 1999; **281**: 61–66.
- 50 Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* 2011; **11**: 355–62.
- 51 Dong H, Bogg L, Rehnberg C, Diwan V. Health financing policies. Providers' opinions and prescribing behavior in rural China. *Int J Technol Assess Health Care* 1999; **15**: 686–98.
- 52 qxc16070. Proceedings of the 2nd National Workshop on Rational Use. Docstoc.com. <http://www.haiaiapacific.org/wp-content/uploads/2014/03/Antibiotics-Rational-Use-report-China-2005.pdf> (accessed June 25, 2014).
- 53 Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infect Dis* 2011; **11**: 692–701.
- 54 Mölstad S, Erntell M, Hanberger H, et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. *Lancet Infect Dis* 2008; **8**: 125–32.
- 55 Goossens H, Guillemot D, Ferech M, et al. National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006; **62**: 373–79.
- 56 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; **374**: 893–902.
- 57 WHO. Children: reducing mortality factsheet. <http://www.who.int/mediacentre/factsheets/fs178/en/> (accessed Dec 19, 2013).
- 58 MacKenzie FM, Gould IM. Quantitative measurement of antibiotic use. In: Gould IM, van der Meer JWM, eds. Antibiotic policies: theory and practice. New York: Springer, 2005: 105–18.
- 59 Pharmaceutical Services Negotiating Committee. Disposal of unwanted medicines. <http://psnc.org.uk/services-commissioning/essential-services/disposal-of-unwanted-medicines/> (accessed April 14, 2014).
- 60 Leeb M. Antibiotics: a shot in the arm. *Nature* 2004; **431**: 892–93.