

Incomplete use of global data for aetiological attribution of diarrhoeal disease in the Global Burden of Disease study

The Global Burden of Disease study (GBD) for 2016 makes a bold attempt to estimate the aetiology of diarrhoeal disease for all ages.¹ Understanding of this burden, especially among non-paediatric populations, has been inadequate, and these necessary estimates will influence policy and prioritisation. However, we are concerned that GBD estimates are highly sensitive to key assumptions, some of which seem arbitrary and do not integrate all relevant data.

In the GBD approach to aetiological attribution, age-specific episodes and deaths for each aetiology are estimated as the product of three variables: the incidence of diarrhoea, the proportion of diarrhoeal episodes in which a given pathogen is detected, and the odds that detection of that pathogen indicates the cause of diarrhoea.¹ It is the third variable, known as attributable fraction, that merits further consideration.

The odds ratios for the attributable fraction used by GBD come solely from the Global Enteric Multicenter Study (GEMS).² GEMS was a rigorous multicentre study with comprehensive aetiological testing of moderate to severe diarrhoea among children aged 0–4 years in four African and three Asian low-income and middle-income countries. In GBD, the attributable fraction from GEMS is extrapolated to all age groups, countries, and the full clinical spectrum of diarrhoeal disease. Such a generalisation presents some serious limitations and potentially results in inaccurate burden estimates for several key pathogens.

However, GEMS is not the only source of data available to inform attributable fraction. For example, the English Infectious Intestinal Disease

study could provide data across the age range and would have led to different estimates.³ That study found the presence of *Campylobacter* spp, enteroaggregative *Escherichia coli*, sapovirus, and norovirus to be strongly associated with diarrhoea, whereas GEMS did not. Another example is our systematic review of norovirus, in which we identified 20 studies worldwide with data on the relative frequency of norovirus among cases of acute gastroenteritis versus controls without acute gastroenteritis.⁴ Data from that review were used to generate the WHO Foodborne Disease Burden Epidemiology Reference Group global norovirus estimates of 685 million episodes and 212 000 deaths annually.⁵ By comparison, the GBD estimates are an order of magnitude lower, at 140 million episodes and 19 000 deaths annually. These sources, and others, could collectively provide a diverse set of study populations and represent a more complete spectrum of ages, disease severity, and development levels. Future estimates of the global burden of diarrhoeal disease should integrate this wider range of data.

BL has served as an advisor to Takeda Pharmaceutical Company outside of the submitted work. AH declares no competing interests. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Attributable deaths caused by infections with antibiotic-resistant bacteria in France

We read with interest the paper by Alessandro Cassini and colleagues¹ on deaths attributable to antibiotic-resistant bacterial infections in the EU in 2015, in which it was estimated that 33 110 deaths each year are caused by infections with antibiotic-resistant bacteria. The method used to provide this estimation is based on mathematical constructs developed in the EU as part of the Burden of Communicable Disease in Europe project, in the context of widespread anxiety about antibiotic resistance and the risk of present and future mortality due to antibiotic-resistant bacteria.

In the report by Cassini and colleagues,¹ the number of deaths due to multidrug-resistant bacteria in France was estimated to be 5543 per year (out of 29 000 deaths due to bacterial infections per year). At the IHU Méditerranée Infection (Marseille, France), we examine, on a weekly basis, the microbiological results of most hospital and private laboratories in the southern region of France (which has around 5 million inhabitants), accounting for about 300 000 bacterial isolates per year.^{2,3} We also examine the results of antibiotic susceptibility testing of all isolated bacteria in the University

Hospital of Marseille (a 3800-bed hospital),² as well as all deaths that occur each week in our hospitals (between 50 and 70 deaths) in patients with a positive bacterial isolate in any kind of microbiological sample in the preceding months. From these patients, we look for 30-day attributable mortality per multidrug-resistant bacteria and any infection site of these patients.⁴ In practice, we have only reported one case of a bacterium resistant to all antibiotics tested within the last 5 years, associated with a death in intensive care unit (ICU), probably for multifactorial reasons.^{4,5}

Because of this large discrepancy between estimation and real deaths, we asked an ICU doctor (ML) associated with our research unit to conduct a short survey within Société Française d'Anesthésie et de Réanimation (the French Society of Anaesthesia and Intensive Care Medicine, which comprises more than 350 ICU practitioners and anaesthetists in France) on their practice over the past 10 years. Participants were asked if they had dealt with patient deaths directly linked to an antibiotic therapeutic impasse despite treatment adjusted to antibiotic susceptibility test results. Among the 251 respondents, 116 (46%) had seen no cases of death and 106 (42%) had seen between one and five cases over the past 10 years. Thus, among 222 (88%) of the 251 participants with more than 10 years of experience, there were probably around 45 deaths per year (IQR 22–73, calculated from the median of responses) due to an antibiotic therapeutic impasse.

In France, the mortality of patients hospitalised in ICUs is around 19% (26 600 of 140 000 patients). This reflects the risk of drift without verifying and counting the number of real deaths. In France, the 2015 BURDEN study reported an estimated 12 500 deaths per year in France due to antibiotic resistance,⁶ whereas the

number of deaths due to bacterial infections in all French hospitals is less than 29 000 per year. The model used in the BURDEN study predicted a number of deaths per year that is more than two times higher than the number (5543 deaths) predicted by the model used by Cassini and colleagues.¹ In fact, Cassini and colleagues' report does not represent true data on number of deaths. Mathematical models for estimation of deaths are disconnected from the reality of clinical practice of hospital doctors and clinical microbiologists, who look daily for deaths and antibiotic resistance. In practice, we believe that it is becoming essential to create a national account register recording the true instances of deaths related to the presence of a bacterium in a pathogenic situation resistant to all antibiotics available. This is crucial to obtain a reasonable understanding of mortality due to antibiotic resistance, which cannot be acquired by unrealistic estimations using inappropriate mathematical models based on extrapolation of multiple and non-controlled studies.

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Authors' reply

"All models are wrong, but some are useful"—George E P Box¹

We thank Didier Raoult and colleagues for their comments and agree that large population studies such as our estimation of the health burden of infections with antibiotic-resistant bacteria in the EU and European Economic Area carry frustrating limitations. We acknowledged these limitations in our Article and corresponding appendix,² including those limitations that affected estimations of the attributable mortality related to infections with antibiotic-resistant bacteria. In particular, the disease models were based on data retrieved from systematic literature reviews, which varied in availability and quality of evidence. For this reason, evidence was scored according to ad-hoc criteria reflecting the quality of the studies included in the reviews. Most studies were observational, matching cases and controls and following clinical outcomes for 7 or 30 days. The studies that scored the highest were used for extrapolation of the risk difference between cases (infected with antibiotic-resistant bacteria) and controls (non-infected or infected with antibiotic-susceptible bacteria). When other risk factors for death had been controlled for, we found that most studies showed an association between death and infection