Authors' reply

We agree with Timothy Baker and colleagues that the burden of critical illness is likely to be underestimated in developing countries and we made this point in our paper, along with emphasising that the estimates in table 1 are for illustration purposes only. Unfortunately, reliable population-based estimates of the incidence and outcomes of critical illness are limited even in high-income countries, and such data are virtually non-existent in low-income and middle-income countries. This important gap in knowledge arises from a scarcity of primary research rather than publication bias, which usually refers to the non-publication of completed randomised trials for which the intervention is harmful or its effect is statistically indeterminate.

The correspondents point to the fact that WHO's estimate of number of deaths caused by infection is highest in sub-Saharan Africa and exceeds the number of deaths due to sepsis we estimated on the basis of North American epidemiology and intensive-care capacity. Unfortunately, many of these deaths occur at home or in the field (for example, neonatal[1] and paediatric[2] deaths in Africa), and such patients thus never have the opportunity to present to hospital with critical illness. The number of deaths due to infection is therefore an extremely liberal upper limit for deaths due to sepsis that might not be sufficiently informative for clinicians, researchers, or health-system planners. A robust estimate of the burden of critical illness in developing nations would require more complex modelling and incorporate data from a sampling strategy based on geography, macroeconomic and health indicators, and critical care resources.

Putting aside the debate about the precise burden of critical illness in developing countries, it undoubtedly exceeds the ability of these countries' health systems to care for it. It is well-established that patients who present to hospital with critical illness in the developing world lack access to safe intraoperative care,[3] intensive care beds, trained staff, and evidence-based tools to treat common syndromes such as sepsis;[4] mortality is therefore high. Research and quality improvement in this area must recognise that context-appropriate acute care is complementary to primary care and should determine whether selected critical care techniques and approaches to the delivery and organisation of care can be implemented in low-resource settings, respecting local priorities, resource constraints, and clinical training.[5]

We declare that we have no conflicts of interest.

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Global health aid: raise more, spend better

In his Perspectives piece, Jeffrey Sachs (Sept 18, p 950)[1] emphasises that the key to making rapid progress towards the Millennium Development Goals (MDGs) is to increase the amount of global health aid substantially and to channel it through multilateral global health initiatives such as the Global Fund to fight AIDS, Tuberculosis and Malaria, the GAVI Alliance, and UNICEF. Both recommendations are sensible. We disagree though on "how" this increased multilateral funding should reach countries.

In Niger, most funding available through UNICEF is earmarked for the implementation of interventions with a short-term effect on maternal and child survival—the so-called "quick win" interventions.[2] Massive funds are for example invested in the supply of artemisinin-based combination therapies, bednets, and oral rehydration solution that will yield results in the short term but fail to improve the long-term capacity of the system to provide high-impact interventions sustainably.

Furthermore, more often than not these funds are poorly aligned to national planning and management mechanisms. Most funding is made available in an unpredictable manner and has to be spent within a year or two. This situation is favoured by the still common "raise it, spend it, prove it" culture[3] of multilateral institutions. We would rather see funding mechanisms that reinforce the ability of the government to exercise ownership[4] and engage in health-system-strengthening activities such as the recruitment and motivation of health workers.[5] Otherwise it is like providing intravenous glucose to a hungry child while his parents cannot feed his siblings.

MF was Health Minister in Niger from June, 2009, to February, 2010, and was previous to that General Secretary for more than 3 years. DH worked with UNICEF in Niger from 2005 to 2008.

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Clostridium difficile PCR ribotype 176 in the Czech Republic and Poland

A hospital-based survey of *Clostridium difficile* infection in Europe (Jan 1, p 63)[1] revealed a low prevalence (5%) of the highly virulent PCR ribotype 027. This type has not been found in the Czech Republic but was found in Poland in two hospitals in 2005 and 2007.

After completion of the European survey in the Czech Republic, outbreaks of *C difficile* infection suspected as being of type 027 were found in some areas of the country (eastern Bohemia and Moravia). Detailed analysis of ten isolates showed that the strains belonged to PCR ribotype 176 but shared many similarities with PCR ribotype 027, including the presence of binary toxin genes and a single-base-pair deletion at nucleotide 117 within the gene encoding a negative regulator of toxin production. In Poland, PCR ribotype 176 was detected during two outbreaks in hospitals in the region of Mazovia in late 2008 and early 2009.

To investigate the relatedness of type 176 with type 027 isolates, we applied multiple-locus variable-number tandem-repeat analysis[2] to 59 type 027 strains collected in 14 different European countries, 11 type 176 isolates from Poland, and ten 176 isolates from the Czech Republic. Type 176 isolates clearly differed from 027 isolates in three of the seven loci tested, with a sum tandem repeat difference of 14, whereas all tested type 176 isolates correlated with one another (see webappendix).

We conclude that a new *C difficile* type highly related to 027 has emerged in the Czech Republic and Poland, underscoring the need for local and regional surveillance to detect and control *C difficile* infection.[3] The commercially available molecular diagnostic tests are unable to differentiate between these types.

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Nutritional status and vitamin D_3 during antimicrobial treatment

We welcome the study by Adrian Martineau and colleagues (Jan 15, p 242),[1] which assessed the potential of 10 mg supplemental vitamin D_3 in four divided doses to accelerate rates of sputum culture conversion in pulmonary tuberculosis. Although Martineau and colleagues did not find a significant difference between treatment groups, a small subset of patients with the *tt TaqI* vitamin D receptor genotype seemed to have enhanced sputum culture conversion rates with vitamin D.

Might poor adherence to the vitamin-D_3-containing vigantol oil have obscured a larger—significant—effect? On the other hand, is Martineau and colleagues' supplementation schedule safe? They noted hypercalcaemia in two of 71 patients. Moreover, other treatment effects such as nutritional factors might have confounded the outcome. Severe weight loss in untreated tuberculosis is common.[2] In Martineau and colleagues' study, a weight gain of 6% in the vitamin D_3 group and 5% in the placebo group was seen at day 56. Low gain in bodyweight[3] and low serum creatinine (reflected a low protein mass)[4] are associated with treatment failure. Low serum 25-hydroxyvitamin D might be a common feature of the acute-phase response, occurring separately from true dietary deficiency.[5] Perhaps data on nutrition and inflammation should be included in future regression models to estimate the full potential of vitamin D_3.

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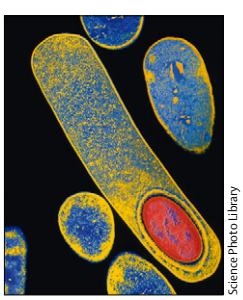
See Online for webappendix



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