

In view of previous knowledge that the two drugs, given separately, increase blood pressure, awareness of the cardiovascular effects of this drug combination is a major issue. Greenway and colleagues report that treatment with naltrexone plus bupropion produced initial and transient increases in blood pressure. After 56 weeks, blood pressure was not reduced as much as would normally be seen with a 5-kg weight loss, and the reduction was less than that in the placebo group. Additionally, the combination treatment did not reduce LDL cholesterol more than did placebo. The investigators concluded that the combination improved several cardiometabolic risk factors; but how relevant are improvements in plasma triglycerides, HDL cholesterol, and high-sensitivity C-reactive protein when the reductions in blood pressure and LDL cholesterol that normally occur with weight loss are absent? Experience with sibutramine perhaps suggests that more data are needed to get a better overall assessment of cardiovascular risk of this otherwise promising combination therapy for obesity.

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Rotavirus: realising the potential of a promising vaccine

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In 2006, two studies that described the efficacy and safety of two new oral rotavirus vaccines were joint winners of *The Lancet's* Paper of the Year.¹⁻³ These trials had been done in infants in high-income and middle-income countries in the Americas and Europe, but no efficacy data were available for infants in low-income populations in Africa and Asia where 85% of the more than 500 000 deaths from rotavirus occur.⁴ Unlike parenteral vaccines, live oral vaccines have behaved differently in high-income and low-income populations because of various immunological factors such as higher titres of transplacental or breast-milk antibodies, host problems related to micronutrient malnutrition, interfering gut flora (tropical enteropathy), intercurrent infections, or an altered distribution of circulating strains.⁵

In 2007, WHO recommended routine immunisation of infants against rotavirus only for those in regions where the effectiveness of the vaccines had been proven.⁶ WHO also recommended that further trials of both vaccines be done for children in poor countries of Africa and Asia. In April, 2009, WHO's Strategic Advisory Group of Experts (SAGE)⁷ reviewed data from the first trials of Rotarix in Malawi and South Africa, together with post-introduction effectiveness data from El Salvador and Nicaragua. In Malawi, the efficacy of Rotarix was 49%, lower than in any high-income or middle-income country.⁸ Despite this lower efficacy, the incidence of severe disease was greater in Malawi than elsewhere; therefore the vaccine was still quite beneficial. On the basis of these data, SAGE recommended that rotavirus vaccines be included in

all national immunisation programmes, particularly in countries where diarrhoeal deaths account for more than 10% of deaths in children younger than 5 years.⁷

Two studies in *The Lancet* today provide new data for the efficacy of Merck's pentavalent rotavirus vaccine, RotaTeq.^{9,10} These randomised trials, undertaken in Ghana, Kenya, Mali, Bangladesh, and Vietnam, enrolled over 7000 infants in urban and rural settings. Over 2 years, vaccine efficacy against severe rotavirus gastroenteritis was lower in the African countries (39.3%, 95% CI 19.1–54.7) than in the Asian countries (48.3%, 95% CI 22.3–66.1). Again, the increased prevalence of severe disease meant that the vaccines could still substantially improve child health and survival (figure^{11–14}). Consequently, in December, 2009, on the basis of the results from today's two studies, WHO decided to extend their recommendation to include all children.¹⁵ This recommendation would allow the GAVI Alliance to accelerate introduction of the vaccine into the national immunisation programmes of the world's 72 lowest-income countries by subsidising vaccine purchase for a limited time at a price of US\$0.10–0.30 per dose.

Will national decision makers in low-income countries now heed WHO's advice and introduce rotavirus vaccines? Although the reduced price might entice some policy makers, many are concerned that without a guaranteed reduction in price in the future, their rotavirus immunisation programmes will become unsustainable when the subsidy ends. The price of vaccines is expected to decrease when developing country manufacturers enter the market but, for now, rotavirus vaccine is only available from the two multinational manufacturers.

The introduction of rotavirus vaccines in national programmes, even in high-income countries, has been slow.⁴ Apart from issues of their lower effectiveness in low-income countries and concerns about vaccine price, there are still some perceptions about adverse effects and intussusception from the earlier vaccine, Rotashield. The finding of DNA fragments of porcine circovirus in both the Rotarix and RotaTeq vaccines has raised questions about vaccine safety despite reviews by WHO, the US Food and Drug Administration, and the European Medicines Agency that deemed the vaccines to be safe.

Criticism of the industry's potential role in formulating WHO's pandemic H1N1 recommendations might negatively skew decision makers who wish to demonstrate their immunity to outside influence.¹⁶ All these issues, however, should not detract from the

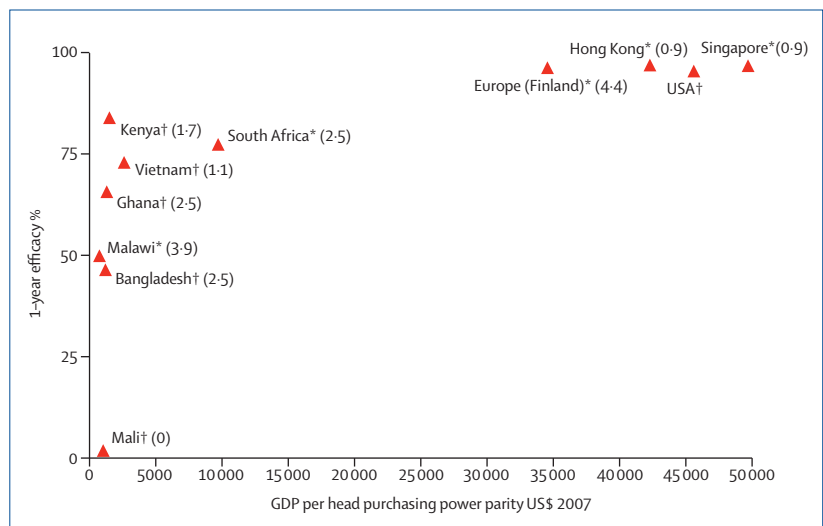


Figure: Point estimates of Rotarix* and RotaTeq† vaccine efficacy, and cases of severe rotavirus gastroenteritis prevented per 100 vaccinated infants by gross domestic product (GDP) per head
 Data for Hong Kong and Singapore from pooled estimates over 2-year follow-up. Cases of severe rotavirus gastroenteritis (Vesikari score ≥ 11 or admission to hospital or emergency department visit for USA) prevented per 100 vaccinated infants are shown in parenthesis.^{11–14}

fact that rotavirus is the most common cause of severe diarrhoea in children that kills more than 1500 children a day. Because diarrhoea is responsible for an estimated 1.5 million deaths per year, and nearly 20% of mortality in children less than 5 years old, rotavirus vaccination will be needed as part of a package of strategies to improve child survival and to achieve Millennium Development Goal 4.¹⁷

Some countries that introduced rotavirus vaccines into their national programmes early on have already begun to see tremendous benefit. In the USA, high vaccine-coverage has resulted in a more than 50% decrease in hospital admissions for childhood diarrhoea,¹⁸ and in Mexico, diarrhoea-related deaths have been markedly reduced.¹⁹ Furthermore, in the USA, the effectiveness of the vaccine seems to be greater than that predicted by initial trials, suggesting herd protection not appreciated from the earlier trials.¹⁸

What is needed next to promote the rotavirus agenda worldwide and to assess the impact of this important intervention to improve children's health? First, we will not be able to assess the true effectiveness of the vaccines in low-income settings and the possible benefit of herd protection until these products are more widely used and their effects are properly evaluated. Reassuring governments in low-income countries that they will be able to purchase vaccine at a reasonable price, when support from the GAVI Alliance ends, will be the quickest

way to encourage their introduction and to establish whether these vaccines will stand alongside smallpox, measles, and poliomyelitis vaccines in their public health benefits.¹ Beyond this, there is a clear need for further research to understand why the efficacy of both live oral rotavirus vaccines is lower among children in low-income countries than high-income countries. Could simple interventions, such as slightly delaying immunisation, adding an additional dose of vaccine, or withholding breast milk around the time of vaccine administration, improve the efficacy of the vaccine in these challenging settings? Finding an answer to these questions could add value to these new vaccines while doing much to improve the health and survival of children.

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Childhood cancer survivors: stillbirth and neonatal death

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As an oncologist, one assumes that the benefit of survivorship outweighs the cost of side-effects, justifying complex multidisciplinary care, including the mainstay treatments of surgery, chemotherapy, and radiotherapy. Children with cancer do not typically make the choice, as adults do, of whether to receive treatment or not, and parents understandably want to provide their children with every possible option for cure. These options can include aggressive, novel treatment strategies with unknown potential consequences decades later. Suffering severe sequelae of cancer treatment might substantially affect long-term quality of life, including the ability to bear children.

In *The Lancet* today, Lisa Signorello and collaborators report a retrospective cohort analysis of the Childhood Cancer Survivor Study (CCSS), looking at the rates of stillbirth and neonatal death.¹ Enrolled cohort members were diagnosed between 1970 and 1986 with leukaemia, lymphoma, sarcoma, CNS cancer, Wilms’ tumour, kidney cancer, or neuroblastoma. Whereas previous reports from the CCSS and others analysed the rates of acute ovarian failure,^{2,3} premature menopause,⁴ miscarriage,⁵ and babies with low birthweight^{5–7} in female survivors, today’s analysis includes both male and female cancer survivors and reports the risk of stillbirth (defined as a fetal death occurring after the 20th gestational week) and