application of 5 mg of cidofovir per kilogram of body weight were ~5-fold higher than an inhibitory concentration of 90% (IC90) against HAdV-B14a (table 1) [7]. Thus, cidofovir holds promise to be active against HAdV-B14a replication in vivo. In the case of ribavirin, the low 50% inhibitory concentration (IC50) value suggested an in vitro susceptibility of HAdV-B14a that is similar to that of HAdV-C5 (table 1). However, a 90% inhibition of HAdV-B14a replication was not achieved with noncytotoxic concentrations (table 1; 50% cytotoxic concentration of ribavirin, 802 μM). For comparison, 90% inhibitions of HAdV-C5 and HAdV-B11, which is closely related to HAdV-B14a, were achieved with noncytotoxic ribavirin concentrations of 29 μM and 38 μM, respectively [5]. Therefore, the interpretation of HAdV-B14a in vitro susceptibility data requires caution, in spite of very high concentrations (>1000 μM ribavirin) achieved in respiratory secretions by high-dose aerosol therapy.

In conclusion, intravenous application of cidofovir should reach a plasma concentration well above in vitro IC50 and IC90 values for HAdV-14a. Although lung concentrations may be lower and early initiation of therapy may be crucial, cidofovir holds promise as an antiviral agent for the treatment of severe lower respiratory tract infections caused by HAdV-B14a. By contrast, high IC50 values of ribavirin in the range of cytotoxic concentrations may lead to clinical failure, although high alveolar concentrations can be achieved using aerosolized ribavirin.

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Glycerol and Dexamethasone in Bacterial Meningitis in Low-Income Countries: Response to the Editorial Commentary by Sáez-Llorens and McCracken Jr.

To the Editor—Some of the comments and observations by Sáez-Llorens and McCracken Jr. [1] regarding the study by Peltola et al. [2], in which the role of glycerol and dexamethasone in acute bacterial meningitis has been evaluated, are provocative and need discussion, particularly after the response by Peltola and Roine [3].

Sáez-Llorens and McCracken Jr. [1] raised ethical concerns about the use of placebo and contend that, because of the use of placebo, many children with bacterial meningitis were subjected to an unnecessary risk of sequelae. Given the current evidence, we do not believe that this is true. A recent meta-analysis supports the use of adjunctive corticosteroids for children in high-income countries only [4]. For children in low-income countries, corticosteroids had no beneficial effect on mortality (risk ratio [RR], 0.96; 95% CI, 0.78–1.18), severe hearing loss (RR, 1.04; 95% CI, 0.66–1.63), and short-term neurological sequelae (RR, 1.08; 95% CI, 0.82–1.44). For children in low-income countries, the use of corticosteroids was not associated with either beneficial or harmful effects [4].

In low-income countries, many of the patients have underlying malnutrition and frequent infections, and they often do not approach a health care facility until late in the course of an illness. These factors are likely to affect cortisol production and levels of cortisol in plasma and may affect the outcome of a critical illness. Malnourished children with or without acute infection have hypercortisolemia and impaired clearance of exogenous cortisol [5–7]. However, the expected metabolic effects of increased cortisol and other glucocorticoid agonists are blunted in these children, because of resistance to glucocorticoids secondary to downregulation of glucocorticoid receptor protein, expression of an inactive form of the glucocorticoid receptor protein, or repression of phosphorylation of the glucocorticoid receptor/hormone complex [7, 8].

In a study from our center, serum cortisol levels in patients who had acute bacterial meningitis were very high. Only 2 of 30 patients had serum cortisol levels in the normal range (20 ng/mL in 1 patient and 50 ng/mL in the other) [9]. The levels correlated with the severity of illness as assessed using the Glasgow Coma Scale. We contend that the therapeutic use of exogenous steroids in patients in low-income countries who already have very high endogenous corticosteroid secretion may not be effective, and this may explain the lack of benefit from dexamethasone.
treatment that has been reported in studies from developing countries [10]. Until such time that new data or meta-analyses are available to define the reasons for different outcomes in high-income versus low-income countries and to identify those children in low-income countries who could benefit form corticosteroids, the role of adjunctive corticosteroids for the treatment of acute bacterial meningitis in low-income countries remains uncertain.

We have also conducted a study [11] that used a protocol similar to that used by Pelto et al. [2]. Our study was approved by the ethics committee of our institution without any concerns. We did not find any difference in outcomes among patients treated with glycerol, dexamethasone, or placebo. However, we found that children who received glycerol had a mean 3% elevation of serum osmolality during the first 6 h after treatment, and this elevation was sustained for 24 h. This could have contributed to lowered intracranial pressure and improved cerebral perfusion and, therefore, reduction of sequelae associated with bacterial meningitis [12].

A prerequisite for a “favorable” effect of dexamethasone treatment in patients who have bacterial meningitis is that it be administered before the first dose of antibiotic. In reality, a large number of patients in developing countries report to the hospital late in the course of the disease and may have received ≥1 antibiotics before reporting to a hospital [13]. Therefore, not using dexamethasone as an adjunct is not unreasonable.

In the absence of clear proof of the benefit of dexamethasone therapy for the treatment of bacterial meningitis, the deleterious effect of a high cortisol level on neurological outcome cannot be discounted. Glucocorticoids produce a generalized metabolic vulnerability in neurons that possess a high concentration of corticosterone receptors [14]. The use of dexamethasone in such a scenario could perhaps raise ethical concerns.

Acknowledgments
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Reply to Singhi et al.
To the Editor—In the concluding paragraph of our commentary regarding the study by Pelto et al. [1], we stated “that the most effective strategy of managing bacterial meningitis and its associated sequelae is prevention by implementing large-scale immunization strategies against the common meningal pathogens….We urgently need to dedicate collaborative effort between vaccine manufacturers, philanthropic foundations, global health organizations, and national governments to make these vaccines available for those who need them most: the infants and children living in less advantageous areas of the world [2, pp. 1288–9].”

We do not believe that additional discussion of whether dexamethasone or glycerol is more effective as adjunctive therapy for bacterial meningitis in infants and children from very low income nations is a useful exercise. These agents have a relatively small impact in those who are most severely affected, compared with the impact of prevention of disease by vaccination.

Singhi and Singh [3] took issue with our concern regarding the use of placebo in children with bacterial meningitis in the study by Pelto et al. [1]. They misread our commentary. We questioned the use