

# Reducing stunting among children: the potential contribution of diagnostics

Authors: **Karen A. Ricci<sup>1</sup>**, **Federico Girosi<sup>1</sup>**, **Phillip I. Tarr<sup>2</sup>**, **Yee-Wei Lim<sup>1</sup>**, **Carl Mason<sup>3</sup>**, **Mark Miller<sup>4</sup>**, **James Hughes<sup>5</sup>**, **Lorenz von Seidlein<sup>6</sup>**, **Jan M. Agosti<sup>7</sup>** & **Richard L. Guerrant<sup>8</sup>**

**Author Affiliations:** <sup>1</sup>RAND Corporation, 1776 Main Street, PO Box 2138, Santa Monica, California 90407-2138, USA

<sup>2</sup>Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8208, St Louis, Missouri 63110, USA

<sup>3</sup>Armed Forces Research Institute of Medical Sciences, APO AP 96546-5000, Thailand

<sup>4</sup>National Institutes of Health, 16 Center Drive, Bethesda, Maryland 20892, USA

<sup>5</sup>Emory University, Mail Stop 1370/004/1AD, 1462 Clifton Road, Atlanta, Georgia 30322, USA

<sup>6</sup>International Vaccine Institute, San 4-8 Bongcheon-7-dong, Kwanak-gu, Seoul, Korea 151-818, and the Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand

<sup>7</sup>Bill & Melinda Gates Foundation, PO Box 23350, Seattle, Washington 98102, USA

<sup>8</sup>University of Virginia, PO Box 80-1379, Charlottesville, Virginia 22908-1379, USA

## PREFACE

Stunting is a major burden in developing countries, affecting ~147 million children. Repeated or prolonged episodes of diarrhoea during childhood increase the risk of stunting, which is believed to be associated with significant morbidity. Although the relationships between malnutrition, environment and diarrhoeal illnesses are complex, studies have suggested a connection between stunting and pathogens that are known to cause diarrhoea, including *Giardia lamblia*, *Cryptosporidium parvum* and enteroaggregative *Escherichia coli* (EAaggEC). In this study, we examine the potential of a new diagnostic for these enteric (intestinal) pathogens to reduce stunting among children presenting with diarrhoeal illness.

## INTRODUCTION

Enteric infections, particularly diarrhoea, are significant causes of morbidity and mortality among children aged <5 years in the developing world. Although childhood mortality from diarrhoeal diseases has decreased substantially since 1980, some evidence suggests that morbidity rates might be increasing<sup>1-5</sup>. A recent review of diarrhoeal morbidity reported that every child aged <5 years in the developing world experiences an average of three episodes of diarrhoea per year<sup>1</sup>, and in some of the poorest areas the rates are consistently higher<sup>6,7</sup>. In acute diarrhoea, dehydration is the most pressing concern. However, diarrhoea also affects food intake and nutrient absorption, both of which are known to contribute to undernutrition. Repeated episodes or persistent diarrhoea significantly increase the risk of growth delays or stunting, which in turn can contribute to long-term cognitive impairment<sup>6,8-12</sup>.

The diarrhoeal diseases working group of the Bill & Melinda Gates Foundation Global Health Diagnostics Forum was asked to identify scenarios in which new individual-level diagnostics for diarrhoeal disease could have the greatest health impact in the developing world. The task of identifying an appropriate and effective individual-level diagnostic for

diarrhoeal diseases posed special challenges. Unlike the other diseases addressed by the forum, diarrhoea does not require a test to determine its presence; rather, it is a symptom of an infection that can be caused by a number of different bacterial, viral and parasitic organisms. Regardless of aetiology, diarrhoeal disease typically does not require specific or symptomatic interventions, and is treated primarily by oral rehydration therapy (ORT), which is both effective and inexpensive. Moreover, most diarrhoeal diseases in the developing world are the result of contaminated water or food and poor sanitation. With this in mind, our view was that scarce resources should generally be focused on efforts to increase access to clean water in the developing world, thereby broadly preventing — rather than specifically diagnosing and treating — enteric infections. However, individual-level diagnostics might be of benefit in certain scenarios.

Various potential diagnostic intervention points were considered, including a test for dehydration. However, we concluded that a tool to measure dehydration would not be useful in a health-care setting, because moderate-to-severe dehydration can be detected through a physical examination, and empiric hydration therapy poses little or no harm. Furthermore, diarrhoea-induced dehydration is a dynamic process that requires continuous monitoring, whereas a single test can provide only a snapshot in time. There were also concerns that a home dehydration test might inappropriately shift the focus of caregivers away from ORT, which is an inexpensive and effective treatment.

We also considered the potential impact of rapid diagnostic tests to identify specific causes of acute diarrhoea. Among the organisms discussed were *Vibrio cholerae*, shigellosis with an emphasis on *Shigella dysenteriae* type 1 (Sd1) and enterotoxigenic *E. coli* (ETEC). We noted that rapid diagnostic tests for cholera are becoming commercially available<sup>13</sup>, and have been used by researchers to identify outbreaks and plan early interventions. We also agreed that rapid diagnostics for Sd1 and ETEC would probably be welcome. A rapid diagnostic test



*C. parvum* and EAggEC. Considering the morbidity burden associated with stunting, we theorized that even a small reduction in stunting prevalence could lead to a substantial reduction in morbidity. Therefore, introducing a test capable of detecting one or more of these pathogens would identify children at risk for stunting. In other words, children with diarrhoea who carry one or more of these pathogens are at higher risk of stunting than uninfected children within the same general population. Once identified, these children could be treated with an intervention designed to reduce their risk of stunting. In this scenario, treatment is assumed to comprise both a drug that eradicates the pathogen and, most importantly, supplemental nutrition.

The data critical for estimating the benefit of a diagnostic intervention are lacking. An important unknown element is the risk of stunting for children with diarrhoea and one of the three pathogens of interest compared with the risk in the general population. The relationship between interventions — in this case, a drug regimen and nutritional supplementation — and reduction in risk of stunting is also unclear. Finally, regional epidemiological prevalence data for the pathogens of interest are scant, and evidence of the efficacy of various drug regimens is sparse, particularly for EAggEC. Therefore, the nature of this study is exploratory, and it is not intended to predict the result of an intervention. Rather, it shows what could happen if a number of assumptions prove to be valid, and how the results of an intervention vary as a function of selected clinical and epidemiological parameters.

might, for example, distinguish between shigellosis, which requires antibiotic therapy, and amoebiasis, which requires antiprotozoal therapy. Similarly, an inexpensive and rapid test for ETEC could allow better understanding of the burden of disease caused by this organism, therefore improving the evaluation of interventions. However, after much debate, our consensus view was that diagnostics for these pathogens would be most valuable at the level of populations (that is, in preventing and controlling diseases within populations) rather than individuals. Moreover, several pathogens are of interest, each of which is responsible for limited overall morbidity and mortality from diarrhoeal disease. The impact of a diagnostic test for a specific organism is therefore likely to be small and not suitable for analytic modelling.

We next turned our attention to the relationship between diarrhoeal diseases and stunting. Even though the rate of stunting has been declining worldwide for the past two decades<sup>14</sup>, it remains a major burden among children in developing countries. In addition to reflecting poor nutrition, stunting also predicts cognitive impairment<sup>6,8–12,15</sup>. A study by de Onis and colleagues in 2004, using the World Health Organization (WHO) Global Database on Child Growth and Malnutrition, estimated that the overall prevalence of stunting in the developing world is 27% or ~147 million children<sup>14</sup>. Its prevalence is highest in Africa at 34.5%, corresponding to 48.5 million stunted children, with lower values in Asia (25.7%) and Latin America (11.8%) corresponding to 92.4 million and 6.5 million stunted children, respectively. The relationships between enteric infections, malnutrition and environmental factors are complex;

however, recurrent or persistent diarrhoeal illnesses have been shown to represent a risk factor for stunting in children aged <5 years in the developing world<sup>18–10,12,16,17</sup>. Epidemiological studies indicate that various pathogens can cause persistent diarrhoea, with *G. lamblia*, *C. parvum* and EAggEC being frequently implicated<sup>10,17,18</sup>. There is a growing body of evidence documenting the relationship between growth retardation and infections with these pathogens<sup>19–22</sup>.

In view of these data, our analytic efforts focused on understanding the potential reduction in morbidity from diarrhoeal diseases, specifically growth shortfalls or stunting, associated with a new individual-level diagnostic for the enteric pathogens *G. lamblia*,



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**METHODS**

**Analytic overview**

We developed a probability tree model depicting the effects of a potential new strategy for identifying the presence of one or more of the three target pathogens. The model focuses on children in the developing world (Africa, Asia and Latin America including the Caribbean) who are aged <5 years, present with diarrhoea, and carry *G. lamblia*, *C. parvum* and/or EAggEC. This scenario assumes that these children are at greater risk of stunting than those in the general population. An alternative strategy of identifying the three pathogens in the general population, regardless of the presence of diarrhoea, is discussed later and elsewhere<sup>23</sup>.

The model was used to calculate health benefits in terms of the number of stunting cases averted among children as a result of the data provided by a new diagnostic test. We define a child as stunted if his or her height-for-age is more than two standard deviations below the WHO international reference. Although, at an individual level, stunting status is not an informative health indicator, it becomes more useful when applied at a population level. A preferable approach would be to base the analysis on the entire growth trajectory of a child, or at least on his or her length velocity. However, it is unlikely that currently available data on individualized growth could support such an analysis; therefore, we chose stunting, as defined above, as our primary outcome.

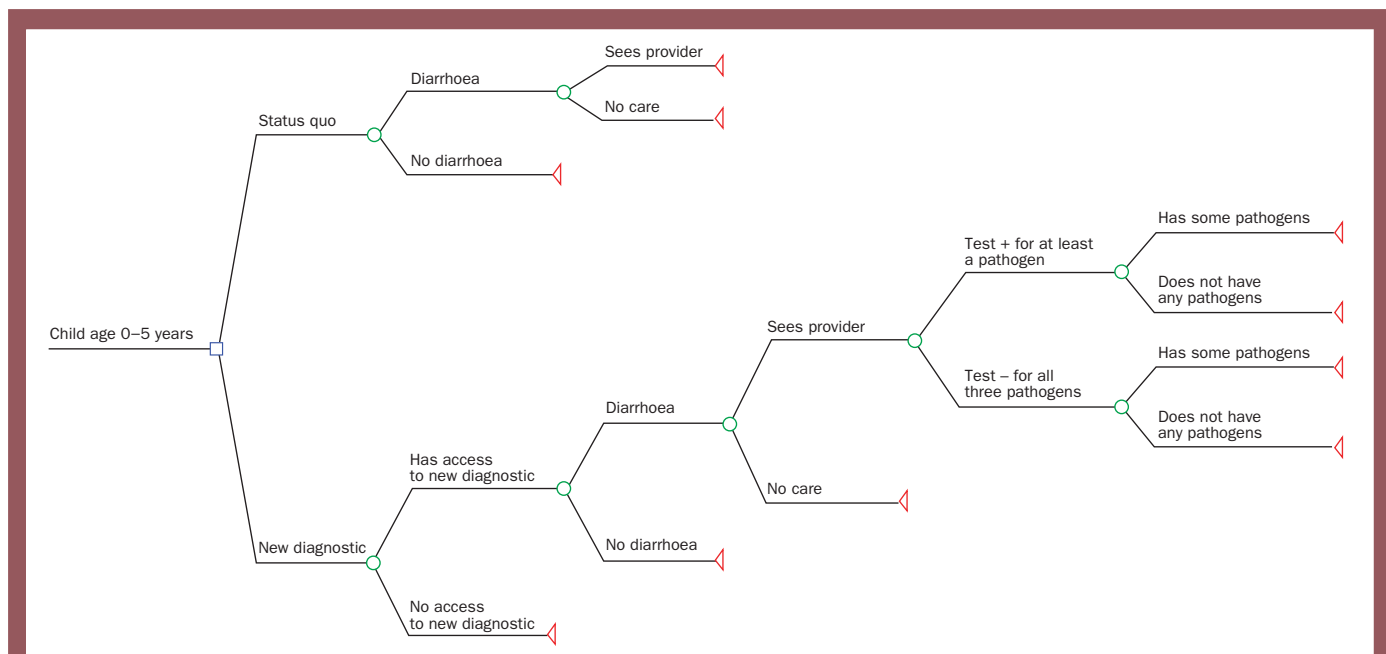
The model is static and compares the probability of becoming stunted over a period of 3 months in the status quo with that in a world with the new diagnostic. The model assumes that a reduction in the probability of stunting translates into an equal reduction in the prevalence of stunting. A more complex compartmental model for stunting, which explicitly takes into account the probability of dying or recovering, was also developed and is described elsewhere<sup>23</sup>. However, we found that the additional complexity did not lead to different insights into the problem; therefore, we believe that the static model is adequate for the purpose of this study.

The choice of 3 months as the base period does not reflect clinical considerations at an individual level, and this should not be interpreted as the time required for stunting to develop after an episode of diarrhoea. Although children can grow at different rates during the first few years of life, and some research indicates that there are seasonal variations in saltatory growth<sup>24–27</sup>, it might take >3 months for an individual child to develop stunting following an insult, such as a diarrhoeal illness. At the aggregate level, however, significant changes occur over a period of 3 months. For example, in Africa, the prevalence of stunting increases by 7.3 percentage points every 3 months among children who are aged <2 years. Therefore, in our initial compartmental model of stunting, it was necessary to use a 3-month period to capture the basic shape of the prevalence–age

profile. This motivated our choice of 3 months as the base period.

To model the potential effects of the new diagnostic, we varied the test performance characteristics (sensitivity and specificity) and the diagnostic infrastructure requirements (minimal and moderate/advanced) corresponding to the level of health-care access. The infrastructure levels are taken from Girosi and colleagues<sup>28</sup>. The model assumes that children at risk of stunting are provided with appropriate treatment in the form of a drug to treat the pathogen and, most importantly, supplemental nutrition. Although a child who is already stunted might also benefit from nutritional supplements, there are few data on catch-up growth, so we decided not to include the benefits accruing to these children in the model.

The main health outcome used in our model is the reduction in the prevalence of stunting provided by the new diagnostic test compared with the status quo, where almost no testing is performed. We also estimated the number of disability-adjusted life years (DALYs) saved because of the reduced prevalence of stunting. DALYs is a health-gap measure that extends the concept of potential years of life lost due to premature death, to include equivalent years of ‘healthy’ life lost owing to illness or disability. The DALY combines, in one measure, the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of healthy life, and the burden of disease can be viewed as a measurement of the gap between current health



**Figure 1 | Core probability tree.** In the status quo, no test for any of the three pathogens is performed. In a world where the new diagnostic is available, only a proportion of children aged <5 years have access to it. Among the children with access to the new test, some will have diarrhoea at some point during a period of 3 months. Of those who have diarrhoea, some will see a health-care provider and be tested. Those who have been tested will experience different outcomes than those who have not been tested.

status and an ideal situation in which everyone lives into old age free from disease and disability. Finally, we considered the potential harm associated with treatment, which we define in terms of the resources used to treat a child that could have been directed towards other more effective interventions (see below).

### Modelling diarrhoeal disease pathogens to reduce stunting in children

Figure 1 illustrates the model for the introduction of a new diagnostic and the sequence of events for the scenario. The upper branches show the status quo, whereas the lower branches depict the world with the new diagnostic. In the latter, children with diarrhoea who access a health-care facility are evaluated by a trained provider and a new diagnostic might or might not be available. If the test is available, and if the child is diagnosed as positive for one or more of the three pathogens, he or she will receive a pathogen-specific eradication regimen and nutritional supplementation. Children testing negative are given the standard treatment recommended for their clinical presentation, which is typically ORT.

### Model parameters

Table 1 shows the parameters used in our model and the estimates applied in the analysis. The latter were obtained from a targeted literature review and through discussions with forum experts. A consensus was reached on the plausible ranges of all estimates used in the model.

The availability of the new diagnostic was determined according to the level of

health-care infrastructure needed to support it and the level of access to an evaluating facility. The model divides health-care facilities into those with minimal infrastructure (such as a village clinic) and those with moderate/advanced infrastructure (such as a hospital)<sup>28</sup>. In general, more children will have access to the former than the latter. A diagnostic test that requires advanced infrastructure will probably be hospital based, whereas a test that requires less support could be clinic based. For example, in Africa, a test that requires moderate-to-advanced infrastructure would be available to only 28% of the population. If the test required only minimal infrastructural support, an additional 47% of the population would have access to it (75% in total). These access estimates were produced by a multinomial logit model using data from the Demographic and Health Surveys (DHS) conducted from 2000 to 2005 in 17 African, 6 Asian and 6 Latin American countries. The results of this analysis and the precise definition of the different types of infrastructure can be found elsewhere<sup>28</sup>. Estimates of diarrhoea prevalence over a period of 3 months were converted from DHS data for prevalence over a period of 2 weeks, assuming an average duration of 3 days per episode.

The prevalence data for *G. lamblia* and *C. parvum* in children with diarrhoea were obtained from Lanata and Mendoza<sup>29</sup>, and are based on an extensive literature search. Data on the prevalence of EAggEC are much scarcer, and come from few settings<sup>7,22,30–39</sup>. Therefore, we treat this parameter with particular care and show results for values ranging from 10 to 30%.

Estimates of the prevalence of stunting were derived from de Onis and colleagues<sup>14</sup>. These values correlate well with those that we independently derived using DHS data.

The efficacy of treatment measures the percentage reduction in the probability of becoming stunted in the near future as a consequence of being treated. Therefore, if we state that a treatment is 50% effective, we mean that it reduces the probability that a child becomes stunted in the next 3 months by 50%. The true efficacy of the treatment depends on the drugs administered, the provision of adequate nutritional support and adherence to the prescribed regimen.

The effectiveness of pathogen-specific therapy combined with nutritional supplementation in preventing near-term stunting is not known. The efficacies of different drug-treatment options vary widely. For example, a recent Cochrane Database study utilizing a controlled trials registry demonstrated the value of nitroimidazoles for the treatment of giardiasis<sup>40</sup>. Most clinical experience has been with metronidazole, although tinidazole has a similar parasitological cure rate (in the 90% range) and a higher rate of clinical cure<sup>41</sup>. Nitazoxanide has been used to treat cryptosporidiosis, and has a good safety profile and an 80% efficacy rate in children<sup>42</sup>. It has also been used to effectively treat giardiasis. Few studies have evaluated the treatment of EAggEC infections in humans to provide interpretable conclusions regarding efficacy and safety. EAggEC infections are plausibly, although not definitely, treatable by antibiotics. However, resistance to a variety of antibiotics

**Table 1 | Main model parameters for three regions**

Parameter	Africa		Asia		Latin America		References
	Base	Range	Base	Range	Base	Range	
Epidemiology and prevalence							
Population aged <5 years (millions)	142		357		57		United Nations World Population Database*
Diarrhoea prevalence (3 month period)	96%	80–100%	84%	70–95%	82%	70–95%	Demographic and Health Surveys†
Prevalence of <i>C. parvum</i>	4.4%	1.5–7.2%	4.8%	1.7–8%	7.8%	2.7–12.8%	29
Prevalence of <i>G. lamblia</i>	10.4%	3.7–17.2%	7.7%	2.7–12.8%	16.7%	5.9–27.6%	29
Prevalence of EAggEC	20%	10–30%	20%	10–30%	20%	10–30%	7,22,30–39
Average stunting prevalence (aged <5 years)	34.5%	31.7–37.4%	25.7%	22.5–28.9%	11.8%	7–17%	14
Number of stunted children aged <5 years (millions)	48.5		92.4		6.5		14
Health-care access							
Proportion of children with diarrhoea visiting health facility	31%	20–40%	49%	35–65%	32%	20–40%	Demographic and Health Surveys†
Health outcomes							
Efficacy of treatment	50%	25–75%	50%	25–75%	50%	25–75%	Expert opinion
Differential risk of stunting for children with diarrhoea	3	1.5–4.5	3	1.5–4.5	3	1.5–4.5	Expert opinion

\*Data from the 2004 Revision of the United Nations World Population Database (<http://esa.un.org/unpp>). †Data from the Demographic and Health Surveys Database 2005 (<http://www.measuredhs.com>). *C. parvum*, *Cryptosporidium parvum*; EAggEC, enteroaggregative *Escherichia coli*; *G. lamblia*, *Giardia lamblia*.

(for example, ampicillin, erythromycin, spectinomycin, streptomycin, tetracycline and trimethoprim/sulfamethoxazole) has been reported<sup>38,39,43</sup>. Ciprofloxacin and rifaximin are potential treatments, but the durability of the susceptibility of EAggEC to these agents has not yet been determined<sup>36,38,39,44</sup>. Although a drug regimen might be a sensible option to treat children infected with *G. lamblia*, *C. parvum* or EAggEC, it is not clear whether eliminating pathogens alone would reduce the risk of stunting. We hypothesized, however, that combining a drug regimen with nutritional supplementation would decrease the risk of stunting over a period of 3 months. To account for variations and uncertainty in treatment efficacy, our model considers three scenarios in which this parameter is set, respectively, to 25, 50 and 75%.

Another important parameter in the model is the differential risk of stunting. This value, which is  $>1$ , refers to the risk over the next 3 months that a child who has diarrhoea and is infected with at least one of the three pathogens will become stunted (see above), compared with an average child in the same general population. Although we predicted that the differential risk for stunting might be large, there is little evidence regarding its magnitude. Therefore, our model considers three scenarios in which this parameter is set, respectively, to 1.5, 3 and 4.5.

### Outcomes

Our main outcome measure is the reduction in the prevalence of stunting, which we predict by region. For simplicity, however, we aggregate the results and report our findings for the developing world as a whole. Regional details



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are provided elsewhere<sup>23</sup>. The reduction in prevalence of stunting is translated into the number of cases averted using the current number of stunted children (~147 million) in the developing world according to de Onis and colleagues<sup>14</sup>.

We also calculate the number of DALYs saved because of reduced stunting prevalence. The DALY calculation for stunting has not been established in the literature; therefore, we estimate this value by adjusting the DALYs associated with diarrhoeal disease published by Guerrant and colleagues<sup>9</sup>. The estimates take into account the potential lifelong disabilities associated with diarrhoeal disease and its negative sequelae, such as fitness

impairment, growth shortfalls and cognitive impairment. Although reduced stunting prevalence would improve DALYs, the extent of this effect is not clear *a priori*. We attribute 50% of the burden of diarrhoeal disease to stunting, with the understanding that this important assumption is not supported by solid evidence. As a measure of diarrhoeal disease DALYs, we use a figure of 306.5 million globally, which is the median estimate presented by Guerrant and colleagues<sup>9</sup>. This value corresponds to a scenario in which 10% of the children are at risk of at least one diarrhoeal attack that could cause lifelong disability. The disability weight applied is a low value of 0.096, the life expectancy is 81.25 years, and standard formulae for age-weighting and discounting at 3% are applied. The chosen life expectancy allows comparison with standard estimates of disease burden; however, using a discounting of 3% means that this parameter has little influence on the results. Based on these figures, each 1% reduction in prevalence of stunting is associated with a reduction of  $0.5\% \times 306.5$  million DALYs = 1.53 million DALYs.

We also report the total number of treatments required by the interventions. This variable is important because it determines the size of the potential negative effects (that is, those that are not dose related or cumulative) or externalities associated with treatment.

As with any treatment, each intervention has a cost to society and a potential harm to the recipient. We refer to the sum of all the negative externalities associated with treatment as the harm of treatment, which we represent as the parameter *C*. In the model, the harm of treatment includes the opportunity cost (that is, the resources used to treat a child that could



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have been used in other more effective interventions, thereby missing the opportunity to realize a certain number of DALYs) as well as the potential increase in the presence of resistant pathogens and the possibility of adverse reactions to drug treatment. These effects can be quantified by estimating that for every treatment, a certain fraction, *C*, of DALYs is lost because of the harm of treatment (see ref. 23 for more details). Therefore, if the harm of treatment and the number of treatments are both high, it is possible that the DALYs saved because of the reduction in prevalence of stunting could be outweighed by the aggregate harm associated with the treatment.

Alternatively, we must consider the fact that there are also positive externalities associated with treatment, in addition to the reduction in stunting prevalence. For example, appropriate nutrition might boost immune response in children, leading to a reduction in the large disease burden associated with infectious

diseases. Therefore, both positive and negative externalities must be considered in the analysis, and the benefit of a new test will depend on their balance.

## RESULTS

We describe the outcomes as functions of the characteristics of the new diagnostic and other parameters of the model. Because there are three pathogens to identify, the new diagnostic must have three sets of sensitivities and specificities. However, it would be impractical to study each simultaneously. Therefore, we assume that all three tests have the same characteristics, and deal with a single sensitivity and a single specificity only.

We start by discussing the reduction in the prevalence of stunting, assuming that the negative and positive externalities associated with treatment balance out. Because there is much uncertainty regarding the value of three key model parameters (differential risk of stunting,

efficacy of treatment and prevalence of EAggEC), we begin by illustrating how this uncertainty is reflected in the outcomes for one particular test. We focus on a test that requires a setting with only minimal infrastructure, and has 100% sensitivity and 100% specificity, which corresponds to the best-case scenario. We allow the three key parameters to assume three values: low, medium and high. The differential risk of stunting is allowed to take the values 1.5, 3 and 4.5, the efficacy of treatment is allowed to take the values 25, 50 and 75%, and the prevalence of EAggEC is allowed to take the values 10, 20 and 30%. The other parameters are fixed at the values reported in Table 1.

Table 2 illustrates the reduction in the prevalence of stunting that would be achieved if the three parameter values varied from low to high. Note that the results span a wide range, from 2.5% (Table 2, parameter set 1) to 40.6% (Table 2, parameter set 27). However, these two extremes are not likely, because they are realized only when all three estimates are at their lower or upper bounds simultaneously. To gain a better idea of how the outcomes are distributed, we randomly varied the values of these parameters between their lower and upper bounds, and computed the corresponding distribution of outcomes (Fig. 2). The mean reduction in prevalence of stunting is 14%, with a standard deviation of 7%. Assuming that there are 147 million stunted children aged <5 years<sup>14</sup>, a reduction of 14% translates to ~21 million stunting cases averted. Using the estimated 306.5 million DALYs associated with diarrhoeal disease, as reported by Guerrant and colleagues<sup>9</sup>, and attributing 50% of them to stunting, we estimate 21.5 million DALYs saved. To appreciate the magnitude of this effect, we note that 21.5 million DALYs corresponds to ~50% of the entire burden of disease for malaria in children aged <5 years.

Although these results imply a sizable benefit associated with this intervention, it should be noted that the results correspond to an intermediate scenario, in which the three key parameters assume intermediate values. As noted above, these results also correspond to a scenario in which the test is perfect and requires only minimal infrastructure.

Table 3 demonstrates variation in results if the sensitivity and specificity of the test are changed. The top half of the table reports the results for a test that requires only minimal infrastructure, whereas the lower half of the table reports results for a test that requires moderate/advanced infrastructure. The no-infrastructure category was not considered because the treatment is likely to require at least a minimally trained health-care provider. In addition to the point estimates, we also

**Table 2 | Reduction in the prevalence of stunting associated with a diagnostic test that is 100% sensitive, 100% specific and only requires minimal infrastructure, as a function of three key model parameters**

Parameter set	Differential risk of stunting	Efficacy of treatment (%)	Prevalence of EAggEC (%)	Reduction in prevalence of stunting (%)
1	1.5	25	10	2.50
2	1.5	25	20	3.50
3	1.5	25	30	4.50
4	1.5	50	10	5.00
5	1.5	50	20	7.00
6	1.5	50	30	9.00
7	1.5	75	10	7.50
8	1.5	75	20	10.50
9	1.5	75	30	13.50
10	3	25	10	5.00
11	3	25	20	7.00
12	3	25	30	9.00
13	3	50	10	10.00
14	3	50	20	14.00
15	3	50	30	18.00
16	3	75	10	15.00
17	3	75	20	21.00
18	3	75	30	27.10
19	4.5	25	10	7.50
20	4.5	25	20	10.50
21	4.5	25	30	13.50
22	4.5	50	10	15.00
23	4.5	50	20	21.00
24	4.5	50	30	27.10
25	4.5	75	10	22.60
26	4.5	75	20	31.60
27	4.5	75	30	40.60

EAggEC, enteroaggregative *Escherichia coli*.

report the tenth and ninetieth percentiles of the distribution of outcome obtained with a Monte-Carlo simulation<sup>45</sup>. The simulation was performed by randomly sampling the values of the model parameters from the ranges reported in Table 1. Sampling was performed using a triangular distribution.

The results for a perfect test with 100% sensitivity, 100% specificity and requiring minimal health-care infrastructure are reported in Table 3 (test 1). The reduction in stunting prevalence, the number of stunting cases averted and the number of DALYs saved are linear in the sensitivity of the test: for every 10 percentage points lost in sensitivity, the reduction in stunting prevalence decreases by 1.5 percentage points, the number of stunting cases averted is reduced by 2.2 million and the number of DALYs saved is reduced by 2.3 million. Therefore a test that is 90% sensitive could reduce the prevalence of stunting by 12.5%, whereas a sensitivity of 70% would reduce the prevalence by 9.5%.

#### Tests requiring minimal infrastructure result in greatest benefit

Results for tests that require moderate/advanced health-care infrastructure are also reported in Table 3 (tests 5–8). When these results are compared with those corresponding to a minimal infrastructure requirement (Table 3, tests 1–4), it is clear that a new diagnostic would not be worth developing if it could only be performed in a health-care facility with moderate-to-advanced infrastructure. Even if such a test were 100% sensitive and 100% specific, it would reduce the prevalence of stunting by only 8.5%, which is less than the 9.5% that could be saved by a diagnostic that requires minimal infrastructure and is only 70% sensitive. This finding is robust to variations in all of the model parameters.

#### Large uncertainties surround the externalities associated with treatment

These calculations, however, do not take into account the externalities associated with treatment. We start with the negative externalities, formalized by the harm of treatment parameter,  $C$ , representing the fraction of DALYs lost for each treatment administered to a child. The concept of harm of treatment is highly relevant in this context, because the number of yearly treatments associated with this intervention is large compared with the number of stunting cases averted: a 100% sensitive and 100% specific test would lead to the treatment of 213 million children, averting 20.7 million cases of stunting; by contrast, a test that is 100% sensitive but only 70% specific would lead to the treatment of 528 million children,

while avoiding the same number of stunting cases.

To illustrate the potential size of the effect associated with the harm of treatment, let  $C^{\text{treat}}$  be the cost of treatment for this intervention and  $C^{\text{cc}}$  be the cost of saving one DALY with a cost-effective intervention. If we assume that harm of treatment comes only from opportunity cost, then  $C = C^{\text{treat}}/C^{\text{cc}}$ .

Assuming that a treatment with 50% efficacy costs between US\$1 and US\$10, and that at least one intervention<sup>46</sup> can save one DALY with US\$20,  $C$  would be between 0.05 and 0.5. The perfect diagnostic, in a minimal infrastructure scenario, would save 21.5 million DALYs and involve 213 million treatments per year. This implies that the number of DALYs lost to the harm of treatment would be between 10.6 million and 106 million, which would negate the benefits of the new test.

Although the harm of treatment seems large, it is possible that it could be at least partially balanced by positive externalities that result from treatment, other than reduction in stunting prevalence. Such positive externalities would not have to be large in order to offset the harm of treatment. For example, if the cost of the intervention were US\$5, the harm of treatment would be  $C = 0.25$ . Treating a child with diarrhoea would need to have a benefit of 0.25 DALYs, in addition to the benefit from the decreased probability of stunting, to offset the negative externalities related to the opportunity cost. If this were the case, we would still find significant benefits from the new diagnostic, and the net DALYs saved would be those shown in Table 3.

The balance between positive and negative externalities is delicate. For example, under the assumption of a cost of treatment of US\$5 and a positive externality of 0.25 DALYs per treatment, the positive externalities would

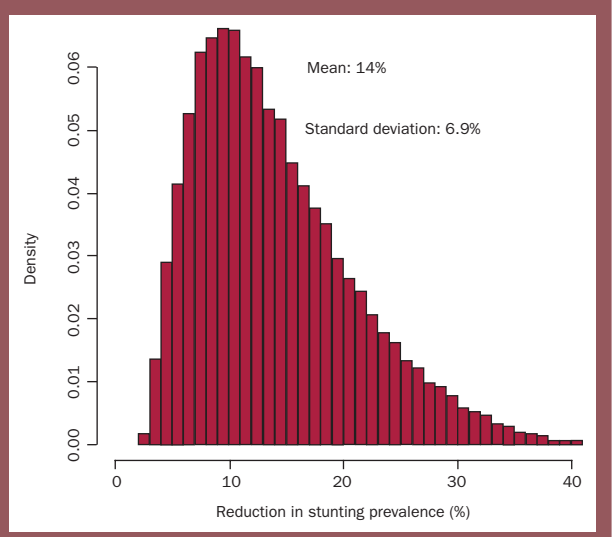
perfectly offset the negative externalities, and 19.2 million DALYs would be saved by a test that is 90% sensitive, 90% specific and requires minimal infrastructure (Table 3, test 4). However, if the cost of treatment were to increase to US\$6, the net DALYs benefit would drop to 2.8 million (data not shown). A further increase of US\$1 in the cost of treatment would make the diagnostic useful only if its specificity were >99%, in which case it would save only 200,000 DALYs. An interactive spreadsheet that allows the user to see how changes in the assumptions about negative and positive externalities affect the results of Table 3 is available elsewhere<sup>23</sup>.

Too little is known about the size of the negative and positive externalities associated with treatment to draw firm conclusions. In the most pessimistic scenario, the harm of treatment would be so large that there would be no benefit from a new test. An intermediate although conservative scenario, which we prefer, is that the positive externalities would only partially offset the negative ones, leaving some significant harm associated with treatment. In this case, it would be important for the new test to have a high specificity. Finally, it is also possible that the positive externalities would outweigh the negative ones. In this case, treating all children would be the optimal strategy.

#### An alternative community-based screening scenario would not be practical

The rationale for the scenario discussed so far is that children with diarrhoea who carry any of the three pathogens are at higher than average risk of stunting, and therefore are a good target population. An alternative is to focus on all children who carry any of the pathogens, regardless of whether they have diarrhoea. This is a larger population, but it has a lower risk of stunting because only one risk factor

**Figure 2 |** Distribution of the reduction in stunting prevalence for a test that requires only minimal infrastructure, and is 100% sensitive and 100% specific. This distribution has been obtained by randomly varying the three key parameters (differential risk of stunting, efficacy of treatment and prevalence of enteroaggregative *Escherichia coli*) in their range, from low to high.



(pathogens) is present instead of two (pathogens and diarrhoea). This population could be reached with a screening programme; for example, 50% of the population could be screened twice a year. Whether this alternative scenario would provide greater benefit than that described above depends mainly on differences in the prevalence of the pathogens and the risks of stunting in children with diarrhoea compared with the general population. If we assume that pathogens are only 20% more likely to be found in children with diarrhoea than in the general population, and that the risk of stunting is only 20% higher in children with diarrhoea and any pathogen than in those with any pathogen and no diarrhoea, a simple calculation<sup>23</sup> shows that for a screening programme to have at least the same benefit as the scenario described above, wherein we targeted children with diarrhoea, 50% of the population would have to undergo screening 4.4 times a year. This is not practical and the scenario is therefore not attractive.

#### Sensitivity analysis highlights effects of model parameters on results

Because of the large uncertainty in many of the model variables, it is important to know how errors in the parameters affect the results. We consider the reduction in the percentage of stunting as the main outcome of interest, because the discussion of the other outcomes follows similar lines. This outcome is directly proportional to the following metrics: prevalence of diarrhoea, proportion of children with diarrhoea visiting a health facility, proportion of children with access to the new diagnostic, differential risk of stunting and

efficacy of treatment. This implies that a percentage increase in each of these parameters leads to an equal percentage increase in outcome. Therefore, to determine what the values in Table 3 would be if the efficacy of treatment were 100% rather than 50%, we simply double all the numbers in Table 3. Although this is technically not correct for the sensitivity of the test, it is a good approximation. The parameters that have the least influence on the outcomes are the prevalence of the pathogens. A 10% increase in the prevalence of *C. parvum*, *G. lamblia* and EAggEC leads to percentage increases in outcome, respectively, of ~1, 2.5 and 5%. Therefore, the model is relatively insensitive to errors in prevalence of *C. parvum* and *G. lamblia*, but is moderately sensitive to changes in prevalence of EAggEC.

### DISCUSSION

After considering multiple scenarios in which an individual-level diagnostic might be of benefit, we developed an intervention scenario whereby new diagnostic technology could potentially reduce the prevalence of stunting in children aged <5 years. We identified assumptions under which there would be a significant benefit from the introduction of a diagnostic tool that can identify the presence of *C. parvum*, *G. lamblia* and EAggEC in children with diarrhoea. The most important condition is that the positive externalities associated with treatment at least partially offset the negative ones, so that the DALYs lost to the harm of treatment (for example, the opportunity cost of overtreatment) do not outweigh those saved by the reduction in stunting.

Another critical assumption is that the test

must be useful in a setting with minimal infrastructure. This implies that such a test would probably not require electricity, water or any external reagents, could be performed with only minimal expertise (low-level medical training), would be portable or able to be performed on a bench top (and require minimal maintenance), and would be thermostable and simple to use (for example, a test with pictorial instead of written instructions). In general, the test would need to be robust, and would probably require a stool specimen as the sample type. Sample preparation would need to be simple, and at least minimal test results should be rapidly available (that is, within 2 h). We summarize our key points in Box 1.

Existing diagnostics might provide a starting point for the development of new tests. Current stool diagnostics for cultures are sensitive and specific, but are also expensive and therefore not practical for minimal-infrastructure settings. Consequently, one challenge for technology developers is to create less-expensive tests with similar performance levels. Polymerase chain reaction (PCR) testing with primers that are based on pathogen DNA is proving to be an accurate and sensitive technique, which might be worth pursuing. Of additional interest is the enzyme immunoassay test for giardiasis that is currently on the market, which might be suitable for adaptation in the developing world. However, research is needed to identify and validate other potential biomarkers, as well as technology and platform development for use in resource-limited settings.

A sensitivity of 70% could provide a benefit by reducing the prevalence of stunting by ~10%. This result, however, depends on the

**Table 3 | Attributable benefit of a new diagnostic test in children with diarrhoea assuming no net externalities associated with treatment**

Test	Sensitivity (%)	Specificity (%)	Reduction in prevalence of stunting (%) <sup>*</sup>	Stunting cases averted (M)	Number of Treatments (M)	DALYs saved by reduction in stunting (M) <sup>†</sup>
Minimal infrastructure <sup>‡</sup>						
1 Perfect test	100	100	14.0 (7.8–21.5)	20.7 (11.4–31.8)	212.9 (157.9–271.6)	21.5 (11.9–33)
2 Low sensitivity/perfect specificity	70	100	9.5 (5.5–14.6)	14.1 (8.1–21.5)	153.5 (113.6–195.6)	14.6 (8.4–22.3)
3 Perfect sensitivity/low specificity	100	70	14.0 (7.9–21.6)	20.7 (11.7–31.9)	527.8 (427.5–632)	21.5 (12.2–33.1)
4 Good sensitivity and specificity	90	90	12.5 (7–18.9)	18.4 (10.3–27.9)	327.1 (260.3–398.4)	19.2 (10.8–29)
Advanced/moderated infrastructure <sup>‡</sup>						
5 Perfect test	100	100	8.5 (4.7–13.2)	12.6 (6.9–19.4)	136.5 (101–173)	13.1 (7.1–20.2)
6 Low sensitivity/perfect specificity	70	100	5.8 (3.2–9)	8.5 (4.8–13.2)	98.5 (73.9–125.1)	8.9 (4.9–13.7)
7 Perfect sensitivity/low specificity	100	70	8.5 (4.9–13.2)	12.6 (7.2–19.5)	336.2 (275.1–407.1)	13.1 (7.4–20.2)
8 Good sensitivity and specificity	90	90	7.6 (4.1–12)	11.2 (6.1–17.7)	208.8 (165–258.3)	11.6 (6.3–18.4)

<sup>\*</sup>The numbers in parentheses are the tenth and ninetieth percentiles of the distribution of outcome obtained with a Monte-Carlo simulation. The simulation was performed by randomly sampling the values of the model parameters from the ranges reported in Table 1. Sampling was performed using a triangular distribution. <sup>†</sup>These correspond to the DALYs saved under the assumption that the negative and positive externalities associated with treatment cancel out, the total DALYs for diarrhoea is 306.5 million and stunting contributes to 50% of the diarrhoeal disease burden. <sup>‡</sup>A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and can be performed in a clinic by staff with minimal training. A test can be performed in a setting with moderate/advanced infrastructure if electricity and water are available, and a laboratory is at least minimally equipped (for example in African hospitals). Staff requirements include nurses, a physician and a technician with minimal training. See ref. 28 for details on calculating the percentage of people with access to a new diagnostic requiring minimal or moderate/advanced infrastructure. DALYs, disability-adjusted life years; M, millions.

model parameters precisely matching the values shown in Table 3. Taking into account the high degree of uncertainty in these parameters, we find that, at this level of sensitivity, there is an 80% probability that the reduction in stunting prevalence would be between 5.5 and 14.6%. A higher sensitivity of 90% would give us more confidence that the diagnostic would have a significant impact on the prevalence of stunting, as there is an 80% probability that the reduction in stunting prevalence would be between 7 and 18.9%, with an average of 12.5%.

It is difficult to provide a clear recommendation for the specificity of the test, due to the uncertainty of the negative and positive externalities associated with treatment. We can, however, make an assumption about these unknowns and consequently provide a recommendation based on that assumption. Assuming that the cost of treatment is US\$6, the only source of harm is the opportunity cost of treatment and there is a positive externality of 0.25 DALYs per treatment, then a test that is 90% sensitive, 90% specific and requires only minimal infrastructure would save a total of 2.8 million DALYs. The cost of treatment is assumed to be high because treatment is complex, and involves both a drug regimen and nutritional supplements. To put this in perspective, US\$6 is comparable to the cost of one 'bed day' in a primary level hospital in sub-Saharan Africa<sup>47</sup>. In addition, the cost of more intensive nutrition programmes is estimated to be between US\$5 and US\$10 per child<sup>48</sup>.

An important caveat is that, due to the large number of treatments, small changes in the cost of treatment and in the DALYs associated with the positive externalities would lead to large changes in the number of DALYs saved, and potentially greater benefits. For example, if the positive and negative externalities were to cancel each other out, the reduction in DALYs associated with such a test would be much larger (equal to 19.2 million DALYs).

The large size of this potential benefit suggests that it is worth gaining a better understanding of the externalities associated with treatment and of the conditions under which such improvements could be realized. It also suggests that preventive strategies for reducing stunting (such as diarrhoea prevention), which do not involve treatment and its associated harm, would be extremely beneficial. It is important to note that all of these findings rely on the assumption that stunting contributes to 50% of the DALYs for diarrhoea, and that the total figure is 306.5 million, which is the median estimate reported by Guerrant and colleagues<sup>9</sup>. The large size of the diarrhoeal disease burden explains why even a small reduction in stunting leads to a large number of DALYs saved.

There are clearly important limitations to our analysis. Epidemiological data on diarrhoeal illnesses worldwide are scarce. In particular, the prevalence of the three pathogens of interest is not well measured, and could vary significantly across and between regions. Moreover, there are few data on correlations among pathogens. Although we modelled the pathogens as independent, there is no way to estimate the strength of that assumption. On the positive side, prevalence parameters exert the least influence on the model outcome. More important are the differential risk of stunting for children with diarrhoea and the efficacy of treatment. An empirical basis exists for the differential risk of stunting, although it is weak. The efficacy of treatment depends on the details of the intervention, some of which are likely to be highly effective but impractical (such as relocating the child to a better environment).

There are two situations in which the introduction of a new test at the individual level would not bring any benefit. The first is the case in which the positive externalities outweigh the negative externalities, which implies that every child should be treated, thereby eliminating the need for a test. This would happen, for example, if the treatment cost US\$5 and was associated

with a benefit of 0.25 DALYs, in addition to the reduced risk of stunting. The second is the case in which the harm of treatment outweighs the positive externalities. This would happen, for example, if the treatment cost \$7 and was associated with a benefit of 0.25 DALYs, in addition to the reduced risk of stunting.

Although it might not be worthwhile introducing an individual-level diagnostic for diarrhoeogenic pathogens, tests could still play a role in reducing the huge burden associated with diarrhoeal diseases. It might simply be more efficient to shift the focus of the intervention from the individual to the community, and from treatment to prevention. It is also important to consider diagnostics not only for the three pathogens of interest in the model, but also for others that cause diarrhoeal illness.

In contrast to the other papers in this series, the benefit of a new diagnostic tool to identify the presence of *C. parvum*, *G. lamblia* and EAggEC in children with diarrhoea is unclear due to the significant uncertainty of the externalities associated with treatment. Although broad upper and lower bounds on the negative externalities can be obtained by estimating the cost of treatment, we are currently unable to estimate the size of the positive externalities (that is, the benefits associated with treatment other than reducing stunting). Although it is plausible that these benefits are large, the degree of uncertainty is substantial. Further research is needed to clarify these uncertainties before recommending the development of this tool.

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### Box 1 | Key messages

- A test requiring minimal infrastructure that is 90% sensitive and 90% specific for each of the pathogens *Giardia lamblia*, *Cryptosporidium parvum* and enteroaggregative *Escherichia coli* (EAggEC) could reduce the prevalence of stunting by 12.5%, and save 2.8 million disability-adjusted life years (DALYs). This result assumes that the cost of treatment is US\$6 and that the positive externalities associated with treatment are equal to 0.25 DALYs.
- Assuming that the negative and positive externalities associated with treatment cancel each other out, such a test could save 19.2 million DALYs.
- The large potential benefits associated with the diagnosis of the pathogens *G. lamblia*, *C. parvum* and EAggEC assume that stunting contributes to 50% of the burden of diarrhoeal diseases, which is assumed to be 306.5 million DALYs.
- Ideally, a new diagnostic for *G. lamblia*, *C. parvum* and EAggEC should require minimal training for use, and no electricity, refrigeration or access to clean water. Stool samples are preferred and the results should be available within 2 h.

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Correspondence and requests for materials should be addressed to K.A.R. (e-mail: karen\_ricci@rand.org)

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