WORKING
PAPER

A Technical Supplement: Reducing Stunting Among Children

The Potential Contribution of Improved Diagnostics

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This is supporting material to Ricci KA, Girosi F, Tarr PI et al. Reducing stunting among children: the potential contribution of diagnostics. Nature S1; 29-38 (2006)

HEALTH

PREFACE

This working paper contains technical material supporting the article by Ricci, et. al. "Reducing stunting among children: the potential contribution of diagnostics" *Nature* S1; 29-38 (2006). It is intended to be read in conjunction with that article. This supplement includes additional material referred to in the published article as well as secondary analyses and tables that were not included in the published paper. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding *Nature* paper, was reviewed by two outside experts and was revised in response to their comments. The work was funded by the Bill & Melinda Gates Foundation to support the Global Health Diagnostics Forum.

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INTRODUCTION

Enteric infections, particularly diarrhea, are significant causes of morbidity and mortality among children aged <5 years in the developing world. Although childhood mortality from diarrheal diseases has decreased substantially since 1980, some evidence suggests that morbidity rates might be increasing[1–5]. The relationships between enteric infections, malnutrition and environmental factors are complex; however, recurrent or persistent diarrheal illnesses have been shown to represent a risk factor for stunting in children aged <5 years in the developing world[8–10,12,16,17]. Epidemiological studies indicate that various pathogens can cause persistent diarrhea, with *Giardia lamblia (G. lamblia)*, *Cryptosporidium parvum (C. parvum)* and enteroaggregative *Escherichia coli* (EAggEC) being frequently implicated[10,17,18]. There is a growing body of evidence documenting the relationship between growth retardation and infections with these pathogens[19–22].

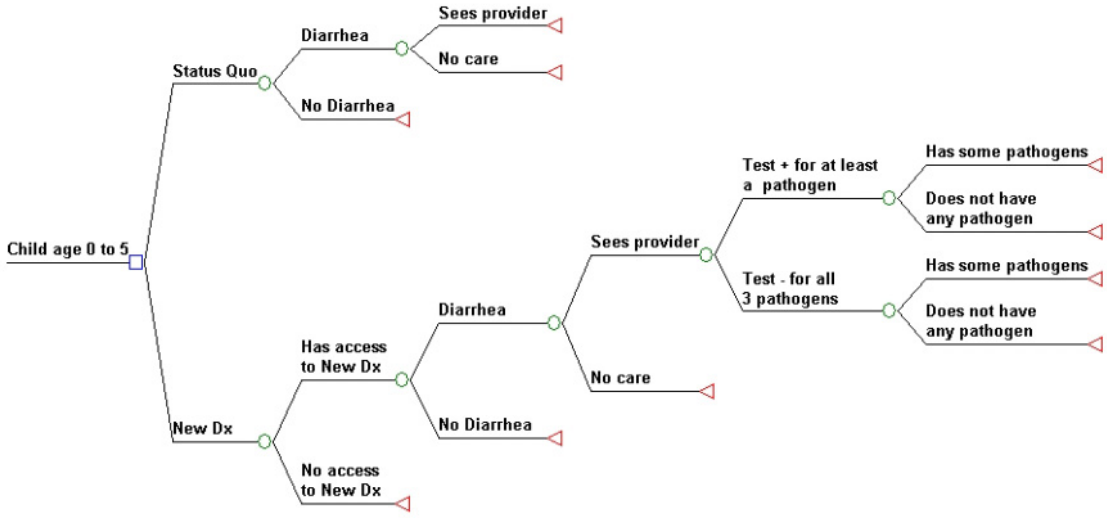
The analysis in Ricci, et. al. "Reducing stunting among children: the potential contribution of diagnostics" *Nature* S1; 29-38 (2006), and the additional materials included here are focused on understanding the potential reduction in morbidity from diarrheal diseases, specifically growth shortfalls or stunting, associated with a new individual-level diagnostic for the enteric pathogens *G. lamblia*, *C. parvum* and EAggEC. 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.

METHODS

Analytic overview

We developed a probability tree model (Fig. 1) 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 diarrhea, 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

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 diarrhea at some point during a period of 3 months. Of those who have diarrhea, 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.



identifying the three pathogens in the general population, regardless of the presence of diarrhea, is discussed later.

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, described in Appendix A, explicitly takes into account the probability of dying or recovering. 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 diarrhea. 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[24–27], it might take >3 months for an individual child to develop stunting following an insult, such as a diarrheal 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. Infrastructure levels are taken from Girosi and colleagues[28]. 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. 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 status and an ideal situation in which everyone lives into old age free of 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).

Modeling diarrheal disease pathogens to reduce stunting in children

In order to quantify the magnitude of the effect of the new test, we start by defining as γ the probability that an average child who is not stunted at some point in time becomes stunted in the next period. Since γ determines the number of new cases in the next period, we may refer to it as incidence in the following sections. Let us define as target population a generic subset of the population of children under age 5, and let P be the probability that a non-stunted child belongs to the target population. Then, in the status quo the probability γ of becoming stunted can be decomposed as:

$$\gamma = \gamma_{\text{target}} P + (1-P)\gamma_{\text{not target}}$$

where γ_{target} and $\gamma_{\text{not target}}$ are the probabilities of becoming stunted in the next period in the target and non-target population respectively. Let us choose as target population the set of children who would be tested and treated if the new diagnostic were introduced. In a world where the new test has been introduced the probability of becoming stunted in this population is reduced by a factor $1 - p_{\text{eff}}$, where p_{eff} is the efficacy of treatment. Therefore in the world with the new test the probability of becoming stunted is:

$$\gamma^{\text{new}} = (1-p_{\text{eff}})\gamma_{\text{target}} P + (1-P)\gamma_{\text{not target}}$$

Using the definition of γ for the status quo we derive the following simple expression:

$$\gamma^{\text{new}} = \gamma\left(1 - p_{\text{eff}} P \frac{\gamma_{\text{target}}}{\gamma}\right)$$

Therefore, as a result of the introduction of the new test the risk of becoming stunted is reduced by a factor p_{eff} P (γ_{target}/γ). It is important to notice that the quantities P, γ_{target} and γ are not independent, and satisfy the constraint P $\gamma_{target} < \gamma$. We refer to the quantity γ_{target}/γ as the "differential risk of stunting for the target population", since it quantifies how much children in the target population are more likely to become stunted, relative to the average population.

The reduction in the probability of becoming stunted now needs to be converted to a more concrete health outcome, such as the prevalence of stunting in the general population. The connection between the risk of becoming stunted and the prevalence of stunting is in principle a complicated one, which also depends on other quantities, such as the probability of recovering from stunting or the probability of dying, which are all age-specific. We originally developed a compartmental model for stunting which allows us to predict changes in prevalence of stunting given changes in the risk of stunting (see Appendix A). However, we found that the large uncertainty of the model parameters makes it of little use, negating the benefit of a more accurate model. Instead, we make the simple assumption that the prevalence of stunting is proportional to the incidence of stunting. Under this assumption a percentage reduction in incidence (γ) leads to an equal percentage reduction in prevalence of stunting. Since we have seen above that the introduction of the new test leads to a percentage reduction in incidence equal to p_{eff} P (γ_{target}/γ), we then conclude the following:

percentage reduction in stunting prevalence = treatment effectiveness x
x size of target population x
x differential risk of stunting

This expression underscores that whenever we design an intervention which introduces the new test, we have to face a trade-off between the size of the target population and the risk of stunting in that population. We want to specifically target high-risk children, since

high differential risk of stunting improves outcome, but the more specific we are the smaller the target population is, worsening outcome.

The Forum experts agreed that children under age 5 with diarrhea and who carry at least one of the three pathogens are much more likely than average children to become stunted, and therefore have a high differential risk of stunting. This makes this population a likely candidate for the target population. However, we must take into account that with the new test we can only reach those children who visit a health facility upon an episode of diarrhea, that not all of those children may have access to the new test and treatment, and that only those who test positive actually receive treatment. Therefore the target population is defined as the set of children who at some point during a three month period have diarrhea, visit a health facility as a consequence, are tested with the new test, and test positive for any of the three pathogens of interest.

Figure 1 illustrates the model for the introduction of a new diagnostic and the sequence of events defining the target population. The upper branches show the status quo, whereas the lower branches depict the world with the new diagnostic. In the latter, children with diarrhea 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 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.

We can now formalize this model as follows. Let $p_{diarrhea}$ be the probability that a child has an episode of diarrhea during a period of three months, p_{hf} the probability that such a child visits a health facility, p^{new}_{hf} the probability that the new test is available at the health facility, p_{path} the prevalence of any pathogen in such children and *sens* the sensitivity of the new test for the detection of any pathogen. Then the probability that a non-stunted child belongs to the target population is:

$$P = p_{\text{diarrhea}} p_{\text{hf}} p^{\text{new}} p_{\text{path}} sens$$

Since P is the product of several probabilities, we expect it to be quite small. This is compensated for by the fact that we are focusing on a high-risk population for which the differential risk of stunting is expected to be high. Denoting by PR the percentage reduction in prevalence of stunting following the introduction of the new test, we have:

$$PR = p_{\text{eff}}\, p_{\text{diarrhea}}\, p_{\text{hf}}\, p^{\text{new}}\, p_{\text{path}}\, sens\left(\gamma_{\text{target}} / \gamma\right)$$

This simple model is now ready to be parameterized.

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 hospitals)[28].

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, for a total of 75%. 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, six Asian and six Latin American countries. The results of this analysis and the precise definition of the different types of infrastructure can be found elsewhere[28]. Estimates of diarrhea 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.

Table 1: Main model parameters for three regions

Parameter	Africa		Asia		Latin America		Reference
	Base	Range	Base	Range	Base	Range	
Epidemiology and prevalence							
Population < 5 years (millions)	142		357		57		United Nations World Population Database*
Diarrhea prevalence (3 month period)	96%	80-100%	84%	70-95%	82%	70-95%	Demographic and Health Surveys†
Prevalence of *C. parvum*	4.4%	1.5-7.2%	4.8%	1.7-8%	7.8%	2.7-12.8%	29
Prevalence of *G. lamblia*	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 diarrhea 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%	Forum Experts' Opinion
Differential risk of stunting for children with diarrhea	3	1.5-4.5	3	1.5-4.5	3	1.5-4.5	Forum Experts' 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*.

The prevalence of *G. lamblia* and *C. parvum* in children with diarrhea was taken from Lanata and Mendoza[29], and are based on an extensive literature search. Data on the prevalence of EAggEC are much scarcer and come from very few settings[7,22,30–39]. 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[14]. 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[40]. 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[41]. Nitazoxanide has been used to treat cryptosporidiosis, and has a good safety profile and an 80% efficacy rate in children[42]. 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 (for example, ampicillin, erythromycin, spectinomycin, streptomycin, tetracycline and trimethoprim/sulfamethoxazole) has been reported[38,39,43]. Ciprofloxacin and rifaximin are potential treatments, but the durability of the susceptibility of EAggEC to these agents has not yet been determined[36,38,39,44]. 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 diarrhea 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 the purpose of discussion we find that it is sufficient to look at the results at the aggregate level, for the entire developing world. However, we report the regional analysis as well in Appendix B.

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[14].

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 diarrheal disease published by Guerrant and colleagues[9]. The estimates take into account the potential lifelong disabilities associated with diarrheal 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 diarrheal disease to stunting, with the understanding that this important assumption is not supported by solid evidence. As a measure of diarrheal disease DALYs, we use 306.5 million globally, which is the median estimate presented by Guerrant and colleagues[9]. This value corresponds to a scenario in which 10% of the children are at risk of at least one diarrheal 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% × 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 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 are lost because of the harm of treatment. 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 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: Sensitivity of outcome with respect to three critical parameters. Reduction in the prevalence of stunting associated with a diagnostic test that is 100% sensitive and 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*.

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 bound 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[14], a reduction of 14% translates to ~21 million stunting cases averted. Using the estimated 306.5 million DALYs associated with diarrheal disease, as reported by Guerrant and colleagues[9], 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.

Figure 2: Distribution of outcomes under Monte Carlo simulation.
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.

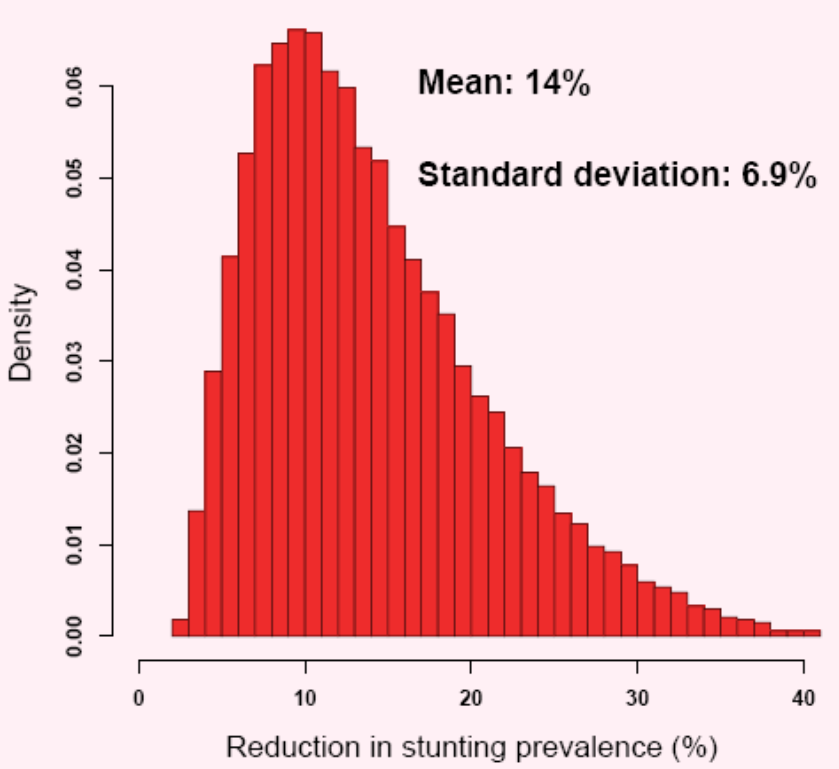


Table 3 demonstrates variation in results if the sensitivity and specificity of the test are changed. The top half of the table reports the results for a test that requires only minimal infrastructure, whereas the lower half of the table reports results for a test that requires moderate/advanced infrastructure. 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 report the tenth and ninetieth percentiles of the distribution of outcome obtained with a Monte-Carlo simulation[45]. 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.

Table 3: Attributable benefit of a new diagnostic test in children with diarrhea, assuming no externalities associated with treatment.

	Test	Sensitivity (%)	Specificity (%)	Reduction in prevalence of stunting (%)*	Stunting cases averted (M)	Number of Treatments (M)	DALYs saved by reduction in stunting (M) †
Minimal Infrastructure‡							
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	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)*
Moderate/Advanced Infrastructure‡							
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)*

*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. †These correspond to the DALYs saved under the assumption that the negative and positive externalities associated with treatment cancel out, that the total DALYs for diarrhea are 306.5 million, and that stunting contributes to 50% of the diarrheal disease burden. ‡A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and is able to 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 more details on calculating the percentage of people with access to a new diagnostic requiring minimal or moderate/advanced infrastructure.

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, 100% specific test would lead to 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 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^{treat} be the cost of treatment for this intervention and C^{ce} 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 $C = C^{treat}/C^{ce}$.

Assuming that a treatment with 50% efficacy costs between US$1 and US$10, and that at least one intervention[46] can save one DALY with $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 diarrhea would need to have a benefit of 0.25 DALYs, in addition to the benefit from 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 (`externalities.xls`) that allows the user to see how changes in the assumptions about negative and positive externalities affect the results of Table 3 has been made available with this document.

Too little is known regarding 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 diarrhea who carry any of the three pathogens are at higher risk of stunting than average, 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 diarrhea. This is a larger population, but it has a lower risk of stunting because only one risk factor (pathogens) is present instead of two risk factors (pathogens and diarrhea). This population could be reached with a screening program: 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 diarrhea compared with the general population. In fact, in this scenario the percentage reduction in prevalence of stunting is simply as follows:

$$PR = p_{\text{eff}}\left(f/4\right)p^{\text{new}}\,p_{\text{screen}}\overline{p}_{\text{path}}sens$$

where f is the *annual* screening frequency, the factor 4 accounts for the fact that our time period is three months and therefore there are 4 periods in a year, p_{screen} is the percentage of the population screened and $\overline{p}_{\text{path}}$ is the prevalence of any pathogen in the general population. It is now possible to compare the reduction in stunting under this scenario to the one obtained using our main scenario. In particular, we can find the screening frequency that would make the two scenarios identical. Equating the percentage reduction in stunting under both scenarios we obtain:

$$p_{\text{eff}}\, p_{\text{diarrhea}}\, p_{\text{hf}}\, p^{\text{new}}\, p_{\text{path}}\, sens\left(\gamma_{\text{target}}/\gamma\right) = p_{\text{eff}}\left(f/4\right) p^{\text{new}}\, p_{\text{screen}}\, \overline{p}_{\text{path}}\, sens$$

Solving for the screening frequency f we have:

$$f = \frac{4 p_{\text{diarrhea}}\, p_{\text{hf}}\, p_{\text{path}}}{p_{\text{screen}}\, \overline{p}_{\text{path}}}\left(\gamma_{\text{target}}/\gamma\right)$$

For the purpose of this computation, let us assume that pathogens are only 20% more likely to be found in children with diarrhea than in the general population so we set $p_{\text{path}}/\overline{p}_{\text{path}} = 1.2$. Similarly, we make a very mild assumption on the differential risk of stunting and also set it to 1.2 (we use values between 1.5 and 4.5 in our simulations). If we assume that only half of the population gets screened, so that $p_{\text{screen}} = 0.5$, and using an average access to a health facility of 40%, then screening should occur 4.4 times a year. This is not practical and this 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 diarrhea, proportion of children with diarrhea 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 of 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.

For a discussion of results, please see Ricci, et. al. "Reducing stunting among children: the potential contribution of diagnostics" *Nature* S1; 29-38 (2006).

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REFERENCES

1. Kosek, M., Bern, C. & Guerrant, R. L. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull. World Health Organ.* **81**, 197–204 (2003).

2. Guerrant, R. L. *et al.* Magnitude and impact of diarrheal diseases. *Arch. Med. Res.* **33**, 351–355 (2002).

3. Pierce, N. F. How much has ORT reduced child mortality? *J. Health Popul. Nutr.* **19**, 1–3 (2001).

4. Thielman, N. M. & Guerrant, R. L. Clinical practice. Acute infectious diarrhea. *N. Engl. J. Med.* **350**, 38–47 (2004).

5. Victora, C. G., Bryce, J., Fontaine, O. & Monasch, R. Reducing deaths from diarrhoea through oral rehydration therapy. *Bull. World Health Organ.* **78**, 1246–1255 (2000).

6. Moore, S. R. *et al.* Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering. *Int. J. Epidemiol.* **30**, 1457–1464 (2001).

7. Vu Nguyen, T., Le Van, P., Le Huy, C., Nguyen Gia, K. & Weintraub, A. Etiology and epidemiology of diarrhea in children in Hanoi, Vietnam. *Int. J. Infect. Dis.* **10**, 298–308 (2006).

8. Berkman, D. S., Lescano, A. G., Gilman, R. H., Lopez, S. L. & Black, M. M. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. *Lancet* **359**, 564–571 (2002).

9. Guerrant, R. L., Kosek, M., Lima, A. A., Lorntz, B. & Guyatt, H. L. Updating the DALYs for diarrhoeal disease. *Trends Parasitol.* **18**, 191–193 (2002).

10. Guerrant, R. L., Schorling, J. B., McAuliffe, J. F. & de Souza, M. A. Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration. *Am. J. Trop. Med. Hyg.* **47**, 28–35 (1992).

11. Niehaus, M. D. *et al.* Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. *Am. J. Trop. Med. Hyg.* **66**, 590–593 (2002).

12. Schorling, J. B. & Guerrant, R. L. Diarrhoea and catch-up growth. *Lancet* **335**, 599–600 (1990).

13. Nato, F. *et al.* One-step immunochromatographic dipstick tests for rapid detection of *Vibrio cholerae* O1 and O139 in stool samples. *Clin. Diagn. Lab. Immunol.* **10**, 476–478 (2003).
14. de Onis, M., Blossner, M., Borghi, E., Morris, R. & Frongillo, E. A. Methodology for estimating regional and global trends of child malnutrition. *Int. J. Epidemiol.* **33**, 1260–1270 (2004).
15. Adair, L. S. & Guilkey, D. K. Age-specific determinants of stunting in Filipino children. *J. Nutr.* **127**, 314–320 (1997).
16. Black, R. E., Brown, K. H. & Becker, S. Effects of diarrhea associated with specific enteropathogens on the growth of children in rural Bangladesh. *Pediatrics* **73**, 799–805 (1984).
17. Schorling, J. B. *et al.* A prospective study of persistent diarrhea among children in an urban Brazilian slum. Patterns of occurrence and etiologic agents. *Am. J. Epidemiol.* **132**, 144–156 (1990).
18. McAuliffe, J. F. *et al.* Prolonged and recurring diarrhea in the northeast of Brazil: examination of cases from a community-based study. *J. Pediatr. Gastroenterol. Nutr.* **5**, 902–906 (1986).
19. Checkley, W., Epstein, L. D., Gilman, R. H., Cabrera, L. & Black, R. E. Effects of acute diarrhea on linear growth in Peruvian children. *Am. J. Epidemiol.* **157**, 166–175 (2003).
20. Checkley, W. *et al.* Effects of *Cryptosporidium parvum* infection in Peruvian children: growth faltering and subsequent catch-up growth. *Am. J. Epidemiol.* **148**, 497–506 (1998).
21. Lima, A. A. *et al.* Persistent diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort study among children in northeastern Brazil. *J. Infect. Dis.* **181**, 1643–1651 (2000).
22. Steiner, T. S., Lima, A. A., Nataro, J. P. & Guerrant, R. L. Enteroaggregative *Escherichia coli* produce intestinal inflammation and growth impairment and cause interleukin-8 release from intestinal epithelial cells. *J. Infect. Dis.* **177**, 88–96 (1998).
24. Karlberg, J., Jalil, F., Lam, B., Low, L. & Yeung, C. Y. in *Causes and Mechanisms of Linear Growth Retardation. Proceedings of an I/D/E/C/G Workshop held in London*,

U.K. (eds Waterlow, J. C. & Schürch, B.) [online] <http://www.unu.edu/unupress/food2/UID06E/uid06e09.htm> (15-18 January 1993).

25. Maleta, K., Virtanen, S. M., Espo, M., Kulmala, T. & Ashorn, P. Seasonality of growth and the relationship between weight and height gain in children under three years of age in rural Malawi. *Acta Paediatr.* **92**, 491–497 (2003).

26. Stoltzfus, R. J., Albonico, M., Tielsch, J. M., Chwaya, H. M. & Savioli, L. Linear growth retardation in Zanzibari school children. *J. Nutr.* **127**, 1099–1105 (1997).

27. Maleta, K. in *Acta Universitatis Tamperensis.* Thesis, Univ. Tampere [online] http://acta.uta.fi/english/teos.phtml?8377 (2003).

28. Girosi, F. *et al.* Developing and interpreting models to improve diagnostics in developing countries. *Nature* **SI**, 3-8 (2006).

29. Lanata, C. & Mendoza, W. *Improving Diarrhoea Estimates* (WHO, Geneva, 2002).

30. Adachi, J. A. *et al.* Enteroaggregative *Escherichia coli* as a major etiologic agent in traveler's diarrhea in 3 regions of the world. *Clin. Infect. Dis.* **32**, 1706–1709 (2001).

31. Bhan, M. K. *et al.* Enteroaggregative *Escherichia coli* and *Salmonella* associated with nondysenteric persistent diarrhea. *Pediatr. Infect. Dis. J.* **8**, 499–502 (1989).

32. Germani, Y., Begaud, E., Duval, P. & Le Bouguenec, C. Prevalence of enteropathogenic, enteroaggregative, and diffusely adherent *Escherichia coli* among isolates from children with diarrhea in new Caledonia. *J. Infect. Dis.* **174**, 1124–1126 (1996).

33. Lima, A. A. *et al.* Persistent diarrhea in Northeast Brazil: etiologies and interactions with malnutrition. *Acta Paediatr.* **81 (suppl 381)**, 39–44 (1992).

34. Sarantuya, J. *et al.* Typical enteroaggregative *Escherichia coli* is the most prevalent pathotype among *E. coli* strains causing diarrhea in Mongolian children. *J. Clin. Microbiol.* **42**, 133–139 (2004).

35. Cohen, M. B. *et al.* Prevalence of diarrheagenic *Escherichia coli* in acute childhood enteritis: a prospective controlled study. *J. Pediatr.* **146**, 54–61 (2005).

36. Glandt, M. *et al.* Enteroaggregative *Escherichia coli* as a cause of traveler's diarrhea: clinical response to ciprofloxacin. *Clin. Infect. Dis.* **29**, 335–338 (1999).

37. Nataro, J. P. Enteroaggregative *Escherichia coli* pathogenesis. *Curr. Opin. Gastroenterol.* **21**, 4–8 (2005).

38. Sang, W. K. *et al.* Multidrug-resistant enteroaggregative *Escherichia coli* associated with persistent diarrhea in Kenyan children. *Emerg. Infect. Dis.* **3**, 373–374 (1997).
39. Yamamoto, T., Echeverria, P. & Yokota, T. Drug resistance and adherence to human intestines of enteroaggregative *Escherichia coli*. *J. Infect. Dis.* **165**, 744–749 (1992).
40. Zaat, J. O., Mank, T. G. & Assendelft, W. J. A systematic review on the treatment of giardiasis. *Trop. Med. Int. Health* **2**, 63–82 (1997).
41. Escobedo, A. A. *et al.* Comparison of chloroquine, albendazole and tinidazole in the treatment of children with giardiasis. *Ann. Trop. Med. Parasitol.* **97**, 367–371 (2003).
42. Ortiz, J. J., Ayoub, A., Gargala, G., Chegne, N. L. & Favennec, L. Randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from Northern Peru. *Aliment Pharmacol. Ther*. **15**, 1409–1415 (2001).
43. Haider K, F. S. *et al.* Enteroaggregative *Escherichia coli* infections in Bangladeshi children: clinical and microbiological features. *J. Diarrhoeal Dis. Res.* **9**, 318–322 (1991).
44. Wanke, C. A., Gerrior, J., Blais, V., Mayer, H. & Acheson, D. Successful treatment of diarrheal disease associated with enteroaggregative *Escherichia coli* in adults infected with human immunodeficiency virus. *J. Infect. Dis.* **178**, 1369–1372 (1998).
45. Doubillet, P., Begg, C. B., Weinstein, M. C., Braun, P. & McNeil, B. J. Probabilistic sensitivity analysis using Monte Carlo simulation: a practical approach. *Med. Decis. Making* **5**, 157–177 (1985).
46. Adam, T. *et al.* Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. *BMJ* **331**, 1107 (2005).
47. Mulligan, J.-A., Fox-Rushby, J. A., Adam, T., Johns, B. & Mills, A. *Unit Costs of Healthcare Inputs in Low and Middle Income Regions. DCPP Working Paper No. 9* [online].http://www.dcp2.org/file/24/wp9.pdf (June 2005)
48. Caulfield, L. E., Richard, S. A., Rivera, J. A., Musgrove, P. & Black, R. E. in *Disease Control Priorities in Developing Countries* (eds Jamison, D. T. *et al*.) [online] http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dcp2.chapter.3990> (Oxford Univ. Press, Washington, DC, 2006).

APPENDIX A:

A MORE COMPLEX COMPARTMENTAL MODEL

Our original approach was to explicitly model the dynamics of stunting: we would model a population of children going in and out of the stunting state according to certain transition probabilities, and the output of the model would be the age profile of stunting prevalence. Diagnostic interventions would affect those transition probabilities, and therefore would change the age profile of stunting prevalence. By comparing the stunting prevalence in a world with and without the diagnostic intervention we could compute the benefit of the diagnostic. In particular, we would be able to relate a change in the probability of becoming stunted (denoted by γ in the paper, and referred to as the incidence of stunting) to a change in prevalence of stunting.

While this approach is quite general, we found that we do not have enough data to parameterize the model, and therefore the advantage of having a more precise model is lost. For this reason we decided to assume that the prevalence of stunting is simply proportional to the incidence of stunting. This implies that a percentage reduction in incidence leads to an equal percentage reduction in prevalence.

While we eventually ended up not using the more complex compartmental model, it is still worth writing down the main equations, which could serve as the basis for future work, once a better understanding of the main parameters has been gained.

The standard compartmental model with two groups, death, "infection" and recovery is written as follows:

$$\begin{aligned} S_{a+1} &= S_a\left(1-m_a^s-\delta_a\right)+\gamma_a NS_a \\ S_0 &= 0 \\ NS_{a+1} &= NS_a\left(1-m_a^{ns}-\gamma_a\right)+\delta_a S_a \\ NS_0 &= b_0 \end{aligned} \tag{1}$$

where we have defined the following quantities:

- S_a: number of stunted children of age a;
- NS_a: number of non-stunted children of age a;

- m_a^s: mortality rate for stunted children of age *a*;
- m_a^{ns} : mortality rate for non-stunted children of age *a*;
- γ_a: probability of becoming stunted at age *a*+1 conditional on not being stunted at age *a* (incidence);
- δ_a: probability of recovering from stunting at age *a*+1 is stunted at age *a*;
- b_0: the number of children born each period.

Here age is measured in units of 3 months, so that age *a*+1 is equivalent to age *a* plus three months. Equation 1 simply says that children who are stunted can exit that state by either dying, at rate m_a^s or by recovering, at rate δ_a. Children who are not stunted can exit that state by either dying, at rate m_a^{ns}, or by becoming stunted, at rate γ_a. Notice that the initial condition is $S_0 = 0$ and that all the b_0 children born each period are not stunted.

Since we are interested in the prevalence of stunting, we wish to rewrite equation 1 so that we can derive an equation for this quantity. We start by converting 1 to a set of differential equations:

$$\begin{aligned}
&\frac{dS}{da} = -\left(m^s(a) + \delta(a)\right)S + \gamma(a)NS \\
&S(0) = 0 \\
&\frac{dNS}{da} = -\left(m^{ns}(a) + \gamma(a)\right)NS + \delta(a)S \\
&N(0) = b_0
\end{aligned} \tag{2}$$

Summing the equations for stunted and non-stunted children we obtain an equation for the size of the entire population, which we denote by *N*:

$$\begin{aligned}
&\frac{dN}{da} = -m^s(a)S - m^{ns}(a)NS = -m^s(a)S - m^{ns}(a)(N - S) \\
&N(0) = b_0
\end{aligned} \tag{3}$$

Denoting the prevalence of stunting by $p \equiv \frac{S}{N}$, we have:

$$\frac{dp}{da} = \frac{1}{N}\frac{dS}{da} - \frac{S}{N^2}\frac{dN}{da} \tag{4}$$

Substituting the expression of equation 2 and 3 in equation 4 we find, after some algebra:

$$\frac{dp}{da} = -p\left[\left(m^s(a) - m^{ns}(a)\right)(1-p) + \delta(a) + \gamma(a)\right] + \gamma(a) \qquad (5)$$

Equation 5 shows that the age prevalence of stunting only depends on three sets of parameters: the differential mortality between stunted and non-stunted children, the rate of recovery from stunting (δ), and the incidence of stunting (γ). It is interesting to notice that the prevalence does not depend on the overall level of mortality.

If we knew the values of the parameters of equation 5 for a certain region we could integrate the differential equation and reproduce the status quo age profile of the prevalence of stunting. Then, using the model described in an earlier section we could simulate the introduction of a diagnostic and treatment for any of the three pathogens of interest, altering the value of γ, and estimating the corresponding change in prevalence of stunting. Unfortunately the age-dependent parameters appearing in equation 5 are largely unknown, in particular the values of γ and δ. Although in principle some of these parameters can be estimated empirically using observed data on the prevalence of stunting, the problem remains highly underdetermined. Therefore this more principled approach it is not of high value, at least not until we have a better understanding of the crucial parameters of equation 5.

Equation 5 is a quadratic differential equation with non-constant coefficients for which a solution is not known. However, there is one case in which we can gain insight in the shape of the solution - that is when the differential mortality risk is 0. In this case the equation becomes a linear differential equation with non-constant coefficients, for which the general form of the solution is known:

$$p(a) = \int_0^a \gamma(s) e^{-\int_s^a (\delta(z)+\gamma(z))dz} ds \qquad (6)$$

Equation 6 shows that, under the assumption of no differential mortality risk, the prevalence of stunting is, at least at the first order, proportional to the risk of stunting γ. This proportionality has been assumed throughout our analysis, and it seems useful to know at least some conditions under which it is correct.

APPENDIX B:

REGIONAL ANALYSIS

In this appendix we report, for completeness, the results of the regional analysis. The following tables have the same format of Table 3, and do not require a special discussion since they are qualitatively similar to it. The only notable thing is that the benefit of the diagnostic would be higher in Asia and Latin America than in Asia. This is because in Africa access to health facilities is more limited, and therefore fewer people would benefit from the test.

Table B1: Africa - attributable benefit of a new diagnostic test in children with diarrhea, assuming no externalities associated with treatment.

	Test	Sensitivity (%)	Specificity (%)	Reduction in prevalence of stunting (%)*	Stunting cases averted (M)	Number of Treatments (M)	DALYs saved by reduction in stunting (M) †
Minimal Infrastructure‡							
1	Perfect test	100	100	10.5 (4.7 - 17.8)	5.1 (2.3 - 8.7)	40.0 (26.9 - 54.6)	4.1 (1.8 – 7)
2	Low Sensitivity/Perfect Specificity	70	100	7.1 (3.1 - 12.4)	3.5 (1.5 - 6.1)	28.6 (19.1 – 39.8)	2.8 (1.2 - 4.8)
3	Perfect Sensitivity/Low Specificity	100	70	10.6 (4.6 - 18.9)	5.2 (2.3 - 9.2)	96.1 (71.1 – 120)	4.2 (1.8 - 7.4)
4	Good Sensitivity and Specificity	90	90	9.5 (4.4 - 15.2)	4.6 (2.1 - 7.5)	61.0 (44.6 - 77.2)	3.7 (1.7 – 6)
Moderate/Advanced Infrastructure‡							
5	Perfect test	100	100	4.0 (1.7 – 6.9)	2.0 (0.8 - 3.4)	14.9 (9.9 - 20.4)	1.6 (0.7 - 2.7)
6	Low Sensitivity/Perfect Specificity	70	100	2.7 (1.2 - 4.4)	1.3 (0.6 - 2.2)	10.6 (7.1 - 14.5)	1.0 (0.5 - 1.7)
7	Perfect Sensitivity/Low Specificity	100	70	3.9 (1.7 - 6.7)	1.9 (0.9 - 3.3)	36.4 (27.2 - 44.8)	1.5 (0.7 - 2.6)
8	Good Sensitivity and Specificity	90	90	3.6 (1.6 - 6.1)	1.8 (0.8 – 3)	22.7 (16.6 - 28.7)	1.4 (0.6 - 2.4)

*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. †These correspond to the DALYs saved under the assumption that the negative and positive externalities associated with treatment cancel out, that the total DALYs for diarrhea in Africa are 78.2 million, and that stunting contributes to 50% of the diarrheal disease burden. ‡A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and is able to 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 more details on calculating the percentage of people with access to a new diagnostic requiring minimal or moderate/advanced infrastructure.

Table B2: Asia - attributable benefit of a new diagnostic test in children with diarrhea, assuming no externalities associated with treatment.

	Test	Sensitivity (%)	Specificity (%)	Reduction in prevalence of stunting (%)*	Stunting cases averted (M)	Number of Treatments (M)	DALYs saved by reduction in stunting (M) †
Minimal Infrastructure‡							
1	Perfect test	100	100	15.8 (6.8 - 26.1)	14.5 (6.2 - 24)	150.8 (99.7 - 208)	15.6 (6.7 - 25.7)
2	Low Sensitivity/Perfect Specificity	70	100	10.8 (4.7 - 18.4)	9.9 (4.3 - 16.9)	109.4 (73.2 - 147.4)	10.6 (4.6 - 18.1)
3	Perfect Sensitivity/Low Specificity	100	70	15.7 (6.9 - 27.2)	14.4 (6.3 - 24.9)	384.6 (286.6 - 493.8)	15.4 (6.8 - 26.8)
4	Good Sensitivity and Specificity	90	90	14.6 (6.3 - 25.5)	13.4 (5.8 - 23.4)	236.4 (174.7 - 299)	14.4 (6.2 - 25.1)
Moderate/Advanced Infrastructure‡							
5	Perfect test	100	100	10.7 (4.9 - 18.2)	9.9 (4.5 - 16.7)	101.3 (67.8 - 139.5)	10.6 (4.9 - 17.9)
6	Low Sensitivity/Perfect Specificity	70	100	7.1 (3.1 - 12.2)	6.5 (2.9 - 11.2)	72.2 (49.5 - 99.1)	7.0 3.1 - 12)
7	Perfect Sensitivity/Low Specificity	100	70	10.5 (4.8 - 18)	9.7 (4.4 - 16.6)	258.3 (193.2 - 326.9)	10.4 (4.7 - 17.8)
8	Good Sensitivity and Specificity	90	90	9.4 (4.2 - 15.8)	8.6 (3.8 - 14.5)	158.1 (116.6 - 204.1)	9.3 (4.1 - 15.5)

*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. †These correspond to the DALYs saved under the assumption that the negative and positive externalities associated with treatment cancel out, that the total DALYs for diarrhea in Asia are 196.8 million, and that stunting contributes to 50% of the diarrheal disease burden. ‡A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and is able to 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 more details on calculating the percentage of people with access to a new diagnostic requiring minimal or moderate/advanced infrastructure.

Table B3: Latin America - attributable benefit of a new diagnostic test in children with diarrhea, assuming no externalities associated with treatment.

	Test	Sensitivity (%)	Specificity (%)	Reduction in prevalence of stunting (%)*	Stunting cases averted (M)	Number of Treatments (M)	DALYs saved by reduction in stunting (M) †
Minimal Infrastructure‡							
1	Perfect test	100	100	14.3 (6.3 - 24.5)	1.0 (0.4 - 1.6)	21.9 (14.8 - 29.7)	1.6 (0.7 - 2.8)
2	Low Sensitivity/Perfect Specificity	70	100	9.6 (4.3 - 16.1)	0.6 (0.3 - 1.1)	16.1 (10.4 - 21.7)	1.1 (0.5 - 1.9)
3	Perfect Sensitivity/Low Specificity	100	70	14.6 (6.8 - 24.9)	1.0 (0.5 - 1.7)	45.1 (33.5 - 56.4)	1.7 (0.7 – 3)
4	Good Sensitivity and Specificity	90	90	13.1 (6.1 - 21.9)	0.9 (0.4 - 1.5)	29.9 (22.1 - 38.3)	1.5 (0.7 - 2.4)
Moderate/Advanced Infrastructure‡							
5	Perfect test	100	100	13.9 (6.1 - 23.4)	0.9 (0.4 - 1.6)	21.0 (14.3 - 27.9)	0.6 (0.3 - 1.1)
6	Low Sensitivity/Perfect Specificity	70	100	9.1 (4.2 - 15.5)	0.6 (0.3 - 1)	15.3 (10.1 - 20.8)	0.4 (0.2 - 0.7)
7	Perfect Sensitivity/Low Specificity	100	70	13.6 (6.1 - 23.2)	0.9 (0.4 - 1.6)	42.6 (31.9 - 52.9)	0.6 (0.3 - 1.1)
8	Good Sensitivity and Specificity	90	90	12.1 (5.4 - 20.7)	0.8 (0.4 - 1.4)	28.3 (20.7 - 36.2)	0.6 (0.2 - 1)

*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. †These correspond to the DALYs saved under the assumption that the negative and positive externalities associated with treatment cancel out, that the total DALYs for diarrhea in Latin America are 31.4 million, and that stunting contributes to 50% of the diarrheal disease burden. ‡A test can be performed in a setting with minimal infrastructure if it does not require water or electricity and is able to 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 more details on calculating the percentage of people with access to a new diagnostic requiring minimal or moderate/advanced infrastructure.