Reducing the global burden of acute lower respiratory infections in children: the contribution of new diagnostics

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PREFACE

Acute lower respiratory infections (ALRIs) are the primary cause of death among children aged <5 years in developing countries, despite increased access to antibiotics. Many children with ALRIs fail to receive adequate care, and overuse of antibiotics has led to an increase in drug-resistant bacteria. An accurate, easy-to-use and widely available new diagnostic test could improve the identification of bacterial ALRI among children, thereby reducing the inappropriate use of antibiotics and the long-term negative impacts of drug resistance. A new diagnostic test for severe ALRI could also reduce mortality if access to hospital care is significantly increased.

INTRODUCTION

ALRI is the leading cause of childhood mortality and morbidity. For the purposes of this paper, we use the term ALRI to refer to viral or bacterial bronchiolitis or pneumonia, which is defined as the infection of lung parenchyma and includes bronchopneumonia and lobar pneumonia. A recent study by the Child Health Epidemiology Reference Group (CHERG) estimated that from 2000 to 2003, ALRI contributed annually to the deaths of >2 million children aged <5 years, 75% of whom were in Africa and southeast Asia[1]. Despite some progress in reducing the number of ALRI-related deaths in developing countries, many children are still not being diagnosed or are not receiving adequate care. Bacterial ALRI is easily treatable with antibiotics, whereas more severe cases of ALRI require hospitalization for intravenous antibiotics, oxygen therapy or inpatient supportive care.

Although many children do not receive adequate care for ALRI, others with similar symptoms but without antibiotic-treatable infection receive unnecessary therapy. Over-prescription of antibiotics by both qualified and unqualified medical practitioners is common in developing countries[2], and self-medication through the purchase of antibiotics from drug vendors and pharmacies is also widespread[3,4]. The overuse of antibiotics has increased resistance among common ALRI-causing bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. The former was once universally sensitive to penicillin, but is now only ~50% sensitive in many countries and <25% sensitive in some[3]. Moreover, multiple drug resistance is increasing; for example, 25.5% of *S. pneumoniae* strains in South Africa, 53.2% in the Far East and 21.1% in Mexico are resistant to any three classes of drugs, excluding penicillin, from among the following: β-lactams, macrolides, tetracyclines, phenicols, folate-pathway inhibitors and quinolones. For *H. influenzae* type b, resistance rates to penicillin and amoxicillin of 30–50% have been reported in Indonesia, Singapore, Thailand, the Philippines and Vietnam, 25–30% in Argentina and Venezuela, and ≤50% in hospital isolates in Guatemala[4].

The prevalence of antibiotic resistance probably reduces the possibility of treating ALRI effectively (that is, significantly altering the probability of death) and increases the risk of complications and mortality. Resistant strains of bacteria can quickly multiply and spread within a community where antibiotic use is common. In addition, the failure of first-line treatments prompts health-care workers to seek more-expensive and often less-available antibiotics. For example, the management of meningitis must be adjusted even in response to low levels of resistance among circulating strains of *S. pneumoniae* and *H. influenzae*. Consequently, antibiotic resistance often results in various societal costs, including increased drug costs, additional health-service costs (such as laboratory tests and hospitalizations), greater drug resistance-related morbidity and mortality, and productivity losses.

The high incidence of childhood ALRI deaths and the growth of antibiotic resistance are due, in part, to the shortcomings of current diagnostic methods. The most common way of diagnosing ALRI in resource-limited countries is through clinical assessment as part of case management. Over the past 20 years, many countries have implemented case-management algorithms developed by the World Health Organization (WHO), and evidence indicates that these protocols have

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helped to reduce the number of deaths due to ALRI[5]. Recently, protocols for the management of ALRI have been incorporated into the Integrated Management of Childhood Illness (IMCI) approach, which seeks to train providers at the primary care level to better manage the conditions of children presenting at health-care facilities. ALRI guidelines train providers to look for two key clinical signs: elevated respiratory rate and inward movement of the lower chest wall on breathing. Community health workers with basic training in the protocol use an algorithm to diagnose bacterial ALRI cases that require antibiotic treatment and severe ALRI cases that require referral for hospital care.

Although the IMCI approach has helped to further the diagnosis and management of ALRI, the large number of related deaths in developing countries demonstrates that better diagnostic tools and treatment approaches are needed. To address these issues, the Global Health Diagnostics Forum convened by the Bill & Melinda Gates Foundation established a working group of international ALRI experts to identify diagnostic intervention points and evaluate the potential health benefits of hypothetical new tests in resource-limited settings. The current paper presents our findings.

We quickly came to the consensus that a new diagnostic test that focused on the identification of bacterial ALRI in young children might have a significant impact on survival by guiding individual treatment. We discussed other possible modelling scenarios, such as the use of a diagnostic test to identify antibiotic resistance as a means of guiding appropriate antibiotic use, and the possibility of combining an individual diagnostic test with a research function (such as collecting epidemiological data on pathogens to estimate pathogen-specific disease burden and, therefore, to guide future vaccine-development priorities). However, these were felt to be of a lower immediate priority than improving the accuracy of ALRI diagnosis for children.

We therefore decided to explore two scenarios in which better diagnostic technology could potentially reduce the burden of ALRI among children aged <5 years: first, the diagnosis of bacterial ALRI cases without necessarily identifying specific pathogens (the bacterial ALRI test); and second, the diagnosis of severe ALRI requiring referral to a hospital (the severe ALRI test). We hypothesized that the former would reduce the inappropriate use of antibiotics and might facilitate broader access to antibiotic treatment in some areas, and that the latter would reduce mortality among children who could benefit from inpatient support (such as supplemental oxygen and intravenous antibiotics) and would minimize unnecessary referral, which is costly for both the family and the community, and can be dangerous (see below).

METHODS

Analytic overview

We have developed decision-tree models to quantify the potential health benefits of new tests for bacterial and severe ALRI among children aged <5 years in Africa, Asia and Latin America. The analyses compare outcomes associated with current practice (that is, the status quo) to those associated with new tests. The outcomes include lives saved due to better diagnosis and reduction in overtreatment, and are a function of the test characteristics (sensitivity and specificity), the associated infrastructure requirements (advanced/moderate, minimal or none) and, when applicable, the level of access to effective hospital care. We have varied the assumptions about the model input parameters extensively in the sensitivity analyses to test the robustness of our results. The outcomes are estimated by calculating the incremental number of true-positive and false-positive cases of bacterial or severe ALRI relative to the status quo following the introduction of a new diagnostic test. One of our outcomes of interest is the number of children saved due to increased true-positive rates. We refer to this outcome as individual lives saved, to emphasize the fact that it relates to individual children. The number of individual lives saved is computed using data from the published literature and the opinions of experts from the working group on the risk of ALRI-related mortality in treated and untreated children.

We also calculate a societal outcome that considers the harm associated with unnecessary treatment. We quantify the harm of treatment in terms of the fraction of lives lost due to the treatment of one child. As these lives are lost as the result of indirect and unintended effects of treatment, we refer to them as indirect lives lost. The reduction in indirect lives lost associated with a reduction in the number of treatments is described as indirect lives saved. Indirect lives are a public-health concept: one indirect life cannot be matched to one particular individual. We also note that indirect lives are saved conditional on some behavioural assumptions (for example, that health-care workers will not find alternative reasons for prescribing antibiotics). Details of the method used to quantify the harm of treatment were reported by Girosi and co-workers[6], and specific calculations of the harm of treatment for bacterial and severe ALRI were described by Lim and colleagues[7].

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In addition to individual and indirect lives saved, we also consider the number of unnecessary treatments saved. By multiplying this number by the cost of treatment in US$, we can derive the treatment cost savings associated with the introduction of the new test.

Modelling a new diagnostic test for bacterial ALRI

Figure 1 presents the decision tree for bacterial ALRI. The model focuses on children with acute respiratory infection (ARI) symptoms that are severe enough to trigger health-care-seeking behaviour. We assume that ~33% of ARI episodes are severe enough to motivate caregivers to seek help, and that all cases of bacterial and severe ALRI fall into this category.

In the status quo (the upper branches of the tree), we account for three possible clinical paths. First, in a limited proportion of cases that vary by region, the caregiver might take the child to a trained provider, who then performs a clinical diagnosis. This is modelled as a test for bacterial ALRI with the same sensitivity and specificity as the clinical algorithm-based guidelines (for example, the IMCI guidelines). Children identified as having bacterial ALRI are treated with antibiotics and have a lower case-fatality rate than those who do not receive treatment. Second, in some countries antibiotics are readily available (for example, from a local pharmacy or drug vendor) and some caregivers might self-treat a child with antibiotics without seeking formal care. We model self-treatment as a test that is 100% sensitive and 0% specific. All children in this group are assigned the case-fatality rate of treated bacterial ALRI. Third, in many cases the caregiver is unable to provide any type of effective help. All children in this group are assigned the case-fatality rate of untreated bacterial ALRI. This category includes those who have no physical access to any type of care, as well as those who might have physical access but do not have the resources or knowledge to access care, and those who have access to ineffective forms of care (for example, expired or otherwise ineffective antibiotics, or treatment with ineffective traditional herbal medicine).

The lower branch shown in Fig. 1 illustrates the introduction of a hypothetical new diagnostic test for bacterial ALRI. In this scenario, the population is first divided into children with and without access to the new diagnostic, and then into the three access categories found in the status quo (as described above). We assume that when a new test is introduced, children who have access to a trained provider in the status quo receive it first, followed by those who self-treat and finally those who have no access to effective care[6]. In other words, access to the new test is correlated with levels of access to care, as found in the status quo. We also assume that, given access to the new diagnostic test, it would be used in children only if the outcomes for society were better than the status quo.

Modelling a new diagnostic test for severe ALRI

Figure 2 shows the decision tree for severe ALRI. In this scenario, a child with ARI symptoms that are severe enough to trigger health-care-seeking behaviour is either taken to a health provider (trained or untrained) or does not receive effective care. Trained and untrained providers differ only in their ability to diagnose severe ALRI. Both types of health provider refer the child to a hospital if the diagnosis is positive. In the severe ALRI

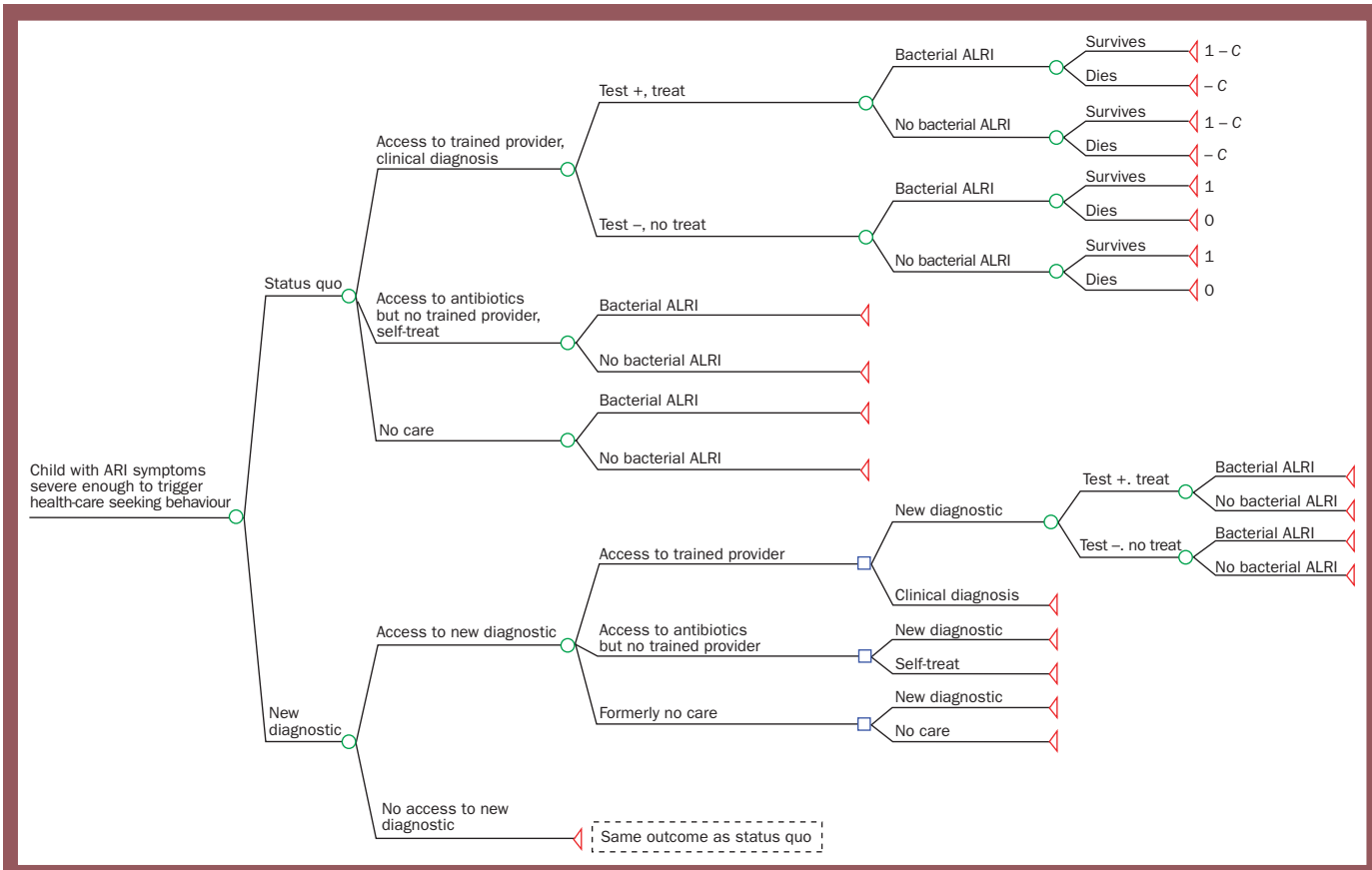

Figure 1 | Decision tree for the bacterial ALRI model. This figure has been drawn using the TreeAge Pro Suite Software (TreeAge Software, Inc.). The outcome here is the sum of individual and indirect lives. Individuals are assigned an outcome of 1 if they survive, 0 if they die and –*C* if they have been treated, where *C* is the harm of treatment. For simplicity, we show only the basic structure of the tree here and not all of the outcomes. The complete tree can be found in Lim *et al.* (ref.7). ARI, acute respiratory infection; ALRI, acute lower respiratory infection.

model, however, we assume that only a fraction of children who are referred to a hospital receive effective treatment. A lack of effective treatment might result from not having access to a hospital or from having access to a hospital that lacks the resources to treat a severe case of ALRI (for example, owing to inadequate or inconsistent oxygen supplies). As in the bacterial ALRI model, we then apply different case fatalities to children with and without effective treatment. We can vary access to the effective hospital-care parameter in the model, to examine its potential impact on our outcome of interest.

We note that there is a large overlap in our model between cases of bacterial and severe ALRI. This implies that if we were to introduce tests for both disorders in one model, the number of lives saved would be far fewer than the sum of the number of lives saved in the two models. In a sense, the interventions target children at different stages of the disease: in the bacterial ALRI model, the assumption is that treating the child with antibiotics will help to prevent disease progression, whereas in the severe ALRI model, the infection has already led to a serious form of the disease. The overlap between bacterial and severe ALRI is clearly a limitation of the model, and is mostly dictated by a lack of reliable data on the clinical course of the disease under different treatment conditions.

Model parameters

The parameter estimates used for the two analyses are shown in Tables 1 and 2. These estimates were obtained from a variety of sources, including the published and unpublished literature, databases of international agencies (such as the United Nations Children's Fund and the WHO) and expert opinion. Expert consensus was reached for the parameter estimates and the plausible ranges of all key inputs for both models.

The ability of a health facility to use a new diagnostic test is characterized by its infrastructure requirements, which follow those described by Olmsted and colleagues[8]. Advanced/moderate infrastructure implies consistent access to running water and electricity, a need for minimal laboratory equipment and a trained provider (such as a nurse or laboratory technician). Minimal infrastructure implies unreliable access to water and electricity, a physical location with no laboratory equipment and a minimally trained health provider (such as a pharmacist or village health worker). No infrastructure refers to settings with no water or electricity, and no trained personnel; a test that can be performed in these settings is essentially a home diagnostic tool.

The estimates of access to different levels of health-care and infrastructure used in these

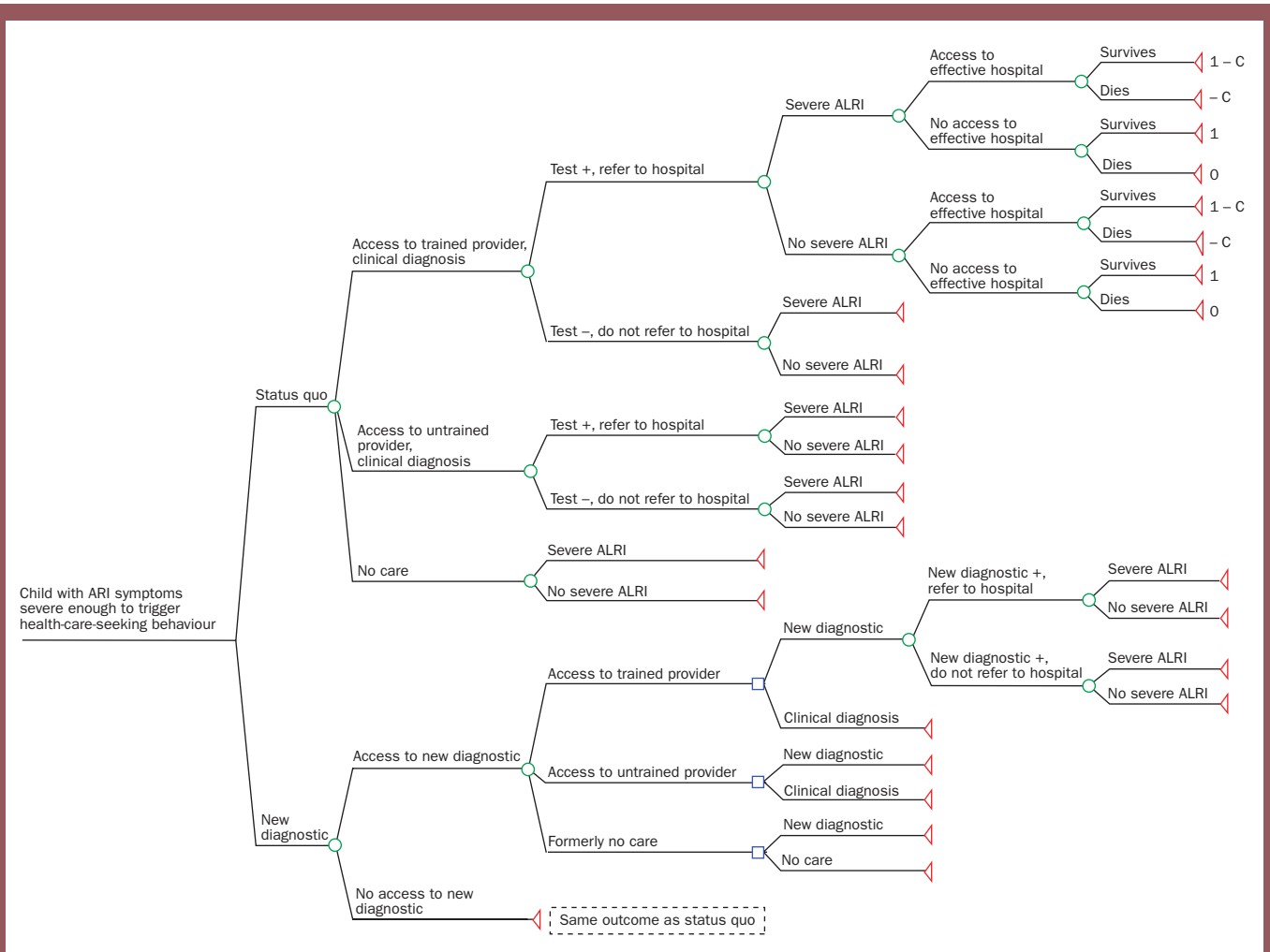

Figure 2 | Decision tree for the severe ALRI model. This figure has been drawn using the TreeAge Pro Suite Software (TreeAge Software, Inc.). The outcome here is the sum of individual and indirect lives. Individuals are assigned an outcome of 1 if they survive, 0 if they die and $-C$ if they have been treated, where C is the harm of treatment.For simplicity, we show only the basic structure of the tree here and not all of the outcomes. The complete tree can be found in Lim *et al.* (ref.7). ARI, acute respiratory infection; ALRI, acute lower respiratory infection.

analyses were derived from a multinomial logit model using data from the Demographic and Health Surveys conducted from 2000 to 2005 for 17 African, six Asian and six Latin American countries[8]. For example, in sub-Saharan Africa, a test that requires advanced/moderate infrastructural support would be available to only 28% of the population[8]. If the test requires only minimal infrastructural support, an additional 47% of the population might have access to it (75% in total). By contrast, a test that requires advanced/moderate infrastructure would be already accessible to 58 and 90% of the Asian and Latin American populations, respectively (Table 3)[8].

The parameter that carries the most uncertainty is the harm of treatment, which we define as the fraction of lives lost as a consequence of treating one child. For example, if we assume the only negative effect of treatment to be that for 1 in 10,000 cases a child would experience a deadly anaphylactic reaction, then the harm of treatment would be equal to 0.0001. This parameter, which we represent as *C*, is intended to summarize all the negative effects of treatment. In the bacterial ALRI model, the harm of treatment accounts for the development of resistant bacterial strains, the opportunity cost of treatment (that is, the health loss due to the capital and labour that are used to treat a child, which could otherwise be used in a more cost-effective intervention), the possibility of anaphylactic reaction and other potential harms (such as colitis). For the severe ALRI model, the harm of treatment accounts for the opportunity cost of hospitalization, the time lost to the family members who take the child to the hospital, the possibility of hospital-acquired (nosocomial) infections and medical errors.

The calculation of *C* does not rely on an explicit calculation of the number of lives lost due to the sum of specific adverse effects of treatment, as the data necessary for such a detailed calculation are not available. Rather, *C* is calculated using a revealed-preference approach: if the medical community is in agreement that a diagnostic test with certain characteristics should be used, then the harm associated with treatment can be neither too low (otherwise it would be preferable to treat everybody) nor too high (otherwise it would be preferable to treat no one). Details of the method used to estimate *C* were reported previously by Girosi and co-workers[6].

For the bacterial ALRI model, we estimate[7] that *C* is between 0.00026 and 0.0052. In the absence of other information, our estimate for *C* is the midpoint of this interval (0.0027). This implies that for every 1 / 0.0027 = 370 antibiotic treatments administered, one indirect life is lost. In order to ascertain whether our estimates are of the right order of magnitude, we can calculate a lower limit to *C* using an alternative method, assuming that the financial cost of treatment is the only source of harm. Using this approach, if the cost of treating bacterial ALRI with antibiotics is 50 US cents, then for every 1,000 treatments administered, US$500 is spent. If there is at least one intervention that can save one child at the cost of US$500, then for every 1,000 treatments administered we miss the opportunity to save one child and the calculated harm of treatment is $C = 0.001$. This simple calculation gives us confidence that the harm of treatment is ≥0.001, as other crucial components have not been included.

For the severe ALRI model, we estimate that $C = 0.0048$, with a lower limit of 0.001 and an upper limit of 0.006, so that for every 1 / 0.004 = 250 children referred to a hospital with effective care, one indirect life is lost. It has been suggested by field experts that, in this case, the main component of the harm of treatment is a lack of hospital beds: if a child uses the last bed, the next child coming to the hospital cannot be admitted because it is at full capacity. The parameter *C* also captures other costs of hospitalization, which include increased risk of nosocomial infections, risk to siblings of having their mother busy in the hospital taking care of the sick child and risk of family resources being exhausted for the episode of hospitalization. We can use this argument to estimate the order of magnitude of the harm of treatment. For example, if we assume that 10% of the time a child hospitalized with severe ALRI would occupy the last bed, and that on average a child not admitted to hospital would experience a 5 percentage point increase in the risk of dying because of the missed treatment, then the harm of treatment would be $C = 0.1 \times 0.05 = 0.005$, which is within our estimated limits.

Table 1 | Parameters used in the bacterial acute lower respiratory infection (ALRI) model for the developing world

Parameter	Africa		Asia		Latin America		References
	Base	Range	Base	Range	Base	Range	
Epidemiology and prevalence							
Population (M)	141.9		356.8		56.9		United Nations Population Division*
ARI incidence (per child per year)	6	5–7	5	4–6	5	4–6	Child Health Epidemiology Reference Group
Bacterial ALRI incidence (per child per year)	0.03	0.02–0.05	0.03	0.02–0.05	0.03	0.02–0.05	Child Health Epidemiology Reference Group
Proportion of ARI cases prompting the parent to seek care	0.33	0.25–0.42	0.33	0.25–0.42	0.33	0.25–0.42	Expert opinion
Test characteristics							
Sensitivity of clinical diagnosis	0.9	0.8–0.95	0.9	0.8–0.95	0.9	0.8–0.95	9,10
Specificity of clinical diagnosis	0.7	0.6–0.8	0.7	0.6–0.8	0.7	0.6–0.8	9,10
Health-care access							
Access to trained provider	0.39	0.3–0.5	0.56	0.45–0.65	0.56	0.45–0.65	UNICEF†
Access to antibiotics (self-treat)	0.05	0–0.1	0.36	0.25–0.4	0.36	0.25–0.4	11–14
Health outcomes							
Case fatality: treated	0.1	0.08–0.15	0.1	0.08–0.15	0.1	0.08–0.15	15,16 and expert opinion
Case fatality: untreated	0.2	0.18–0.25	0.2	0.18–0.25	0.2	0.18–0.25	15,16 and expert opinion
C‡	1.2	0.9–1.6	1.2	0.9–1.6	1.2	0.9–1.6	7

*Data from the 2004 Revision of the World Population Prospects Database (http://esa.un.org/unpp/index.asp?panel=2). †Data from the United Nations Children's Fund (UNICEF) statistical tables (www.unicef.pt/sowc06/statistics/tables.html). ‡Harm of treatment per 1,000 treatments. ARI, acute respiratory infection.

RESULTS

Validation of the model parameters was performed by comparing the number of ALRI deaths predicted by our status quo models with estimates from the CHERG study[1]. The parameter estimates were then calibrated within the range of uncertainty that we identified, to ensure that the numbers of deaths projected by the models were consistent with current epidemiological estimates. Our models underestimated the number of ALRI deaths by <20%, but were well within the margin of error.

Diagnosing bacterial ALRI

Table 4 shows the impact of the sensitivity, specificity and infrastructure requirements of a new test on health outcomes compared with the status quo for Africa, Asia, Latin America and the developing world as a whole, which we define as the sum of the three aforementioned regions. Each numbered row in Table 4 corresponds to a potential new diagnostic defined by its sensitivity, specificity and infrastructure requirements.

As the value of the reduction in overtreatment is directly proportional to that of the harm of treatment parameter *C*, we follow a conservative strategy to avoid overestimating the benefit of a new test by using a lower limit of 0.001 in our calculations. The lower limit is computed under the assumption that harm comes exclusively from the opportunity cost of treatment, and we are confident that the true value of *C* is larger. As described below, using the lower limit is in itself sufficient to generate significant benefits from a new test and to recommend a set of characteristics. The advantage of this approach is that we are much more confident in the estimate of the lower limit (0.001) than in the midpoint estimate (0.0027) for *C*.

To establish a benchmark for comparison, we initially report the results for a test that is 100% sensitive, 100% specific and requires no infrastructure. Such an 'ideal' test would be universally available, although only ~33% of children with ARI symptoms would seek care. We assume that children who gain access to a diagnostic test also gain access to treatment. The results indicate that a 100% sensitive and 100% specific test that is universally available in the developing world would save the lives of ~424,000 children per year relative to the status quo (Table 4, test 11). In addition, ≥400,000 indirect lives could be saved by reducing overtreatment (Table 4, test 11), so that the total number of lives saved would be >800,000 per year. These savings of indirect lives are due to the better use of resources currently employed for treatment. The number of indirect lives has been computed using a lower limit for the harm of treatment ($C = 0.001$), which includes only the opportunity cost of treatment and disregards other important negative externalities, such as increased antibiotic resistance. Our analysis[7] shows that the harm of treatment could be five-times higher. In this case, the number of indirect lives saved would also be five-times higher (that is, 2 million lives).

Our results also indicate that, when advanced/moderate infrastructure is required, few individual lives would be saved globally, regardless of the characteristics of the test. Infrastructure requirements would have the greatest impact in Africa, where only a minority of the population would have access to an advanced/moderate infrastructure test. In Asia and Latin America, such a test would be available to significant proportions of the population; however, as antibiotics are already available to some extent within these regions, increased test sensitivity has limited potential to improve the number of individual lives saved over the status quo. For example, a 100%

Table 3 | Proportion of individuals with access to health facilities with different types of infrastructure

Region	Access to advanced/ moderate infrastructure (%)	Access to at least minimal infrastructure (%)
Africa	28	75
Asia	58	87
Latin America	90	95

Table 2 | Parameters used in the severe acute lower respiratory infection (ALRI) model for the developing world

Parameter	Africa		Asia		Latin America		References
	Base	Range	Base	Range	Base	Range	
Epidemiology and prevalence							
Population (M)	141.9		356.8		56.9		United Nations Population Division*
ALRI incidence (per child per year)	0.3	0.25–0.35	0.3	0.25–0.35	0.3	0.25–0.35	Child Health Epidemiology Reference Group
Proportion of ARI cases prompting the parent to seek care	0.33	0.25–0.42	0.33	0.25–0.42	0.33	0.25–0.42	Expert opinion
Proportion of ALRI that is severe	0.1	0.05–0.15	0.1	0.05–0.15	0.1	0.05–0.15	Expert opinion
Test characteristics							
Sensitivity of clinical diagnosis of trained provider	0.95	0.85–1	0.95	0.85–1	0.95	0.85–1	17,18
Specificity of clinical diagnosis of trained provider	0.8	0.7–0.9	0.8	0.7–0.9	0.8	0.7–0.9	17,18
Sensitivity of clinical diagnosis of untrained provider	0.85	0.75–0.95	0.85	0.75–0.95	0.85	0.75–0.95	Expert opinion
Specificity of clinical diagnosis of untrained provider	0.7	0.6–0.8	0.7	0.6–0.8	0.7	0.6–0.8	Expert opinion
Health-care access							
Access to trained provider	0.39	0.3–0.5	0.56	0.45–0.65	0.56	0.45–0.65	19 and UNICEF†
Access to untrained provider	0	0–0	0.38	0.26–0.48	0.38	0.26–0.48	Expert opinion
Access to effective hospital	0.1	0.05–0.2	0.3	0.2–0.4	0.3	0.2–0.4	20–23
Health outcomes							
Case fatality: treated	0.08	0.06–0.15	0.08	0.06–0.15	0.08	0.06–0.15	24
Case fatality: untreated	0.16	0.14–0.3	0.16	0.14–0.3	0.16	0.14–0.3	24
C‡	4	1–6	4	1–6	4	1–6	7

*Data from the 2004 Revision of the World Population Prospects Database (http://esa.un.org/unpp/index.asp?panel=2). †Data from the United Nations Children's Fund (UNICEF) statistical tables (www.unicef.pt/sowc06/statistics/tables.html). ‡Harm of treatment per 1,000 treatments. ARI, acute respiratory infection.

sensitive test requiring advanced/moderate infrastructure would save only 82,000 children globally (Table 4, test 5) or ~20% of the 424,000 individual lives that could be saved with an ideal test. A 95% sensitive test could save only 5% of these 424,000 individual lives, because most children either already have access to a relatively good test (for example, clinical algorithms with 90% sensitivity) or self-treat.

A test requiring advanced/moderate infrastructure could result in some gains in indirect lives saved if test specificity were improved over the status quo. As the specificity of IMCI for the identification of pneumonia requiring antibiotics is estimated to be only 70%, we find that by increasing the specificity of the new test to 85% (leaving sensitivity unaltered), ≥100,000 indirect lives could be saved, mostly in Asia and Latin America (Table 4, test 2). This result is due to a reduction in the opportunity cost of treatment. We notice that there is great potential for reducing the overtreatment rate: at the current level of 70% specificity, the ratio between false positives and true positives is large (18:1). Increasing the specificity to 85% would reduce this ratio to 9:1, producing a significant reduction in the overtreatment rate. However, although 100,000 is a large number of indirect lives, it is small compared with the number of individual and indirect lives that could be saved by a test requiring only minimal infrastructure to operate.

Minimal infrastructure tests improve outcomes

In terms of individual lives, the greatest benefit for a new bacterial ALRI diagnostic test occurs when it can be performed with minimal infrastructure support, which would greatly increase access in Africa. Introducing a minimal infrastructure test with the same sensitivity as clinical algorithm-based diagnosis (90%) would save 117,000 individual lives in Africa (Table 4, test 6). However, the test would require a higher sensitivity in order to be adopted worldwide. A figure of 90% sensitivity would be too low for Asia and Latin America: indeed, the model predicts a negative number of individual lives saved for these regions (that is, an increase in mortality), because self-treatment would be replaced by a test that is less sensitive. This result emphasizes an important problem: it might be difficult to introduce a new diagnostic in a population that self-treats unless the sensitivity is high enough (~95%) to ensure that the overall number of individual lives saved is positive.

A test with 95% sensitivity and 85% specificity produces significant gains

Large gains in indirect lives could be obtained in Asia and Latin America by improving the specificity of the test. Globally, a test that is 95% sensitive, 85% specific and requires only minimal infrastructure could save ~152,000 individual lives (mostly in Africa) and ≥253,000 indirect lives (mostly outside Africa; Table 4, test 9). These figures represent, respectively, 36% of the number of individual lives and 63% of the number of indirect lives that could be saved with an ideal test. A one percentage point increase in sensitivity would save an additional 14,000 individual lives, while a one percentage point increase in specificity would save an additional 8,000 indirect lives. As the number of indirect lives saved is a lower limit and is obtained using a conservative value for the harm of treatment, the actual number could be as much as five-times larger.

Further improvements upon the status quo, especially in terms of individual lives, would require a test with no infrastructure requirements. Although children requiring a no-infrastructure test constitute a relatively small proportion of the overall population (~10% in Asia and Latin America,

Table 4 | Results for the bacterial acute lower respiratory infection (ALRI) model in the developing world

			Africa			Asia			Latin America			Developing World		
Test	Sensitivity	Specificity	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved
Advanced/moderate infrastructure														
1	0.9	0.7	0 (3)	0 (2)	0 (2,200)	–2 (17)	8 (20)	8,200 (20,000)	–6 (5)	22 (5)	21,900 (4,300)	–8 (18)	30 (21)	30,100 (20,600)
2	0.9	0.85	0 (5)	12 (4)	11,700 (4,200)	–2 (23)	59 (29)	59,000 (28,700)	–6 (6)	35 (7)	34,500 (6,200)	–8 (24)	106 (30)	105,200 (29,600)
3	0.9	1	0 (5)	23 (5)	23,500 (4,700)	–2 (25)	110 (36)	109,800 (33,700)	–6 (6)	47 (9)	47,000 (7,700)	–8 (26)	180 (37)	180,300 (34,800)
4	0.95	0.85	6 (5)	12 (4)	11,700 (3,600)	29 (26)	59 (27)	59,000 (26,100)	2 (6)	34 (7)	34,500 (5,800)	37 (27)	105 (28)	105,200 (27,000)
5	1	1	12 (6)	23 (5)	23,500 (4,500)	60 (30)	109 (35)	109,800 (33,400)	10 (7)	47 (9)	47,000 (7,500)	82 (31)	179 (36)	180,300 (34,500)
Minimal infrastructure														
6	0.9	0.7	117 (43)	–17 (8)	–16,200 (7,400)	–33 (25)	127 (28)	126,700 (24,500)	–2 (7)	23 (5)	22,700 (4,200)	82 (50)	133 (30)	133,200 (25,900)
7	0.9	0.85	117 (44)	14 (9)	15,200 (8,500)	–33 (28)	203 (42)	203,000 (35,100)	–2 (8)	36 (7)	35,900 (6,200)	82 (53)	253 (44)	254,200 (36,700)
8	0.9	1	117 (41)	46 (11)	46,700 (10,100)	–33 (32)	280 (51)	279,200 (42,600)	–2 (8)	49 (9)	49,200 (7,400)	82 (53)	375 (53)	375,100 (44,400)
9	0.95	0.85	133 (52)	14 (9)	15,200 (8,600)	13 (35)	203 (44)	203,000 (38,900)	6 (9)	36 (7)	35,900 (5,900)	152 (63)	253 (45)	254,200 (40,200)
10	1	1	149 (59)	45 (11)	46,700 (10,000)	60 (40)	279 (52)	279,200 (46,600)	14 (10)	49 (9)	49,200 (7,400)	223 (72)	373 (54)	375,100 (48,200)
No infrastructure														
11	1	1	255 (84)	44 (11)	46,700 (9,600)	146 (73)	307 (58)	308,400 (47,900)	23 (12)	49 (9)	49,200 (7,600)	424 (112)	400 (60)	404,300 (49,400)

The developing world includes Africa, Asia and Latin America. All figures are expressed in thousands. The figures in parentheses are standard deviations, computed using Monte-Carlo simulations, and reflect uncertainty in the model parameters except for sensitivity and specificity.

and 25% in Africa), they would disproportionately benefit from a new test because they currently receive little or no care, and therefore bear the greatest burden of pneumonia mortality.

Identifying severe ALRI cases

Table 5 presents results for the severe ALRI analysis and is similar to Table 4, except that access to effective hospital care has been added as a variable so that we can explore its impact on treatment.

Increased access to hospital care is key

In the case of a 100% sensitive and 100% specific diagnostic test that is universally available and followed by effective hospital treatment, 1 million children aged <5 years could be prevented from dying of severe ALRI (Table 5, test 15). Table 5 shows that the benefit of any new diagnostic test is conditional on increased access to effective hospital care. As long as this access remains at the status quo level (10–30%), a new test for severe ALRI would not save a large number of lives, even if it were 100% sensitive, 100% specific and required minimal infrastructure (Table 5, test 8). Therefore, in the following analyses we assume that, as the new diagnostic test is introduced, access to effective hospital care is also increased to ≥50%.

New test requires 85% sensitivity and 90% specificity

Similar to the bacterial ALRI model, the benefits of a new diagnostic test for severe ALRI in Africa depend on the level of infrastructure required. Table 5 shows that, assuming 50% access to effective hospital care, a new test that is 100% sensitive, 100% specific and requires advanced/moderate infrastructure would save only 39,000 individual lives in Africa (Table 5, test 6). However, if the same test required only minimal infrastructure, this number would almost triple (Table 5, test 13). The situation is different for Asia and Latin America, where levels of access to advanced/moderate infrastructure are already substantial (58 and 90%, respectively), and a new 100% sensitive and 100% specific test requiring advanced/moderate infrastructure would save 135,000 individual lives (107,000 in Asia and 28,000 in Latin America; Table 5, test 6). This number would increase by 50% if the infrastructure requirement were changed from advanced/moderate to minimal (Table 5, test 13).

Table 5 | Results for the severe acute lower respiratory infection (ALRI) model in the developing world

				Africa			Asia			Latin America			Developing World		
Test	Access to effective hospital in world with new test	Sensitivity	Specificity	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved	Individual lives saved	Indirect lives saved	Unnecessary treatments saved
Advanced/moderated infrastructure															
1	Status quo	1	1	0 (2)	6 (3)	1,600 (500)	8 (21)	82 (34)	20,700 (5,800)	3 (6)	24 (9)	6,000 (1,400)	12 (22)	112 (35)	28,200 (6,000)
2	0.5	0.85	0.8	31 (20)	–27 (13)	–6,300 (3,000)	70 (46)	–56 (28)	–13,200 (6,700)	19 (11)	–11 (6)	–2,400 (1,400)	120 (52)	–93 (32)	–21,900 (7,500)
3	0.5	0.95	0.8	36 (22)	–27 (13)	–6,300 (2,900)	95 (54)	–58 (30)	–13,200 (6,700)	25 (14)	–11 (6)	–2,400 (1,400)	156 (60)	–95 (33)	–21,900 (7,400)
4	0.6	0.85	0.8	40 (25)	–33 (16)	–7,800 (3,800)	112 (70)	–86 (40)	–20,000 (9,600)	29 (17)	–18 (8)	–4,100 (1,900)	181 (76)	–137 (44)	–31,900 (10,500)
5	0.5	0.85	0.9	31 (12)	–11 (4)	–2,300 (600)	70 (35)	11 (21)	3,700 (4,900)	19 (9)	6 (5)	1,800 (1,100)	120 (38)	7 (22)	3,200 (5,000)
6	0.5	1	1	39 (15)	4 (2)	1,600 (500)	107 (45)	77 (32)	20,700 (5,600)	28 (12)	23 (9)	6,000 (1,400)	174 (49)	104 (33)	28,200 (5,800)
7	1	1	1	86 (32)	2 (2)	1,600 (500)	356 (127)	65 (31)	20,700 (5,800)	89 (34)	19 (8)	6,000 (1,400)	531 (135)	86 (32)	28,200 (6,000)
Minimal infrastructure															
8	Status quo	1	1	13 (6)	8 (4)	2,200 (700)	19 (33)	143 (52)	35,900 (8,400)	4 (6)	25 (9)	6,300 (1,500)	36 (34)	176 (53)	44,400 (8,600)
9	0.5	0.85	0.8	96 (61)	-80 (38)	–18,800 (9,000)	112 (66)	–65 (36)	–14,900 (8,500)	20 (12)	–11 (7)	–2,600 (1,500)	229 (90)	–156 (53)	–36,200 (12,500)
10	0.5	0.95	0.8	109 (66)	–81 (39)	–18,800 (8,700)	150 (78)	–67 (37)	–14,900 (8,300)	27 (14)	–12 (7)	–2,600 (1,500)	285 (103)	–159 (54)	–36,200 (12,100)
11	0.6	0.85	0.8	118 (73)	–98 (48)	–23,000 (11,200)	176 (97)	–109 (49)	–25,100 (11,300)	31 (17)	–19 (9)	–4,300 (2,000)	325 (122)	–226 (70)	–52,400 (16,000)
12	0.5	0.85	0.9	96 (39)	–38 (14)	–8,300 (2,100)	112 (58)	36 (30)	10,500 (6,900)	20 (10)	6 (6)	1,900 (1,200)	229 (71)	5 (34)	4,100 (7,300)
13	0.5	1	1	115 (42)	3 (4)	2,200 (700)	168 (74)	135 (52)	35,900 (8,700)	30 (13)	24 (9)	6,300 (1,500)	313 (86)	162 (53)	44,400 (8,800)
14	1	1	1	243 (92)	–3 (4)	2,200 (700)	541 (210)	117 (48)	35,900 (8,600)	95 (37)	20 (8)	6,300 (1,400)	878 (232)	134 (49)	44,400 (8,800)
No infrastructure															
15	1	1	1	328 (121)	–8 (5)	2,200 (700)	638 (223)	126 (51)	39,400 (9,000)	102 (40)	20 (8)	6,300 (1,400)	1,067 (257)	138 (52)	47,900 (9,200)

The developing world includes Africa, Asia and Latin America. All figures are expressed in thousands except for access to effective hospital, sensitivity and specificity. The figures in parentheses are standard deviations computed using Monte-Carlo simulations and reflect uncertainty in the model parameters.

As Africa accounts for ~33% of the lives that could potentially be saved by a new ALRI diagnostic, a test requiring only minimal infrastructure has the potential to produce the greatest benefit. Table 5 shows that, if access to an effective hospital is reasonably great, such a test need not be highly sensitive.

For example, a test that is only 85% sensitive would save 229,000 individual lives with 50% access to effective hospital care (Table 5, test 9). Increasing the sensitivity to 95% would only save an additional 56,000 lives (Table 5, test 10). A similar increase in access to hospital care to 60% would lead to a much larger benefit, saving an additional 96,000 lives (Table 5, test 11). These results indicate that it would not be worth investing much effort in producing a test that is highly sensitive. Rather, it would be more efficient to invest in increasing access to effective hospital care. A test sensitivity as low as 85% already brings significant benefits, as long as access to hospital care is >50%.

In order to understand the recommended specificity requirements of a test, we need to consider the interplay with access to effective hospital care. If the latter is increased but specificity and sensitivity are unchanged relative to the status quo, more children will be treated; some of these will need and benefit from the intervention, while many others will be unnecessarily treated, leading to a loss of indirect lives and negating some of the benefits achieved in terms of individual lives. The loss of indirect lives can be eliminated by judiciously raising the specificity of the test. When increasing access to effective hospital care to 50%, a specificity of 90% would be sufficient to guarantee little change in the number of unnecessary treatments, and therefore no saving or loss of indirect lives (Table 5, test 12). Above this level of specificity, a one percentage point increase would lead to the saving of an additional 16,000 indirect lives.

DISCUSSION

Our analyses indicate that there are significant benefits to introducing a new diagnostic test for bacterial ALRI. There is also a large potential benefit to introducing a new test for severe ALRI, but it can only be realized if access to effective hospital care is improved. The benefits depend largely on the infrastructure required to conduct the test and the corresponding levels of access. This is particularly relevant for Africa, where much of the ALRI disease burden exists and only a small fraction of children has access to health-care facilities with advanced/moderate infrastructure. Therefore, the impact of a new diagnostic for bacterial and severe ALRI can be maximized only if the test can be used in an environment that requires minimal infrastructure.

Our analyses also indicate the performance characteristics necessary for new diagnostic tests for bacterial and severe ALRI in young children. We show that, for bacterial ALRI, efforts should be directed towards developing a test that is highly specific (≥85%). A test with this level of specificity, a sensitivity that is slightly higher than that of the current clinical algorithm-based diagnosis (95%) and a requirement for minimal infrastructure support would save a total of 405,000 lives every year (152,000 individual and 253,000 indirect lives). Most of the individual lives saved would be in Africa, where access to tests and antibiotic treatment is currently limited. Most of the indirect lives saved would be in Asia and Latin America, where the main problem is overtreatment. Superficially, it might seem that the benefit to Africa should be attributed to treatment, rather than diagnostics; however, this is not the case. Although it is true that having access to a diagnostic tool without treatment is worthless, universal access of this type would create a situation similar to that currently seen in urban Asia, where many indirect lives are lost due to unnecessary treatment.

The benefit of any diagnostic test for severe ALRI depends on access to effective hospital care. Our analyses found that it is not meaningful to develop a new test for severe ALRI unless access to effective hospital care can be substantially increased to ≥50% of the population. In addition, we found that, in the trade-off, it is always better to invest in expanding access to hospital care rather than in increasing the sensitivity of the test. If access to effective hospital care could be increased to 50%, even a sensitivity of 85% would be more than adequate. However, greater access to hospital care implies greater potential for overtreatment or over-referral. Therefore, we conclude that the specificity of any new test for severe ALRI must be ≥90%.

Our analyses has several important limitations, some of which stem from the lack of reliable epidemiological data. For example, there are few data documenting the incidence of bacterial ALRI compared with non-bacterial ALRI. Similarly, the difficulty in quantifying the overlap between bacterial and severe ALRI restricts us to conducting separate and mutually exclusive analyses of these conditions (that is, the results cannot be used additively). In addition, for both bacterial and severe ALRI, the estimates of case fatalities for treated and untreated individuals carry significant uncertainty. Despite these limitations, however, the standard deviations of our estimates, obtained with a multi-way Monte-Carlo simulation, are not large enough to alter our conclusions.

Our ALRI models do not account for the fact that children who present with symptoms such as fever and fast breathing might have other diseases, such as malaria. For example, children with malaria who receive a false-positive test result might suffer because they receive the wrong treatment while their malaria goes untreated, even though the IMCI specifies that malaria should be treated, regardless of whether or not a child has pneumonia according to the algorithm. By contrast, sick children who are falsely identified as having severe ALRI might benefit from hospitalization and continued care, despite a wrong initial diagnosis. In addition, our model does not predict how the introduction of a new diagnostic test might change health-care-seeking behaviour among patients. For example, as outcomes improve, the perception of the quality of health services might also improve, leading to an increased use of health-care services and overall better care. It is also conceivable that the introduction of a new diagnostic might lead to a reduction in health-care-seeking behaviour, because people could be less willing to seek such services if they are not certain to receive antibiotics.

Another limitation of the model is the assumption that the distribution of ALRI cases is equal across populations. In fact, those with no access to a health-care system might have a higher burden of illness and might present with more severe disease. As a result, the introduction of a diagnostic test to those who currently are most vulnerable and have little or no access might result in a benefit greater than that indicated by the model. We recognize that the cost of introducing and sustaining the logistics chain needed to support a test that could be used far from a health-care system is a significant consideration. However, our results indicate that the greatest mortality reductions can be gained by introducing a new diagnostic to populations who currently have no access. Our findings confirm that the impact of a diagnostic test for those who currently have no formal access to care is considerable.

There is clearly a role for new diagnostic tests for ALRI. Our analyses indicate that a diagnostic test for bacterial ALRI requires at least 95% sensitivity and 85% specificity, whereas a diagnostic test for severe ALRI requires at least 85% sensitivity and 90% specificity. A key requirement for both tests is that they can be used in a minimal infrastructure health-care setting, which imposes some constraints. Ideally, a test should not need power to be operated, although disposable or rechargeable batteries and solar-powered systems are viable options. Refrigeration and access to clean water should not be required, and users should be able to store a test at 40 °C

Box 1 | Key messages

- A new diagnostic test for bacterial ALRI with at least 95% sensitivity, 85% specificity and minimal infrastructure requirements could significantly improve global efforts to control ALRI, saving at least 405,000 children's lives every year.
- A new diagnostic for severe ALRI could also have benefit provided access to effective hospital care is increased globally. If 50% of the population had access to effective hospital care, a new diagnostic for severe ALRI would require at least 85% sensitivity, 90% specificity and minimal infrastructure requirements. Such a diagnostic would save 229,000 children per year.
- Ideally, new diagnostics for bacterial and severe ALRI should require minimal training to use and no electricity, refrigeration, or access to clean water. Preferred sample types include saliva, urine, or a dried blood spot, and results should be available within 1 h.

and 70% humidity for ≥6 months. The test sample should require neither preparation nor the use of external reagents. Preferred sample types include saliva, urine and a dried blood spot, and test results should be available within 1 h. Health-care providers should need only 1–5 days of training to learn how to use a test. Furthermore, in the case of severe ALRI, increased access to effective hospital care is a prerequisite to realizing the potential impact of any new diagnostic tool. We summarize our key points in Box 1.

So far, there has been limited research emphasis and funding specifically for ALRI, with further studies being needed to identify pathogen-specific biomarkers. Current non-specific biomarkers, such as C-reactive protein (CRP) and procalcitonin, have been used in experimental settings; however, they have not been sufficiently validated as diagnostic biomarkers for clinical use. Urine tests for pathogen-specific antigens exist, but are not useful in children, largely because naso-pharyngeal carriage of the organisms, which is common in developing countries, produces an excessive numbers of false positives. Therefore, more work is needed in the area of pathogen-specific markers, especially those for bacterial disease. Another area to explore is host-specific response to infection. In order to make progress in this field, test developers would need to tackle a number of challenges, including the confounding presence of maternal antibodies in neonates and young infants, the poorer antibody response to infection among these groups, the lack of specificity among markers for acute-phase inflammation, which are subject to the influence of other factors, and the fact that markers for bacterial ALRI might be used only when the disease is severe.

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