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Economics and financing of vaccines for diarrheal diseases

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The considerable burden of infectious disease-caused diarrhea around the world has motivated the continuing development of a number of vaccine candidates over the past several decades with some reaching the market. As with all major public health interventions, understanding the economics and financing of vaccines against diarrheal diseases is essential to their development and implementation. This review focuses on each of the major infectious pathogens that commonly cause diarrhea, the current understanding of their economic burden, the status of vaccine development, and existing economic evaluations of the vaccines. While the literature on the economics and financing of vaccines against diarrhea diseases is growing, there is considerable room for more inquiry. Substantial gaps exist for many pathogens, circumstances, and effects. Economics and financing studies are integral to vaccine development and implementation.

Introduction

The considerable burden of infectious disease-caused diarrhea around the world has motivated the continuing development of a number of vaccine candidates over the past several decades with some reaching the market. According to the Global Burden of Disease 2010 update, diarrhea is the fourth leading cause of disability-adjusted life years (DALYs) and years of life lost (YLLs) and the seventh leading cause of death globally.[1,2] Among children under 5-y-old, diarrhea causes an estimated 801 000 deaths worldwide (second leading cause of all infectious complications) in 2010.[3] However, even these numbers may be underestimates of the true burden, given the lack of readily available diagnostics, accurate surveillance, and adequate reporting. Existing prevention strategies include improved water and sanitation, safe drinking water, breastfeeding, education, safe food storage and preparation, and basic hygiene practices such as hand washing with soap. But these measures can be difficult and take years to implement broadly, making vaccines an important potential intervention.[4-6]

As with all major public health interventions, understanding the economics and financing of vaccines against diarrheal diseases is essential to their development and implementation.[7] Funders and policy makers have many competing priorities, quantifying the burden of the different diarrheal diseases can better determine whether and how much resources to invest toward vaccine development and implementation. Determining the cost-effectiveness of vaccines can assist in choosing among different possible control strategies and interventions. Manufacturers will be more apt dedicate their time and effort toward those projects likely to yield higher profits and returns-on-investment (ROI). So, knowing these metrics can help manufacturers make decisions and funders and policy makers structure and offer the proper financial incentives. Even after a vaccine successfully reaches the market, economics and finance form the basis of many ongoing key decisions. Choosing the right target populations depends on a balance between impact, feasibility, and cost. Convincing populations and their responsible decision-makers such as governments, third party payers, or organizational leaders of the need for a vaccine often involves presenting a cogent financial argument (i.e., this vaccine is worth purchasing). Finally, getting the vaccines to their points of use requires time and resources and an accurate perception of the relevant logistics and financial trade-offs to design the most efficient and cost-effective processes and systems.

Therefore, this review will walk through each of the major infectious pathogens that commonly cause diarrhea, the current understanding of their economic burden, the status of vaccine development, and existing economic evaluations of the vaccines and the relevant processes and logistics to get the vaccines to the populations. **Table 1** summarizes information on the economic burden and value of such vaccines.

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Pathogens

Human caliciviruses (norovirus and sapovirus)

Economic burden: high income country

Some existing studies have attempted to quantify the overall economic burden of norovirus (which along with sapovirus, is the major calcivirus that causes diarrhea in humans) but many of these studies may in fact underestimate the true burden. As the most frequent cause of viral gastroenteritis outbreaks in healthcare settings and in the community[8,9] (one published study estimates 21 million cases annually in the US[10]), symptomatic norovirus infections can result in lost productivity and health care costs.

However, quantifying these effects can be challenging since the reported incidence of norovirus infections in developed countries is highly variable,[10-18] due to the lack of reporting requirements, routine testing for norovirus, and need for most infected persons to interface with the healthcare system. Moreover, the size (and thus the impact) of a given norovirus outbreak can vary considerably so that projections from one or a limited number of outbreaks may not reflect the true variability that exists. Nonetheless, existing estimates are substantial. Two studies aimed to capture the health care costs associated with norovirus infections by using medical billing data[19] and MarketScan insurance claims[17] to tabulate the healthcare costs per symptomatic norovirus case and then multiplied these per case costs by the estimated number of norovirus-related healthcare visits nationally, leading to total treatment costs in the US exceeding $270 million annually.[17,19] An economic modeling study incorporated both age-specific treatment costs and age-specific lost productivity (from symptom induced missed work) found the total annual costs in the US to be considerably higher at over $5.5 billion,[20] highlighting the substantial contribution of lost productivity. In fact, since a large percentage of people with norovirus infections do not seek formal healthcare, productivity losses may be the primary cost.

Quantifying the burden of various types of norovirus infections can be help identify specific target populations for a vaccine. One study that focused solely on food borne cases of norovirus and included both treatments costs and productivity losses estimated annual costs to be around $2 billion.[21] Several studies specifically evaluated the cost of various norovirus hospital outbreaks (range: $37 968 to ≤201 690 per outbreak) in developed countries.[22-25] One study found that over a two year period outbreaks in the United Kingdom cost up to ≤1.2 million.[25] These studies do show wide variation in the cost impact of an outbreak due in part to the wide variety in scope, size, and number of outbreaks but also due to variability in the types of cost included (e.g., interventions, attributable sick leave for staff and overtime salary, cleaning expenses, diagnosis costs), costs of various items and services, and reimbursement policies. Weaknesses of these studies include the generalizablity, as they are specific to the outbreak hospital, some focus only on extra costs and lost revenue,[23-25] used a case definition of symptoms only,[22] and small sample size.[24] Modeling studies, which may overcome some of these limitations, estimate a case of norovirus to the hospital is an average $6237[26] and provide cost estimates for outbreaks of various sizes in differing size hospital wards.[27] However, all models are limited by their data inputs and estimates may change with more information.

Sapovirus burden estimates are even more sparse. There was an estimated 1 898 561 cases in Canada 2006[11] and an estimated incidence of 900 per 100 000 persons in the community in the US in 2004.[28] Among persons hospitalized for acute gastroenteritis, saprovirus has not been frequently isolated; 0.6% in adults and ranging from to 1.4% to 5.4% among children under 5 y.[29-31] A MEDLINE search found no published economic evaluations of saprovirus infection.

Economic burden: middle/low income country

There have been no published economic evaluations of norovirus or sapovirus in developing countries.

Economic value of vaccines: disease in high income country

Although no vaccines for human caliciviruses are currently licensed, norovirus vaccine candidates are currently undergoing human clinical trials. Economic evaluations of vaccines early in development can help guide development while vaccine characteristics and implementation plans can still be readily altered.[7,32] To date, the only readily available published economic evaluation of norovirus vaccines is a computational model that evaluated the potential cost-effectiveness (2012 $US) of a norovirus vaccine in the US community and explored how varying different key vaccine and implementation characteristics would affect cost-effectiveness, total costs, and number of norovirus gastroenteritis outcomes.[20] Experiments found that vaccinating young children (<5-y-old) and older adults (>65-y-old) could provide net cost-savings (i.e., when the cost of the vaccine and vaccination is <$25, the result could be cost savings). Moreover, the vaccine would not need to have very high efficacy to result in cost savings (e.g., in children ≤ 4-y old, ≥50% efficacy and a cost of $25); and a higher costing vaccine was cost-saving when protecting for ≥24 mo. For those aged 5 to 65 y a 50% efficacious vaccine that cost $25 and protected for 12 mo cost $380 to $950 per case averted. For adults ≥65 y of age, a $25 vaccine protecting for 24 mo saved $147 per case averted.[20]

This study evaluated the thresholds of key parameters to help identify vaccine characteristics, such as target population and vaccine price, efficacy, and duration of protection, which can help guide vaccine development. Once more clinical trials have been performed to evaluate the vaccine efficacy and protection duration, a model such as the one by Bartsch et al. can be updated to re-evaluate the vaccine's potential economic value.

Economic value of vaccines: disease in middle/low income country

A MEDLINE search found no published economic evaluations of vaccines for norovirus or saprovirus in developing countries.

Economic value of vaccines: travelers from high income to middle/low income country

A MEDLINE search found no published economic evaluations of vaccines for human *Caliciviruses* among travelers.

No other studies evaluating the economic value of a norovirus vaccine have been done. There is a need for such studies, like ROI and logistic evaluations. This is especially important now while norovirus vaccines are being developed and key characteristics can be changed (e.g., price points, target populations, vaccine efficacy, and protection duration). Once on the market, economic evaluations become less valuable as certain vaccine characteristics evaluated by such studies cannot be modified.

Campylobacter

Campylobacter is a frequent bacterial cause of acute gastroenteritis globally (both sporadic and out-break cases in developed and developing countries as well as travelers' diarrhea) and is associated with the development of extraintestinal sequelae and may contribute to chronic gastrointestinal conditions.[33]

Economic burden: high income country

Over the past 20 y, the incidence of *Campylobacter* disease in developed countries has steadily risen, and likely is significantly underestimated.[33] Estimated rates are higher than laboratory confirmed cases, with several thousand estimated annually

in developed countries (range: 7000 to 845 024),[10,11,34,35] and rates of 10.9 (95% CI: 7.4 to 15.9) cases per 1000 person-years (2008–2009).[13] Estimates are variable as it's underreported and laboratory diagnostics are not always performed. Foodborne cases (based on Scallan et al.'s annual numbers) cost an estimated $1747 million (2009 $US) annually in the US and is responsible for a average of 13 256 QALYs lost (in addition to the detail of this study described above, costs [treatment and productivity losses] and QALYs for physical and mental disabilities resulting from *Campylobacter*-associated Guillain-Barre Syndrome [GBS] were included).[21] While in Sweden, it cost an estimated €26.1 million (2006 values) annually in direct (e.g., general practitioner, hospitalization, and drug costs) and indirect costs (productivity loss due to sick leave from work or care of sick children), including the short- and long-term outcomes of GBS.[35]

Economic burden: middle/low income country

Campylobacter rates in developing countries are similarly high, but a lack of surveillance systems hinders an accurate estimate.[33] The recent Global Enteric Multicenter Study (GEMS) study (conducted in six low-income developing countries in children <5 y of age), found *C. jejuni* to have regional importance being significantly associated with moderate-to-severe diarrhea in at least one age group at three Asian sites.[36] This is a large prospective, matched case-control study (36 mo across 7 sites with 487 386 child-years of observation) in a highly relevant population (where more than 80% of child deaths occur) with a range of health indicators, healthcare accessibility, economic development, and environmental conditions. However, this study may have underestimated the attributable fraction of some pathogens as they are endemic in the studied sites and can be detected in asymptomatic controls. A MEDLINE search found no reports on the cost of *Campylobacter* in developing countries.

There are several gaps in the economic burden literature for *Campylobacter*; more studies are needed to characterize the cost of illness due to *Camploybacter*, especially for uncomplicated cases and non-foodborne illnesses. Evaluations of *Campylobacter* illness costs in developing countries are particularly important as they are currently lacking from the literature. While the evaluations mentioned help paint the picture of the burden of *Campylobacter* for developed countries, they are limited. Weaknesses of the current economic cost evaluations are the inclusion of only foodborne cases (as in the case of the US study) and certain outcomes (e.g., irritable bowel syndrome which is an important outcome) were not included due to lack of reliable estimates. One study did report the cost of its chronic outcomes (e.g., irritable bowel syndrome, inflammatory bowel disease, celiac disease, and functional syspepsia), but not the disease itself.[33] Additionally, these costs were not age-stratified to account for potential differences in disease incidence, health outcomes, and treatment costs.

Economic value of vaccines: disease in high income country

A MEDLINE search found no published economic evaluations of vaccines in developed countries.

Economic value of vaccines: disease in middle/low income country

Likewise, there have been no economic evaluations of a *Campylobacter* vaccine for populations in developing countries.

Economic value of vaccines: travelers from high income to middle/low country

Currently, there is no vaccine available for *Campylobacter*. Only one study to date has been published looking at the potential economic value of a *Campylobacter* vaccine. Riddle et al. utilized a model to determine the cost-effectiveness (in 2006 $US) of enteric vaccines for the US military, measuring effectiveness in duty days lost due to diarrhea (DDL) averted.[37] This evaluation estimated that a *Campylobacter* vaccine acquisition strategy could avert $191 947 in care costs annually for the US military and had a cost-effectiveness ratio of $1243/DDL averted (assuming a $24.74 per dose vaccine with two-doses), including vaccine research and development costs.[37] If a vaccine were immediately available (excluding front end costs for research and development), the vaccine had a marginal cost-effectiveness ratio of $692/DDL averted. This study also looked at vaccination of a smaller number of troops deployed to specific regions. For troops in Southeast Asia, the vaccine would cost $170 per duty day lost.[37] As there is no vaccine close to market, there are no financing studies.

The study by Riddle et al. is well designed, included appropriate costs and costing methods, included research and development costs for the vaccine (which many other studies like this lack), performed apt sensitivity analyses, and, by using DDL as an outcome measure, was especially relevant for the modeled population. However, this outcome limits the studies generalizability to other potential target populations. It would be ideal if this study could be expanded to evaluate other populations, such as travelers and persons who live in high-risk areas. Additional economic evaluations such as ROI studies and logistic studies should also be conducted to help decision makers prioritize scare resources and determine investment for a *Campylobacter* vaccine.

Cholera

Cholera is a water-borne acute secretory diarrheal disease caused by the bacteria *Vibrio cholerae* and can be epidemic or endemic.[38] In 2012, 48 countries from all continents reported 245 393 cases to the WHO; 3034 deaths reported from 30 countries (global case-fatality rate (CFR) of 1.2%), with African countries reporting 67% of the total (2042 deaths).[39] This is a 58% decrease in the number of cases compared with 2011 (589 854 cases reported), however, the actual number of cases is known to be much higher than reported, due to limited surveillance and inconsistent case definitions, among other reasons.[39] Cholera notification is compulsory, yet countries can be reluctant to report cases due to fear of possible commercial sanction.[38] Several studies have evaluated the cost of cholera illness in developing countries.[40-43]

Economic burden: high income country

A MEDLNE search found no studies evaluating the economic burden of cholera in developed countries.

Economic burden: middle/low income country

One study evaluated the cost for all of the cases reported to the WHO in 2005, 2006, and 2007 in the African region (in 2002 $US).[41] This study focused on the costs of the hotel component of hospitalization, diagnosis, medicines, costs borne by patients (and accompanying family member), and productivity losses.

Table 1. Summary of the economic burden and economic value of vaccine for seven diarrheal diseases in high income and middle/low income countries (continued)

Pathogen	Economic Burden		Economic Value of Vaccine			Status of Vaccine Development
	High Income Country	Middle/Low Income Country	Disease in High Income Country	Disease in Middle/ Low Income Country	Travelers from High Income to Middle/ Low Income Country	
Norovirus	10 studies, total treatment costs in the US exceed $270 million annually,[17,19] costing over $5.5 billion with inclusion of productivity losses,[20] foodborne cases cost $2 billion annually,[21] cost of hospital outbreaks range from $37 968 to ≤201 690,[22-25,27] one case is estimated to cost the hospital $623 726	no published evaluations found*	1 study, vaccinating children <5 y and adults >65 y could provide net cost-savings when the cost of vaccination is <$25, for those 5- to 65-y-old vaccination cost $380 to $950 per case averted (50% efficacious, $25 cost, 12 mo protection), for adults ≥65 y of age, a $25 vaccine saved $147 per case averted ($25 cost, 24 mo protection20	no published evaluations found*	no published evaluations found*	candidates in clinical trials
Sapovirus	no published evaluations found*	no published evaluations found*	no published evaluations found*	no published evaluations found*	no published evaluations found*	none under development
Campylobacter	2 studies, cost ranged from $1747 million[21] (in the US) to €26.1 million (in Sweden) annually[35]	no published evaluations found*	no published evaluations found*	no published evaluations found*	1 study, vaccine could avert $191 947 in annual care costs for the US military, cost-effectiveness ratio of $1243/duty day lost averted[37]	none under development
Cholera	no published evaluations found*	2 studies, total costs ranged from $53.2 million to $128.1 million for all cases reported to the WHO and cost $541 per case in 2007,[41] in Indonesia, India, Bangladesh, and Mozambique, for all ages, a hospitalized case incurred a mean total cost ranging from $31.5 to $205.7 and total outpatient cost was $28.1[42]	no published evaluations found*	4 cost-effectiveness studies, cost-effectiveness varied by location and vaccination program[43-46] 1 study evaluated global stockpile, projected costs totaled $147 to $360 million for 54 million doses from 2013–2020, for an annual cost of $27–51 million[45]	no published evaluations found*	3 oral vaccines are currently licensed
Clostridium difficile	2 review studies,[47,50] the median cost per case ranges from $6117[53] to $16 464,[51] annual excess cost estimates range from ≥$496 million[51] to $4.8 billion[52]	no published evaluations found*	1 study, both a preventative vaccine and a recurrence preventative vaccine would be cost-effective or economically dominant (less costly and more effective) for almost every vaccine cost and efficacy tested[54]	no published evaluations found*	no published evaluations found*	candidates in clinical trials

*Based on MEDLINE search using various combinations of the following and considered studies published before December 2013: disease or pathogen name (e.g., norovirus, Norwalk virus, saprovirus, calicivirus, Campylobacter, campylobacteriosis, cholera, Clostridium difficile, CDI, enterotoxigeneic Escherichia coli, ETEC, E. coli, rotavirus, Shigella, shigellosis, travelers diarrhea), cost, economic, burden, disease burden, vaccine, cost-effectiveness, return on investment, cost-benefit.

Table 1. Summary of the economic burden and economic value of vaccine for seven diarrheal diseases in high income and middle/low income countries (continued)

Pathogen	Economic Burden		Economic Value of Vaccine			Status of Vaccine Development
	High Income Country	Middle/Low Income Country	Disease in High Income Country	Disease in Middle/ Low Income Country	Travelers from High Income to Middle/ Low Income Country	
Enterotoxigenic Escherichia coli (ETEC)	1 study, traveler's diarrhea cost an estimated $1460 for leisure travelers and $1996 for business travelers[56]	no published evaluations found*	no published evaluations found*	no published evaluations found*	2 studies, the WC/rBS oral cholera vaccine used for ETEC generated $24 to $41 in cost-savings for travelers (depending on ETEC risk),[56] for the US military ETEC vaccination would avert $334 672 care costs and its cost-effectiveness ranges from $821 to $1188 per duty day lost to diarrhea averted[37]	candidates in pre-clinical and clinical trials
Rotavirus	3 individual studies[61-63] 1 review study, cost €166 to €473 in the primary care setting and €1525 to €2101 in the hospital setting in areas for Belgium, France, Germany, Italy, Spain, Sweden, and the UK[59]	4 individual studies[64-67] 1 review study, cost $423 million ($3.47 per child) annually across all developing countries (without vaccination)[59] 1 systematic review, (reports data from 35 countries) inpatient care ranged from $79.91 to $858.40 and outpatient care ranged from $13.06 to $64.10[68]	10 studies, cost-effectiveness is variable, tending to be cost-effective only from the societal perspective[61,63,69-76]	7 studies, vaccination tends to be cost-effective or highly cost-effective,[64,66,67,77-80] vaccination was highly cost-effective across all the GAVI-eligible countries ($42/DALY; range: $31-$64/DALY)[80] 1 public financing and financial risk protection study[82] 1 study on the affordability of vaccination[79] 1 evaluation of fiscal consequences, changes in morbidity and mortality due to vaccination estimated to generate $2.5 billion in net taxes (in Ghana) and $28.8 million (in Vietnam)[83]	no published evaluations found*	2 vaccines are currently licensed
Shigellosis	1 study, foodborne cases resulted in an estimated cost of $120.9 million (range: $8.1 to $639.3 million; 2009 $US) annually[21]	1 study, average treatment cost for children <5 y was $8.65 (95% CI: $4.79 and 12.51 $US in Thailand[85]	no published evaluations found*	1 study, cross-sectional survey (in Bangladesh) 83% of households would pay a median of $0.05 (range: $0.01 to $0.15) for a vaccine with a life-time protection[89]	1 study, vaccination would avert $196 436 in military care costs and had a cost-effectiveness ratio ranged from $781 to $1860 per duty day lost due to diarrhea averted[37]	candidates under development and in clinical trials

*Based on MEDLINE search using various combinations of the following and considered studies published before December 2013: disease or pathogen name (e.g., norovirus, Norwalk virus, saprovirus, calicivirus, Campylobacter, campylobacteriosis, cholera, Clostridium difficile, CDI, enterotoxigeneic Escherichia coli, ETEC, E. coli, rotavirus, Shigella, shigellosis, travelers diarrhea), cost, economic, burden, disease burden, vaccine, cost-effectiveness, return on investment, cost-benefit.

The sum of the appropriate costs was multiplied by the number of reported cases that incurred each cost. Total costs ranged from $53.2 million (for 125018 cases in 2005) to $128.1 million (for 203564 cases in 2006) and cost an average $541 per case in 2007.[41] Strengths of this study include country-specific costs, appropriate cost inclusions and methodology, relevant populations, evaluation of various scenarios to account for differences in life-expectancy, evaluation of data over several years (as the number of cases varied from year to year), and a detailed breakdown of results. Limitations, pointed out by the authors, include the use of standard treatment guidelines (which may not be followed), assuming all cases would receive a diagnostic test, and the total economic cost of morbidity and mortality may not be captured as the study estimated the loss in the country's gross national income.

Poulos et al. determined various costs of culture-confirmed cholera in four endemic areas—Indonesia, India, Bangladesh, and Mozambique.[42] A hospitalized case incurred a mean total cost ranging from $31.5 (Bangladesh) to $205.7 (Indonesia) for all ages and $36.0 to $223.0 for children <5 y (2005 $US); total outpatient costs of illness were $28.1 for all ages and $23.5 for children under 5 y in Indonesia.[42] This study prospectively followed cases (both community and hospital cases) and included extensive and comprehensive costs. However, costs were obtained from questionnaires for post-cholera confirmed cases, which may induce recall bias; additionally cost for hospitalized cases came from a few facilities and offered a high level of care which may limit generalizability.

These reports vary by cost inclusions (e.g., medications, diagnostics, hospitalization, and clinic visits), perspectives (e.g., household, public, provide, and patient costs), methodology and data sources (e.g., models, questionnaires, and hospital and community-based studies), and regions of the world. However, they do show the substantial economic burden caused by cholera. Additional studies should evaluate the cost of cholera in an epidemic setting, which may be different than endemic illness.

Economic value of vaccines: disease in high income country

No published economic evaluations have been performed for cholera vaccination in developed countries.

Economic value of vaccines: disease in middle/low income country

There are a few economic and cost-effectiveness studies that examine cholera vaccination in different endemic areas, including Bangladesh, India, Indonesia, Mozambique, and Zanzibar.[43-46] One study evaluated different immunization strategies and looked at the impact of herd immunity,[44] while two studies evaluated the cost of a mass vaccination campaign - determining the total cost, cost per person (ranging from $3.93 to $30 per fully immunized person) and potential cost-savings.[43,46] These estimates varied with cost inclusions, for example $3.93 is for the vaccine only, while the $30 figure includes other components of the campaign (only 68% of this was vaccine cost).

In some locations, cholera vaccination was cost-effective (e.g., school based programs in India and Mozambique) and in others (e.g., Zanzibar, Indonesia) it was not cost-effective as the cost per DALY averted was more than three times the country's gross domestic product (GDP) per capita.[43,44] Cost-effectiveness depended on target population, vaccine cost, inclusion of herd immunity, and vaccination coverage rate. In one study, even if the vaccines were donated (i.e., no cost), vaccination would still cost more than the avoided public cost of illness and would still not be cost-effective.[43] On the other hand, including herd immunity made vaccination very cost-effective (i.e., ICER less than the GDP per capita), in some instances.[44]

It is difficult to compare across these studies as they employed differing methodologies (e.g., evaluating a targeted or mass oral cholera vaccination campaign, cluster randomized trial, and a model) and costs. For example, the cost per vaccine dose tends to be a key parameter in economic evaluations, and these studies utilized values that may not be comparable—ranging from $0.60 to $5 per dose, while in others it was calculated based on program costs for vaccination campaigns. While these studies had several strengths (e.g., evaluated relevant populations,[43,44,46] large populations/sample size,[46] included appropriate costs and factors impacting vaccination and costs,[43,44,46] performed sensitivity analysis,[44] explored various realistic scenarios,[44] and had appropriate cost inclusions[44]), limitations include interviews and questionnaires to gather costs (which may incur recall bias),[43,44] no probabilistic sensitivity analysis were performed in one study,[43] and the effects of waning immunity were not considered (although this most likely would have a little effect).[43,44] Additionally, herd protection is location specific, and with limited data, assumptions were made.[44] Evaluation of an actual campaign[43,46] can be helpful, but also limits generalizability to areas with other target populations, disease incidence, and other key factors.

Another analysis projected annual costs of a global cholera vaccine stockpile, for outbreak situations (using the at risk populations for epidemic cholera), and possible donor share of financing.[45] Projected costs totaled $147 to $360 million for 54 million doses from 2013–2020, for an annual cost of $27–51 million. The estimate contributions for donor financing ranged from $177 to $221 million. These estimates assume a vaccine price of $2.13 per dose, including 15% for insurance and shipping.[45] A vaccine stockpile can help make vaccine readily available during an epidemic and could motivate investment in vaccine capacity, ensuring an adequate supply. This study greatly adds to the literature and helps fill a gap that occurs for most other vaccines. It takes into account many relevant costs and factors, such as vaccine deployment, coverage rates, availability of vaccine and funding, it included the costs of vaccine purchase and delivery, but excluded stockpile management, monitoring, and research costs (which the authors point out may be minor or donated). This study also performs appropriate sensitivity analysis, which shows the robustness of the model and evaluates the stockpile under different circumstances.

Economic value of vaccines: travelers from high income to middle/low income country

A MEDLINE search found no studies evaluating the economic value of cholera vaccination in travelers from developed to developing countries. This is an important population to consider, especially for traveling healthcare workers who aid during outbreaks.

Additional studies should evaluate the economic benefit of cholera vaccination in an epidemic or outbreak scenario (some already evaluate vaccination's epidemiologic impact). These analyses may need to incorporate other concepts different from current studies, such as additional costs and campaign logistics to make large scale vaccination possible, to make them applicable to these situations. ROI and other investment studies can add to the growing body of literature on cholera vaccination and help garner support for to increase the vaccination supply and the generation of a stockpile.

Clostridium difficile (C. difficile)

Economic burden: high income country

Clostridium difficile (C. difficile) is the leading cause of infectious diarrhea in hospitalized patients and especially affects elderly and frail patients.[47] The incidence of *C. difficile* infection (CDI) has been on the rise,[48] more than doubling from 1991 to 2003 (from 65.6 to 156.6 per 100000 population).[49] More than a 2.5-fold increase (139000 to 349000) in the number of hospitalizations with any CDI discharge diagnosis has been noted in the US from 2000 to 2008 (with a 3.5-fold increase for a primary diagnosis), while the number of CDI-related hospitalizations appears to have leveled off between 2008 and 2010.[49] Similar tends have been seen in Europe since 2007 and may be declining; a 61% reduction in the incidence was noted in England from 2007 to 2010.[49] Of noticeable importance is the increased incidence of community-associated CDI in populations once considered to be low-risk; approximately 20% to 27% of all CDI cases are community-associated.[48,49]

Several papers have been published reporting the costs of CDI and two separate review articles highlight the economic burden of *C. difficile* reported by these studies.[47,50] The costs reported by these studies, as the reviews point out, vary greatly. This is in part explained by reports in various study populations (e.g., irritable bowel syndrome patients), differing methodology, cost inclusion and exclusion criteria, and the review articles found that few studies reported the true attributable cost of CDI.[47,50] An economic model (simulating up to 3 episodes for healthcare-acquired CDI in elderly patients) found the median cost per case ranges from $9179 to $16464, depending on perspective, with most of the cost incurred during a patient's primary episode.[51] This extrapolates to an annual burden of ≥$496 million (hospital perspective) to ≥$547 million (third party payer perspective) in the US alone.[51] A review analyzing the healthcare costs in US acute-care facilities (based on 2008 prevalence data from the Healthcare Cost and Utilization Project [HCUP]) suggests that CDI resulted in $4.8 billion in excess costs.[52] Analysis of clinical data in a propensity score matching study of adult inpatients in six Pennsylvanian hospitals estimates that healthcare-onset CDI cases had an attributable cost of $6117 (95% CI: $1659 – $10574; 2008 $US).[53] Cost estimates vary as they are driven by length of stay and total prevalence. These studies highlight the market for a *C. difficile* vaccine, which could potentially prevent substantial morbidity and save costs in developed countries.

Economic burden: middle/low income country

A MEDLINE search found no studies evaluating the economic burden of *C. difficile* in developing countries.

Economic value of vaccines: disease in high income country

C. difficile candidate vaccines are currently in clinical trials. Only one study has been done exploring the potential cost-effectiveness of a vaccine for *C. difficile*.[54] Lee et al. utilized a simulation model to evaluate two *C. difficile* vaccination scenarios: (1) a prevention vaccine for at-risk patients, and (2) a vaccine to prevent CDI recurrence from the hospital and third party payer perspectives. From the third party payer perspective, a preventative vaccine would be cost-effective or economically dominant (i.e., less costly and more effective) when the risk of CDI was ≥5% at almost every vaccine cost and efficacy tested. When preventing recurrences, vaccination was cost-effective and frequently dominant under most conditions simulated. Even if the vaccine cost $1600, a 75% efficacious vaccine was cost-effective ($5081/disability-adjusted life year [DALY] prevented). Both vaccine types were cost-effective in some scenarios when analyzed from the hospital perspective. While this study uses sound methodology and evaluates two different types of vaccinations under varying scenarios and presents results for a wide range of sensitivity analyses, results are limited to elderly patients (median age 71-y-old). Additionally, DALYs were used to evaluate effectiveness, which are typically used for health states in developing countries or those with a long duration.

No other economics evaluations have been done for a *C. difficile* vaccine. Future studies should evaluate the cost-effectiveness of such a vaccine under other conditions such as with updated data on the NAP1/BI/027 strain (which may be more severe) and with other patient populations (e.g., younger patients) to help identify a target population. Additionally, future studies should measure effectiveness in quality-adjusted life years (QALYs). Utilizing QALYs can help make these results comparable to other cost-effectiveness studies for other diarrheal pathogens to help prioritize research and funding for these vaccines as QALYs are traditionally used as a measure for developed countries (vs. DALYs which are traditionally used for developing countries or disease with outcomes lasting longer periods of time). Additionally, vaccine financing and ROI studies should be pursued, especially with a *C. difficile* vaccine on the horizon—there have been completed and ongoing clinical trials. These studies can help guide the development and licensure of a vaccine to help ensure success after it reaches the market.[7,32]

Economic value of vaccines: disease in middle/low income country

There have not been any studies published evaluating a potential *C. difficile* vaccine in a developing country.

Economic value of vaccines: travelers from high income to middle/low income country

Similarly, there have been no economic evaluations for a *C. difficile* vaccine among travelers.

Enterotoxigenic *Escherichia coli* (ETEC)

Enterotoxigenic *Escherichia coli* (ETEC) causes profuse watery diarrhea, is the most common cause of bacterial diarrhea in African, Asian, and Latin American children, and is the most common pathogen isolated (up to 60%) from those with travelers' diarrhea.[55,56]

Economic burden: high income country

A MEDLINE search did not find studies examining the cost of ETEC in developed countries; however, a cost-effectiveness analysis determined the cost of traveler's diarrhea to be an estimated $1460 for leisure travelers and $1996 for business travelers (2007 prices for a Canadian traveler).[56] These values are estimated using adequate assumptions with the little data that is available (e.g., there is no consensus of value for lost vacation day and authors utilized the net income for a work day after taxes in Canada); however, this may limit generalizability. Additionally, it is difficult to put a value on travel, and the duration of symptoms vary between travelers and destinations.

Economic burden: middle/low income country

ETEC is one of the two leading causes of hospitalization for diarrheal disease in low and middle income countries, identified in 28.1% of hospitalized patients[4] and is responsible for an estimated 300000 to 500000 deaths per year.[57] A systematic review of population based studies reported the incidence of ETEC in developing countries to range from 39 to 4460 infections per 1000 persons per year.[55] This review was through and included studies published between 1984 and 2005; however, living, environmental, sanitation, and other conditions affecting diarrheal disease may have changed since the mid-1980s, impacting ETEC's incidence. Additionally, the pathogen-specific incidence of diarrhea may not be generalizable outside study sites or even to the same population during a different season or year. As with developed countries, a MEDLINE search did not find any studies examining the cost of ETEC in developing countries.

The economic burden of ETEC needs to be clearly established, especially in endemic countries where is it a major cause of hospitalization. While the burden to travelers is important, it is necessary to determine the economic burden to those who are at great risk of infection and live in endemic areas, as they may be the more appropriate target population for vaccination. Quantifying the burden is essential to prioritize research and available funding for gastrointestinal diseases and to help determine how much to invest in prevention measures like vaccination.

Economic value of vaccines: disease in high income country

An ETEC specific vaccine does not yet exist, but there are candidates in pre-clinical and clinical trials. The economic value of a potential ETEC vaccine has not been evaluated in a developed country.

Economic value of vaccines: disease in middle/low income country

The cost-effectiveness of an ETEC vaccine has also not been evaluated in developing countries. An investment report by PATH reports on the market of an ETEC vaccine in endemic countries.[58]

Economic value of vaccines: travelers from high income to middle/low income country

To date there are no vaccines that have been approved that specifically target ETEC. However, the whole-cell/recombinant-B-subunit (WC/rBS) oral cholera vaccine also protects against ETEC in travelers. A cost-benefit analysis of vaccination for ETEC caused traveler's diarrhea with the oral cholera vaccine for leisure and business travelers determined that vaccination would be cost-effective at incidence rates of ETEC caused travelers' diarrhea above 13% for leisure travelers and 9% for business travelers.[56] Vaccination only generated $41 in cost-savings for leisure travelers when the risk of ETEC diarrhea was 20% and $24 for business travelers if the ETEC rate was 13% (costs are for Canadian travelers in 2007 prices).[56] In addition to those mentioned above, strengths include estimates for leisure and business travelers, which may vary, while a potential weakness of this study, is the lack of an effectiveness measure (i.e., not a cost-effectiveness model) as there are no studies on the loss of health or quality of life for travelers' diarrhea; however, a proxy could have been utilized to estimate this value. As the cost-benefit is highly dependent on the individual's value of the trip, it may be difficult to generalize results to various types of travelers and destinations.

The cost-effectiveness of an ETEC vaccine (costing $24.74 per dose in a two dose regimen) for the US military has been evaluated.[37] The annualized cost of care averted by a vaccine acquisition strategy was $334672 (2006 $US) and would cost $1188 per duty day lost to diarrhea (DDL) averted; without research and development costs (i.e., vaccination available immediately) the cost-effectiveness ratio would be $672/DDL averted. If given to troops deploying to the Middle East, it would cost $821 to avert one DDL.[37] Several strengths of this study include its design, inclusion (and exclusion) of vaccine development costs and timeframe, including various levels of treatment for the military population, and its outcome measure (DDL) was especially relevant for the modeled population, which was varied by treatment type and pathogen. However, the results cannot be expanded to other potential target populations with similar risks for ETEC as DDL are specific to military populations.

An investment report by PATH reported that ETEC vaccines may have an estimated potential of $600 million in revenue annually, 10 y after a global launch.[58] Their analysis resulted in an attrition-adjusted $339 to $624 million, without preclinical costs and before return on investment costs.[58] This report additionally outlines an ETEC vaccine target product profile (TPP) and reports on the different markets of these vaccines (i.e., endemic countries, travelers, and military). This report evaluated a wide range for vaccine uptake in each market investigated and performed sensitivity analyses to show impact on revenues, which help account for future uncertainties that may affect results such as the burden of disease, vaccine strain coverage and efficacy, and travel and endemic country market uptake.

Although an ETEC specific vaccine does not yet exist and there are candidates in pre-clinical and clinical trial, early economic studies can help guide its development and prioritize research funding. Beyond the studies highlighted above, additional work is needed to evaluate the economic value of an ETEC vaccine in non-traveler populations and where the risk of disease is higher. As the report by PATH shows, an ETEC vaccine could have a substantial monetary benefit. Reports such as these are extremely beneficial before a vaccine is licensed to determine its TPP and provide great insight into the markets and economic of vaccines prior to licensure, when it is most applicable. Additional studies can evaluate an individual's willingness to pay for a vaccine, as this may be different between persons living in endemic areas

and travelers. This information may be especially useful for traveler vaccinations as they may not be reimbursable by third party payers.

Rotavirus

Rotavirus is the leading cause of gastroenteritis worldwide. Although the true burden of rotavirus infection is likely an underestimate, annually it results in 25 million clinic visits, more than 2 million hospital admissions, and 527 000 deaths in children <5 y of age. In addition, it is estimated to cause 111 million gastroenteritis episodes for which care is not sought.[59] Globally, in 2004, rotavirus accounted for 527 000 deaths (95% CI: 475 000–580 000) among children <5-y-old; more than half of these deaths were in 6 countries (India, Nigeria, Congo, Ethiopia, China, and Pakistan), with 23% in India alone.[60]

Economic burden: high income country

Additional studies provide more detailed disease burdens for developed countries from 2004 to 2009.[11,13,14,31,61] While the mortality is rare in high income countries, the economic burden is considerable.[59] Rotavirus cost €166 to €473 in the primary care setting and €1525 to €2101 in the hospital setting in areas for Belgium, France, Germany, Italy, Spain, Sweden, and the UK (societal costs per case, in 2006 values). There are many studies determining the cost of rotavirus for many developed countries, several focusing on children less than 5 y of age.[61-63]

Economic burden: middle/low income country

Beyond the overall burden reported above, an additional study provides more detail for the rotavirus burden in Kenya.[64] The annual cost of rotavirus across all developing countries without vaccination is an estimated $423 million ($3.47 per child).[59] The cost of rotavirus in individual developing countries has also been reported.[64-67] Takemoto et al. preformed a systematic review of rotavirus cost of illness and productivity loss in Caribbean and Latin American countries.[68] The study reports data from 35 countries and results show that illness costs reported for the same country utilizing similar methods varied. For example, inpatient care ranged from $79.91 to $858.40 and outpatient care ranged from $13.06 to $64.10.[68] The authors conclude that although the studies included were conducted in the same geographic area and had a similar time frame, because of different methodologies, data sources, and perspectives, they could not be considered comparable.

The literature is rich with many studies determining the cost of rotavirus for many developed and developing countries, many focusing on the costs for children less than 5 y of age.[61-67] These studies vary in methodology (e.g., models, evaluation of survey data or medical records), costs included (e.g., only direct costs, direct and indirect costs, nonmedical costs such as transportation and food for caregivers staying at the hospital with ill children, healthcare facility and personnel costs, and testing and medication costs), and perspectives (e.g., healthcare system, societal, family costs, hospital). Additional differences in costs come from the different healthcare systems in these countries and their reimbursement rates. They also report on different outcomes, as some delineate costs for hospitalizations, outpatient visits, cost per child under 5 y, and costs to families with a child illness. As Takemoto et al. pointed out, these differences in studies make it difficult for them to be compared. However, all of these studies delineate the substantial burden of rotavirus around the world, showing its importance as a global player in gastrointestinal illness and its associated economic burden.

Economic value of vaccines: disease in high income country

Currently, there are two rotavirus vaccines available and both have been extensively studied and are cost-effective in various settings. There is a substantial body of literature on the economics of rotavirus vaccination in developed countries that have been published in the last few years.[61,63,69-76] The cost-effectiveness of rotavirus vaccination in developed countries is variable. For many developed countries, rotavirus vaccination is not cost-effective from a hospital perspective, but is from a societal perspective (as many cases are not hospitalized), in others it is cost-effective (but not cost-saving), and in others still it is not cost-effective.[63,69,71-75] As its cost-effectiveness is controversial, programs are not implemented in many European countries.[75] While one economic evaluations has shown that target vaccination of high-risk infants (i.e., prematurity, low birth weight, and complex chronic conditions) in developed countries may be a viable and cost-effective option.[75] Additional considerations such as herd immunity have improved the cost-effectiveness of vaccination.[73,74] In one study, herd protection significantly reduced the overall disease burden, making rotavirus vaccination more cost-effective, while ignoring these indirect effects made vaccination not cost-effective.[73] The cost-effectiveness of rotavirus vaccination in developed countries tended to be dependent on the model of administration, perspective, and vaccine cost price and efficacy, influence of productivity losses (or income loss) and case fatality rate. The cost-effectiveness also varied by the presentation of the vaccine (i.e., the 2-dose Rotarix and the 3-dose RotaTeq).[63,71,72]

Many studies evaluated the impact of vaccination on rotavirus outcomes and costs averted in developed countries, potentially saving millions of dollars.[61,70,76] Many studies also provided break-even price points (ranging from $7.98 to $42 per dose, depending on the perspective and number of doses required),[61,63,69] which can be helpful before a vaccine comes to the market to help decision-makers adopt an appropriate price to allow the vaccine to be successful in the market.

The studies evaluated in developed countries may have differing results and may not be comparable due to the differences between them. The type of study and methodology employed differed (e.g., Markov model, decision model, transmission model, Monte Carlo analysis), as was the time horizon evaluated also differed across studies (some were 5 y duration and one was 10 y). Cost-effectiveness was also evaluated with different costing inclusions, some considering only direct medical costs, others including direct and indirect, and still others including direct medical and nonmedical and indirect costs.

Economic value of vaccines: disease in middle/low income country

There is a substantial body of literature showing that rotavirus vaccination tends to be cost-effective or highly cost-effective for most developing countries from both the healthcare system and societal perspectives.[64,66,67,77-80] A few studies evaluated the economics of rotavirus vaccination with regards to other important considerations in developing countries. One of these

studies included the impact of rotavirus vaccine presentations in the cold chain. This study found Rotarix is preferred (over RotaTeq) as it is more cost-effective, its thermo-stable, and as it requires fewer doses, requires less storage space.[77] Another study included breastfeeding patterns (as it is considered protective against rotavirus) and determined that even with an increased uptake in breastfeeding, rotavirus vaccination would be highly cost-effective.[79] One study modeled the health and economic impact of rotavirus vaccination in 72 GAVI-eligible countries.[80] Between 2011–2030, vaccination in the these countries would avert more than 2.4 million childhood deaths and prevent >83 million DALYs, with >95% of this averted burden in African, Eastern Mediterranean, and Southeast Asian regions. Vaccination was highly cost-effective (2010 $US) across all the GAVI-eligible countries ($42/DALY; range: $31-$64/DALY); this varied across regions, but remained highly cost-effective in all 72 countries.[80]

A few studies determined the medical break-even cost of vaccination (ranging from $0.65 to $1.19 per dose).[64,66,78] A systematic review found that the break-even vaccine price ranged from $1 to $10 ($US), depending on the perspective taken by the study.[81] Many of the studies evaluated the total cost of vaccination, its potential savings, and the costs averted per child. Although these varied by country of interest and perspective, rotavirus vaccination was found to save millions of dollars (range: $0.3 million to $61.4 million) in several countries.[64,66,77-79] Other outcomes of interest evaluated include outpatient visits, hospitalization, deaths, and DALYs averted. Although these studies varied with cost inclusions, perspectives, rotavirus vaccine (2 vs. 3-dose vaccination), they all provided consistent results that rotavirus vaccination is highly cost-effective in developing countries. A systematic review focused on developing and low-income countries determined that all of the reviewed studies provide clear evidence that universal rotavirus vaccination was very cost-effective or cost-effective at a price of $7 per dose and could remain cost-effective at a price up to $25 per dose.[81] Although rotavirus vaccination is cost-effective in these countries, it may not be financially possible, especially at higher vaccine prices.[81]

A few other economic studies have evaluated the financial impact of rotavirus vaccination including a public financing and financial risk protection study,[82] an evaluation of fiscal consequences of changes in morbidity and mortality due to vaccination,[83] and the affordability of vaccination.[79] Kotsopoulos et al. evaluated the fiscal consequences of changes in morbidity and mortality due to rotavirus immunization by measuring the lifetime productivity capacity and government related taxes while taking into account vaccination costs.[83] In Ghana, rotavirus immunization was estimated to generate $2.5 billion in net taxes up to 65 y of age, in Vietnam, this was estimated to be $28.8 million; both suggesting a positive return for the government in the long run.[83] These studies provide additional information on the economic landscape to the rotavirus vaccine literature; however may have limited generalizability as countries have differing tax systems and there is heterogeneity in income within as well as across countries. ROI studies are still missing from the wealth of rotavirus vaccination literature.

Economic value of vaccines: travelers from high income to middle/low income country

A MEDLINE search found no studies evaluating the economic value of rotavirus vaccination in travelers.

It is important to note that a majority of these studies (both in developed and developing countries) have been published after the rotavirus vaccine had been licensed. Once a vaccine reaches the market, it is extremely difficult to change characteristics such as price, efficacy, and target population, all of which studies such as these attempt to delineate. This makes these studies have less of an impact and is a substantial limitation. While a study like Fischer et al., which evaluated the economic value of the rotavirus vaccine pre-licensure, is beneficial not only to developers, manufacturers, but also policy makers, especially for countries with scarce economic resources.

Shigellosis

Economic burden: high income country

The *Shigella* bacteria is a major cause of dysentery. *Shigella* outbreaks occur globally and are a common cause of travelers' diarrhea. Few reports of shigellosis burdens exist for developed countries and they vary widely.[10,11,34] Reports vary widely as not all cases are identified, for example, *Shigella* was responsible for an estimated 131 254 (90% credible interval: 24 511–374 789) foodborne cases in 2006 in the US, of which only 14 864 cases were laboratory confirmed.[10] These cases resulted in an estimated annual cost of $120.9 million (range: $8.1 to $639.3 million; 2009 $US) and in the loss of 545 (range: 14 to 3372) QALYs annually.[21] As mentioned above, this study includes costs for physician visits, hospitalization, and self-liming disease, and productivity losses (adjusted for the employment rate). However, the costs and QALYs utilized by the authors were an age-weighted national average and cost and health outcomes vary by age, which may limit their results.

Economic burden: middle/low income country

In developing countries, *Shigella* was isolated (utilizing passive surveillance in health centers and hospitals) from 5% of diarrhea episodes in six Asian countries (China, Vietnam, Thailand, Bangladesh, Pakistan, and Indonesia) between 2000 and 2004.[84] This ranged from 2% to 13% across countries, for an incidence of treated shigellosis of 2.1 episodes per 1000 per year in all ages and 13.2 per 1000 per year in children under 5 y.[84] This was a large, prospective, population-based study that utilized standardized protocols and had a large sample size (over 600 000 persons across 6 study sites) for duration of 3 y. This time period is adequate as some *Shigella* serotypes vary geographically and temporally. However, as passive surveillance was used, this may actually be an underestimate of the burden of shigellosis. In the GEMs study, *Shigella* was significantly associated with moderate-to-severe diarrhea individually at all seven study sites (in Africa and Asia) in children <5 y.[36] The strengths and weaknesses of this study have already been described.

Additionally, individual studies have reported incidences and annual cases in a number in other countries, including Thailand, Israel, Jordan, and Argentina.[85-88] Only one of these studies evaluated treatment cost of shigellosis: for children <5 y in Thailand the average cost was $8.65 (95% CI: $4.79 and 12.51;

2006 $US) with a majority of costs borne by hospitalized cases.[85] This study only included the public treatment cost (cost to the health facility) and is limited to those seeking care in one district in Thailand, costs may not be generalizable to the entire country.

There is very limited data on the cost of shigellosis. Studies are limited to foodborne cases in the US and the cost in children in <5 y old Thailand, which is from a limited number of episodes (137) in one district.[85] Other cost of illness and economic evaluations are necessary to help delineate the true burden of *Shigella* to aid in the prioritization of funds and research. Determining the burden in other endemic regions, especially as it is significantly associated with diarrhea, can provide additional insight into the scope of the problem caused by *Shigella* and determine how much can be invested in prevention measures.

Economic value of vaccines: disease in high income country

Currently, *Shigella* vaccines are under development and undergoing clinical trials. However, the economic value of a *Shigella* vaccine has not been evaluated in developed countries.

Economic value of vaccines: disease in middle/low income country

A MEDLINE search found no studies evaluating the cost-effectiveness of vaccination for developing countries. However, in a different approach, a cross-sectional survey study conducted in Dhaka, Bangladesh found that 93% of respondents thought a vaccine could prevent bloody diarrhea (of which, 80–90%, is caused by *Shigella* spp.) and 99% reported being willing to receive a vaccine if one were available. If a vaccine could provide life-time protection, 83% of households said they would pay a median of $0.05 (range: $0.01 to $0.15) for the vaccine, which is <1% of their median weekly income.[89] A strength of this study is its design in utilizing household surveys to gather information on individual perspectives. While this study provides useful information for public health officials, its results may be limited as it was conducted in urban slum area and may not represent persons living in other areas or locations.

Economic value of vaccines: travelers from high income to middle/low income country

A modeling study by Riddle et al. determined the potential economic value of a *Shigella* vaccine for the US military. They reported the annualized cost of care averted by a *Shigella* vaccination acquisition strategy would be $196436 and marginal cost-effectiveness ratio of $1860 per duty day lost due to diarrhea (DDL) averted (2006 $US).[37] This estimate includes upfront costs for research and development. If the vaccine were available immediately, it would cost $1104/DDL averted and if given to only troops in sub-Sahara Africa, vaccination would cost $781/DDL. Strengths and weakness of this study have already been described.

These studies show the value of a *Shigella* vaccine and how much it is worth to an individual and its economic value for military. Expanding the cost-effectiveness analysis to include other outcomes measures besides DDL and other potential populations could make this analysis more generalizable and help determine its value in other populations. Additional studies are also needed to determine target populations, vaccine price points, and efficacy thresholds. Vaccine financing, ROI, and logistic studies would also be beneficial to help decision makers make a case for continued vaccine development.

Other pathogens

There are several diarrheal pathogens for which there are no vaccines available and few to no analyses of their potential economic value. These include: cyclospora, *giardia*, astrovirus, *Clostridium perfringens*, *Entamoeba histolytica*, *Cryptosporidium, Enteropathogenic E. coli,* and non-typhoid *Salmonella*. These pathogens contribute to the substantial burden of gastroenteritis worldwide. Together, *Entamoeba histolytica*, *Cryptosporidium, Enteropathogenic E. coli,* and non-typhoid *Salmonella* account for 333 DALYs per 100000 population and 325.3 thousand deaths worldwide in 2010.[1,2] *Giardia*, *Cryptosporidium, Entamoeba,* and, *Cyclospora* are among the most common enteric protozoa causing illness in developed countries.[90]

Considering the burden of these pathogens, cost of illness and other studies to determine their economic burden would be extremely beneficial. These studies can help us understand the impact that these pathogens have and help prioritize limited funding for research and interventions. Without studies like these it is difficult for policy makers to adequately distribute scarce resources or determine investment options for funders.

Conclusions

While there have been studies on the economic burden for diarrheal diseases and the potential (for vaccines under development) and estimated (for vaccines currently on the market) economic value of vaccines to prevent diarrhea diseases, many gaps remain. A surge of economic studies tends to emerge close to or immediately after the licensing of a vaccine, as has been seen with the rotavirus vaccines. However, this may be too late to substantially change the characteristics and implementation of the vaccine. Earlier explorations, while the vaccines and their roll-out plans are more malleable may be helpful to provide earlier guidance. More and earlier economic information are important for the whole range of vaccine stakeholders such as:

- Scientists and vaccine developers: adjust target product profiles (TPPs) and development plans accordingly.[7]
- Funders: identify which vaccines to fund and at what levels.
- Policy makers and public health officials: select target populations and make other recommendations.
- Third party payers: determine reimbursement policies.
- Healthcare workers: choose whom should receive the vaccine and under what circumstances
- Vaccine suppliers and distributors: determine strategies and operations.

Economic and financing studies are particularly important for populations with limited financial resources such as those in lower and middle income countries. Often, as in the case of the rotavirus vaccine in Asia, the true cost of a vaccine to a particular stakeholder may vary quite substantially based on available co-funding or negotiated prices.[91] Economic and financing studies can help structure the appropriate financing

to make purchase and distribution of the vaccines more feasible. For instance, in the case of *Shigella* and oral cholera vaccines in Asia, uncertainty about the disease burden and high prices of the current vaccines and their moderate protection levels have inhibited their adoption.[92] Moreover, the cost of vaccine delivery in middle and low income countries should not be overlooked, as large new vaccines such as rotavirus can lead to bottlenecks that inhibit the delivery of other vaccines.[93-95]

Evaluating the economics of vaccines for nearly all types of diarrheal diseases bring particular common challenges. Since many episodes of diarrheal diseases go undiagnosed, burden may be underestimated or mistakenly ascribed to the wrong causes or pathogens. Moreover, the existence of genetic diversity and multiple serotypes (e.g., *Shigella* and norovirus) and interactions with co-morbidities can lead to highly variable health outcomes and thus substantial variability in costs. Moreover, asymptomatic rates are in many cases unclear. Also, the efficacy and effectiveness of vaccines can be difficult to measure. Improving the amount and quality of different types of clinical and epidemiological data in turn will improve the precision of economic studies. Many existing studies do not fully account for the indirect effects of diarrheal diseases such as impairment of cognitive and physical growth and productivity losses. It is also important to remember that the economics of such vaccines may evolve over time. As the incidence of disease decreases so may the value of the vaccine. Changes in vaccine cost, efficacy, and other types of treatments and preventive measures can also have impact. Economic models can help explore the effects of changes in different parameters.

While the literature on the economics and financing of vaccines against diarrhea diseases is growing, there is considerable room for more inquiry. Substantial gaps exist for many pathogens, circumstances, and effects. Economics and financing studies are integral to vaccine development and implementation. Without the proper funding and incentives, potential vaccines may not reach the market or appropriate populations to the detriment of millions and potentially billions of lives.

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