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Systematic Review Of The Economic Value Of Diarrheal Vaccines

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Abstract

Diarrheal disease is a leading cause of child mortality in low-income settings and morbidity across a range of settings. A growing number of studies have addressed the economic value of new and emerging vaccines to reduce this threat. we conducted a systematic review to assess the economic value of diarrheal vaccines targeting a range of pathogens in differ- ent settings. The majority of studies focused on the economic value of rotavirus vaccines in different settings, with most of these concluding that vaccination would provide significant economic benefits across a range of vaccine prices. There is also evidence of the economic benefits of cholera vaccines in specific contexts. For other potential diarrheal vaccines data are limited and often hypothetical. Across all target pathogens and contexts, the evidence of economic value focuses the short-term health and economic gains. Additional information is needed on the broader social and long-term economic value of diarrhea vaccines.

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Systematic review of the economic value of diarrheal vaccines

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Diarrheal disease is a leading cause of child mortality in low-income settings and morbidity across a range of settings. A growing number of studies have addressed the economic value of new and emerging vaccines to reduce this threat. we conducted a systematic review to assess the economic value of diarrheal vaccines targeting a range of pathogens in different settings. The majority of studies focused on the economic value of rotavirus vaccines in different settings, with most of these concluding that vaccination would provide significant economic benefits across a range of vaccine prices. There is also evidence of the economic benefits of cholera vaccines in specific contexts. For other potential diarrheal vaccines data are limited and often hypothetical. Across all target pathogens and contexts, the evidence of economic value focuses the short-term health and economic gains. Additional information is needed on the broader social and long-term economic value of diarrhea vaccines.

Introduction

Diarrheal disease is a leading cause of child mortality in many low-income countries, accounting for 700 000 deaths annually among children under 5 y of age.[1] It is also a leading cause of hospitalization among children under 5 in low and upper income countries.[2] Over the past several years, two rotavirus diarrhea vaccines have been developed and licensed by the US Food and Drug Administration and pre-qualified by the World Health Organization.[3] This has sparked the first wide-scale introduction of a diarrheal vaccine into routine vaccination schedules in developed and developing countries. The successful development of a third vaccine with a substantially lower cost (ROTAVAC) could accelerate introduction into additional low-income settings, including India.[4] The introduction process for rotavirus vaccines included substantial attention to documenting the economic value at the national and global levels[5].

Although rotavirus is often the most common cause of moderate to severe diarrhea in children under 5,[6] other diarrheal pathogens contribute substantial health and economic burden. Vaccines currently exist for other diarrheal infections, including cholera and typhoid.[7] Additional vaccines against *Shigella* and enterotoxigenic *Escherichia coli* (ETEC) are also under development. This raises a question of whether there is adequate evidence of the economic value of these other vaccines in different settings. While there is substantial work on the economic value of rotavirus vaccines, this may not be directly transferable to other anti-diarrheal vaccines. Unlike rotavirus, other enteric pathogens (e.g., cholera, typhoid, *Shigella* and ETEC) tend to be more heterogeneous in their distributions, in part due to their transmission through poor water, sanitation and hygiene.[6] In addition, these other pathogens can affect a much broader age range of individuals and not just children under 5 y.

Assessments of economic value of vaccines typically include analyses of the economic benefits themselves (e.g., averted medical costs or productivity losses), as well as assess whether the health benefits of vaccine introduction provided good economic value in comparison to the investment cost. The most common economic benefits include direct medical costs averted (i.e., reduced medications, diagnostics, and services), other direct expenses such as travel, and reduced productivity losses (indirect costs). Evaluations also assess the economic value of vaccines as an investment, in comparison to the health or economic gains. Although terminology differs slightly, cost-effectiveness analyses compare net costs of vaccines to the health gains measured as Disability-Adjusted Life Years (DALYs). Cost-utility analyses compare net costs to health gains measured as Quality-Adjusted Life Years (QALYs). Cost-benefit analyses compare economic costs of vaccines to the total monetized value of benefits, either as a Benefit-Cost Ratio (BCR) or net benefit.

In general, assessments of the economic value of rotavirus vaccines have focused on the costs associated with acute illness and mortality. However there is growing evidence that diarrheal illness can have important long-term consequences including under-nutrition,[8] cognitive function,[9] chronic gastrointestinal conditions,[10] metabolic syndrome,[11] and rheumatologic conditions.[12,13] It is unclear the extent to which these outcomes may affect the overall economic value of the vaccines.

Several authors have also argued that traditional economic evaluations may underestimate the value of the vaccines, by ignoring broader health and social effects. Barnighausen and colleagues identify three categories of broader benefits.[14] These include outcome-related productivity gains behavior-related productivity gains, and community externalities. Outcome-related productivity gains refer to improved cognitive function

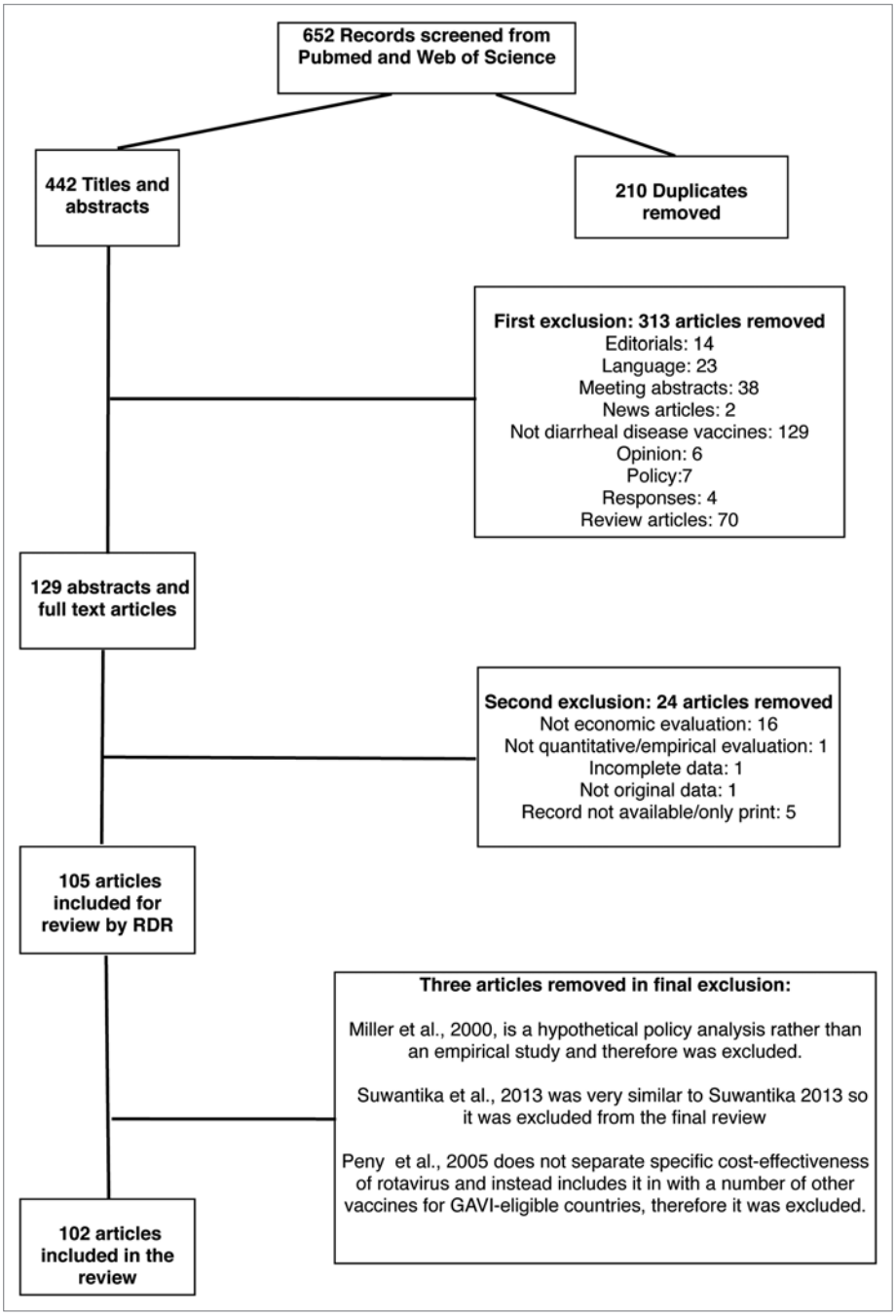

Figure 1. Article exclusion and selection flowchart.

and educational attainment. Behavior-related productivity gains are based on the potential effect of reduced child mortality on reduced fertility. This demographic response would presumably result in an increased per child investment in health and education, thus increasing human capital. It is also possible that the full household economic value of a vaccine may exceed the expected cost reduction if they are willing to pay a risk premium to avoid worrying about whether their child gets sick. Drummond and colleagues refer to this as "utility in anticipation."[15] Others have argued that the household costs associated with diarrheal disease may have a disproportional effect on poor households and may contribute to structural impoverishment and poverty traps which can create a macro-economic drag on an economy.[16,17]

The purpose of this paper is to systematically review the evidence of the economic value of diarrheal vaccines. Our primary questions include whether there is evidence of the economic value of diarrheal vaccines, and how these benefits differ by setting, vaccine type, and other factors. This includes assessing the economic benefits of vaccination, as well as the economic value of vaccination as an investment (compared with the health benefits). We also explore the extent to which the literature addresses the potential broader economic benefits of diarrheal vaccines.

Methods

Eligibility criteria

A systematic search to locate peer-reviewed articles on economic evaluations of enteric vaccines was conducted in two of the major electronic databases (PubMed and Web of Science). The search was performed in March of 2014 and the limits of the search were: English language and a publication date ranging from 2000 to 2014. We followed the guidelines set forth by.[18]

The articles selected for the final review had to be specific to enteric vaccines and economic evaluations. No restriction was placed on type of population. Similarly, there were no restrictions in the country or region studied. Articles not related to enteric vaccines or that were not economic evaluations were excluded in the final review. Other exclusion criteria included articles with incomplete data, articles without original data, editorials, meeting abstracts and reviews.

Search strings

The search string used in the different databases (modified according to each of the search features) was: ("cost-effectiveness" OR "economic evaluation" OR "cost of illness" OR "cost benefit analysis") AND ("diarrhea" OR "diarrhoea" OR "rotavirus" OR "salmonella" OR "norwalk virus" OR "cholera" OR "ETEC" OR "shigella" OR "gastroenteritis" OR "norovirus") AND ("vaccine" OR "vaccination" OR "immunization")

Eligibility assessment and study selection

Table 1. Summary of economic evaluations of diarrheal vaccines in low- and middle-income counties, by pathogen. All base case and range values are in 2014 inflation-adjusted US$

Author (Reference)	Year	Location	Vaccine	Target population	Type of analysis*	Base case	Range	Units
Abbott et al.[45]	2012	Ghana	Rotavirus	Universal child	CeA	46	2–72	$/DALY
Atherly et al.[46]	2009	72 GAVI-eligible countries	Rotavirus	Universal child	CeA	96–515	17–515	$/DALY
Atherly et al.[47]	2012	72 GAVI-eligible countries	Rotavirus	Universal child	CeA	47	34–260	$/DALY
Bakir et al.[48]	2013	Turkey	Rotavirus	Universal child	CBA	-31,161,329	(-29,371,560)-(-32,221,605)	US$ offset with vaccine
Berry et al.[27]	2010	Malawi	Rotavirus	Universal child	CeA	6	6–89	$/DALY
Centenari et al.[35]	2010	Northeast Brazil	Rotavirus	Mass campaign	CBA	(-10,106)-1,428,824	-	US$ offset with vaccine
Chang et al.[49]	2013	Taiwan	Rotavirus	Universal child	CeA	CS-95,382	-	$/DALY
Chotivitayatarakorn et al.[50]	2010	Thailand	Rotavirus	Universal child	CeA	455	228–933	$/DALY
Clark et al.[51]	2009	Peru	Rotavirus	Universal child	CeA	779	289–787	$/DALY
Connolly et al.[33]	2012	egypt	Rotavirus	0–72 y after vaccination	CBA	6,955,644–64,919,348	-	Incremental Net Present Value (US$)
Constenla et al.[52]	2008	Brazil	Rotavirus	Universal child	CeA	890	472–890	$/DALY
Constenla et al.[36]	2009	Mexico	Rotavirus	Universal child	CeA	1,401	373–1,401	$/DALY
Cook et al.[53]	2008	Kolkata, India; North Jakarta, Indonesia; Hue, Vietnam; Karachi, Pakistan	Typhoid	Adults and children (2–15 y old)	CeA	181–4,648	181–4,817	$/DALY
Cook et al.[29]	2009	Kolkata, India	Typhoid	Adults and children (2–15 y old)	CeA	181–558	-	$/DALY
Cook et al.[28]	2009	Kolkata, India	Cholera	Adults and Children	CBA	779,032	-	Total Social Benefits (US$)
de Blasio et al.[54]	2014	Kazakhstan	Rotavirus	Universal child	CeA	19,143–25,347	-	US$/Life year gained
De la Hoz et al.[55]	2010	Colombia	Rotavirus	Universal child	CeA	10,779	-	$/DALY
de Soarez et al.[56]	2008	Brazil	Rotavirus	Universal child	CeA	525–875	-	US$/Life Years Saved
esposito et al.[57]	2011	India	Rotavirus	Universal child	CeA	26	CS-239	$/DALY
Fischer et al.[58]	2005	Vietnam	Rotavirus	Universal child	CeA	122	CS-258	$/DALY
Flem et al.[59]	2009	Kyrgyzstan	Rotavirus	Universal child	CeA	260	CS-260	$/DALY
Ho et al.[60]	2008	Hong Kong, China	Rotavirus	Universal child	CeA	CS-587,413	CS-651,573	$/DALY
Isakbaeva et al.[61]	2007	Uzbekistan	Rotavirus	Universal child	CeA	657	126–1,322	$/DALY
Jeuland et al.[30]	2009	Mozambique	Cholera	Children, adolescents, and mass campaign	CBA	1.3	1.2–6.4	Benefit-Cost ratio
Jeuland et al.[62]	2009	Bangladesh, India, Indonesia, Mozambique	Cholera	All ages	CeA	2,150–28,797	1,329–28,797	$/DALY
Jeuland et al.[63]	2009	Low-income countries	Cholera	Children, adolescents, and mass campaign	CBA	1.1	0.1–9.4	Benefit-Cost ratio
Jit et al.[64]	2011	Armenia	Rotavirus	Universal child	CeA	50–957	50–10,692	$/DALY
Kim et al.[21]	2008	Hue, Vietnam	Cholera	All ages	wTP	71	-	Average willingness to pay (US$)
Kim et al.[65]	2009	Vietnam	Rotavirus	Universal child	CeA	726	-	$/DALY
Kim et al.[66]	2010	72 GAVI-eligible countries	Rotavirus	Universal child	CeA	CS-37,112	-	$/DALY

Abbreviations: *CeA, Cost-effectiveness analysis; CUA, Cost-utility analysis; CBA, Cost-benefit analysis; wTP, willingness to pay.

Table 1. Summary of economic evaluations of diarrheal vaccines in low- and middle-income counties, by pathogen. All base case and range values are in 2014 inflation-adjusted US$ (continued)

Author (Reference)	Year	Location	Vaccine	Target population	Type of analysis*	Base case	Range	Units
Kim et al.[67]	2011	Zimbabwe	Cholera	Mass campaign	CeA	CS-3,308	-	$/DALY
Kim et al.[68]	2011	72 GAVI-eligible countries	Rotavirus	Universal child	CeA	1,135	CS-37,156	$/DALY
Kotsopoulos et al.[34]	2013	Ghana and Vietnam	Rotavirus	Universal child	CBA	9,229,830–29,705,200	-	Incremental Benefit (immunization tax)
Lauria et al.[31]	2009	South and Southeast Asia	Typhoid	Mass campaign	CBA	283	-	Median US$/ case avoided
Liu et al.[69]	2012	China	Rotavirus	Universal child	CeA	1,648–8,142	CS-12,471	$/DALY
Muangchana et al.[70]	2012	Thailand	Rotavirus	Universal child	CeA	148,460–164,784	148,460–172,869	$/DALY
Ortega et al.[71]	2009	Arab Republic of egypt	Rotavirus	Universal child	CBA	474	-	$/DALY
Patel et al.[72]	2013	Pakistan	Rotavirus	Universal child	CeA	159	-	$/DALY
Podewils et al.[73]	2005	Asia	Rotavirus	Universal child	CeA	150–12,177	CS-21,997	$/DALY
Poulos et al.[74]	2004	India	Typhoid	Universal child	CBA	CS-142	-	US$ / case averted
Rheingans et al.[75]	2009	Low and middle-income countries grouped by wHO regions	Rotavirus	Universal child	CeA	16–501	CS-55,424	$/DALY
Rheingans et al.[37]	2012	25 GAVI-eligible countries	Rotavirus	Universal child	CeA	32–158	21–276	$/DALY
Rose et al.[76]	2009	India	Rotavirus	Universal child	CeA	247	245–247	US$ / Life year saved
Sardar et al.[22]	2013	Zimbabwe	Cholera	Outbreak	CeA	18,990–1,113,945	-	US$ / case averted
Schaetti et al.[23]	2012	Tanzania	Cholera	Adult	CeA	34,778	-	$/DALY
Smith et al.[77]	2011	Bolivia	Rotavirus	Universal child	CeA	162	CS-505	$/DALY
Stack et al.[78]	2011	72 GAVI-eligible countries	Rotavirus	Universal child	CBA	40,100,449,504	-	US$ saved / case averted
Suwantika et al.[79]	2013	Indonesia	Rotavirus	Universal child	CeA	190–198	160–222	$/QALY
Tate et al.[38]	2009	Kenya	Rotavirus	Universal child	CeA	33	CS-713	$/DALY
Tate et al.[80]	2011	Uganda	Rotavirus	Universal child	CeA	5	-	$/DALY
Tu et al.[81]	2012	Vietnam	Rotavirus	Universal child	CeA	771	CS-771	$/QALY
Valencia-Mendoza et al.[82]	2008	Mexico	Rotavirus	Universal child	CeA	5,426	-	US$ / life-year saved
van Hoek et al.[83]	2012	Kenya	Rotavirus	Universal child	CeA	155–315	155–320	$/DALY
Verguet et al.[39]	2013	India and ethiopia	Rotavirus	Universal child	CeA	8,742–17,484	8,742–28,411	Financial risk protection afforded (US$)
wang et al.[84]	2009	China	Rotavirus	Universal child	CBA	CS	All CS	US$ saved / case averted
whittington et al.[85]	2012	Developing Countries	Cholera	Mass campaign	CBA	0–2	0–2	Benefit cost ratio
wilopo et al.[86]	2009	Indonesia	Rotavirus	Universal child	CeA	148	-	$/DALY

Abbreviations: *CeA, Cost-effectiveness analysis; CUA, Cost-utility analysis; CBA, Cost-benefit analysis; wTP, willingness to pay.

To analyze the search results author RDR set the eligibility criteria. Following this, authors MPA and JDA identified the exclusion criteria to use for both the first and second exclusion. Two teams were formed with authors PC and JA as one team and authors MPA and JDA on the other to independently review the results and apply the selection criteria. Each author performed the eligibility assessment in a standardized manner. Each team followed an identical search strategy.

After removal of duplicates, the titles and abstracts were read to ascertain the article r[illegible]cording to each author's interpretation. This step was the first exclusion, which involved the removal through a categorization of articles by editorials language, meeting abstract, news articles, not enteric vaccines, opinion articles, policy briefs, responses and reviews. After the first exclusion, teams compared results and settled disagreements on inclusion of articles through consensus (**Fig. 1**). A second exclusion was performed based on a more rigorous full text examination of the articles selected in the first exclusion. The second exclusion included articles that did not have complete data, articles that were not economic evaluations, articles without original data, studies that did not have quantitative or empirical data and those records whose full text was not available.

Data collection and data items

For the final set of selected articles, a data extraction sheet (see **Supplemental Material**) was developed that was used throughout this step. An initial pilo*t* test of the table was performed with 15 articles, in order to clarify and modify categories. After this JC, JDA, JA, and MPA extracted the following information from the included articles: Data were extracted on citation, sponsor, location, pathogen, population, type of analysis (cost-effectiveness, cost-utility, cost-benefit, or other), perspective, types of costs included, health outcomes included, base currency, and whether distributional effects were considered. The main outcomes included summary measures (cost/DALY, cost/QALY, benefit-cost ratio), range, key variables influencing results, and authors conclusions. All cost measures were recorded in the published currency, and were subsequently converted to 2014 US dollars for comparison. For the full variable list, see Appendix 1 in **Supplemental Material**. The extraction results were validated by having authors JDA, JA and PC manually identify the extracted data within the articles and cross checking each entry. Disagreements on placement of items or classifications in the table were resolved through consensus.

Results

A total of 102 articles were included in the final review (**Fig. 1**). The systematic search of PubMed and Web of Science provided a total of 652 citations. Following the removal of duplicates, 442 articles remained. Of these, 313 were discarded after reviewing the titles and abstracts because they did not meet the inclusion criteria (for example, they were editorials, meeting abstracts, policy briefs or review articles). The full text of the remaining 129 citations was studied in greater detail, after which 24 additional articles were removed during the second exclusion. 105 studies were retained for review by author RDR, who identified three additional articles to be excluded.

Our search identified a total of 102 eligible studies on the economic value of diarrheal vaccines (**Tables 1,2, and 3**, **Fig. 2**). The most widely studied pathogen was rotavirus, accounting for 82% (84) of the eligible studies. This was followed by cholera with 11% (11) and typhoid with 5% (5). One study considered Norovirus[19] and Riddle et al.[20] considered *Campylobacter*, ETEC, *Shigella* vaccines and a hypothetical multiplex vaccine in deployed soldiers. The studies also covered a wide range of settings. A total of 45 studies (44%) focused on high-income settings and 57 (56%) examined low- and middle-income settings.

Most studies focused on universal access to childhood vaccination. This was in part a reflection of the high number of studies on rotavirus. Other studies considered targeted introduction in outbreak settings[21-23] or among travelers.[20,24-26]

The studies varied in what benefits were included in the analysis. The majority of studies (98%) included estimates of the direct medical costs averted through vaccination. Sixty-four studies (63%) included other direct costs. Productivity losses for caregivers or patients were included in 62 studies (61%) and were more likely to be included in studies in high-income settings compared with low-income settings (**Fig. 3**). A small number of studies included the consumer surplus or willingness to pay among parents.[21,27-32]

We found no studies that included long-term health consequences of diarrheal disease or the economic value of preventing them. However, two studies did estimate the long-term fiscal consequences of rotavirus mortality and morbidity in terms of labor productivity and tax revenue differences in immunized vs. non-immunized cohorts.[33,34] We also found no studies that estimated changes in fertility due to reduced child mortality, nor the economic value of such reductions. Only 14 studies considered the distributional effects of diarrheal vaccines.[21,22,27-33,35-39]

The studies predominantly used one of three summary measures: cost-effectiveness ratio (cost/DALY), cost-utility ratio (cost/QALY), or benefit cost ratio (BCR). A number of studies also included net costs as a secondary summary measure. Studies in low-and middle-income settings were more likely to consider cost per DALY and those in high-income setting were more likely to report cost per QALY or BCR as a summary measure.

While the studies used a wide range of criteria, the majority concluded that the diarrheal vaccine would provide good economic value over a range conditions considered. Most studies provided a base case estimate, many emphasized that the actual realized economic value would depend on the price of vaccines and the cost of delivery. This was particularly true for rotavirus vaccines during early stages of introduction and for other diarrheal vaccines that have not fully introduced.

Discussion

Substantial evidence exists for the economic value of preventing rotavirus diarrhea in a wide range of settings. In high-income settings, studies emphasized economic value in terms of the direct and indirect costs averted, in comparison to the costs of vaccination. In low-income settings the authors often emphasized economic value in terms of the health returns (DALYs) to the financial investment in vaccination. In middle-income settings, both types of value were evidenced. The evidence of economic value for rotavirus vaccine introduction appears to have been important in justifying investment by national governments, international partners, and in some settings households

Table 2. Distribution of diarrheal pathogens considered in studies of economic value of vaccines, by income setting. All base case and range values are in 2014 inflation-adjusted US$ (continued)

Author (Reference)	Year	Location	Vaccine	Target population	Type of analysis*	Base case	Range	Units
Atkins et al.[87]	2012	england and wales	Rotavirus	Universal child	CUA	CS-58,820	CS-92,566	$/QALY
Bartsch et al.[19]	2012	USA	Norovirus	Mass campaign	CBA	CS-3,497	-	Cost savings (US$)
Bilcke et al.[88]	2009	Belgium	Rotavirus	Universal child	CUA	85,329–109,971	12,661–109,971	$/QALY
Bruijning-Verhagen et al.[89]	2013	Netherlands	Rotavirus	Universal child and adolescents	CUA	3,693–230,128	-	$/QALY
Chodick et al.[90]	2009	Israel	Rotavirus	Universal child	CUA	13,522–37,725	13,522–62,089	$/QALY
Coyle et al.[91]	2012	Canada	Rotavirus	Universal child	CUA	CS-134,360	-	$/QALY
Dhont et al.[92]	2008	Belgium	Rotavirus	Universal child	CBA	12,655,402–21,694,975	-	Costs saved (US$)
Diez-Domingo et al.[93]	2010	Spain	Rotavirus	Universal child	CBA	32,189,552–55,600,135	-	Costs avoided (US$)
Fisman et al.[94]	2012	Canada	Rotavirus	Universal child	CeA	2,450	2,450–14,597	$/QALY
Giammanco et al.[95]	2009	Italy	Rotavirus	Universal child	CeA	160	45–499	N/A
Goosens et al.[96]	2008	Netherlands	Rotavirus	Universal child	CUA	34,004	34,004–54,462	$/QALY
Huet et al.[97]	2007	France	Rotavirus	Universal child	CBA	136,145,586	72,522,903–136,145,586	US$ avoided
Imaz et al.[98]	2014	Spain	Rotavirus	Universal child	CUA	298,552	298,552–398,233	$/QALY
Jit and edmunds[99]	2007	United Kingdom (wales and england)	Rotavirus	Universal child	CUA	158,033–207,254	-	$/QALY
Jit et al.[100]	2009	Belgium, england and wales, Finland, France, Netherlands	Rotavirus	Universal child	CUA	25,082–183,935	CS-493,123	$/QALY
Jit et al.[64]	2011	Belgium, england and wales, Finland, France, Netherlands	Rotavirus	Universal child	CUA	25,082–183,935	-	$/QALY
Kang et al.[101]	2012	Republic of Korea	Rotavirus	Universal child	CBA	470	-	US$ / case averted
López-Gigosis et al.[24]	2009	Spain	Cholera	Adult travelers	CBA	2.2	-	N/A
Lorgelly et al.[102]	2008	UK	Rotavirus	Universal child	CeA	397,701	-	US$ / life year saved
Lundkvist et al.[25]	2009	Canada	Cholera	Travelers	CBA	CS-102	-	US$ saved/ person vaccinated
Mangen et al.[103]	2010	Netherlands	Rotavirus	Universal child	CeA	81,935–96,984	-	$/DALY
Martin et al.[104]	2009	UK	Rotavirus	Universal child	CUA	57,846	28,451–140,602	$/QALY
Melliez et al.[105]	2007	France	Rotavirus	Universal child	CUA	215,346	-	$/QALY
Milne and Grimwood[106]	2009	New Zealand	Rotavirus	Universal child	CUA	40,872	40,872–65,398	$/QALY
Newall et al.[107]	2007	Australia	Rotavirus	Universal child	CUA	57,219–64,465	CS-64,465	$/QALY
Panatto et al.[108]	2009	Genoa Province, Italy	Rotavirus	Universal child	CUA	CS-15,360	-	$/QALY
Papadimitropoulos et al.[26]	2004	USA	Typhoid	Travelers	CeA	249–7,450	-	US$ / case averted
Perez-Rubio et al.[109]	2011	Castilla y Leon, Spain	Rotavirus	Universal child	CUA	33,292–106,483	-	$/QALY
Riddle et al.[20]	2008	US Military personnel	Multiplex	Travelers	CeA	1,730	950–1,730	US$ / Duty days lost

Abbreviations: *CeA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; wTP, willingness to pay.

Table 2. Distribution of diarrheal pathogens considered in studies of economic value of vaccines, by income setting. All base case and range values are in 2014 inflation-adjusted US$ (continued)

Author (Reference)	Year	Location	Vaccine	Target population	Type of analysis*	Base case	Range	Units
Riddle et al.[20]	2008	US Military personnel	eTeC	Travelers	CeA	1,505	877–1,505	US$ / Duty days lost
Riddle et al.[20]	2008	US Military personnel	Campylobacter	Travelers	CeA	1,575	851–1,575	US$ / Duty days lost
Riddle et al.[20]	2008	US Military personnel	Shigella	Travelers	CeA	2,356	1,444–2,356	US$ / Duty days lost
Rozenbaum et al.[110]	2011	Netherlands	Rotavirus	Universal child	CUA	11,923–127,939	CS-243,713	$/QALY
Sansom et at.[32]	2001	USA	Rotavirus	Universal child	wTP	87–163	-	willingness-to-pay (US$)
Sato et al.[111]	2011	Japan	Rotavirus	Universal child	CeA+CUA	124,721	11,013–124,721	$/QALY
Shim et al.[112]	2009	USA	Rotavirus	Universal child	CUA	128,657–236,259	99,300–236,259	$/QALY
Standaert et al.[113]	2008	France	Rotavirus	Universal child	CUA	69,223	-	$/QALY
Standaert et al.[114]	2013	Belgium	Rotavirus	Universal child	CUA	81,045	81,045–92,204	$/QALY
Syriopoulou et al.[115]	2011	Greece	Rotavirus	Universal child	CBA	8,433,442	-	US$ saved
Tilson et al.[116]	2011	Ireland	Rotavirus	Universal child	CUA	185,749	CS-185,749	$/QALY
Tu et al.[117]	2013	Netherlands	Rotavirus	Universal child	CUA	23,352	4,790–23,352	$/QALY
wang et al.[118]	2010	USA	Rotavirus	Universal child	CBA	12,600	-	US$ / 1000 person-years
weycker et al.[119]	2009	USA	Rotavirus	Universal child	CeA	94,886,612	77,379,627–94,886,612	Net economic benefits (US$)
widdowson et al.[120]	2007	USA	Rotavirus	Universal child	CeA	265,007–632,620	-	US$ / life-year saved
wu et al.[121]	2009	Taiwan	Rotavirus	Universal child	CeA	130–190	-	$US / case averted
Zhou et al.[122]	2014	USA	Rotavirus	Universal child	CBA	379,082,622–689,768,074	-	US$ saved
Zlamy et al.[123]	2013	Austria	Rotavirus	Universal child	CBA	10,129–290,420	-	US$ saved
Zomer et al.[124]	2008	Netherlands	Rotavirus	Universal child	CeA	200,350–208,768	-	$/DALY

Abbreviations: *CeA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; wTP, willingness to pay.

themselves. In most instances, the case for the economic value of rotavirus vaccination did not require estimates of the additional economic benefits from long-term health improvements or broader societal benefits.

However there is substantially less evidence of the economic value of other diarrheal vaccines. This may be the result of several factors. First, there are no licensed vaccines for some of the pathogens or they may have demonstrated effectiveness in a limited number of settings. Second, the relatively high and consistent attributable fraction from rotavirus among cases of moderate to severe diarrhea may also have contributed to the proliferation of studies of economic value, many of which use the same model.

This raises the question of whether the evidence of economic value of rotavirus vaccine can be extended to vaccines for other enteric pathogens. Several biological factors may contribute to the limited ability to extrapolate rotavirus vaccine results to other pathogens. First, other leading diarrheal pathogens individually account for a smaller attributable fraction than rotavirus. Although higher case fatality rates for some (e.g., cholera) may offset this, the smaller attributable fraction implies fewer health or economic benefits to balance against vaccine costs. Second, other leading diarrheal pathogens tend to affect individuals across a wider age range, while rotavirus primarily affects children under 3 y of age. However the implication is that vaccination may need to be repeated throughout life for these other vaccines.

This suggests that informed decision making about the economic value of these other diarrheal vaccines might require a more complete accounting of the long-term and broader economic benefits. One element of this would be more complete estimates of the long-term health benefits of diarrheal prevention. While these connections remain uncertain, there is growing evidence that the effects of diarrhea infections extend well beyond the acute consequences. A number of studies have documented the association between enteric infection and under-nutrition even in the absence of acute diarrheal illness.[8,40] Fischer-Walker and colleagues further demonstrated that repeated diarrheal episodes can have a long-term negative impact on cognitive function, independent of the effect mediated through nutrition.[9]

Table 3. Health and economic benefits of diarrheal vaccines

Value or benefit	Summary	Studies reporting
Narrow Benefits		
Reduced diarrheal morbidity and mortality	episodes and mortality of diarrheal disease; measured as DALYs, QALYs, or the monetized value	19-32,35-38,45-92,94-96,98-121,124,125
Averted medical costs from diarrhea	Reduced costs associated with inpatient, outpatient and informal medical care	19,20,22-33,35-39,45-47,49-57,59-63,65-99,101-112,114-117,119-122,124,125
Direct non-medical costs	Non-medical out of pocket costs to households such as travel; including disrupted travel	21,23,24,26,28-31,34,35,38,39,50,51,53,55,58,59,61-66,69,70,74-76,79,81,83-86,88,89,91-93,95-98,100-108,110-113,116,117,119-121,123,125
Indirect or productivity costs	Lost time from work for caregivers or patients	19,23-25,28,30,33,34,39,50,53-56,58,59,61,62,64,69,70,74-76,78,79,81,83-86,88-90,92,93,95-104,106-112,115-117,119-122,124,125
Broader Benefits		
Herd immunity	Indirect protection of non-vaccinated individuals due to reduced force of infection	28,31,39,46,65,87,89,100,103,112,114,117
Non-diarrheal health benefits	Benefits from improved nutrition, reduced co-infection, or long-term health improvements (e.g., cardiovascular, chronic GI, rheumatologic)	None
Adaptive and averting costs	Costs to household, healthcare facilities and public health system to avoid infections which could be avoided with vaccination	None
Long-term averted medical costs	Medical costs associated with chronic health conditions resulting from diarrhea	None
Long-term productivity	Costs associated with reduced cognitive function due to diarrhea and/or associated malnutrition	None
Demographic adaptive response	Reduced child mortality is expected to result in reduced fertility; increased per capita investment in health and education	None
Macro-economic effects from impoverishment	Reduced macroeconomic costs associated with impoverishment due to repeated high medical treatment costs	None
Distributional or equity effects	Value or willingness to pay for benefits that equally or disproportionately benefit the poor	21,22,27-33,35-39
Risk premium or utility in anticipation	Value of safety or piece of mind associated with reduced risk of illness. This separate from the expected value of health or economic outcomes.	None

Adapted from[14,15]

Porter and colleagues have demonstrated that some diarrheal infections are associated with subsequent chronic gastrointestinal problems including irritable bowel syndrome, GERD and dyspepsia.[10] DeBoer also found an association with metabolic syndrome.[11] Lastly, several studies have found an association with rheumatologic conditions.[12,13] In addition to these long-term consequences Ashraf and colleagues found that diarrheal disease episodes increased the likelihood of subsequent respiratory illness in children in Pakistan.[41] Associated with each of these conditions, there are likely to be direct medical costs, reduced economic productivity and morbidity that could be measured as DALYs.

Endemic and epidemic diarrheal disease can force households to take additional protective steps, incurring costs (referred to as averting costs).[42] Presumably, effective vaccination could reduce these costs. Outbreaks can also result in costs associated with social disruption and infection. These measures in health facilities and communities have associates costs, may divert resources from other investments, and may result in increased antibiotic resistance.[43]

In low-income settings, repeated diarrheal episodes can result in out-of-pocket costs that are high in comparison to household income, even though they may be small in relative terms.[17] These costs can force households to take out expensive loans, sell productive resources, or forgo important investments like food or education, resulting in persistent poverty. This suggests that the short-term out-of-pocket costs greatly underestimate the long-term cost of illness. Few assessments of the economic value of vaccines directly estimated these consequences of out-of-pocket costs and none included the long-term costs associated with the impoverishment they might create.

Given the heterogeneity of burden from diarrheal pathogens such *Shigella*, cholera, ETEC, and typhoid, it may be increasingly

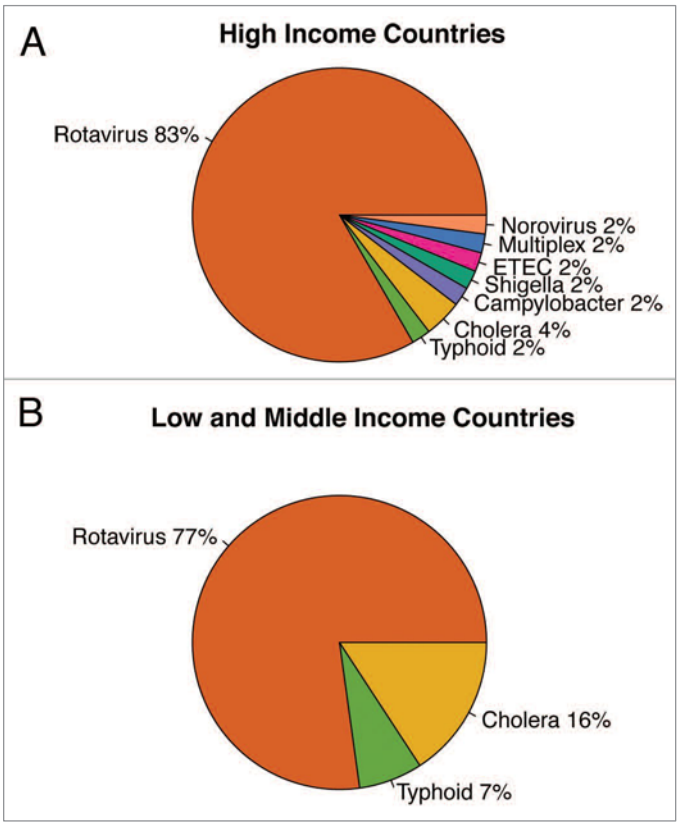

Figure 2. Distribution of diarrheal pathogens considered in studies of economic value of vaccines, by income setting.

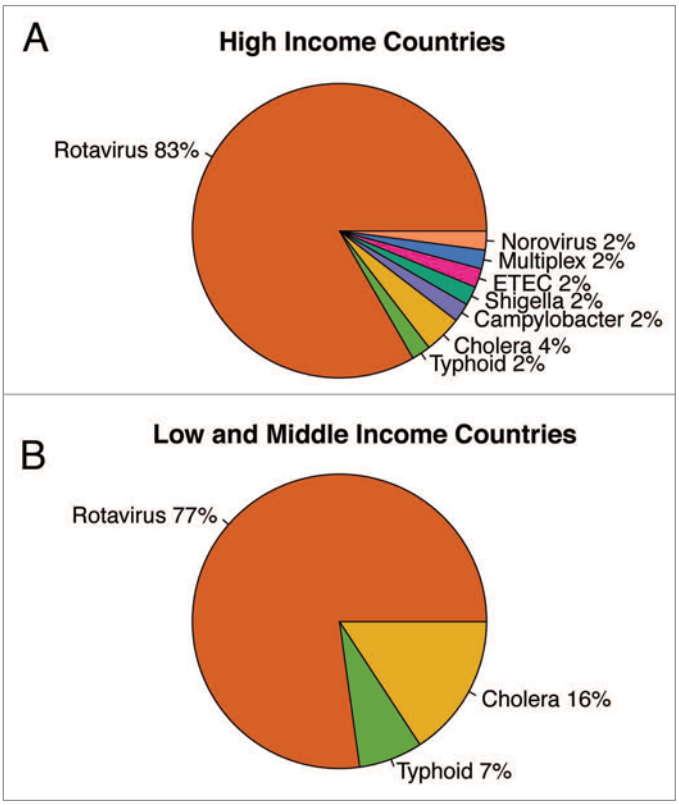

Figure 3. Health and economic benefits considered in evaluations of diarrheal vaccines by income setting.

important to assess the distributional effects of vaccination and economic value of vaccinating higher risk subpopulations. In settings where universal vaccination may not be cost-effective, target vaccination of high exposure groups may provide greater economic value.

A final potential economic value of diarrheal vaccines is the social externality of reduced fertility associated with declining child mortality. Although there is no direct evidence that reducing child mortality from diarrhea can spur such a response, this is a basic tenet of the demographic transition. If diarrheal vaccines can catalyze even a modest response in fertility, it could result in the refocusing of health and social investments and stimulating long-term development.

An additional opportunity for increasing the economic value of diarrheal vaccines is the development of combined vaccines. For pathogens with similar distributions, this could reduce the delivery costs while increasing the overall reduction in diarrheal disease.

One of the most commonly cited uncertainties in vaccine economic value in the reviewed studies was the price of vaccines. Economic market theory would suggest that high economic benefits or value of a given product (in this case a vaccine) would create an upward pressure on price. However the value of diarrheal vaccines in a global context is dependent upon maintaining prices that are affordable and can be sustained by donors and national governments. Global efforts to reduce the price of future diarrheal vaccines can greatly increase their economic value. This may be in the form of advanced market commitments that guarantee demand in exchange for reduced prices or creative research and development initiatives such as the partnership among Bharat Biotech, the Government of India's Department of Biotechnology, PATH, and the US National Institutes of Health that resulted in the development of the low-cost ROTAVAC vaccine.[44]

Limitations

The current study has several important limitations. First, the reviewed studies utilized a wide range of designs and assumptions, making it difficult to directly compare results. Second, the studies were conducted across different settings and the threshold for what represents sufficient economic value varies across settings and is subject to interpretation. Third, the majority of the studies considered rely on assumptions regarding critical variables such as vaccine price, and in some cases efficacy. As a result, the conclusions drawn by authors are often dependent upon the feasibility of these assumptions. Lastly, most studies capture only a fraction of the potential economic value of diarrheal vaccines. When the measured value is sufficient to justify introduction this may not represent a problem. However, when measured benefits are lower the omission of this unmeasured economic value may bias decision-making.

Conclusions

Our systematic review of the economic value of diarrheal vaccines demonstrates a growing literature on the issue, in response to the increased availability of vaccines and the expanded use of economic analysis in related decision-making. The reviewed studies suggest substantial economic value of rotavirus vaccines across a range of settings, although this is dependent in part on vaccine costs. A smaller but important literature suggests that other diarrheal vaccines could provide economic value for specific populations and conditions. Existing studies rely heavily on traditional measures of economic value including averted medical costs and productivity losses. However less evidence is available on the potential value of diarrheal vaccines in preventing related non-diarrheal health conditions or in producing broader economic benefits. Assessing the full economic value of new or underutilized diarrheal vaccines may require better estimates of the broader benefits.

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