

SYSTEMATIC REVIEW

Cost-effectiveness of measles treatment: a systematic reviewNam Xuan Vo,¹ Anh Thi Van Nguyen,¹ Ha Thi Mai Tran,¹ Linh Thi Thuy Truong,¹ Nghi Ngoc Bao Nguyen¹**Abstract**

Objective: Measles is still common in many developing countries, and its outbreaks have been on the rise since 2009 even though the disease is almost entirely preventable through safe and effective vaccination. This paper aims to provide evidence about the systematic review of the cost-effectiveness of measles treatment in different regions worldwide.

Methods: The methodical search began on 10th January 2019 to look for all articles on the cost-effectiveness of measles treatment published from January 2019 to April 2019 in SCOPUS, Pubmed (www.ncbi.nlm.nih.gov) and Cochrane (www.cochrane.org). We summarised the articles by using a data table to extract all information using health economic evaluation methods.

Results: We identified 14 articles from the 69 total articles searched. These articles showed favourable cost-effectiveness or cost-benefit ratios in high- and middle-income countries based on data organised by World Bank Income Level in 2018: the United States, Canada, Japan, India and Zambia. However, research is still limited in low-income countries and thus the effectiveness of vaccination programmes cannot be conclusively identified.

Conclusion: This review shows the overview of the research in health economic evaluations of measles in different places, years and using different methods of intervention. Overall, it evaluates the cost-effectiveness of measles treatment.

Keywords: Cost-effectiveness analysis, Measles, Systematic review, Literature review. (JPMA 69: S-148 (Suppl. 2); 2019)

Introduction

Measles, which is caused by morbillivirus, is one of the world's most infectious diseases. It affects mostly children, especially poorly nourished young children, those with insufficient vitamin A and those who have weak immune systems of any age, such as HIV/AIDS patients. In 2017, measles caused close to 110,000 deaths.¹ Even in high-income countries, complications can result in hospitalisation in up to a quarter of the cases of measles infections, and could lead to lifelong disability from brain damage, blindness or hearing loss.²

There is no specific antiviral treatment that exists for the measles virus, but measles is preventable and can be eliminated by two doses of a safe, effective and inexpensive vaccine which has been in use since the 1960s, when it was immediately identified as highly cost-effective.³ The World Health Organization (WHO) recommends immunisation for all susceptible children and adults for whom measles vaccination is not contraindicated. Inoculating all children with two doses of the measles vaccine, either alone or in a measles-rubella (MR), measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) combination should be the

standard for all National Immunisation Programmes.⁴ All six WHO regions have measles elimination goals before or by 2020, and the Global Vaccine Action Plan has a goal to eliminate measles in five of the six WHO regions by 2020.² Achieving global measles-mortality reduction goals would require a further increase in measles vaccine coverage. Through a combination of innovation, resources and political action, we can work together to achieve and maintain the global elimination of measles.¹

However, measles is still common in many developing countries, particularly in parts of Africa and Asia. The overwhelming majority of measles deaths today occur in countries with low per capita income and weak health infrastructure. Outbreaks of measles have been on the rise since 2009, particularly in the African, South-East Asia and European Regions, and also in North America.² There is a clear trend that many countries are in the midst of sizeable measles outbreaks. As of 15th April 2019, 170 countries have reported 112,163 measles cases to the WHO.⁵ In contrast, in April 2018 there were 28,124 measles cases from 163 countries. Preliminary global data shows a 300% increase in reported cases in the first three months of 2019, compared to same period in 2018.⁵

Due to the availability of an inexpensive and effective vaccine, measles immunisation is one of the most cost-effective public health interventions in a wide range of developed regions.¹ The first health economic analysis of

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the measles vaccine was published in 1969⁴ and over the past 50 years, many research articles explored a wide range of immunisation interventions for measles using cost-benefit analysis (CBA) and or cost-effectiveness analysis (CEA). The motivation for this paper is to provide a systematic review of the cost-effectiveness of measles treatments in different region worldwide.

Materials and Methods

The search for materials began on 10th January 2019 and continued through to 10th April 2019. We searched for all articles on the cost-effectiveness of measles treatments published from January 2019 to April 2019 in SCOPUS, Pubmed (www.ncbi.nlm.nih.gov) and Cochrane (www.cochrane.org). Our search strategy included the following terms: 'measles', 'treatment', 'regimen', 'cost-effectiveness' and 'economic evaluation'. After checking for duplication, the selected articles were reviewed one-by-one by reading their

titles, abstracts and full text to identify the most appropriate articles. The details and results of our selection process are shown in Figure-1.

After reviewing the selected studies, we categorised them by year and by different methods of health economic evaluations, and then were compared the results together to assess the cost-effectiveness of measles treatments. We summarised them by using a data table to extract all article information using methods of health economic evaluations like CBA and CEA, as well as cost-utility analysis (CUA) and cost-minimisation analysis (CMA), to make a comparison of these studies together.

Results

Figure-1 shows our results from searching the syntax mentioned in the methods section. We found 1 article on Cochrane, 27 articles on SCOPUS and 54 articles on Pubmed. Because 13 of these were duplications, a total

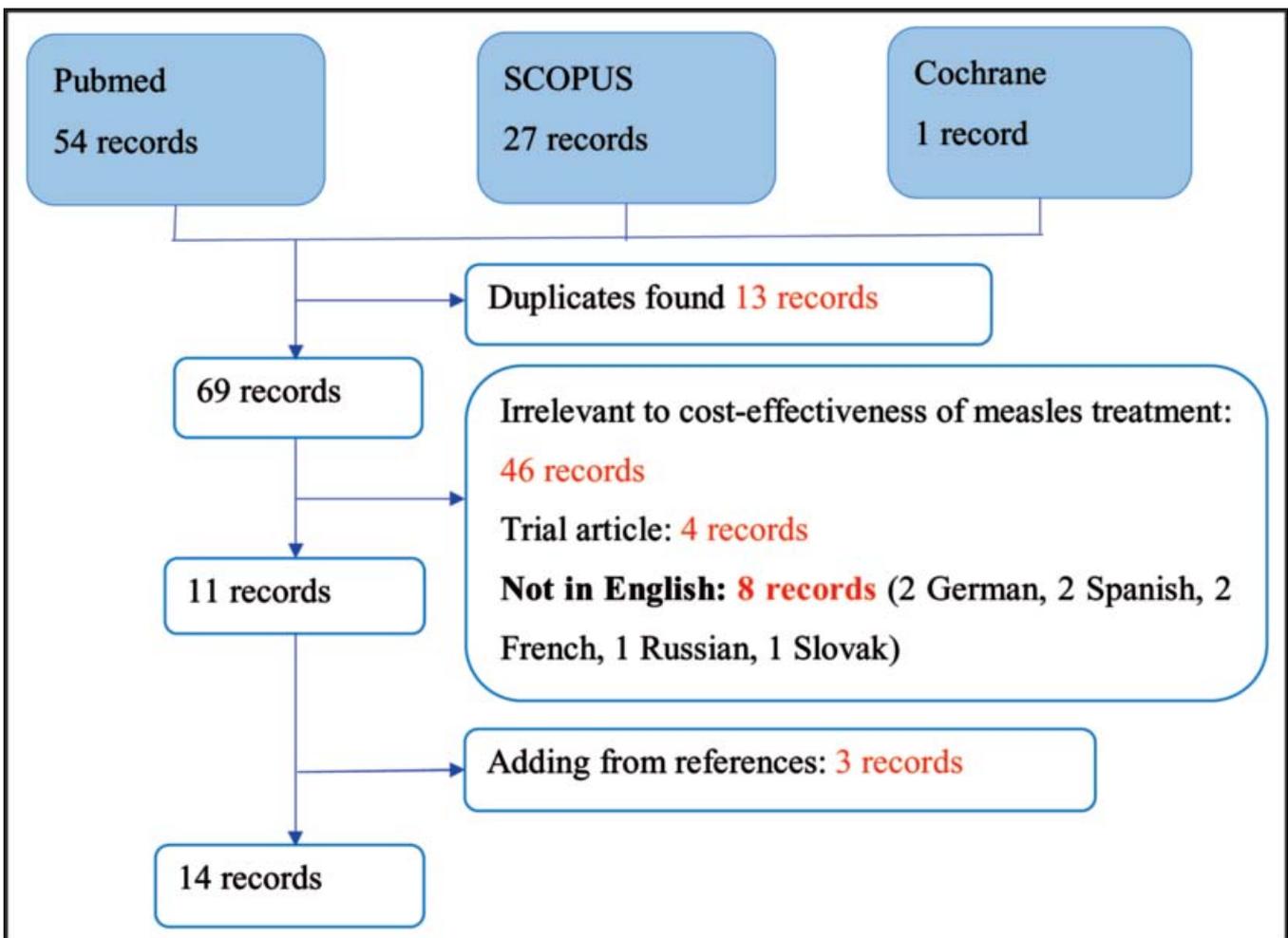


Figure-1: Flow chart shows process used to identify relevant reports.

Table-1: Types of economic evaluation of identified articles.

Types of economic evaluation	Number of publications
CBA	7
CEA	5
CBA and CEA	1
ECEA	1
Others	11

CBA: Cost-benefit analysis. CEA: Cost effectiveness analysis. ECEA: Estimated cost-effectiveness analysis.

Table-2: Interventions and results of selected articles using the cost-benefit analysis.

No.	Authors	Year	Title	Intervention vs. comparator	Result
1	Zhou F, Reef S, Massoudi M, Papania MJ, Yusuf HR, Bardenheier B, et al ³	2004	An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States	In this study, there were two base case scenarios: the absence of the MMR vaccination and the present level of implementation of the 2-dose MMR vaccination program, and the impact of the second dose of the MMR vaccine.	Analysis of the incremental benefit-cost of the second dose showed that the direct and societal benefit-cost ratios were 0.31 and 0.49, respectively. The national 2-dose MMR vaccination program is highly cost-beneficial and results in substantial cost savings.
2	Takahashi K, Ohkusa Y, Kim JY. ⁶	2011	The economic disease burden of measles in Japan and a benefit cost analysis of vaccination, a retrospective study	Measles immunisation was compared with no measles immunisation.	The nationwide total cost for measles treatment was estimated to be US\$ 404 million, while the vaccination cost was US\$165 million. The benefit-cost ratio of the base case was 2.48 and ranged from 2.21 to 4.97 in sensitivity analysis.
3	Uzicanin A, Zhou F, Eggers R, Webb E, Strebel P ⁸	2004	Economic analysis of the 1996-1997 mass measles immunization campaigns in South Africa	A 2-dose routine immunisation program was compared with the combined vaccination strategy, which was a routine 2-dose immunisation program plus the 1996-1997 campaign.	Net savings per measles case averted: US\$40 in Mpumalanga and US\$7 in Western Cape. Net savings per hospitalisation averted: US\$278 in Mpumalanga and US\$46 in Western Cape. Net savings per death averted: US\$7,984 in Mpumalanga and US\$1,369 in Western Cape. Benefit-cost ratio of the 1996-1997 campaigns was 2.27 and 0.89 for Mpumalanga and Western Cape, respectively.
4	Pelletier L, Chung P, Duclos P, Manga P, Scott J. ⁷	1998	A benefit-cost analysis of two-dose measles immunization in Canada	The current single-dose program was compared with a 2-dose immunisation program.	The resulting benefit-cost ratios vary between 2.61:1 and 4.31:1, depending on the strategy used and the age of the children targeted. Given the parameters established for this analysis, the benefits of a 2-dose vaccination program against measles far outweigh the costs of such a program in all scenarios.
5	Rivière M, Tretiak R, Leventon C, Fitzsimon C, Lederc C. ⁹	1997	Economic benefits of a routine second dose of combined measles, mumps and rubella vaccine in Canada	A routine second dose of the MMR vaccine was compared to no routine second dose of MMR.	The routine second dose immunisation of the MMR vaccine is cost saving. A second dose of MMR administered at 18 months of age would prevent 9,200 cases of measles, 6,120 cases of mumps and 1,960 cases of rubella, producing a savings of US\$6.34 for every dollar spent from the ministry of health perspective and US\$3.25 from the societal perspective
6	Ginsberg GM, Tulchinsky TH. ¹⁰	1990	Costs and benefits of a second measles inoculation of children in Israel, the West Bank, and Gaza	This study compared three options. Option A: a continued measles immunisation at 15 months, plus a routine second measles immunisation at early school age. Option B: Option A, plus a mass immunisation campaign of 7-17-year-olds. Option C: Option A, plus a mass immunisation campaign of 7-27-year-olds.	A policy of immunising all Israeli children at age 6, which Option A represents, would cost around US\$1 million and have estimated benefits of US\$4.5 million, yielding a benefit-cost ratio of 4.53:1. Despite relatively lower medical care costs and work absence costs as a result of the lower per capita GNP and lower female participation rate in the workforce, the West Bank and Gaza situations yield benefit-cost ratios of 5.74:1 and 9.59:1, respectively, because of their relatively higher incidence rates. If implemented in Israel, a vaccination programme such as Option A would prevent, over the next 10 years, approximately 28,700 simple cases, 3,400 hospital admissions, 8 non-fatal cases of encephalitis and 2.2 cases of SSPE. It would save 28 lives directly. The adoption of Option A is expected to reduce incidence of measles infection and mortality from measles by around 13,600 and 32 cases, respectively, in the West Bank, and by 18,000 and 64 cases, respectively, in Gaza.
7	White CC, Koplan JP, Orenstein WA. ¹¹	1985	Benefits, risks and costs of immunization for measles, mumps and rubella	The MMR vaccine was compared to no immunisation.	The benefit-cost ratio for measles is 11.9:1. The benefit-cost ratio for MMR is 14.4:1.

of 69 articles were identified. From these, 58 articles were eliminated because of our exclusion criteria: 4 articles were trial articles, 8 articles were not written in English (2 in German, 2 in Spanish, 2 in French, 1 in Russian and 1 in Slovak) and 46 articles were irrelevant to the cost-effectiveness measles treatments. Therefore, 11 articles from our initial search were included. After consulting the reference list of these 11 articles, three more articles were added referring to the

Table-3: Interventions and results of selected articles using the cost-effectiveness analysis.

No.	Authors	Year	Title	Intervention vs. comparator	Result
1	Bishai D, Johns B, Nair D, Nabyonga-Orem J, Fiona-Makmot B, Simons E, et al. ¹²	2011	The cost-effectiveness of supplementary immunization activities for measles: stochastic model for Uganda	MCV1 with SIAs was compared to MCV1 without SIAs	It is a cost-effective intervention. The ICER per DALY averted is US(2010)\$1.50
2	Levin A, Burgess C, Garrison LP Jr, Bauch C, Babigumira J, Simons E, et al. ⁵	2011	Global eradication of measles: an epidemiologic and economic evaluation	A baseline scenario consisting of a global goal of 90% measles-associated mortality reduction was compared to 95% and 98% mortality reduction.	Measles eradication by 2020 was found to be the most cost-effective scenario, both in the six countries studied and globally. Eradicating measles by 2020 is projected to cost an additional discounted US\$7.8 billion and avert a discounted 346 million DALYs
3	Dabral M. ¹³	2009	Cost-effectiveness of supplementary immunization for measles in India	Routine measles immunisation alone was compared with measles vaccination by supplementary immunisation strategy.	The cost per measles vaccine dose delivered is 30 and the cost per DALY averted is 430.
4	Vijayaraghavan M, Lievano F, Cairns L, Wolfson L, Nandy R, Ansari A, et al. ¹⁵	2006	Economic evaluation of measles catch-up and follow-up campaigns in Afghanistan in 2002 and 2003	Catch-up and follow-up campaigns were compared to no measles campaigns.	The cost per death prevented is US\$23.60. More than 42,000 measles deaths were avoided for US\$1 million spent.
5	Edejer TT, Aikins M, Black R, Wolfson L, Hutubessy R, Evans DB. ¹⁴	2005	Cost effectiveness analysis of strategies for child health in developing countries	Interventions were compared to no interventions. Interventions included case management pneumonia, oral rehydration therapy, supplementation or fortification of staple foods with vitamin A or zinc, provision of supplementary food with counselling on nutrition and immunisation against measles.	For measles immunisation, the Afr-E region cost US\$82-\$164 per DALY and the Sear-D region cost US\$240 per DALY.

Table-4: Interventions and results of selected articles using both CBA and CEA method.

No.	Authors	Year	Title	Intervention vs. comparator	Result
1	Beutels P, Gay NJ. ¹⁶	2003	Economic evaluation of options for measles vaccination strategy in a hypothetical Western European country	This study compared cost-effectiveness and cost-benefit of five strategies, labelled 0-4.	For society, all strategies are cost-saving, with strategy 3 yielding the greatest savings. The total ICER of strategy 4 vs. strategy 3 is £20,678 per discounted life-year gained. A strategy with incremental costs of £1,000 and benefits of £300,000 yields net savings of £29,000 and a BCR of 30, whereas a strategy with incremental costs of £1 million and benefits of 2 million yields net savings of £1 million and a BCR of 2.

searching topic. In total, the number of reviewed articles was 14.

The types of economic evaluation used with the articles identified are summarised in Table-1. There were seven cost-benefit analyses, five cost-effectiveness analyses, one extended cost-effectiveness analysis and one article used both cost-benefit analysis and cost-effectiveness analysis. In the cost-benefit analyses, the measles immunisation, 2-dose MMR vaccine, 2-dose measles immunisation and measles vaccine catch-up schedule were all proven to be cost-effective.^{3,6-11} The cost-effectiveness analyses indicated that the measles immunisation, measles eradication, measles-containing-vaccine first-dose (MCV1) combined with supplemental immunisation activities

(SIAs), catch-up schedule and follow-up measles campaign appear to be cost-effective.^{5,12-15} The article which used both the cost-effectiveness analysis and the cost-benefit analysis showed that the 2-dose measles vaccination at 95% coverage is cost-effective in a hypothetical Western Europe country.¹⁶ The article with the extended cost-effectiveness analysis showed that the measles vaccination averted the most deaths per dollar spent in Ethiopia.¹⁷

Tables-2, 3, 4 and 5 summarise the interventions and results of selected articles by cost-benefit analysis, cost-effectiveness analysis, extended cost-effectiveness analysis and the article that used both cost-benefit analysis and cost-effectiveness analysis.

Table-5: Interventions and results of selected articles using ECEA method.

No.	Authors	Year	Title	Intervention vs. comparator	Result
1	Verguet S, Olson ZD, Babigumira JB, Desalegn D, Johansson KA, Kruk ME, et al. ¹⁷	2015	Health gains and financial risk protection afforded by public financing of selected interventions in Ethiopia: an extended cost-effectiveness analysis	This study compared nine interventions to each other: measles vaccination, rotavirus vaccination, pneumococcal conjugate vaccination, diarrhoea treatment, malaria treatment, pneumonia treatment, caesarean section surgery, hypertension treatment and tuberculosis treatment.	Per dollar spent by the Ethiopian government, the intervention that averted the most deaths was the measles vaccination at 367 deaths per US\$100,000 spent. For the measles vaccine, government intervention cost US\$(2011)260,000, the household expenditure averted was US\$(2011)9,000, deaths averted were 890 and cases of poverty averted were 14.

Measles immunisation appears to be more cost-effective compared to no measles immunisation, with the benefit-cost ratio at 2.48 in Japan.⁶ Measles vaccination is also cost-saving in other regions: the cost per case averted was US\$71.75 and the cost per death averted was US\$15,000 in Latin America and the Caribbean;¹⁸ meanwhile the net savings per measles case averted were US\$40 in Mpumalanga and US\$7 in Western Cape.⁸ In the Afr-E region and Sear-D region, the costs per disability-adjusted life year (DALY) averted for measles immunisation were, respectively, US\$82-\$164 and US\$240.¹⁴ Another article, which studied 73 low- and middle-income countries supported by Gavi, the Vaccine Alliance, also proved that measles vaccination is highly cost-effective and saved US\$142 billion in the cost of illness from 2001 to 2020 and US\$27,000 in the cost of illness per death averted.¹⁹ Sear-D includes the following countries: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor Leste. Afr-E includes the following countries: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe

When compared to other interventions, such as the rotavirus vaccination, pneumococcal conjugate vaccination, diarrhoea treatment, caesarean section surgery, hypertension treatment and tuberculosis treatment, measles vaccination is the intervention that averted the most deaths: 367 deaths per US\$100,000 spent by the Ethiopian Government.¹⁷ Measles eradication is cost-effective,^{5,20-22} and eliminating measles by 2020 is cost-effective in Uganda. The incremental cost-effectiveness ratio (ICER) per DALY averted was US\$556 for a 2030 time horizon and US\$284 per DALY averted for a 2050 time horizon.²⁰ Eradication by 2020 would save US\$800 million compared to measles control in high income countries,²¹ while the incremental cost-effectiveness of control is similar to eradication in low- and middle- income countries.²¹ Measles eradication by 2020 is predicted to cost an additional discounted

US\$7.8 billion and avert 346 million DALYs,⁵ indicating that the ICER per DALY averted was US\$22.5.

In 72 of the world's poorest countries, increasing the measles vaccine coverage to 90% is cost-effective. The total cost averted was US\$ 9.65 million and the number of deaths averted was 360,000,²³ indicating that the incremental cost per death averted is approximately US\$26.82. However, raising measles immunisation rates would not appear to be cost-effective, except during measles outbreaks in very low immunisation rate areas.²⁴

The use of a 2-dose measles vaccination is more cost-effective than a single-dose vaccination in Canada, with the benefit-cost ratios ranging from 2.61:1 to 4.31:1, depending on the target population and the strategy used.⁷ Another study in a Western European country shows that a 2-dose measles vaccination at 95% coverage is cost-effective, with the benefit-cost ratio ranging from 2.47 in the base case of single-dose vaccination at 90% coverage to 3.96 in the base case of single-dose vaccination at 70% coverage. The ICER per life-year gained was €1209 compared to the base case of 90% vaccination coverage.

The use of the first dose through routine immunisation and the second dose through supplemental immunisation activities is cost-effective in Uganda, Zambia and India, with the ICER per DALY averted being US (2010) \$1.50 in Uganda,¹² the ICER per death averted being \$US155.84 in Zambia²⁵ and the cost per DALY averted being 30 in India.¹³ SIAs are also cost-effective in Bangladesh and Ethiopia, with the estimated cost-effectiveness ratios per DALY averted being US\$19.20 in Bangladesh and US\$2.50 in Ethiopia.²² The catch-up vaccine schedule is also cost-effective.^{8,15} The benefit-cost ratios for a catch-up campaign in Mpumalanga and Western Cape were 2.27 and 0.89, respectively,⁸ and the cost per death averted was US\$23.60 in Afghanistan.¹⁵ In India, West Bank and Gaza, continuing measles immunisation at 15 months plus a routine second measles immunisation at early school age is cost-beneficial, with cost-benefit ratios of 4.53:1 in Israel, 5.74:1

in West Bank and 9.59:1 in Gaza.¹⁰

The measles and rubella vaccination is cost-beneficial, with a benefit-cost ratio of 14:1. The use of the MMR vaccine is cost-effective, with a benefit-cost ratio of 14.4:1 in the United States.¹¹ One study, which also took place in the United States, shows that two doses of the combined MMR vaccine is more cost-beneficial compared to the absence of the MMR vaccine, with benefit-cost ratios of 0.31 and 0.49 from direct cost and societal perspectives, respectively.³ Another study shows that routine second-dose immunisation with MMR vaccine is cost-effective, with net gains of US\$6.34 per dollar spent from the ministry of health perspective and US\$3.25 from the societal perspective.⁹ However, when the 2-dose MMR vaccine is compared with either the single-dose or 2-dose MR vaccine, the MR vaccine appears to be more cost-saving than the 2-dose MMR vaccine, with savings of a single MR vaccine being US\$4.1 billion at a 3% discount rate or US\$2.1 billion at a 5% discount rate.²⁶

Discussion

This review shows a variety of evidence accumulated in a 35-year period from 1982 to 2017 that demonstrates the cost-effectiveness and economic benefits of different kinds of measles vaccines, such as the 2-dose measles vaccination, supplemental immunisation and MMR. In addition, this review also shows the effectiveness achieved on benefit-cost ratios and the incremental cost-effectiveness ratio per quality-adjusted life year (QALY) or DALY in a data source.

Moreover, this assessment compares the costs of vaccination to the cost of treatment after being infected with measles in some countries. The vaccination cost was assessed to be US\$165 million, while the whole nationwide cost for measles treatment was US\$404 million in Japan.⁶ Other research shows that a vaccination policy averts a single case of measles at the cost of US\$71.75 and prevents a death due to measles at the cost of US\$15,000.¹⁸ A vaccination strategy saves a total of US\$208 million in treatment costs due to reduced incidences of measles.¹⁸ Therefore, the benefit of vaccination not only minimises costs, but also provides high efficiency in preventing measles in infants.

Our analysis has a number of limitations. Some research we used was from the 1980s and 1990s, when researchers did not use optimal economic evaluation methods such as cost-minimisation, cost-benefit, cost-effectiveness or cost-utility analyses. Therefore, the cost-effectiveness has not been specifically assessed on life years gained, DALYs or QALYs. Another limitation mentioned is that all

research was studied in different regions of the world, so it is impossible to compare the results between developed and developing countries.

The cost-effectiveness of most health interventions of measles not only depends on how well the health systems function in different countries,²⁷ but also on a mother's knowledge of measles epidemics during and after pregnancy. We hope that this review provides useful background about the cost-effectiveness of the treatment of measles and the differences in costs, as well as the benefits of vaccination immunisation compared to measles treatment. Therefore, the economic analyses likely play a vital role in measles eradication.

Conclusion

This review shows the overview of the research in health economic evaluations of measles in different places, years and using different intervention methods. Measles prevention by vaccination programmes is the most effective intervention. It shows favourable cost-effectiveness or cost-benefit ratios in high- and middle-income countries based on data organised by World Bank Income Level in 2018: The United States, Canada, Japan, India and Zambia. However, research is still limited in low-income countries, and thus the effectiveness of these vaccination programmes cannot be conclusively identified. Therefore, it is necessary to advance the scope of research in low-income countries to evaluate the effectiveness of vaccination programmes in these countries.

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