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Evaluations of training and education interventions for improved infectious disease management in low- and middle-income countries: a literature review

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ABSTRACT

Objectives To identify most vital input and outcome parameters required for evaluations of training and education interventions aimed at addressing infectious diseases in low- and middle-income countries.

Design Systematic review

Data sources PubMed/Medline, Web of Science and Scopus were searched for eligible studies between January 2000 and October 2020.

Study selection Health economic and health-outcome studies on infectious diseases and antimicrobial resistance covering an education or training intervention in low- and middle income countries were included.

Results A total of 57 eligible studies covering training or education interventions for infectious diseases were found; infectious diseases were categorized as acute febrile infections (AFI), non-acute febrile infections (non-AFI) and other non-acute infections. With regard to input parameters, the costs (direct and indirect) were most often reported. As outcome parameters, five categories were most often reported including final health outcomes, intermediate health outcomes, cost outcomes, prescription outcomes and health economic outcomes. Studies showed a wide range of per category variables included and a general lack of uniformity across studies.

Conclusions Further standardization is needed on the relevant input and outcome parameters in this field. A more standardized approach would improve generalizability and comparability of results and allow policy makers to make better informed decisions on the most effective and cost-effective interventions.

Strengths and limitations of this study

- This is the first review (to our knowledge) to systematically assess health economic and health-outcome literature of training or education interventions on input and outcome parameters used for improved management of infectious diseases.
- This review covers a wide variety of infectious diseases, allowing for comparisons across disease areas but also introducing high heterogeneity of results
- This study is prone to publication bias as it includes only data from published literature

INTRODUCTION

Infectious diseases continue to be one of the greatest health challenges worldwide, with the highest burden in low- and middle-income countries (LMICs)[1]. Over the past decades, improvements have been made in the management of infectious diseases by, amongst others, the introduction of widespread vaccine programs[2], health programs on malaria[3], human immunodeficiency virus (HIV) prevention[4] and the widespread use of antimicrobials for bacterial infections[5]. To further reduce the global burden of infectious diseases, there is a need of (new) effective strategies that can be implemented at high speed with high coverage levels[6]. These strategies should enable effective management of infectious diseases but also limit inappropriate use of antimicrobials to prevent further increase of antimicrobial resistance.

A variety of programs have been implemented to address the management of specific diseases such as HIV, malaria or tuberculosis (TB)[7] or the prescription of antimicrobials[8]. Across the different disease programs, commonalities can be found on two major topics. First, the implementation of diagnostics is an often used strategy across programs, such as rapid diagnostic tests (RDTs) for malaria diagnosis[9] or home based testing for HIV detection[10,11]. Second, education or training interventions are used across different infectious disease programs. For example, physicians are trained and educated on improved prescription of antimicrobials[8], patients are taught about the importance of treatment adherence for antiretroviral therapy[12] and individuals are informed on preventive measures that can be taken to prevent HIV or malaria infections[13]. Evidently, there are similarities in the approaches that are used by the different programs, but within a program the interventions are often focused on one specific disease (e.g. malaria, HIV). Hence, with finite financial resources, a decision needs to be made by policy makers on the programs to be incorporated in national health policy.

Policymakers are informed by health economic analyses to maximize the impact on health and equity. The health economic impact is often expressed in costs per quality-adjusted life year gained (cost per QALY) or cost per disability-adjusted life year averted (cost per DALY), both of which combine morbidity and mortality (i.e. quality and length of life)[14]. QALYs are predominantly used in higher-income countries and DALYs in global health studies[15]. Expressing health economic impact in cost per QALY or cost per DALY allows for comparing different health interventions across diseases[16].

There are no consistent guidelines with input parameters and outcomes to report on in health economic evaluations of infectious disease interventions in LMICs[17,18]. To close this gap, previous endeavors have been undertaken by the VALUE-Dx consortium to review health economic assessments of diagnostic interventions for infectious diseases[19]. One of the conclusions of this consortium was that there is a lack of universal outcomes in the assessment of diagnostics.

Parameter categories that were found across a multitude of studies included final health outcomes (QALY, DALY), antibiotic consumption and diagnostic test performance. This provides valuable insight in parameters to use for the health economic assessment of diagnostics. However, to our knowledge, comparable research is lacking on educational or training interventions for improved management of infectious diseases.

It is important to get a better understanding of input parameters and outcomes that have been used previously to guide future research efforts, to improve the quality of health economic assessments as well as the generalizability of results. Such guidance would specifically be relevant for LMICs, where the need for improved management of infectious diseases is most urgent[20,21], where health economic frameworks are less formalized, and where limitations are encountered in applying results from health economic studies into policymaking[22]. Therefore, the objective of this review is to close the knowledge gap by identifying input parameters and outcomes reported in health economic and health-outcome studies on training or education interventions for infectious diseases in LMICs.

METHODS

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23] were used for this study (Appendix A). A systematic search of databases was performed, including PubMed/Medline, Web of Science and Scopus. The detailed search strategy per database can be found in Appendix B. Five queries were combined in the main query, including the following aspects:

- Population: individuals in LMICs[24];
- Intervention: programs that include an education or training intervention, including antimicrobial stewardships;
- Disease focus: infectious diseases and antimicrobial resistance;
- Type of research: health economic and health-outcomes articles; and
- Time period: January 2000 – October 2020.

Duplicate articles were removed after which the title and abstract were scanned independently by two researchers (PvD and ADIvA). Full-text analysis was performed on potentially relevant articles.

Study selection

We included studies which, based on full text analysis, met the following inclusion criteria: (i) assessing the impact of either a training or education or stewardship intervention; (ii) to improve either infectious disease management or appropriate use of antibiotics; (iii) in low- and middle-income countries; (iv) in humans; (v) and reporting the impact of the intervention in either health or health economic outcomes. Studies were excluded if no intervention was applied (e.g. review, protocol, cross-sectional or descriptive study), if the intervention didn't include a training or educational aspect, in case the training was merely focused on the introduction of RDTs as test-and-treat strategy (which was the scope of the Value Dx consortium), and if the full text was not available or not available in English.

Data extraction

Included studies were systematically analyzed and documented using a digital form (Google Forms; see appendix C). Within the digital form, a distinction was made between health economic articles and health-outcomes articles. For health economic articles, a total of 57 variables were listed for

data extraction, using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist as a basis[25]. A total of 23 variables were listed for health-outcome articles. Variables captured were related to study design, disease focus, interventions, input parameters and outcomes.

Categorization of results

To structure the findings of the review, a categorization of the infectious diseases was made between acute febrile infections (AFI) (fever for < 7 days), non-acute febrile infections (non-AFI) (fever for > 7 days)[26] and other infectious diseases that are not primarily febrile.

For the training and education interventions that were found in the review, further clarity was given by positioning the different interventions on the healthcare spectrum, for which the definition from O'Connel et al. (2009) was used. The interventions were positioned in four distinct phases, including (i) promotion of health, (ii) prevention of developing a disease, (iii) treatment, including patient identification and start of the treatment, and (iv) maintenance/post-intervention care, which includes patient compliance in long-term care and provision of after-care[27].

Input parameters found were categorized into four categories. The first category was *costs* which entailed all cost parameters that were used to calculate a final cost outcome (e.g. cost of medication, cost of personnel). The second category was defined as *etiology specific characteristics*, covering disease specific parameters that could impact other parameters (e.g. average duration of a disease to calculate QALYs or DALYs). The third category was *population background*, defined as population related parameters that could impact other input or outcome parameters (e.g. % of population at risk in a country). The fourth and final category consisted of *intervention details*, which put the intervention in a broader perspective (e.g. percentage of individuals at risk targeted by the intervention).

Outcome parameters were also categorized, in nine separate categories. The first two categories were related to health effects, in which the distinction between final and intermediate outcomes was made. *Final health outcomes* were defined as a quantification of the health effect of an intervention, reported in a final outcome for a health (status) change (e.g. death, QALYs, DALYs). *Intermediate health outcomes* were quantified as a change in a clinical indicator that might or might not lead to final health outcomes[28]. The third category was defined as *cost outcomes*, which included parameters that reported the cost outcomes of a whole program or a single intervention. The fourth category was defined as *prescription outcomes*, which included parameters that quantify the prescription practices like doses and frequency, often described in standardized units like the Defined Daily Doses (DDD). The fifth category, *health economic outcomes*, entailed outcomes that were reported as incremental cost per unit of outcome, indicating the cost-effectiveness of an intervention (i.e. cost per QALY). The sixth category was defined as *behavioral outcomes*, indicating the effect of an intervention on the behavior of the targeted individual. The seventh category consisted of *time related outcomes*, which included outcomes that indicated important time related aspects as a result of the intervention. Category eight was defined as *macro-level outcomes*, compromising outcomes that expressed the impact of a program at hospital or population level. The final category was classified as *miscellaneous*, covering outcomes that couldn't be placed in one of the other categories, but which were of importance for the patient or broader society[28].

Patient and public involvement

As this paper is a review comprising an assessment of the academic literature, there was no direct patient and public engagement on the paper.

RESULTS

Search results

The search strategy resulted in 1269 references, of which 291 were duplicates. Removing duplicates resulted in 978 studies that were scanned on Title and Abstract. Full-text analysis was done on 103 articles and 57 were considered to meet the study inclusion criteria (see figure 1).

Insert Figure 1

Baseline characteristics

Out of the 57 included studies, the majority was performed in Africa (44%) and Asia (33%). Also, the majority of the articles was published between 2012 and 2020 (68%). Out of the 57 studies, 20 studies were cost-effectiveness studies. For a complete overview see Table 1.

Table 1. General characteristics of studies included (n = 57). ASP: Antimicrobial stewardship program; FI: febrile illness; HIV: human immunodeficiency virus; STD: Sexually transmitted disease.

Characteristics	Number	Percentage of total
Year		
2000-2002	3	5%
2003-2005	2	4%
2006-2008	6	11%
2009-2011	7	12%
2012-2014	11	19%
2015-2017	12	21%
2018-2020	16	28%
Geography		
Africa	25	44%
Asia	19	33%
Latin-America	8	14%
Europe	4	7%
Middle East	1	2%
Study design		
Cost-effectiveness	20	35%
Quasi experimental cohort study	19	33%
Randomized control trial	10	18%
Quasi experimental retrospective cohort study	4	7%
Retrospective case-control study	2	4%
Non-randomized controlled trial	2	4%
Classification of infectious diseases		
Acute febrile infections	**30**	**53%**
- Inpatient infections (ASPs)	17	
- Malaria	6	
- Respiratory tract infection	2	
- Upper respiratory tract infection	2	
- Group of acute infectious diseases (caused by parasitic-, bacterial-, viral infections)	2	
- Post-discharge infectious disease	1	
Non-acute febrile infections	**20**	**35%**
- HIV	16	

- Tuberculosis	3	
- HIV and tuberculosis	1	
Other non-acute infections	**7**	**12%**
- *Enterobius vermicularis*	1	
- Lymphatic filariasis	1	
- *Schistosoma haematobium*	1	
- *Schistosoma japonicum*	1	
- Leprosy	1	
- STD	1	
- Candidiasis	1	

Interventions identified

Across the 57 studies that met the inclusion criteria, 34 unique interventions were identified (Table 2). The list of interventions includes non-training and non-educational interventions that were combined with a training or educational intervention.

The studies in the current review described interventions targeting three different groups, including patients, physicians and non-physician professionals. The group of non-physician professionals consisted of retail shopkeepers and pharmacists. Most interventions were targeting patients (21/34; 62%), followed by interventions targeting physicians (13/34; 38%) and a minority targeting non-physician professionals (6/34; 18%). Some interventions were targeted at more than one group.

Among the interventions that targeted patients or caregivers, the most prevalent interventions were focused on the education of patients or caregivers by peers, community workers, or health advisors. The educational goals and topics differed across the studies. Studies on HIV covered sexual- and reproductive health education for adolescents and youth[29–32], and education aiming to change sexual behavior for individuals at high risk (i.e. sexually active individuals, sex workers)[29,33–36]. Also, studies on HIV incorporated educational interventions to prevent pregnancy-related HIV transmission[37–39] and more general health education for (pregnant) women on the prevention of HIV infections[40,41]. Educational interventions in studies not targeting HIV, were focused on improving knowledge of the disease (i.e. infections with *Enterobius vermicularis*, TB, lymphatic filariasis, leprosy, malaria) and promoted preventive behavior for specific groups (i.e. youth, adolescents, patients, pregnant women) or across the general population[30,40,42–49].

Interventions targeting the physician were mainly focused on the promotion of adequate use of antimicrobial drug therapy by physicians[50–67]. In addition, physician-targeted interventions aimed to improve adequate use of antifungal therapy[68] and improved management of infectious diseases[69–72].

Four studies described interventions that targeted drug retail locations (e.g. pharmacies, shopkeepers) that play a vital role in appropriate drug use. By improving the health skillset of people at pharmacies and drug retailers, appropriate use of antimalarials and improved syndromic management of STD was promoted[73–76].

Table 2. Overview of interventions with number of studies reporting the respective intervention (% of total number of studies), categorized per healthcare value chain, per target group, per condition. AMR: Antimicrobial resistance; FI: Febrile illness; HIV: human immunodeficiency virus; STI: Sexually transmitted infection;

	Acute febrile infections			Non-acute febrile infections		Other non-acute infections	
Intervention	**Patient**	**Physician**	**Non-physician professionals**	**Patient**	**Non-physician professionals**	**Patient**	**physician**
Health promotion							
Media campaigns	-	-	1 (2%)	3 (5%)	-	1 (2%)	-
Improvement of basic needs (safe water, sanitation)	-	-	-	1 (2%)	-	1 (2%)	-
Primary school education	-	-	-	1 (2%)	-	-	-
Support to receive school education (non-disease related)	-	-	-	1 (2%)	-	-	-
Prevention							
Free commodities supplies (soap, oral rehydration salts, mosquito nets, condoms, medication)	2 (4%)	-	1 (2%)	5 (9%)	-	-	-
Health education from health advisors	1 (2%)	-	-	9 (16%)	-	3 (5%)	-
Peer-led/community-based support workers outreach and education	-	-	-	9 (16%)	-	-	-
HIV testing	-	-	-	7 (12%)	-	-	-
Prescription of preventive medication	-	-	-	3 (5%)	-	2 (4%)	-
Case finding of leprosy by dedicated team traveling from city to city	-	-	-	-	-	1 (2%)	-
Treatment							
Physician instructed care support via teachers/community-based support workers	3 (5%)	-	-	1 (2%)	-	-	-
Presentation and discussion of (newly created) clinical guideline	-	14 (25%)	-	-	1 (2%)	-	1 (2%)
Training on AMR	-	13 (23%)	-	-	-	-	1 (2%)
Feedback on baseline antibiotic prescription practices	-	12 (21%)	-	-	-	-	1 (2%)
Create new guideline for optimal prescription	-	8 (14%)	-	-	-	-	1 (2%)
Antimicrobial order form	-	6 (11%)	-	-	-	-	-

Review/modification of prescription by AMR team	-	5 (9%)	-	-	-	-	-
Bedside discussions among AMR expertise group	-	3 (5%)	-	-	-	-	1 (2%)
Face-to-face (individual) interactive discussions	-	4 (7%)	-	-	-	-	-
Antimicrobial susceptibility patterns shared with physicians	-	3 (5%)	-	-	-	-	-
Peer review/presentation and discussion of the guideline, and presentation of clinical scenarios	-	3 (5%)	-	-	-	-	-
Motivational interventions (fine based)	-	1 (2%)	-	-	-	-	-
Restricted use of specific drugs	-	-	-	-	-	-	1 (2%)
Introduction of an antibiotic prescription chart	-	1 (2%)	-	-	-	-	-
Skill-based training on management of diseases	-	-	3 (5%)	1 (2%)	1 (2%)	-	-
Facilitation of community mobilization	-	-	1 (2%)	1 (2%)	-	-	-
Financial support (free treatment of disease, reimbursement of travel cost, care and assistance)	-	-	-	8 (14%)	-	-	-
Offering free food to reduce food insecurity and encourage clinic visits	-	-	-	2 (4%)	-	-	-
Prioritization of patients with HIV over other patients	-	-	-	1 (2%)	-	-	-
Syndromic management of STI			-	1 (2%)	-	-	-
Maintenance/post-intervention care							
Educational materials for caregivers, patients and communities	2 (4%)	-	1 (2%)	3 (5%)	-	2 (4%)	-
Scheduling post-discharge follow-up visits	1 (2%)	-	-	-	-	-	-
Sending post-discharge reminders for treatment adherence	-	-	-	1 (2%)	-	-	-
HIV counseling	-	-	-	7 (12%)	-	-	-

Input parameters identified

A total of 42 unique input parameters were found. Categorization of the input variables resulted in four overarching parameter types: (i) cost parameters, (ii) disease-specific parameters, (iii) population background characteristics, and (iv) intervention details (see table 3).

The majority of the input parameters detailed the costs of an intervention (27 unique parameters). Within the cost category, a clear distinction was present between cost related to the program, cost for care and cost for the patient and caregiver. Great variety existed amongst the studies, none of the cost parameters was used across all studies.

Acute febrile infections

No consistent approach was found amongst studies that included cost input parameters. A large proportion of the studies only included the cost of medication, not taking any other program or care related costs into account[50,51,53,58,60,63,65]. Though, there were also studies that took a more extensive approach by reporting both cost of care (e.g. cost of medication, cost of consultation) and program costs (e.g. cost of personnel, cost of training and cost of program management)[55–57,61,71,74,75,77,78]. Across all studies in the review, only three studies included the cost for the patient and caregiver. These studies were cost-effectiveness studies of malaria interventions performed from a societal perspective[71,75,77].

Non-acute febrile infections

All non-AFI studies that reported costs as input parameters, included at least one variable on the cost of care and one variable on costs of the program[29,30,33,34,36,38,40,41,45,79–82]. The cost of supplies such as condoms and medication was reported most frequently[29,33,34,38,40,41,45,79,81]. None of the studies included the costs for the patient and caregiver.

Other non-acute infections

Studies that included costs for interventions targeting non-acute infections, reported costs in different ways. One study on candidiasis only included the cost of medication[68], while studies on sexually transmitted diseases (STD), *S. japonicum* and leprosy incorporated both costs of care and cost of the program[42,73,83]. None of the studies included the costs for the patient and caregiver.

Table 3. Overview of input parameters. ANC: Antenatal Care; ART: antiretroviral therapy; FI: Febrile illness; HIV: human immunodeficiency virus; ICU: Intensive Care Unit.

Category	Definition	Input variables	Reported in N studies (% of total; % of total within the respective category)		
			Acute febrile infection	Non-acute febrile infections	Other non-acute infections
Cost	Costs related to the intervention/the program	**Program cost:** Cost of travel and accommodation for personnel; cost of buildings; cost of overhead; cost of refreshments; start-up costs; cost of training or education; program management costs; program development cost; program implementation cost; recurring costs for training; personnel cost; cost of transportation of supplies; cost of equipment; cost for data capture and use; **Cost of care:** Routine care costs; daily cost of ICU admission; average cost of one inpatient day; cost of social mobilization; pharmacists costs; cost of consultation; cost of lifetime treatment; cost of diagnostic tests; cost of death; cost of supplies/medication; **Cost for the patient/caregiver:** Travel cost; cost of time lost for caregiver; out-of-pocket costs	19 (33%; 63%)	13 (23%; 65%)	4 (7%; 57%)
Disease specific characteristics	Disease related characteristics that have impact on the intervention outcomes	ART initiation age; awareness of HIV status; bacterial resistance rates; disease transmission rates; average duration of the disease; disease prevalence	5 (9%; 17%)	7 (12%; 35%)	4 (7%; 57%)
Population background	Background information on the targeted population which could affect the outcomes of the intervention	number of people at risk in the area; average life expectancy; average number of sex clients per month; average time span men buy sex; average time span women sell sex; proportion of individuals using condoms	-	4 (7%; 20%)	1 (2%; 14%)
Intervention details	Details of the intervention that put the intervention in a broader perspective	number of individuals reached with the intervention; efficacy of the intervention; the proportion of the population at risk targeted by the intervention	-	5 (9%; 20%)	1 (2%; 14%)

Outcomes identified

A total of 74 unique outcomes were reported in 57 studies which are categorized into nine categories (see Table 4). In the section below, the five categories that were reported in most studies are reviewed in more detail.

Final health outcomes

Out of the 57 studies, 19 studies reported final health outcomes. Final health outcomes - reported in DALYs averted, QALYs gained, Years of Life Saved (YLS), mortality rate, cured rate and deaths averted - were found in studies across all three infectious disease categories.

Acute febrile infections

Amongst the studies on AFI, one study on malaria reported DALYs and deaths averted, calculated based on the probability of death for a child with fever for whom treatment is first sought from a shop, with and without the intervention[74]. Six studies on inpatient infections reported mortality rates (increase/decrease) as a result of the intervention[50,54,56,59,61,84]. One study on post-discharge infections reported final health outcomes in deaths averted, defined as hospitalized patients that survive 30 days after discharge[62].

Non-acute febrile infections

In total, six studies on HIV reported DALYs averted, calculated from the number of infections averted[29,34,36,38,40,81]. Besides the studies reporting DALYs averted, there was one study on HIV reporting QALYs to quantify the impact of the prevention of mother-to-child HIV transmission [41]. To estimate QALYs, the difference between the expected number of QALYs of a child living with and without HIV was calculated[41]. One study on HIV reported outcomes in YLS calculated from the life years lost as a result of loss-to-follow-up from antiretroviral therapy (ART)[79]. One study on TB reported the final health outcomes as the number of patients cured, defined as individuals who are smear- or culture negative in the last month of treatment[43], and another study on TB reported the outcome as the reduction in mortality rate as a result of the intervention[45].

Other non-acute infections

Only one study in the category of other non-acute infections reported a final health outcome. The study on leprosy reported the number of patients cured, defined as individuals completing the therapy[42].

Intermediate health outcomes

Acute febrile infections

Amongst the studies reporting on AFI, the most frequently reported intermediate health outcome was the number of patients that are correctly treated, covered in studies on inpatient infections, malaria and acute respiratory tract infections[50,51,55,56,64,67,70–72,75,75,76]. The recurrence rate, also indicated as unexpected readmission rates, was reported in five studies covering inpatient infections, respiratory tract infection and post-discharge infections[54,56,59,61,84]. Other intermediate health-outcomes reported in studies on AFI were less widely reported. These outcomes included the number of cases diagnosed with malaria[71], the decrease of inpatient infections as a result of an antimicrobial stewardship program (ASP)[58], and the number of adverse events occurred after implementation of ASPs for improved management of inpatient infections[64,65].

Non-acute febrile infections

The two most reported intermediate health-outcomes in studies on HIV or TB were the number of cases diagnosed[82,85] and the number of infections averted[29,34,41]. Across all studies in the review, only one study reported the quality of life of the patient, which was measured using the EQ-5D with TB patients[43]. Disease specific clinical outcomes were also found in studies on HIV and TB. Examples of disease specific outcomes were reduced TB stigma or CD4 count slope[30,86].

Other non-acute infections

One study on STD reported intervention outcomes in the number of patients correctly treated[73]. Two studies, on STD and candidiasis, reported the results in the number of unexpected readmissions[68,73]. The number of cases diagnosed was reported in one study on leprosy[42] and the increase/decrease of infections as a result of the intervention was reported in two studies, covering *S. japonicum* and *E. vermicularis* infections[44,83].

Cost outcomes

The cost impact of an intervention was reported in an aggregate form (i.e. total program costs and total cost saved) or on a per-unit basis (e.g. per person reached). The aggregated total costs of the program/intervention[34,36,38,42,48,53,57,63,66,70,74,75,77,78,80–83] and the costs saved as a result of the intervention[36,41,53,54,56–58,61,61,65,68] were often reported across all three infectious disease categories.

Only studies on non-AFI reported the cost per unit. Three studies on HIV reported cost per person reached[29,33,36] and one study on HIV indicated the cost per individual tested[33].

Health economic outcomes

Acute febrile infections

Only six studies in the category of AFI reported health economic outcomes, out of which four were on malaria. Studies on malaria reported health economic outcomes as the cost per case adequately treated[71,74,75,77], cost per DALY averted[74] and cost per death averted[74]. Cost per death averted was also reported in a study on inpatient infections[62]. The cost per percentage reduction in antibiotic prescription was reported once in a study on upper respiratory tract infection[78].

Non-acute febrile infections

Health economic outcomes were most often reported in studies on non-AFI. Twelve out of the seventeen studies on HIV reported on the cost-effectiveness of the intervention. Variables included were cost per infection averted[34,36,41,85], cost per QALY[41], cost per HIV case detected[82,85], cost per DALY averted[29,34,36,38,40,81], cost per averted loss-to-follow-up[30,80] and cost per YLS[79].

Cost-effectiveness thresholds, which indicates the maximum amount a country or organization is willing to pay for a unit of health-outcome, were only applied in studies on HIV. The thresholds ranged between one to five times Gross Domestic Product (GDP) per capita per DALY averted[29,36,38,40] or per YLS[79]. For all five studies that applied cost-effectiveness thresholds, the cost per DALY averted or cost per YLS of the interventions fell below the cost-effectiveness thresholds. Hence, these interventions were considered cost-effective compared to the standard of care[29,36,38,40,79].

Other non-acute infections

In the category of other non-acute infections, health economic outcomes were rarely reported. One study on *S. japonica* reported cost per infection averted[83] and one study on STD reported the cost per case adequately treated[73].

Prescription outcomes

The category of prescription outcomes included outcomes reported in studies that aimed for more appropriate use of antimicrobials and antifungals by physicians, and was only found in studies on AFI. The category of prescription outcomes provided insight into three main factors: (i) the overall prescription practices by physicians, (ii) the quality of the prescription practices, and (iii) the quantitative prescription details (see Table 4).

As an indicator of the overall prescription practices, three outcomes were reported: the antibiotic prescription rate (number of times antibiotics prescribed)[55,57,63,66,68,69,78], percentage of the prescriptions containing more than one antibiotic[66] and percentage of prescriptions containing broad-spectrum antibiotics[66].

The quality of the prescription practices was reflected by the number of inappropriate prescriptions, defined as incorrect antimicrobial prescribed, incorrect dose prescribed, incorrect duration prescribed or incorrect decision to prescribe antimicrobials[52,63,68]. Another outcome that indicated the quality of prescription practices was the number of times adjustment of prescription was done[50].

The quantitative details of the prescription were reported in a variety of ways. Two studies reported the total DDD prescribed[65,78]. The DDD is a validated method to standardize the number of doses consumed and is developed by the World Health Organization (WHO). Eight studies reported the total DDD per 1000 patient days or 100 patients treated[51,53,54,56,58,60,61,68]. One study reported the total antibiotic days of therapy per 1000 patient days, defined as the days of antibiotic therapy administered to the patients independent of the doses. The days of therapy was calculated by multiplying the number of doses received by the dosing interval (in hours) and then divided by 24 hours for each antibiotic the patient received[59]. The antibiotic use density (AUD) was given once, which was equal to DDD per 100 patient days, and was calculated by multiplying the DDD by 100, divided by the number of patient[67]. All studies on inpatient infections that reported on antibiotic consumption reported a decrease in the total antibiotics consumed[51,53,54,56,58–61,65,67,68] with some small increases on individual antibiotics[50,51,53,57,60,61,63,65].

Table 4. Overview of outcome variables. ANC: Antenatal Care; DALY: Disability Adjusted Life Years; DDD: Defined Daily Doses; FI: Febrile illness; GP: General Practitioner; HIV: human immunodeficiency virus; ICU: Intensive Care Unit; QALY: Quality Adjusted Life Year; YLS: Years of Life Saved.

Category	Definition	Outcome variables	Reported in N studies (% of total; % of total within the respective category)		
			Acute febrile infections	Non-acute febrile infections	Other non-acute infections
Final health outcomes	Quantification of the health effect of an intervention, addressing the length or quality of life	QALY; DALY; YLS; deaths averted; mortality rate; mortality increase/decrease; cured rate	8 (14%; 27%)	10 (18%; 50%)	1 (2%; 14%)
Intermediate health outcomes	Quantification of the health effects of an intervention as a change in clinical indicator that may or may not lead to final health outcomes[28]	Disease specific outcomes; number of cases correctly treated; infections averted; number cases detected with disease; infection rates; recurrence rates; number of adverse drug reactions; % positive and negative tests; number of individuals receiving treatment; quality of life	19 (33%; 63%)	8 (14%; 40%)	5 (9%; 71%)
Cost outcomes	Quantification of the costs as a result of the whole program or single intervention	Total cost; cost reduction/costs saved; cost of intervention per patient; cost per individual tested; costs per person reached	18 (32%; 60%)	11 (19%; 55%)	3 (5%; 43%)
Prescription outcomes	Quantification of the impact of an intervention on prescribing practices	Antibiotic use density; DDD/100 patients; (antibiotic) prescription rate; DDD/1000 or 100 patient days; number of inappropriate prescriptions; total antibiotic Days of Therapy/1000 patient days; % of prescriptions containing more than one antibiotic; % of prescriptions having broad spectrum antibiotics; number of times adjustment of antibiotic prescription done	19 (33%; 63%)	-	-
Health economic outcomes	Outcomes reflecting the incremental cost per single unit of outcome	Cost per infection averted; cost per individual adequately treated; cost per HIV case detected; costs per averted loss-to-follow-up; cost per decrease in antibiotic prescription rate; Cost per QALY; cost per DALY averted; Cost per YLS; cost per death averted	6 (11%; 20%)	12 (21%; 60%)	2 (4%; 29%)

Behavior outcomes	Outcomes that indicate the effect of the intervention on health-related behavior of the targeted individual	Adherence rates; attrition rates (including loss-to-follow-up and mortality); number of admissions; loss-to-follow-up rate; averted loss-to-follow-up; % retention in care; completion of follow-up visits; number of referrals to secondary health clinics by GP; number of women giving birth at health facility; number of ANC visits; number of cases that did postpartum check-up; number performing exclusive breastfeeding; % using family planning;	6 (11%; 20%)	8 (14%; 40%)	1 (2%; 14%)
Time related outcomes	Quantification of the time related component of an intervention	Time efficiency gain; time to event; duration of hospital stay; per person life-expectancy losses due to loss-to-follow-up; time till loss-to-follow-up	6 (11%; 20%)	4 (7%; 20%)	-
Macro-level outcomes	Expressing the impact of a program/intervention at hospital or population level	% tested; medical care utilization days; number of diagnostic tests done; ICU admissions; absolute risk ratio; number needed to treat; % receiving treatment; Bacterial resistance rates	8 (14%; 27%)	4 (7%; 20%)	-
Miscellaneous	Intervention specific outcomes, which are not direct measures of health but are of societal importance or of importance for the patient[28]	Number of times replacement drug is provided; number of male partners attending care visits; number of physicians receiving fines; number of times education provided to the patient; number of early infant diagnosis done; population knowledge of the disease; number of times combined medication provided; number of couple HIV testing and counseling	4 (7%; 13%)	3 (5%; 15%)	1 (2%; 14%)

DISCUSSION

The results of the current review provide insight in the wide range of programs that aim for improved infectious disease management and antibiotic prescriptions in LMICs. The programs consisted of one or more interventions that span across the healthcare pathway and target different stakeholder groups including patients, physicians and non-physician professionals. The input and outcome parameters reported in the studies did not show a consistent and generalizable set of metrics used across all studies. However, by grouping the individual variables into categories, it became evident that four input categories and nine outcome categories could be considered when reporting the impact of a program targeting infectious diseases.

Heterogeneity in outcomes is a well-known factor of influence in clinical research[87]. Several initiatives have started to improve the standardization of metrics measured and reported in clinical studies. One of these initiatives is the Core Outcome Measures in Effectiveness Trials (COMET; https://www.comet-initiative.org/) initiative, which launched in 2010 to coordinate efforts in the development of core outcome sets (COS) across a wide range of areas of health. The definition of COS is "an agreed standardized collection of outcomes that should be measured and reported for a specific area of health"[88]. Unfortunately, for infectious disease, the number of COS developed is limited, existing COS on infectious diseases have not been updated recently[89,90] and the involvement of LMICs in the development of the COS was low[91]. Therefore, we suggest that further research will continue with a critical assessment of the categories and metrics found in the current review. These efforts could function as valuable input to establish an initial COS for infectious disease management programs in LMIC.

Reporting on final health outcomes is crucial to allow comparisons between interventions. Final health outcomes are standardized and widely used outcomes across multiple disease areas, as opposed to intermediate health outcomes that could be disease specific and thereby making it difficult to extrapolate and compare with other disease areas. The most used final health outcome in global health studies and in LMICs is the DALYs averted, which is used to define the burden of the disease[15]. Also within the current review, DALYs averted was the most frequent reported final health outcome, mostly found in studies on non-AFI (e.g. HIV)[29,34,36,38,40,81] and only one time in a study on AFI (e.g. malaria)[74]. Studies on AFI more often report on an increase or decrease in mortality rate. However, as opposed to DALYs, mortality rates do not quantify the impact of a disease on morbidity[92], which is why the DALY is preferred over the mortality rate. One of the potential reasons for not reporting the DALYs could be the lack of local data for estimating the DALYs, which appeared to be an important reason for researchers in LMIC to not include the DALYs averted[93]. Also, infectious diseases are often self-limiting and of short duration, thereby having a small impact on the estimated DALYs per patient, but on population level could still result in a substantial disease burden[1]. To encourage researchers in reporting on important outcome parameters like DALYs averted, the Guide to Economic Analysis and Research (GEAR; http://www.gear4health.com/) online resource was introduced as a reliable aid for researchers in LMICs that provide solutions for methodological difficulties[22]. Although it could be a helpful resource, none of the studies in the current review mentioned or referred to the GEAR resource. Hence, further dissemination of the GEAR resource amongst researchers performing health-economic analyses for LMICs could be of benefit to improve standardization across studies.

The impact of a health intervention should logically be expressed in health outcomes, but also the financial impact should be considered. Being able to compare interventions on health-related and economic outcomes, allows policy makers to create health policy with the intervention that maximizes the health impact per monetary unit spent. There are different approaches researchers

could take when calculating the cost of an intervention, considering direct and indirect costs. Within the current review, most of the studies reporting the costs of an intervention only included direct costs, with substantial variations in the type of direct costs included. These methodological variations have impact on the results and make comparisons between studies less reliable. A more standardized approach for calculating costs would improve generalizability of results and thereby enhance the ability to compare outcomes between different studies. Wider implementation of existing guidelines could be an important step towards more generalizable results for studies in LMICs. For example, for health economic studies, the CHEERS provides guidance in the reporting of health economic assessments. The CHEERS guideline includes some high-level recommendations in the decision on what costs to include, depending on the perspective that is taken (e.g. healthcare system, societal)[25]. Also, for studies on ASPs, the US guideline incorporated recommendations to include costs on program management, salary for stewardship personnel, and medication purchasing costs[94]. With the US guideline for studies on ASPs and the CHEERS guideline for health economic assessments, some guidance already exists and could be more broadly applied as an initial step towards more generalizable cost outcomes.

Indicating the impact of an intervention on prescription practices has been considered as an important outcome variable. As such, standardized approaches are introduced by WHO to enable clear and concise reporting of prescription outcomes[95]. Especially in the case of antimicrobial prescriptions, the dose, frequency and duration are important to assess the impact of an intervention on the consumption and the related antimicrobial resistance. Within the current review, the DDD was the most reported outcome in the category of prescriptions outcomes. The DDD is a standardized approach but is impacted by weight-based dosing as done for pediatrics[94]. Therefore, instead, days of therapy is suggested as a more valuable parameter since it is not impacted by dose adjustments. When following the guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, days of therapy is the preferred option[94]. In the present review, only one study reported the outcomes in days of therapy[59]. Moving forward, it would be advised to report the antimicrobial use in days of therapy if possible.

Studies targeting antimicrobial prescription reported the DDD or days of therapy as the main outcome measure[51,53,54,56,58–61,65,67,68]. None of these articles reported final health outcomes in DALY, QALY or YLS. Translating antimicrobial use into a value that indicates the burden of the disease, such as DALYs, is challenging and comes with great uncertainty[96]. Calculating the DDD or days of therapy requires no significant assumptions, thereby making DDD or days of therapy reliable parameters to indicate the effect of an intervention. However, these measures are not relevant for interventions not targeting antimicrobial prescription practices. In theory, to make these measures more generalizable, antimicrobial use could be converted to costs per antimicrobial prescribed. Some studies estimated the cost of antimicrobial resistance per antibiotic prescription[97,98], but these estimates come with high uncertainty and there is a risk that the actual costs are far higher than the best estimates[99]. However, not incorporating any impact of future antimicrobial resistance should not be an option. Health systems have finite resources; underestimating the impact of ASPs now could result in further de-prioritization of the implementation of ASPs with a higher change of antimicrobial resistance in the future.

The current literature review is limited in the following aspects: firstly, the variables found in this review show a high heterogeneity resulting in low generalizability. This could be a result of the wide scope of etiologies included, in addition to the fact that the input and outcome parameters are often context specific. However, generalizability should, to a certain extent, also apply to interventions targeting different etiologies to allow policy makers to decide on the most cost-effective strategy.

There should at least be a set of core outcomes across etiologies that functions as the minimum of what should be included, still allowing for additional disease specific measures to be added. Secondly, the results of the current review could guide researchers in the process of defining input and outcome parameters to report on for health economic research on infectious diseases but does not offer a concrete list of input and outcome parameters. Further research is needed to come to a core outcome set for infectious diseases along with broad implementation and knowledge dissemination of currently available guidelines.

To our knowledge, the current study is the first review that provides an overview of health economic and health-outcome studies on training or education interventions for improved management of infectious diseases. Thereby, the current study offers valuable insights for future health economic assessments on programs in which education is integral part of the intervention.

CONCLUSION

In conclusion, it can be said that standardization of parameters is lacking across studies on infectious disease programs. For input parameters, the most reported category was costs. For outcomes, studies reported most often on final health outcomes, intermediate health outcomes, cost outcomes, prescription outcomes and health economic outcomes. We recommend that further research will be performed on the definition of a core outcome set for infectious diseases in LMICs.

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Figure legends

Figure 1. Prisma flow diagram.

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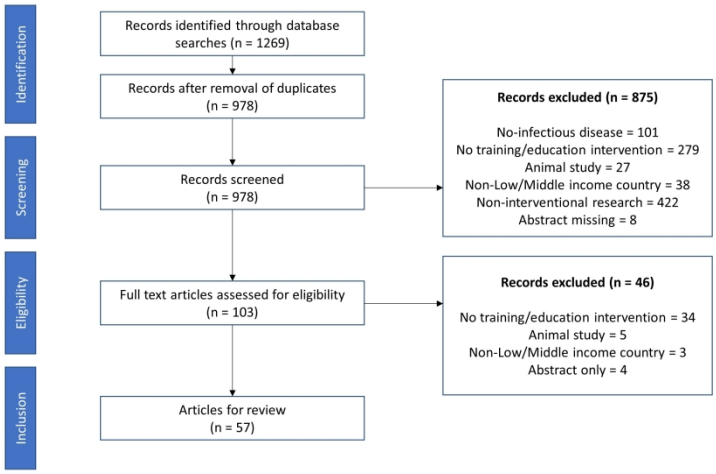

Figure 1 - PRISMA flow diagram

338x190mm (300 x 300 DPI)

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Appendix C
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix C
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

Topic	No.	Item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16 - Page 17
	23b	Discuss any limitations of the evidence included in the review.	Page 17 - Page 18

Topic	No.	Item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Page 18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 18
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 18
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18
Competing interests	26	Declare any competing interests of review authors.	Page 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 18

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

APPENDIX A – Detailed search strategy per database

PubMed/Medline

(febrile* OR infectious OR "bacterial infection" OR "viral infection" OR antibiotic* OR antimicrobial) AND

("Antimicrobial Stewardship"[Mesh] OR "Education"[Mesh] OR Stewardship*[tiab] OR train*[tiab] OR educat*[tiab] OR campaign*[tiab] OR behavior change*[tiab] OR behavioral change*[tiab] OR behaviour change*[tiab] OR behavioural change*[tiab]) AND

(cost-effectiv*[tiab] OR economic analys*[tiab] OR economic evaluation*[tiab] OR pharmacoeconomic*[tiab] OR Health outcome*[tiab] OR health-related outcome*[tiab] OR health technology assessment*[tiab] OR Cost-saving*[tiab] OR Cost-benefit*[tiab]) AND

(middle-income[tiab] OR Low-income[tiab] OR "Afghanistan"[Mesh] OR Afghan*[tiab] OR "Albania"[Mesh] OR Alban*[tiab] OR "Algeria"[Mesh] OR Algeria*[tiab] OR "Angola"[Mesh] OR Angol*[tiab] OR "Antigua and Barbuda"[Mesh] OR Antigua*[tiab] OR "Argentina"[Mesh] OR Argentin*[tiab] OR "Armenia"[Mesh] OR Armenia*[tiab] OR "Azerbaijan"[Mesh] OR Azerbaijan*[tiab] OR "Bangladesh"[Mesh] OR Bangladesh*[tiab] OR "Republic of Belarus"[Mesh] OR Belarus*[tiab] OR "Belize"[Mesh] OR Belize*[tiab] OR "Benin"[Mesh] OR Benin*[tiab] OR "Bhutan"[Mesh] OR Bhutan*[tiab] OR "Bolivia"[Mesh] OR Bolivia*[tiab] OR "Bosnia and Herzegovina"[Mesh] OR Bosnia*[tiab] OR "Botswana"[Mesh] OR Botswan*[tiab] OR "Brazil"[Mesh] OR Brazil*[tiab] OR "Burkina Faso"[Mesh] OR Burkino faso*[tiab] OR "Burundi"[Mesh] OR Burundi*[tiab] OR "Cabo Verde"[Mesh] OR Cabo Verde*[tiab] OR "Cambodia"[Mesh] OR Cambodia*[tiab] OR "Cameroon"[Mesh] OR Cameroon*[tiab] OR "Central African Republic"[Mesh] OR Central African Republic*[tiab] OR Africa*[tiab] OR "Chad"[Mesh] OR Chad*[tiab] OR "China"[Mesh] OR Chin*[tiab] OR "Colombia"[Mesh] OR Colombia*[tiab] OR "Comoros"[Mesh] OR Comor*[tiab] OR "Congo"[Mesh] OR Congo*[tiab] OR "Polynesia"[Mesh] OR Cook Islander*[tiab] OR "Costa Rica"[Mesh] OR Costa Rica*[tiab] OR "Côte d'Ivoire"[Mesh] OR Côte d'Ivoir*[tiab] OR "Cuba"[Mesh] OR Cuba*[tiab] OR "Djibouti"[Mesh] OR Djibouti*[tiab] OR "Dominica"[Mesh] OR Dominic*[tiab] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh] OR Ecuador*[tiab] OR "Egypt"[Mesh] OR Egypt*[tiab] OR "El Salvador"[Mesh] OR salvador*[tiab] OR "Equatorial Guinea"[Mesh] OR Equatorial Guinea*[tiab] OR "Eritrea"[Mesh] OR Eritrea*[tiab] OR "Ethiopia"[Mesh] OR Ethiopia*[tiab] OR "Fiji"[Mesh] OR Fiji*[tiab] OR "Gabon"[Mesh] OR Gabon*[tiab] OR "Gambia"[Mesh] OR Gambia*[tiab] OR "Georgia"[Mesh] OR Georgia*[tiab] OR "Ghana"[Mesh] OR Ghana*[tiab] OR "Grenada"[Mesh] OR Grenad*[tiab] OR "Guatemala"[Mesh] OR Guatemala*[tiab] OR "Guinea"[Mesh] OR Guinea*[tiab] OR "Guinea-Bissau"[Mesh] OR Guinea-Bissau*[tiab] OR "Guyana"[Mesh] OR Guyan*[tiab] OR "Haiti"[Mesh] OR Haiti*[tiab] OR "Honduras"[Mesh] OR Hondura*[tiab] OR "India"[Mesh] OR India*[tiab] OR "Indonesia"[Mesh] OR Indonesia*[tiab] OR "Iran"[Mesh] OR Iran*[tiab] OR "Iraq"[Mesh] OR Iraq*[tiab] OR "Jamaica"[Mesh] OR Jamaica*[tiab] OR "Jordan"[Mesh] OR Jordan*[tiab] OR "Kazakhstan"[Mesh] OR kazakhstan*[tiab] OR "Kenya"[Mesh] OR Kenya*[tiab] OR "Micronesia"[Mesh] OR Kiribati*[tiab] OR "Korea"[Mesh] OR Korea*[tiab] OR "Kosovo"[Mesh] OR kosovo*[tiab] OR "Kyrgyzstan"[Mesh] OR Kyrgyzstan*[tiab] OR "Laos"[Mesh] OR Laos*[tiab] OR "Lebanon"[Mesh] OR Leban*[tiab] OR "Lesotho"[Mesh] OR Lesotho*[tiab] OR "Liberia"[Mesh] OR Liberia*[tiab] OR "Libya"[Mesh] OR Libya*[tiab] OR "Republic of North Macedonia"[Mesh] OR Macedonia*[tiab] OR "Madagascar"[Mesh] OR Madagasca*[tiab] OR Malagasy*[tiab] OR "Malawi"[Mesh] OR Malawi*[tiab] OR "Malaysia"[Mesh] OR Malaysia*[tiab] OR maldiv*[tiab] OR "Mali"[Mesh] OR Mali*[tiab] OR Marshall*[tiab] OR "Mauritania"[Mesh] OR Mauritania*[tiab] OR "Mauritius"[Mesh]

OR Mauriti*[tiab] OR "Mexico"[Mesh] OR Mexic*[tiab] OR "Micronesia"[Mesh] OR Micronesia*[tiab] OR "Moldova"[Mesh] OR Moldova*[tiab] OR "Mongolia"[Mesh] OR Mongolia*[tiab] OR "Montenegro"[Mesh] OR Montenegr*[tiab] OR Montserrat*[tiab] OR "Morocco"[Mesh] OR Morrocc*[tiab] OR "Mozambique"[Mesh] OR Mozambic*[tiab] OR "Myanmar"[Mesh] OR Myanmar*[tiab] OR "Namibia"[Mesh] OR Namibi*[tiab] OR Nauru*[tiab] OR "Nepal"[Mesh] OR Nepal*[tiab] OR "Nicaragua"[Mesh] OR Nicaragua*[tiab] OR "Niger"[Mesh] OR Niger*[tiab] OR "Nigeria"[Mesh] OR Niue*[tiab] OR "Pakistan"[Mesh] OR Pakistan*[tiab] OR "Palau"[Mesh] OR Palau*[tiab] OR "Panama"[Mesh] OR panama*[tiab] OR "Papua New Guinea"[Mesh] OR Papua New Guinea*[tiab] OR "Paraguay"[Mesh] OR paraguay*[tiab] OR "Peru"[Mesh] OR Peru*[tiab] OR "Philippines"[Mesh] OR Philippin*[tiab] OR "Rwanda"[Mesh] OR Rwanda*[tiab] OR "Atlantic Islands"[Mesh] OR Saint helena*[tiab] OR "Samoa"[Mesh] OR Samoa*[tiab] OR "São Tomé and Príncipe"[Mesh] OR São Tomé and Príncip*[tiab] OR "Senegal"[Mesh] OR Senegal*[tiab] OR "Serbia"[Mesh] OR Serbia*[tiab] OR "Sierra Leone"[Mesh] OR Sierra leon*[tiab] OR "Melanesia"[Mesh] OR Solomon island*[tiab] OR "Somalia"[Mesh] OR Somalia*[tiab] OR "South Africa"[Mesh] OR South Africa*[tiab] OR "South Sudan"[Mesh] OR South Sudan*[tiab] OR "Sri Lanka"[Mesh] OR Sri Lanka*[tiab] OR "Saint Lucia"[Mesh] OR Saint lucia*[tiab] OR "Saint Vincent and the Grenadines"[Mesh] OR vincent*[tiab] OR "Sudan"[Mesh] OR Sudan*[tiab] OR "Suriname"[Mesh] OR Suriname*[tiab] OR "Eswatini"[Mesh] OR Swaziland*[tiab] OR "Syria"[Mesh] OR Syria*[tiab] OR "Tajikistan"[Mesh] OR Tajikistan*[tiab] OR "Tanzania"[Mesh] OR tanzania*[tiab] OR "Thailand"[Mesh] OR Thai*[tiab] OR "Timor-Leste"[Mesh] OR Timor*[tiab] OR "Togo"[Mesh] OR Togo*[tiab] OR Tokelau*[tiab] OR "Tonga"[Mesh] OR Tonga*[tiab] OR "Tunisia"[Mesh] OR Tunisia*[tiab] OR "Turkey"[Mesh] OR Turk*[tiab] OR "Turkmenistan"[Mesh] OR Tuvalu*[tiab] OR "Uganda"[Mesh] OR Uganda*[tiab] OR "Ukraine"[Mesh] OR Ukrain*[tiab] OR "Uzbekistan"[Mesh] OR Uzbek*[tiab] OR "Vanuatu"[Mesh] OR Vanuatu*[tiab] OR "Venezuela"[Mesh] OR Venezuala*[tiab] OR "Vietnam"[Mesh] OR Vietnam*[tiab] OR Furtun*[tiab] OR Gaza*[tiab] OR "Yemen"[Mesh] OR Yemen*[tiab] OR "Zambia"[Mesh] OR Zambia*[tiab] OR "Zimbabwe"[Mesh] OR Zimbabwe*[tiab]) AND

("2000/01/01"[Date - Publication]: "2020/11/01"[Date - Publication])

Web of Science

TS=((""bacterial infection"" OR ""viral infection"" OR antibiotic* OR antimicrobial OR infectious) AND

(Educat* OR Stewardship* OR train* OR campaign* OR ""behavior change"" OR ""behavioral change"" OR ""behaviour change"" OR ""behavioural change"") AND

(cost-effectiveness OR ""economic analysis"" OR ""economic evaluation"" OR pharmacoeconomic* OR ""Health outcome"" OR ""health-related outcomes"" OR ""health technology assessment"" OR Cost-saving OR Cost-benefit) AND

(middle-income OR Low-income OR Afghan* OR Alban* OR Algeria* OR Angol* OR Antigua* OR Argentin* OR Armenia* OR Azerbaijan* OR Bangladesh* OR Belarus* OR Belize* OR Benin* OR Bhutan* OR Bolivia* OR Bosnia* OR Botswan* OR Brazil* OR ""Burkino faso"" OR Burundi* OR Cabo Verde* OR Cambodia* OR Cameroon* OR ""Centrial African Republic"" OR Africa* OR Chad* OR Chin* OR Colombia* OR Comor* OR Congo* OR ""Cook Island"" OR ""Costa Rica"" OR ""Côte d'Ivoir"" OR Cuba* OR Djibouti* OR Dominic* OR Ecuador* OR Egypt* OR salvador* OR ""Equatorial Guinea"" OR Eritrea* OR Ethiopia* OR Fiji* OR Gabon* OR Gambia* OR Georgia* OR Ghana* OR Grenad* OR Guatemala* OR Guinea* OR Guinea-Bissau* OR Guyan* OR Haiti* OR Hondura* OR

India* OR Indonesia* OR Iran* OR Iraq* OR Jamaica* OR Jordan* OR kazakhstan* OR Kenya* OR Kiribati* OR Korea* OR kosovo* OR Kyrgyzstan* OR Laos* OR Leban* OR Lesotho* OR Liberia* OR Libya* OR Macedonia* OR Madagasca* OR Malagasy* OR Malawi* OR Malaysia* OR maldiv* OR Mali* OR Marshall* OR Mauritania* OR Mauriti* OR Mexic* OR Micronesia* OR Moldova* OR Mongolia* OR Montenegr* OR Montserrat* OR Morrocc* OR Mozambic* OR Myanmar* OR Namibi* OR Nauru* OR Nepal* OR Nicaragua* OR Niger* OR Niue* OR Pakistan* OR Palau* OR panama* OR ""Papua New Guinea"" OR paraguay* OR Peru* OR Philippin* OR Rwanda* OR ""Saint helena"" OR Samoa* OR ""São Tomé and Príncipe"" OR Senegal* OR Serbia* OR ""Sierra leone"" OR ""Solomon islands"" OR Somalia* OR ""South Africa"" OR ""South Sudan"" OR ""Sri Lanka"" OR ""Saint lucia"" OR ""Saint vincent"" OR Sudan* OR Suriname* OR Swaziland* OR Syria* OR Tajikistan* OR tanzania* OR Thai* OR Timor* OR Togo* OR Tokelau* OR Tonga* OR Tunisia* OR Turk* OR Tuvalu* OR Uganda* OR Ukrain* OR Uzbek* OR Vanuatu* OR Venezuala* OR Vietnam* OR ""Wallis and furtuna"" OR Gaza* OR Yemen* OR Zambia* OR Zimbabwe*))) AND

Time period 2000 – 2020

Scopus

(TITLE-ABS-KEY (febrile*) OR TITLE-ABS-KEY (antibiotic*) OR TITLE-ABS-KEY (infectious) OR TITLE-ABS-KEY ("bacterial infection") OR TITLE-ABS-KEY ("viral infection")) AND

(TITLE-ABS-KEY(Educat*) OR TITLE-ABS-KEY(Stewardship*) OR TITLE-ABS-KEY(train*) OR TITLE-ABS-KEY(campaign*) OR TITLE-ABS-KEY("behavior change") OR TITLE-ABS-KEY("behavioral change") OR TITLE-ABS-KEY("behaviour change") OR TITLE-ABS-KEY("behavioural change")) AND

(TITLE-ABS-KEY(cost-effectiveness) OR TITLE-ABS-KEY("economic analysis") OR TITLE-ABS-KEY("economic evaluation") OR TITLE-ABS-KEY(pharmacoeconomic) OR TITLE-ABS-KEY("Health outcome") OR TITLE-ABS-KEY("health-related outcomes") OR TITLE-ABS-KEY("health technology assessment") OR TITLE-ABS-KEY(Cost-saving) OR TITLE-ABS-KEY(Cost-benefit)) AND

(TITLE-ABS-KEY(middle-income) OR TITLE-ABS-KEY(Low-income) OR TITLE-ABS-KEY(Afghan*) OR TITLE-ABS-KEY(Alban*) OR TITLE-ABS-KEY(Algeria*) OR TITLE-ABS-KEY(Angol*) OR TITLE-ABS-KEY(Antigua*) OR TITLE-ABS-KEY(Argentin*) OR TITLE-ABS-KEY(Armenia*) OR TITLE-ABS-KEY(Azerbaijan*) OR TITLE-ABS-KEY(Bangladesh*) OR TITLE-ABS-KEY(Belarus*) OR TITLE-ABS-KEY(Belize*) OR TITLE-ABS-KEY(Benin*) OR TITLE-ABS-KEY(Bhutan*) OR TITLE-ABS-KEY(Bolivia*) OR TITLE-ABS-KEY(Bosnia*) OR TITLE-ABS-KEY(Botswan*) OR TITLE-ABS-KEY(Brazil*) OR TITLE-ABS-KEY("Burkino faso") OR TITLE-ABS-KEY(Burundi*) OR TITLE-ABS-KEY(Cabo Verde*) OR TITLE-ABS-KEY(Cambodia*) OR TITLE-ABS-KEY(Cameroon*) OR TITLE-ABS-KEY("Centrial African Republic") OR TITLE-ABS-KEY(Africa*) OR TITLE-ABS-KEY(Chad*) OR TITLE-ABS-KEY(Chin*) OR TITLE-ABS-KEY(Colombia*) OR TITLE-ABS-KEY(Comor*) OR TITLE-ABS-KEY(Congo*) OR TITLE-ABS-KEY("Cook Island") OR TITLE-ABS-KEY("Costa Rica") OR TITLE-ABS-KEY("Côte d'Ivoir") OR TITLE-ABS-KEY(Cuba*) OR TITLE-ABS-KEY(Djibouti*) OR TITLE-ABS-KEY(Dominic*) OR TITLE-ABS-KEY(Ecuador*) OR TITLE-ABS-KEY(Egypt*) OR TITLE-ABS-KEY(salvador*) OR TITLE-ABS-KEY("Equatorial Guinea") OR TITLE-ABS-KEY(Eritrea*) OR TITLE-ABS-KEY(Ethiopia*) OR TITLE-ABS-KEY(Fiji*) OR TITLE-ABS-KEY(Gabon*) OR TITLE-ABS-KEY(Gambia*) OR TITLE-ABS-KEY(Georgia*) OR TITLE-ABS-KEY(Ghana*) OR TITLE-ABS-KEY(Grenad*) OR TITLE-ABS-KEY(Guatemala*) OR TITLE-ABS-KEY(Guinea*) OR TITLE-ABS-KEY(Guinea-Bissau*) OR TITLE-ABS-KEY(Guyan*) OR TITLE-ABS-KEY(Haiti*) OR TITLE-ABS-KEY(Hondura*) OR TITLE-ABS-KEY(India*) OR TITLE-ABS-KEY(Indonesia*) OR TITLE-ABS-KEY(Iran*) OR TITLE-ABS-KEY(Iraq*) OR TITLE-ABS-KEY(Jamaica*) OR TITLE-ABS-KEY(Jordan*) OR TITLE-ABS-KEY(kazakhstan*) OR TITLE-ABS-KEY(Kenya*) OR TITLE-ABS-KEY(Kiribati*) OR TITLE-ABS-KEY(Korea*)

OR TITLE-ABS-KEY(kosovo*) OR TITLE-ABS-KEY(Kyrgyzstan*) OR TITLE-ABS-KEY(Laos*) OR TITLE-ABS-KEY(Leban*) OR TITLE-ABS-KEY(Lesotho*) OR TITLE-ABS-KEY(Liberia*) OR TITLE-ABS-KEY(Libya*) OR TITLE-ABS-KEY(Macedonia*) OR TITLE-ABS-KEY(Madagasca*) OR TITLE-ABS-KEY(Malagasy*) OR TITLE-ABS-KEY(Malawi*) OR TITLE-ABS-KEY(Malaysia*) OR TITLE-ABS-KEY(maldiv*) OR TITLE-ABS-KEY(Mali*) OR TITLE-ABS-KEY(Marshall*) OR TITLE-ABS-KEY(Mauritania*) OR TITLE-ABS-KEY(Mauriti*) OR TITLE-ABS-KEY(Mexic*) OR TITLE-ABS-KEY(Micronesia*) OR TITLE-ABS-KEY(Moldova*) OR TITLE-ABS-KEY(Mongolia*) OR TITLE-ABS-KEY(Montenegr*) OR TITLE-ABS-KEY(Montserrat*) OR TITLE-ABS-KEY(Morrocc*) OR TITLE-ABS-KEY(Mozambic*) OR TITLE-ABS-KEY(Myanmar*) OR TITLE-ABS-KEY(Namibi*) OR TITLE-ABS-KEY(Nauru*) OR TITLE-ABS-KEY(Nepal*) OR TITLE-ABS-KEY(Nicaragua*) OR TITLE-ABS-KEY(Niger*) OR TITLE-ABS-KEY(Niue*) OR TITLE-ABS-KEY(Pakistan*) OR TITLE-ABS-KEY(Palau*) OR TITLE-ABS-KEY(panama*) OR TITLE-ABS-KEY("Papua New Guinea") OR TITLE-ABS-KEY(paraguay*) OR TITLE-ABS-KEY(Peru*) OR TITLE-ABS-KEY(Philippin*) OR TITLE-ABS-KEY(Rwanda*) OR TITLE-ABS-KEY("Saint helena") OR TITLE-ABS-KEY(Samoa*) OR TITLE-ABS-KEY("São Tomé and Príncipe") OR TITLE-ABS-KEY(Senegal*) OR TITLE-ABS-KEY(Serbia*) OR TITLE-ABS-KEY("Sierra leone") OR TITLE-ABS-KEY("Solomon islands") OR TITLE-ABS-KEY(Somalia*) OR TITLE-ABS-KEY("South Africa") OR TITLE-ABS-KEY("South Sudan") OR TITLE-ABS-KEY("Sri Lanka") OR TITLE-ABS-KEY("Saint lucia") OR TITLE-ABS-KEY("Saint vincent") OR TITLE-ABS-KEY(Sudan*) OR TITLE-ABS-KEY(Suriname*) OR TITLE-ABS-KEY(Swaziland*) OR TITLE-ABS-KEY(Syria*) OR TITLE-ABS-KEY(Tajikistan*) OR TITLE-ABS-KEY(tanzania*) OR TITLE-ABS-KEY(Thai*) OR TITLE-ABS-KEY(Timor*) OR TITLE-ABS-KEY(Togo*) OR TITLE-ABS-KEY(Tokelau*) OR TITLE-ABS-KEY(Tonga*) OR TITLE-ABS-KEY(Tunisia*) OR TITLE-ABS-KEY(Turk*) OR TITLE-ABS-KEY(Tuvalu*) OR TITLE-ABS-KEY(Uganda*) OR TITLE-ABS-KEY(Ukrain*) OR TITLE-ABS-KEY(Uzbek*) OR TITLE-ABS-KEY(Vanuatu*) OR TITLE-ABS-KEY(Venezuala*) OR TITLE-ABS-KEY(Vietnam*) OR TITLE-ABS-KEY("Wallis and furtuna") OR TITLE-ABS-KEY(Gaza*) OR TITLE-ABS-KEY(Yemen*) OR TITLE-ABS-KEY(Zambia*) OR TITLE-ABS-KEY(Zimbabwe*)) AND

(PUBYEAR > 1999) AND (PUBYEAR < 2021)

APPENDIX B – Data extraction form content

Section	Variables captured	Answer options (empty is open question)
General section	Email Address	
	Title	
	First author (last name)	
	Year published	
	Disease area	(General) respiratory tract infection Influenza Pneumonia (specifically) Urinary tract infection gastroenteritis General reflux complaints Tuberculosis Malaria Dengue HIV Fungal infection Appendicitis Typhoid Other
	Specific pathogens (if given, separate by semicolon ;)	
	Objective (from abstract)	
	Research question(s)	
	Health economic study?	Yes No
Health economic study	Explicit statement on the context of the study	Yes No
	Explanation of relevance for health policy or practise decision	Yes No
	Country	
	Is the model used based on a previously published model? (If yes, give author and year)	
	Target population and subgroups	
	Setting (Primary care, hospital, home, etc.)	Home Primary care Emergency department Hospital Other:
	Study perspective	Societal perspective Healthcare payer's perspective Healthcare centre's perspective Other:
	Interventions or strategies being compared [separate different strategies with a semicolon ;]	
	Duration of the intervention (years)	
	Treatment options included in the analysis [separate different strategies with a semicolon ;]	
	Time horizon (years)	
	Is a time framework and reasoning provided by the authors (are reasons given for the chosen time horizon, e.g. one flue season (when the time horizon is a couple of months to a year) or in concordance with the national guidelines, for a lifetime horizon)	Yes No
	Discount rate for base case (health outcomes)	
	Discount rate for base case (economic outcomes)	
	Study type [As qualified by the authors]	
	Study type [As qualified by the reviewer (use Drummond book for background)]	
	What input parameters were used? (separate by semicolon ;)	
	What were the reported output variables? (separate by semicolon ;)	Life years Life expectancy QALYs DALYs Quality-adjusted life expectancy (QALE) Antibiotic prescriptions saved Hospitalizations saved Days free from disease Other:

	Measurement of effectiveness	Single-study based estimates Synthesis-based estimates Other:
	Did the authors describe the following: for Single study–based estimates: describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data; for synthesis-based estimates: describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	Yes No
	Did the authors describe the population and methods used to elicit preferences for outcomes?	Yes No N/A
	Are the resource and cost estimations explained in the article?	Yes No
	Costs of training method (in reported currency) [separate different strategies with a semicolon ;]	
	Costs of treatment options (in reported currency) [separate different strategies with a semicolon ;]	
	Currency/currencies reported	US dollars Euros Pound Sterling Japanese yen Other:
	Currency year used	
	Is the method for currency conversion described?	Yes No
	Type of model	Decision tree Markov (compartimental) model Discrete-event simulation Individual sampling model Dynamic compartmental model Individual-contact model / agent-based model Network model Other:
	Is the model stochastic or deterministic	Stochastic (or probabilistic) Deterministic Other:
	Description of model	
	Software used to program the model and statistical analyses	Microsoft Excel TreeAge Pratt Medical Decision maker IBM SPSS R Python C++ Not reported Other:
	Is the model design thoroughly described in the article?	Yes No
	Are structural or other assumptions underpinning the decision-analytical model described?	Yes No
	Is a description given for the analytical methods supporting the evaluation? (e.g. methods for dealing with missing data, skewed data, uncertainty)	Yes No
	Is antibiotic resistance included in the model?	Yes No
	If yes, how is antibiotic resistance included?	
	Unit of incremental costs and outcomes	Costs or savings /QALY Costs or savings /DALY Costs or savings /LYG Costs or savings /antibiotic prescription saved Costs or savings /patient QALYs/DALYs Correct diagnoses Time to correct diagnosis Hospital length-of-stay Disease duration Other:
	How is the uncertainty reported?	Deterministic sensitivity analysis (DSA) Table of DSA

		Tornado diagram of DSA Sensitivity analysis graph (with one parameter varied) Two-way sensitivity analysis graph Three-way (or more) sensitivity analysis graph Probabilistic sensitivity analysis (PSA) Cost-effectiveness plane of PSA Cost-effectiveness acceptability curve(s) Cost-efficiency/efficiency frontier Other:
	Have subgroup analyses been performed? (If yes, which subgroups and how?)	
	Main findings	
	Are limitations of the study described?	Yes No
	Specific limitations/gaps in the assessment of Training	
	Is generalisability discussed?	Yes No
	To what extend do authors consider the results generalizable?	Specific hospital/healthcare center Nationwide Continental Worldwide Other:
	Have the results been linked to current knowledge?	Yes No
	What is the main conclusion or conclusions? The strategy/strategies being compared was...	Cost-saving Cost-effective Not cost-effective Unclear Other:
	If reported, which willingness-to-pay threshold(s) was/were used?	
	Source of funding	Industrial Governmental grant Academic grant No funding Not reported Other:
	Is a statement on the conflicts of interest present?	Yes No
Non-Health economic study	What is the research design?	
	Country	
	Target population and subgroups	
	Setting (Primary care, hospital, home, etc.)	Home Primary care Emergency department Hospital Other:
	Interventions or strategies being analyzed [separate different strategies with a semicolon ;]	
	Treatment options included in the analysis [separate different strategies with a semicolon ;]	
	Duration of the intervention (years)	
	Variables reported/used (please specify all)	Life years Life expectancy QALYs DALYs Quality-adjusted life expectancy (QALE) Antibiotic prescriptions saved Hospitalizations saved Days free from disease Prescription of right antibiotics Money spent on antibiotics Mortality increase/decrease De-escalation/escalation of antibiotic use Duration of hospital stay Number of diagnostic tests done Other:
	Is antibiotic resistance included in the research?	Yes No
	If yes, how is antibiotic resistance included?	

	Have subgroup analyses been performed? (If yes, which subgroups and how?)	
	Main findings	
	Are limitations of the study described?	Yes No
	Source of funding	Industrial Governmental grant Academic grant No funding Not reported Other:
	Is a statement on the conflicts of interest present?	Yes No

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Evaluations of training and education interventions for improved infectious disease management in low- and middle-income countries: a systematic literature review

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Evaluations of training and education interventions for improved infectious disease management in low- and middle-income countries: a systematic literature review

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ABSTRACT

Objectives To identify most vital input and outcome parameters required for evaluations of training and education interventions aimed at addressing infectious diseases in low- and middle-income countries.

Design Systematic review

Data sources PubMed/Medline, Web of Science and Scopus were searched for eligible studies between January 2000 and November 2021.

Study selection Health economic and health-outcome studies on infectious diseases covering an education or training intervention in low- and middle income countries were included.

Results A total of 59 eligible studies covering training or education interventions for infectious diseases were found; infectious diseases were categorized as acute febrile infections (AFI), non-acute febrile infections (non-AFI) and other non-acute infections. With regard to input parameters, the costs (direct and indirect) were most often reported. As outcome parameters, five categories were most often reported including final health outcomes, intermediate health outcomes, cost outcomes, prescription outcomes and health economic outcomes. Studies showed a wide range of per category variables included and a general lack of uniformity across studies.

Conclusions Further standardization is needed on the relevant input and outcome parameters in this field. A more standardized approach would improve generalizability and comparability of results and allow policy makers to make better informed decisions on the most effective and cost-effective interventions.

Strengths and limitations of this study

- This is the first review (to our knowledge) to systematically assess health economic and health-outcome literature of training or education interventions on input and outcome parameters used for improved management of infectious diseases.
- This review covers a wide variety of infectious diseases, allowing for comparisons across disease areas but also introducing high heterogeneity of results.
- This study is prone to publication bias as it includes only data from published literature.

INTRODUCTION

Infectious diseases continue to be a major health challenge worldwide, with the highest burden in low- and middle-income countries (LMICs)[1]. Over the past decades, improvements have been made in the management of infectious diseases by, amongst others, the introduction of widespread vaccine programs[2], health programs on malaria[3], human immunodeficiency virus (HIV) prevention[4] and the widespread use of antimicrobials for bacterial infections[5]. As a downside, widespread overuse of antimicrobials (amongst others) for treatment of infectious diseases, has resulted in an increase of antimicrobial resistance (AMR) which could make future infections difficult or impossible to treat. Thus, to further reduce the global burden of infectious diseases, there is a need for (new) effective strategies that can be implemented at high speed with high coverage levels[6]. These strategies should enable effective management of infectious diseases but also limit inappropriate use of antimicrobials to prevent further increase of AMR.

A variety of programs have been implemented to address the management of specific diseases such as HIV, malaria or tuberculosis (TB)[7] or the prescription of antimicrobials[8]. Across the different disease programs, commonalities can be found on two major topics. First, the implementation of diagnostics is an often used strategy across programs, such as rapid diagnostic tests (RDTs) for malaria diagnosis[9] or home based testing for HIV detection[10,11]. Second, education or training interventions are used across different infectious disease programs. For example, physicians are trained and educated on improved prescription of antimicrobials[8], patients are taught about the importance of treatment adherence for antiretroviral therapy[12] and individuals are informed on preventive measures that can be taken to prevent HIV or malaria infections[13]. Evidently, there are similarities in the approaches that are used by the different programs, but within a program the interventions are often focused on one specific disease (e.g. malaria, HIV). Hence, with finite financial resources, a decision needs to be made by policy makers on a limited number of disease specific programs that can be incorporated in national health policy.

Policymakers are informed by health economic analyses to maximize the impact on health and equity. The health economic impact is often expressed in costs per quality-adjusted life year gained (cost per QALY) or cost per disability-adjusted life year averted (cost per DALY), both of which combine morbidity and mortality (i.e. quality and length of life)[14]. QALYs are predominantly used in higher-income countries and DALYs in global health studies[15]. Expressing health economic impact in cost per QALY or cost per DALY allows for comparing different health interventions across diseases[16].

There are no consistent guidelines with input parameters and outcomes to report on in health economic evaluations of infectious disease interventions in LMICs[17,18]. To close this gap, previous endeavors have been undertaken by the VALUE-Dx consortium to review health economic

assessments of diagnostic interventions for infectious diseases[19]. One of the conclusions of this consortium was that there is a lack of universal outcomes in the assessment of diagnostics. Parameter categories that were found across a multitude of studies included final health outcomes (QALY, DALY), antibiotic consumption and diagnostic test performance. This provides valuable insight in parameters to use for the health economic assessment of diagnostics. However, to our knowledge, comparable research is lacking on educational or training interventions for improved management of infectious diseases.

It is important to get a better understanding of input parameters and outcomes that have been used previously to guide future research efforts, to improve the quality of health economic assessments as well as the generalizability of results. Such guidance would specifically be relevant for LMICs, where the need for improved management of infectious diseases is most urgent[20,21], where health economic frameworks are less formalized, and where limitations are encountered in applying results from health economic studies into policymaking[22]. Therefore, the objective of this review is to close the knowledge gap by identifying input parameters and outcomes reported in health economic and health-outcome studies on training or education interventions for infectious diseases in LMICs.

METHODS

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23] were used for this study (Appendix A). A systematic search of databases was performed, including PubMed/Medline, Web of Science and Scopus. The detailed search strategy per database can be found in Appendix B. Five queries were combined in the main query, which aimed to include studies that matched the following elements:

- Population: individuals in LMICs (i.e. countries and territories that are eligible to receive official development assistance as per the Organization for Economic Co-operation and Development (OECD)) [24];
- Intervention: programs that include an education or training intervention;
- Disease focus: infectious diseases;
- Type of research: health economic and health-outcomes articles; and
- Time period: January 2000 – November 2021.

Duplicate articles were removed after which the title and abstract were scanned independently by two researchers (PvD and ADIvA). Full-text analysis was performed on potentially relevant articles.

Study selection

We included studies which, based on full text analysis, met the following inclusion criteria: (i) assessing the impact of either a training or education intervention; (ii) focused on infectious diseases; (iii) in low- and middle-income countries; (iv) in humans; (v) and reporting the impact of the intervention in either health or health economic outcomes. Studies were excluded if no intervention was applied (e.g. review, protocol, cross-sectional or descriptive study), if the intervention didn't include a training or educational aspect, in case the training was merely focused on the introduction of RDTs as test-and-treat strategy (which was the scope of the Value Dx consortium), and if the full text was not available or not available in English.

Data extraction

Included studies were systematically analyzed and documented using a digital form (Google Forms; see appendix C). Within the digital form, a distinction was made between health economic articles and health-outcomes articles. For health economic articles, a total of 57 variables were listed for data extraction, using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist as a basis[25]. A total of 23 variables were listed for health-outcome articles. Variables captured were related to study design, disease focus, interventions, input parameters and outcomes.

Categorization of results

To structure the findings of the review, a categorization of the infectious diseases was made between acute febrile infections (AFI) (fever for < 7 days), non-acute febrile infections (non-AFI) (fever for > 7 days)[26] and other infectious diseases that are not primarily febrile. This categorization is used throughout the results section, which consists of the following three sub-sections: interventions identified, input parameters identified, and outcomes identified. Further breakdown of the results in each sub-section is explained below.

For the training and education interventions that were found in the review, further clarity was given by positioning the different interventions on the healthcare spectrum, for which the definition from O'Connel et al. (2009) was used. The interventions were positioned in four distinct phases, including (i) promotion of health, (ii) prevention of developing a disease, (iii) treatment, including patient identification and start of the treatment, and (iv) maintenance/post-intervention care, which includes patient compliance in long-term care and provision of after-care[27].

Input parameters found were categorized into four categories. The first category was *costs* which entailed all cost parameters that were used to calculate a final cost outcome (e.g. cost of medication, cost of personnel). The second category was defined as *etiology specific characteristics*, covering disease specific parameters that could impact other parameters (e.g. average duration of a disease to calculate QALYs or DALYs). The third category was *population background*, defined as population related parameters that could impact other input or outcome parameters (e.g. % of population at risk in a country). The fourth and final category consisted of *intervention details*, which put the intervention in a broader perspective (e.g. percentage of individuals at risk targeted by the intervention).

Outcome parameters were also categorized, in nine separate categories. The first two categories were related to health effects, in which the distinction between final and intermediate outcomes was made. *Final health outcomes* were defined as a quantification of the health effect of an intervention, reported in a final outcome for a health (status) change (e.g. death, QALYs, DALYs). *Intermediate health outcomes* were quantified as a change in a clinical indicator that might or might not lead to final health outcomes[28]. The third category was defined as *cost outcomes*, which included parameters that reported the cost outcomes of a whole program or a single intervention. The fourth category was defined as *prescription outcomes*, which included parameters that quantify the prescription practices like doses and frequency, often described in standardized units like the Defined Daily Doses (DDD). The fifth category, *health economic outcomes*, entailed outcomes that were reported as incremental cost per unit of outcome, indicating the cost-effectiveness of an intervention (i.e. cost per QALY). The sixth category was defined as *behavioral outcomes*, indicating the effect of an intervention on the behavior of the targeted individual. The seventh category consisted of *time related outcomes*, which included outcomes that indicated important time related aspects as a result of the intervention. Category eight was defined as *macro-level outcomes*, compromising outcomes that expressed the impact of a program at hospital or population level. The

final category was classified as *miscellaneous*, covering outcomes that couldn't be placed in one of the other categories, but which were of importance for the patient or broader society[28].

Patient and public involvement

As this paper is a review comprising an assessment of the academic literature, there was no direct patient and public engagement on the paper.

RESULTS

Search results

The search strategy resulted in 1445 references, of which 310 were duplicates. Removing duplicates resulted in 1135 studies that were scanned on Title and Abstract. Full-text analysis was done on 111 articles and 59 were considered to meet the study inclusion criteria (see figure 1).

Insert Figure 1

Baseline characteristics

Out of the 59 included studies, the majority was performed in Africa (46%) and Asia (34%). Also, the majority of the articles was published between 2012 and 2020 (64%). Out of the 59 studies, 20 studies were cost-effectiveness studies. For a complete overview see Table 1.

Table 1. General characteristics of studies included (n = 59). ASP: Antimicrobial stewardship program; FI: febrile illness; HIV: human immunodeficiency virus; STD: Sexually transmitted disease.

Characteristics	Number	Percentage of total
Year		
2000-2002	3	5%
2003-2005	2	3%
2006-2008	6	10%
2009-2011	7	12%
2012-2014	9	15%
2015-2017	11	19%
2018-2020	18	31%
2021	3	5%
Geography		
Africa	27	46%
Asia	20	34%
Latin-America	8	13%
Europe	3	5%
Middle East	1	2%
Study design		
Cost-effectiveness	20	34%
Quasi experimental cohort study	17	29%
Randomized control trial	11	19%
Quasi experimental retrospective cohort study	8	13%
Retrospective case-control study	1	2%
Non-randomized controlled trial	2	3%
Classification of infectious diseases		
Acute febrile infections	**30**	**51%**
- Inpatient infections (ASPs)	17	

- Malaria	6	
- Respiratory tract infection	2	
- Upper respiratory tract infection	2	
- Group of acute infectious diseases (caused by parasitic-, bacterial-, viral infections)	2	
- Post-discharge infectious disease	1	
Non-acute febrile infections	**22**	**37%**
- HIV	17	
- Tuberculosis	4	
- HIV and tuberculosis	1	
Other non-acute infections	**7**	**12%**
- Lymphatic filariasis	1	
- *Schistosoma haematobium*	1	
- *Schistosoma japonicum*	1	
- Leprosy	1	
- STD	1	
- Candidiasis	1	
- Soil-transmitted helminthiases and Clonorchiasis	1	

Interventions identified

Across the 59 studies that met the inclusion criteria, 36 unique interventions were identified (Table 2). The list of interventions includes non-training and non-educational interventions that were combined with a training or educational intervention.

The studies in the current review described interventions targeting three different groups, including patients, physicians and non-physician professionals. The group of non-physician professionals consisted of retail shopkeepers, pharmacists and lay health workers. Most interventions were targeting patients (21/36; 58%), followed by interventions targeting physicians (13/36; 36%) and a minority targeting non-physician professionals (8/36; 22%). Some interventions were targeted at more than one group.

Among the interventions that targeted patients or caregivers, the most prevalent interventions were focused on the education of patients or caregivers by peers, community workers, or health advisors. The educational goals and topics differed across the studies. Studies on HIV covered sexual- and reproductive health education for adolescents and youth[29–32], and education aiming to change sexual behavior for individuals at high risk (i.e. sexually active individuals, sex workers)[29,33–37]. Also, studies on HIV incorporated educational interventions to prevent pregnancy-related HIV transmission[38–40] and more general health education for (pregnant) women on the prevention of HIV infections[41,42]. Educational interventions in studies not targeting HIV, were focused on improving knowledge of the disease (i.e. infections with TB, lymphatic filariasis, leprosy, malaria, soil-transmitted helminthiasis (STH)) and promoted preventive behavior for specific groups (i.e. youth, adolescents, patients, pregnant women) or across the general population[30,41,43–49].

Interventions targeting the physician were mainly focused on the promotion of adequate use of antimicrobial drug therapy by physicians[50–68]. In addition, physician-targeted interventions aimed to improve adequate use of antifungal therapy[69] and improved management of infectious diseases[70–73].

Four studies described interventions that targeted drug retail locations (e.g. pharmacies, shopkeepers) that play a vital role in appropriate drug use. By improving the health skillset of people at pharmacies and drug retailers, appropriate use of antimalarials and improved syndromic management of STD was promoted[74–77]. One study described an intervention that aimed to improve the knowledge and skills of lay health workers to improve TB care provided to patients and subsequently improve treatment adherence[78].

Table 2. Overview of interventions with number of studies reporting the respective intervention (% of total number of studies), categorized per healthcare value chain, per target group, per condition. AMR: Antimicrobial resistance; FI: Febrile illness; HIV: human immunodeficiency virus; STI: Sexually transmitted infection;

	Acute febrile infections			Non-acute febrile infections		Other non-acute infections	
Intervention	**Patient**	**Physician**	**Non-physician professionals**	**Patient**	**Non-physician professionals**	**Patient**	**physician**
Health promotion							
Media campaigns	-	-	1 (2%)	3 (5%)	-	2 (3%)	-
Improvement of basic needs (safe water, sanitation)	-	-	-	1 (2%)	-	2 (3%)	-
Primary school education	-	-	-	2 (3%)	-	-	-
Support to receive school education (non-disease related)	-	-	-	1 (2%)	-	-	-
Prevention							
Free commodities supplies (soap, oral rehydration salts, mosquito nets, condoms, medication)	2 (3%)	-	1 (2%)	6 (10%)	-	-	-
Health education from health advisors	-	-	-	9 (15%)	-	2 (3%)	-
Peer-led/community-based support workers outreach and education	-	-	-	9 (15%)	-	-	-
HIV testing	-	-	-	8 (14%)	-	-	-
Prescription of preventive medication	-	-	-	3 (5%)	-	3 (5%)	-
Case finding of leprosy by dedicated team traveling from city to city	-	-	-	-	-	1 (2%)	-
Treatment							
Physician instructed care support via teachers/community-based support workers	2 (3%)	-	-	1 (2%)	-	-	-
Presentation and discussion of (newly created) clinical guideline	-	13 (22%)	-	-	1 (2%)	-	1 (2%)
Training on AMR	-	15 (25%)	-	-	-	-	-
Feedback on baseline antibiotic prescription practices	-	11 (19%)	-	-	-	-	1 (2%)
Create new guideline for optimal prescription	-	10 (17%)	-	-	-	-	1 (2%)
Antimicrobial order form	-	7 (12%)	-	-	-	-	-

Review/modification of prescription by AMR team	-	5 (8%)	-	-	-	-	-
Bedside discussions among AMR expertise group	-	3 (5%)	-	-	-	-	1 (2%)
Face-to-face (individual) interactive discussions	-	4 (7%)	-	-	-	-	-
Antimicrobial susceptibility patterns shared with physicians	-	3 (5%)	-	-	-	-	-
Peer review/presentation and discussion of the guideline, and presentation of clinical scenarios	-	3 (5%)	-	-	-	-	-
Motivational interventions (fine based)	-	1 (2%)	-	-	-	-	-
Restricted use of specific drugs	-	1 (2%)	-	-	-	-	1 (2%)
Introduction of an antibiotic prescription chart	-	1 (2%)	-	-	-	-	-
Skill-based training on management of diseases	-	-	3 (5%)	1 (2%)	2 (3%)	-	-
Facilitation of community mobilization	-	-	1 (2%)	1 (2%)	-	1 (2%)	-
Financial support (free treatment of disease, reimbursement of travel cost, care and assistance)	-	-	-	8 (14%)	-	-	-
Offering free food to reduce food insecurity and encourage clinic visits	-	-	-	2 (3%)	-	-	-
Prioritization of patients with HIV over other patients	-	-	-	1 (2%)	-	-	-
Introduction of medication dosing table					1 (2%)		
Syndromic management of STI			-	1 (2%)	-	-	-
Maintenance/post-intervention care							
Educational materials for caregivers, patients and communities	2 (3%)	-	1 (2%)	4 (7%)	-	2 (3%)	-
Scheduling post-discharge follow-up visits	1 (2%)	-	-	-	-	-	-
Sending post-discharge reminders for treatment adherence	-	-	-	1 (2%)	-	-	-
HIV counseling	-	-	-	7 (12%)	-	-	-
Peer support network					1 (2%)		

Input parameters identified

A total of 42 unique input parameters were found. Categorization of the input variables resulted in four overarching parameter types: (i) cost parameters, (ii) disease-specific parameters, (iii) population background characteristics, and (iv) intervention details (see table 3).

The majority of the input parameters detailed the costs of an intervention (27 unique parameters). Within the cost category, a clear distinction was present between cost related to the program, cost for care and cost for the patient and caregiver. Great variety existed amongst the studies, none of the cost parameters was used across all studies.

Acute febrile infections

No consistent approach was found amongst studies that included cost input parameters. A large proportion of the studies only included the cost of medication, not taking any other program or care related costs into account[50,51,53,59,62,64,67,68]. Though, there were also studies that took a more extensive approach by reporting both cost of care (e.g. cost of medication, cost of consultation) and program costs (e.g. cost of personnel, cost of training and cost of program management)[55–57,60,72,75,76,79,80]. Across all studies in the review, only three studies included the cost for the patient and caregiver. These studies were cost-effectiveness studies of malaria interventions performed from a societal perspective[72,76,79].

Non-acute febrile infections

All non-AFI studies that reported costs as input parameters, included at least one variable on the cost of care and one variable on costs of the program[29,30,33,34,36,37,39,41,42,45,81–84]. The cost of supplies such as condoms and medication was reported most frequently[29,33,34,37,39,41,42,45,81,83]. None of the studies included the costs for the patient and caregiver.

Other non-acute infections

Studies that included costs for interventions targeting non-acute infections, reported costs in different ways. One study on candidiasis only included the cost of medication[69], while studies on sexually transmitted diseases (STD), *S. japonicum,* STH and leprosy incorporated both costs of care and cost of the program[43,49,74,85]. None of the studies included the costs for the patient and caregiver.

Table 3. Overview of input parameters. ANC: Antenatal Care; ART: antiretroviral therapy; FI: Febrile illness; HIV: human immunodeficiency virus; ICU: Intensive Care Unit.

Category	Definition	Input variables	Reported in N studies (% of total; % of total within the respective category)		
			Acute febrile infection	Non-acute febrile infections	Other non-acute infections
Cost	Costs related to the intervention/the program	**Program cost:** Cost of travel and accommodation for personnel; cost of buildings; cost of overhead; cost of refreshments; start-up costs; cost of training or education; program management costs; program development cost; program implementation cost; recurring costs for training; personnel cost; cost of transportation of supplies; cost of equipment; cost for data capture and use; **Cost of care:** Routine care costs; daily cost of ICU admission; average cost of one inpatient day; cost of social mobilization; pharmacists costs; cost of consultation; cost of lifetime treatment; cost of diagnostic tests; cost of death; cost of supplies/medication; **Cost for the patient/caregiver:** Travel cost; cost of time lost for caregiver; out-of-pocket costs	20 (34%; 67%)	14 (24%; 64%)	5 (8%; 71%)
Disease specific characteristics	Disease related characteristics that have impact on the intervention outcomes	ART initiation age; awareness of HIV status; bacterial resistance rates; disease transmission rates; average duration of the disease; disease prevalence	6 (10%; 20%)	7 (12%; 32%)	4 (7%; 57%)
Population background	Background information on the targeted population which could affect the outcomes of the intervention	number of people at risk in the area; average life expectancy; average number of sex clients per month; average time span men buy sex; average time span women sell sex; proportion of individuals using condoms	-	4 (7%; 18%)	1 (2%; 14%)
Intervention details	Details of the intervention that put the intervention in a broader perspective	number of individuals reached with the intervention; efficacy of the intervention; the proportion of the population at risk targeted by the intervention	-	5 (8%; 23%)	1 (2%; 14%)

Outcomes identified

A total of 81 unique outcomes were reported in 59 studies which are categorized into nine categories (see Table 4). In the section below, the five categories that were reported in most studies are reviewed in more detail.

Final health outcomes

Out of the 59 studies, 21 studies reported final health outcomes. Final health outcomes - reported in DALYs averted, QALYs gained, Years of Life Saved (YLS), mortality rate, cured rate and deaths averted - were found in studies across all three infectious disease categories.

Acute febrile infections

Amongst the studies on AFI, one study on malaria reported DALYs and deaths averted, calculated based on the probability of death for a child with fever for whom treatment is first sought from a shop, with and without the intervention[75]. Seven studies on inpatient infections reported mortality rates (increase/decrease) as a result of the intervention[50,54,56,58,60,67,86]. One study on post-discharge infections reported final health outcomes in deaths averted, defined as hospitalized patients that survive 30 days after discharge[61].

Non-acute febrile infections

In total, six studies on HIV reported DALYs averted, calculated from the number of infections averted[29,34,36,39,41,83]. Besides the studies reporting DALYs averted, there was one study on HIV reporting QALYs to quantify the impact of the prevention of mother-to-child HIV transmission [42]. To estimate QALYs, the difference between the expected number of QALYs of a child living with and without HIV was calculated[42]. One study on HIV reported outcomes in YLS calculated from the life years lost as a result of loss-to-follow-up from antiretroviral therapy (ART)[81]. Two studies on TB reported the final health outcomes as the number of patients cured, defined as individuals who are smear- or culture negative in the last month of treatment[44,78], and another study on TB reported the outcome as the reduction in mortality rate as a result of the intervention[45].

Other non-acute infections

Only one study in the category of other non-acute infections reported a final health outcome. The study on leprosy reported the number of patients cured, defined as individuals completing the therapy[43].

Intermediate health outcomes

Acute febrile infections

Amongst the studies reporting on AFI, the most frequently reported intermediate health outcome was the number of patients that are correctly treated, covered in studies on inpatient infections, malaria and acute respiratory tract infections[50,51,55,56,63,66,71–73,76,76,77]. The recurrence rate, also indicated as unexpected readmission rates, was reported in six studies covering inpatient infections, respiratory tract infection and post-discharge infections[54,56,58,60,67,86]. Other intermediate health-outcomes reported in studies on AFI were less widely reported. These outcomes included the number of cases diagnosed with malaria[72], and the number of adverse events occurred after implementation of ASPs for improved management of inpatient infections[63,64].

Non-acute febrile infections

The two most reported intermediate health-outcomes in studies on HIV or TB were the number of cases diagnosed[84,87] and the number of infections averted[29,34,42]. Across all studies in the review, only one study reported the quality of life of the patient, which was measured using the EQ-5D with TB patients[44]. Disease specific clinical outcomes were also found in studies on HIV and TB. Examples of disease specific outcomes were reduced TB stigma or CD4 count slope[30,88].

Other non-acute infections

One study on STD reported intervention outcomes in the number of patients correctly treated[74]. Two studies, on STD and candidiasis, reported the results in the number of unexpected readmissions[69,74]. The number of cases diagnosed was reported in one study on leprosy[43] and the increase/decrease of infections as a result of the intervention was reported in two studies covering *S. japonicum* and STH infections[49,85].

Cost outcomes

The cost impact of an intervention was reported in an aggregate form (i.e. total program costs and total cost saved) or on a per-unit basis (e.g. per person reached). The aggregated total costs of the program/intervention[34,36,39,43,49,53,57,62,65,67,68,71,75,76,79,80,82–85] and the costs saved as a result of the intervention[36,42,53,54,56,57,60,60,64,67–69] were often reported across all three infectious disease categories.

Only studies on non-AFI reported the cost per unit. Three studies on HIV reported cost per person reached[29,33,36] and one study on HIV indicated the cost per individual tested[33].

Health economic outcomes

Acute febrile infections

Only six studies in the category of AFI reported health economic outcomes, out of which four were on malaria. Studies on malaria reported health economic outcomes as the cost per case adequately treated[72,75,76,79], cost per DALY averted[75] and cost per death averted[75]. Cost per death averted was also reported in a study on inpatient infections[61]. The cost per percentage reduction in antibiotic prescription was reported once in a study on upper respiratory tract infection[80].

Non-acute febrile infections

Health economic outcomes were most often reported in studies on non-AFI. Twelve out of the seventeen studies on HIV reported on the cost-effectiveness of the intervention. Variables included were cost per infection averted[34,36,42,87], cost per QALY[42], cost per HIV case detected[84,87], cost per DALY averted[29,34,36,39,41,83], cost per averted loss-to-follow-up[30,82], cost per YLS[81], cost per reduction in male sexual partners[37] and cost per % increase in condom use[37].

Cost-effectiveness thresholds, which indicates the maximum amount a country or organization is willing to pay for a unit of health-outcome, were only applied in studies on HIV. The thresholds ranged between one to five times Gross Domestic Product (GDP) per capita per DALY averted[29,36,39,41] or per YLS[81]. For all five studies that applied cost-effectiveness thresholds, the cost per DALY averted or cost per YLS of the interventions fell below the cost-effectiveness thresholds. Hence, these interventions were considered cost-effective compared to the standard of care[29,36,39,41,81].

Other non-acute infections

In the category of other non-acute infections, health economic outcomes were rarely reported. One study on *S. japonica* reported cost per infection averted[85] and one study on STD reported the cost per case adequately treated[74].

Prescription outcomes

The category of prescription outcomes included outcomes reported in studies that aimed for more appropriate use of antimicrobials and antifungals by physicians, and was predominantly found in studies on AFI and in one study on other non-AFI. The category of prescription outcomes provided insight into three main factors: (i) the overall prescription practices by physicians, (ii) the quality of the prescription practices, and (iii) the quantitative prescription details (see Table 4).

As an indicator of the overall prescription practices, three outcomes were reported: the antibiotic prescription rate (number of times antibiotics prescribed)[55,57,62,65,67,69,70,80], percentage of the prescriptions containing more than one antibiotic[65] and percentage of prescriptions containing broad-spectrum antibiotics[65].

The quality of the prescription practices was reflected by the number of inappropriate prescriptions, defined as incorrect antimicrobial prescribed, incorrect dose prescribed, incorrect duration prescribed or incorrect decision to prescribe antimicrobials[52,62,68,69]. Another outcome that indicated the quality of prescription practices was the number of times adjustment of prescription was done[50].

The quantitative details of the prescription were reported in a variety of ways. Four studies reported the total DDD prescribed[64,67,68,80]. The DDD is a validated method to standardize the number of doses consumed and is developed by the World Health Organization (WHO). Nine studies reported the total DDD per 1000 patient days or 100 patients treated[51,53,54,56,59,60,67–69]. One study reported the total antibiotic days of therapy per 1000 patient days, defined as the days of antibiotic therapy administered to the patients independent of the doses. The days of therapy was calculated by multiplying the number of doses received by the dosing interval (in hours) and then divided by 24 hours for each antibiotic the patient received[58]. The antibiotic use density (AUD) was given once, which was equal to DDD per 100 patient days, and was calculated by multiplying the DDD by 100, divided by the number of patient[66]. One study reported the antibiotic prescription in total grams [68]. All studies on inpatient infections that reported on antibiotic consumption reported a decrease in the total antibiotics consumed[51,53,54,56,58–60,64,66–69] with some small increases on individual antibiotics[50,51,53,57,59,60,62,64,67].

Table 4. Overview of outcome variables. ANC: Antenatal Care; DALY: Disability Adjusted Life Years; DDD: Defined Daily Doses; FI: Febrile illness; GP: General Practitioner; HIV: human immunodeficiency virus; ICU: Intensive Care Unit; QALY: Quality Adjusted Life Year; YLS: Years of Life Saved.

Category	Definition	Outcome variables	Reported in N studies (% of total; % of total within the respective category)		
			Acute febrile infections	Non-acute febrile infections	Other non-acute infections
Final health outcomes	Quantification of the health effect of an intervention, addressing the length or quality of life	QALY; DALY; YLS; deaths averted; mortality rate; mortality increase/decrease; cured rate	11 (19%; 37%)	9 (15%; 41%)	1 (2%; 14%)
Intermediate health outcomes	Quantification of the health effects of an intervention as a change in clinical indicator that may or may not lead to final health outcomes[28]	Disease specific outcomes; number of cases correctly treated; infections averted; number cases detected with disease; infection rates; recurrence rates; number of adverse drug reactions; % positive and negative tests; number of individuals receiving treatment; quality of life	19 (32%; 63%)	8 (14%; 36%)	5 (8%; 71%)
Cost outcomes	Quantification of the costs as a result of the whole program or single intervention	Total cost; cost reduction/costs saved; cost of intervention per patient; cost per individual tested; costs per person reached; cost per 100 bed-days	18 (31%; 60%)	11 (19%; 50%)	4 (7%; 57%)
Prescription outcomes	Quantification of the impact of an intervention on prescribing practices	Antibiotic use density; DDD/100 patients; (antibiotic) prescription rate; DDD/1000 or 100 patient days; number of inappropriate prescriptions; total antibiotic Days of Therapy/1000 patient days; % of prescriptions containing more than one antibiotic; % of prescriptions having broad spectrum antibiotics; grams of antibiotics prescribed; number of times adjustment of antibiotic prescription done	19 (32%; 63%)	-	1 (2%; 14%)
Health economic outcomes	Outcomes reflecting the incremental cost per single unit of outcome	Cost per infection averted; cost per individual adequately treated; cost per HIV case detected; costs per averted loss-to-follow-up; cost per decrease in antibiotic prescription rate; Cost per QALY; cost per DALY averted;	6 (10%; 20%)	13 (22%; 59%)	3 (5%; 43%)

		Cost per YLS; cost per death averted; cost per reduction in male sexual partners; cost per % increase in condom usage			
Behavior outcomes	Outcomes that indicate the effect of the intervention on health-related behavior of the targeted individual	Adherence rates; attrition rates (including loss-to-follow-up and mortality); number of admissions; loss-to-follow-up rate; averted loss-to-follow-up; % retention in care; completion of follow-up visits; number of referrals to secondary health clinics by GP; number of women giving birth at health facility; number of ANC visits; number of cases that did postpartum check-up; number performing exclusive breastfeeding; % using family planning;	6 (10%; 20%)	10 (17%; 45%)	1 (2%; 14%)
Time related outcomes	Quantification of the time related component of an intervention	Time efficiency gain; time to event; duration of hospital stay; per person life-expectancy losses due to loss-to-follow-up; time till loss-to-follow-up	7 (12%; 23%)	4 (7%; 18%)	-
Macro-level outcomes	Expressing the impact of a program/intervention at hospital or population level	% tested; medical care utilization days; number of diagnostic tests done; ICU admissions; absolute risk ratio; number needed to treat; % receiving treatment; Bacterial resistance rates	7 (12%; 23%)	4 (7%; 18%)	1 (2%; 14%)
Miscellaneous	Intervention specific outcomes, which are not direct measures of health but are of societal importance or of importance for the patient[28]	Number of times replacement drug is provided; number of male partners attending care visits; number of physicians receiving fines; number of times education provided to the patient; number of early infant diagnosis done; population knowledge of the disease; number of times combined medication provided; number of (couple) HIV testing and counseling; number of individuals with access to clean water; % increase in condom use; reduction in number of sexual partners	4 (7%; 13%)	4 (7%; 18%)	1 (2%; 14%)

DISCUSSION

The results of the current review provide insight in the wide range of programs that aim for improved infectious disease management in LMICs. The programs consisted of one or more interventions that span across the healthcare pathway and target different stakeholder groups including patients, physicians and non-physician professionals. The input and outcome parameters reported in the studies did not show a consistent and generalizable set of metrics used across all studies. However, by grouping the individual variables into categories, it became evident that four input categories and nine outcome categories could be considered when reporting the impact of a program targeting infectious diseases.

Heterogeneity in outcomes is a well-known factor of influence in clinical research[89]. Several initiatives have started to improve the standardization of metrics measured and reported in clinical studies. One of these initiatives is the Core Outcome Measures in Effectiveness Trials (COMET; https://www.comet-initiative.org/) initiative, which launched in 2010 to coordinate efforts in the development of core outcome sets (COS) across a wide range of areas of health. The definition of COS is "an agreed standardized collection of outcomes that should be measured and reported for a specific area of health"[90]. Unfortunately, for infectious disease, the number of COS developed is limited, existing COS on infectious diseases have not been updated recently[91,92] and the involvement of LMICs in the development of the COS was low[93]. Therefore, we suggest that further research will continue with a critical assessment of the categories and metrics found in the current review. These efforts could function as valuable input to establish an initial COS for infectious disease management programs in LMIC.

Reporting on final health outcomes is crucial to allow comparisons between interventions. Final health outcomes are standardized and widely used outcomes across multiple disease areas, as opposed to intermediate health outcomes that could be disease specific and thereby making it difficult to extrapolate and compare with other disease areas. The most used final health outcome in global health studies and in LMICs is the DALYs averted, which is used to define the burden of the disease[15]. Also within the current review, DALYs averted was the most frequent reported final health outcome, mostly found in studies on non-AFI (e.g. HIV)[29,34,36,39,41,83] and only one time in a study on AFI (e.g. malaria)[75]. Studies on AFI more often report on an increase or decrease in mortality rate. However, as opposed to DALYs, mortality rates do not quantify the impact of a disease on morbidity[94], which is why the DALY is preferred over the mortality rate. One of the potential reasons for not reporting the DALYs could be the lack of local data for estimating the DALYs, which appeared to be an important reason for researchers in LMIC to not include the DALYs averted[95]. Also, infectious diseases are often self-limiting and of short duration, thereby having a small impact on the estimated DALYs per patient, but on population level could still result in a substantial disease burden[1]. To encourage researchers in reporting on important outcome parameters like DALYs averted, the Guide to Economic Analysis and Research (GEAR; http://www.gear4health.com/) online resource was introduced as a reliable aid for researchers in LMICs that provide solutions for methodological difficulties[22]. Although it could be a helpful resource, none of the studies in the current review mentioned or referred to the GEAR resource. Hence, further dissemination of the GEAR resource amongst researchers performing health-economic analyses for LMICs could be of benefit to improve standardization across studies.

The impact of a health intervention should logically be expressed in health outcomes, but also the financial impact should be considered. Being able to compare interventions on health-related and economic outcomes, allows policy makers to create health policy with the intervention that maximizes the health impact per monetary unit spent. There are different approaches researchers

could take when calculating the cost of an intervention, considering direct and indirect costs. Within the current review, most of the studies reporting the costs of an intervention only included direct costs, with substantial variations in the type of direct costs included. These methodological variations have impact on the results and make comparisons between studies less reliable. A more standardized approach for calculating costs would improve generalizability of results and thereby enhance the ability to compare outcomes between different studies. Wider implementation of existing guidelines could be an important step towards more generalizable results for studies in LMICs. For example, for health economic studies, the CHEERS provides guidance in the reporting of health economic assessments. The CHEERS guideline includes some high-level recommendations in the decision on what costs to include, depending on the perspective that is taken (e.g. healthcare system, societal)[25]. Also, for studies on ASPs, the US guideline incorporated recommendations to include costs on program management, salary for stewardship personnel, and medication purchasing costs[96]. With the US guideline for studies on ASPs and the CHEERS guideline for health economic assessments, some guidance already exists and could be more broadly applied as an initial step towards more generalizable cost outcomes.

Indicating the impact of an intervention on prescription practices has been considered as an important outcome variable. As such, standardized approaches are introduced by WHO to enable clear and concise reporting of prescription outcomes[97]. Especially in the case of antimicrobial prescriptions, the dose, frequency and duration are important to assess the impact of an intervention on the consumption and the related antimicrobial resistance. Within the current review, the DDD was the most reported outcome in the category of prescriptions outcomes. The DDD is a standardized approach but is impacted by weight-based dosing as done for pediatrics[96]. Therefore, instead, days of therapy is suggested as a more valuable parameter since it is not impacted by dose adjustments. When following the guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, days of therapy is the preferred option[96]. In the present review, only one study reported the outcomes in days of therapy[58] which could imply that the impact of weight-based dosing has been overlooked in the other studies. Moving forward, to give a more complete picture of antimicrobial prescription, researchers could consider to include the antimicrobial use expressed in days of therapy if possible.

The studies on infectious diseases that reported antimicrobial consumption in DDD or days of therapy as the main outcome measure[51,53,54,56,58–60,64,66,69], did not report final health outcomes in DALY, QALY or YLS. Thereby making it challenging to compare the effect of these interventions with interventions not reporting DDDs or days of therapy. Translating antimicrobial use into a value that indicates the burden of the disease in more generalizable outcomes, such as DALYs, is challenging and comes with great uncertainty[98]. Another possibility is to convert antimicrobial use to costs per antimicrobial prescribed to account for future resistance, as is done in some studies[99,100]. However, these estimates also come with high uncertainty and there is a risk that the actual costs are far higher than the best estimates[101]. Therefore, future research should focus on the quantification of antimicrobial use in more generalizable outcomes to better reflect the actual value of interventions that aim for appropriate antimicrobial use as part of the infectious disease management strategy.

The current literature review is limited in the following aspects: firstly, the variables found in this review show a high heterogeneity resulting in low generalizability. This could be a result of the wide scope of etiologies included, in addition to the fact that the input and outcome parameters are often context specific. However, generalizability should, to a certain extent, also apply to interventions targeting different etiologies to allow policy makers to decide on the most cost-effective strategy.

There should at least be a set of core outcomes across etiologies that functions as the minimum of what should be included, still allowing for additional disease specific measures to be added. Secondly, the results of the current review could guide researchers in the process of defining input and outcome parameters to report on for health economic research on infectious diseases but does not offer a concrete list of input and outcome parameters. Further research is needed to come to a core outcome set for infectious diseases along with broad implementation and knowledge dissemination of currently available guidelines.

To our knowledge, the current study is the first review that provides an overview of health economic and health-outcome studies on training or education interventions for improved management of infectious diseases. Thereby, the current study offers valuable insights for future health economic assessments on programs in which education is integral part of the intervention.

CONCLUSION

In conclusion, it can be said that standardization of parameters is lacking across studies on infectious disease programs. For input parameters, the most reported category was costs. For outcomes, studies reported most often on final health outcomes, intermediate health outcomes, cost outcomes, prescription outcomes and health economic outcomes. We recommend that further research will be performed on the definition of a core outcome set for infectious diseases in LMICs.

Competing interests Professor Maarten J Postma received grants and honoraria from various pharmaceutical companies all unrelated to this research. The other authors have no conflicts of interest to declare.

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Availability of data and material The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contributions All authors (PvD, SvdP, OS, SD, PO, MP, CB, ADIvA) contributed to the study conception and design. Material preparation, data collection and analysis were performed by PvD, ADIvA and SvdP. The first draft of the manuscript was written by PvD and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Prisma flow diagram.

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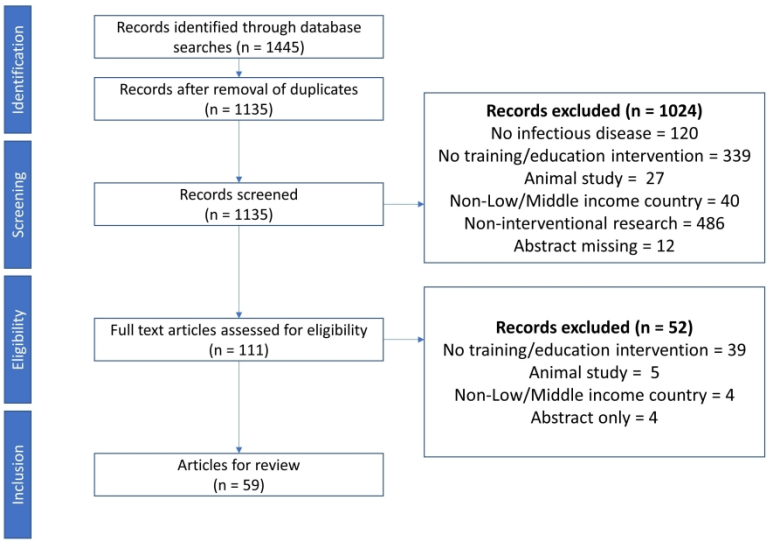

Figure 1 - PRISMA flow diagram

338x190mm (300 x 300 DPI)

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2/ Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3/ Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Appendix C
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix C
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

Topic	No.	Item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5 / Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5
Study characteristics	17	Cite each included study and present its characteristics.	Page 5 - Page 16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 17 - Page 19
	23b	Discuss any limitations of the evidence included in the review.	Page 18 - Page 19

Topic	No.	Item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Page 18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 19
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 19
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19
Competing interests	26	Declare any competing interests of review authors.	Page 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 19

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

APPENDIX B – Detailed search strategy per database

PubMed/Medline

(febrile* OR infectious OR "bacterial infection" OR "viral infection" OR antibiotic* OR antimicrobial) AND

("Antimicrobial Stewardship"[Mesh] OR "Education"[Mesh] OR Stewardship*[tiab] OR train*[tiab] OR educat*[tiab] OR campaign*[tiab] OR behavior change*[tiab] OR behavioral change*[tiab] OR behaviour change*[tiab] OR behavioural change*[tiab]) AND

(cost-effectiv*[tiab] OR economic analys*[tiab] OR economic evaluation*[tiab] OR pharmacoeconomic*[tiab] OR Health outcome*[tiab] OR health-related outcome*[tiab] OR health technology assessment*[tiab] OR Cost-saving*[tiab] OR Cost-benefit*[tiab]) AND

(middle-income[tiab] OR Low-income[tiab] OR "Afghanistan"[Mesh] OR Afghan*[tiab] OR "Albania"[Mesh] OR Alban*[tiab] OR "Algeria"[Mesh] OR Algeria*[tiab] OR "Angola"[Mesh] OR Angol*[tiab] OR "Antigua and Barbuda"[Mesh] OR Antigua*[tiab] OR "Argentina"[Mesh] OR Argentin*[tiab] OR "Armenia"[Mesh] OR Armenia*[tiab] OR "Azerbaijan"[Mesh] OR Azerbaijan*[tiab] OR "Bangladesh"[Mesh] OR Bangladesh*[tiab] OR "Republic of Belarus"[Mesh] OR Belarus*[tiab] OR "Belize"[Mesh] OR Belize*[tiab] OR "Benin"[Mesh] OR Benin*[tiab] OR "Bhutan"[Mesh] OR Bhutan*[tiab] OR "Bolivia"[Mesh] OR Bolivia*[tiab] OR "Bosnia and Herzegovina"[Mesh] OR Bosnia*[tiab] OR "Botswana"[Mesh] OR Botswan*[tiab] OR "Brazil"[Mesh] OR Brazil*[tiab] OR "Burkina Faso"[Mesh] OR Burkino faso*[tiab] OR "Burundi"[Mesh] OR Burundi*[tiab] OR "Cabo Verde"[Mesh] OR Cabo Verde*[tiab] OR "Cambodia"[Mesh] OR Cambodia*[tiab] OR "Cameroon"[Mesh] OR Cameroon*[tiab] OR "Central African Republic"[Mesh] OR Central African Republic*[tiab] OR Africa*[tiab] OR "Chad"[Mesh] OR Chad*[tiab] OR "China"[Mesh] OR Chin*[tiab] OR "Colombia"[Mesh] OR Colombia*[tiab] OR "Comoros"[Mesh] OR Comor*[tiab] OR "Congo"[Mesh] OR Congo*[tiab] OR "Polynesia"[Mesh] OR Cook Islander*[tiab] OR "Costa Rica"[Mesh] OR Costa Rica*[tiab] OR "Côte d'Ivoire"[Mesh] OR Côte d'Ivoir*[tiab] OR "Cuba"[Mesh] OR Cuba*[tiab] OR "Djibouti"[Mesh] OR Djibouti*[tiab] OR "Dominica"[Mesh] OR Dominic*[tiab] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh] OR Ecuador*[tiab] OR "Egypt"[Mesh] OR Egypt*[tiab] OR "El Salvador"[Mesh] OR salvador*[tiab] OR "Equatorial Guinea"[Mesh] OR Equatorial Guinea*[tiab] OR "Eritrea"[Mesh] OR Eritrea*[tiab] OR "Ethiopia"[Mesh] OR Ethiopia*[tiab] OR "Fiji"[Mesh] OR Fiji*[tiab] OR "Gabon"[Mesh] OR Gabon*[tiab] OR "Gambia"[Mesh] OR Gambia*[tiab] OR "Georgia"[Mesh] OR Georgia*[tiab] OR "Ghana"[Mesh] OR Ghana*[tiab] OR "Grenada"[Mesh] OR Grenad*[tiab] OR "Guatemala"[Mesh] OR Guatemala*[tiab] OR "Guinea"[Mesh] OR Guinea*[tiab] OR "Guinea-Bissau"[Mesh] OR Guinea-Bissau*[tiab] OR "Guyana"[Mesh] OR Guyan*[tiab] OR "Haiti"[Mesh] OR Haiti*[tiab] OR "Honduras"[Mesh] OR Hondura*[tiab] OR "India"[Mesh] OR India*[tiab] OR "Indonesia"[Mesh] OR Indonesia*[tiab] OR "Iran"[Mesh] OR Iran*[tiab] OR "Iraq"[Mesh] OR Iraq*[tiab] OR "Jamaica"[Mesh] OR Jamaica*[tiab] OR "Jordan"[Mesh] OR Jordan*[tiab] OR "Kazakhstan"[Mesh] OR kazakhstan*[tiab] OR "Kenya"[Mesh] OR Kenya*[tiab] OR "Micronesia"[Mesh] OR Kiribati*[tiab] OR "Kosovo"[Mesh] OR kosovo*[tiab] OR "Kyrgyzstan"[Mesh] OR Kyrgyzstan*[tiab] OR "Laos"[Mesh] OR Laos*[tiab] OR "Lebanon"[Mesh] OR Leban*[tiab] OR "Lesotho"[Mesh] OR Lesotho*[tiab] OR "Liberia"[Mesh] OR Liberia*[tiab] OR "Libya"[Mesh] OR Libya*[tiab] OR "Republic of North Macedonia"[Mesh] OR Macedonia*[tiab] OR "Madagascar"[Mesh] OR Madagasca*[tiab] OR Malagasy*[tiab] OR "Malawi"[Mesh] OR Malawi*[tiab] OR "Malaysia"[Mesh] OR Malaysia*[tiab] OR maldiv*[tiab] OR "Mali"[Mesh] OR Mali*[tiab] OR Marshall*[tiab] OR "Mauritania"[Mesh] OR Mauritania*[tiab] OR "Mauritius"[Mesh] OR Mauriti*[tiab] OR "Mexico"[Mesh] OR Mexic*[tiab] OR

"Micronesia"[Mesh] OR Micronesia*[tiab] OR "Moldova"[Mesh] OR Moldova*[tiab] OR "Mongolia"[Mesh] OR Mongolia*[tiab] OR "Montenegro"[Mesh] OR Montenegr*[tiab] OR Montserrat*[tiab] OR "Morocco"[Mesh] OR Morrocc*[tiab] OR "Mozambique"[Mesh] OR Mozambic*[tiab] OR "Myanmar"[Mesh] OR Myanmar*[tiab] OR "Namibia"[Mesh] OR Namibi*[tiab] OR Nauru*[tiab] OR "Nepal"[Mesh] OR Nepal*[tiab] OR "Nicaragua"[Mesh] OR Nicaragua*[tiab] OR "Niger"[Mesh] OR Niger*[tiab] OR "Nigeria"[Mesh] OR Niue*[tiab] OR "Pakistan"[Mesh] OR Pakistan*[tiab] OR "Palau"[Mesh] OR Palau*[tiab] OR "Panama"[Mesh] OR panama*[tiab] OR "Papua New Guinea"[Mesh] OR Papua New Guinea*[tiab] OR "Paraguay"[Mesh] OR paraguay*[tiab] OR "Peru"[Mesh] OR Peru*[tiab] OR "Philippines"[Mesh] OR Philippin*[tiab] OR "Rwanda"[Mesh] OR Rwanda*[tiab] OR "Atlantic Islands"[Mesh] OR Saint helena*[tiab] OR "Samoa"[Mesh] OR Samoa*[tiab] OR "São Tomé and Príncipe"[Mesh] OR São Tomé and Príncip*[tiab] OR "Senegal"[Mesh] OR Senegal*[tiab] OR "Serbia"[Mesh] OR Serbia*[tiab] OR "Sierra Leone"[Mesh] OR Sierra leon*[tiab] OR "Melanesia"[Mesh] OR Solomon island*[tiab] OR "Somalia"[Mesh] OR Somalia*[tiab] OR "South Africa"[Mesh] OR South Africa*[tiab] OR "South Sudan"[Mesh] OR South Sudan*[tiab] OR "Sri Lanka"[Mesh] OR Sri Lanka*[tiab] OR "Saint Lucia"[Mesh] OR Saint lucia*[tiab] OR "Saint Vincent and the Grenadines"[Mesh] OR vincent*[tiab] OR "Sudan"[Mesh] OR Sudan*[tiab] OR "Suriname"[Mesh] OR Suriname*[tiab] OR "Eswatini"[Mesh] OR Swaziland*[tiab] OR "Syria"[Mesh] OR Syria*[tiab] OR "Tajikistan"[Mesh] OR Tajikistan*[tiab] OR "Tanzania"[Mesh] OR tanzania*[tiab] OR "Thailand"[Mesh] OR Thai*[tiab] OR "Timor-Leste"[Mesh] OR Timor*[tiab] OR "Togo"[Mesh] OR Togo*[tiab] OR Tokelau*[tiab] OR "Tonga"[Mesh] OR Tonga*[tiab] OR "Tunisia"[Mesh] OR Tunisia*[tiab] OR "Turkey"[Mesh] OR Turk*[tiab] OR "Turkmenistan"[Mesh] OR Tuvalu*[tiab] OR "Uganda"[Mesh] OR Uganda*[tiab] OR "Ukraine"[Mesh] OR Ukrain*[tiab] OR "Uzbekistan"[Mesh] OR Uzbek*[tiab] OR "Vanuatu"[Mesh] OR Vanuatu*[tiab] OR "Venezuela"[Mesh] OR Venezuala*[tiab] OR "Vietnam"[Mesh] OR Vietnam*[tiab] OR Furtun*[tiab] OR Gaza*[tiab] OR "Yemen"[Mesh] OR Yemen*[tiab] OR "Zambia"[Mesh] OR Zambia*[tiab] OR "Zimbabwe"[Mesh] OR Zimbabwe*[tiab]) AND

("2000/01/01"[Date - Publication]: "2021/11/30"[Date - Publication])

Web of Science

TS=((""bacterial infection"" OR ""viral infection"" OR antibiotic* OR antimicrobial OR infectious) AND

(Educat* OR Stewardship* OR train* OR campaign* OR ""behavior change"" OR ""behavioral change"" OR ""behaviour change"" OR ""behavioural change"") AND

(cost-effectiveness OR ""economic analysis"" OR ""economic evaluation"" OR pharmacoeconomic* OR ""Health outcome"" OR ""health-related outcomes"" OR ""health technology assessment"" OR Cost-saving OR Cost-benefit) AND

(middle-income OR Low-income OR Afghan* OR Alban* OR Algeria* OR Angol* OR Antigua* OR Argentin* OR Armenia* OR Azerbaijan* OR Bangladesh* OR Belarus* OR Belize* OR Benin* OR Bhutan* OR Bolivia* OR Bosnia* OR Botswan* OR Brazil* OR ""Burkino faso"" OR Burundi* OR Cabo Verde* OR Cambodia* OR Cameroon* OR ""Centrial African Republic"" OR Africa* OR Chad* OR Chin* OR Colombia* OR Comor* OR Congo* OR ""Cook Island"" OR ""Costa Rica"" OR ""Côte d'Ivoir"" OR Cuba* OR Djibouti* OR Dominic* OR Ecuador* OR Egypt* OR salvador* OR ""Equatorial Guinea"" OR Eritrea* OR Ethiopia* OR Fiji* OR Gabon* OR Gambia* OR Georgia* OR Ghana* OR Grenad* OR Guatemala* OR Guinea* OR Guinea-Bissau* OR Guyan* OR Haiti* OR Hondura* OR India* OR Indonesia* OR Iran* OR Iraq* OR Jamaica* OR Jordan* OR kazakhstan* OR Kenya* OR

Kiribati* OR kosovo* OR Kyrgyzstan* OR Laos* OR Leban* OR Lesotho* OR Liberia* OR Libya* OR Macedonia* OR Madagasca* OR Malagasy* OR Malawi* OR Malaysia* OR maldiv* OR Mali* OR Marshall* OR Mauritania* OR Mauriti* OR Mexic* OR Micronesia* OR Moldova* OR Mongolia* OR Montenegr* OR Montserrat* OR Morrocc* OR Mozambic* OR Myanmar* OR Namibi* OR Nauru* OR Nepal* OR Nicaragua* OR Niger* OR Niue* OR Pakistan* OR Palau* OR panama* OR ""Papua New Guinea"" OR paraguay* OR Peru* OR Philippin* OR Rwanda* OR ""Saint helena"" OR Samoa* OR ""São Tomé and Príncipe"" OR Senegal* OR Serbia* OR ""Sierra leone"" OR ""Solomon islands"" OR Somalia* OR ""South Africa"" OR ""South Sudan"" OR ""Sri Lanka"" OR ""Saint lucia"" OR ""Saint vincent"" OR Sudan* OR Suriname* OR Swaziland* OR Syria* OR Tajikistan* OR tanzania* OR Thai* OR Timor* OR Togo* OR Tokelau* OR Tonga* OR Tunisia* OR Turk* OR Tuvalu* OR Uganda* OR Ukrain* OR Uzbek* OR Vanuatu* OR Venezuala* OR Vietnam* OR ""Wallis and furtuna"" OR Gaza* OR Yemen* OR Zambia* OR Zimbabwe*))) AND

Time period 2000-01-01 - 2021-11-30

Scopus

(TITLE-ABS-KEY (febrile*) OR TITLE-ABS-KEY (antibiotic*) OR TITLE-ABS-KEY (infectious) OR TITLE-ABS-KEY ("bacterial infection") OR TITLE-ABS-KEY ("viral infection")) AND

(TITLE-ABS-KEY(Educat*) OR TITLE-ABS-KEY(Stewardship*) OR TITLE-ABS-KEY(train*) OR TITLE-ABS-KEY(campaign*) OR TITLE-ABS-KEY("behavior change") OR TITLE-ABS-KEY("behavioral change") OR TITLE-ABS-KEY("behaviour change") OR TITLE-ABS-KEY("behavioural change")) AND

(TITLE-ABS-KEY(cost-effectiveness) OR TITLE-ABS-KEY("economic analysis") OR TITLE-ABS-KEY("economic evaluation") OR TITLE-ABS-KEY(pharmacoeconomic) OR TITLE-ABS-KEY("Health outcome") OR TITLE-ABS-KEY("health-related outcomes") OR TITLE-ABS-KEY("health technology assessment") OR TITLE-ABS-KEY(Cost-saving) OR TITLE-ABS-KEY(Cost-benefit)) AND

(TITLE-ABS-KEY(middle-income) OR TITLE-ABS-KEY(Low-income) OR TITLE-ABS-KEY(Afghan*) OR TITLE-ABS-KEY(Alban*) OR TITLE-ABS-KEY(Algeria*) OR TITLE-ABS-KEY(Angol*) OR TITLE-ABS-KEY(Antigua*) OR TITLE-ABS-KEY(Argentin*) OR TITLE-ABS-KEY(Armenia*) OR TITLE-ABS-KEY(Azerbaijan*) OR TITLE-ABS-KEY(Bangladesh*) OR TITLE-ABS-KEY(Belarus*) OR TITLE-ABS-KEY(Belize*) OR TITLE-ABS-KEY(Benin*) OR TITLE-ABS-KEY(Bhutan*) OR TITLE-ABS-KEY(Bolivia*) OR TITLE-ABS-KEY(Bosnia*) OR TITLE-ABS-KEY(Botswan*) OR TITLE-ABS-KEY(Brazil*) OR TITLE-ABS-KEY("Burkino faso") OR TITLE-ABS-KEY(Burundi*) OR TITLE-ABS-KEY(Cabo Verde*) OR TITLE-ABS-KEY(Cambodia*) OR TITLE-ABS-KEY(Cameroon*) OR TITLE-ABS-KEY("Centrial African Republic") OR TITLE-ABS-KEY(Africa*) OR TITLE-ABS-KEY(Chad*) OR TITLE-ABS-KEY(Chin*) OR TITLE-ABS-KEY(Colombia*) OR TITLE-ABS-KEY(Comor*) OR TITLE-ABS-KEY(Congo*) OR TITLE-ABS-KEY("Cook Island") OR TITLE-ABS-KEY("Costa Rica") OR TITLE-ABS-KEY("Côte d'Ivoir") OR TITLE-ABS-KEY(Cuba*) OR TITLE-ABS-KEY(Djibouti*) OR TITLE-ABS-KEY(Dominic*) OR TITLE-ABS-KEY(Ecuador*) OR TITLE-ABS-KEY(Egypt*) OR TITLE-ABS-KEY(salvador*) OR TITLE-ABS-KEY("Equatorial Guinea") OR TITLE-ABS-KEY(Eritrea*) OR TITLE-ABS-KEY(Ethiopia*) OR TITLE-ABS-KEY(Fiji*) OR TITLE-ABS-KEY(Gabon*) OR TITLE-ABS-KEY(Gambia*) OR TITLE-ABS-KEY(Georgia*) OR TITLE-ABS-KEY(Ghana*) OR TITLE-ABS-KEY(Grenad*) OR TITLE-ABS-KEY(Guatemala*) OR TITLE-ABS-KEY(Guinea*) OR TITLE-ABS-KEY(Guinea-Bissau*) OR TITLE-ABS-KEY(Guyan*) OR TITLE-ABS-KEY(Haiti*) OR TITLE-ABS-KEY(Hondura*) OR TITLE-ABS-KEY(India*) OR TITLE-ABS-KEY(Indonesia*) OR TITLE-ABS-KEY(Iran*) OR TITLE-ABS-KEY(Iraq*) OR TITLE-ABS-KEY(Jamaica*) OR TITLE-ABS-KEY(Jordan*) OR TITLE-ABS-KEY(kazakhstan*) OR TITLE-ABS-KEY(Kenya*) OR TITLE-ABS-KEY(Kiribati*) OR TITLE-ABS-KEY(kosovo*) OR TITLE-ABS-KEY(Kyrgyzstan*) OR TITLE-ABS-KEY(Laos*) OR TITLE-ABS-KEY(Leban*)

OR TITLE-ABS-KEY(Lesotho*) OR TITLE-ABS-KEY(Liberia*) OR TITLE-ABS-KEY(Libya*) OR TITLE-ABS-KEY(Macedonia*) OR TITLE-ABS-KEY(Madagasca*) OR TITLE-ABS-KEY(Malagasy*) OR TITLE-ABS-KEY(Malawi*) OR TITLE-ABS-KEY(Malaysia*) OR TITLE-ABS-KEY(maldiv*) OR TITLE-ABS-KEY(Mali*) OR TITLE-ABS-KEY(Marshall*) OR TITLE-ABS-KEY(Mauritania*) OR TITLE-ABS-KEY(Mauriti*) OR TITLE-ABS-KEY(Mexic*) OR TITLE-ABS-KEY(Micronesia*) OR TITLE-ABS-KEY(Moldova*) OR TITLE-ABS-KEY(Mongolia*) OR TITLE-ABS-KEY(Montenegr*) OR TITLE-ABS-KEY(Montserrat*) OR TITLE-ABS-KEY(Morrocc*) OR TITLE-ABS-KEY(Mozambic*) OR TITLE-ABS-KEY(Myanmar*) OR TITLE-ABS-KEY(Namibi*) OR TITLE-ABS-KEY(Nauru*) OR TITLE-ABS-KEY(Nepal*) OR TITLE-ABS-KEY(Nicaragua*) OR TITLE-ABS-KEY(Niger*) OR TITLE-ABS-KEY(Niue*) OR TITLE-ABS-KEY(Pakistan*) OR TITLE-ABS-KEY(Palau*) OR TITLE-ABS-KEY(panama*) OR TITLE-ABS-KEY("Papua New Guinea") OR TITLE-ABS-KEY(paraguay*) OR TITLE-ABS-KEY(Peru*) OR TITLE-ABS-KEY(Philippin*) OR TITLE-ABS-KEY(Rwanda*) OR TITLE-ABS-KEY("Saint helena") OR TITLE-ABS-KEY(Samoa*) OR TITLE-ABS-KEY("São Tomé and Príncipe") OR TITLE-ABS-KEY(Senegal*) OR TITLE-ABS-KEY(Serbia*) OR TITLE-ABS-KEY("Sierra leone") OR TITLE-ABS-KEY("Solomon islands") OR TITLE-ABS-KEY(Somalia*) OR TITLE-ABS-KEY("South Africa") OR TITLE-ABS-KEY("South Sudan") OR TITLE-ABS-KEY("Sri Lanka") OR TITLE-ABS-KEY("Saint lucia") OR TITLE-ABS-KEY("Saint vincent") OR TITLE-ABS-KEY(Sudan*) OR TITLE-ABS-KEY(Suriname*) OR TITLE-ABS-KEY(Swaziland*) OR TITLE-ABS-KEY(Syria*) OR TITLE-ABS-KEY(Tajikistan*) OR TITLE-ABS-KEY(tanzania*) OR TITLE-ABS-KEY(Thai*) OR TITLE-ABS-KEY(Timor*) OR TITLE-ABS-KEY(Togo*) OR TITLE-ABS-KEY(Tokelau*) OR TITLE-ABS-KEY(Tonga*) OR TITLE-ABS-KEY(Tunisia*) OR TITLE-ABS-KEY(Turk*) OR TITLE-ABS-KEY(Tuvalu*) OR TITLE-ABS-KEY(Uganda*) OR TITLE-ABS-KEY(Ukrain*) OR TITLE-ABS-KEY(Uzbek*) OR TITLE-ABS-KEY(Vanuatu*) OR TITLE-ABS-KEY(Venezuala*) OR TITLE-ABS-KEY(Vietnam*) OR TITLE-ABS-KEY("Wallis and furtuna") OR TITLE-ABS-KEY(Gaza*) OR TITLE-ABS-KEY(Yemen*) OR TITLE-ABS-KEY(Zambia*) OR TITLE-ABS-KEY(Zimbabwe*)) AND

(PUBYEAR > 1999) AND (PUBYEAR < 2022)

APPENDIX C – Data extraction form content

Section	Variables captured	Answer options (empty is open question)
General section	Email Address	
	Title	
	First author (last name)	
	Year published	
	Disease area	(General) respiratory tract infection Influenza Pneumonia (specifically) Urinary tract infection gastroenteritis General reflux complaints Tuberculosis Malaria Dengue HIV Fungal infection Appendicitis Typhoid Other
	Specific pathogens (if given, separate by semicolon ;)	
	Objective (from abstract)	
	Research question(s)	
	Health economic study?	Yes No
Health economic study	Explicit statement on the context of the study	Yes No
	Explanation of relevance for health policy or practise decision	Yes No
	Country	
	Is the model used based on a previously published model? (If yes, give author and year)	
	Target population and subgroups	
	Setting (Primary care, hospital, home, etc.)	Home Primary care Emergency department Hospital Other:
	Study perspective	Societal perspective Healthcare payer's perspective Healthcare centre's perspective Other:
	Interventions or strategies being compared [separate different strategies with a semicolon ;]	
	Duration of the intervention (years)	
	Treatment options included in the analysis [separate different strategies with a semicolon ;]	
	Time horizon (years)	
	Is a time framework and reasoning provided by the authors (are reasons given for the chosen time horizon, e.g. one flue season (when the time horizon is a couple of months to a year) or in concordance with the national guidelines, for a lifetime horizon)	Yes No
	Discount rate for base case (health outcomes)	
	Discount rate for base case (economic outcomes)	
	Study type [As qualified by the authors]	
	Study type [As qualified by the reviewer (use Drummond book for background)]	
	What input parameters were used? (separate by semicolon ;)	
	What were the reported output variables? (separate by semicolon ;)	Life years Life expectancy QALYs DALYs Quality-adjusted life expectancy (QALE) Antibiotic prescriptions saved Hospitalizations saved Days free from disease Other:

	Measurement of effectiveness	Single-study based estimates Synthesis-based estimates Other:
	Did the authors describe the following: for Single study–based estimates: describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data; for synthesis-based estimates: describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	Yes No
	Did the authors describe the population and methods used to elicit preferences for outcomes?	Yes No N/A
	Are the resource and cost estimations explained in the article?	Yes No
	Costs of training method (in reported currency) [separate different strategies with a semicolon ;]	
	Costs of treatment options (in reported currency) [separate different strategies with a semicolon ;]	
	Currency/currencies reported	US dollars Euros Pound Sterling Japanese yen Other:
	Currency year used	
	Is the method for currency conversion described?	Yes No
	Type of model	Decision tree Markov (compartimental) model Discrete-event simulation Individual sampling model Dynamic compartmental model Individual-contact model / agent-based model Network model Other:
	Is the model stochastic or deterministic	Stochastic (or probabilistic) Deterministic Other:
	Description of model	
	Software used to program the model and statistical analyses	Microsoft Excel TreeAge Pratt Medical Decision maker IBM SPSS R Python C++ Not reported Other:
	Is the model design thoroughly described in the article?	Yes No
	Are structural or other assumptions underpinning the decision-analytical model described?	Yes No
	Is a description given for the analytical methods supporting the evaluation? (e.g. methods for dealing with missing data, skewed data, uncertainty)	Yes No
	Is antibiotic resistance included in the model?	Yes No
	If yes, how is antibiotic resistance included?	
	Unit of incremental costs and outcomes	Costs or savings /QALY Costs or savings /DALY Costs or savings /LYG Costs or savings /antibiotic prescription saved Costs or savings /patient QALYs/DALYs Correct diagnoses Time to correct diagnosis Hospital length-of-stay Disease duration Other:
	How is the uncertainty reported?	Deterministic sensitivity analysis (DSA) Table of DSA

		Tornado diagram of DSA Sensitivity analysis graph (with one parameter varied) Two-way sensitivity analysis graph Three-way (or more) sensitivity analysis graph Probabilistic sensitivity analysis (PSA) Cost-effectiveness plane of PSA Cost-effectiveness acceptability curve(s) Cost-efficiency/efficiency frontier Other:
	Have subgroup analyses been performed? (If yes, which subgroups and how?)	
	Main findings	
	Are limitations of the study described?	Yes No
	Specific limitations/gaps in the assessment of Training	
	Is generalisability discussed?	Yes No
	To what extend do authors consider the results generalizable?	Specific hospital/healthcare center Nationwide Continental Worldwide Other:
	Have the results been linked to current knowledge?	Yes No
	What is the main conclusion or conclusions? The strategy/strategies being compared was...	Cost-saving Cost-effective Not cost-effective Unclear Other:
	If reported, which willingness-to-pay threshold(s) was/were used?	
	Source of funding	Industrial Governmental grant Academic grant No funding Not reported Other:
	Is a statement on the conflicts of interest present?	Yes No
Non-Health economic study	What is the research design?	
	Country	
	Target population and subgroups	
	Setting (Primary care, hospital, home, etc.)	Home Primary care Emergency department Hospital Other:
	Interventions or strategies being analyzed [separate different strategies with a semicolon ;]	
	Treatment options included in the analysis [separate different strategies with a semicolon ;]	
	Duration of the intervention (years)	
	Variables reported/used (please specify all)	Life years Life expectancy QALYs DALYs Quality-adjusted life expectancy (QALE) Antibiotic prescriptions saved Hospitalizations saved Days free from disease Prescription of right antibiotics Money spent on antibiotics Mortality increase/decrease De-escalation/escalation of antibiotic use Duration of hospital stay Number of diagnostic tests done Other:
	Is antibiotic resistance included in the research?	Yes No
	If yes, how is antibiotic resistance included?	

	Have subgroup analyses been performed? (If yes, which subgroups and how?)	
	Main findings	
	Are limitations of the study described?	Yes No
	Source of funding	Industrial Governmental grant Academic grant No funding Not reported Other:
	Is a statement on the conflicts of interest present?	Yes No