01 04 2020

Ref. Ares(2020)1857340 - 31/03/2020

UNIVERSITY OF LA RIOJA: PAULA **ROJAS GARCIA**, MARINO J. **GONZÁLEZ,** FERNANDO **ANTOÑANZAS VILLAR**
UNIVERSITY MEDICAL CENTER GRONINGEN: SIMON **VAN DER POL**, THEA **VAN ASSELT**, MAARTEN **POSTMA**

Review of health-economic approaches for diagnostic-driven antibiotic use

Deliverable 5.1

VALUE-Dx

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 820755. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and bioMérieux SA, Janssen Pharmaceutica NV, Accelerate Diagnostics S.L., Abbott, Bio-Rad Laboratories, BD Switzerland Sàrl, and The Wellcome Trust Limited.



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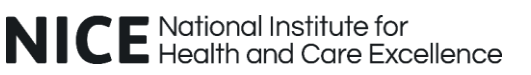
NICE National Institute for
Health and Care Excellence

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ESCMID
EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES

ERS
EUROPEAN
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SOCIETY
every breath counts

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Executive summary

In many European countries, health-technology assessment (HTA) is very common, often even mandatory, for new pharmaceutical treatments. However, for the introduction of non-pharmaceutical innovations, HTA is much less established. In research focussing on clinical diagnostics, HTA is not the default and specific diagnostic appraisal procedures are absent in many countries. In addition, HTAs of diagnostics are vastly different from HTAs of pharmaceuticals; instead of directly affecting clinical endpoints, diagnostics influence intermediate decisions (i.e. the treatment decision) and often, diagnostics are used in sequence. To assess the cost effectiveness of a diagnostic, not only the clinical effectiveness of the test needs to be considered, but also the population has a greater influence on the results, as well as the treatment options that follow. In the case of infectious diseases, matters are even more complicated: early diagnosis may influence the transmission of a disease, seasonal variation may be present and targeted therapy, although possible, is seldom practised in primary care. This feeds into the threat of antimicrobial resistance (AMR), which is increasing in Europe.

This systematic review has three aims: to review current health-economic frameworks, applied to diagnostic strategies for infectious disease; to identify gaps in current practice in these frameworks and to select preferred strategies for both the short- and long-term health-economic models within the VALUE-Dx project.

Three large databases of scientific literature were searched (Scopus, Web of Science and PubMed) for the period 2000-2018, to find economic evaluations focussing on diagnostic strategies of infectious disease. A diagnostic strategy was defined as: “identifying the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care”. Data from the included studies were extracted using a standardized form, based on the CHEERS checklist, which is often used in the field of HTA.

Out of 3586 articles included in the initial search, 129 were included in the review, they were subdivided in eight categories (respiratory tract infection, vector-borne disease, gastrointestinal infection, urinary tract infection, fungal infection, sexually transmitted disease, sepsis and other), with respiratory tract infection being the largest category, containing 60 articles. A slight increase in the number of published articles is present towards the later 2010s.

Regarding the modelling approaches, most models used a decision tree, of which the majority was programmed using TreeAge, over a relatively short time horizon (in many cases less than one year, or not reported). Other frequent modelling approaches included Markov models, regression analyses and dynamic models, in general, Markov models allowed for a longer time horizon to be assessed as compared to decision tree models. Some articles used generic health outcomes (e.g. Quality-Adjusted Life Years), but often also outcomes specific to infectious disease diagnostics were used, such as correct diagnoses or outcomes related to the number of antibiotics prescribed. AMR was not considered by most studies; for the studies which included this, several methods were applied, such as adding a cost to all antibiotic prescriptions, varying the efficacy of treatment (based on AMR projections or sensitivity analyses) or, for diagnostic tests which can detect resistant organisms, changing the treatment to a usually more expensive option.

Opportunities in the field of HTA of diagnostics for infectious disease, mainly lie in the inclusion of generic quality-of-life outcomes, as opposed to (disease-)specific outcomes, and in the inclusion of time in the analyses, mainly in assessing more extensive time horizons (over 10 years).

Within work package 5 of VALUE-Dx, two health-economic models will be developed, one short-term, trial-based model and one long-term model. The trial-based model will be used to follow the data

captured during the trial as closely as possible using decision trees. The long-term model will allow the exploration of extended time horizons, beyond the trial, including the effects improved diagnosis and subsequent antibiotic prescribing have on AMR.

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List of abbreviations

ACT	Artemisinin-based Combination Therapy
ADR	Adverse Drug Reaction
AMR	Antimicrobial Resistance
AP	Acute pharyngitis
ARTI	Acute Respiratory Tract Infection
BIA	Budget Impact Analysis
C.	Chlamydia
CA-ARTI	Community-Acquired Acute Respiratory Tract Infection
CAP	Community-Acquired Pneumonia
CBA	Cost Benefit Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CT	Computed Tomography
CUA	Cost–Utility Analysis
DALY	Disability-Adjusted Life Year
DSA	Deterministic Sensitivity Analysis
ED	Emergency Department
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EQ-5D	European Quality of life index version 5D
EU	European Union
GM	Galacomannan
GP	General Practitioner
GRACE	Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection in Europe
H.	Helicobacter
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HTA	Health-Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ILI	Influenza-Like Illness
L	Litre
lgMFA	Lateral Flow Analysis Of Immunoglobin M
LMIC	Low- And Middle- Income Country
LRTI	Lower Respiratory Tract Infections
LYG	Life Years Gained
mg	Milligram
MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis
n	No
NA	Not Available
NAAT	Nucleic Amplification Test For Chlamydia Trachomatis
NICE	National Institute for Clinical Excellence
OECD	Organization for Economic Co-operation and Development
PCR	Polymerase Chain Reaction
PCT	Procalcitonin Test
pH	Potential Hydrogen
PID	Pelvic Inflammatory Diseases
POC	Point Of Care
PPI	Proton Pump Inhibitor

PRG	Paula Rojas García
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALD	Quality-Adjusted Life Day
QALY	Quality-Adjusted Life Year
QALE	Quality-Adjusted Life Expectancy
R	Software environment for statistical computing and graphics
RIF	Resistance To Rifampicin
RSV	Respiratory Syncytial Virus
RUT	Rapid Urease Test
S.	Streptococcus
SHPAb	Serum Helicobacter Pylori Igg Antibody
SIR	Susceptible-Infected-Recovered
SP	Streptococcus Pneumoniae
SPSS	Statistical Package For The Social Sciences
STATA	Statistical Software Package
STD	Sexually Transmitted Diseases
SvdP	Simon van der Pol
T2DT	T2Candida-Directed Therapy
TB	Tuberculosis
UBT	Urea Breath Test
UGI	Upper GI Radiography
UK	United Kingdom
USA	United States of America
USD	United States Dollar
WinBUGS	Windows operating system version of Bayesian Analysis Using Gibbs Sampling
WTP	Willingness-To-Pay
y	yes

1. Introduction

Healthcare expenditure has been growing in Europe over the past decades[1], as the European population continues to grow older[2]. Innovations in healthcare are to thank for the increasing life expectancy: improved hygiene for all; vaccinations for the very young and chronic medication for the elderly. This certainly has its price: in many Western European countries, healthcare spending is now over 10% of the gross domestic product[1]. This has led to many countries implementing economic assessment criteria for new healthcare technologies. For the pharmaceutical market these criteria are most clear: after a drug is approve on the European level by the European Medicines Agency (EMA) on safety and efficacy, many countries assess the cost-effectiveness of the drug to decide whether it should be included in national reimbursement schemes[3]. Generally, this approach focusses on expressing the costs per Quality-Adjusted Life Year (QALY), which enables comparisons between many different disease areas. The Incremental Cost-Effectiveness Ratio (ICER) is a measure to compare the costs/QALY of one intervention to another: usually the innovative treatment compared to current care[4].

1.1. Health technology assessment of diagnostics

In many European countries, health-technology assessment (HTA) is very common, often even mandatory, for new pharmaceutical treatments. However, for the introduction of non-pharmaceutical innovations, HTA is much less established. Research focussing on clinical diagnostics less often incorporates HTA[3,5] and specific diagnostic procedures are absent in many countries[6]. As a major difference compared to HTA of new treatments, diagnostic tests directly influence intermediate outcomes, as opposed to clinical endpoints, complicating the assessment of diagnostics[7]. An important influence on the performance of diagnostics is the population the test is applied to. Additionally, diagnostics often are incorporated in sequence as part of an algorithm with other diagnostics, as opposed to being used in isolation. To assess the cost effectiveness of a diagnostic, not only the clinical effectiveness of the test needs to be considered, but also the population it will be applied to and the treatment options that follow. See also Figure 1 for an overview of the determinants for the cost-effectiveness of diagnostics.

For infectious disease diagnostics, there are additional factors to consider. First, quick diagnosis may limit the transmission of the disease, which prevents others from getting ill[8], this may be hard to quantify, unless an epidemiological transmission model is included. Second, seasonal variations[9] and vaccination efficacy, such as for influenza, influence the cost-effectiveness of the diagnostic method. Third, by informing treatment decision, clinicians can tailor treatment to the patient, including prescribing targeted antibiotics or, if the infection is viral, refrain from prescribing an antibiotic. This is an important effect, as the annual number of infections with

Figure 1 determinants of cost-effectiveness of diagnostics

resistant bacteria is estimated to be more than 650.000, causing over 30.000 attributable deaths in Europe[10].

1.2. Antimicrobial resistance

In recent years, there has been increased attention for AMR-related problems, however, antibiotic prescribing rates remain high for patients with community-acquired acute respiratory tract infections (CA-ARTI). To fight the threat of AMR in the context of CA-ARTI, it has been suggested that more targeted prescriptions of antibiotics, informed by quick diagnostics, are an important tool[11,12]. Increasingly, the economic case for reducing AMR is being made. In light of the evidence of significant costs of AMR for society, it has also been suggested that the costs of AMR need to be included in health-economic assessments. However, this is not an easy feat, as the exact mechanisms for the development of resistance and the spread of resistant bacteria are not clear[13]. In assessing POC diagnostic strategies for CA-ARTI, economic evaluations have been performed, e.g. for C-reactive protein (CRP) testing[14,15]. If included, AMR is considered indirectly, e.g. by calculating the threshold cost of resistance that would change the conclusion of the compared strategy being cost-effective[16]; an incremental cost-effectiveness ratio using prescriptions saved as an outcome measure[15]; or as a total percentage of infections[17–20].

1.3. Aims of this systematic review

This systematic review aims to assess current practises on health-economic approaches for diagnostics methods for infectious disease, using the PRISMA standards[21,22]. We will specifically assess the (modelling) methods, as well as the outcomes generated, to establish current best practice and identify room for improvement. Then, we can use these collected data to improve upon what has been done previously and develop innovative health-economic models for CA-ARTI diagnostics within VALUE-Dx later.

This systematic review has the following objectives:

1| Review health-economic frameworks that have been applied to diagnostic strategies for infectious disease within scientific literature.
2| Identify gaps in current practice related to health-economic models for infectious disease diagnostics.
3| Select preferred strategies for both the short-term and long-term health-economic models within VALUE-Dx.

2. Methodology

2.1. Search strategy

We conducted a systematic review of articles contained in two large general databases: Scopus and Web of Science and a specific database in biomedical literature: PubMed. These three repositories include only peer-reviewed articles and employ Boolean operators, which allow to perform advanced searches that yield more targeted results.

The specific syntax (Table 1) for this study was designed, aimed at finding economic evaluations, whose object of study was "antibiotics" or "infectious disease". In addition, the words "diagnostic" and "test" were included in the syntax, in all their possible variations (e.g. diagnose, testing). The results were not geographically limited but with the purpose of reflecting recent clinical practice, we only included articles published between 2000 and 2018, both years inclusive.

Table 1 search criteria for systematic review

Syntax used in Scopus	Syntax used in PubMed	Syntax used in Web of Science
(TITLE-ABS-KEY (pharmacoeconomic*) OR TITLE-ABS-KEY(cost-effectiveness) OR TITLE-ABS-KEY("economic evaluation") OR TITLE-ABS-KEY("health technology assessment")) AND (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("diagnostic") OR TITLE-ABS-KEY("diagnostics") OR TITLE-ABS-KEY("test") OR TITLE-ABS-KEY("tests") OR TITLE-ABS-KEY("testing")) AND PUBYEAR > 1999 AND PUBYEAR < 2019	(infectious OR "bacterial infection" OR "viral infection" OR antibiotic* OR antimicrobial) AND ("diagnostic" OR "diagnostics" OR "test" OR "tests" OR "testing") AND ("2000/01/01"[Date - Publication]: "2018/12/31"[Date - Publication]) AND (pharmacoeconomic* OR "cost-effectiveness" OR "economic evaluation" OR "health technology assessment")	TS=(((“bacterial infection" OR "viral infection" OR antibiotic* OR antimicrobial OR infectious) AND ("diagnostics" OR "diagnostic" OR "test" OR "tests" OR "testing") AND (pharmacoeconomic* OR cost-effectiveness OR "economic evaluation" OR "health technology assessment"))) Period of time: 2000-2018

2.2. Definition of diagnostic strategy

The words "diagnostic", "test" and "screening" could have various meanings, depending on the article. We defined a diagnostic strategy as[23]:

"Identifying the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care"

Furthermore, population screenings, disease monitoring or genotyping were explicitly not considered as diagnostic strategies.

2.3. Eligibility criteria

Following the recommendations of the PRISMA standards[24], two reviewers (PRG & SvdP) independently screened all abstracts and conducted an exercise of consensus. In case of not reaching an agreement, a third person was asked. See Table 2 for an overview.

The titles and abstracts were examined in order to determine the suitability of each article to be included in the review. The article that met the eligibility criteria performed an economic or cost-effectiveness analysis (CEA) that compared at least two diagnostic strategies for bacterial or viral infections. Not testing compared to performing a diagnostic test was also considered to be a comparison of two diagnostic strategies. An example of this would be empirical antiviral treatment for influenza, based on clinical symptoms assessed by a General Practitioner (GP), compared to performing an influenza Rapid Diagnostic Test (RDT) and basing the prescription decision on this test. Other exclusion criteria were studies focused on animals, review articles, study protocols, comments on articles or individual case reports, and languages other than English, Spanish, Dutch, German or French.

The full-text screening phase was performed by the same two reviewers, applying the same criteria. In addition to the inclusion and exclusion criteria above, this phase was used to separate the diagnostic and screening strategies, as this distinction often was not clear from the abstract.

Table 2 exclusion criteria

Round 1: Reading title and abstract (articles from databases searching results)

- Is it a duplicate? -> if yes, excluded
- Is the abstract available? -> if no, excluded
- The language used is one of the following: English, Spanish, Dutch, German or French?-> if no, excluded
- Is it related to infectious disease? -> if no, excluded
- Does it include a cost-effectiveness or cost-benefit analysis (as defined by Drummond *et al*[4])? -> if no, excluded
- Does it compare two diagnostic strategies? -> if no, excluded
- Is it a human study? -> if no, excluded
- Is it a review, study protocol, letter-to-the-editor or case report -> if yes, excluded

Round 2: Reading full text (articles included in round 1)

- Is the full text available? -> if no, excluded
- Same criteria as round 1
- Does it concern a screening programme (as opposed to a diagnostic strategy, as specified in Chapter 2.2)?-> if yes, excluded

= Record included in the review

2.4. Study selection

Reading the full texts, a classification of the articles was conducted based on the infectious disease. In this sense, the following groups and subgroups were defined:

- respiratory tract infection
    - general
    - tuberculosis (TB)
    - influenza
    - pneumonia
- sexually transmitted disease
- vector-borne disease
    - malaria
    - others
- gastroenteritis
- urinary tract infection
- sepsis
- fungal infection.

We used the reference manager Zotero and created a common folder to store all full texts.

2.5. Data extraction

Using a standardized digital (Google) form to manage all the extraction and following the CHEERS checklist[25], the data included different items classified in four groups depending on where they can be found in the text: general items, methodology items, results items and discussion items. See Table 3 for an overview and Appendix I for a printout.

In the general and introduction parts, identification information such as title, main author, year of publication or objective were included. In the methodology, we emphasize the type of model performed and its characteristics in terms of perspective, time horizon, setting, population included and incorporation of uncertainty analysis in parameter values (stochastic or deterministic). A section was included to assess whether the model included the effect of AMR, as well as a segment to complete with its full description. In the results items, we pay attention to the unit of incremental costs and outcomes, techniques to report uncertainty in the model and currency used. Finally, the discussion items were focused on main findings, limitations, specific limitations in the assessment of diagnostics of the study and advantages/disadvantages of the modelling technique discussed by the authors.

Table 3 list of items checked for data extraction

General part
Title
First author last name
Year published
Disease area: *General respiratory tract infection, Influenza, Pneumonia, Urinary tract infection, Gastroenteritis, General reflux complaints, Tuberculosis, Malaria, Dengue, HIV, Fungal infection, Appendicitis, Other.*
Specific pathogens
Objective from abstract

Introduction
Research question
Explicit statement on the context of the study *(y/n)*
Explanation of relevance for health policy or practise decision *(y/n)*
Country
Methodology
Model used based on a previously model? *(y/n)*
Target population
Setting: *Primary care, ED, Hospital, Other*
Study perspective: *Societal, Healthcare payer's/ Healthcare centre's.*
Interventions or strategies being compared
Treatment options included in the analysis
Time horizon
Is a time framework and reasoning provided? *(y/n)*
Discount rate for base case
Study type: *Cost Analysis, Cost Effectiveness analysis, Cost Utility Analysis, Cost Benefit analysis, Cost-minimization analysis, Budget Impact Analysis.*
Reported clinical outcomes: *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 or Synthesis-based estimates.
Costs of diagnostic method
Costs of treatment options
Currency/currencies reported
Type of model: *Decision tree, Markov (compartmental) model, Discrete-event simulation, Individual sampling model, Dynamic compartmental model, Individual-contact model / agent-based model, Network model, Other.*
Is stochasticity incorporated in the model?
Description of model
Software used to program the model
Is the model design thoroughly described? *(y/n)*
Is antibiotic resistance included in the model? *(y/n)*
If yes, how is antibiotic resistance included?
Results
Incremental costs and outcomes (value)
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, 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), Other.*
For the DSA, which ranges of values are used?
For the PSA, how many replications are used?
Discussion
Main findings
Limitations
Specific limitations in the assessment of diagnostics
Generalisability
Have the results been linked to current knowledge? *(y/n)*
What is the main conclusion of conclusions? *Cost-saving, Cost-effective, Not cost-effective, Unclear.*
Which willingness-to-pay threshold was used?
Specific advantages/disadvantages of the modelling technique discussed in the article
Other

Source of funding: *Industrial, Governmental grant, Academic grant, No funding, Not reported, Other.*
Is a statement on the conflicts of interest present? *(y/n)*

3. Results

3.1. Selection criteria

In Figure 2 the PRISMA flow diagram[22] is displayed. The search using the syntax as described in the methods was run on July 3rd, 2019. After the removal of duplications, a total of 3586 articles were included in the title and abstract screening. Of these, 3186 were excluded, mainly as they were no CEA (2066 records) or because they were not considering infectious disease (534 records). 500 records were included in the full-text screening, 371 of which were excluded from the final analysis. The main exclusion criterium here (304 records), was that no diagnostic strategy was evaluated by the authors. Many papers dealt with screening strategies within a largely healthy population, as opposed to a pure diagnostic strategy, i.e. a healthcare provider is looking for the most likely cause of a patient's illness. Eventually, 129 articles were included in this systematic review.

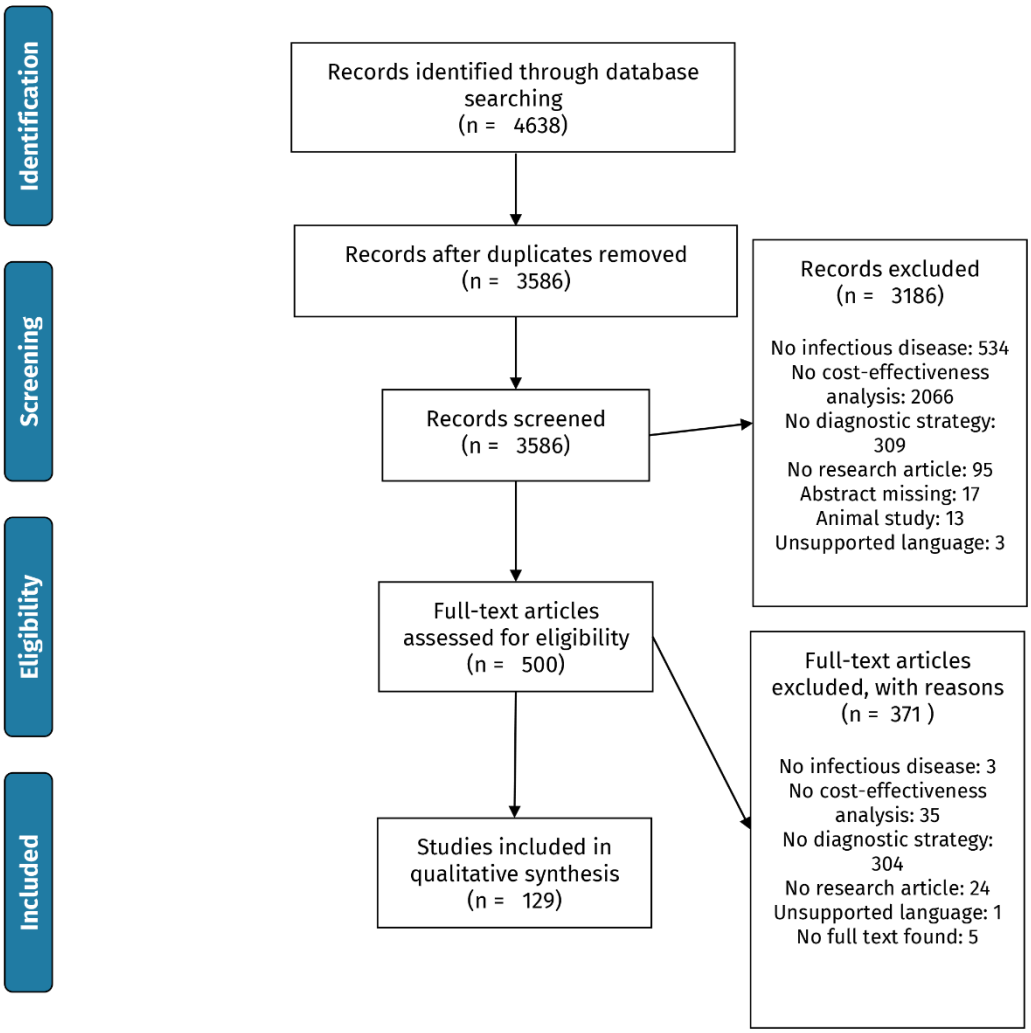

Figure 2 PRISMA flow diagram

3.2. Characteristics of included studies

This subchapter will first give a high-level overview of the economic evaluations of diagnostics that were included in this review, focussing on the modelling approaches used. The articles will be described more in-depth in Chapter 3.3, where the results for the specific disease areas are discussed.

3.2.1. Disease categories

Table 4 number of articles per disease category

	NUMBER OF ARTICLES
Respiratory tract infection	60
Vector-borne disease	16
Infections of the gastrointestinal tract	12
Sepsis	11
Urinary tract infection	11
Fungal infection	6
Sexually transmitted disease	6
Other	7

Table 4 shows the number of articles included per disease category. Almost half (60/129) of all studies deal with respiratory tract infections. From the other disease areas, 16 or less articles are included.

3.2.2. Chronology

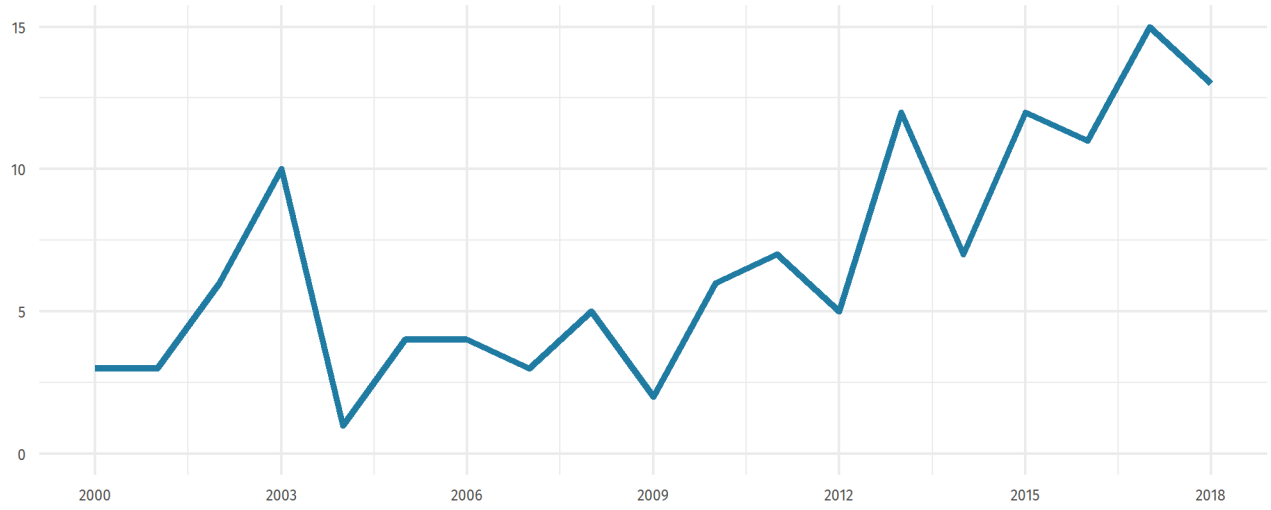

Figure 3 chronology of included studies

Figure 3 shows the number of studies included per year. A rising trend is visible, with three studies in 2000 and 2001, increasing to fifteen and thirteen in 2017 and 2018 respectively.

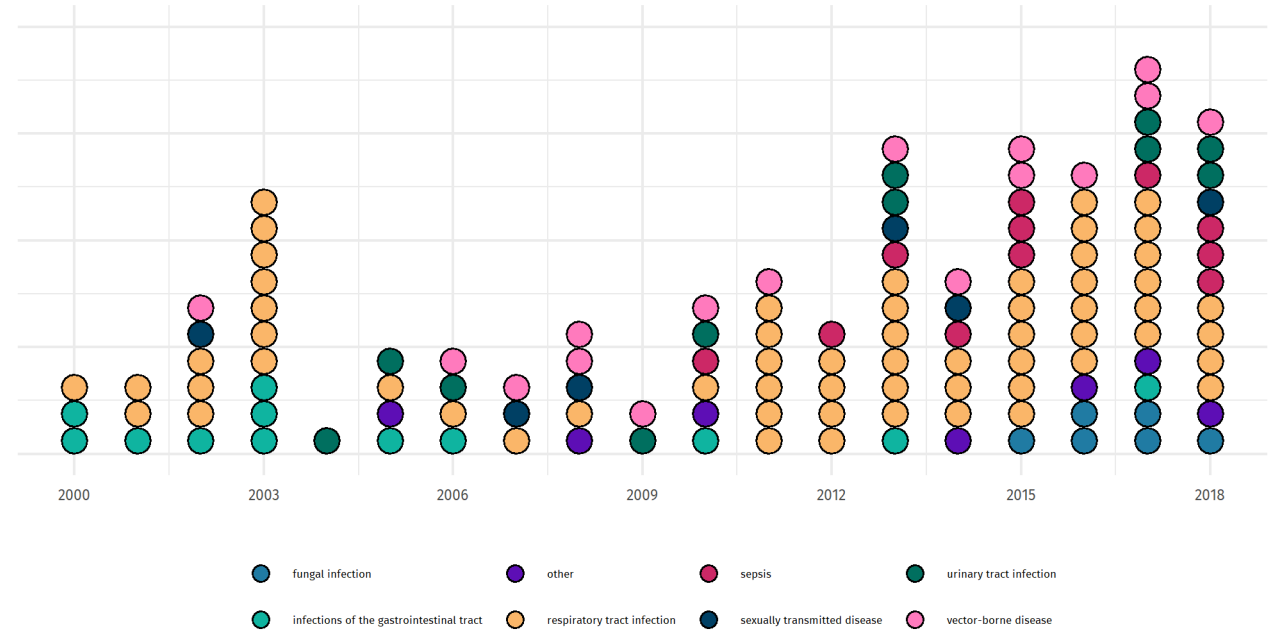

Figure 4 chronology of included studies, per disease category

Figure 4 shows the number of included articles per year per disease category. Over the years, the interests of specific disease categories have shifted: respiratory tract infections are a rather stable category, in most years accounting for half to two thirds of published papers. In the early 2000s gastrointestinal tract infections were a focus, for example focussing on helicobacter infections[26–31]. Papers focussing on sepsis became more popular towards the mid 2010s[32–37]. 2003 shows a relatively high number of articles compared to the surrounding years. This year was characterized for relatively many articles on gastrointestinal infections[38–40] and influenza[41–43].

3.2.3. General modelling approaches

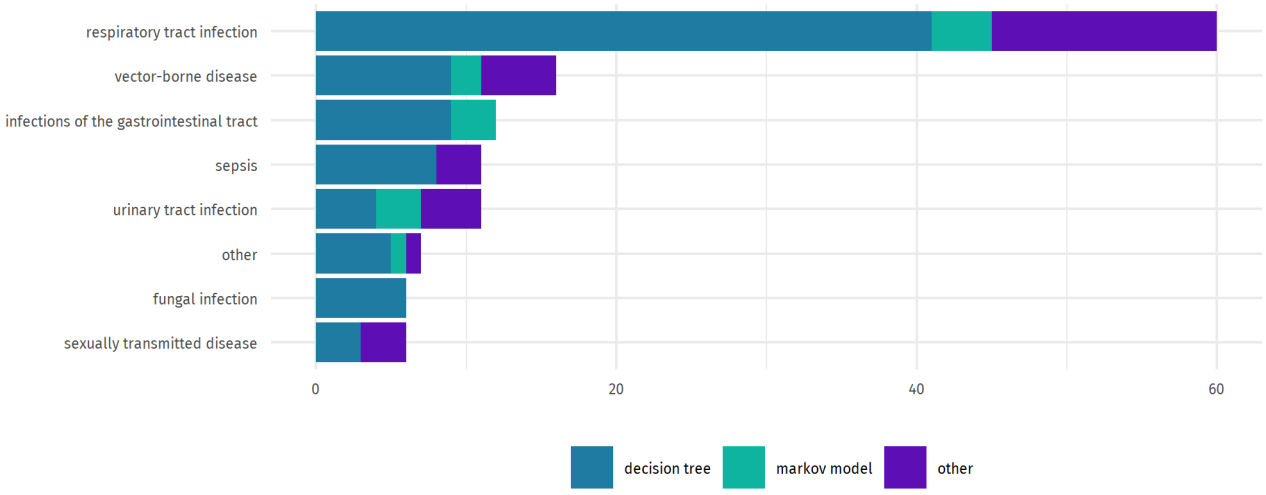

Figure 5 model types used for the various disease categories

Figure 5 shows the modelling approach taken for the different disease categories. Decision trees are the most used modelling approach, with 65% of papers using this approach. This varies between the disease areas however, for urinary tract infections, vector-borne disease and sexually transmitted disease, this percentage is lower.

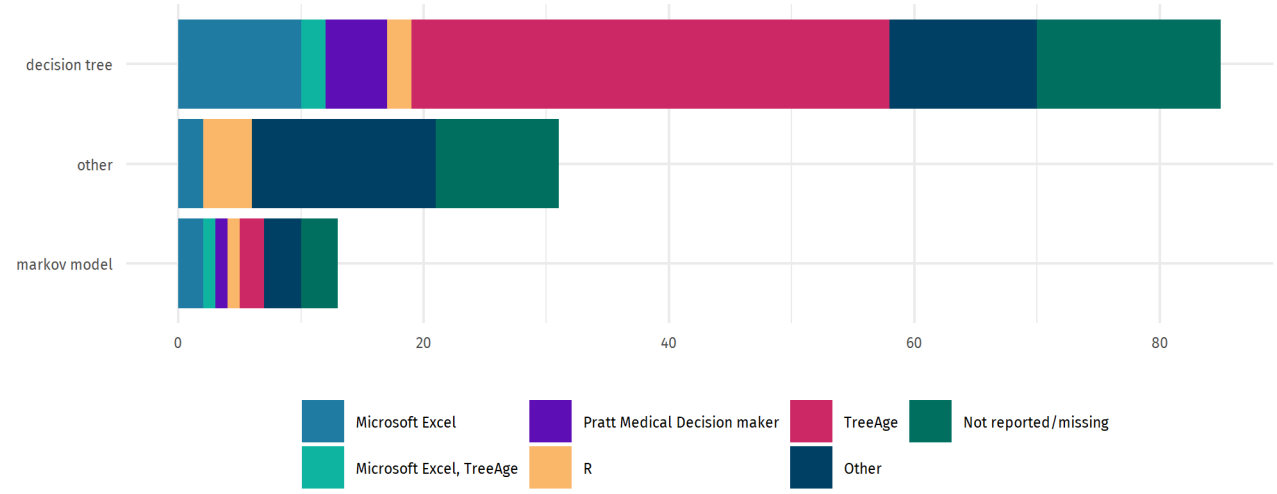

Figure 6 software used for model development

Figure 6 shows the software used to develop the various models. TreeAge seems rather popular to build decision trees: around 50% of decision trees are built with this package. This is interesting, as Microsoft Excel is generally regarded to be the most popular software for HTA model development[44], but is used in few papers assessing diagnostics (24/129). Many articles did not report the software used to perform their analysis.

Figure 7 shows whether the models were probabilistic or deterministic, about half of all decision tree models did not incorporate stochasticity, while over three quarters of Markov models did.

The time horizon considered for the included papers is shown in Figure 8. 45 articles did not clearly indicate the time horizon considered within the analysis; 32 articles used a time horizon

of less than one year. A lifetime horizon, now often recommended for national appraisals, is used in twelve articles.

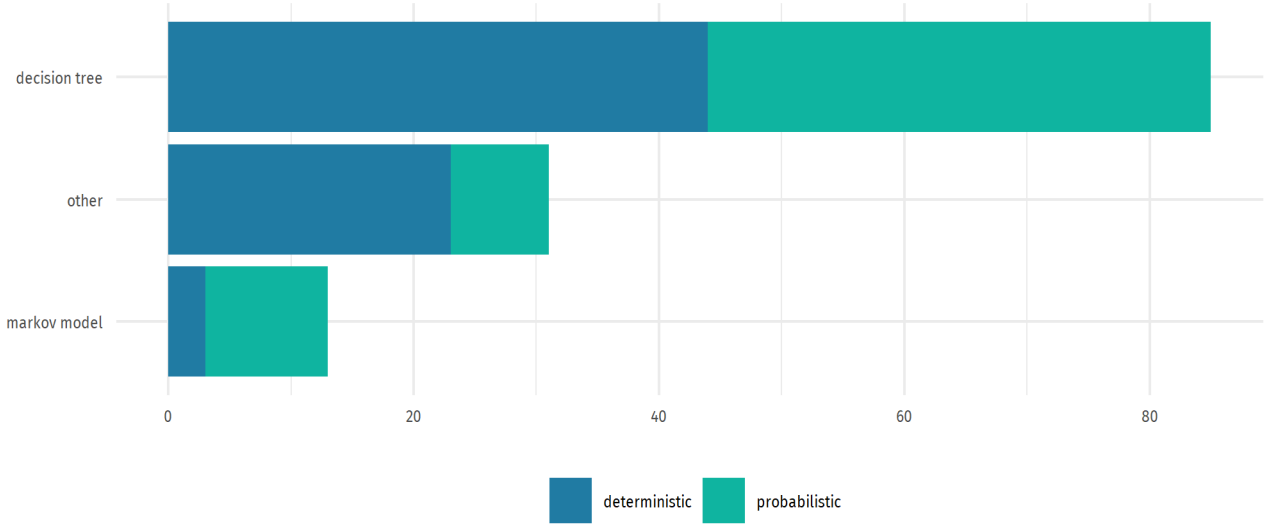

Figure 7 stochastic and deterministic models per model type

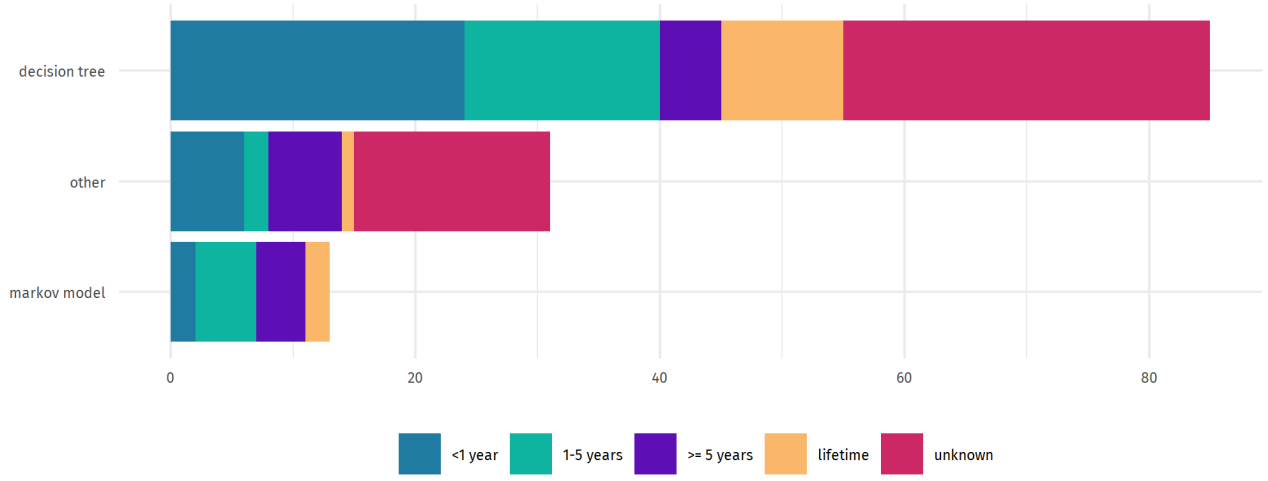

Figure 8 modelled time horizon for the various model types

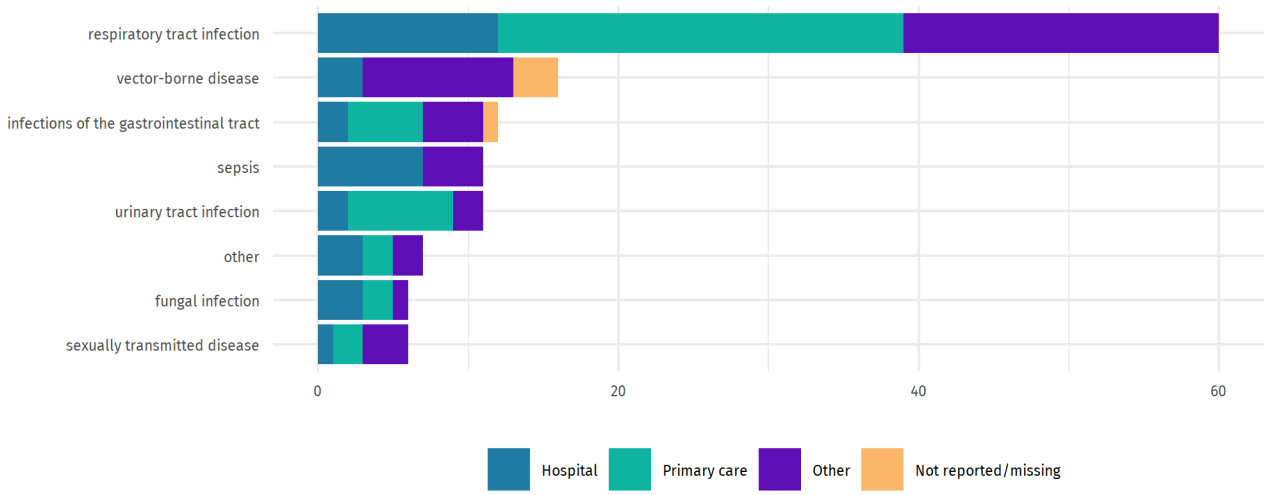

Figure 9 settings analysed for the different disease categories

The setting analysed in the included articles is displayed in Figure 9. The settings are quite different for the various disease categories. Sepsis is often assessed within the context of hospitals, while respiratory tract infections are more often assessed within primary care. Vector-borne diseases and tuberculosis (TB, part of respiratory tract infections) are more often relevant for Low- and Middle-Income Countries (LMICs), which more often include settings that are categorized as "Other".

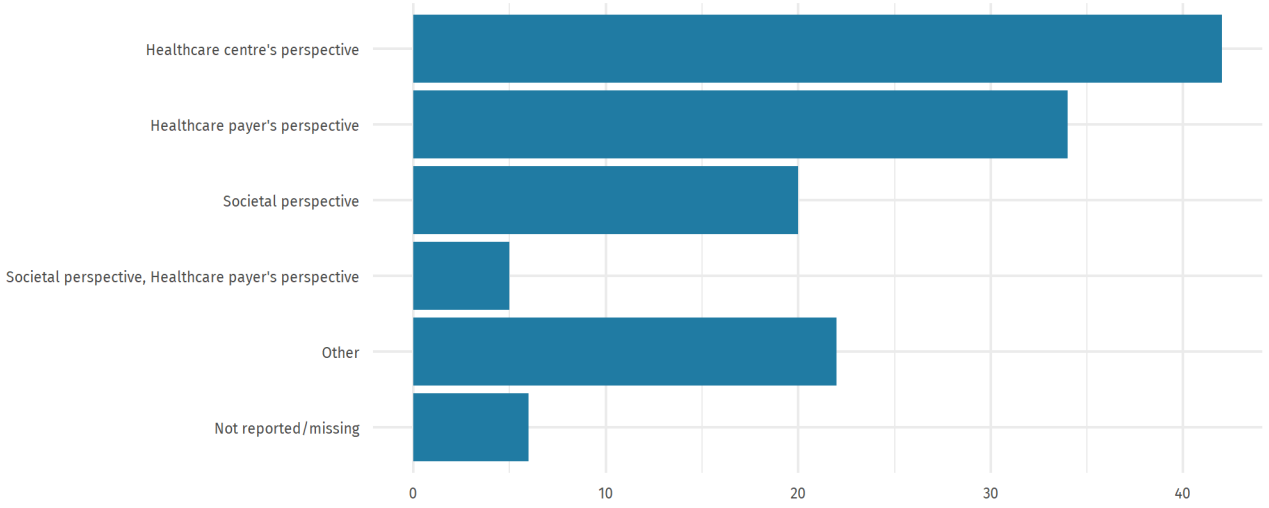

Figure 10 perspective reported for analyses

The perspective used for the analyses is shown in Figure 10, about one third uses the healthcare centre's perspective, followed by the healthcare payer's perspective. The healthcare centre's perspective assessed one healthcare centre, such as a single hospital, while the payer's perspective would be from the viewpoint of a healthcare system or insurer. A societal perspective is considered in about one sixth of all included articles.

3.2.4. Inclusion of antimicrobial resistance

Figure 11 shows the inclusion of AMR in the modelling. Most studies did not include this, and it seems AMR is most relevant in respiratory tract infections and sepsis. For fungal infections this is never considered, these infections are obviously not caused by bacteria. In vector-borne

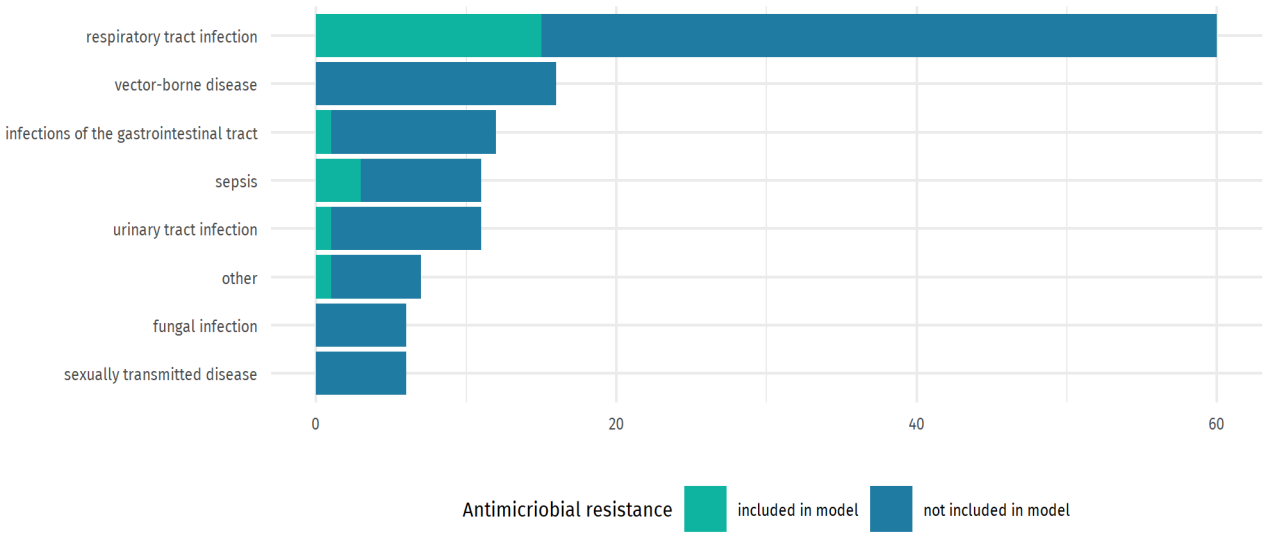

Figure 11 Inclusion of AMR in modelling work, per disease area

diseases, mostly malaria, the issue of resistance against treatment is discussed, but not modelled.

3.2.5. Outcomes

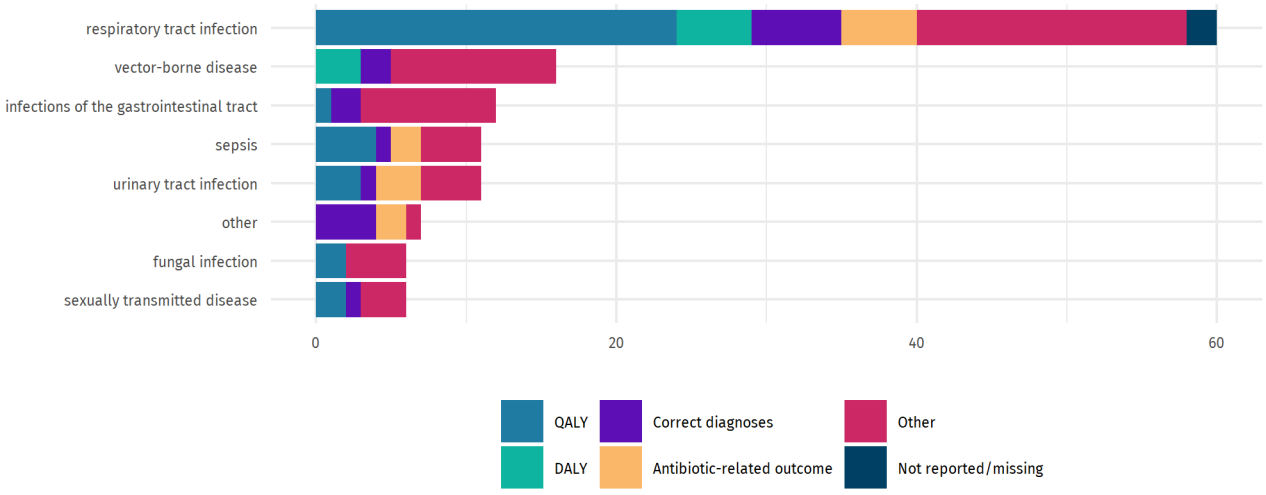

Figure 12 clinical outcomes considered

Figure 12 shows the clinical outcomes considered for the disease categories. Next to the standard DALYs and QALYs, we included specific categories for correct diagnoses and antibiotic-related outcomes (e.g. decrease in antibiotic prescriptions). There are many outcomes classified as "Other" and these can vary a lot, also depending on the disease considered. In Chapter 3.3 these other outcomes are considered for each of the disease categories.

Figure 13 shows the main conclusions reported by the articles. Around half of all papers report a cost-effective outcome, while almost a quarter of the included papers report a cost-saving result. Ten articles reported the diagnostic method not to be cost-effective.

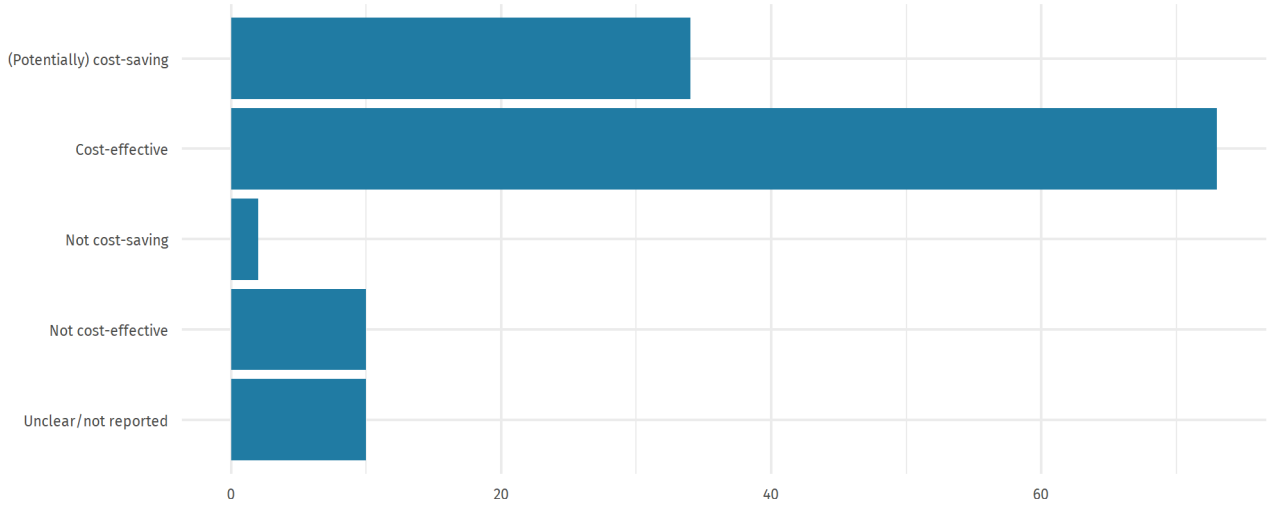

Figure 13 main conclusion reported

3.3. Disease areas

In this subchapter, we go in-depth to discuss the models and outcomes that were built for the various disease categories that were included in this analysis. Results from the data extraction from each individual study, are presented in Appendix II.

3.3.1. Respiratory tract infections

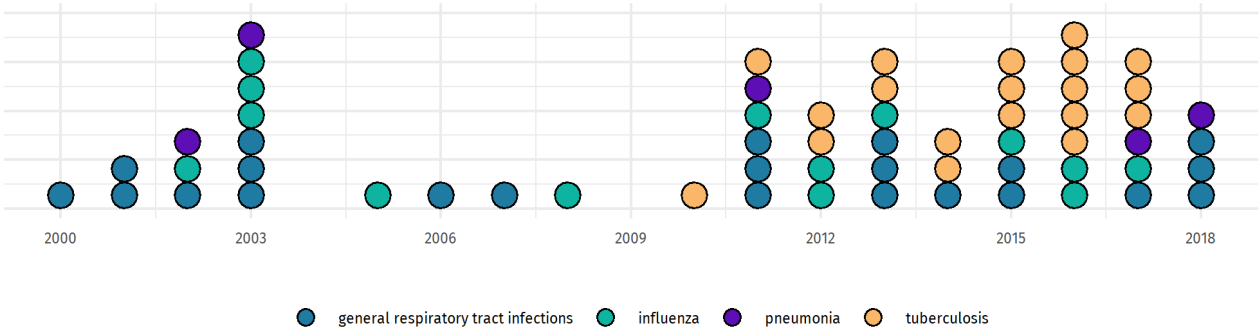

Figure 14 timeline of published respiratory tract infection models, per subcategory

First, we will discuss the models developed to diagnose several types of respiratory tract infections. As displayed in Figure 14, the number of articles has increased quite dramatically since the 2010s, as compared to the 2000s. This is mainly caused by the increase of TB models, which is mainly traceable to the introduction of the Xpert MTB/RIF test[45]. Five articles on influenza diagnostics were published in the period 2002-2005, three of which were written by the same team[41,42,46].

3.3.1.1. General respiratory tract infections

Twenty-two articles assessed the introduction of different diagnostic tests to detect general respiratory tract infections diseases in adults[14,15,47–58] or children[52,59–62] with symptoms of respiratory tract infection (for less than four weeks[49,63], for more than twelve hours[57], with cough[14,64], sore throat[65,66] or meningeal signs[61,62]) where the antibiotic decision was not clear. The setting most studied was primary care under a healthcare system perspective[14,47,48,50,53,56,65], a healthcare payer`s perspective[15,52,55,57,60,64] or a societal perspective[49,51,59] followed by the hospital

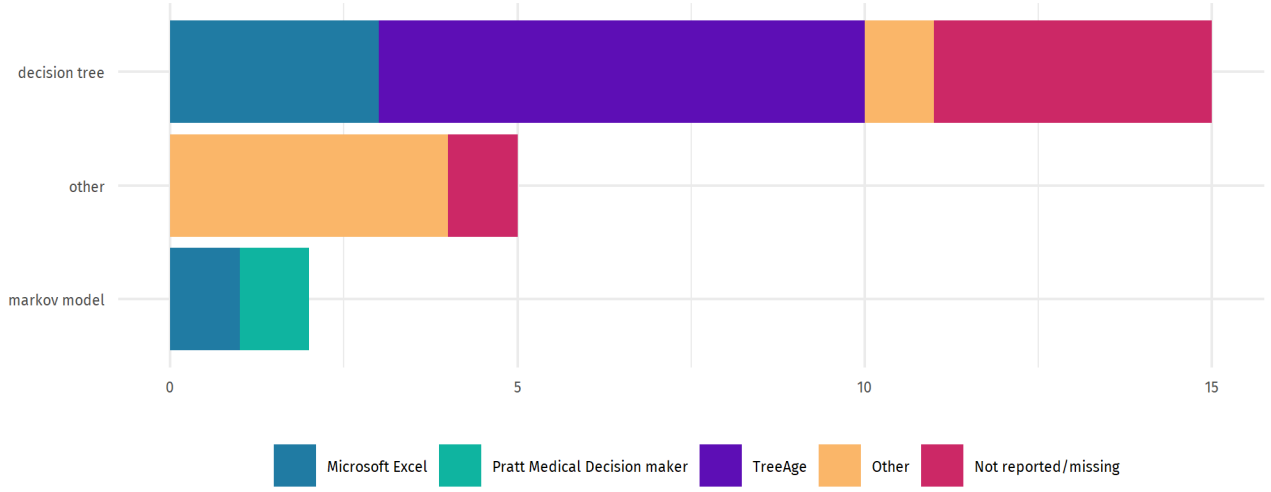

Figure 15 model types for general respiratory tract infections

setting with a healthcare centre's perspective. Country-specific assessments were performed for eight countries: the United States[50,51,53,54,59], the Netherlands[48,61,62,64], Spain[47,60], Switzerland[65], Canada[66], Uganda[58], France[52] and the United Kingdom (UK)[63]. Two articles included more than one country: Norway and Sweden[14] and Belgium, the UK, the Netherlands, Poland and Spain[15].

Tests differ from each other by the type of result yielded (quantitative or qualitative outcome). The tests studied in each article had a chronological component; they appear in the literature, around the moment they were fully available for clinical practice. In this sense, the four oldest articles[47–50], published from 2000 to 2003, studied the incorporation of simple radiography and ultrasound techniques. The following five articles[51,52,59,60,65] published from 2003 to 2011, studied the rapid detection test for group A *Streptococcal*. This test yields a qualitative result, which identifies infection cases and allows for rapid antibiotic treatment. Four articles[53,54,56,58] assessed the procalcitonin test (PCT), published from 2013 to 2017. One article[63] published in 2014 studied the Polymerase Chain Reaction (PCR) test, used to differentiate between influenza A and B. Influenza A is the most prevalent and is associated with serious epidemics, whereas type B is associated with milder health consequences. In case of influenza detection, antiviral treatment is prescribed and for bacterial infection, antibiotic treatment. From 2011 to 2018, five articles studied CRP testing[14,15,55,57,64]. This test yields a quantitative result (in mg/L) and as in the NICE protocol[67], it guides the clinical decision as follows: in case of a low result, do not prescribe antibiotics, in case of a medium result, delay prescription and, in case of a high result, prescribe antibiotics.

With a decision tree model, authors assess the economic and clinical results of different diagnostic strategies, known as "arms". In the most simple model, a "rapid test" strategy and a "usual care" strategy were compared[47,51,53,54,56,57,61]. However, some authors included in the decision tree other types of strategies such as a "clinical scoring strategy"[52,59,60,65] or a "deferred prescription" strategy[48,57]. See also Figure 15 for an overview.

The "clinical scoring" strategy is based on clinical observation (e.g. fever >38.8ºC, pus in nasal cavities, etc.). When the patient presents one of these symptoms, a point is given. Patients with a low score were neither tested nor treated and those with a high score were always treated with antibiotics. Thus, the test was only applied to patients with a middle score because there was a suspicion of a bacterial infection. Conclusions showed that in three[52,60,65] of the four articles the "clinical scoring" was the most cost-effective strategy as it dominated the rest of strategies. In one article[59], in which the scoring strategy was not cost-effective, the authors argued that it was because a "culture to all patients" strategy was included (in this reimbursement setting, performing a throat culture for all patients with pharyngitis has the best cost-utility).

In the "deferred prescription" strategy, patients were advised to take analgesics for pain symptoms, and they were asked to return for antibiotic prescription if there was no improvement after one week. This was the most cost-effective strategy and the authors[48,57] concluded that further testing did not improve health outcomes.

Decision tree models have some advantages for the evaluation of the introduction of a diagnostic test. They enable representing the real clinical patterns[57] and can be applied in different groups of patients (adult population and paediatrics)[52]. Also, they can take into account test cost variations[57,64], different clinical settings[54], the incorporation of new clinical strategies[60] and all possible outcomes of the patient[51,60]. In this sense, some models[52,57,59,60] included an alternative treatment, which broadens the spectrum of antibiotics, if the first antibiotic did not succeed and the patient undergoes an adverse reaction. Four articles modelled the impact of AMR, assuming that the value of an antibiotic prescription safely avoided equals the cost of antibiotic resistance[53,54,56,57].

The main reason provided to justify the choice of a decision tree model was that this was the most appropriate method to select when working under uncertainty conditions and considering a short period. In fact, the time horizon of the previous decision tree models did not exceed one year: 7 days[48], 28-30 days[54,56,57,64], one year[60] and number of days from the beginning of the treatment to the final recovery. In three articles[52,59,65] the time horizon was not explicitly mentioned. In order to extend the time horizon (from short to long term) in an article[55] the decision tree model led to a Markov model, in which after performing the test and prescribing the appropriate treatment, the patient could go to either a "be healthy" or "suffer complications" state. In another article[49] a Markov model was used to simulate possible transitions of the patient`s health such as "continue being sick", "serious complication" or "cured".

EXAMPLE DURSKI *ET AL.*

Three strategies for general respiratory tract infections were compared using decision trees

Comprehensive testing, all available diagnostic tests were ordered simultaneously by the clinician and the laboratory ran all diagnostic tests simultaneously. This resulted in 93.3% correct diagnoses, costing $32.00 per patient

Stepwise testing, where the number and order of test were limited, prioritizing tests with high sensitivity for the most prevalent diseases. This yielded 93.8% correct diagnoses, for on average $9.72 per patient

Minimalist testing, where the number and order were limited to high-yield tests only, eliminating tests with poor sensitivity/specificity. 91.1% was correctly diagnosed, costing an average of $6.17 per patient.

The conclusion was that strategically choosing the order and type of testing was most efficient.

Another method used was a regression model with a time horizon of 28 days[14,15]. It was used in analyses where more than one country was analysed: Norway and Sweden[14] and Belgium, the UK, the Netherlands, Poland and Spain[15] (as part of the Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infections in Europe, GRACE). Its main advantage was the wider applicability and it can incorporate into the model as many variables as considered relevant by the author (e.g. cost and quantity of antibiotic prescription, price of the test and enhancing communication skills of the GP). Different results were obtained in each country: improving the communication skills of GP through training courses was the driving variable to reach a cost-effective intervention in Spain and Poland, whereas performing a rapid test had more impact in Belgium, the UK and the Netherlands.

Software used to develop the models (Figure 15) were TreeAge[48,51–53,58–60,64], Microsoft Excel[54–57], Pratt Medical Decision maker[49] and WinBUGS 1.4.3 (MRC Biostatistics Unit)[63]. The ICER was mainly expressed as costs/QALY[51,57,59,61,63,68], cost/prescription of antibiotic saved[14,53,57,64,68], cost/patient[47,48,50,54,62,65,66] and cost/correct diagnosis[58]. Oppong *et al.*[68] found that communication skills training was the most cost-effective strategy since it dominated all other interventions in Belgium, the UK and the Netherlands and testing was only cost-effective in the Netherlands if the threshold was €27,000 per QALY gained. Giraldez-Garcia *et al.*[60] pointed out that the most cost-effective method for the diagnoses of pharyngitis was the "clinical scoring + rapid test" strategy of the six strategies analysed. This relationship held up under all conditions studied in the sensitivity analyses except when the clinical scoring sensitivity was <91% and its specificity was ≤9%. In this case, the "rapid test" strategy became the most cost-effective. Michaelidis *et al.*[53] found that testing was unlikely to be preferred over usual care when costs alone were considered, but was likely to be cost-effective when the costs of antibiotic resistance were included and the test was used only in patients judged to require antibiotics by their physicians.

In conclusion, except of the previously indicated articles, which include a "clinical scoring" strategy[52,60,65] or enhancing GPs' communication skills (in some countries)[15] the rest of the studies concluded that the incorporation of a rapid test in the clinical practice for the diagnosis of general respiratory tract infection diseases was cost- saving[49,50,54,56] or /and cost-effective[14,15,47–49,51,53,55,57,59,63,64]. This result depends most on the cost of the rapid test[15,49,53,59], the sequence of application when different test are available[58], test accuracy in terms of specificity and sensitivity[60], the cost of antibiotic resistance or side effects[52,53,59] and the prevalence of the disease[49].

3.3.1.2. Influenza

Fourteen papers explicitly assessed diagnostics for influenza[41–43,46,69–78]. The most-researched country is the United States, with eight assessments[41–43,46,69,71,72,76], followed by three for China (including Hong Kong)[74,77,78], and one for the UK[75], Canada[73] and Mexico[70]. Eleven papers assessed the outpatient setting[41–43,46,70,71,73–76,78] and four the hospital or emergency care settings[69,72,73,77] (one assessed both[73]). The population in most articles consisted of patients presenting with influenza-like illness (ILI)[41–43,46,69–72,74–78], although characteristics such as the age category or vaccination status were specified in many cases as well. One study included a population model of a whole

EXAMPLE
NSHIMYUMUKIZA *ET AL.*

This study compared an RDT followed by antiviral treatment to empiric antiviral treatment, for the whole of Quebec, a Canadian province. The model consisted of two parts:

An SIR model was used to model influenza transmission. Using three differential equations, three states were modelled: susceptible, infected and recovered using single-day cycles. The authors assumed homogenous mixing, meaning influenza spreads at random.

The economic analytical model was used to simulate infected persons, which could remain asymptomatic and did not seek medical care; a fraction of symptomatic people was modelled not to consult a physician (they did not feel very sick). Patients who did seek care, within 48 hours, received oseltamivir, reducing the probability of complications such as pneumonia and death.

The authors concluded that the testing strategy was dominant (less deaths and less costs) compared to empirical antiviral treatment.

Canadian province (Quebec)[73]. In some articles the exact strain of influenza was specified [70,71,77] and/or virus type (Influenza A and B)[41,46,70,71,73,77,78].

The strategies compared in most articles are both a specific diagnostic method in combination with antiviral treatment. The diagnostic tests are not specified in all articles, but the most common specified diagnostic method seems to be the Quickvue® (Quidel Corporation, San Diego CA, United States), which was specifically mentioned in three articles (all by Rothberg *et al.*)[41,42,46], while other articles specifically mentioned a PCR-based test[69,70,72,77]. All papers included antiviral treatment, the majority specified oseltamivir[41,42,46,69–71,73–78]. Five papers also included antibiotic treatment[42,43,46,69,72]. In seven analyses empiric antiviral treatment (i.e. not performing any RDT) was included as well[43,69,71,74–77].

Thirteen articles used a decision tree to model the cost-effectiveness[41–43,46,69–72,74–78] and one used an agent-level Markov model combined with a dynamic deterministic model[73] (see also Figure 16). Most decision trees incorporated three basic strategies: no treatment, systematic treatment and test and treat (based on the test result), which were the first branches of the tree. The next branch was the decision to treat or not to treat (most often with oseltamivir). The following branch incorporated whether a patient has influenza, with the final branches assessing the complications following this disease.).

The most-used perspective is the societal perspective[41–43,46,69,71,73,76], followed by the healthcare centre's or provider's perspective[60,72,77,78]. A lifetime horizon was applied in six models[41,46,69,72,77,78] 1 year in two [71,73] and the duration of an illness episode in another two[43,76]. Three articles did not report a time horizon[70,74,75]. Due to the small time horizon, no discount rate was reported for a majority of articles[41–43,46,70,71,73,74,76]. Most models were stochastic[41,46,69–73,75–78] and (in part) developed using TreeAge[43,69,71,76–78]. Viral resistance to oseltamivir is included in one model, as a percentage[71]. The clinical outcome assessed in most articles is the QALY[41,42,46,69,71,72,74,75,77,78], and three papers assessed an outcome related to the duration of the disease[43,70,76]. Most papers included a thorough description of the model[41–43,46,69,71,73–78]. See also Figure 17 for an overview of the influenza model characteristics.

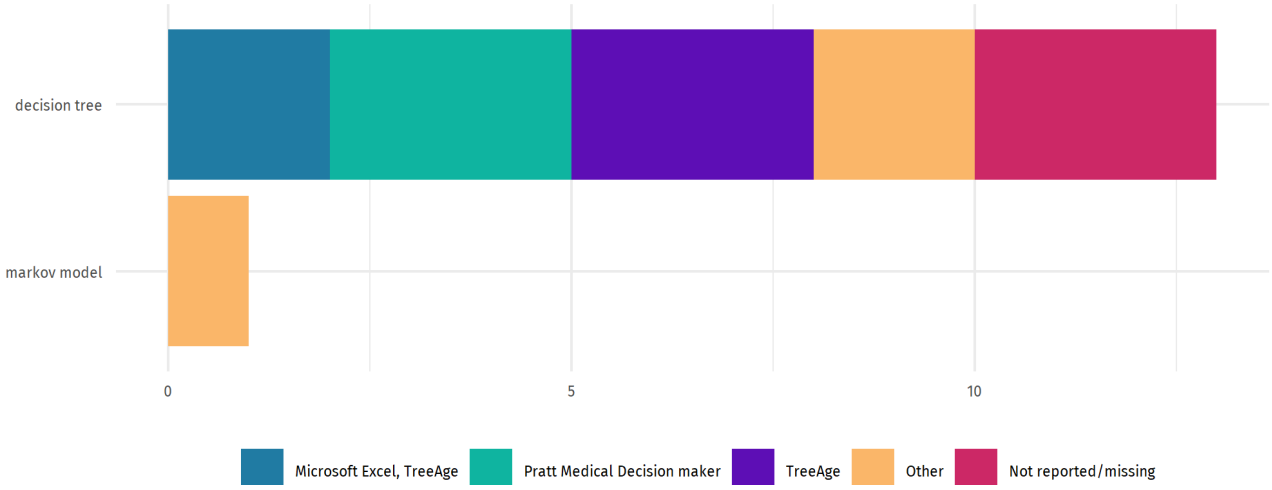

Figure 16 model types for influenza

Most papers reported an ICER as the cost/QALY[41,46,69,71,72,74,75,78]. Other incremental outcomes reported were the amount saved for each suspected case[70], amount saved per 100,000 person years[73], amount saved or invested per averted influenza day[43,76] and stockpiling costs[75]. The outcome is highly dependent on the setting and population in which the test is performed, only considering the US-based Cost-Utility Analyses (CUA) in emergency care, the ICER values range from $1389/QALY[69] to $228,000/QALY[72] (both 2011 USD). Uncertainty was explored in all papers, most often using a Tornado diagram[69,73–76,78] and/or a Cost-Effectiveness Acceptability Curve (CEAC)[69,71–73,76–78].

The main findings also often incorporated the dependency on the influenza prevalence; testing was mainly considered in the influenza season[41–43,69,71,74,75,77]. In some studies, the incidence was also included in sensitivity analyses, often as a proportion of patients with ILI symptoms that had influenza[41–43,46,69,72,74–78]. This uncertainty regarding the number of ILI patients that have influenza, is described as a limitation in some papers[69,70,74]. Other reported uncertainties deal with the influenza transmission rates and the effect of rapid diagnostics on this[43,71,78], development of antiviral resistance[43,46,69,71,75], vaccination coverage[41,42,71,74] and ADRs from antiviral treatment[42,43,73,77]. In the conclusion, the majority of studies reported that the diagnostic intervention was cost-effective or cost-saving[41–43,69–73,78]. Considering the generalizability of these studies, this conclusion is specific to the regions and populations for which the analysis was performed.

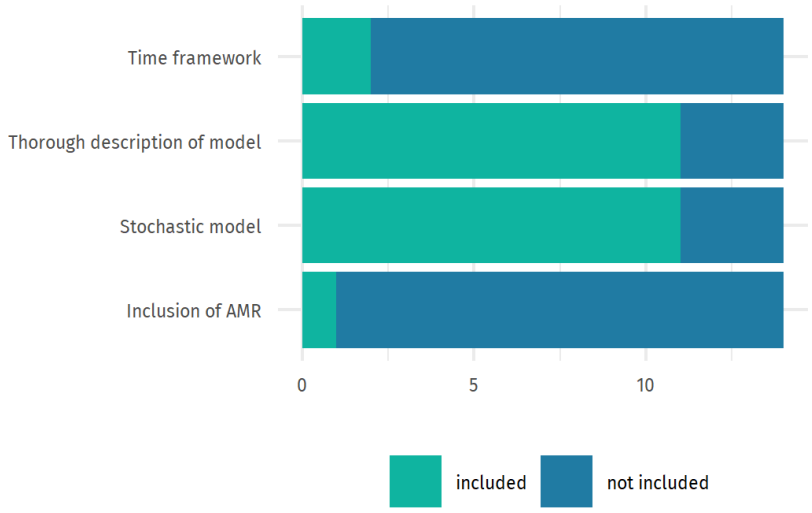

Figure 17 overview of model characteristics for influenza

3.3.1.3. Pneumonia

Five articles assessed diagnosis for pneumonia[79–83] in Germany[79], France[80], South Africa[81], the United States[82] and Canada[83]. Two papers studied the hospital setting[79,83] and one an emergency department[80], intensive care unit[82] or primary care[81]. The population of the studies focused mainly

on hospitalized patients [79,82,83] or who consulted with community-acquired pneumonia[80,81]. Some of the pathogens studied were *Streptococcus pneumoniae*[80,83] and *Pneumocystis jiroveci*[81].

The strategies compared consisted of usual care and a diagnostic test such as PCR-based test[81], mini bronchoalveolar lavage [82], inquaro[79], pneumococcal urine antigen test[80] and BinaxNOW™ *S. pneumoniae* Antigen Card[83]. Three articles also included a culture strategy[81–83]. All articles included antibiotics as treatment in case of positive result. Furthermore, three articles considered two kinds of antibiotic treatment in case the test detects a specific pathogen. In this sense, Böhmer *et al.*[79] considered eight antibiotics agents from levofloxacin to doxycycline. Dinh *et al.*[80] pointed out that if *S. pneumoniae* was detected, penicillin A was prescribed and if no microbiological identification was achieved the treatment was based on broad-spectrum antibiotics. Ost *et al.*[82] also considered that if pathogens were identified, treatment would be adjusted to cover the identified pathogen and unnecessary antibiotics would be discontinued.

Three papers assessed the cost-effectiveness of the strategies, two used a decision tree model (one with a stochastic approach[83] and the other deterministic[82]) and in one paper[81] the model type was not explicitly declared. Two papers also performed a cost analysis[79,80]. The most used perspective was the healthcare centre's[79,80,82,83] followed by the healthcare payer's perspective[81]. All time horizons were shorter than one year; thus, no discount rate was applied. Two articles included the bacterial resistance into the models by taking antibiotic use as a cost, in terms of promoting antibiotic resistance[82] and assuming that the rapid diagnosis could help reduce the antimicrobial spectrum because streptococcus pneumonia, the main bacteria involved, is susceptible to penicillin A[80]. To perform the analyses SPSS[80], OpenBUGS[83] and TreeAge[82] were used.

Some ICERs were based on savings/year[80], cost/LYG[81], cost/antibiotic used[80] and cost/case correctly identified[83]. The main findings showed that tests should be used only for patients with suspected infection[80] and its cost-effectiveness depend on the proportion of the total diagnostic and treatment cost[81]. In Böhmer *et al.*[79] improvements were found in terms of fewer infusions, faster symptom resolution and a shorter length-of-stay, with savings for the hospital and insurance providers. All of the diagnostic strategies were cost-effective[81–83] or cost-saving[79,80]. Uncertainty was studied with deterministic sensitivity analysis[81–83]. As limitation, it was argued that performing the rapid test depended on physicians and could vary from a physician to another, which could not be entered in the model[80] and indirect costs were also not included (buildings, equipment, and technical know-how needed to carry out more advanced molecular diagnostics)[81]. In Ost *et al.*[82] if test yielded a negative result it was better to stop antibiotic treatment, however, practice physicians did not consider this option, although it would yield favourable results. Results cannot be easily generalized worldwide, as there are fluctuations regarding resistance, patient population and diagnostics and therapy[79].

3.3.1.4. Tuberculosis

Nineteen papers assessed the use of diagnostics in TB[84–102]. Most studies dealt with specific LMICs: Kenya[86,101], South Africa[89,92,93,97,98], Uganda[95,98,99], Tanzania[90], Mozambique[100], Lesotho[92], Namibia[92], Botswana[92], Swaziland[92], Brazil[94] and India[96,98]. One study looked at generic 'resource-limited countries in sub-Saharan Africa[84]. Studies in high income countries are from Singapore[85], the US[87], Spain[88], England[91] and Hong Kong[102]. Nine studies were assessing the cost-effectiveness of diagnostics within in a clinic or hospital[85–88,95,96,98,101,102], seven within primary care[84,86,94,95,97,99,100] and three within a laboratory[89,90,93]. The assessed population in most studies are TB-suspected patients[85–90,92–100,102], with some making a distinction based on the HIV status[84,90,95,99] or the presence of cough for a certain period of time[86,97,101].

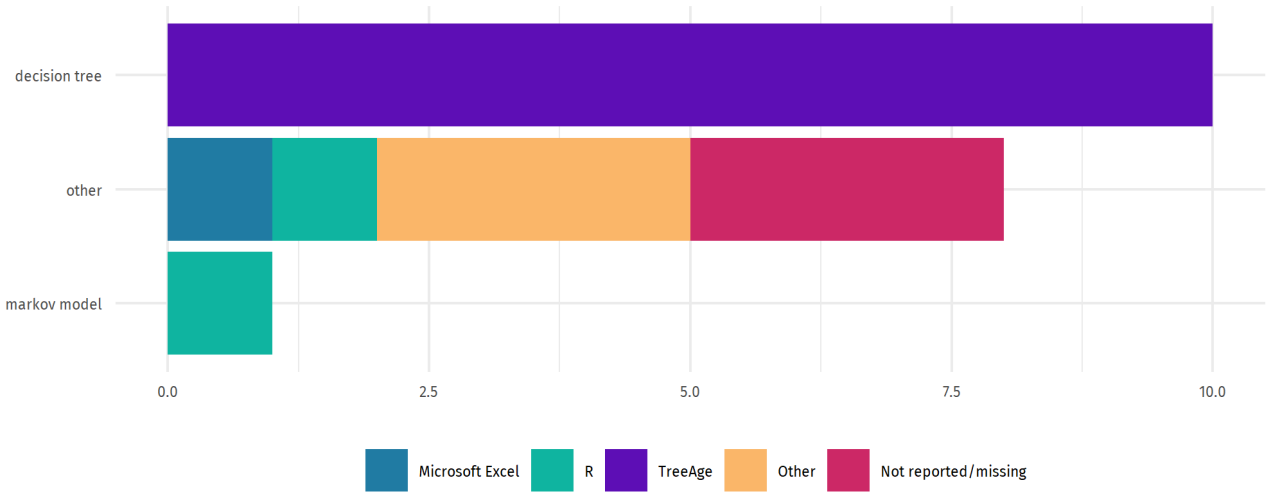

Figure 18 model types for tuberculosis

In many studies, the main considered diagnostic method was the Xpert MTB/RIF test, which detects *Mycobacterium tuberculosis* and resistance to rifampin[45]. In 2011 the WHO TB guidelines were updated to include Xpert[84]. A total of fifteen studies[84,87–90,92–100,102] included an Xpert-based strategy. A frequent comparator to Xpert was bleach smear microscopy, included in fifteen studies[84,86,87,89,90,93,95,97,98,100,102], often as a component in a more elaborate diagnostic algorithm. TB therapy was not specified in many articles, although in some cases a distinction was made between drug-susceptible and drug-resistant TB[88–90,95,96,98,102]. One study made a distinction between early and late treatment[102], some studies detailed the treatment regimen in full detail[91,98].

Decision trees were the most common type of model, included in ten articles[78,84–88,94,95,98,99] (all developed using TreeAge), two studies used a dynamic model[91,92] one study used a discrete-event simulation, combined with a dynamic model[90], one a dynamic microsimulation model[96] and one a Markov model[100]. Four articles used other means of assessing the cost-effectiveness or did not fully describe the model[89,93,97,101]. See Figure 18 for an overview of model types and software used.

The healthcare provider's perspective was used in seven studies [86–88,99–102], the healthcare payer's perspective in five [89,90,92,95,98] and the societal perspective in one[96]. The assessed outcomes were QALYs in five studies [85,88,91,96,102], DALYs in five studies[90,92,95,98,100] and number of (correct) TB diagnoses in seven studies[86,89,93–95,98,101] (see also Figure 19). The clinical outcomes came from a single study in eight models[85–87,89,93,95,97,101] and were synthesized from several studies in eleven models[84,88,90–92,94,96,98–100,102]).

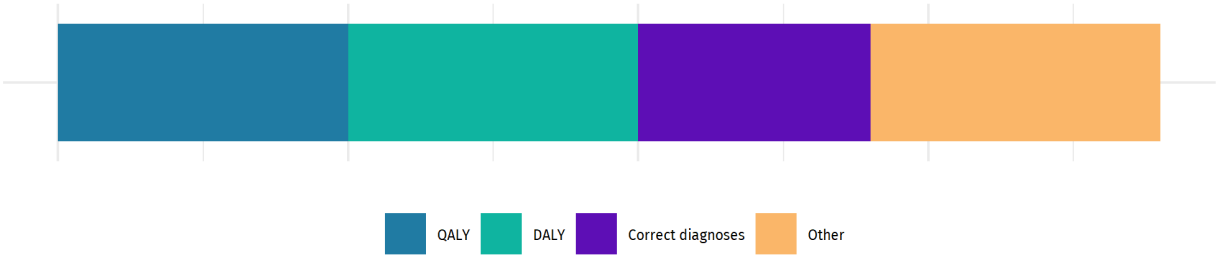

Figure 19 primary clinical outcomes considered for analysis (tuberculosis models)

Bear in mind that some papers reported several outcomes, in which case the main outcome is displayed here

The decision tree structure of the papers that used this method[78,84–88,94,95,98,99], were quite similar. In some papers, the various diagnostic options were included as separate branches after the first node, followed by the test results[84,85,88,95,98], in one article the true and false positives and negatives were explicitly stated[85]. Four articles[87,94,99,102] used a different approach, where the first branch after the decision on which diagnostic to use, was whether the patient had TB, including in one article whether it was of a resistant variety[102]. In most articles the final branch was the treatment strategy to be followed[85–88,95,98]. In some articles, complications, such as survival or death were modelled as well[85,102]. The four dynamic models[90–92,96] all modelled a certain population of TB susceptible persons and the resulting complications after an infection occurs (active TB infection, latent TB infection, recovery) using compartmental differential equations. Two papers reported monthly cycles[92,96], while one reported weekly cycles[91]. For the UK situation, Mears *et al.* also included contact tracing in their analyses[91]. Two models also considered HIV status of the modelled individuals[90,92]. Langley *et al.* used a discrete event simulation to be able to model the patient and sputum samples pathways in more detail within a typical Tanzanian diagnostic centre[90]. This detailed model was linked to the before mentioned dynamic transmission model[90]. A Markov model approach was used in one article, in which the risk of TB infection was dependent on the prevalence of TB[100]. One study primarily used a costing tool to assess the cost-effectiveness, which considered unit costs to compare Xpert to a smear-culture based strategy[93], this analysis did not include patient outcomes however[93].

There were five studies that considered the African setting and reported DALYs[90,92,95,98,100], all of which also incorporated Xpert. For the Xpert strategy, the cost-effectiveness was in the range of $37/DALY for Uganda at $27.55 per Xpert test (both 2010 USD)[98] to $784/DALY for Southern Africa, without a specified country at an Xpert cost of $20 (both 2011 USD)[92]. In general, there are large differences between results, depending on the country, diagnostic algorithm and considered outcome. A limitation mentioned in several articles, is the lack of transmission modelling or, if transmission was modelled, improvements thereof, which is expected to improve the cost-effectiveness, due to a reduction in TB incidence[87,90,95,96,98]. Some studies also mention general long-term effects that are not included in the analysis[89,92,102]. Patient costs were not included in most included studies, yet they may be very important for diagnostics uptake in LMICs – this limitation was included in two articles[86,98]. Uncertainties surrounding resistance

EXAMPLE
HOLLINGWORTH *ET AL.*

The authors estimated the cost-effectiveness of a two-step clinical rule using symptoms, signs and dipstick testing to guide the diagnosis and antibiotic treatment of urinary tract infection in young children presenting to primary care.

A **short-term decision tree** models testing and treatment during the index consultation. The acute illness phase is handled by a nine-state Markov model estimating the time taken to recover (maximum 21 days).

Another **Markov model** is used to calculate the number of recurrent UTIs and PAs in the 3 years after the index consultation.

Finally, a **lifetime decision tree** models the impact of renal scarring in the earlier phases on the model, which is an important risk factor for long-term, potentially life-limiting renal complications such as end-stage renal disease.

Compared with GPs' clinical judgment, the clinical rule could substantially reduce urine sampling, achieving lower costs and equivalent patient outcomes.

prevalence was mentioned in several articles as well[87,90,94]. Interestingly, one study considers the lack of modelled resistant TB transmission an underestimation of the cost-effectiveness[90], as Xpert will enable a reduction in resistance on the long term. Another study hypothesizes that the improved detection of resistant TB will increase treatment costs[94], without mentioning the longer term. Although two out of nineteen papers included HIV status in their modelling[90,92], three other papers mention the lack of this as a limitation[89,94,99].

A diagnostic strategy was assessed as being cost-effective in thirteen articles[84–90,95,96,98–100,102] and cost-saving in one[97]. This indicates that in many settings Xpert can be considered cost-effective, although some papers question the affordability in resource-limited settings[89,92,93,98,99,101]. This may be a result of the system changes that may be needed to implement novel diagnostics in the healthcare system[84,98,99].

3.3.2. Urinary tract infections

Eleven articles assessed diagnostics for urinary tract infection, four in the Netherlands[103–106], four in the United Kingdom[107–110], two in the United States[111,112] and one included different countries; England, the Netherlands, Spain and Wales[113]. Nine papers studied the primary care setting[103,106–113] and two the hospital setting[104,105]. The population of the studies focused mainly on women visiting their GP with painful or frequent micturition that had been present for no longer than seven days[103,109,111–113], children with complaints of any acute illness episode associated with at least one potential marker for urinary tract infection[107,110] and men attending genitourinary medicine services[108]. Specific pathogens studied were *Legionella*[104], *Trichomonas vaginalis*[112] and *Mycoplasma genitalium*[108].

The strategies compared consisted of usual care and a diagnostic test and if positive antibiotics (nitrofurantoin[103], penicillin monotherapy[104], amoxicillin[107] or quinolone treatment[111]). Diagnostic tests used in this area of disease were: dipsticks[103,106,108–110], flexicult tests[113], urinary antigen tests for *Legionella*[105], PCR testing[104], pH testing and gram's stain for *Bacterial vaginosis*[112]. Some articles also included cultures[107,110–112].

Nine papers assessed the cost-effectiveness of the strategies, six used a decision tree model (one with a deterministic approach[111]) and in two papers[107,110] the decision tree was followed by a Markov model. One paper included a standalone Markov model[106], in another a comparison of clinical groups were performed[109] and in another one the type of model was not declared[113]. Two papers performed a deterministic cost analysis[104,105]. The most used perspective was the healthcare payer's[103,106–111,113] followed by the healthcare centre's perspective [104,105] and the societal perspective[112]. In three articles time horizons were shorter than one year[103,111,113], thus no discount rate was applied. In other articles the time horizons were 3 years[110], 7 years[104], 20 years[108] all with a discount rate (outcomes and costs) of 3.5%, 30 years[106] with a discount rate of 4% and one used a lifetime horizon with a discount rate of 3.5%[107]. Three articles did not explicitly declare the time horizon[105,109,112]. One article included AMR, by considering that when the rate of resistance increases, the percentage of patients failing empiric therapy also increases[111]. Software used to model the analyses were Microsoft Excel[109,110], Pratt Medical Decision maker[111,112] and STATA[107].

Some papers reported an ICER of cost/correct diagnosis[103], cost/antibiotic prescription saved[113], cost/symptom days avoided[111,112], cost/positive result[105], cost/treatment day[104], cost/QALY[106] and cost/case averted[108,110]. The main findings showed benefits of testing. Timely detection on average 13 days earlier as compared with culture[104] and most sequential testing strategies resulted in higher proportions of correctly classified women and lower costs than parallel testing strategies[103]. The testing strategy was associated with the shortest duration of symptoms, compared with the group given immediate antibiotics, the strategy cost £10 per additional day of

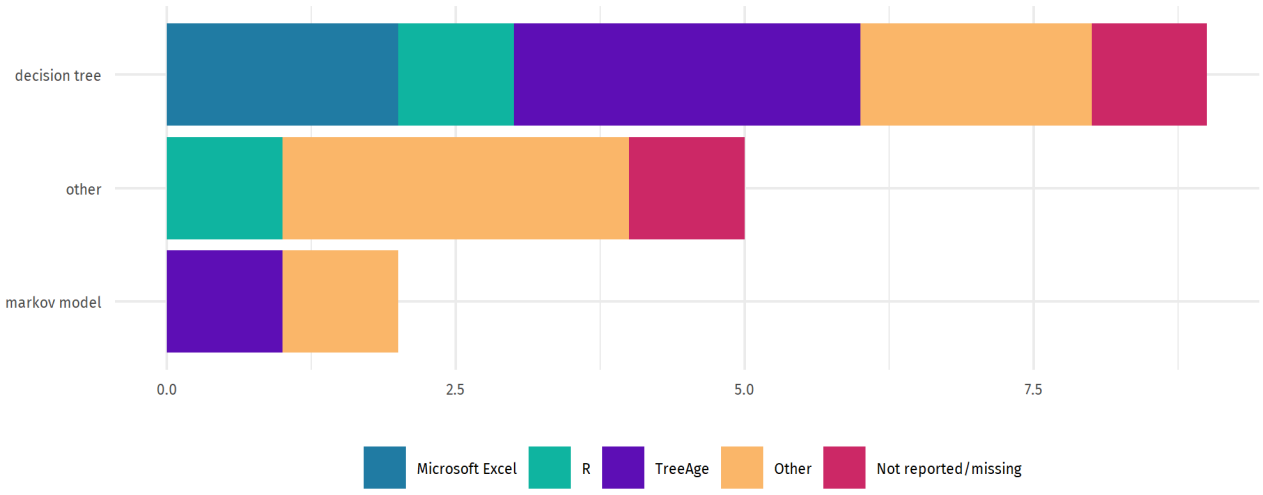

Figure 20 model type and software package used to develop CE model for vector-borne diseases

symptoms avoided[109]. Some diagnostic strategies were not cost-effective[108,113], only cost-effective if the rate of resistance to trimethoprim-sulfamethoxazole exceeded 40%[111], or not cost-saving, because this strategy was €1,162 more expensive than usual care[104]. Uncertainty was studied using DSA[103,104,107,108,110–112] or PSA[106,113]. A reported limitation was that antibiotic therapy based on clinical observations would have occurred irrespective of the test result and protocols were not followed, driving to different outcome measures[104]. Also, studies had limited available data[106,112] and resistance rates were difficult to add into the model because they differ substantially between antibiotics and regions. The majority of costs associated with antimicrobial resistance are not related to the use of expensive antibiotics for an individual patient, but with the possible cost savings associated with prudent antibiotic use in the long term[103]. Regarding generalizability, studies had similar characteristics to national attending samples and results are therefore considered to be representative of routine clinical practice[108,109,113].

3.3.3. Vector-borne diseases

Sixteen articles included in this study specifically assessed vector-borne diseases[114–129], of which malaria is the most commonly assessed[116–120,122,123,125–129]. Other diseases are visceral leishmaniasis (kala-azar)[114,121], Chagas disease[115] and dengue (together with scrub typhus and general febrile patients)[124]. The most-researched area is sub-Saharan Africa, with two articles discussing a hypothetical sub-Saharan country[126,127], three studies including Tanzania[119,123,125], three studies Uganda[116,118,125], one Nigeria[128], one Mozambique[129], one Angola[125] and one Cameroon[122]. Morocco was also assessed in one study[114]; and outside Africa, Laos[124] and Afghanistan[117]. The settings of the analyses were quite different, varying from drug shops[117] to various health centres[116,117,119,122,126–128] and hospitals[114,123,124]. Not all

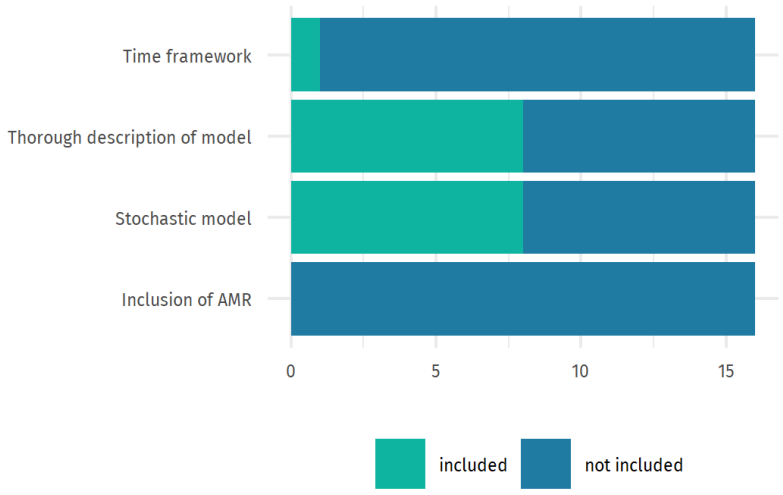

Figure 21 overview of vector-borne disease model characteristics

studies specifically mentioned the setting in which the diagnostic would be performed[115,121,125,129]. The populations assessed also vary between papers, two studies looked specifically to a paediatric population[114,125], the other studies did not specify age categories. Some studies considered patients presenting with fever or other symptoms[116,120,122,124,126,128,129], while two studies considered all patients for which the clinician deemed a test necessary[119,123]. All malaria-related studies assessed an RDT[116–120,122,123,125–129], which was unspecified in most cases[116,118,120,122,125–129], and specified (e.g. the brand and type of the test was given) in a few studies[117,119,123]. The RDT was compared to presumptive treatment[116,120,125–129] and/or microscopy[117,119,122,123,127,128]. Generally, antimalarial treatment regimens were well defined, including artemisinin-based combination therapy (ACT)[117,118,122,123,125–128], artesunate-based treatment[117,118,120,129], quinine-based treatment[117,126,129] and artemether-based treatment[116,119,129]. Antibiotic treatment was also mentioned in five studies[116,123,125,127,128]. Outside of the malaria papers, two also looked at RDTs, one for dengue, scrub typhus and CRP[124] and one for visceral leishmaniasis[114]. The visceral leishmaniasis studies included serological tests[114,121] and one parasitological diagnosis as well[121]. The diagnostic method in the Chagas paper was unspecified[115]. Both visceral leishmaniasis studies included antimonials as treatment options[114,121] and all non-malaria papers included antibiotic treatment[114,115,121,124].

All analyses dealing with vector-borne disease were qualified as a CEA[114–129], while two papers were also a cost analysis, linked to a trial[119,120]. Most modelling work was performed using a decision tree analysis[114,116–118,121,127,128] and TreeAge was the most often used development package for decision trees[116,126,128], followed by Excel[114,118]. Two models were a Markov model[115,125], one in combination with a microsimulation[125] and one in combination with a dynamic model[115]. Two papers performed a regression analysis[119,122] and four did not specifically report a model type[120,123,126,129], see also Figure 20 for an overview. Some general characteristics of the models are displayed in Figure 21, one model provided a suitable time framework[125]. The majority of studies did not report a time horizon[114,116–124,128,129], one used a follow-up of 30 days[126], one study 1 year[125], one study 50 years[115] and one study used a lifetime horizon[127]. 50% of the models was stochastic[114,115,117,118,122,124,125,127] and also 50% of models provided a thorough description of the model[114,115,117,118,122,125,127,128]. A societal perspective was taken in five studies[115–118,122], the payer's perspective in four[115,117,118,125] and the perspective of a specific provider in three[120,123,129].

EXAMPLE
PHILLIPS *ET AL.*

To assess the cost-effectiveness of diagnostic testing for malaria in children, a Markov model was combined with a microsimulation model. [127]

The Markov model consisted of three states: fever, no fever and death due to fever, which was used to 'capture the recurrent nature of suspected malaria fevers'[127].

If a fever occurred, patients entered a microsimulation which was similar in structure to the previously discussed decision trees (albeit extended for long-term complications). The first decision was whether a patient would seek care, followed by the result of the RDT, the adherence of clinicians to the test, the treatment decision made and whether the treatment was successful. If a treatment failure occurred, patients could seek care, either to a hospital or another health facility, after which a hospital admission could follow (depending on the severity of malaria) and survival (with or without recurrent fever) or death.

The authors concluded that the RDT was dominant for the Angolan setting and calculated an ICER of $5.54/LYG for Tanzania and $94.28/LYG for Uganda.

Two studies used a combined provider and patient perspective[127,128]. AMR was not modelled in any included study.[114–129]

The malaria decision tree models[116–118,126–128] adhered to similar principles. The first decision node was a choice between the different diagnostic strategies compared (e.g. an RDT or presumptive treatment), then the probability of having malaria was incorporated as opposed to not having malaria (e.g. non malaria febrile illness[127,128]). One study switched these first nodes of the decision tree, the first decision node was whether a patient had malaria or not and the second was the decision to buy a RDT (included as it needed to be paid out-of-pocket by the patient)[118]. After the first two nodes, the branches were dependent on the test characteristics (i.e. sensitivity and specificity was incorporated)[117,118,127,128] and the tree ended with the treatment given[117,118,127,128] and optionally the adherence to treatment[127,128]. Two papers used the same model[127,128], two papers did not report a decision tree in detail[116,126]. Alonso *et al.* used a decision tree to assess a visceral leishmaniasis RDT, the order of nodes is as follows: decision which test to use; result of the test (true or false and positive or negative); the decision which treatment to prescribe and finally whether a patient is cured or diseased[114]. Lubell *et al.* used a similar approach to assess febrile patients with a negative malaria test: the first decision node was which test to use; the next was in combined branches the test result and the treatment decision made, the type of empiric antibiotics prescribed (one outcome of the tree, as per current practice) was based on fixed percentages[124]. Two studies directly modelled the results (costs and effects) of a trial into a cost-effectiveness model using a regression-type model[119,122].

Bartsch *et al.* assessed Chagas disease and included a transmission model[115], with four states for humans: susceptible, acute state, indeterminate state and chronic state. However, they also included animal hosts: such as dogs and chickens. Also, vectors were modelled (as either susceptible or infectious). Economic outcomes and DALYs were modelled using a Markov model[130], in which costs and probabilities for diagnosis, treatment and monitoring of chronic cases were included[115]. This Markov model, which was based on a model used to determine the burden of disease, included productivity losses as well[130].

The most reported clinical outcome is the proportion of accurately diagnosed or treated patients[115–120,122,123,126,129] and the ICER reported for these papers was defined in terms like incremental costs per correctly-diagnosed patient (or similar)[116–118,120,122,123,126,129] with varying results. Three studies included DALYs[115,124,127] and reported the cost per DALY, also with varying results. Four papers mainly considered deaths averted[114,121,125,128] and reported costs per death averted. Numbers of the deterministic sensitivity analysis were included, mostly using a table, in five papers[114–116,118,128] or as a graph in four papers[115,121,123,126]. Probabilistic results were most often reported as a confidence interval[114,115,117,118,120,122,124], and a CEAC was included in three papers[114,122,124]. Limitations of the models include uncertainties in costs, e.g. patient-level costs were

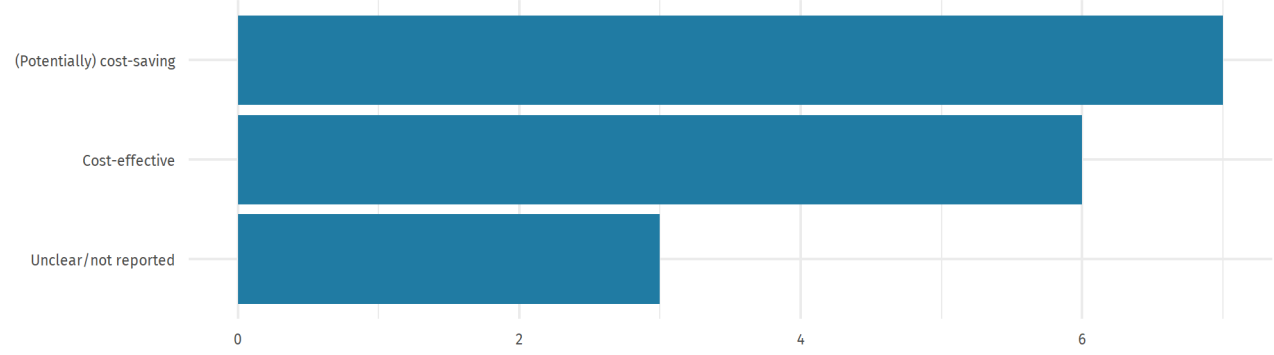

Figure 22 cost-effectiveness of vector-borne disease models

excluded[118,123] or only direct costs were included[120,123]. The difficulties in extrapolating results, or the lack of longer term results, were mentioned as well[114,117,122]. Appropriate malaria diagnosis may result in an increase of antibiotic use for patients where malaria is ruled out[117,123,126,127]. This raises the issue of appropriate antibiotic prescribing in case of a negative result, where after the introduction of a malaria RDT, other RDTs may need to be introduced, which was the focus of the work done by Lubell *et al.*[124]

The majority of studies have a positive conclusion, regarding the diagnostic method as either cost-effective[116,118,120,124,125,127] or cost-saving[114,115,117,119,125,128,129] (which may be depending on the setting). Some studies mention however, that the adherence of clinicians to the diagnostic test results is an important factor[122,123,125,127], as well as patients' adherence to both the diagnostic result[118] (i.e. they do not buy treatment elsewhere) and treatment[125]. See Figure 22 for an overview.

3.3.4. Infections of the gastrointestinal tract

3.3.4.1. Gastritis and ulcers

Six articles specifically assessed the inclusion of a diagnostic test in patients with gastritis[29,38,39,131–133] attending primary care[29,39,131–133] or hospital[38] in India[29,38], Spain[131], Canada[39], United States[133] and Japan[132]. Population included in these studies was middle-aged patients with duodenal ulcer diagnosed at index endoscopy without any other serious comorbid medical conditions[29,38], with uncomplicated dyspepsia[39,131,133] or with atrophic gastritis suggesting *Helicobacter pylori* infection[134]. In fact, all articles included a strategy based on the use of a test to diagnose *H. pylori*. Others strategies compared were endoscopy[30,39,131], histological examination[29,30,132], urease test[38,132] and breath test[39,135]. Four articles included triple therapy (antibiotics in combination with other treatments if positive results such as omeprazol[131], tinidazole[29] or lansoprazol[38,132]).

All articles included a decision tree model to perform a CEA and one also a CUA[38]. Three models had a stochastic approach[29,132,133]. The perspective most used was the healthcare payer`s perspective[29,38,39,131,133] and one paper had a societal perspective[132]. Except Ghoshal *et al.*[38] who studied a 2 year-time horizon, all of the articles had a one-year time horizon. One article studied how AMR affected results. Omata *et al.*[132] took into account an increasing prevalence of resistant H. pylori. Antimicrobial therapy can be a suitable option if the proportion of resistant H. pylori increases to more than 45%. The results of Omata *et al.*[132] indicate that if the prevalence of *H. pylori* in patients with AG is 85% and chloramphenicol-resistant *H. pylori* is 30%, histology, stool *H. pylori* antigen, bacterial culture, and

EXAMPLES
GHOSHAL AND DAS GHOSHAL *ET AL.*

The comparison of the urease test (RUT) was made in two studies. In Ghoshal 2002, the RUT and histological examination and subsequent treatment depending on the outcome was compared with two options: (1) antisecretory therapy, (2) triple therapy (antisecretory plus antibiotics). In Ghoshal 2003 the test was compared with (1) maintenance therapy, and (2) triple therapy.

Both used **decision trees** from the patients' perspective. In the first study, cost minimization was carried out, while in the second cost effectiveness analysis was added taking as reference the measurement of QALYs. The time horizon in the first study was one year and two years in the second study.

Ghoshal, 2002 shows that initial **empirical triple therapy** is the most cost-effective approach to treatment of endoscopically documented duodenal ulcer in India. Ghoshal, 2003 showed that treatment of H. pylori followed by 2 months of **maintenance therapy** was the most cost-effective option.

urine *H. pylori* antibody were dominated by serum *H. pylori* IgG antibody (SHPAb), rapid urease test (RUT), and urea breath test (UBT). Among three undominated methods, the incremental cost-effective ratios (ICER) of RUT versus SHPAb and UBT versus RUT were $214 and $1914, respectively. If the prevalence of chloramphenicol-sensitive *H. pylori* was less than 55%, bacterial culture was not dominated, but its *H. pylori* eradication success rate was 0.86. In general, RUT was the most cost-effective diagnostic procedure given the present prevalence of chloramphenicol -resistant *H. pylori*.

Analyses were mainly performed with TreeAge[29,38,39,132] and in one paper with Microsoft Excel[131]. In García-Altés *et al.*[131] endoscopy was the most effective alternative, whereas testing was the most cost-effective strategy. In Ghoshal *et al.*[29] initial empirical therapy was the least expensive approach per patient treated but if there was an increase in the time horizon of the analysis to more than 1 year, it was expected that the cost of testing H. pylori would lower than therapy alone because of the possibility of a higher number of recurrences with the latter strategy. Also, it was found that testing of *H. pylori* was the most cost-saving strategy for the prevention of recurrence of duodenal-related hemorrhage[38]. In one paper[39] different results were found by age group. In patients under age 45, endoscopy and testing were not cost-effective and in patients over age 45, testing was the most effective, but endoscopy results in the early detection of most gastric cancers. Clinical variables that impacted these findings were the probability of symptomatic relapse in patients with no ulcer dyspepsia after successful versus failed *H. pylori* eradication, the probability of finding a duodenal ulcer in a young dyspeptic patient and the prevalence of *H. pylori*. Outcomes used in the articles were cost/patient[29,38,39,131], cost/QALY[38], cost/eradication of a *H. pylori* case[132] and cost/ulcer cured[133].

EXAMPLE VAKIL *ET AL.*

Vakil et al.[140] studied thirty-six diagnostic testing strategies, which included various sequences of three diagnostic tests (serology ELISA, urea breath test (UBT), fingerstick whole blood test, stool antigen test, rapid urease test (RUT), and histology) were initially evaluated. Five strategies utilized single tests, 20 strategies utilized an additional confirmatory test, and 11 strategies utilized three tests. ELISA had the lowest cost per correct diagnosis at low (30%), intermediate (60%), and high (90%) prevalence ($90 –$95/correct diagnosis), but its diagnostic accuracy was low (80–84%). At low and intermediate prevalence, the stool test was more accurate (93%), with an average cost of $126–$127 per correct diagnosis. Although ELISA results in the lowest cost-effectiveness ratios, in patients at low-intermediate pre-test probability of infection, the stool test provides increased accuracy, with modest incremental costs.

Uncertainty was reported with deterministic sensitivity analysis[38,39,131], and sensitivity analysis graphs[29,38,39132,133]. In general, analysis was robust to changes in the prevalence of H. pylori, the accuracy of diagnostic tests and the age of the patients.

3.3.4.2. Gastroenteritis and pouchitis

Five articles assessed the introduction of different tests to detect gastroenteritis, in patients with uncomplicated ulcer-like dyspepsia[135,136], *H. pylori* suspected infection[137,138] or with symptoms suggestive of pouchitis[139], in primary care[135–137,139] or not explicitly stated[138] using a healthcare payer´s perspective [137,139], societal perspective[135] or healthcare centre´s perspective[136,138].

The type of model most used was the decision tree, found in three articles[136,137,139] all of them had a deterministic approach and a time horizon of 28 days[139]. Some studies included a strategy based on the *H. pylori* testing[135,138],

endoscopy arm[138] and rapid breath testing[135,137]. Decision trees allow to model different clinical situations (e.g. level of disease prevalence) in which the physician performs the diagnostic test. Two articles used a Markov model with a time cycle defined as two weeks[135] or one month[138]. This last one was the only article that included AMR, considering that antibiotic resistance may cause a higher failure rate, and therefore the effect of eradication rate in the model was examined over a range of 50-100%. The main advantage related to using this model was that it allows the use of different clinical data from other countries or settings. ICERs reported were cost/correct diagnosis[135,137], cost/days saved[139] and cost/ulcer treated[138]. Four articles[136–139] concluded that testing was a cost-effective strategy. Of the only article[135] that concluded that there were no benefits in using a rapid diagnostic test, it was indicated that the cost of the alternative diagnostic technique (usually more invasive but with better success rates) was the key factor driving these results.

Uncertainty was reported with deterministic sensitivity analysis[136,139], sensitivity analysis graph[136,137] and probabilistic sensitivity analysis[135]. Sensitivity analysis showed that varying the sensitivity or specificity of the test and cost would alter the results of the CEA[137] and results should not be considered to have validity outside of some assumptions[135].

3.3.4.3. Appendicitis

Kastenberg et al.[140] compared in a hospital setting the use of diagnostic laparoscopy, computed tomography (CT) and magnetic resonance imaging (MRI) following indeterminate ultrasound in pregnant women with suspected appendicitis. As early pregnancy is typically considered a contraindication to MRI (risks of miscarriage and developmental damage to the foetus), they excluded first trimester pregnancies from the analysis.

The authors used a Markov model (stochastic approach) that captured long-term outcomes including the potential development of and treatment for childhood acute lymphoblastic leukaemia, as it is the most common childhood cancer linked to radiation exposure. The women then undergo either expedited operation resulting in no perforated appendicitis (true positive), a negative appendectomy (false positive), a delayed operation with perforated appendicitis (false negative), or no operation (true negative). The pregnant women's surgical outcomes include no complication, complication (simplified to surgical site infection, the most common complication following appendectomy), or death. For surviving mothers, the subsequent foetal outcomes include full-term delivery, pre-term delivery, or foetal death. Surviving children enter a Markov simulation model to capture the risk of developing radiation-associated childhood leukaemia and associated health outcomes and costs. In the model, all children are initially healthy but face risks of developing childhood leukaemia. It is modelled in terms of an initial three years of treatment followed by a period of remission for those children surviving to the end of treatment. Following the tenth year of disease-free remission the child is considered cured. Uncertainty was assessed with deterministic sensitivity analyses, a two-way sensitivity analysis graph and a CEAC.

Magnetic resonance imaging is the most cost-effective strategy, costing $6,767/QALY gained relative to CT, well below the generally accepted $50,000/QALY threshold. In a setting where MRI is unavailable, CT is cost-effective even when considering the increased risk of radiation-associated childhood cancer ($560/QALY gained relative to diagnostic laparoscopy).

3.3.5. Sexually transmitted diseases

Six articles assessed diagnostics for sexually transmitted diseases (STDs) in United States[141–143], the Netherlands[144,145] and Italy[146]. Five articles studied the primary care setting[142,145] (specifically the STD clinic[141,144,146]) and one the hospital setting[143]. The population of the studies included patients of both sexes with STD-related signs or symptoms[146], only men with signs of having

STD[144,145], women with presumptive chlamydial infection[141,142], neonates with fever or cerebrospinal fluid pleocytosis[143].

A paper compared two strategies, performing a Gram stain test to all patients or only those with urogenital symptoms[145]. Another paper did similar analysis using a nucleic amplification test for *Chlamydia trachomatis* (NAAT)[141]. Also, both tests (Gram stain and NAAT) were compared[144]. Another paper compared a rapid immunochromatography test with a traditional ELISA screening test[146]. Different strategies regarding the herpes simplex virus test were studied such as test and treatment while waiting for the results, test and treatment only if positive or treatment without testing[143]. Also, there was the case in which two tests were included in the analysis: test for N gonorrhoeae only, test for *C. trachomatis* only or test both.

All papers assessed the cost-effectiveness of the strategies, three used a decision tree model (two with a stochastic approach[141,143] and the other deterministic[142]). Another article developed a transmission model[144] and a walk-in-clinic model[146]. In one paper, the model type was not explicitly declared. The most used perspective was the healthcare centre's[141,142,145,146] followed by the healthcare payer's perspective[144] and the societal perspective[143]. Only in two articles the time horizons were shorter than one year[143,145]. An article considered time horizons of both 5 and 10 years[141], another article only 10 years[144] and another a lifetime time horizon[142], all of them with a discount rate of 3%.None of the articles included bacterial resistance into the models. Three articles used TreeAge[141–143], one used Microsoft Excel[144] and another STATA[145] to program the model.

ICERs were reported as cost per correct consultation[145] or diagnosis[146], cost/QALY[143,144], cost per case prevented[141,142]. All of the diagnostic strategies were cost-effective. In Gianino *et al.*[146] testing was even less expensive than ELISA and yielded a similar number of correct diagnoses[146]. In Bartelsman *et al.*[145] performing the test to only symptomatic patients as opposed to all patients saved €2.34 per correctly managed consultation, thus Gram stain smear was dominant when offered only to symptomatic patients. In Huang *et al.*[141] test sensitivity, cost and proportion of women willing to wait for the test result were the key factors that determines the cost-effectiveness of the strategy. Some articles warn that the results may not be directly applicable to other populations or healthcare settings because only epidemiological data of the specific clinic were used[141,144].

3.3.6. Fungal infections

Six papers assessed diagnostics for fungal infections[147–152]. The most-researched country is the United States[147,149,151], followed by Canada[152], Australia[148] and France[150]. Three papers assessed the hospital setting[147,148,151], two primary care[149,152] and one the intensive care unit[150]. The population hospitalized consisted of patients presenting candidemia in admission[147] or undergoing allogeneic hematopoietic stem cell transplant or receiving chemotherapy for acute leukaemia[148] or with signs and symptoms sufficient to conduct a blood culture that had at least one risk factor[151]. The population attending primary care consisted on patients with confirmed onychomycosis[149,152] or with peritonitis diagnostic[150]. Some of the articles also specified the fungi diagnosed such as candida[147,150,151] or aspergillus[148].

The strategies compared use a specific diagnostic method with antifungal agents treatment such as fluconazole[147,148,150,151], itraconazole[147,148,152], voriconazole[147,148] or efinaconazole[149]. Different diagnostic method were used: potassium hydroxide[149,153], periodic acid–Schiff[149,152], biomarker-based diagnostic strategy of galactomannan (GM)[148], aspergillus PCR[148], candida PCR[150] and T2Candida® (T_2 Biosystems, Inc.)[151]. All articles used a decision tree (one with a stochastic approach[150]) to assess the cost-effectiveness of the diagnostic strategies and one also performed

a budget impact analysis (BIA)[147]. Most trees included the strategies of immediate treatment, rapid diagnostic and culture. All articles used a decision tree (only one with a stochastic approach[150]) to assess the cost-effectiveness of the diagnostic strategies and one also performed a BIA[147]. Most trees included the strategies of immediate treatment, rapid diagnostic and culture.

The most-used perspective is the healthcare centre's[147–149,151], followed by the healthcare payer's perspective[150,152]. A five year horizon was applied in a model[148], 1.4 years in an article[149], 1 year in two[147,150] and a time horizon shorter than one year was applied in two articles[151,152]. No discount rate was reported. Two articles used TreeAge[150,151], two articles Excel[147,149] and one STATA[148] to develop the model. There was no inclusion of resistance in any model. The clinical outcomes assessed were: correctly diagnosed patient[152], life-years saved[148], QALY[150], cost per patient tested[147,149,151].

Different ICERs were reported as cost per test/sensitivity[152], cost/life-year saved[148,151], cost/QALY[150]. Uncertainty was explored in all papers, mostly with a sensitivity analysis graph[147,149,152] and a deterministic sensitivity analysis[147,149–152]. The main findings of these studies showed that a diagnostic tool significantly reduced cost and mortality rates in patients at high risk for candidemia[147]. Performing confirmatory testing prior to treatment decreases the overall cost[152] but it has a direct dependency on the treating physician, the percentage of suspected cases from total[149] and the cost of treatment (if it decreases, strategies involving a diagnostic test became more cost-effective) In Gupta *et al.*[152] the CEA was dependent on the ability of the physicians to detect the infection. Only in one paper the diagnostic test strategy was considered not cost-effective[151]. In this study, disease prevalence and the mortality attributable to candida were the two most important factors affecting model predictions. The optimal use of the test may be in a moderate-risk setting where the prevalence is around 5% and empirical or prophylactic antifungal therapy is prescribed routinely.

3.3.7. Sepsis

Eleven articles assessed diagnostics for sepsis in different European countries[34,35,37,154–156], the United States[32,157,158], Argentina[159] and Ethiopia, Gambia, Papua New Guinea and Philippines[33]. Seven articles studied the hospital setting[33,35,37,156,159–161] and four others studied the intensive care unit[34,154,155,163]. In the former setting, the population included patients with suspected sepsis requiring hospitalization. In the latter setting, the population of the studies included patients admitted with a diagnosis of severe sepsis or septic shock to the intensive care unit[154,155] or with suspected bacterial infection and sepsis[34,163]. One article focused on a paediatric population[159]. The diagnostic strategy included different test such as real-time PCR technique[154,155,159,161,163], procalcitonin-guided treatment[34,159,163] and an testing[37,156,161]. The preferred treatment in case of a positive result was antibiotics. In one hand, articles such as Harrison *et al.*[163] only considered broad spectrum antimicrobial therapy based on vancomycin and cefepime. On the other hand, articles included different treatment options, which depend on the test results. In Brown *et al.*[160] penicillin was prescribed if methicillin-sensitive *Staphylococcus aureus* was found and vancomycin if methicillin-resistant was detected. In Steuten *et al.*[35] the duration of the antibiotic treatment was calculated based on the level of concentration of PCT.

Nine papers assessed the cost-effectiveness of the strategies, seven used a decision tree model (three with a stochastic approach[34,35,159] and four deterministic[33,37,160,161]). Only one of these articles used a time horizon longer than one year[161], which calculated lifetime results. Another article performed a cost-minimization analysis with an individual sampling model[154] and one was a CUA with a decision tree model with a deterministic approach[163]. The most used perspective was the healthcare centre's[33,34,37,154–156,160,161,163] followed by the healthcare payer's perspective[159] and the

societal perspective[35]. Bacterial resistance was included in three articles. Diagnostic test guides the treatment because it can detect and differentiate between methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus*[35,160,163].

The ICERs were reported in terms of cost/correctly diagnosed case[159], cost/LYS[33,160], cost/QALY[37,161,163], cost/episode[156]. In Buendia *et al.*[159] US$937 per correctly diagnosed case was calculated for the use of CRP testing and in Brown *et al.*[160] this test resulted in $820/LYS in the USA and €636/LYS in Europe. All diagnostic strategies were cost-effective or cost-saving. Uncertainty was reported mainly with deterministic sensitivity analysis[33–35,154,159–161,163] or a probabilistic sensitivity analysis[37,155]. The main limitation found was that the model includes outcomes only for 30 days after the blood cultures were ordered and have not accounted for readmission costs or costs associated with antibiotic discontinuation, as such data were not available[161]. Also, assumptions had to be made to estimate costs of productivity losses due to the recovery period and/or premature mortality[155]. Taking into account the analysis that includes data from different European countries, results can be likely generalizable to similar patient populations in developed countries[35].

3.3.8. Other

Four papers did not apply to any of the previous infection diseases. Two papers published from Argentina[162] and Japan[164] and two from United States[165,166].

Two studies were set in a hospital[162,165]. Buendia *et al.*[162] presented a hypothetical cohort of children with fever without a source and compared two strategies: (1) observation, clinical assessment and clinical records and (2) the use of Rochester criteria and CRP test, if positive, an intravenous ceftriaxone was applied. Schroeder *et al.*[165] used a cohort of 10,000 adult inpatients suspected of having Clostridium difficile infection to compare the strategies of traditional technologies (PCR, Enzyme Immunoassay toxin A/B and culture), rapid diagnostic test (on-demand PCR, lateral-flow glutamate dehydrogenase testing) and any kind of diagnostic tool (treat all, treat none).

Another two studies were set in a primary care setting[164,166]. Takemura *et al.*[164] took patients with acute fever (+37.5ºC) and suspected of having an infection to compare the use of PCR in initial consultation (treat if positive with both antibiotics and antiviral agents) with only physician examination plus history of patient. Udeh *et al.*[166] compared the use of the rapid diagnostic test named RPD Adeno Detector to not testing. In this study, the population was not explicitly stated.

All of the four papers performed a CEA with a deterministic decision tree model. One also performed a cost-benefit analysis (CBA)[165]. Most of them used a healthcare centre's perspective and only one a societal perspective[166]. The time horizon of the studies was shorter than one year or the duration of an episode of acute bacterial infection without recurrence[162]. No discount rate was needed. No inclusion of bacterial resistance was found. ICER was reported as cost/correct diagnosis in hospital studies[162,165] and cost/antibiotic prescription saved in primary care studies[164,166]. Uncertainty was reported mostly with deterministic sensitivity analysis[162,165] and a tornado diagram[166]. Three articles used TreeAge and one article[164] StatFlex 5.0 (Artec Inc., Tokyo, Japan) to perform the model.

The main finding of these studies was that the cost-effectiveness of including a diagnostic tests depends on the prevalence. If it is equal or lower than 14%, the best option is only examination without testing[162], which is the case for developed countries where vaccination reduced the prevalence of bacterial infection to 1%. In Takemura *et al.*[164] testing produced savings in

antibiotics consumption but usually they were offset by the use of expensive antiviral agents. If a rapid test is available to a physician, they used as many as available, which increased costs, so the rapid testing did not imply final savings. This was the only study where they concluded the diagnostic not to be cost-effective. As a limitation, one study assumed that the physicians followed the test results, removing the assumption that physicians can ignore test results so the costs and effectiveness of the diagnostic strategies may be different[165]. In another article, information about sensibility and specificity values in tests came from studies made abroad[162].

3.3.8.1. Tropical

Three articles were defined as "other" and considered tropical disease. In this sense, in Fitzpatrick *et al.*[167] patients came from historic endemicity (Ghana, Papua New Guinea, Solomon Island and Vanuatu) presenting to a clinic with infection symptoms. The authors compared the use of BIOLINE Syphilis 3.0 with DPP Yaws Trep Assay. Also, Saito *et al.*[168] studied a hypothetical cohort of 10,000 children visiting a health centre with fever of unknown source. They compared the standard of care (without test) with lateral flow analysis of immunoglobin M (lgMFA). If positive plus fever azithromycin was prescribed and if positive and no fever amoxicillin. Suputtamongkol *et al.*[169] studied a hypothetical cohort of adult patients who present with acute fever. They compared the lateral flow test with agglutination test and if positive doxycycline treatment.

All of the three papers performed a CEA, two[168,169] with a deterministic decision tree model and another with stochastic approach[167]. One also performed a cost analysis[167]. Most of them used a healthcare centre's perspective and only one a societal perspective[169]. The time horizon of the studies was seven days, so no discount rate was needed. None of the articles included AMR into the model but Fitzpatrick *et al.*[167] mentioned that the benefit of testing could be lower because the potential benefit could be reduced in patients with false positive (higher probability to develop resistance). ICER was reported as cost/correct diagnosis. Uncertainty was reported mostly with a two-way sensitivity analysis graph[167,168]. One article used R[167] and another one Microsoft Excel[168] to develop the models.

In one study[167] testing was cost-effective only if the prevalence of the infection in the population was higher than 85% and treat all patients was the best strategy in terms of costs and effectiveness. Limitations reflected that the analysis was performed in countries with low resources in which some treatment such as azithromycin may not be available in health centres which would affect the number of days until treatment successes. Results only can be generalized among developing or low resource countries[167–169].

4. Discussion

4.1. Disease areas

In this section, the quality of the articles described above are discussed in terms of inclusion of an explanation of relevance for health policy, results linked to current knowledge, resource and cost estimations explained in all articles and explicit statement on the context of the study. Also, advantages and disadvantages of the modelling decision were included in this part.

4.1.1. Respiratory tract infections

4.1.1.1. General respiratory tract infections

Twenty-two articles, published along the period of the review, assessed the introduction of different rapid diagnostic tests to diagnose patients with symptoms of respiratory tract infection (mainly with cough[14,64], sore throat[65,66] or meningeal signs[61,62]) where the antibiotic decision was not clear. The setting most studied was primary care under a healthcare system perspective[14,47,48,50,53,56,65], a healthcare payer`s perspective[15,52,55,57,60,64] or a societal perspective[49,51,59] followed by the hospital setting with a healthcare centre perspective. Two articles included in the analysis more than one country: Norway and Sweden[14] and Belgium, United Kingdom, Netherlands, Poland and Spain[15]. The chronological order in which test were assessed for their cost effectiveness in the literature followed the respective availability of these tests for clinical practice: simple radiography and ultrasound techniques, rapid detection test for group A *Streptococcal*, procalcitonin test, PCR tests for influenza A and B and CRP testing. The type of model most used was the decision tree. In this sense, examination of several possible outcomes[51], inclusion of patient`s follow up[57], applicability in different settings[60] and age groups[52] were discussed as advantages of the decision tree modelling technique, while the main disadvantage argued was that several simplifying conditions in creating the decision model were needed[51,55,57]. Regarding hierarchical regression, it was described as a technique with wide applicability[14].

In this area of disease different strategies were assessed such as clinical scoring, improving GP communication skills or deferred prescription. Clinical scoring strategy or an enhancing in GPs communication skills (in some countries)[15] the rest of the studies concluded that the incorporation of a rapid test in the clinical practice for the diagnosis of general respiratory tract infection diseases was cost- saving[49,50,54,56] or /and cost-effective[14,15,47–49,51,53,55,57,59,63,64]. This result depends most on the cost of the rapid test[15,49,53,59], the sequence of application when different test are available[58], its parameters in terms of specificity and sensitivity[60], the cost of antibiotic resistance or side effects[52,53,59] and the prevalence of the disease[49]. Most of the articles found in this section (except three[47,50,65]) had an explicit statement on the context of the study and an explanation of relevance for health policy or practise decision (except two[48,65]). The resource and cost estimations were explained, and the results have been linked to current knowledge in most of the articles.

4.1.1.2. Influenza

Fourteen articles assessed the cost-effectiveness of influenza RDTs between 2000 and 2018. In the early 2000s, five studies were published on influenza diagnostics[41–43,46,76], which can probably be traced back to the introduction of antivirals, such as oseltamivir during that period[170]. In these analyses, doing nothing was compared to empirical treatment and performing an RDT before

treatment. The models that followed later, did follow similar structures and most assessed antivirals (mainly oseltamivir) as empiric treatment as well.

The diagnostic models that specifically assessed influenza, were mostly built using static decision trees[41–43,46,69–72,74–78]. Long-term outcomes were partially assessed, for example by estimating the (quality-adjusted) life-expectancy for all possible end nodes of the trees. Six studies used an approach like this[41,46,69,72,77,78], while three others only assessed a single illness episode[42,43,76]. Only one study (of fourteen) included a dynamic transmission component[73]. This is a relatively low number: De Boer *et al.* performed a systematic review of health-economic models of quadrivalent influenza vaccination and found that five out of sixteen models were dynamic[171]. In the SIR model used in the transmission model[73], the contact rate is an important factor for patients to get infected. In this article, we found no indication that the contact rate was changed by a diagnostic test result[73,172]. In theory, early diagnosis could influence the contact rate in such a model for influenza, if combined with clear clinical advice to patients, e.g. an advice to stay at home[8]. However, more research on these effects is needed. Another factor that could more easily be captured in a dynamic model, as opposed to a static model, is the effect of a shorter disease duration on the transmission, considering Nshimyumukiza *et al.*[73] used cycles of one day, this effect seems to be included in the analysis, although this is not mentioned specifically.

Antiviral resistance was only included in one model[71], although more papers discussed the influence of this phenomenon and its potential effect on the cost-effectiveness of diagnostics. Resistance against antivirals is not as urgent as AMR, especially in the early 2000s, close to the introduction of antiviral treatments such as oseltamivir[170]. Antibiotic treatment was included in a subset of studies[42,43,46,69,72], and AMR in none. The added value of combating AMR, by reducing inappropriate antibiotic treatment, was not included in the influenza diagnosis models.

In general, the models were well explained in the articles, with the exception of the time frameworks, which could be better explained. Although a lifetime horizon usually is preferred in health-economic models, this may be difficult to implement using a decision tree, as only one influenza episode can easily be modelled, and patients may have recurrent episodes over their life course. Life expectancy as an outcome is understandable however, as mortality as a result of an influenza episode can be quantified without much (computational) effort.

Most studies concluded the diagnostic test to be cost-effective, with four studies concluding the RDT to be not cost-effective, while empirical treatment was[46,74,75,77]. Some studies specifically defined the population as being “unvaccinated”[42,71] or included vaccination coverage in a sensitivity analysis[41]. However, to be able to prioritize influenza policy, it may be important to be able to compare vaccination strategies, diagnostics and treatment (and combinations hereof) in one analysis.

4.1.1.3. Pneumonia

Five articles, published in 2002-2003[79,82] and from 2011 to 2018[80,81,83], studied the cost-effectiveness or/and cost analysis of using a diagnostic test such as PCR-based test[81], mini bronchoalveolar lavage [82], inquaro[79], *Pneumococcal* urine antigen test[80] and *S. pneumoniae* Antigen Card[83] for pneumonia detection (*S. pneumoniae*[80,83] and *P. jiroveci*[81]). Some articles considered the test could specify the pathogen. In Dinh *et al.*[80] if *S. pneumoniae* was detected penicillin A was prescribed and if no microbiological identification, treatment was based on broad-spectrum antibiotics. In Ost *et al.*[82] treatment would be adjusted to cover the identified pathogen. Furthermore, bacterial resistance was included into the models by taking antibiotic use as a cost, in terms of promoting AMR[82] or by assuming that the rapid diagnosis could help reduce the antimicrobial spectrum, because *S. pneumonia*, the main bacteria involved, is susceptible to penicillin A[80].

Xie *et al.*[83] argued that using a Bayesian latent class meta-analysis model in advance of a decision tree allows to evaluate the accuracy and economic value of a new test in the absence of a perfect reference test using an evidence-based approach. Articles found in this section had an explicit statement on the context of the study and an explanation of relevance for health policy or practise decision but the resource and cost estimations were not explained in two articles[79,80] and the results have been linked to current knowledge in most of the articles (except one[79]).

4.1.1.4. Tuberculosis

After the WHO recommended the use of Xpert, many studies were performed on the cost-effectiveness of this intervention for TB diagnosis[45], which includes detection of *Mycobacterium tuberculosis* and the detection of rifampin resistance.

Decision trees were used by over half of the included studies[78,84–88,94,95,98,99], with more advanced modelling techniques used in five studies[90–92,96,100]. This proportion of decision trees seems to be rather high, a recently-published review of TB vaccination strategies showed relatively more Markov and transmission models[173]. Not further established models, or no model at all, were used in the four remaining studies[89,93,97,101], which may be a result of the focus of the study being on one clinical trial, which was the case for eight studies[85–87,89,93,95,97,101]. While the decision trees were rather similar in their approach, the more complex models used varying approaches to answer various research questions. The time framework was thoroughly described in only five studies[84,85,87,95,96], with eleven studies not reporting a time horizon[86–89,93,94,97–99,101,102]. The modelling approach taken by Langley *et al.* incorporated an operational component, as well as a transmission component[90]. This operational component included diagnostic machines, staff use and the time to start treatment, which has the potential to also include patient time and costs, caused by a less hospital visits. Even though a key component of Xpert is the detection of rifampin resistance, AMR was only included in six papers[89,90,92,93,96,98]. With TB, modelling this may decrease the cost effectiveness, as treatment of resistant TB is more expensive.

One of the more complex models included is developed by Mears *et al.*[91] While most TB models focussed on LMICs, this study for the UK took a different approach, informed by the setting, with a low TB prevalence, and a well-established single-payer health system. This study used a mixed-methods approach on the use of strain typing to inform the English public health institute, including performing interviews, which were used in a CEA. They concluded that changes needed to be made to the programme (which was already implemented) to improve its effectiveness and reduce costs, by focussing on reducing the diagnostic delay[91]. The importance of case-finding was also stressed in a study for many African countries[92], where this effect was shown to result in a major increase in treatment costs for newly-diagnosed TB. This time element is an important aspect, as it is hard to incorporate using decision trees. Several studies reported a limitation that can be traced back to a limited assessed time horizon.

Reported clinical outcomes were often QALYs or DALYs, ten studies incorporated one of these outcome measures. As some studies did not include a time element, reporting the proportion of correct diagnoses as the main outcome seems to be an appropriate approach. Most studies assessed the cost-effectiveness of Xpert to be favourable, with one exception[91]. However, in several studies, affordability is raised as an important issue. Improved diagnostics will improve case-finding and increase the treatment prescriptions, for which the funds may be lacking in LMICs. This stresses the importance of the link between diagnostics and treatment options, without cost-effective and affordable treatment, improved diagnostics may not be a priority.

4.1.2. Urinary tract infections

Eleven articles, published from 2004 to 2018, assessed the use of dipstick[103,106,108–110], flexicult test[113], urinary antigen test for legionella[105],PCR[104], pH testing and gram's stain for bacterial vaginosis[112]

to diagnose urinary tract infection in women[103,109,111–113], children[107,110] and men[108]. Specific pathogens studied were *legionella*[104], *T. vaginalis*[112] and *M. genitalium*[108]. Nine papers used a decision tree model and in two of these[107,110] the decision tree was followed by a Markov model.

Turner *et al.*[109] concluded that testing shortened the duration of symptoms, compared with the group given immediate antibiotics. In Rothberg *et al.*[111] testing was only cost-effective if the rate of resistance to trimethoprim-sulfamethoxazole exceeded 40%. These authors included the bacterial resistance into the model by considering that when the rate of resistance increased, the percentage of patients failing empiric therapy also increased[111]. Bosmans *et al.*[103] found that costs associated with antimicrobial resistance were not related to the use of expensive antibiotics, but with the possible cost savings associated with prudent antibiotic use in the long term. As general conclusion, testing shortened the period needed to detect the pathogen in comparison with traditional culture, which lead to a discontinuation of unnecessary antibiotics treatments.

Most of the urinary tract infections related studies included an explicit statement on the context of the study (except one[109]) and an explanation of relevance for health policy or practise decision. However, a lack of information on resource and cost estimations was found in several papers[103,104,108,113].

4.1.3. Vector-borne diseases

Sixteen articles regarded vector-borne diseases[114–129], with malaria being the most commonly assessed[116–120,122,123,125–129]. A small number of studies dealt with visceral leishmaniasis[114,121], Chagas disease[115] and dengue[124]. The assessed countries were mostly in Africa, although Laos[124] and Afghanistan[117] were also considered. This resulted in a variety in the settings where the diagnostics were assessed, from drug shops[117] to hospitals[114,123,124]. The choice of setting may have an impact on the results of the analysis, however, the setting was not reported in four papers[115,121,125,129]. We believe specifying the setting in which the diagnostic is performed is very important to be able to interpret and generalize the results. Related to this is the population on which the test is used. This should be close to how the test is implemented in practise, a good example for malaria would be: 'patients presenting with fever or other (specified) malaria symptoms', variations of which were used by seven studies[116,120,122,124,126,128,129]. More difficult to interpret is "all patients for which the clinician deemed a test necessary", used by two studies[119,123], as this may vary between clinicians. Regarding the context, only three studies specifically mentioned the test used[117,119,123], for the interpretation and comparison of the results, this may be very helpful.

Over half of the models were categorized as a decision tree. Half of the studies used a stochastic model to incorporate uncertainty[114,115,117,118,120,122,124,125] and most incorporated a DSA[114–116,118,121,123,126–129] to explore the impact of input parameters on the results. Half of the models were not described in sufficient detail, and only one provided a well-explained time framework[125]. The limitations of the models, in terms of assessing long-term outcomes, may be partly due to the difficulties in performing clinical trials in these countries where the health systems are not as established or as well-funded as in many Western countries. Another factor to consider is that patients in LMICs may experience a burden associated with going to the hospital and long travel and waiting times. These patient costs were not included in all studies – however some studies took a societal or patient perspective, which incorporated these patient costs[115–118,122,127,128]. Registering this is possible during a trial, but with a decision tree it is difficult to further explore this aspect, such as how optimizations in the clinical pathway can reduce the burden on patients.

An example of good practise for modelling diagnostics is the paper by Phillips *et al.*, which was well described and the only vector-borne disease paper which clearly described the time horizon

(of one year)[125]. This model included not only the diagnostic pathway when a patient was seeking care, but also the process of care seeking if a fever occurred and clinical complications in more detail than most other studies. The recurrent nature of fevers was also included, so patients could seek care several times during the one-year horizon. The only model that included a transmission component for vector-borne diseases, was the Chagas diagnostics model by Bartsch *et al.*, which, in addition to humans, included animals[115]. The lack of a transmission component in the other models is interesting, as many agent-based models for malaria are available, which include transmission[174].

No study concluded that the diagnostic intervention was not cost-effective, although some studies incorporated a type of threshold analysis, where they defined the Willingness-To-Pay (WTP) below which the intervention could be considered cost effective (due to a lack of a formal WTP threshold in the analysed country). For malaria diagnostics, affordability seems to play a minor role compared to e.g. tuberculosis diagnostics, as this component was less often mentioned in the malaria-related papers. However, for decision makers to prioritize funding, the models included in this review have a major limitation, that is, they focus on diagnostic strategies only. With limited healthcare budgets, priorities may need to be elsewhere. In the context of malaria elimination, the WHO has developed the integrated vector management approach to prioritize public health interventions to control vector-borne disease in a cost-effective manner[175]. Interventions can include insecticide-treated nets, improving disease monitoring and introducing larvicolous fish[175]. Assessing diagnostics, which can improve disease monitoring if implemented efficiently, within the context of these other interventions, may be an opportunity for further research.

4.1.4. Infections of the gastrointestinal tract

4.1.4.1. Gastritis and duodenal ulcers

Six articles published mainly from 2000 to 2005 assessed the inclusion of a diagnostic test in patients with gastritis[29,38,39,131–133] attending primary care[29,39,131–133] or hospital[38] with suspected gastritis suggesting *H. pylori* infection[134]. Treatments included triple therapy (antibiotics in combination with other treatments such as omeprazol[131]).

All articles included a decision tree model to perform a CEA. The main advantage of using this type of model was that it incorporates the repetition of recurrent symptoms in the model emulating the relevant clinical practice[39]. One article studied how AMR affected results taking into account increasing prevalence of resistant *H. pylori*. In Ghoshal *et al.*[29] initial empirical therapy was the least expensive approach per patient treated but if there was an increase in the time horizon of the analysis to more than 1 year, it was expected that the cost of testing *H. pylori* to be lower than therapy alone because of the possibility of a higher number of recurrences with the latter strategy. Clinical variables that impacted these findings were the probability of symptomatic relapse in patients with no ulcer dyspepsia after successful versus failed *H. pylori* eradication, the probability of finding a duodenal ulcer in a young dyspeptic patient and the prevalence of *H. pylori*.

In the gastritis related articles all papers included an explicit statement on the context of the study, an explanation of relevance for health policy and linked the results to current knowledge.

4.1.4.2. Gastroenteritis and pouchitis

Five articles published mainly from 2000 to 2005 assessed the introduction of different RDTs to detect gastroenteritis. The pathogen considered was *H. pylori* in primary care[135–137,139] from a healthcare payer´s perspective [137,139], a societal perspective[135] and a healthcare centre´s perspective[136,138]. Decision trees and Markov models were used because of their main advantages

in terms of assessing different clinical situations. AMR was included in the model by assuming that antibiotic resistance may cause a higher failure rate.

Adding a rapid test was a cost-effective strategy. Of the only article[135] that concluded that there were no benefits in using a rapid diagnostic test, it was indicated that the cost of the alternative diagnostic technique (usually more invasive but with better success rates) was the key factor driving these results. Papers analysed included high quality articles with an explanation of relevance for health policy, results linked to current knowledge and resource and cost estimations explained in all articles.

4.1.4.3. Appendicitis

One paper explicitly assessed diagnostics for appendicitis in the USA at the hospital setting[140]. The population consisted of 25-year-old primigravid women in the second or third trimester of pregnancy with a valid clinical concern for appendicitis. The strategies compared were diagnostic laparoscopy, CT and MRI following indeterminate ultrasound in pregnant women with suspected appendicitis. Appendicectomy was the indicated treatment. The evaluation used a Markov model. The base case assumes the societal perspective, but it also utilized costs from the payer perspective in sensitivity analyses. The main finding of this study was that for pregnant women with suspected appendicitis, an extremely high level of clinical diagnostic certainty must be reached prior to proceeding to operation without preoperative imaging.

4.1.5. Sexually transmitted diseases

Six articles published from 2002 to 2018 evaluated diagnostics for sexually transmitted diseases in patients with signs of STD[146], such as women with chlamydial infection[141,142], manly in the primary care setting[142,145]. Diagnostic tests assessed were Gram stain test[145], NAAT[141], traditional ELISA screening test[146], herpes simplex virus test[143].

Decision tree models[141–143], a transmission model[144] and a walk-in-clinic model[146] were used to assess the cost-effectiveness. Four articles considered a time horizon longer than one year: 5 years[141], 10 years[141,144], and lifetime time horizon[142], all of them with a discount rate of 3%.

All of the diagnostic strategies were cost-effective. Huang *et al.*[141] found that the key factors that determine this result were: test sensitivity, test cost and the proportion of women willing to wait for the test result. Some articles warned that the results may not be directly applicable to other populations or healthcare settings because only epidemiological data of the specific clinic were used[141,144]. As a general conclusion, in developed countries it was most cost-effective to test only patient with symptoms of having an infection than to test all patients (i.e. screening program).

The sexually transmitted disease articles were of high quality in terms of inclusion of an explanation of relevance for health policy, results linked to current knowledge and resource and cost estimations explained in all articles. Also, an explicit statement on the context of the studies were included in all of them. Bartelsman *et al.*[145] explained that the strength of the study was the large number of consultations analysed but it should be noted that they selected a high-risk population in a large clinic, so these results might not be representative of other populations.

4.1.6. Fungal infections

Six papers published from 2015 assessed diagnostics in primary care[149,152] and hospitals[147,148,150,151] for fungal infections[147–152] with specific diagnostic methods such as potassium hydroxide[149,153], periodic acid–Schiff[149,152], biomarker-based diagnostic strategy of GM[148], aspergillus PCR[148], candida PCR[150] and T2Candida®(Biosystem, Inc.)[151]. The treatment if positive was always antifungal treatment such as fluconazole[147,148,150,151], itraconazole[147,148,152], voriconazole[147,148] or efinaconazole[149].

All articles used a decision tree to assess the cost-effectiveness of the diagnostic strategies and one also performed a BIA[147]. Most trees included the strategies of immediate treatment, rapid diagnostic and culture and a different time horizon were applied: 5 years[148], 1.4 years[149], 1 year[147,150] and shorter than one year[151,152]. As there was no antibiotic therapy, there was also no inclusion of AMR in any model. Only one author included an explanation of the model chosen. In Pàges *et al.*[150] the decision tree model was selected because the interventions of PCR and antifungal treatments were implemented over short period and peritoneal candidiasis is an acute pathology.

Gupta *et al.*[152] concluded that the cost-effectiveness of performing a rapid test depended on the capacity of the physician to diagnose correctly. Also, that the ability of the physicians to detect the infection influenced the result of the CEA. Only in Walker *et al.*[151] the diagnostic test strategy was considered not cost-effective mainly because the disease prevalence and the mortality were important factors, thus the optimal use of the test may be in a setting where the prevalence is around 5% and empirical or prophylactic antifungal therapy is prescribed routinely. As a general conclusion, diagnostic testing in fungal infections became more cost-effective as the cost of treatment or the percentage of suspected cases increases.

The fungal infection papers analysed were of high quality with an explanation of relevance for health policy, results linked to current knowledge and resource and cost estimations explained in all articles. An explicit statement on the context of the study was included in most articles[148,150–152].

4.1.7. Sepsis

Eleven articles, published from 2010, assessed diagnostic for sepsis with real-time PCR technique[154,155,159,161,163], procalcitonin-guided treatment[34,159,163] and a RDT[37,156,161]; in case of positive results, antibiotics were prescribed. Furthermore, some articles included different treatment options which depended on the test results: penicillin for methicillin-sensitive *S. aureus* and vancomycin in case resistance was found[160] and the duration of the antibiotic treatment was calculated based on the level of concentration of PCT[35].

Nine papers assessed the cost-effectiveness of the strategies, mostly used a decision tree model and only one used a time horizon longer than one year[161]. Another article performed a cost-minimization analysis with an individual sampling model[154] and a CUA with a deterministic decision tree model[163]. Bacterial resistance was included assuming that diagnostic test guides the treatment because it can detect and differentiate between methicillin-susceptible and -resistant *S. aureus*[35,160,163].

Diagnostic testing was cost-effective in all articles. It was found that decision models allow to select the best identification strategy of infection but were not able to explore long-term costs and effects beyond 6 months[34]. Furthermore, it is also recommended to perform a cost-minimisation analysis because benefits of both alternatives usually are equivalent. Regarding bacterial resistance, Harrison *et al.*[163] found that incorporating the effect of antimicrobial resistance into the model though increasing the cases of adverse events is difficult because the authors could not quantify these variables[163].

In the sepsis-related articles all papers included an explicit statement on the context of the study, an explanation of relevance for health policy or practise decision and linked the results to current knowledge, except from one[160].

4.1.8. Other

Four papers studied patients with fever of unknown origin attending hospitals[162,165] and primary care[164,166]. As they did not include any further detail, they could not be included in any previous area. Diagnostic test assessed were Rochester criteria plus CRP test[162,164], on demand PCR, lateral-flow glutamate dehydrogenase testing[165] and RPD Adeno Detector[166]. In these studies, the strategies compared were clinical assessment following only a physician examination and checking clinical records of the patients. In case of positive result, antibiotics were prescribed.

All the four papers performed a CEA with a deterministic decision tree model. One also performed a CBA[165]. The time horizon of the studies were shorter than one year or the duration of an episode of acute bacterial infection without recurrence[162] and any inclusion of bacterial resistance was found. No specific comments on the advantages and disadvantages of the modelling technique were discussed in any article.

As seen in previous diseases areas, the prevalence influenced the cost-effectiveness result of including a diagnostic test. Testing produced great savings in antibiotics consumption but can be offset by the cost of antiviral agents and all of the models assumed that physicians followed the test results, which may not be representative of clinical practice. Also, it was found that the more diagnostic tests available for physicians, the more tests they perform, offsetting the benefit of reducing antibiotics consumption. Furthermore, in developed countries vaccination reduced the prevalence of bacterial infection, so testing is not the most cost-effective strategy.

The articles described in the "other" section had an explicit statement on the context of the study, an explanation of relevance for health policy or practise decision and all the resource and cost estimations were explained in the articles. Also, the results have been linked to current knowledge.

4.1.8.1. Tropical

Three articles had a special reference to tropical diseases, one with patients from historic endemicity[167] (Ghana, Papua New Guinea, Solomon Island and Vanuatu) presenting to a clinic with infection symptoms and other two with children visiting health centre with fever without a source[168] and adults presenting with acute fever[169]. Strategies compared included the use of BIOLINE Syphilis 3.0 with DPP Yaws Trep Assay[167], immunoglobin M (lgMFA)[168] and agglutination test[169]. If positive antibiotics such as amoxicillin[168] or doxycycline[169] were prescribed.

All of the three papers performed a CEA and the time horizon of the studies was seven days. None of the articles included AMR into the model but it was mentioned that the benefit of testing could be lower because the potential benefit could be reduced by overtreatment in patients with false positive test results (higher probability to develop resistance)[167].

The main finding was that treat all patient without testing was the best strategy in terms of cost and effectiveness because the analysis was performed in developing countries with few vaccination programs and high prevalence of the disease. Furthermore, in countries with low resources, lack of available treatment should be considered as it increases the number of days to full cure, so results only can be generalized among low resource countries.

This section only included studies performed in low resources countries. All articles found in this section included an explanation of relevance for health policy or practise decision but only two[167,168] also an explicit statement on the context of the study. The resources and cost estimations were explained in two articles[168,169].

4.2. Learnings of health-economic models for diagnostics

This section will include learnings obtained from the review. Specifically, we will discuss the general state of health economics models for diagnostics, highlighting the modelling techniques used and the inclusion of antimicrobial resistance into the models. With this information, recommendations will be made (paragraph 5).

4.2.1. Modelling techniques used

The type of model most frequently found in the revision was a decision tree (deterministic or stochastic) with a short time horizon 28 to 30 days, set in primary care and under a healthcare centre's perspective, mainly modelling a respiratory tract infection disease. The main reason exposed to justify the choice of a tree decision model was that is the most simplest method to select when working under uncertainty conditions and results in a short period.

When using a decision tree model the approach taken can be deterministic or stochastic. In this revision, we found the same number of deterministic decision trees and stochastic decision trees (41 each). The factors that more affected the results in this revision were: the prevalence of infection[71,103] (among other references), the costs of the test[57,84] (among others) and test parameters[78,176] (among others). Most of the articles included the cost/tests. Also, it was also used cost/treatment, which imply per therapy[123] (among others), per week[76] (among others), per day[87] (among others) or per antibiotic prescription[49] (among others). Other costs were physician salary[53] (among others) and[158] (among others).

Most of decision trees considered a time horizon of one month or shorter (7 days[48,103,168,169], 28 days[40,57,64,82] or 30 days[37,54,56]) or one year or shorter (6 months[34,84] or 1 year[102,152,165], among others). For respiratory infection disease, it usually varies from 28 to 30 days. Another option was to give a qualitative information about time horizon: "a single episode of illness"[76], "from the moment the treatment started in primary care to the final healing or clinical failure after a third antibiotic option prescribed in hospital"[47], "a treatment episode"[53], "an episode of acute bacterial infection without recurrence"[162] or "duration of influenza-like illness"[43].

Markov modelling was the second most used model technique (13 of 129). A decision tree can lead into a Markov model, in which after performing the test and prescribing the appropriate treatment, the patient could depict different states. It was mostly applied when it was needed to perform a long-term model with a stochastic approach. Most of them (8) had a long term horizon: 3 years[55,110], 10 years[140], 30 years[106], 50 years[115], 90 years[100] or a life time horizon[107,135] (the preferred discount rate was 3%). This type of technique was used in gastrointestinal articles and respiratory infections and mainly used a healthcare payer's perspective, a societal perspective, or both combined.

Five articles[14,15,20,119,122] used as methodology the regression model, set in primary care and with a short time horizon. It was the preferred method when more than one country were analysed: Norway and Sweden[14] and Belgium, United Kingdom, Netherlands, Poland and Spain[15]. Its main advantage was the wider applicability and the possibility to incorporate into the model as many variables as consider relevant by the author (e.g. cost and quantity of antibiotic prescription, price of the test and enhancing communication skills of the GP). Oppong *et al.*[14] 2013 choose a deterministic healthcare centre's perspective and using hierarchical regression, data were analysed in terms of the effect on antibiotic use, cost and patient outcomes (symptom severity after 7 and 14 days, time to recovery and EQ-5D). Also, they controlled for patient characteristics (self-reported symptom severity, comorbidities and health-related quality of life) at first attendance. Oppong *et al.*[15] 2018 had a stochastic healthcare payer's perspective. They performed

a multilevel modelling, recommended for the economic evaluation of cluster and multinational trials. Dependent variables included total cost, QALYs and antibiotic prescribing. The model controlled for day 1 EQ-5D, gender, age, smoking, sex, wheeze, pulse rate, temperature, respiratory rate, blood pressure and duration of cough. These variables were controlled for to adopt a similar approach to the clinical study. To explore country variation in the cost-effectiveness of the interventions, adjusted country specific cost-effectiveness estimates were also obtained using a Bayesian approach (minimally informative prior distributions were placed on all model parameters).

4.2.2. Antimicrobial resistance

Of the 129 articles, 21 included in the model the appearance of antimicrobial resistance with 6 articles related to the respiratory tract infection disease[49,53,54,56,57,68], 6 to tuberculosis[89,90,92,93,96,98], 3 to sepsis[32,35,160], 2 to pneumonia[80,82] and 1 each to gastrointestinal[138], urinary tract infection[111], influenza[71] and one categorized as other[168].

In respiratory tract infections disease articles AMR was included into the model mainly modifying the cost per antibiotic prescription (applied to 5 of the 6 papers). Oppong *et al.*[15] and Holmes *et al.*[57] added a fixed cost for every antibiotic prescribed. This cost was based on annual cost of resistance in USA ($55 billion), EU (€1.5 billion) and total global resistance over a 35-year period ($2.8 trillion annually). Thus, the calculations were simple as authors divided the previous costs by the annual number of prescriptions in each region. Schuetz *et al.*[54] and Stojanovic *et al.*[56] also followed this method but they calculated the daily costs of antibiotic resistance by dividing the cost per prescription by the average duration (number of days) of a typical antibiotic treatment. Similarly, Michaelidis *et al.*[53] assumed that the intrinsic value of an antibiotic prescription safely avoided would equal the health care system cost of antibiotic resistant infections attributable to that antibiotic prescription. In pneumonia one article also paid the attention to costs. In Ost *et al.*[82] authors consider antibiotic use and survival rate simultaneously. They use the number of antibiotic days per survivor to report ICER so antibiotic use was viewed as a cost (in terms of promoting antibiotic resistance). A drawback of these methods is that they imply to consider that the antibiotic prescription in ambulatory care is the main cause of resistance dissemination while in real practice it depends on several aspects. For instance, the World Health Assembly adopted a global action plan on antimicrobial resistance, which outlines five objectives[177], one of them is to optimize the use of antimicrobial medicines in animal health and specially to avoid antibiotics to growth them[178].

Another approach to introduce AMR into the model was decreasing the efficacy of the treatment as the rate of resistance increases. Balk *et al.*[49] decreased the efficacy of the antibiotic compared to placebo to simulate an increasing AMR to amoxicillin in a paper of respiratory tract infection. Also, You et al.[138] from gastroenteritis disease, introduced the effect of eradication rate into the model taking into account antibiotic resistance over a range of 50-100%. In Saito *et al.*[168], a paper classified as “other infections”, the model assumed that if drug-resistant pathogen was found the treatment had 0% effect if treated with amoxicillin. As they did not find available data for the prevalence of resistance in the community, they assumed to be 50%. This approach needs an assumption about the prevalence of resistance in the population, which had to be made with the only reference that authors have, community resistance has to be lower than in hospital settings. Recently, studies aimed at determining the incidence of infections with resistant bacteria are arising. In this sense, we have found a study that used prevalence data from European Centre for Disease Prevention and Control to determine the annual burden of infection with antibiotic-resistant bacteria[10].

Some tests can detect if the pathogen is resistant to any antibiotic so the treatment could be adjusted in advance. In Dinh *et al.*[80] test can yield not only positive or negative results in terms of diagnosing community-acquired pneumonia but also it can perform a microbiological identification. If *S. pneumoniae* was found, the treatment prescribed had a narrowed spectrum, which can reduce the probability of AMR. Also, in two sepsis articles test can differentiate among *Staphylococcus.* Brown *et al.*[179] test can detect and differentiate between methicillin-susceptible and methicillin-*resistant S. aureus* and in Harrison *et al.* the model included an extra empiric therapy (vancomycin) for possible methicillin-resistant Staphylococcus aureus. Similarly, in Steuten *et al.*[35] the duration of the antibiotic treatment was calculated based on the level of concentration of PCT. In diagnosing sepsis, they used antibiotic days avoided and subsequent cases of infections or Clostridium difficile infections avoided to evaluate two treatment pathways, testing and standard care.

Another approach to introduce AMR into the model is the need of prescribing a second treatment in case of failing first treatment. In Rothberg *et al.*[111], urinary infection article, a patient may fail empiric antibiotic therapy either because of misdiagnosis or antibiotic resistance. In the latter case, an initial culture result confirms the diagnosis, allowing immediate treatment with another antibiotic. When resistance is low, few patients fail therapy. When resistance increased the percentage of patients failing empiric therapy increased, and more benefited from urine culture. When in vivo resistance reached 30%, the cost-effectiveness of routine urine culture, compared to urine culture for negative urinalysis only, fell to $49 per SDA. They found that for patients with pyuria who failed therapy, it was best to immediately retreat with a quinolone, without waiting for a culture result. For strategies that did not include immediate retreatment, initial urine cultures for pyuria were much more cost-effective ($8 per SDA at 30% resistance).

In an influenza related article, authors assumed a given rate of resistance in circulating influenza virus. Lavelle *et al.*[71] create a primary scenario in which prevalence of oseltamivir resistance was 29%. In the absence of any drug resistance, treatment would shorten the duration of uncomplicated influenza symptoms by 36 hours. For the proportion of children infected with a resistant virus, no clinical benefit from treatment will be received. Results found that testing maintains a more favourable cost-effective profile for a higher prevalence of oseltamivir-resistant viruses compared with the empiric treatment strategy. However, this approach can only consider one type of resistance (caused by the H275Y mutation).

All of the previous authors included AMR into the model based on different hypothesis such as AMR was only caused by human antibiotic prescription. In practice, national and international programs against the emergence of antibiotic resistance fight against this phenomenon from the fields of human and veterinary health[177]. However, as indicated in the methodology of this report, articles on animals were excluded. Also, it was considered that a reduction in antibiotic prescription had an equal-direct effect to reduction of AMR. In real world, this consumption-resistance elasticity may not be linear (for example, it could thought that if the consumption of antibiotics is reduced by a certain amount thanks to the introduction of a RDT, the resistance will be reduced by a smaller proportion)[180].

4.3. Recommendations on health-economic models for diagnostics

We have been able to identify 129 health-economic analyses of diagnostic strategies for infectious disease in the period 2000-2018. While this is more than we initially expected, we believe the field of HTA of diagnostics is still in its infancy. The majority of studies used a decision model (as discussed in paragraph 4.2.1), which makes it difficult to capture any time-related consequences

of improved diagnostics in the analysis, even though this is considered to be an important part of the value of RDTs[8]. Compared to pharmacoeconomic analyses, we believe there are some characteristics that should be stated more explicitly when performing a diagnostic-economic analysis. Below, we make some recommendations to be considered when performing a CEA of a diagnostic strategy:

1| The relevant patient-population considered should be clearly defined, including characteristics such as age, comorbidities, vaccination status. If the analysis is linked to a clinical trial, inclusion and exclusion criteria should be stated in the methods and implications regarding the generalizability should be discussed. This includes the reasons for going to a healthcare facility, such as symptoms patients may be suffering from.

2| The clinical setting in which the clinician operates, and the diagnostic test is performed should be specified. Examples include a GP office in Europe or a field hospital in Africa. The setting impacts the severity of complaints that cause patients to seek care, as well as the prevalence of the disease of interest.

3| The diagnostic test should be specified (including brand and type). Regarding the costs of the test, a unit-costing approach is preferred, which includes reagents usage, staff costs and device costs (including depreciation and maintenance). This can be used to explore the different settings where a diagnostic test can be cost-effective (e.g. GP offices with at least 5,000 patients or a laboratory performing 20,000 tests per year). An alternative to this unit-costing approach can be to use a fixed price per test.

4| The overall diagnostic algorithm should be specified, few tests are used in isolation and the capacity of the physician to diagnose correctly without an RDT may affect the cost effectiveness. If possible, different diagnostic algorithms should be compared, for example using a cost-effectiveness frontier to visualize the results. Additionally, the adherence of the clinician to the test results, is important to incorporate. This was seldom included in the studies in this review, but it may have a major influence on the cost-effectiveness of the diagnostic test.

5| Treatment regimens should be specified for the outcomes of the various diagnostic options. As treatment will directly influence clinical outcomes and costs, this is an important factor for CEAs of diagnostics. The availability of effective and affordable treatment for patients with a positive test result, is critical.

6| The time framework and horizon should be clearly defined, also when using a decision tree. The added value of innovative RDTs may in many cases be a time reduction for either patients, clinicians or laboratory technicians. Defining the time horizon may be as simple as stating: “the time horizon considered is one disease episode”, if this is the extent of the trial results. Health-economic modelling does allow for extrapolations after beyond the data collected during a trial and we think longer-term modelling is preferred to assess all consequences of a new test.

7| Many different outcomes were assessed in the articles included in this review, in Figure 12 we mention some categories: QALYs, DALYs, correct diagnoses and antibiotic consumption, still, many papers were categorized as “other” and used something else. Only DALYs and QALYs can be used to compare outcomes between different diseases. For health economic analyses, it is recommended to use outcomes that can be applied to different patient populations and disease areas[4]. Also, regarding the cost-effectiveness outcomes, we recommend the use of the costs per QALY gained or per DALY saved, expressing the cost-effectiveness of a new diagnostic intervention as an ICER.

8| The budget impact was seldom included in the CEAs; however, we believe this may provide important information regarding the affordability of the new diagnostic intervention[181]. Especially if the current standard-of-care is based on the clinician’s expertise, a new

diagnostic test has the potential to cause a major cost increase, even though the intervention may be cost-effective. This should also consider the budget where the investments to implement the test come from and whether it is feasible to either increase the budget or reduce expenditure elsewhere.

The points above should in our view, be covered in any CEA of diagnostics. If it is not possible to incorporate these points in the model, e.g. due to limitations in the clinical data, these omissions should be discussed as limitations. We believe there are some opportunities in general with infectious disease diagnostics, points that only a few studies include:

Firstly, disease transmission, which was only included in a few studies. This is an opportunity to test the public health advantages such as the influence of shorter disease duration due to earlier diagnosis and/or more targeted treatment or differences in the cost-effectiveness that may arise due to varying disease incidence (including the benefits of improved diagnosis in outbreak scenarios). Second, AMR is included in some models, but we believe estimating the increase or decrease of resistance, due to the treatment options after the diagnostic method, may be a relevant aspect for diagnosing both bacterial and viral infections. Lastly, to enable priority setting of infectious disease prevention, it may be interesting to include other public health interventions, such as improved vaccination, contact-tracing and improved (patient) education, as opposed to strictly assessing diagnostic strategies.

5. Conclusions

5.1. General conclusions

Health-economic analysis of diagnostic strategies of infectious disease most often concern respiratory tract infections, followed by vector-borne diseases and infections of the gastrointestinal tract. Most models are decision trees, in which time is not modelled. Time horizons in general are limited and most models primarily assess a single consultation with a clinician. Various settings are considered with primary care being most popular, followed by the hospital-setting. The perspective taken is most-often the healthcare centre's, followed by the healthcare payer's perspective. Few studies manage to include AMR in the analysis. About half of the models incorporate a universal quality-of-life-related clinical outcome (QALYs or DALYs) but supplementing with another measure such as reduction in antibiotics prescription. The conclusion of most studies was positive: either cost-saving or cost-effective.

A main gap identified is the exclusion of a time element in many models; while reducing time often is an important part of a new diagnostic method, only few models managed to incorporate this. Other important gaps identified are the frequent absence of universal outcomes that can be applied to different patient populations and disease areas; and ambiguity regarding the patient population assessed within which clinical setting (i.e. the symptoms are not well defined or the setting in which the clinician operates is not clear). Finally, the scope of most analyses could be a bit broader from a public health perspective, such as how improved diagnostics of infectious disease relate to infection prevention and vaccination strategies.

5.2. Preferred strategies for VALUE-Dx health-economic models

5.2.1. Short-term modelling

For the short-term modelling within VALUE-Dx project, we have found that the most frequent modelling technique was the decision tree. This technique assesses a finite set of alternatives to uncertain events. The decision nodes show the possible actions. Thus, one of the comparison groups should be usual care, so that the effects can be compared with the actual pattern of antibiotic prescribing. When usual care is not included, the comparison of the different tests may not adequately reflect the variation from the actual pattern.

In a decision tree there are also random nodes, in which the result is not controlled by the decision maker. From these points the possible uncertain events will arise, that is, the possible probabilistic responses of the patient to the action taken. For this reason, it is especially important to establish that the inclusion of patients reflects as much as possible the cases of uncertainty regarding the indication of antibiotics. It is also important to collect information on factors affecting uncertainty in the decision on antibiotic use (e.g. characteristics of the treating clinician). These factors are of great importance in order to later analyse whether the differences in the economic evaluation are related to the aspects that affect uncertainty. Especially in multi-centre studies (both multi-country and multi-centre in each country), cost information should reflect as much as possible the particular realities. The use of national or regional aggregates may not adequately reflect these variations. Also, the comparison should be made separately between the outpatient and inpatient settings. Differences in usual practices between the two

settings have an effect on the admission status of patients and on the indication of antibiotics. An article that adapts the analysis based on the setting. Stojanovic *et al.*[56] modelled PCT testing differently for each setting (primary care and hospital). For primary care, they considered patients from ED discharged home or office visits. Same number of patients entered the "usual care" arm or the PCT arm. They assumed a single PCT test to support antibiotic initiation. For hospital patients, they assumed an initial PCT test upon initial presentation (e.g., ED admitted to ward or ICU) and subsequent monitoring tests every other day until discharge.

Intervention groups should not be numerous and should include tests that allow for diagnostic discrimination. In this way, the effects of specific interventions can be separated. If possible, incorporating a group in which the evidence is combined makes it easier to analyse the specific and aggregate effects of the interventions. However, as the current review included not only respiratory tract infection disease, we have learned other aspects related to the tests. In this sense, we have recognized that algorithms are generally made up of more than one test. However, if we want to evaluate this particular, we must be cautious as Takemura *et al.*[164] found that more diagnostic tests available for physician result in more test performed, thus the cost offset the benefit of reducing antibiotics consumption.

In acute respiratory infections, the patient follow-up period should be linked to the evolution of symptoms. In the literature reviewed this period is generally 28 days, although the clinical criterion for defining acute cough (one of the most common symptoms in acute respiratory infections) is 21 days. As seen before, some decision trees can be followed by a Markov model[55,107,110,169], which extends the time horizon, even to reach a life time horizon as seen in Hollingworth *et al.*[107]. With a Markov model authors try to simulate what happens in the disease process. They are especially useful for modelling chronic diseases. Within the duration of follow-up, the number of days of absence of symptoms should be defined to separate episodes of acute respiratory infection. This aspect is relevant in order not to assign effects and costs to different infectious processes.

5.2.2. Long-term modelling

For the long-term modelling within the VALUE-Dx project, there are a couple of articles by which we were inspired. First of all, Nshimuimukiza *et al.* developed an influenza model which incorporates the transmission of the virus using an SIR model within the population of a whole province. A certain proportion of patients infected move into an economic analytic model, where they could either survive or die[73]. An important aspect is that only a certain proportion of patients decides to also seek care, the model considers a percentage of infected that remain asymptomatic and also a percentage of symptomatic patients that do not seek care, as they do not feel very ill[73]. These are important factors to consider when including disease transmission in the long-term health-economic model, especially considering CA-ARTI can have various etiological causes.

Another model was developed by Phillips *et al.* for malaria, which considered children under the age of 5 years old. This is a Markov model linked to a micro-simulation model. Patients in the Markov model, which used cycles of 30 days, could either not have fever, have fever or die of fever. In case of no fever, nothing happened, and the child could get fever in the next cycle. If a fever occurred, the child's caretaker could decide to seek care, after which a diagnostic pathway followed (comparable to a decision tree), including potential hospitalizations.

Considering the papers discussed in this review, we aim to start with three parts in the long-term model:

1| **Population model with a care-seeking component**, which will model the population of certain areas, starting with hypothetical areas, working towards entire countries. This model component considers the seasonal variability of CA-ARTI and factors that influence patients to seek care (such as cultural factors or earlier experiences) and where to seek care (e.g. a GP office or emergency department).
2| **Consultation model**, comparable to the decision trees used in most studies included in this review, which will consider the initial consultation, the treatment decision and short-term complications that may follow. This will likely be the same or very similar to the short-term modelling approach (paragraph 5.2.1). After a disease episode, patients will re-enter the population model.
3| **AMR model**, which will use the increase or decrease in antibiotic prescriptions for the whole population to model AMR levels for the future, using the OECD approach[182].

After these components have been developed, we may pursue adding a disease transmission model, for example influenza, to model the influence of improved diagnostics on disease transmission.

A societal perspective will be used, incorporating patient-level costs as well as productivity losses. The output of the model will focus on the standardized costs/QALY, but also more specific outcomes, such as the proportion of correct diagnoses, reductions in antibiotic prescriptions and eventually, AMR levels. Uncertainty will be analysed using a PSA, where the uncertainty of all parameters will be analysed simultaneously.

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UNIVERSITY MEDICAL CENTER GRONINGEN: SIMON **VAN DER POL**, THEA **VAN ASSELT**, MAARTEN **POSTMA**

Review of health-economic approaches for diagnostic-driven antibiotic use

Deliverable 5.1 - appendix I

Data extraction form

VALUE-Dx

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 820755. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and bioMérieux SA, Janssen Pharmaceutica NV, Accelerate Diagnostics S.L., Abbott, Bio-Rad Laboratories, BD Switzerland Sàrl, and The Wellcome Trust Limited.


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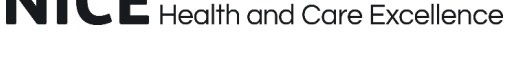
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janssen


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Data extraction form VALUE-Dx task 5.2

* Required

Email address *

Your email

General

Title

Your answer

First author (last name)

Your answer

Year published

Your answer

Disease area

- [ ] (General) respiratory tract infection
- [ ] Influenza
- [ ] Pneumonia (specifically)
- [ ] Urinary tract infection
- [ ] gastroenteritis
- [ ] General reflux complaints
- [ ] Tuberculosis
- [ ] Malaria
- [ ] Dengue
- [ ] HIV
- [ ] Fungal infection
- [ ] Appendicitis
- [ ] Other:

Specific pathogens (if given, separate by semicolon ;)

Your answer

Objective (from abstract)

Your answer

Introduction

Research question(s)

Your answer

Word used to describe "diagnostic strategy" (in research question)

- [ ] Diagnostic
- [ ] Testing
- [ ] Screening
- [ ] Other:

Explicit statement on the context of the study

	1	2	
Yes	○	○	No

Explanation of relevance for health policy or practise decision

	1	2	
Yes	○	○	No

Country

Your answer

Methodology

Is the model used based on a previously-published model? (If yes, give author and year)

- ○ No
- ○ Other: _____

Target population and subgroups

Your answer

Setting

- ☐ 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 (diagnostics) [separate different strategies with a semicolon ;]

Your answer

Treatment options included in the analysis [separate different strategies with a semicolon ;]

Your answer

Time horizon (years)

Your answer

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)

	1	2	
Yes	○	○	No

Discount rate for base case (health outcomes)

Your answer

Discount rate for base case (economic outcomes)

Your answer

Study type

	Cost Analysis	Cost Effectiveness analysis	Cost Utility Analysis	Cost Benefit analysis	Cost-minimization analysis	Budget Impact Analysis
As qualified by the authors	☐	☐	☐	☐	☐	☐
As qualified by the reviewer (use Drummond book for background)	☐	☐	☐	☐	☐	☐

Reported clinical outcomes

- ☐ 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.

	1	2	
Yes	○	○	No

Are the resource and cost estimations explained in the article?

	1	2	
Yes	○	○	No

Costs of diagnostic method (in reported currency) [separate different strategies with a semicolon ;]

Your answer

Costs of treatment options (in reported currency) [separate different strategies with a semicolon ;]

Your answer

Currency/currencies reported

- [ ] US dollars
- [ ] Euros
- [ ] Pound Sterling
- [ ] Japanese yen
- [ ] Other:

Currency year used

Your answer

What are the methods used to convert to a common currency

Your answer

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

Your answer

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?

	1	2	
Yes	○	○	No

Is antibiotic resistance included in the model?

	1	2	
Yes	○	○	No

If yes, how is antibiotic resistance included?

Your answer

Results

Incremental costs and outcomes (value)

Your answer

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
- [ ] Other:

Is the same common currency used as in the methods (if no, explain how this is done for the results)

- ○ Yes
- ○ 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)
- [ ] Other: _____

For the DSA, which ranges of values are used?

Your answer

For the PSA, how many replications are used

- ○ No PSA
- ○ 1,000
- ○ 10,000
- ○ Other: _____

Have subgroup analyses been performed? (If yes, which subgroups and how?)

Your answer

Discussion

Main findings

Your answer

Limitations

Your answer

Specific limitations/gaps in the assessment of diagnostics

Your answer

Generalisability

Your answer

Have the results been linked to current knowledge?

	1	2	
Yes	○	○	No

What is the main conclusion of 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?

Your answer

Specific advantages of the modelling technique discussed in the article

Your answer

Specific DISadvantages of the modelling technique discussed in the article

Your answer

Other

Source of funding

- [ ] Industrial
- [ ] Governmental grant
- [ ] Academic grant
- [ ] No funding
- [ ] Not reported
- [ ] Other: _____

Is a statement on the conflicts of interest present?

	1	2	
Yes	○	○	No

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UNIVERSITY MEDICAL CENTER GRONINGEN: SIMON **VAN DER POL**, THEA **VAN ASSELT**, MAARTEN **POSTMA**

Review of health-economic approaches for diagnostic-driven antibiotic use

Deliverable 5.1 - appendix II

Data extraction results

VALUE-Dx

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 820755. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and bioMérieux SA, Janssen Pharmaceutica NV, Accelerate Diagnostics S.L., Abbott, Bio-Rad Laboratories, BD Switzerland Sàrl, and The Wellcome Trust Limited.



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Table of contents

List of abbreviations

ABR	Antibiotic Resistance
ACT	Artemisinin-based Combination Therapy
AECB	Acute Exacerbation of a Chronic obstructive pulmonary disease
AMR	Antimicrobial Resistance
AP	Acute Pharyngitis
A-PCR	Aspergillus Polymerase Chain Reaction
ARTI	Acute Respiratory Tract Infection
BAL	Bronchoalveolar Lavage
BM	Bone Marrow Aspirate
BC	Bacterial Culture
BCDT	Blood Culture-Directed Therapy
BIA	Budget Impact Analysis
C.	Chlamydia
CA-ARTI	Community-Acquired Acute Respiratory Tract Infection
CAM	Chloramphenicol
CAP	Community-acquired pneumonia
CBA	Cost Benefit Analysis
CD4	Cluster of Differentiation 4
CDI	Clostridium Difficile Infections
CEAC	Cost-Effectiveness Acceptability Curve
CMA	Cost-Minimization Analyses
CNY	Chinese Yuan
COPD	Chronic Obstructive Pulmonary Disease
CP	Control Period
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	Computed Tomography
CTX	Cotrimoxazole
CUA	Cost–utility analysis
DALY	Disability-Adjusted Life Year
DFL	Dutch Florins
DSA	Deterministic Sensitivity Analysis
DST	Drug-Susceptability Testing
DU	Duodenal Ulcer
ED	Emergency Department
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D	European Quality of life index version 5D
ETT	Endotracheal Tube
EU	European Union
FET	Fluconazole Empirical Therapy
FOB	Bronchoscopy
GABHS	Group A Beta-Haemolytic Streptococcus
GAS	Group A Beta-Haemolytic Streptococcus
GDH	Glutamate Dehydrogenase
GM	Galacomannan
GP	General Practitioner
GSS	Gram-stained smear
H.	Helicobacter
H1N1	Hemagglutinin Type 1 and Neuraminidase Type 1
HE	Health Economics
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus

ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IGRA	Interferon-gamma release assay
ILI	Influenza-Like Illness
KOH	Potassium Hydroxide
L	Liter
L-AmB	Liposomal Amphotericin B
LED	Light-Emitting Diode
LF-LAM	Lateral Flow Urine Lipoarabinomannan Assay
lgMFA	Lateral Flow Analysis Of Immunoglobin M
LJ	Löwenstein-Jensen method
LOSE	Length of Sepsis Episodes
LRTI	Lower Respiratory Tract Infections
LSC	LightCycler SeptiFast
LSF	Molecular Test
MD	Microbiological Diagnosis
MDR	Multi-Drug Resistant
mg	Milligram
MODS	Microscopic Observation Drug Susceptibility
mRDT	Molecular Rapid Diagnostic Tests
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-Resistant Staphylococcus Aureus
MSM	Men who have Sex with Men
MSSA	Methicillin-Sensitive Staphylococcus Aureus
MTB	Mycobacterium Tuberculosis
MTZ	Metronidazole
NA	Not Available
NAAT	Nucleic Amplification Test For Chlamydia Trachomatis
NSAID	Nonsteroidal Anti-Inflammatory Drugs
odPCR	On Demand PCR
OIA	Optical Immunoassay
PAS	Periodic Acid–Schiff
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PCT	Procalcitonin Test
pH	Potential Hydrogen
PID	Pelvic Inflammatory Diseases
POC	Point Of Care
POCT	Point Of Care Test
PPI	Proton Pump Inhibitor
PPM	Public-Private Mix
PSA	Probabilistic Sensitivity Analysis
PUA	Pneumococcal Urinary Antigen
PUD	Peptic Ulcer Disease
QALD	Quality-Adjusted Life-Day
QALY	Quality-Adjusted Life Year
RCT	Randomised controlled trial
RDT	Rapid Diagnostic Test
RFT	Rapid Flu Test
RIF	Resistance To Rifampicin
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infections
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RUT	Rapid Urease Test
S.	Streptococcus
SB	Meglumine Antimoniate

SHPAb	Serum Helicobacter Pylori Igg Antibody
SHPAg	Stool Helicobacter Pylori Antigen
SIR	Susceptible-Infected-Recovered
SIRS-SS	Systemic Inflammatory Response Syndrome With Suspected Sepsis
SP	Streptococcus Pneumoniae
SSM	Sputum Smear Microscopy
SSP	Semi-Synthetic Penicillin
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infection
T2DT	T2Candida-Directed Therapy
TB	Tuberculosis
TLA	Thin-Layer Agar
TST	Tuberculin Skin Testing
UBT	Urea Breath Test
UC	Ulcerative Coliti
UGI	Upper GI Radiography
UHPAb	Urine Helicobacter Pylori Antibody
UK	United Kingdom
USA	United States of America
USD	United States dollar
VL	Visceral Leishmaniasis
WHO	World Health Organization
WTP	Willingness-To-Pay
Xpert	GeneXpert
ZN	Ziehl-Neelsen

1. Respiratory tract infections

1.1. General respiratory tract infections

Table 1.1A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Balk (2001)	NA	Primary care	Patients with suspected, uncomplicated, community-acquired, acute bacterial sinusitis who had had symptoms for less than 4 weeks and who had not had recurrent sinusitis	No patients given antibiotic treatment; all patients given empirical amoxicillin treatment; patients given amoxicillin based on the results of a set of clinical criteria; patients given amoxicillin based on the results of sinus radiography (plain film x-ray)	10-day course of amoxicillin, 250 mg 3 times a day.
Bertran (2000)	Spain	Primary care, Hospital	Patients with CAP, less than 65 years old, without hospital admission criteria; Patients with AECB due to respiratory infection.	Performing a diagnostic tests (simple chest x-ray and a blood count). The patient can respond clinically well to treatment and be cured (probability P1, clinical efficacy). In those patients who do not respond well (persistence of fever, probability 1-P1) after 3-5 days of treatment, the possibility of changing antibiotics and obtaining favorable clinical response	Macrolides (erythromycin, clarithromycin, azithromycin, roxithromycin); Fluoroquinolones (ciprofloxacin, ofloxacin); Cephalosporins (cefuroxime, ceftriaxone);

				(probability 1-P2) is raised or refer the patient to a specialized consultation with eventual hospital admission and cure (probability P2). A low percentage of patients will present unfavorable evolution, with therapeutic failure and death in the hospital (P3).	Betalactam (penicillin, amoxicillin, amoxicillin clavulanic acid).
Cals (2011)	The Netherlands	Primary care	Eligible patients were aged 18 years or older, consulting with their GP with a new episode of acute cough of up to 28 days and caused by an lower respiratory tract infections (LRTIs) in the GPs view	GPs managed patients in the usual care group with the availability of the Dutch College of GPs guidelines for acute cough: GP use of CRP; GP communication skills training; GP use of CRP and GP communication skills training	
de Bock (2001)	The Netherlands	Primary care	Patients presenting with Acute sinusitis in primary care	Wait and see (the patient is advised to take analgesics for the headache, and asked to return to the practice for antibiotic treatment after 1 week if there is no improvement in symptoms); Selective prescription (antibiotics are prescribed only to patients selected on the basis of a structured clinical assessment); Antibiotics (antibiotics are prescribed to all patients at first presentation); Ultrasound assessment (antibiotics are	Doxycycline

				prescribed only after a positive result on ultrasound investigation); Radiographic assessment (antibiotics are prescribed only after a positive result on radiographic investigation)	
Durski (2013)	Uganda	Hospital	HIV-infected adults with suspected central nervous system infections	Comprehensive testing (all available diagnostic tests are ordered simultaneously by the clinician with the laboratory running all diagnostic tests simultaneously); stepwise testing (it limited the number and order of diagnostic tests performed, prioritizing tests with a high sensitivity for the most prevalent diseases); minimalist testing (it limited the number and order of diagnostic tests to high-yield tests only, eliminating tests with poor sensitivity/specificity)	2g ceftriaxone intramuscularly once for meningococcal meningitis; five days of ceftriaxone for pneumococcal meningitis.
Giraldez-Garcia (2011)	Spain	Primary care	Patients between the ages of 2 and 14 years who consult with a primary care physician due to AP symptoms. We considered a hypothetical cohort of four million children, based on estimates of the number of	Treat all; clinical scoring; rapid testing; culture; rapid test + culture; clinical scoring + rapid test.	Penicillin; azithromycin (in case of allergy)

			paediatric consultations for sore throat that occur annually in the Spanish primary care centers.		
Holmes (2018)	Wales, UK	Primary care	Adults with symptoms of acute respiratory tract infection (ARTI) for >12 hours where the antibiotic decision is unclear versus immediate antibiotic prescription.	Current standard of care; antibiotic prescribing conditional on POC CRP testing.	Antibiotic: Amoxicillin 500 mg three times daily for 7 days.
Hunter (2015)	England	Primary care	Cohorts of 100 hypothetical patients with RTI	Current GP practice: Patients with RTI symptoms are prescribed antibiotics dependent on GP's views and patient expectation. Three strategies of CRP testing: 1) GP plus CRP; 2) Practice nurse plus CRP; 3) GP plus CRP and communicating training	Antibiotics at index consultation, antibiotics within 28 days of index, antibiotics for subsequent incidents of RTIs after 28 days
Lathia (2018)	Canada	Pharmacy	Patients with sore throat	Current situation (patients receiving care in family physician's office, walk-in clinic or emergency room); patients receive care from a pharmacist in addition to the other three settings	Antibiotics

Maizia (2011)	France	Primary care	Adults (16 years and older) and children (up to 15 years old).	Observation only (reference strategy); clinical scoring; RDT testing; throat culture; clinical scoring combined with RDT testing; RDT testing combined with throat culture; systematic antibiotic therapy.	Amoxicillin penicillin A (6 days) and in case of allergy cefuroxime-axetil (4 days).
Michaelidis (2013)	United States	Primary care	Two hypothetical cohorts were modeled in separate trial-based analyses: adults with ARTIs judged by their physicians to require antibiotics and all adults with ARTIs.	Procalcitonin-guided antibiotic therapy; usual care.	Empiric antibiotic prescription
Neuner (2003)	United States	Primary care	Adults in the general US population.	Observation without testing or treatment; empirical treatment with penicillin; throat culture using a two-plate selective culture technique; optical immunoassay (OIA) followed by culture to confirm negative OIA test results; OIA alone.	Penicillin at a dosage of 250 mg four times a day for 10 days.
Nicholson (2014)	United Kingdom	Hospital	People presenting to medical admissions units, or any ward accepting acute medical admissions, with an	Point-of-care tests (POCTs) for influenza A and B and pneumococcal infection; reverse transcriptase-polymerase chain reaction (RT-PCR) tests for influenza A and B and RSV A and B; and conventional culture for these pathogens.	Broad-spectrum antibiotics (cephalosporins, co-amoxiclav, piperacillin with tazobactam, carbapenems,

			acute exacerbation of chronic cardiopulmonary illness of ≤ 168 hours (7 days) duration or an acute cardiopulmonary illness of ≤ 7 days' duration [including pneumonia, influenza/ILI, exacerbations of chronic obstructive pulmonary disease (COPD), bronchitis, asthma, congestive heart failure or cardiac arrhythmia], who satisfied the study inclusion and exclusion criteria and could be recruited to the study within a 16-hour period of initial assessment by the patient's medical team.		quinolones, tetracyclines, cotrimoxazole, clarithromycin, azithromycin and clindamycin); narrow-spectrum antibiotics (Gram-positive antibiotics benzylpenicillin, flucloxacillin, amoxicillin (and ampicillin), erythromycin, vancomycin, rifampicin, fusidic acid, linezolid, daptomycin, gram-negative antibiotics, gentamicin and other aminoglycosides, aztreonam, trimethoprim, nitrofurantoin, anaerobic antibiotics and metronidazole).
Oostenbrink (2002)	The Netherlands	Hospital, Pediatric	Children (1 month to 15 years) visiting	Practice a lumbar puncture, based on the characteristics of the	Antibiotics

		Emergency Department	the pediatric emergency department of a hospital with meningeal signs	patient's history, physical examination and serum C-reactive protein (CRP) ; do not practice this	
Oostenbrink (2003)	The Netherlands	Hospital	360 children from one month up to fifteen years of age visiting the emergency department of a hospital with meningeal signs between 1988 and 1998	Diagnostic decision rule, based on a clinical score and a CSF score (cell count in cerebrospinal fluid) for lumbar puncture and empirical treatment for bacterial meningitis; current practice (a low threshold to perform a lumbar puncture, and empirical treatment)	3rd generation cefalospsorin; amoxicilin; bemzylpenicilim
Oppong (2013)	Norway and Sweden	Primary care	Patients aged ≥18 years presenting to their GP for the first time with an acute or worsened cough as the main or dominant symptom for up to 28 days, or who had a clinical presentation suggesting lower respiratory tract infections.	Rapid test, point-of-care C-reactive protein.	Antibiotics
Oppong (2018)	Belgium, United Kingdom, Netherlands, Poland and Spain	Primary care	Patients presenting with respiratory tract infections in primary care, from	CRP; communication skills; CRP and communication skills combined; usual care	Antibiotics

			Belgium, the Netherlands, Poland, Spain and the UK (England and Wales).		
Perone (2007)	Switzerland	Primary care	372 patients over 15 years of age who were referred for a sore throat were included between March 1999 and September 2001 if their clinical score was between two and four points.	Rapid test systematique then antibiotic therapy if the test is positive; quick test if the score is 2 or 3 then antibiotic to patients with a positive result or a clinical basis of 4; empiric antibiotic therapy to patients with a clinical score of 3 or 4.	Ten-day penicillin.
Schuetz (2015)	United States	Hospital	The patient population in this study is patients with suspected ARTI infection diagnoses seen in one of three settings: inpatient hospitalsetting (not in the intensive care unit - ICU); hospital ICU; outpatient clinic or emergency department (ED) based on the meta-analysis data	PCT testing and monitoring; usual care	Typical dosages and mix of expected therapy were derived frompublished clinical treatment guidelines (many references, but nothing explicit)

Stankiewicz (2003)	United States	Primary care	One hundred patient were evaluated for criteria meeting the subjective diagnostic criteria for chronic rhinosinusitis as developed by the Task Force for Acute and Chronic Rhinosinusitis. Seventy-eight patients satisfied the criteria for a subjective diagnosis of chronic sinusitis. Each patient filled out a questionnaire identifying and measuring the severity of symptoms.	Subjective-based diagnosis; diagnosed with a screening CT scan.	Amoxicillin or cefuroxime.
Stojanovic (2017)	China	Primary care, Emergency department, Hospital	Patients with suspected ARI infection diagnoses seen in one of three settings (subgroups): (1) inpatient hospital setting (not in the ICU); (2) hospital	Usual care; PCT testing and monitoring	Antibiotic days

			ICU; (3) outpatient clinic or emergency department (ED).		
Van Howe (2006)	United States	Primary care	Children and adolescents presenting with pharyngitis.	Observe without testing or treatment; treat all suspected cases with antibiotics; treat those with positive throat cultures; treat those with positive rapid tests; treat those with positive rapid tests and those with positive throat cultures after negative rapid tests; use a clinical scoring measure to determine the diagnosis/treatment strategy.	Penicillin; cephalosporin.

Table 1.1B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Balk (2001)	CEA	Markov (compartimental) model	Societal perspective	QALYs, Days free from disease	14 days	NA	No	Yes
Bertran (2000)	CEA	Decision tree	Healthcare centre's perspective	Clinical effectiveness of the first antibiotic option	from the moment the treatment started in primary care to the final healing or clinical failure after a third antibiotic option prescribed in hospital administration	NA	No	No
Cals (2011)	CEA	Decision tree	Healthcare payer's perspective	Antibiotic prescriptions saved	28 days	NA	No	No
de Bock (2001)	CEA	Decision tree	Healthcare centre's perspective	Probability of cure	7 days	NA	No	No
Durski (2013)	CEA	Decision tree	Healthcare centre's perspective	percentage of correct diagnosis	NA	NA	No	No
Giraldez-Garcia (2011)	CEA	Decision tree	Healthcare payer's perspective	Proportion of patients cured without complications from the	1 year	NA	No	No

				disease or fro m any adverse reaction to trea tment with pen icillin				
Holmes (2018)	CEA	Decision tree	Healthcare payer's perspective	QALYs	28 days	NA	Yes	Yes
Hunter (2015)	CEA	Decision tree, Markov (compartimental) model	Healthcare payer's perspective	QALYs, number of antibiotics p rescribed and t he number of R TIs over 3 years	3 years	economic: 3.5% for costs and benefits (QALYs multiplied by the willingness to pay; health: NA	No	No
Lathia (2018)	CMA	Decision tree	Healthcare payer's perspective	NA	NA	NA	No	No
Maizia (2011)	CEA	Decision tree	Healthcare payer's perspective	Suppurative co mplication avoi ded	NA	NA	No	No
Michaeli dis (2013)	CEA	Decision tree	Health care system perspective	QALYs, Antibiot ic prescriptions saved	ARTI treatment episode as the time horizon	NA	Yes	Yes
Neuner (2003)	CEA	Decision tree	Societal perspective	QALYs	1 year	NA	Yes	No
Nicholso n (2014)	CEA	Randomised controlled trial (RCT)	Healthcare centre's perspective	QALYs, EQ-5D; time from a dpectrum' anti mission to first administration of narrow antibiotics. Time, from ad	28 days	NA	No	No

				mission to first administration of oral antibiotics; time from admission to prescription of no antibiotics administered to patients with influenza or RSV; proportion of patients in each group who are prescribed.				
Oostenbrink (2002)	CUA	Decision tree	Societal perspective	Hospitalizations saved	15 years	4%	No	No
Oostenbrink (2003)	CA	Cost-minimization analysis	Healthcare centre's perspective	QALYs	NA	NA	No	No
Oppong (2013)	CEA	Hierarchical regression	Healthcare centre's perspective	QALYs, Days free from disease, EQ-5D, symptom information (case report forms).	28 days	NA	No	No
Oppong (2018)	CEA	Multilevel (regression) model	Healthcare payer's perspective	QALYs, EQ-5D	28 days	NA	Yes	Yes

Perone (2007)	CA	Decision tree	Healthcare centre's perspective	Rate of appropriate use of an antibiotic per patients treated	NA	NA	No	No
Schuetz (2015)	CA	Decision tree	Healthcare payer's perspective	NA	30 days	NA	No	Yes
Stankiewicz (2003)	CA	Individual sampling model	Healthcare centre's perspective	Costs saved	NA	NA	No	No
Stojanovic (2017)	BIA	Decision tree	Healthcare centre's perspective	Reduction in antibiotic days	30 days	NA	No	Yes
Van Howe (2006)	CUA	Decision tree	Societal perspective	QALD—quality-adjusted life-day	NA	3%	Yes	No

Table 1.1C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Balk (2001)	34.0 costs/symptom free day (in a mild scenario)	US dollars (NA (probably 2001))	Deterministic sensitivity analysis (DSA), Table of DSA, Sensitivity analysis graph (with one parameter varied)	The best strategy for diagnosing and treating acute sinusitis depends in part on the prevalence of the bacterial sinusitis (or the likelihood that a given patient actually has the disease)	Cost-saving, Cost-effective
Bertran (2000)	Patients with community-acquired pneumonia (CAP): Betalactam antibiotic treatment is the most cost-effective strategy. Hospitalization, directly related to the success rate of the first empirical antibiotic treatment, is the main driver of the final average cost per patient, rating from 50% to 70% of total cost. Acquisition costs of the first empirical antibiotic treatment represents just a small fraction of the total costs (between 2% and 13%)	Spanish peseta (1998.0)	Deterministic sensitivity analysis (DSA)	The model indicates that acquisition costs of the initial empirical antibiotic represent a small fraction of total treatment costs in patients with lower respiratory tract infections acquired in the community	Cost-effective

Cals (2011)	The ICER of GP use of CRP versus usual care was €5.79 and for GP use of both CRP and Communication versus usual care €4.15. This implies that an additional investment of €5.79 or €4.15 is needed for every additional unit of outcome (1% reduction in antibiotic prescribing) in the intervention group compared with the usual care group. Communication was superior to usual care costs or savings /antibiotic prescription saved	Euros (Unclear. 2010)	Probabilistic sensitivity analysis (PSA)	The interventions are cost-effective in any combination (yielding NMB at no willingness-to pay), taking into account GPs' preferences where at least 15% of GPs chose to implementthe communication skills training.	Cost-effective
de Bock (2001)	Wait and see=Reference; Clinical assessement = DFL 515.59; Ultrasound assessement = DFL 5745.38; Radiographic assessement = DFL 3164.98; Antibiotics = DFL 881.67 costs or savings /patient	Three Dutch Florins (DFL) equal about one British pound. (unclear, but it seems to be 2001)	Deterministic sensitivity analysis (DSA), Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	The costs for curing one additional patient were DFL516 when antibiotics were selectively prescribed and DFL882 when antibiotics were prescribed immediately	Cost-effective
Durski (2013)	133.0 costs per additional correct diagnosis	US dollars, South African Rand (2013)	Deterministic sensitivity analysis (DSA)	Through strategically choosing the order and type of testing coupled with disease prevalence rates, algorithms can deliver more	Cost-effective

				care more efficiently.	
Giraldez-Garcia (2011)	51,22 (only rapid test); 50,72 (clinical scoring + rapid test) Costs per patient cured without complications and no adverse reaction to penicillin		Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	The "clinical scoring + rapid test" strategy was the most cost-effective of the six strategies analysed	Cost-effective
Holmes (2018)	In patients with symptoms of ARTI and based on routine practice, the incremental cost-effectiveness ratios of CRP testing were £19,705 per quality-adjusted-life-year (QALY) gained and £16.07 per antibiotic prescription avoided. Following clinical guideline, CRP testing in patients with lower respiratory tract infections (LRTIs) cost £4390 per QALY gained and £9.31 per antibiotic prescription avoided. costs or savings /QALY, costs or savings /antibiotic prescription saved	Pound Sterling (2016-2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	The model suggests that as implemented in routine primary care (for all adults with symptoms of ARTI for >12 hours where the antibiotic decision unclear) POC CRP testing is borderline cost-effective.	Cost-effective, POC CRP testing for adults where the antibiotic decision is unclear, is borderline cost-effective, however the results are favourable when restricted to patients with LRTI symptoms only adhering to protocol.
Hunter (2015)	For 3 years per 100 patients: Total costs (discounted): current practice 18,081 pounds, GP plus CRP 18,039 pounds, Nurse plus CRp 17,401 pounds, GP plus CRP plus communication 18,431 pounds. QALYs:current practice 255.630, GP plus CRP 255.764,039, Nurse plus CRP 255.761, GP plus CRP plus communication 255.588. GP plus CRP and Nurse plus CRP	Pound Sterling (2012/2013)	Deterministic sensitivity analysis (DSA), Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA,	Over a 3-year time horizon, GP plus CRP test and nurse plus CRP test have a higher net monetary benefits than current practice. The additional costs of	Cost-effective

	dominate. These two strategies result in 0.13 additional QALYs per 100 patients (discounted) and costs 42 pounds less per 100 patients the GP plus CRP strategy ; and 680 pounds less for nurse plus CRP. Total costs and QALYs		Cost-effectiveness acceptability curve(s)	the test is outwighted by cost savings and QALY increment associated with a reduction in infections in the long run.	
Lathia (2018)	-18.66 (province AB); -14.86 (province BC); -12.78 (province NS); -12.47 (province ON); -24.36 (province SK) costs or savings /patient		Deterministic sensitivity analysis (DSA)	This analysis estimates that in a scenario where 60% of patients with severe sore throat seek care in a community pharmacy, compared to a scenario where all patients seek care through a family physician, walk-in clinic or emergency room, the healthcare systems in the five provinces saves a mean of $12.47 to $24.36 per patient.	Cost-saving
Maizia (2011)	970€ in children and at 903€ in adults cost per suppurative complication avoided	Euros (2008.0)	Deterministic sensitivity analysis (DSA),	The use of RDT was the most cost-effective strategy from the insurance	Cost-effective

			Tornado diagram of DSA	perspective private US, while the use of culture appeared to be more efficient from the perspective of the system public Medicaid. In acute tonsillitis, in both adults and children, RDT testing by practitioners is the more efficient strategy to identify and treat patients with GAS tonsillitis. Combining RDT testing with throat culture can provide additional effectiveness, but at the cost of a significant extra charge for the community.	
Michaelidis (2013)	149.0 costs or savings /antibiotic prescription saved	US dollars (2012.0)	Probabilistic sensitivity analysis (PSA), Cost-effectiveness acceptability curve(s)	Procalcitonin testing is unlikely to be preferred over usual care when costs alone are considered, but is likely to be	Cost-effective

				cost-effective when the costs of antibiotic resistance are considered and the test is used only in adults with ARTIs judged to require antibiotics by their physicians.	
Neuner (2003)	(culture strategy) 0.2668 quality-adjusted life-day lost and an average cost of $6.66 per patient costs or savings /QALY, costs or savings /patient	US dollars (2000.0)	Deterministic sensitivity analysis (DSA), Probabilistic sensitivity analysis (PSA)	Empirical treatment was the least effective strategy at a GAS pharyngitis prevalence of 10% (resulting in 0.41 lost quality-adjusted life-day), it is reasonable only when probabilities approach 70%, that is, in cases of epidemics of streptococcal infection and perhaps when streptococcal pharyngitis is being spread among family members or	Cost-effective

				patients are at very high probability of having the condition after application of the Centor decision rule.. Although the other four strategies had similar effectiveness (all resulted in about 0.27 lost quality-adjusted life-day), culture was the least expensive strategy.	
Nicholson (2014)	734717.0 costs or savings /QALY	Pound Sterling (2007.0)	Deterministic sensitivity analysis (DSA), Table of DSA, Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	All tests had limitations. We found no evidence that point-of-care tests for influenza or S. pneumoniae, or PCR for influenza or RSV influenced antimicrobial prescribing or clinical outcomes. The total costs and QALYs of each diagnostic strategy were similar,	Cost-effective

				although, incrementally, PCR was the most cost-effective strategy. The analysis does not support routine use of point-of-care tests for either influenza or pneumococcal antigen for adults presenting with acute cardiopulmonary conditions, but suggests that conventional viral culture for clinical diagnosis should be replaced by PCR.	
Oostenbrink (2002)	Vaccination strategies of Streptococcus pneumoniae and Neisseria meningitidis resulted in our model in incremental cost-utility ratios of 401,965 €/QALY and 22,635€/QALY, respectively. costs or savings /QALY	Euros (2001.0)	Deterministic sensitivity analysis (DSA)	Key determinants were the risk of bacterial meningitis or sequelae, costs of treatment, and long-term morbidity. Minimizing lumbar punctures and empirical treatments using a	Cost-effective, Not generalizable for vaccination strategies.

				diagnostic decision rule, without missing a single case of meningitis, was a dominant strategy to actual practice. The vaccination strategies analyzed take different efficiency results.	
Oostenbrink (2003)	Total costs current practice 2.976€; Total costs decision rule 2.684 € costs or savings /patient	Euros (2001)	Deterministic sensitivity analysis (DSA)	The decision rule reduced total costs by 292 euros per patient, 33 euros in the diagnostic phase and 259 euros in the treatment course. The application of the decision rule reduced the number of patients hospitalized.	Cost-saving
Oppong (2013)	€112,7 costs or savings /antibiotic prescription saved	Euros (2007)	Cost-effectiveness acceptability curve(s)	Patients receiving POC CRP did not have significantly different measures of recovery or outcomes compared to	Cost-effective, Reduces the rate of antibiotic prescribing.

				patients not receiving this test.	
Oppong (2018)	Communication skills was associated with an ICER of €68.08 (£55.23) per percentage reduction in antibiotic prescribing when compared with usual care. The ICER for CRP compared with communication skills was €176.53 (£143.20) per percentage reduction in antibiotic prescribing and the ICER for the combined intervention compared with CRP was €338.89 (£274.90) per percentage reduction in antibiotic prescribing. costs or savings /antibiotic prescription saved	Euros (2016)	Deterministic sensitivity analysis (DSA), Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	In terms of cost per percentage reduction in antibiotic prescribing, overall, communication skills was the most cost-effective intervention. Similarly, the CUA also showed that communication skills was the most cost-effective intervention.	Cost-effective
Perone (2007)	$15.30 (rapid test strategy) costs or savings /patient		Deterministic sensitivity analysis (DSA)	The results of this study is that the rapid test is a valid method for the diagnosis of GABHS. The best clinical strategy for the diagnosis and treatment of pharyngitis in adults is the rapid systematic test in patients with a clinical population	Cost-effective

				greater than or equal to two.	
Schuetz (2015)	The costs of PCT-guided care for the one million member cohort was $2,083,545, compared to $2,780,332 for the usual care group, resulting in net savings of nearly $700,000 costs or savings /patient	US dollars (2014.0)	Deterministic sensitivity analysis (DSA), Sensitivity analysis graph (with one parameter varied)	The results show substantial savings associated with the use of PCT to guide antibiotic treatment of ARI in common US treatment settings. Across all three settings PCT-guided care is associated with net savings ranging from $73,326 in the ICU to >$5 million in the outpatient clinic and ED setting, for total savings to the IDN of more than $6 million.	Cost-saving
Stankiewicz (2003)	147.0 costs or savings /patient	NA	NA	With screening CT scanning, patients are diagnosed more accurately, according to whether they have disease or not. This is important because the	Cost-saving

				current subjective method of diagnosis of chronic rhinosinusitis is inaccurate.	
Stojanovic (2017)	In the inpatient setting, the costs of PCT-guided care compared to usual care resulted in net savings of 721,563 CNY Chinese hospital system; In the ICU and outpatient settings, savings were 250,699 CNY and 2.4 million CNY, respectively. The overall annual net savings of PCT-guided care was nearly 3.4 million CNY. total cost/hospital	Chinese yuan (CNY) (2015.0)	Deterministic sensitivity analysis (DSA)	Our results demonstrate substantial savings associated with the use of PCT to guide antibiotic treatment of ARI across common China treatment settings. Across all three settings, PCT-guided care was associated with a total of 3.8 million CNY, compared to 7.2 million CNY for usual care, resulting in an overall net savings to the hospital system of 3.4 million CNY ($561,487 USD) based onall ARI patients treated in a typical urban	Cost-saving

				hospital system in China.	
Van Howe (2006)	$32.132,01 rapid antigen testing had the best cost-utility. It dominated both "treat all" and "rapid test + culture" strategies. costs or savings /QALY	US dollars (2003)	Table of DSA, Tornado diagram of DSA, Probabilistic sensitivity analysis (PSA)	When the cost of a culture is low, in comparison with a paid test, culturing samples for all children may be the best option. As the cost of throat cultures increase, relative to the price of a rapid test, the rapid test becomes the better option. The justification for testing and treating GAS pharyngitis among children is to prevent the sequelae of infection.	Cost-effective

1.2. Influenza

Table 1.2A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Dugas (2013)	USA	Emergency department	Patients presenting with symptoms of an acute respiratory infection at risk or potentially having influenza-related complications.	1: treat none; 2: treat based on provider judgement; 3: treat based on a PCR-based rapid test; 4: treat all	Antiviral treatment: oseltamivir, zanamivir; antibiotics: amoxicillin/expensive antibiotics
Gonzalez-Canudas (2011)	Mexico	Primary care	Patients admitted with suspected ILI	1: diagnosis with gold standard strategy (real-time reverse transcription polymerase chain reaction); 2: diagnosis with influenza RDT + clinical data	Oseltamivir
Lavelle (2012)	USA	Primary care	Unvaccinated children coming to a physician's office with	1: no antiviral treatment; 2: rapid testing for influenza, followed by oseltamivir if results	Oseltamivir

			age-appropriate symptoms of uncomplicated ILI	are positive; 3: empiric oseltamivir treatment	
Nelson (2015)	USA	Emergency department	Children presenting with ILI	1: rapid multiplex PCR; 2: traditional PCR methods; 3: direct-fluorescentantibody staining; 4: Rapid antigen tests.	Antibiotics; antivirals (not further specified)
Nshimyumukiza (2016)	Canada	Outpatient clinic or emergency department	Quebec (Canada) population	1: current care; 2: potential rapid POCT	Oseltamivir
Rothberg (2003)	USA	Physician's office	Unvaccinated, healthy, working adults aged 20-50, presenting with influenza-like illness during the influenza season	1: no diagnostic test; 2: Directigen (influenza A/B); 3: FLU OIA; 4: QuickVue; 5: ZstatFlu	Amantadine; rimantadine; oseltamivir; zanmivir; azithromicin; amoxicillin
Rothberg (2003)	USA	Primary care	Persons aged >65 years, presenting with influenza symptoms during the	1: current care; 2: Quickvue	Amantadine; zanamivir; oseltamivir; rimantidine

			influenza season		
Rothberg (2005)	USA	Primary care	Healthy children at ages 2, 7 and 15 years	1: Quickvue; 2: ZstatFlu	Amantadine; oseltamivir; amoxicillin
Schwarzinger (2003)	USA	Primary care (not stated specifically)	Healthy working adults younger than 65 years of age who consult within 2 days of the onset of influenza-like symptoms	1: no zanamivir; 2: RFT with zanamivir; 3: systematic zanamivir	Nanamivir; (unspecified) antibiotics
Shen (2016)	China	Primary care	Children aged 18 years or below with ILI, had symptoms and signs compatible with influenza.	1: no antiviral therapy; 2: post influenza RDT treatment; 3: empiric treatment	Oseltamivir
Siddiqui (2008)	UK	Primary care	Patients presenting with ILI	1: do not treat with antiviral drugs; 2: treat all patients with antiviral drugs; 3: test then treat those who test positive	Oseltamivir
Smith (2002)	USA	Primary care (not	32-year old patients with	1: no antiviral testing or treatment; 2:	Oseltamavir; zanamivir;

		stated specifically)	typical influenza symptoms and a temperature 37.8°C during an influenza season. Other age categories in sensitivity analysis.	oseltamivir/zanamivir treatment without testing; 3: empiric rimantadine; 4: empiric amantadine; 5: test-treat oseltamivir/zanamivir; 6: test-treat rimantadine; 7: test-treat amantadine	rimantadine; amantadine
You (2012)	China (Hong Kong)	Hospital	Adult patients hospitalized for severe respiratory infection, suspected of influenza	1: immunofluorescence assay; 2: PCR testing to guide antiviral treatment; 3: empirical antiviral treatment plus PCR, to later continue or discontinue treatment based on test result; 4: empirical antiviral treatment	Oseltamivir
You (2017)	China (Hong Kong)	Primary care	Elderly patients with ILI	1: clinical judgement with no POCT; 2: rapid molecular POCT	Oseltamivir

Table 1.2B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Dugas (2013)	CUA	Decision tree	Societal perspective	Synthesis-based estimates	Lifetime horizon	economic: 0%; health: 3%	Yes	No
Gonzalez-Canudas (2011)	CEA, BIA	Decision tree	Healthcare centre's perspective	Synthesis-based estimates	NA	NA	Yes	No
Lavelle (2012)	CEA	Decision tree	Societal perspective	Synthesis-based estimates	1 year	NA	Yes	Yes
Nelson (2015)	CEA	Decision tree (not explicitly stated)	Healthcare centre's perspective	Single-study based estimates	Lifetime horizon	Economic: NA; health: 3%	Yes	No
Nshimyumukiza (2016)	CEA	Dynamic deterministic compartmental models, Agent-level Markov model (SPLMM)	Societal perspective	Synthesis-based estimates	1 year	NA	Yes	No
Rothberg (2003)	CUA	Decision tree	Societal perspective	Synthesis-based estimates	5 days	NA	No	No

Rothberg (2003)	CUA	Decision tree	Societal perspective	Synthesis-based estimates	Lifetime horizon	NA	Yes	No
Rothberg (2005)	CEA	Decision tree	Societal perspective	Synthesis-based estimates	Lifetime horizon	NA	Yes	No
Schwarzinger (2003)	CBA	Decision tree	Societal perspective	Synthesis-based estimates	Duration of influenza-like illness	NA	No	No
Shen (2016)	CEA	Decision tree	Healthcare payer's perspective	Synthesis-based estimates	NA	NA	No	No
Siddiqui (2008)	CEA	Decision tree	Healthcare payer's perspective	Synthesis-based estimates	NA	3.5000000000000003E-2	Yes	No
Smith (2002)	CEA	Decision tree	Societal perspective, Healthcare payer's perspective	Synthesis-based estimates	Single episode of illness	NA	Yes	No
You (2012)	CEA	Decision tree	Healthcare provider	Synthesis-based estimates	Lifetime horizon	0.03	Yes	No
You (2017)	CEA	Decision tree	Healthcare provider	Synthesis-based estimates	Lifetime horizon	economic: NA; health: 3%	Yes	No

Table 1.2C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Dugas (2013)	3: $1389/QALY; 4: $6246/QALY; 1: dominated (all compared to provider judgement)	US dollars (2011)	Tornado diagram of DSA, CEAC	The optimal method of influenza testingand treatment is highly dependent on influenza prevalence, which changes rapidly throughout the influenza season. Assuming a $50,000 per quality-adjusted life-year willingness-to-pay threshold, the most cost-effective treatment option is treatment according to provider judgment from 0% to 3% prevalence, treatment according to a PCR-based rapid influenza test from 3% to 7% prevalence, and treating all at greater than 7% prevalence.	Cost-effective
Gonzalez-Canudas (2011)	$12.60 saved each suspected case	US dollars (2009)	Fagan nomogram	The use of PR as an aid in the diagnosis of H1N1 influenza increases certainty and reduces the average cost per suspect and infected patient.	Cost-saving
Lavelle (2012)	$25,900 to $71,200/QALY, depending on age, compared with the no	US dollars (2008)	Table of DSA, Sensitivity analysis graph	This analysis demonstrates that when seasonal influenza viruses are circulating in the	Cost-effective

	oseltamivir treatment strategy		(with one parameter varied), CEAC	community and antiviral treatment is clinically indicated, empiric oseltamivir treatment of children who are suspected to have influenza illness may be a cost-effective treatment strategy. This conclusion is particularly true for children aged 1 to <12 years, but is highly dependent on the prevalence of oseltamivir resistance in circulating influenza virus strains.	
Nelson (2015)	PCR: $115,556/QALY in children aged 3-36 months, and $228,000/QALY in children aged 3-18 yrs (other alternatives were dominated)	US dollars (2011)	Sensitivity analysis graph (with one parameter varied), CEAC	A rapid multiplex PCR strategy was not only the most effective strategy in terms of maximizing patient QALYs, but was also the most expensive.	Cost-effective
Nshimyumukiza (2016)	$7573 saved /100,000 person years and 1.92 life-years saved /100,000 person years	Canadian dollars (2011-2012)	Tornado diagram of DSA, CEAC	Considering the baseline values of sensitivity, specificity, and cost to be 74%, 99%, and $25, respectively, for a POC test; the antiviral treatment based on this test appears dominant as compared to empirical antiviral treatment based on clinical judgment. In probabilistic sensitivity analyses, the POCT strategy is costeffective in 66% of cases, when a threshold of	Cost-effective

				$50 000 per lifeyear saved is fixed.	
Rothberg (2003)	All testing strategies are dominated by empiric treatment with amantadine	US dollars (2001)	DSA	The economic impact alone validates the use of antiviral therapy in healthy adults with influenza-like illness. The small benefit of shortening symptoms by an average of 1 day is by no means trivial.	Cost-saving, Cost-effective
Rothberg (2003)	Amantadine treatment only: $1129/QALY; test-treat oseltamivir: $5025/QALY, empiric oseltamivir: $10,296/QALY, other test-treat combinations (extended) dominated	US dollars (2001)	Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph, PSA	Community-based older adults benefit from antiviral therapy through an improvement in quality-adjusted life expectancy, if they begin treatment within 48 hours of ILI. The benefit comes at a cost. Under most circumstances, antiviral therapy is reasonably cost-effective and within the range of other widely accepted interventions for older adults, such as cholesterol reduction in patientswith diabetes or screening mammography. The optimal strategy, however, depends on the patient's vaccination status, the probability that he or she has influenza, and the risk for hospitalization	Cost-effective
Rothberg (2005)	Antiviral therapy: $800 - $1800/QALY; testing	US dollars (2003)	Sensitivity analysis graph	During local influenza outbreaks, children with	Testing not cost-effective -

	stategies were dominated in most scenarios		(with one parameter varied), PSA	symptoms of ILI benefit from antiviral therapy if it is initiated within 48 hours of symptom onset. At the same time, antiviral therapy saves money if parents return to work sooner. In that case, there is no trade-off between cost and effectiveness.	empirical treatment is cost-effective
Schwarzinger (2003)	2: $-14.40 for 0.65 averted influenza days; 3: $-29.80 for 0.81 averted influenza day (1)	US dollars (1999)	Table of DSA, Sensitivity analysis graph (with one parameter varied)	During influenza epidemics, when unvaccinated healthy working adults consult within 2 days of the onset of influenza-like symptoms, systematic zanamivir prescription without rapid influenza test is a dominant strategy from a societal perspective.	Cost-saving
Shen (2016)	RMB32,810/QALY (compared to no antiviral therapy, dominated by empiric treatment)	Chinese yuan (no year)	Tornado diagram of DSA, cost-effectiveness plane	The empiric oseltamivir treatment of children who are suspected to have influenza illness may be a dominant or a very cost-effective treatment strategy in comparison against post RIDT treatment with oseltamivir and no antiviral therapy, respectively in Chinese setting, when seasonal influenza viruses are circulating and antiviral treatment is indicated.	Not cost-effective

Siddiqui (2008)	For stockpiling: £1900 and £13700/QALY for the 1918 and 1957/69 scenarios; test-treat £31000 and £228000/QALY	Pound Sterling (2004)	Tornado diagram of DSA, Sensitivity analysis graph (with one parameter varied), cost-effectiveness plane	Near-patient testing is unlikely to be a cost-effective approach to conserving AV stocks but might be considered early in a pandemic. A more cost-effectivestrategy would be to increase the stockpile of AV drugs.	Not cost-effective
Smith (2002)	4: $9.06 per illness day avoided; 2: $198 per illness day avoided; other strategies (extended) dominated	US dollars (2000)	Tornado diagram of DSA, CEAC	Amantadine, zanamivir, and oseltamivir cost about $250 or less per quality-adjusted day gained or illness day avoided for patients with fever and typical influenza symptoms. Rapid testing was, forthe most part, more costly and less effective than treatment without testing.	"Economically reasonable"
You (2012)	Empirical treatment dominates testing	US dollars (2011)	Two-way sensitivity analysis graph, CEAC	In a season when the 'seasonal influenza' virus strains are predominant, "empirical antiviral treatment alone" would be a cost-effective option at influenza prevalence levels of 2.5% or above, whereas the 'PCRguided treatment' approach would be cost-effective at a low prevalence of less than 2.5%.	Not cost-effective
You (2017)	$29582/QALY	US dollars (2017)	Table of DSA, Tornado diagram of DSA, cost-	POCT-PCR saves QALYs by reducing the rates of subsequent hospitalization for	Cost-effective

			effectiveness plane, CEAC	influenza and mortality. The POCT-PCR incurred higher total direct cost when compared to the clinical judgement group by USD33.2 per patients tested. The expected ICER of POCT-PCR is SD29,582, lower than 1x GDP per capita of Hong Kong (USD43,497). The base-case ICER is therefore highly cost-effective from the perspective of healthcare provider in Hong Kong.	

1.3. Pneumonia

Table 1.3A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Böhmer (2002)	Germany	Hospital	Patients hospitalized with community-acquired pneumonia in the internal medicine department	1: Current practise; 2: inquaro, a computer system to aid in diagnosing community-acquired pneumonia patients	Levofloxacin, clarithromycin, ampicillin/sulbactam; ceftriaxon; erythomycin; ampicillin; cefazolin; doxycyclin
Dinh (2018)	France	Emergency department	Patients who consulted for community-acquired pneumonia in emergency departments	1: Pneumococcal urinary antigen test; 2: usual care	Antimicrobial treatment (penicillin A if Streptococcus pneumoniae), broad-spectrum antibiotics without microbiological identification
Harris (2011)	South Africa	Primary care	Ambulatory HIV-infected patients in South Africa	33 diagnostic options, involving combinations of specimen collection methods (oral washes induced and expectorated sputum and bronchoalveolar lavage); PCR or clinical diagnosis with chest x-ray alone	Treatment costs are based on a single, 21-day regimen with oral CTX
Ost (2003)	United States	ICU	Immunocompetent patients in the intensive care unit, intubated for 7 days, with	1: Empiric treatment only; 2: quantitative nonprotected	Antibiotics

			evidence of lateonset ventilator-associated pneumonia based on centers of disease control criteria of fever, purulent secretions, leukocytosis and radiographic infiltrates	endotracheal cultures; bronchoscopy; 3: nonbronchoscopic mini-bronchoalveolar lavage (mini-BAL)	
Xie (2017)	Canada	Hospital	Hospsitalized community acquired pneumoniae	1: BinaxNow-SP and culture; 2: culture alone	Ceftriaxone plus azithromycin for empirical treatment; penicillin G for treAtment of SP

Table 1.3B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Böhmer (2002)	CA, CEA	Differences are calculated using T tests	Healthcare centre's perspective	Days with symptoms, days with antibiotics, hospital length of stay, application time	Hospital addmission	NA	No	No
Dinh (2018)	CEA	Retrospective real life pragmatic study	Healthcare centre's perspective	Antibiotic prescriptions saved	NA	NA	No	Yes
Harris (2011)	CEA	Analysis for decision-making	Healthcare payer's perspective	Life years, Proportion of ill patients successfully treated	1 year	NA	No	No
Ost (2003)	CEA	Decision tree	Healthcare centre's perspective	Hospital survival	28 days	NA	No	Yes
Xie (2017)	CEA	Decision tree	Healthcare centre's perspective	Case correctly classified	3 days	NA	Yes	No

Table 1.3C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Böhmer (2002)	No incremental cost-effectiveness outcomes reported, only individual costs (microbiology: -11.77; imaging procedures: 8.32; antibiotic costs: -114.04; application costs: -100.41) and individual effects (application time (h): -5.4; days with symptoms: -3.5; days with antibiotics: -3; hospital length-of-stay (days): -3) All costs and effects here is the difference of fase 2 - fase 1.	NA	Deterministic sensitivity analysis (DSA)	Improvements were found for the patients (fewer infusions, faster symptom resolution and a shorted length-of-stay)	Cost-saving
Dinh (2018)	As only 7 PUA tests led to appropriate antimicrobial modification, we deemed that the potential cost savings, if the test had not been used, would have been 26,244 € during 3 years, that is 8748 € per year.	NA	Deterministic sensitivity analysis (DSA)	The test should be used only for patients with probable CAP	Cost-saving
Harris (2011)	At 50% disease prevalence, diagnostic procedures involving expectorated sputum with any PCR method, or induced sputum with nested or real-time PCR, were all highly cost-effective, successfully treating 77–90% of patients at $26–51 per life-year gained.	NA	Deterministic sensitivity analysis (DSA)	Three metrics are relevant: proportion of PCP patients successfully treated, proportion of well persons unnecessarily treated, and	Cost-effective

				the total diagnostic and treatment cost per life-year gained.	
Ost (2003)	No. of Initial Antibiotics: Zero: Empiric=Na; Empiric + ETT asp=72847; Empiric + mini-BAL=101479; Empiric + FOB=433261; One antibiotic: Empiric=Na; Empiric + ETT asp=20734; Empiric + mini-BAL=86184; Empiric + FOB=634288; Two antibiotics:Empiric + ETT asp=NA; Empiric + mini-BAL=4854; Empiric + FOB=819710; Empiric=dominated; Three antibiotics: Empiric + mini-BAL=NA; Empiric + ETT asp= dominated; Empiric + FOB= 1375978; Empiric= Dominated	NA	Deterministic sensitivity analysis (DSA), Two-way sensitivity analysis graph, Three-way (or more) sensitivity analysis graph, Probabilistic sensitivity analysis (PSA)	From the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was three antibiotics with mini-BAL.	Cost-effective
Xie (2017)	Incremental cost per patient 36 dollars. Incremental costs per case correctly classified 582 dollars	Canadian dollars	Deterministic sensitivity analysis (DSA)	An overall increase in diagnostic accuracy of 6.2% due to the addition of BinaxNOW-SP	Cost-effective

1.4. Tuberculosis

Table 1.4A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Abimbola (2012)	Resource-limited countries in sub-Saharan Africa	Primary care	A group of patients eligible for antiretroviral therapy based on the presence of clinical illness and/or a CD4 cell count of <200 cells/microliter.	1: current practice (symptom screening, sputum smear microscopy, and chest radiography); 2: culture as recommended by WHO guidelines (2007); 3: the WHO algorithm as updated in 2011 and is based on the Xpert MTB/RIF test.	Non-specified TB therapy
Ang (2015)	Singapore	Hospital	Patients visiting an eye centre with signs suggestive of TB uveitis	1: TST only; 2: IGRA following a positive TST; 3: IGRA only; 4: TST and IGRA simultaneously	Non-specified TB therapy
Bonnet (2010)	Kenya	Primary care/urban health clinic	TB-suspected patients (cough of at least 2 weeks)	Bleach smear (B) and direct smear (D) (under microscope) in various combinations and orders: D1+D2; B1; B1+B2; D1+B1; B1+D2; D1+B2; D1+B1+D2; D1+D2+B2; D1+B1+B2; B1+D2+B2	Not specified
Cowan (2017)	United States	Hospital	Inpatients placed in airborne infection isolation for presumptive pulmonary TB.	1: 1 Xpert on an unconcentrated sputum sample; 2: 1 Xpert on a concentratedsample; 3: 2 Xperts on concentrated sputum samples; 4: 2 smears; and 5: 3 smears	Non-specified TB therapy

Herráez (2017)	Spain	Hospital	Patients with suspected TB	1: the routine TB diagnosis method used; 2: the theoretical application of Xpert MTB/RIF technology.	Routine (sensitive) TB treatment
Jha (2016)	South Africa	Laboratory	Patients with (clinically) suspected TB	1: sputum smear microscopy alone; 2: TBDx automated microscopy alone; 3: TBDx automated microscopy,with confirmation of low positive results by Xpert MTB/RIF; 4: TBDx automated microscopy, with confirmation of all positive results by Xpert MTB/RIF; 5: Xpert MTB/RIF performed on all specimens	Non-specified TB therapy (both drug-susceptible and drug-resistant)
Langley (2014)	Tanzania	Diagnostic centre	Patients with presumptive TB - different algorithms for patients with and without HIV.	1: Ziehl-Neelsen (ZN) microscopy; 2: LED fluorescence microscopy; 3: same-day LED fluorescence microscopy; 4: full Xpert rollout; 5: Xpert for known HIV-+ cases; 6: Xpert for HIV-+ cases with additional HIV screening; 7: Xpert for smear-negative and known HIV-+ cases; 8: Xpert for smear-negative and HIV-+ cases with additional HIV testing	Standard regimen; retreatment regimen; resistant TB regimen
Mears (2016)	England	Multiple interacting components (laboratory, public health	Population of England, taking into consideration the age distribution of the	National TB strain typing service	Latent infection treatment (rifampicin, isoniazid, pyridoxine);

		and clinical services)	population and medium TB incidence		management of active disease (rifater, ethambutol, rifanah, pyridoxine)
Menzies (2012)	Botswana, Lesotho, Namibia, South Africa, and Swaziland	Health facility	General population (with dynamic model). For TB diagnosis patients presenting to a health facility with suspected TB	1: Current diagnostic algorithms; 2: implementing Xpert in accordance with current WHO recommendations	Non-specified TB therapy
Naidoo (2016)	South Africa	Laboratory	Patients with presumptive TB	1: a smear/culture-based algorithm; 2: an Xpert-based algorithm	Not specified
Pinto (2016)	Brazil	Primary care	Presumptive TB patients undergoing an initial consultation	1: standard of care (presumptive TB patients undergoing an initial consultation, a chest X-ray, two SSM examinations and HIV testing, those with HIV co-infection undergo culture and DST); 2: SSM testing of two samples was replaced by Xpert testing of one sputum sample	The WHO-recommended standard first-line drug regimen
Shah (2013)	Uganda	Primary care, Hospital	HIV-infected individuals presenting with signs/symptoms of active TB disease	1: ZN smear-microscopy testing of two sputa; 2: same as 1 plus one urine sample for point-of-care LF-LAM testing; 3: Xpert on one sputum (rifampin resistance is confirmed with conventional culture and DST for all patients);	TB treatment; TB treatment category 2; MDR-TB treatment; Annual HIV care costs

				4: same as 3 plus one urine sample for point-of-care LF-LAM testing	
Suen (2015)	India	Public sector clinics and private clinics	Individuals are followed from birth to death, TB suspects for TB diagnosis	1: current standard of care; 2: GeneXpert for DST; 3: GeneXpert for initial diagnoses and DST in public clinics; 4: PPM; 5: PPM combined with GeneXpert for DST; 6: PPM combined with GeneXpert for initial diagnoses and DST in public clinics	Various treatment courses (categories 1,2 and 4)
Van Rie (2013)	South Africa	Primary care	individuals with prolonged (>2 weeks) cough and/or other TB symptoms, presenting at a primary care clinic	1: smear plus culture; 2: Xpert	Not specified
Vassall (2011)	India, South Africa, Uganda	(unspecified) clinic	Individuals suspected of having TB	1: two sputum microscopy, followed by clinical diagnosis that might include chest Xray and antibiotic trial; 2: Xpert after two negative smear examinationss; 3: Xpert instead of smear examination	Specified treatment protocol of TB treatment, also including what to do if resistance is found
Walusimbi (2016)	Uganda	Primary care	The study population comprised adult HIV-infected patients older than 18 years, with presumptive active pulmonary TB	1: microscopic observation drug susceptibility (MODS) assay; 2: Xpert MTB/Rif test.	Not specified

Wikman (2017)	Mozambique	Primary care	TB suspects	1: SSM; 2: Xpert replacing SM; 3: Xpert after smear-negative SSM; 4: MODS as a replacement; 5: MODS as an add-on for smear-negative SSM	Non-specified TB therapy
Yakhelef (2014)	Kenya	Hospital	Study population: aged >=15 years living within a 10 km radius of the hospital, with a cough of at least 2 weeks and two negative smears	1: conventional diagnostic algorithm (based on clinical findings, radiological features and an antibiotic trial); 2: culture-based algorithm that uses TLA and LJ cultures in addition to the conventional algorithm	Non-specified TB therapy
You (2015)	Hong Kong (China)	Hospital	Patients hospitalized for suspected active pulmonary TB	1: conventional approach; 2: smear plus Xpert (for smear-negative); 3: Xpert	Early treatment; late treatment; both split up in first- and second line (based on whether or not multi-drug resistant)

Table 1.4B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Abimbola (2012)	CEA	Decision tree	Health system perspective	Synthesis-based estimates	182 days	NA	Yes	No
Ang (2015)	CEA	Decision tree	Not specified	Single-study based estimates	30 years	economic: NA; health: 3%	Yes	No
Bonnet (2010)	CEA	Decision tree	Health service provider's perspective	Single-study based estimates	NA	NA	No	No
Cowan (2017)	CEA	Decision tree	Healthcare centre's perspective	Single-study based estimates	NA	NA	Yes	No
Herráez (2017)	CEA	Decision tree	Healthcare centre's perspective	Synthesis-based estimates	NA	NA	Yes	No
Jha (2016)	CEA	Non-specified model	Healthcare payer's perspective	Single-study based estimates	NA	economic: 3% was used to annualized costs of equipment (no discount rate for outcomes); health: NA	Yes	Yes
Langley (2014)	CEA	Discrete-event simulation, Compartmental	Healthcare payer's perspective	Synthesis-based estimates	10 years	3%	Yes	Yes

		differential equation model						
Mears (2016)	CEA	Dynamic deterministic compartmental models	Public sector perspective	Synthesis-based estimates	20 years	3.5000000000000003E-2	No	No
Menzies (2012)	CEA	Dynamic compartmental model	Healthcare payer's perspective	Synthesis-based estimates	20 years	3%	Yes	Yes
Naidoo (2016)	Cost Analysis, CEA	Unspecified costing tool	Laboratory perspective	Single-study based estimates	NA	economic: 3% for equipment; health: NA	No	Yes
Pinto (2016)	CEA	Decision tree	National TB programmes perspective	Synthesis-based estimates	NA	No discounting	Yes	No
Shah (2013)	CEA	Decision tree	Healthcare payer's perspective	Single-study based estimates	Lifetime horizon	3%	No	No
Suen (2015)	CEA	Dynamic transmission microsimulation model	Societal perspective	Synthesis-based estimates	Lifetime horizon	0.03	Yes	Yes
Van Rie (2013)	Cost Analysis	Standard descriptive statistics	Not specified	Single-study based estimates	NA	economic: 5% (capital goods); health: NA	No	No

Vassall (2011)	CEA	Decision tree	Healthcare payer's perspective	Synthesis-based estimates	NA	economic: 3%; health: NA	Yes	Yes
Walusimbi (2016)	CEA	Decision tree	Healthcare centre's perspective	Synthesis-based estimates	NA	economic: 3%; health: NA	No	No
Wikman (2017)	CUA	Markov (compartimental) model	Healthcare provider's perspective	Synthesis-based estimates	90 years	3%	Yes	No
Yakhelef (2014)	CEA	No model	Healthcare centre's perspective	Single-study based estimates	NA	NA	No	No
You (2015)	CEA	Decision tree	Healthcare provider's perspective	Both single- and synthesis-based(for different diagnostic strategies)	Not stated (appears to be 1 year)	economic: 3%; health: NA	Yes	No

Table 1.4C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Abimbola (2012)	2: $60,430/death averted; 3: dominated	US dollars (2010)	Tornado diagram of DSA, CEAC	A diagnostic approach that includes culture was most effective at averting early deaths, but it was not the least costly approach compared with other algorithms considered. The algorithm with Xpert cost less and was more effective in reducing early mortality compared with the current practice.	Cost-effective
Ang (2015)	1: $3611/QALY; 3: dominated; 4: 11506/QALY (using 2 as reference)	Singapore dollars (2010)	Table of DSA, Tornado diagram of DSA, Sensitivity analysis graph (with one parameter varied), CEAC	In the context of our study population, while recognising the difficulties of diagnosing TB uveitis, our results suggest that the dual-test strategy of performing TST and IGRA simultaneously appears to be the most cost-effective strategy relative to the other strategies.	Cost-effective
Bonnet (2010)	B1+B2: €50; D1+B1: €276; : €71; D1+B1+D2, D1+B2, B1+D2, D1+D2+B2, D1+B1+B2, B1+D2+B2: dominated, measure of effectiveness: costs / proportion of smear-positive patients detected among the total number of PTB suspects (using D1+D2 and B1 as references)	Euros (2006)	Table of DSA	Considering all potential combinations of direct smear and smear after overnight NaOCl sedimentation, the approaches based on the single examination of the first concentrated specimen or based on the examination of two concentrated specimens were the most cost-effective: B1 due to its low cost, and B1+B2 dueto its	Cost-effective

				effectiveness and low ICER compared to B1.	
Cowan (2017)	XPERT 2 concentrated: $2826682/accurately diagnosed case; 2 smears: $-320893/accurately diagnosed case; 3 smears: $-363987/accurately diagnosed case (reference 1 Xpert concentrated and unconcentrated, which are expected to have equal performance)	US dollars (unknown year)	Tornado diagram of DSA, Two-way sensitivity analysis graph, Probabilistic sensitivity analysis (PSA), CE plane, CEAC	The present study supports analyses suggesting that Xpert implementation in the United States is cost-effective and can reduce AII duration. .A single-Xpert strategy was cost-saving in a variety of sensitivity analyses, suggesting that replacement of 3 AFB smears with Xpert to determine the need for AII would result in cost savings for most US hospitals.	Cost-effective
Herráez (2017)	€2960/QALY	Euros (2016)	Table of DSA, Tornado diagram of DSA, Probabilistic sensitivity analysis (PSA), CEAC	The implementation of a molecular microbiological technique in the diagnosis of tuberculosisis extremely cost-effective compared to the usual method. Its introduction into the routine diagnostic procedure could lead to an improvement in quality care for patients, given that it would avoid both unnecessary hospitalisations and treatments, and reflected in economic savings to the hospital.	Cost-effective
Jha (2016)	Main outcome reported: $1280 per incremental TB diagnosis, for strategy 3	US dollars (2015)	Table of DSA, Tornado diagram of DSA, Uncertainty ranges (95%) around results	In settings where universal XpertMTB/RIF is affordable, and health systems are willing to pay at least $1927 per incremental TB diagnosis made, universal Xpert is generally preferred.	Cost-effective

Langley (2014)	2: $29/DALY; 3: $45/DALY; 4: $169/DALY; others dominated	US dollars (2011)	Table of DSA, Tornado diagram of DSA, Probabilistic sensitivity analysis (PSA), CEAC, 95% credible intervals	We have assessed the effect of several promising tuberculosis diagnostic options that are being considered by many national tuberculosis programmes, and have identified three cost-effective strategies in the context of Tanzania: full rollout of Xpert MTB/RIF (B1), followed by same-day LED fluorescence microscopy (A3) and LED fluorescence microscopy(A2).	Cost-effective
Mears (2016)	£95,628/QALY (LTBI detecting increase from 3% to 4%); £54,539/QALY (LTBI detecting increase from 3% to 13%); cost-saving if diagnostic delay was reduced with 1 week	Pound sterling (unknown year)	Table of DSA, Sensitivity analysis graph (with one parameter varied)	This analysis failed to demonstrate that the TB-STS is a cost-effective use of NHS resources. It suggests that it is unlikely that earlier identification of false positive cases related to laboratory contamination, or increases in the identification and prophylactic treatment of contacts with a latent infection could, on their own, justify the cost of the system.	Not cost-effective
Menzies (2012)	$784/DALY; $810/life-year saved	US dollars (2011)	Table of DSA, Tornado diagram of DSA, Three-way sensitivity analysis graph, CEAC, uncertainty interval (2.5 and 97.5 percentiles)	Along with the projected health benefits of scaling up Xpert will come significantly increased demands on healthcare resources. The large increase in funding required under the Xpert scenario raises the question of affordability. Although our cost-effectiveness results suggest that the	-

				introduction of Xpert represents good value for money according to typical international benchmarks, it does not automatically follow that TB program budgets will be able toabsorb these changes.	
Naidoo (2016)	$6274 per additional MDR-TB case diagnosed	US dollars (2013)	-	The introduction of the Xpert-based algorithm has resulted in substantial increases in cost which are in line with modelling exercises undertaken in South Africa. However, these were not matched by an increase in TB diagnostic efficacy; massive cost increases persist even when temporal trends of a possible declining TB prevalence were taken into consideration. One of the benefits of the Xpert-based algorithm was the modest increase in the number of MDR-TB cases diagnosed, which comes at high cost.	-
Pinto (2016)	$943 per additional TB diagnosis; US$356 per additional TB diagnosis with bacteriological confirmation	US dollars (2014)	Table of DSA, Tornado diagram of DSA, Two-way sensitivity analysis graph, PSA: uncertainty ranges	Xpert is more costly than SSM, but has been shown to be more accurate, and potentially more costeffective in low and high-burden countries with high MDR-TB and HIV co-infection rates. In a setting with low MDR-TB and moderate HIV coinfection rates such as Brazil, implementation of single-sample Xpert testing	-

				replacing two-sample SSM tests would result in a modest increase (US$1.2 million per year, or 1.7% of Brazil's NTP budget) in total health system costs for the additional TB confirmation of 3344 patients.	
Shah (2013)	2: $33/DALY; 3: $58/DALY; 4: $57/DALY (1 as reference)	US dollars (2013)	Sensitivity analysis graph (with one parameter varied), CEAC	Compared with an algorithm of Xpert testing alone, the combination of Xpert with LFLAM was considered highly cost-effective. Addition of urine LF-LAM testing to smear-microscopy was a less effective strategy than Xpert replacement of smear-microscopy, but was less costly and also considered highly cost-effective compared with continued usage of smear-microscopy alone.	Cost-effective
Suen (2015)	4: $72/QALY; 5: 145/QALY; 6: 1104/QALY (others dominated)	US dollars (2013)	CEAC, partly PSA (on the simultaneous effect of uncertainty about the quality of life lost due to TB and the costs of care)	Our results illustrate that there is no silver bullet for combating the TB epidemic – introducing rapid and accurate diagnostic systems, either for initial diagnosis or DST, will have limited ability to control the epidemic and, in a context where PPM is available, is not cost-effective if implemented without substantial effort to bring the fragmented public and private treatment systems together.	Cost-effective
Van Rie (2013)	Cost savings of $3.28 per valid Xpert result	US dollars (2010)	-	The cost per Xpert was only US$1.88 higher than the cost for smear	Cost-saving

				microscopy and culture, and US$14.05 higher than smear microscopy only. Due to the low error rate, the cost per valid Xpert result was US$3.28 lower than the cost per valid smear microscopy plus culture result. The cost per case diagnosed was similar for both strategies (US$266 vs. US$260).	
Vassall (2011)	2: India: $55/DALY, South Africa: $110/DALY, Uganda: $41/DALY; 3: India: $68/DALY, South Africa: $138/DALY, Uganda: $37/DALY	US dollars (2010)	Table of DSA, Sensitivity analysis graph (with one parameter varied), Three-way sensitivity analysis graph, CEAC	Our results suggest that Xpert is likely to be more cost-effective than a base case of smear microscopy and clinical diagnosis of smear-negative TB.	Cost-effective
Walusimbi (2016)	1: $34 per TB patient diagnosed; 2: $71 per TB patient diagnosed	US dollars (2014)	Table of DSA, Tornado diagram of DSA	The algorithm using MODS was more cost-effective compared to the algorithm using Xpert for a wide range of different values of accuracy, cost and TB prevalence. The cost (threshold value), where the algorithm using Xpert was optimal over the algorithm using MODS was $5.92	Cost-effective
Wikman (2017)	5: $5648/DALY; 4: $5375/DALY; 3: $346/DALY; 2: $122/DALY	US dollars (2013)	Tornado diagram of DSA, Probabilistic sensitivity	Our results suggest that in this rural African setting substituting SM by Xpert MTB/RIF would be the most cost-effective strategy compared to its implementation as an add-on	Cost-effective

			analysis (PSA), CE plane	strategy or MODS implementation. However, the degree of uncertainty is high.	
Yakhelef (2014)	Varying between €452-€3121 per case depending on exact algoritm used	Euros (2009)	DSA	Using TLA/LJ in addition to the conventional algorithm made it more expensive, although its cost-effectiveness would improve if the number of screened patients increased. The decision to adopt rapid culture for TB epends on the government/community's willingness to pay for it.	culture-based algorithm may be hard to afford for resource-limited countries
You (2015)	$99/QALY	US dollars (2014)	Sensitivity analysis graph (with one parameter varied), CEAC	Using a simple sputum test of Xpert at inital assessment was the most cost-effective option	Cost-effective

2. Vector-borne diseases

Table 2A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Alonso (2017)	Morocco	Hospital	Child living in a visceral leishmaniasis-endemic area in Morocco presenting with visceral leishmaniasis symptoms: persistent fever and splenomegaly.	1: Current practice: diagnosis: bone marrow aspirate (BM) for diagnosis, treatment: meglumine antimoniate (SB) for 20 days for treatment; 2: diagnosis: BM, treatment: 6-day course L-AmB for treatment; 3: diagnosis: BM, treatment: 2-day course L-AmB; 4: diagnosis: RDT, treatment: SB for 20 days; 5: diagnosis: RDT, treatment: 6-day course L-AmB; 6: diagnosis: RDT,	Meglumine antimoniate; L-AmB

				treatment: 2-day course L-AmB	
Bartsch (2018)	Mexico	Population-level (specific diagnostic method not described)	Mexican population, diagnosed at different disease stages, representing the village in the Yucatán,	1: baseline, routine treatment of chronic cases; 2: identifying and treating in the acute phase; 3: intermediate stage; 4: acute and intermediate stages	Benznidazole
Batwala (2011)	Uganda	Public health centers	Outpatients presenting with fever	1: microscopy; 2: RDT; 3: presumptive diagnosis	Artemether-lumefantrine; other non-specified treatment (antibiotics/analgesics)
Boelaert (2002)	Not specified	Not specified	Clinically suspect patients for visceral leishmaniasis/kala-azar	1: Treat all; 2: parasitological diagnosis; 3: serological test (direct agglutination test)	(Unspecified) antimonials; stibogluconate
Hansen (2015)	Afghanistan	Health centres	Suspected malaria patients visiting study health centres	1: standard of care (depending on setting microscopy or presumptive malaria diagnosis); 2:Malaria RDT (Access- Bio	Confirmed Plasmodium vivax: chloroquine; P. falciparum or mixed infections receive artemisinin combination therapy; and clinically diagnosed patients with suspected malaria receive combination therapy with sulfadoxine-pyrimethamine and

				CareStart malaria RDT Pf (HRPII)/Pan (pLDH))	chloroquine (complying to national guidelines)
Hansen (2017)	Uganda	Drug shop	Not specified	1: no RDT for malaria; 2: malaria RDT	ACT; rectal artesunate
Harchut (2013)	Tanzania	Private dispensary and government-owned public health centre	Any patient for whom the clinician judged a malaria diagnostic test necessary, based on case history and presenting symptoms	1: RDTs (ICT Malaria Combo Cassette, ICT Diagnostics, Cape Town, South Africa); blood slide microscopy	Artemether-lumefantrine; sulphadoxine-pyrimethamine combination therapy,;
Lubell (2007)	Tanzania	Hospital	Patients for whom the clinician had requested a parasitologic test for malaria; in low and high transmission environments	1: Routine microscopy; 2: a RDT for the detection of Pf Histidine Rich Protein 2 antigen (Paracheck)	ACT; antibiotics
Lubell (2016)	Laos	Hospital	Febrile patient with a negative malaria test	1: current practice; 2: dengue RDT; 3: scrub typhus RDT; 4: crp RDT	tetracycline; fluoroquinolone; macrolide; beta-lactam; gentamicin;
Ly (2010)	The objectives of this study were to evaluate, under field conditions, the accuracy of Paracheck®				

	compared to TBS in two areas with different levels of malaria endemicity and to conduct a cost-effectiveness analysis of the				
	diagnostic and treatment strategy recommended by the Senegalese NMCP, taking into account the public health impact of the introduction of ACT and RDTs. Field research dispensary Patients consulting at a field research dispensary and presenting with	clinically-suspectied malaria (fever or suspicion of fever, cephalgia, diarrhoea or vomiting) requiring a thick blood smear. 1: presumptive treatment of all the febrile e	pisodes; 2: presumptive treatment of some episodes of illness according to the healthcare provider's feeling; 3: treatment of all episodes of illness RDT positive; 4: treatment of febrile illness wi	th positive RDT; 5: treatment of all children under six and treatment of all episodes of illness RDT positive for patients over six Artesunate-amodiaquine	
Mangham (2014)	Cameroon	Public and mission health facilities	Patients seeking treatment for fever or suspected malaria	1: Current practise (microscopy); 2: rapid diagnostic test with basic training; 3: rapid diagnostic test with enhanced training	Revised malaria treatment guidelines: patients to receive an ACT if they have a positive malaria test result, and patients not to receive an antimalarial if they have a negative malaria test result
Phillips (2015)	Angola, Tanzania, Uganda	Not reported	Children younger than age 5 in 2010	1: presumptive treatment; 2: RDT	ACT; other antimalarials; antibiotics

			with fever with their caregivers seeking care		
Rolland (2006)	Hypothetical sub-Saharan country (data from Sudan and Ethiopia)	Temporary malaria treatment centres	All patients with fever or a history of fever	1: presumptive strategy in which all patients with fever or a history of fever receive antimalarial; 2: a RDT-based strategy in which all patients with fever or a history of fever are tested by the Paracheck-Pf® test (Orchid Biomedical Systems, India), and receive antimalarial only if they are test-positive	ACT; quinine for pregnant women for whom ACT is contra-indicated; paracetamol
Shillcutt (2008)	Region: sub-Saharan Africa	Mixed (typical facilities would include health centres and dispensaries staffed by nurses and perhaps clinical	Ambulatory patients presenting with fever to health facilities in rural sub-Saharan Africa.	1: presumptive treatment; 2: RDT; 3: Microscopy diagnosis	ACT; antibiotic; no treatment

		officers, and outpatient departments of district hospitals)			
Uzochukwu (2009)	Nigeria	Health facilities (consisting of 12 public health centres, 30 private clinics, and hospitals)	Patients who come to the health facility with malaria symptoms	1: Presumptive treatment; 2: RDT; 3: Microscopy	ACT; Amoxicillin
Zikusooka (2008)	Mozambique (pilot data from two districts in the south: Namaacha and Matutuine)	Not reported	Clinically suspected malaria cases	1: clinical diagnosis; 2: RDT	Artesunate plus sulfadoxine/pyrimethamine; chloroquine; artemether-lumefantrine; sulfadoxine/pyrimethamine

Table 2B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Alonso (2017)	CEA	Decision tree	Not reported	Synthesis-based estimates	NA	3%	Yes	No
Bartsch (2018)	CEA	Markov (compartimental) model, Dynamic compartmental model	Societal perspective, Healthcare payer's perspective	Synthesis-based estimates	50 years	3%	Yes	No
Batwala (2011)	CEA	Decision tree	Societal perspective	Single-study based estimates	NA	economic: 3% (for capital goods); health: NA	No	No
Boelaert (2002)	CEA	Decision tree	Not reported	Synthesis-based estimates	NA	NA	No	No
Hansen (2015)	CEA	Decision tree	Societal perspective, Healthcare payer's perspective	Single-study based estimates	NA	economic: 3% (for capital goods); health: NA	Yes	No
Hansen (2017)	CEA	Decision tree	Societal perspective, Healthcare payer's perspective	Single-study based estimates	NA	economic: 3% for capital goods; health: NA	Yes	No

Harchut (2013)	Cost Analysis, CEA	Regression analysis	Not reported	Single-study based estimates	NA	NA	No	No
Lubell (2007)	CEA	Not reported	Healthcare centre's perspective	Single-study based estimates	NA	NA	No	No
Lubell (2016)	CEA	Not reported specifically (although a decision tree is displayed)	Not reported	Synthesis-based estimates	NA	NA	Yes	No
Ly (2010)	Cost Analysis, CEA	Not reported	Senegalese National Malaria Control Programme perspective	Single-study based estimates	NA	NA	No	No
Mangham (2014)	CEA	Bivariate multilevel model with covariates	Societal perspective, provider's perspective	Single-study based estimates	NA	economic: 3%(for capital goods); health: NA	Yes	No
Phillips (2015)	CEA	Markov (compartimental) model, Microsimulation	Healthcare payer's perspective	Synthesis-based estimates	1 year	NA	Yes	No
Rolland (2006)	CEA	Not reported	Not reported	Synthesis-based estimates	30 days	NA	No	No

Shillcutt (2008)	CEA	Decision tree	Joint perspective of providers and patients	Single-study based estimates	Lifetime horizon	NA	Yes	No
Uzochukwu (2009)	CEA	Decision tree	Consumer and provider perspectives	Single-study based estimates	Not clearly stated. Possibly 21 days (patient follow-up)	NA	No	No
Zikusooka (2008)	CEA	Not reported	Healthcare centre's perspective, public sector provider's perspective	Single-study based estimates	NA	NA	No	No

Table 2C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Alonso (2017)	Compared to 4: 1,2,3,5: dominated; 6: 1165 per death averted	US dollars (2014)	Table of DSA, CEACs, 95% CIs; threshold analysis (at which price L-AmB becomes cost-effective)	RDT to diagnose paediatric patients should be implemented with visceral leishmaniasis without further delay. Treatment should also be reviewed: L-AmB should be used to treat VL in children in Morocco. Price negotiations should aim at reducing the cost of an L-AmB phial below US$140.	Cost-saving
Bartsch (2018)	Identifying and treating in the acute stage (5% to 100% of cases annually): cost-savings totaling $694 to $7,419 from the third-party payer perspective, $6,976 to $79,950 from the societal perspective, and averting 0.6 to 10.8 DALYs over the lifetime of all chronic cases occurring over the 50-year period. Over the 50-year period, cost-savings totaled $7,666 to $21,938 from the third-party payer perspective, $90,530 to $243,068 from the societal perspective, while 11.7 to 31.1 DALYs were averted.	US dollars (2018)	Table of DSA, Sensitivity analysis graph (with one parameter varied), PSA results are provided using 95% CI	Identifying and treating Chagas disease in its earlier stages (i.e., acute and indeterminate) would result in reduced transmission, better health outcomes, and cost-savings. Treatment in either stage could save up to $279,379 or $2.6 million (varying with the cost of a chronic Chagas case) and 35.7 DALYs in a 2,000-person village in the Yucatán. In fact, the cost-savings would outweigh the cost of identifying and treating	Cost-saving

				earlier, meaning that earlier treatment may pay for itself.	
Batwala (2011)	RDT: $5 per additional case correctly diagnosed and treated; microscopy: $9.61 (dominated) per additional case correctly diagnosed and treated	US dollars (2011)	DSA	RDT was the most cost effective. However, with the reduction in the cost of RDT and AL, the Malaria Control Programme and stakeholders need a contingencyplan regarding malaria diagnosis. Further, there is need to sensitize health service users about the benefits of appropriate malaria diagnosis.	Cost-effective
Boelaert (2002)	1: $1107.95; 2: serotology: $125.80; 3: $554.40 per death averted	US dollars (year unknown)	Sensitivity analysis graph (with one parameter varied)	District doctors in endemic areas treating VL suspects on clinical evidence only, do clearly not use the most costeffective strategy. Furthermore, this practice might cause considerable harm to patients if the potential cardiotoxicity of generic stibogluconate is considered.	Cost-effective
Hansen (2015)	Moderate transmission region: RDT dominant compared to microscopy; low transmission region: RDT dominant compared to microscopy - $2.5/% increase in patients appropriately treated	US dollars (2009)	CIs from PSA	In this context, introducing malaria RDTs with a standard training package is shown to be a desirable intervention on cost-effectiveness grounds. In both the moderate and low	Cost-saving, Cost-effective

	from health sector perspective ($4.5 from societal perspective)			transmission areas, RDT diagnosis dominates microscopyand is therefore cost-effective. In settings currently without parasitological diagnosis, the introduction of RDTs leads to a large improvement in the proportion of patients appropriately treated at a low cost, particularlyfrom a health sector perspective. The analyses presented in this paper suggest that the RDT intervention provides value for money in terms of appropriately treated febrile patient in each of the trial settings.	
Hansen (2017)	$0.55 / patient appropriately treated	US dollars (2011)	Table of DSA, 95% CI of PSA	The present research suggests that the introduction of subsidised RDTs in private drug shops in Uganda is desirable from a pure cost-effectiveness perspective compared to a situation with presumptive diagnosis. It was found that the availability of this parasitological test in drug shops significantly increased the proportion of patients	Cost-effective

				appropriately treated of malaria (from 32% to 75%) at a low incremental cost of US$0.55 per appropriately treated patient from a health sector perspective and US$3.83 from a societal perspective.	
Harchut (2013)	$96/month (total cost savings, without considering clinical outcomes)	US dollars (2011)	Not reported	The introduction of RDTs at the public clinic proved to be cost-effective, resulting in a net saving of 96 USD/month for the Tanzanian government. As the estimated RDT-diagnosed prevalence of malaria in this study was 14%, RDT introduction is recommended given WHO findings that RDTs are predicted to be cost-effective in prevalence areas of less than 20%.	Cost-saving
Lubell (2007)	$25.2/$7 per additional patient correctly treated (for low/high transmission settings)	US dollars (2005)	Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	We showed that, in both high and low transmission settings, the use of microscopy results in lower average costs per patient correctly treated than the use of RDTs. However, the slide results in this study were both less sensitive and specific than RDT results. The	Not reported

				incremental cost for each additional patient correctly treated because of the higher accuracy of RDTs ranged from $7 to $26, depending on transmission intensity.	
Lubell (2016)	2: dominated; 3: $48/DALY; 4: $94/DALY	US dollars (Not reported, probably 2012)	Cost-effectiveness plane of PSA, CEAC, 95% credible intervals	This analysis suggests that tools that are already available can vastly improve patient management. The model predicts that pathogen-specific tests for treatable and prevalent infections such as scrub typhus in the Mekong region could offer a cost-effective strategy over current practice when considering direct health benefits to the patients. This is particularly advantageous when empirical treatment practices are ill-suited to local etiologies, as appears to be the case in Laos	Cost-effective
Ly (2010)	No ICER reported	Euros (no year reported)	95% Cis	The cost of the scenario was estimated around 700€ per 1,000 episodes of illness, approximately twice as expensive as the others scenarios considered, except for scenario 5. Nevertheless,	Cost-effective

				it still appeared to us cost-effective as it ensured the correct diagnosis and treatment of 100% of malaria attacks and an adequate management of 98.4% of episodes of illness. The other scenarios, while less costly, were also less effective. Scenario 4 was close to the reference scenario when considering the primary measure of effectiveness, but it wouldhave resulted in the correct diagnosis and treatment of only 50% of malaria cases and thus cannot be recommended for ethical and public health reasons. Scenario 5 could be a possible alternative to the reference scenario when the primary measure of effectiveness is considered.	
Mangham (2014)	Basic training: $10.13/$8.40 per febrile patient correctly treated; Enhanced training: $6.70/$3.71 per febrile patient correctly treated [provider perspective/societal perspective)	US dollars (2011)	Probabilistic sensitivity analysis (PSA), Cost-effectiveness acceptability curve(s), Confidence	The cluster randomized trial evaluated the introduction of RDTs with either basic or enhanced training in health facilities in which microscopy was available. The interventions had a positive effect on health workers'	Cost-effective depending on WTP

			intervals for costs and effects	practice in the diagnosis and treatment of febrile illness, though were also more costly than current practice. The enhanced intervention was more cost-effective than the basic intervention when each intervention was compared with current practice, which indicates that the additional 2 days of training represent good value for money. Because there is no established cost-effectiveness threshold in Cameroon, however, the question of whether it is cost-effective to introduce RDTs (with training) in health facilities in which microscopy is already available will depend on the government's willingness to pay for improvements in the diagnosis and treatment of febrile patients. The incremental cost of introducing RDTs with enhanced training for the trial was $3.71 per patient correctly treated from a societal perspective.	

Phillips (2015)	Angola: cost-saving; Tanzania: $5.54 per life-year gained, $155 per death averted; Uganda: $94.28 per life-year gained, $2640 per death averted	US dollars (2010)	Results (quadrants) of cost-effectiveness plane in table with percentages	This study comprehensively explored the cost-effectiveness of adopting RDT for children. We improved on the analytic methods of previous studies, used household data, and accounted for the effect on those with nonmalaria fevers. Incorporating extensive sensitivity analyses, our results suggest that diagnostic testing should be adopted in Angola and Tanzania and strongly considered in Uganda. Our costs per life-year gained fell well below the WHO standard value. They also did not exceed the value of each country's per capita gross national product, another cost-effectiveness guideline.	Angola: Cost saving; Tanzania: cost-effective; Uganda: cost-effective
Rolland (2006)	Considering a prevalence of 50%: €6.80 /true malaria case detected, €-0.2 /false positive averted	Euros (2004)	Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	Our results suggest that if financing bodies were willing to tolerate an added cost of up to 1 € per false positive averted (namely a total cost increase of less than 20%), RDTs would be favoured in a majority of scenarios.	Not clearly cost-effective

Shillcutt (2008)	Not reported	-	Threshold analysis and probability graph	This study demonstrates that taking both antimalarial and antibiotic treatments into account, RDTs are cost-effective compared with presumptive treatment up to high levels of P. falciparum malaria prevalence among patients with febrile illness presenting to rural health facilities.	Cost-effective
Uzochukwu (2009)	RDT vs Presumptive treatment: -$27,860 and 4 additional deaths averted; Microscopy vs presumptive treatment: $28,821 and 4 additional deaths averted	US Dollars	Table of DSA	At the prevalence level of 43.1%, RDT was a cost-effective strategy for diagnosis of malaria in Nigeria	Cost-effective
Zikusooka (2008)	In first line for 25% cases positive: -$0.19 per malaria positive case up to $0.82 per positive case if 75% cases positive; in second line these numbers are -$2.12 and $0.61 respectively	US dollars (2004 for treatment; 2003 for RDT)	DSA	While the use of RDTs in all suspected cases has been shown to be cost-saving when parasite prevalence among clinically diagnosed malaria cases is low to moderate, findings show that targeting RDTs at the group older than six years and treating children less than six years on the basis of clinical diagnosis is even more cost-saving. In semi-immune populations, young children carry the highest risk of severe malaria and many	Cost-saving, Cost-effective (depending on assumptions)

				healthcare providers would find it harder to deny antimalarials to those who test negative in this age group.	

3. Infections of the gastrointestinal tract

Table 3A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Chey (2001)	USA	Primary care	Patients with uncomplicated, ulcer-like dyspepsia who had not been previously tested for H. pylori	1: antibody test followed -if positive- by treatment; 2: active H pillory infection test followed -if positive- by treatment.	14-day course of a combination of lansoprazole, clarithromycin and amoxicillin.
García-Altés (2005)	Spain	Primary care	Patients that consult at primary care with uncomplicated dyspepsia, excluding patients with clinical suspicion of isolated reflux disease and patients with alarm clinical symptoms suggestive of malignant disease.	1: Endoscopy; 2: Score and scope; 3: Test and scope; 4: Test and treat; 5: Empirical antisecretory treatment.	Clarithromycin; amoxicillin; Omeprazole
Ghoshal (2002)	India	Primary care	Middle-aged patients with DU diagnosed at index	1: anti-secretory therapy alone was administered	Anti-secretory therapy (Hz receptor antagonist

			endoscopy (any serious comorbid medical conditions, and without any confounding factors such as smoking or use of non-steroidal anti-inflammatory drugs).	for 8 weeks; 2: urease test and histological examination for H. pylori and subsequent management based on the results; 3: empirical triple therapy for possible H. pylori infection.	and Proton pump inhibitor); triple therapy (antisecretory therapy, amoxycillin, and tinidazole)
Ghoshal (2003)	India	Hospital	Middle-aged, patients with bleeding from duodenal, which has already been controlled with endoscopic treatment (injection or thermal therapy) and pharmacotherapy (intravenous PPIs and somatostatin) but had no co-morbid illness and had not recently been using NSAIDs.	1: Anti-secretory therapy for 8 weeks without considering H. pylori status; 2: Urease test and histological examination at the time of initial endoscopy to establish H. pylori status. 3: Patients who were positive on either test at the time of initial endoscopy were given triple therapy. 4: Comprised empirical triple therapy for possible H. pylori infection in all patients, without performing any test.	The anti-H. pylori therapy included a combination treatment with three antibiotics (clarithromycin 1 g/day, ampicillin 1.5 g/day and tinidazole 1 g/day, all in divided doses) and a PPI (omeprazole 40 mg or lansoprazole 60 mg/day).
Holmes (2010)	United States of America (USA)	Primary care	Patients with uninvestigated dyspepsia	1: IgG/IgA (with H. pylori IgG and IgA tests). 2: IgG (Begin with H. pylori IgG test; 3: Stool Antigen; 4: IgG with reflex to stool Antigen; 5: Breath Test (Begin with H. pylori urea	Therapy or empiric PPI

				breath test; 6: PPI trial (Skip noninvasive testing and begin instead with PPI trial)	
Kastenberg (2013)	United States	Hospital	25-year-old primigravid women in the second or third trimester of pregnancy with a valid clinical concern for appendicitis following an indeterminate ultrasound	1: Diagnostic laparoscopy; 2: computed tomography (CT); 3: magnetic resonance imaging (MRI) following indeterminate ultrasound	Appendectomy
Makris (2003)	Canada	Primary care	dyspeptic patients; (< > 45 years); > 45 years with gastric cancer	1: initial endoscopy; 2: Barium Examination; 3: empirically prescribed eradication therapy; 4: 4-week antisecretory regimen: 5: urea breath test – UBT; 6: laboratory serology testing and pharmacotherapy is then chosen according to the presence or absence of H. pylori infection; 7: H. pylori–positive serology test with a UBT before initiating appropriate treatment	3: empirically prescribed eradication therapy; 4: 4-week antisecretory regimen; 6: laboratory serology testing and pharmacotherapy is then chosen according to the presence or absence of H. pylori infection
Omata (2017)	Japan	Primary care	Patients diagnosed with AG suggesting H. pylori infection	1: Rapid urease test (RUT); 2: histology; bacterial culture (BC); 3: serum H. pylori IgG antibody (SHPAb), 4: urea breath	Iansoprazole, amoxicillin omeprazole, lansoprazole, metronidazole

				test (UBT), 5: stool H. pylori antigen (SHPAg), 6: urine H. pylori IgG antibody (UHPAb)	
Rich (2000)	USA	Services that have the resources to perform serology and x-rays	Patients with uncomplicated ulcer-like dyspepsia who were not taking nonsteroidal anti-inflammatory agents (NSAIDs)	1: Test and Treat—initial HP serology; 2: initial UGI series; 3: initial UGI series, HP serology if ulcer present.	Antibiotics; antisecretory agents
Shen (2003)	USA	Primary care	Adult ulcerative coliti (UC) patients with symptoms suggestive of pouchitis	1: Pouch endoscopy with biopsy; 2: pouch endoscopy without biopsy	Metronidazol; ciprofloxazin (CIP)
Vakil (2000)	United States	Primary care	Patients undergoing H. pylori testing	36 diagnostic testing strategies: Stool with none confirmatory test (CT); Stool + urea breath test (UBT) for positives; Stool+UBT for negatives; UBT + none CT; UBT+Fingerstick for negatives; UBT+Serology for negatives; UBT+Stool for positives; UBT+Stool for negatives; ELISA + none CT; ELISA + UBT for positives; Fingerstick + none CT; Fingerstick + UBT for positives; Rapid urease test + none CT; Rapid	NA

				urease test +Breath test for negatives	
You (2006)	Hong Kong, China	NA	Patients presenting with weekly attacks of heartburn or acid regurgitation	1: No therapy; 2: empirical PPI therapy; 3: H. pylori "test and treat"; 4: initial endoscopy.	PPI, eradication therapy; eradication therapy, PPI; eradication therapy, PPI

Table 3B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Chey (2001)	CEA	Decision Analytic Model	Healthcare centre's perspective	Incremental cost per unnecessary treatment avoided	NA	NA	No	No
García-Altés (2005)	CEA	Decision tree	Healthcare payer's perspective	Rate of asymptomatic patients one year after the end of the treatment.	1 year	NA	No	No
Ghoshal (2002)	CMA	Decision tree	Patient perspective	Rate of ulcer cured.	1 year	economic: 3%; health: NA	Yes	No
Ghoshal (2003)	CEA, CUA CMA	Decision tree	Patients' perspective	QALYs	2 years	NA	No	No
Holmes (2010)	CEA	Markov (compartimental) model	Societal perspective	Days free from disease	Lifetime horizon	NA	Yes	No
Kastenberg (2013)	CEA	Markov (compartimental) model	Societal perspective, Healthcare payer's perspective	Positive appendectomy, negative appendectomy, maternal perioperative complications, preterm delivery, fetal loss,	10 years	3%	Yes	No

				childhood cancer, lifetime costs, discounted life expectancy, and incremental cost-effectiveness ratios.				
Makris (2003)	CEA	Decision tree	Healthcare payer's perspective	Days free from disease	1 year	NA	No	No
Omata (2017)	CEA	Decision tree	Societal perspective	Eradication of H. pylori	1 year	NA	Yes	No
Rich (2000)	CEA	Decision tree, Simulation based on data obtained from peer-reviewed journals	Healthcare payer's perspective	Ulcer cured	1 year	NA	Yes	No
Shen (2003)	CEA	Decision tree	Healthcare payer's perspective	Length of time to correct diagnosis and appropriate treatment	28 days	NA	No	No
Vakil (2000)	CEA	Decision tree	Healthcare payer's perspective	Correct diagnosis	NA	NA	No	No
You (2006)	CEA	Markov (compartimental) model	Healthcare centre's perspective	Ulcer treated	1 year	NA	Yes	Yes

Table 3C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Chey (2001)	Active testing led to a substantial reduction in unnecessary treatment for patients without active infection (antibody, 23.7; active, 1.4 per 100 patients) at an incremental cost of $37 per patient	US dollars (1999)	Sensitivity analysis graph (with one parameter varied)	Active testing led to a substantial reduction in unnecessary treatment	Cost-effective
García-Altés (2005)	Score & scope = 483,17; Test & treat = Dominated; Endoscopy = 1396,85; Test & scope = Dominated costs or savings /patient	Euros (2003)	Deterministic sensitivity analysis (DSA), Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	Endoscopy was the most effective alternative, whereas score and scope was the most cost-effective strategy	Cost-effective
Ghoshal (2002)	In the baseline analysis, the cost per patient managed with initial anti-secretory therapy alone was Rs 544, cost of performing the urease test and histological examination at the time ofinitial endoscopy and subsequent treatment was Rs 692, and strategy III of empirical triple therapy for H.	NA	Two-way sensitivity analysis graph	If there is an increase in the time horizon of the analysis to more than 1 year, it is expected the cost of anti-H. pylori treatment (empirical and test-based) to be lower than anti-secretory therapy alone because of the possibility of a higher number of recurrences with the latter strategy	Not cost saving

	pylori yielded a cost per patient of Rs 523. Sensitivity analysis with a wide range of clinical probabilities and cost estimates and a second-order Monte Carlo simulation supported the conclusions of the baseline analysis				
Ghoshal (2003)	All the strategies resulted in similar QALY (1.9 years). Therefore, per QALY, empirical treatment for H. pylori, test-and-treatstrategy and maintenance treatment with PPIs alone were associated with INR 3937.4 (US$82.0), INR 4314.7 (US$89.9) and INR 7631.6 (US$158.9) expenditure, respectively	US dollars, Indian National Rupees: INR ((2002) in US, US = INR 48)	Deterministic sensitivity analysis (DSA), Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	Treatment of H. pylori (empirical or test-based) is the most cost-saving strategy	Cost-effective
Holmes (2010)	Empiric PPI Trial = 122.13; Stool Ag = 123.23; IgG serology = 125.76; IgG serology w/reflex to Stool Ag = 126.17; Breath test = 128.31; IgG/IgA binary serology = 129.04 cost (US$) per symptom-free year, cost per Correct Diagnosis	US dollars (2009)	Probabilistic sensitivity analysis (PSA)	The cost-effectiveness ratios for the six initial management strategies were similar	Not cost-effective
Kastenberg (2013)	Magnetic resonance imaging costing $6,767 per (QALY). In a setting where MRI is unavailable, CT is cost-effective even when	US dollars (2012)	Deterministic sensitivity analysis (DSA), Table of DSA, Two-way sensitivity analysis graph,	Magnetic resonance imaging is the most cost-effective strategy, costing $6,767 per quality adjusted life year (QALY)	Cost-effective

	considering the increased risk of radiation-associated childhood cancer ($560 per QALY gained relative to diagnostic laparoscopy). costs or savings /QALY		Cost-effectiveness acceptability curve(s)		
Makris (2003)	Group A: Patients Between 18 and 45 Years Old - endoscopy, sequential testing, and barium examination were not cost-effective strategies; laboratory serology=2,970; empirical antisecretory erradication = 6,412; Urea breath test=10,429; Group B: Patients over 45 Years - four strategies were cost-effective. These were, in order of increasing cost and effectiveness, empirical antisecretory therapy, barium examination, empirical eradication treatment, and UBT. Compared with empirical eradication treatment, UBT cures 0.46 additional patients/100 treated for a cost of $10,835 for each additional cure. Compared with barium testing, UBT can provide an additional cure at	Canadian dollars (2003)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA, Sensitivity analysis graph (with one parameter varied), Two-way sensitivity analysis graph	Clinical variables that impacted these findings were the probability of symptomatic relapse in patients with nonulcer dyspepsia (NUD) after successful versus failed H. pylori eradication, the probability of finding a duodenal ulcer (DU) in a young dyspeptic patient, the specificity of UBT, and the prevalence of H. pylori in patients with DU	Cost-effective

	an extra cost of $4,114 costs or savings /patient				
Omata (2017)	If the prevalence of H. pylori in the patients with AG is 85% and CAM-resistant H. pylori is 30%, histology, stool H. pylori antigen (SHPAg), bacterial culture (BC), and urine H. pylori antibody (UHPAb) were dominated by serum H. pylori IgG antibody (SHPAb), rapid urease test (RUT), and urea breath test (UBT). Among three undominated methods, the incremental cost effective ratios (ICER) of RUT versus SHPAb and UBT versus RUT were $214 and $1914, respectively. If the prevalence of CAM-sensitive H. pylori was less than 55%, BC was not dominated, but its H. pylori eradication success rate was 0.86. Cost/erradication of H. Pylori	NA	Sensitivity analysis graph (with one parameter varied), Cost-effectiveness acceptability curve(s)	The results can be applied to choosing a diagnostic method for H. pylori infection mainly in the context of a screening population undergoing EGD	Cost-effective, RUT was the most cost-effective diagnostic procedure given the present prevalence of CAM-resistant H. pylori.
Rich (2000)	The estimated cost per ulcer cured for each strategy were as follows: test and treat, $3,025; initial UGI, $3,690; and UGI with serology, $3,790. The estimated cost per patient treatment were: test and	NA	Sensitivity analysis graph (with one parameter varied)	Test test and treat provides similar outcomes and an economic advantage over UGI strategies even when we assumed UGI to be a perfect test for detection of PUD. The cost-effective	Not cost-effective

	treat, $498; initial UGI, $610; and UGI with serology, $620. When UGI reimbursement was decreased to less than $50, the UGI strategies yielded a lower cost per patient treated than the test and treat strategy. cost/ ulcer cured			advantage of test and treat was sensitive to the cost of invasive testing. If the cost of UGI was less than $50, UGI would be preferred given similar cost per patient treated, increased diagnostic accuracy, and decreased unnecessary antibiotic use. For individuals with suspected PUD, the test and treat strategy for HP is preferred when compared to strategies that use UGI initially, at reimbursement rates greater than $50.	
Shen (2003)	The pouch endoscopy without biopsy strategy costs $50 more per patient than the MTZ trial strategy but results in an additional 15 days for early diagnosis and thus initiation of appropriate treatment (incremental cost-effectiveness ratio $3 per additional day gained).	US dollars (2003)	Deterministic sensitivity analysis (DSA)	The results of base-case analysis were robust in sensitivity analyses	Cost-effective
Vakil (2000)	The enzyme-linked immunosorbent assay (ELISA) test had the lowest cost per correct diagnosis at low (30%), intermediate (60%),	US dollars (2000)	Sensitivity analysis graph (with one parameter varied)	If the cost of the breath test was <$50 or if the cost of the stool test is >$82, breath testing became preferable to stool testing.	Cost-effective

	and high (90%) prevalence($90–$95/correct diagnosis), but its diagnostic accuracy was low (80–84%). At low and intermediate prevalence the stool test was more accurate (93%), with an average cost of $126–$127 per correct diagnosis.			If the cost of the stool test fell to <$20, it became preferable to ELISA. Similarly, if the cost of the ELISA serology was >$39 then stool testing became preferable at all prevalence rates.	
You (2006)	The analysis showed that the H. pylori 'test and treat'' strategy, was associated with the lowest ICER, suggesting that it is more cost-effective than empirical PPI therapy and endoscopy for treating undiagnosed PUD	US dollars	Sensitivity analysis was explained in the text.	The sensitivity analysis showed that the ICER of the H. pylori "test and treat'' arm was sensitive to the prevalence of H. pylori infection among patients with typical reflux symptoms and that the ICER increased as the prevalence decreased	Cost-effective

4. Sexually transmitted diseases

Table 4A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Bartelsman (2014)	The Netherlands	NA	Patients who were identified as 'high-risk' patients irrespective of signs or symptoms (having STI-related complaints, notified of a STI by a sex partner, paid for sexual contact, men who had sex with men or uninsured patients from sub-Sahara Africa)	1: Retrospective comparison of a Gram stain POC system to all high-risk patients (2008–2009); 2: with only those with urogenital symptoms (2010–2011) on diagnostic accuracy	Ceftriaxone 500 mg parentally; azithromycin 1000 mg orally to treat presumed co-infection with chlamydia.
Caviness (2014)	United States	Hospital	Neonates, aged from birth to 28 days, with fever (rectal temperature =38°C) with no other symptoms and neonates with fever with cerebrospinal fluid (CSF) pleocytosis	1: HSV testing and empirical treatment while awaiting test results; 2: HSV testing and treatment if test results were positive for HSV or the patient had symptoms of HSV; 3: treatment alone without testing; no HSV testing or treatment unless the patient exhibited symptoms	Acyclovir sodium, 60 mg/kg/d intravenously (21-days therapy in neonates with disseminated or central nervous system disease; 14-days therapy in neonates with skin, eyes, and mouth disease.

Gianino (2014)	Italy	Primary care, STI clinic	316 patients with suspected infectious syphilis, either symptomatic for dermatological or genital lesions, or asymptomatic patients belonging to an high-risk for STI/syphilis group, who visited between June 1st 2003 and September 30th 2006 the STI clinic	1: Rapid immunochromatography test; 2: traditional ELISA screening test	NA
Gift (2014)	United States	Primary care	A hypothetical cohort of 1.000 asymptomatic women, who had no indication (signs or partners with symptoms) for presumptive treatment because up to 70% of chlamydial infections and 30% to 80% of gonococcal infections in women are asymptomatic and who visited a Center for Disease Control and Prevention to be tested for a potential infection with N gonorrhoeae	1:Co-Treat (test for N gonorrhoeae, not for C trachomatis); 2: test (test both infections separately and treat women only for the disease which has resulted positive in the test); 3: test/Co-Treat (test both infections separately)	Chlamydia: Azithromycin; doxycycline. Gonorrhoea: Cefixime; Ceftriaxone
Huang (2014)	United States	STI clinic	154 women who were recruited from STD clinics between April 2010 and	1: Vaginal swab NAAT assay; 2: vaginal swab POC test.	Azithromycin (1g); Ceftriaxone (250mg);

			February 2011 for an evaluation of a new chlamydia POC test in development. Age = 18 years, no antibiotic treatment within the past 21 days, 1h since last urine void, requiring a pelvic examination on the day of the visit		Doxycycline (100mg bid for 14 days)
Zwart (2014)	The Netherlands	Primary care, STI clinic	Men who visit STI clinic with suspected anogenital gonorrhoea (symptomatic or asymptomatic) after having sex with other men (MSM)	1: Gram-stained smear (GSS) evaluation only in symptomatic MSM (reference strategy); 2: no GSS, only nucleic acid amplification tests (NAAT) for all MSM (budget-saving strategy); 3: GSS and NAAT performed in all MSM, irrespective of the symptoms (health-gaining strategy).	Gonorrhea treatment

Table 4B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Bartelsman (2014)	CA, CEA	NA	Healthcare centre's perspective	Proportion of confirmed and treated urogenital gonorrhea infections	84 days	NA	No	No
Caviness (2008)	CEA	Decision tree	Societal perspective	QALYs, 12-month survival	1 year	3%	Yes	No
Gianino (2007)	CEA	British walk-in-clinic model	Healthcare centre's perspective	Nº of right diagnoses; Cost per additional right diagnose	NA	NA	No	No
Gift (2002)	CEA	Decision tree	Healthcare centre's perspective	Nº of PID (pelvic inflammatory disease) cases prevented	Lifetime	3%	No	No
Huang (2013)	CEA	Decision tree	Healthcare centre's perspective	Number of pelvic inflammatory diseases (PID) and its sequelae (chronic pelvic pain, ectopic pregnancy, tubal infertility) averted; Costs averted through PID prevention.	10 years (infertility); 5 years (ectopic pregnancy); 2 years (chronic pelvis pain).	3%	Yes	No

Zwart (2018)	CEA	Transmission model	Healthcare payer's perspective	QALYs, Epididymitis cases	10 years	3%	No	No

Table 4C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Bartelsman (2014)	A saving of €2.40 per consultation (a reduction of 8%); a saving of €2.34 per correctly managed consultation (a reduction of 7.7%) cost per correctly managed consultation.	Euros (2014)	Deterministic sensitivity analysis (DSA)	There were no differences between the two time periods in loss to follow-up (7.1% vs 7.0%)	Cost-saving
Caviness (2008)	Using $100.000 per QALY gained as a threshold only strategy 1 (test+empirical treatment) using HSV CSF PCR in febrile neonates with CSF pleocytosis was cost-effective ($55.562/QALY gained)	US dollars (2006)	Deterministic sensitivity analysis (DSA); Table of DSA; Sensitivity analysis graph (with one parameter varied); Probabilistic sensitivity analysis (PSA)	In febrile neonates with CSF pleocytosis, the strategy of testing with CSF HSV PCR and treating with empirical acyclovir therapy is cost-effective as long as those without disease are discharged by the end of the third day of hospitalization	Cost-effective
Gianino (2007)	Rapid test was less expensive than ELISA (€ 26.46 vs € 40.57) and yielded a similar number of right diagnoses.	Euros (2003)	Sensitivity analysis graph (with one parameter varied)	Rapid test has a high sensitivity and specificity, which can equal that of the ELISA screening test	Cost-effective
Gift (2002)	Nucleic acid hybridization assay for C trachomatis; culture for N gonorrhoeae: test $130 and test+co-treat $143; Nucleic acid hybridization assay for both	US dollars (2000)	Deterministic sensitivity analysis (DSA); Table of DSA; Sensitivity analysis graph (with one parameter varied)	In settings where the Test algorithm is determined to be cost-effective, the Test/Co-Treat algorithm usually will be, as well, except in populations that	Cost-saving

	C trachomatis and N gonorrhoeae test $149 and test+co-treat $148.			have very low coinfection rates.	
Huang (2013)	The point-of-care test strategy would save US$28 and avert 14 pelvic inflammatory disease (PID) cases.	US dollars (2011)	Deterministic sensitivity analysis (DSA); Table of DSA; Sensitivity analysis graph (with one parameter varied); Two-way sensitivity analysis graph; Probabilistic sensitivity analysis (PSA); Cost-effectiveness acceptability curve(s)	A new vaginal swab POC is likely to be cost-effective compared with a traditional NAAT strategy in the typical STD clinical setting	Cost-saving; Cost-effective
Zwart (2018)	No testing compared with testing in symptomatic patients only (current strategy) resulted in nine extra epididymitis cases 72 QALYs lost and €7300 additional costs over 10 years	Euros (2016)	Deterministic sensitivity analysis (DSA); Table of DSA; Tornado diagram of DSA; Probabilistic sensitivity analysis (PSA); Cost-effectiveness plane of PSA	Among the parameters of the transmission model, the most influential for the value of the ICER were the percentage of gonorrhea infections with symptoms and the frequency of acts of unprotected anal intercourse with casual partners	Cost-saving; Cost-effective

5. Fungal infections

Table 5A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Bilir (2015)	USA	Hospital	High-risk patient (+18) with a candidemia admission or discharge diagnosis. Excluded if admitted from or discharged to another hospital or acute care facility	1: blood culture diagnostic; 2: T2Candida panel adjunct to the blood culture diagnostic	Triazole antifungal agents: fluconazole, itraconazole, voriconazole; Echinocandin: micafungin, caspofungin, anidulafungin; amphotericin B, abelcet, amBisome
Gupta (2018)	Canada	Primary care	Dermatophyte-confirmed onychomycosis (HIV-positive patients excluded)	1: potassium hydroxide test (KOH); 2: culture; 3: periodic acid–Schiff (PAS)	Onychomycosis treatment: efinaconazole, ciclopirox, terbinafine, itraconazole
Macesic (2017)	Australia	Hospital	Adults undergoing allogeneic hermatopoietic stem cell transplant or receiving chemotherapy for acute leukemiain	1: biomaker-based diagnostic strategy (BDS) of galacomannan (GM); 2: apergillus polymerase chain reaction (A-PCR); 3: standard diagnostic strategy (SDS) of culture and histology	Fluconazole; itraconazole; voriconazole; posaconazole; liposomal amphotericin B
Mikailov (2016)	USA	Primary care	Onychomycosis patients	1: empirical therapy without confirmatory testing; 2: pretreatment confirmatory testing with potassium hydrixide (KOH) stain followed	Full 12-week treatment course of oral terbinafine, 250mg; Full treatment of 1 nail with efinaconazole, 10%.

				by periodic acid-Schiff (PAS) evaluation if KOH testing is negative; 3: pretreatment testing with PAS	
Pagès (2017)	France	ICU	Adult patients with peritonitis receiving empirical antifungal therapy in the ICU according to severity criteria	1: fluconazole or echinocandin as an empirical therapy; 2: diagnosis by fungal culture 3: PCR of all Candida species; 4: use of PCR detects most fluconazole-resistant Candida species	An empirical therapy was started with echinocandin or injectable fluconazole
Walker (2016)	United States	Hospital	Inpatients with signs and symptoms sufficient to conduct a blood culture that had at least one risk factor	1: in vitro diagnostic assay for direct detection of Candida, the T2Candida (T2 Biosystems, Inc.); 2: empirical treatment	T2Candida-directed therapy (T2DT); echinocandin empirical therapy (EET); fluconazole empirical therapy (FET); blood culture-directed therapy (BCDT)

Table 5B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Bilir (2015)	CEA, BIA	Decision tree	Healthcare centre's perspective	Candidemia-related deaths	1 year	NA	No	No
Gupta (2018)	CEA	Decision tree	Healthcare payer's perspective	Mycological cure (1 course of antifungal treatment/mycological cure)	1 year	NA	No	No
Macesic (2017)	CEA	Decision tree	Healthcare centre's perspective	QALYs, Mortality, IA Incidence, Length of hospital stay	5 year	NA	No	No
Mikailov (2016)	CEA	Decision tree	Healthcare centre's perspective	Proportion of correct and incorrect (FP) treatments, Liver failures associated with terbinafine	1.4 year	NA	No	No
Pagès (2017)	CEA	Decision tree	Healthcare payer's perspective	QALYs, Reduction in mortality	1 year	NA	Yes	No
Walker (2016)	CEA	Decision tree	Healthcare centre's perspective	Life expectancy, Survival of infected patients	21 days	NA	No	No

Table 5C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Bilir (2015)	2: T2Candida versus BC, a 47.6% decrease in candidemia diagnosis and treatment budget ($1149/patient tested), while averting 60.6% of candidemia-related mortality	US dollars (2015)	Deterministic sensitivity analysis (DSA), Tornado diagram of DSA, Sensitivity analysis graph (with one parameter varied)	T2Candida has the potential to significantly reduce costs and mortality rates in patients at high risk for candidemia	Cost-saving
Gupta (2018)	1: KOH the least expensive strategy; 2: culture; 3: PAS was determined to be the most sensitive confirmatory test. Comparatively, performing confirmatory testing prior to treatment decreases the overall cost to $320 to $930, depending on the therapy, physician, and test	Canadian dollars (2015)	Sensitivity analysis graph (with one parameter varied)	PAS was the most sensitive confirmatory test and KOH the least expensive	Cost-saving
Macesic (2017)	Costs at 180 days and mortality rate. 1: BDS US$81,279, 10.1% for BDS, (P = .573); 3: SDS US$78,774, 14.7%. Costs per life-year saved were $325.448 (0,008 life-years saved) $81.966 (0,023 life-years saved) and $3.670 (0,266 life-years saved) for a time horizon of 180 days one year and five years	US dollars (2015)	NA	Diagnostic strategy was cost-effective, but this was dependent on a survival benefit and was only apparent after several years of follow-up	Cost-effective
Mikailov (2016)	Prevalence 75%, per-patient cost savings of 1: empirical terbinafine therapy without confirmatory testing was $47, 2: KOH screening model and $135, 3: PAS testing. 2: KOH screening	US dollars (2015)	Deterministic sensitivity analysis (DSA), Sensitivity analysis	The value of confirmatory testing before initiation of	Cost-saving, Cost-effective

	and 3: PAS testing before treatment with efinaconazole 10% saved $272 and $406 per patient per nail, respectively.		graph (with one parameter varied)	treatment is largely driven by drug costs	
Pagès (2017)	3: PCR to detect all Candida species is more cost-effective with incremental cost-effectiveness ratio of €40,055/quality-adjusted life-year).	Euros (2015)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA, Probabilistic sensitivity analysis (PSA), Cost-effectiveness acceptability curve(s)	The use of fluconazole empirical treatment and PCR to detect all Candida species is more cost-effective than using fluconazole empirical treatment without PCR	Cost-effective
Walker (2016)	1: T2DT was more effective. Average cost per patient tested ($) T2DT=1,384.	US dollars (2015)	Deterministic sensitivity analysis (DSA), Probabilistic sensitivity analysis (PSA)	Although T2DT is less costly and more effective than BCDT, it remains unclear whether T2DT is a costeffective alternative to empirical therapy	Not cost-effective

6. Sepsis

Table 6A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Alvarez (2012)	Spain	Hospital, ICU	Patients admitted with a diagnosis of severe sepsis or septic shock to the intensive care unit of a university hospital	1: Real-time polymerase chain reaction technique (PCR); 2: LightCycler SeptiFast (LSC group) followed by adequate treatment.); 3: usual care (broad-spectrum antibiotic treatment (control group)	Antibiotics
Antonio Buendía (2013)	Argentina	Hospital	Children who were 1 to 3 months of age and had a fever of >39ºC and no source of infection	1: Procalcitonin; 2: C reactive protein; 3: Rochester criteria	NA
Brown (2010)	EU and USA	Hospital	Patients who have not received anti-staphylococcal antibacterials before PCR results are available	1: Empiric treatment, semi-synthetic penicillin (SSP); 2: rapid MRSA (methicillin-resistant Staphylococcus aureus)	Penicillin if MSSA (methicillin-sensitive Staphylococcus aureus) and vancomycin if MRSA (methicillin-resistant Staphylococcus aureus)
Cambau (2017)	France	Hospital	Patients aged =18 years were consecutively enrolled when meeting the diagnosis of SES (including	1: Blood cultures (BC); 2: molecular test (LSF)	Beta-lactams (carbapenems, third-generation); cephalosporins (others

			septic shock) a first episode of FN or suspicion of infective endocarditis		beta-lactams); Aminoglycosides; Glycopeptides; Fluoroquinolones; Anti-fungal
Harrison (2015)	USA	Hospital, Intensive care unit	Hypothetical cohort of 10,000 adult patients admitted to an ICU with suspected bacterial infection and sepsis. Inclusion and exclusion criteria matched those described in the PRORATA trial and included patients admitted with suspected infections who were not receiving antimicrobials or those who received antimicrobials for <24 hours	1: Procalcitonin-guided treatment; 2: standard care	Broad-spectrum antimicrobial therapy (vancomycin and cefepime)
Kip (2018)	The Netherlands	Hospital, Intensive care unit	Patients admitted to the ICU of 4 university medical centres and 12 teaching hospitals in the Netherlands. ICU patients were eligible for inclusion if they were aged = 18 years and received their first dose of antibiotics for a presumed or proven infection = 24 h before trial inclusion	1: PCT guidance treatment; 2: standard of care	Antibiotics

Mancini (2014)	Italy	Hospital	Hematological patients with signs of systemic inflammatory response syndrome possibly related to an infectious cause (SIRS with suspected sepsis SIRS-SS)	1: SIRS-SS managed with standard diagnostic assays; 2: SIRS-SS managed with a molecular diagnostic assay (SeptiFast)	Antibiotics
Penno (2015)	Ethiopia, Gambia, Papua New Guinea and Philippines.	Hospital	Febrile patients presenting at the district hospital level in a low-resource setting	1: Clinical assessment; 2: Point-of-care test (POCT)	Emergency dose + standard 5-days treatment with ampicillin and gentamicin; Emergency dose + standard 5-days treatment with ceftriaxone
Pliakos (2018)	USA	Hospital	Adult hospital inpatients with suspected bacteremia for whom blood cultures were ordered	Different rapid diagnostic test (mRDT PCR, MALDI-TOF, PNA-FISH, Gram-negative.	Antibiotics
Steuten (2018)	United Kingdom, Germany, and the Netherlands	Hospital	A hypothetical population of intensive care unit (ICU) patients with suspected sepsis and, separately, COPD patients with exacerbations requiring hospitalization	1: PCT-guided antibiotic prescription strategy; 2: current care strategy in chronic obstructive pulmonary disease (COPD)	Antibiotics
Westwood (2015)	United Kingdom	Emergency department, Intensive care unit	Adults and children with confirmed or highly suspected sepsis in intensive care settings; adults or children	1: Procalcitonin (PCT); 2: usual care	5-day course of a single antibiotic to patients with low-severity CAP, consider a macrolide or tetracycline for patients

			presenting to the emergency department with suspected bacterial infection		who are allergic to penicillin

Table 6B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Alvarez (2012)	CMA	Individual sampling model	Healthcare centre's perspective	ICU and hospital length-of-stay after the diagnosis of septic shock, mortality rate and the antibiotics used	6 months	NA	No	No
Antonio Buendía (2013)	CEA	Decision tree	Healthcare payer's perspective	Additional correct diagnosis	NA	NA	Yes	No
Brown (2010)	CEA	Decision tree	Healthcare centre's perspective	Life time	NA	3%	No	Yes
Cambau (2017)	CEA	Decision tree	Healthcare centre's perspective	The primary endpoint was MD, i.e. detection of pathogens in the blood samples using results of BCs during CP and of both BCs and molecular tests during IP	30 days	NA	No	No
Harrison (2015)	Cost Utility Analysis, Cost-minimization analysis	Decision tree	Healthcare centre's perspective	QALYs	1 year	NA	Yes	Yes

Kip (2018)	CEA	Prospective, multicentre, randomised, open-label intervention trial	Healthcare centre's perspective	QALYs, The impact on the duration of antibiotic treatment, in-hospital mortality, and healthcare costs	1 year	NA	Yes	No
Mancini (2014)	CEA	Observational, propensity score-matched analysis	Healthcare centre's perspective	Sepsis-related mortality; Length of Sepsis Episodes (LOSE)	2 year	NA	No	No
Penno (2015)	CEA	Decision tree	Healthcare centre's perspective	Antibiotic prescriptions saved, Patient survival	NA	NA	No	No
Pliakos (2018)	CEA	Decision tree	Healthcare centre's perspective	QALYs, Bloodstream infection deaths averted	Lifetime	3%	No	No
Steuten (2018)	CEA	Decision tree	Societal perspective	reduce antibiotic resistence (reduce the number of ABR cases)	1 year	NA	Yes	Yes
Westwood (2015)	CEA	Decision tree	Healthcare centre's perspective	QALYs, Hospitalizations saved, Reduction in antibiotic therapy duration (days)	6 months	NA	Yes	No

Table 6C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Alvarez (2012)	The total cost was €42,198 in the control group versus €32,228 in the LCS group with statistically significant differences (P <0.05), giving rise to an average net saving of €9970 per patient. The mortality rate was similar in both groups.	Euros (2017)	Table of DSA, Non-parametric bootstrapping	Significant economic savings afforded by using the LCS technique, due to shorter of length-of-stay in the ICU and less use of antibiotics.	Cost-saving
Antonio Buendía (2013)	C reactive protein result in US$ 937 per correctly diagnosed cases of SBI. The additional cost per additional correct diagnosis using procalcitonin versus C reactive protein was US$ 6127 while Rochester criteria resulted dominated	US dollars (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA	The variables that have the greatest influence on the results were: costs of integration by IBS, probability of IBS, costs of false negatives, probability of IBS due to pneumococcus, sensitivity of procalcitonin and costs of false positives.	Cost-effective
Brown (2010)	Rapid PCR, EU: €636; USA: $820	US dollars (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Sensitivity analysis graph (with one parameter varied)	Rapid PCR testing for MRSA (methicillin-resistant S. aureus (MRSA)) appears to have the potential to reduce mortality rates while being less costly than empiric therapy in the EU and US, across a wide range of	Cost-effective

				MRSA prevalence rates and PCR test costs.	
Cambau (2017)	Unclear (no values, only cost-effectiveness scatterplot, were the scatterplot for patients with SES indicated a weak dominance with a positive effectiveness effect and a reduced hospital cost as shown by the higher density below the horizontal axis)	Euros (2017)	Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA	Overall, turn-around time was shorter during IP than during CP (22.9 vs. 49.5 h, P < 0.001) and hospital costs were similar (median, mean ± SD: IP €14,826, €18,118 ± 17,775; CP €17,828, €18,653 ± 15,966). Bootstrap analysis of the incremental cost-efectiveness ratio showed weak dominance of intervention in SES patients.	Cost-effective
Harrison (2015)	0.0002 QALYs and decreased overall treatment costs ($65)	US dollars (2017)	Deterministic sensitivity analysis (DSA), Probabilistic sensitivity analysis (PSA)	The combination of procalcitonin testing with an evidence-based treatment algorithm may improve patients' quality of life while decreasing costs in ICU patients with suspected bacterial infection and sepsis; however, results were highly dependent on a number of variables and assumptions.	Cost-saving, Cost-effective
Kip (2018)	The results of this trial-based cost-effectiveness analysis indicate that the expected in-hospital costs per patient are €46,081/patient in the PCT group, compared with €46,146/patient in the standard of care group. This	Euros (2017)	Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	Although the impact of PCT guidance on total healthcare-related costs during the initial hospitalization episode is likely negligible, the lower in-hospital mortality may lead to a non-significant increase in	Cost-effective

	indicates an average decrease of €65/patient (95% CI - €6314 to €6107, a relative decrease of 0.14%)			costs over a one-year time horizon.	
Mancini (2014)	Significant savings were observed in the prospective cohort, especially due to reduced costs in antifungal therapy €151,62	Euros (2017)	NA	The reduction in spending did not exert any negative effect on the clinical outcomes investigated (SIRS-SS-related mortality and average LOSE).	Cost-saving
Penno (2015)	POCT for sepsis with a sensitivity of 0.83 and a specificity of 0.94 was cost-effective, resulting in parity in survival but costing $1.14 less per live saved	US dollars (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Sensitivity analysis graph (with one parameter varied)	A POCT with accuracy equivalent to the best malaria rapid diagnostic test was cheaper and more effective than clinical assessment.	Cost-saving, Cost-effective
Pliakos (2018)	MALDI-TOF analysis with an ASP was the most cost-effective strategy, resulting in savings of $29,205 per quality-adjusted life year and preventing 1 death per 14 patients with suspected bloodstream infection tested compared to conventional laboratory methods without an ASP	US dollars (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA, Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	mRDTs are cost-effective for the diagnosis of patients with suspected bloodstream infection and can reduce health care expenditures. Notably, the combination of mRDT and an ASP can result in substantial health care savings	Cost-effective
Steuten (2018)	Reduce in 6% the number of antibiotic resistance (ABR); reduce in 21% the cases of Clostridium difficile infections (CDI); Total hospital costs of	Euros (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA, Sensitivity analysis graph (with	Model outcomes were most sensitive to the impact of the PCT guided strategy on the number of intensive care unit	Cost-saving, Cost-effective

	care per patient are expected to decrease with €1071 (Germany), €1124 (the Netherlands), and €1163 (United Kingdom)		one parameter varied), Probabilistic sensitivity analysis (PSA)	days and general hospital ward days	
Westwood (2015)	Cost-savings ranged from £368 to £3268	Pound Sterling (2017)	Deterministic sensitivity analysis (DSA), Table of DSA, Probabilistic sensitivity analysis (PSA), Cost-effectiveness plane of PSA, Cost-effectiveness acceptability curve(s)	The addition of a PCT algorithm to the information used to guide antibiotic treatment may reduce antibiotic exposure in adults being treated for suspected or confirmed sepsis in ICU settings and in adults presenting to the ED with respiratory symptoms and suspected bacterial infection, without any adverse consequences	Cost-saving

7. Other

Table 7A overview of setting, comparators and treatment

Author (year)	Country/countries	Setting	Population	Compared strategies	Included treatment
Buendia (2016)	Argentina	Hospital	Babies aged from 1 to 3 months presenting with fever without a source	1: rochester criteria (clinical assessment, clinical records, urine test and hemogram); 2: rochester criteria plus C reactive protein test; 3: Rochester criteria plus procalcitonin test; 4: Expectant observation (not lab tests, just clinical assessment)	Intravenous ceftriaxone
Carr (2005)	United States	Primary care	Healthy women with symptoms of vaginitis undiagnosed after an initial pelvic exam	28 diagnostic strategies comprised of combinations of pH testing, vaginal cultures for yeast and Trichomonas vaginalis, Gram's stain for bacterial vaginosis, and DNA probes for Neisseria gonorrhoeae and Chlamydia	Treatment guided by vaginal pH (treatment with single dose fluconazole for Candida when the pH is less than 4.9 or treatment with 2 g of metronidazole to cover Trichomonas and/or BV when the pH is greater than 4.9 and treatment with both fluconazole and metronidazole

Saito (2018)	Cambodia	Primary care	Children aged from 0 to 14 years, who visited a health center with undifferentiated fever (shock, encephalopathy, convulsions, bleeding, deep jaundice or suspected gut perforation excluded)	1: lateral flow analysis of immunoglobulin M (IgMFA); 2: current standard of presumptive clinical diagnosis without an RDT	Azithromycin (250 mg per day) for five days; amoxicillin (1500 mg per day) for five days
Schroeder (2014)	United States	Hospital	Adult inpatients suspected of having Clostridium difficile infection	Strategies based on traditional technologies (batch PCR, EIA toxin A/B, and direct tissue culture cytotoxicity); Based on rapid diagnostics (stand-alone odPCR, lateral-flow GDH testing with positive results confirmed by odPCR and lateral-flow testing of both GDH and C. difficile toxin A/B with concordant positives treated); Based on non-diagnostic strategies for purposes of comparison (treat none and treat all)	12 days treatment
Supputomongkol (2010)	Thailand	Hospital	Adult patients (>14 years) who present with acute fever (<15 days) suspected of leptospirosis i.e. no obvious focus of	1: lateral flow; 2: microcapsule agglutination test; 3: latex agglutination test	Doxycycline

			infection without severe complications or impaired consciousness and are suitable for oral antimicrobial therapy		
Takemura (2005)	Japan	Primary care	Patients who showed acute fever (+37.5 ºC) and were suspected of having an infection	1: CRP and WBC immediate testing before the physician's initial consultation with test results made available to the physician during the consultation; 2: not testing before the consultation, diagnosis decisions based on history and physical examination	Oral and parenteral antibiotics and oral antiviral agents, the sames for two strategies
Udeh (2008)	United States	Primary care	NA	1: Adeno Detector, hereafter referred to as AVD for cases of acute conjunctivitis (viral and bacterial); 2: no use of a point-of-care test (hereafter referred to as NAVD)	Antibiotics

Table 7B overview of model parameters

Author (year)	Type of economic evaluation	Model type	Perspective	Clinical outcomes	Time horizon	Discount rate	Inclusion of stochasticity	Inclusion of AMR
Buendia (2016)	CEA	Decision tree	Healthcare centre's perspective	Additional cost per patient correctly diagnosed	Duration of an episode of acute bacterial infection without recurrence.	NA	No	No
Carr (2005)	CEA	Decision tree	Societal perspective	Symptom-days	NA	NA	Yes	No
Saito (2018)	CEA	Decision tree	Healthcare centre's perspective	The number of correctly diagnosed typhoid fever cases (i.e. true-positives)	7 days	NA	No	Yes
Schroeder (2014)	CEA, CBA	Decision tree	Healthcare centre's perspective	True-positive case treated	1 year	NA	No	No
Supputomongkol (2010)	CEA, CBA	Decision tree, Markov (compartimental) model	Societal perspective	Duration of fever with or without doxycycline treatment	7 days	NA	No	No

Takemura (2005)	CEA	NA	Healthcare centre's perspective	Antibiotic prescriptions saved	NA	NA	No	No
Udeh (2008)	CEA	Decision tree	Societal perspective	Cases of inappropriate antibiotic treatment avoided	NA	NA	No	No

Table 7C overview of results

Author (year)	ICER	Currency (year)	Reporting of uncertainty	Main findings	Cost-effectiveness verdict
Buendia (2016)	1: rochester criteria + C reactive protein test" resulted in the most cost-effective strategy among those studied, with a cost of $784 per correct diagnosis. 3: "Rochester criteria + procalcitonin test" obtains a slightly better success ratio (84,33% vs 83%), the additional cost per patient correctly diagnosed associated with this strategy ($5.378) makes it less cost-effective.	US dollars (2010)	Deterministic sensitivity analysis (DSA), Table of DSA, Tornado diagram of DSA, Sensitivity analysis graph (with one parameter varied), Probabilistic sensitivity analysis (PSA)	At a prevalence lower than 14%, the best option would be expectant observation. The case in developed countries, where vaccination has successfully reduced the bacterial infection prevalence to a ratio lower than 1%	Cost-effective
Carr (2005)	The least expensive strategy was to perform yeast culture, gonorrhoeae and Chlamydia probes at the initial visit, and Gram's stain and Trichomonas culture only when the vaginal pH exceeded 4.9 ($330, 7.30 symptom days). Other strategies cost $8 to $76 more and increased	US dollars (2003)	Deterministic sensitivity analysis (DSA), Table of DSA, Probabilistic sensitivity analysis (PSA)	The least expensive strategy was to perform yeast culture, gonorrhoeae and Chlamydia probes at the initial visit	Cost-effective

	duration of symptoms by up to 1.3 days.				
Saito (2018)	Correctly diagnosed typhoid fever cases 1: with test 38.45, 2: without test 32.59; difference 5.87. Treatment success among typhoid fever cases; with test 46.78; without test 43.17; difference 3.61 Cost: Total cost (not inclusive of start-up costs); with test $8465; without test $2765; difference $5700	US dollars (2016)	Table of DSA, Tornado diagram of DSA, Two-way sensitivity analysis graph, Probabilistic sensitivity analysis (PSA)	The particular IgMFA studied, with a sensitivity of 59% and cost of $3.25, was estimated to be more effective but more costly than the clinical diagnosis in the base-case analysis	Cost-effective
Schroeder (2014)	Algorithms incorporating rapid testing were cost-effective relative to non rapid algorithms. $1,600 per additional true-positive case treated. Stand-alone odPCR was more effective and more expensive, identifying 174 additional true-positive cases at $6,900 per additional case treated	US dollars (2012)	Deterministic sensitivity analysis (DSA), Table of DSA, Two-way sensitivity analysis graph, Probabilistic sensitivity analysis (PSA)	Under most reasonable scenarios, stand-alone odPCR as a one-step test is the strategy that minimizes false-negative results and costs to the health care system	Cost-effective
Supputomongkol (2010)	Empirical treatment dominating (-1.57); 3: latex test: 2.68; 1: lateral flow test: 0.71; MCAT: 0.75	US dollars (NA)	Deterministic sensitivity analysis (DSA), Table of DSA	Empirical treatment with doxycycline was found to be the most cost-effective strategy, being both cheap and effective in treating uncomplicated leptospirosis and other causes of febrile illness.	Not cost-effective

Takemura (2005)	Total cost in the 1: advance-testing patients was slightly higher than that in the 2: non-advance testing patients (1,028,827 vs. 984,105) with 74 antibiotic prescriptions reduced by 1: advance testing.	Japanese yen (2005)	NA	Massive reduction in antibiotic prescription in patients with advance testing produced great savings in the antibiotic cost subcategory: however, the savings were largely offset by more frequent use of expensive antiviral agents and physicians ordered more additional tests	Not cost-effective
Udeh (2008)	1: Adeno detector USD =225.40; (entire US population per annun); 2: no point-of-care test = Dominated	US dollars (2006)	Tornado diagram of DSA, Two-way sensitivity analysis graph	Extrapolating these costs to the entire U.S. population per annum, society could potentially save nearly $430 million currently spent on unnecessary medical care and avoid over 1 million cases of unnecessary antibiotic treatment.	Cost-effective

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