The background of the entire image is a close-up photograph of red and blue ink swirling and mixing in water. The red ink is more concentrated on the left side, while the blue ink is more prominent on the right, creating a dynamic, organic pattern.

SIMON VAN DER POL

MAKING INFORMED DECISIONS

THE VALUE OF TESTING STRATEGIES IN HEALTHCARE

Online appendix

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Cover image: Lucas Kapla

Chapter 2: A Review of Workforce Expenditure Across Five Countries

Table 2.1 – public data sources

	Austria	Estonia	Finland	Iceland	Norway
Data year	2018	2017	2017	2018	2016
Population 4-18 year olds (Eurostat)	1277309	205248	904671	67258	955476
Conversion factor to 2018 euros, corrected for PPP (OECD)	0.879388 819	0.624720 371	0.996246 295	155.2012 143	12.06252 753
Percentage incurred by "other labour costs" (Eurostat)	36%	35%	28%	25%	22%
Healthcare spending in data year, local currency (millions) (OECD)	€39,883	€1,518	€20,621	233,780 kr	328,134 kr

PPP: purchasing power parities

Table 2.2 – survey results

		Austria	Estonia	Finland	Iceland	Norway
FTEs	School nurses	NA	281*	1073	59.23	1408
	School doctors	532^	5*	158	0	56.8
	Psychologists	157*	NA	265	0	110.4
	Social workers	NA	NA	0	0	68.8
	Dentists	NA	NA	0	0	1218
	Physical therapists	NA	NA	0	0	72.6
	Healthcare assistants	NA	NA	0	0	40.8
	Supportive staff	NA	NA	0	0	0
	Others	NA	NA	NA	NA	70.5
Salaries	School nurses	€ 14,208	€ 33,125	6,804,000 kr	kr 530,000	NA
	School doctors	€ 18,300	€ 81,975	NA	kr 830,000	€ 69,500
	Psychologists	NA	€ 44,125	NA	kr 573,000	€ 59,309
	Social workers	NA	€ 41,938	NA	kr 481,800	NA
	Dentists	NA	€ 77,450	NA	kr 707,160	NA
	Physical therapists	NA	NA	NA	kr 460,000	NA
	Healthcare assistants	NA	NA	NA	kr 432,000	NA
	Supportive staff	NA	NA	NA	NA	NA
	Others	NA	NA	NA	kr 607,320	NA
	Type of employmnet	Salaried	Salaried	Salaried	Salaried	Salaried
	Year	2017	2017	2018	2016	2018

*only a number of professionals was provided, not the number of full-time equivalents

^estimated based on 0.25 FTE for 600 children in the Austrian population

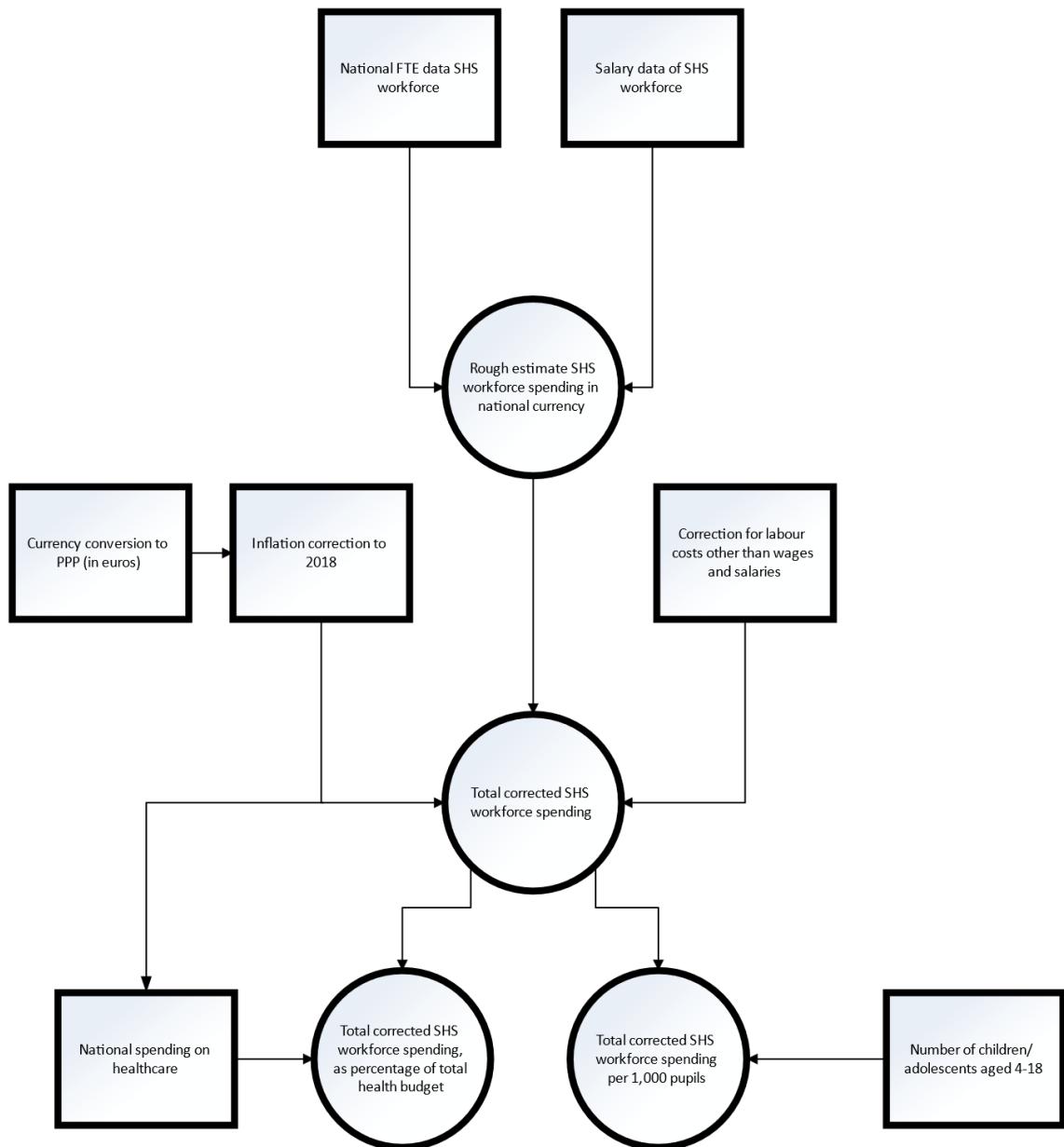
Table 2.3 – workforce cost estimations

Country	Total estimated spending on SHS workforce (% of total healthcare spending)	Estimated spending on SHS workforce, per 1,000 pupils
Austria	€71,817,209 (0.16%)	€56,225
Estonia	€8,852,043 (0.36%)	€43,129
Finland	€77,097,560 (0.37%)	€85,222
Iceland	€3,234,405 (0.21%)	€48,090
Norway	€186,612,220 (0.69%)	€195,308

Currencies corrected using purchasing power parities and consumer price indexes (to the year 2018)

SHS: School Health Services

Figure 2.1 – calculation steps



Calculation steps to get outcomes of the analysis, the squares indicate inputs and the circles indicate outcomes

FTE: full-time equivalents; SHS: School Health Services; PPP: Purchasing Power Parity

File 2.1 – questionnaire

Link to file: https://static-content.springer.com/esm/art%3A10.1186%2Fs12913-020-05077-w/MediaObjects/12913_2020_5077_MOESM2_ESM.xlsx

Chapter 3: Costs of two vancomycin-resistant enterococci outbreaks in a Dutch academic hospital

Figure 3.1: Time series used for opportunity costs 2017 outbreak

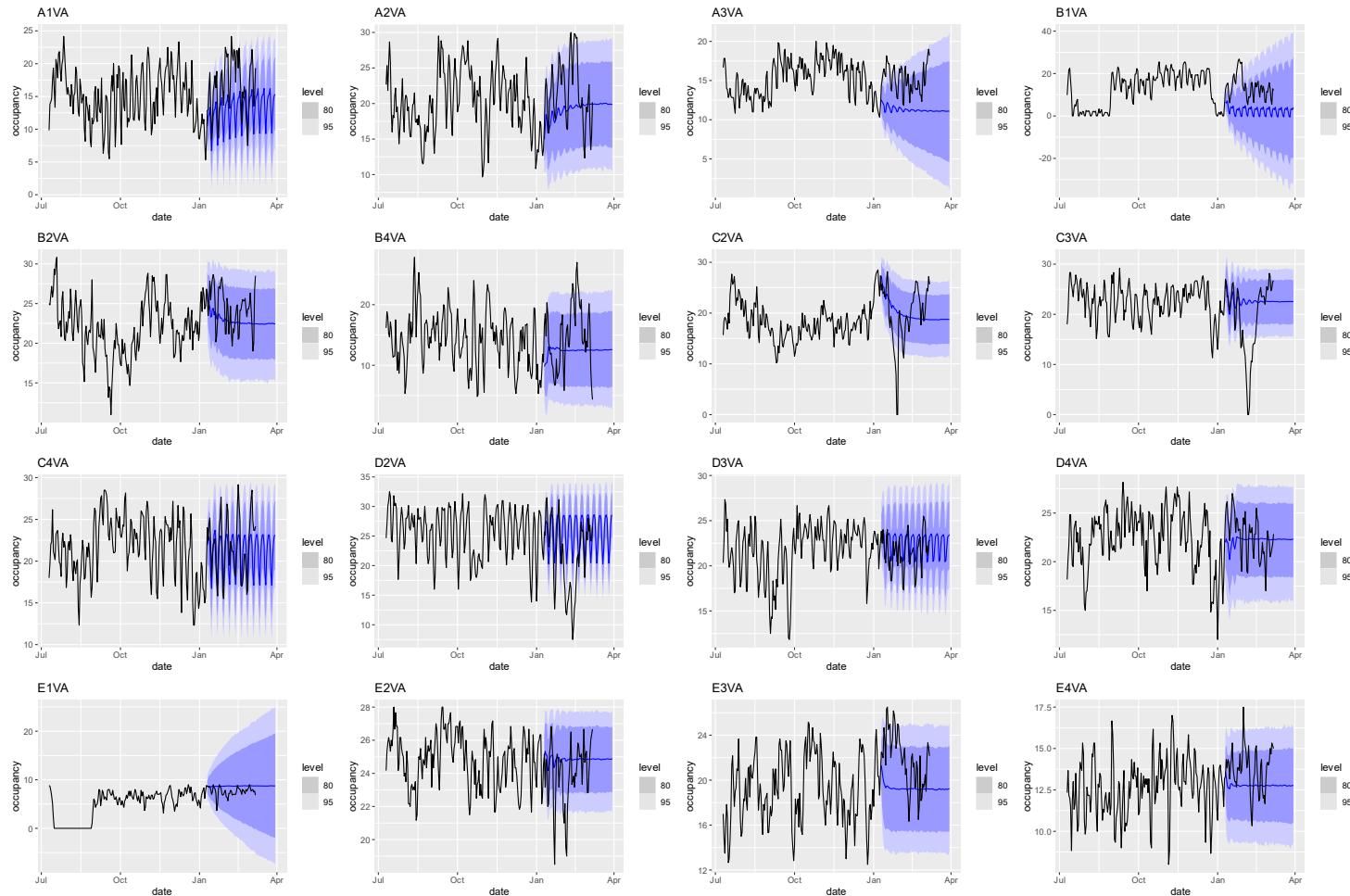
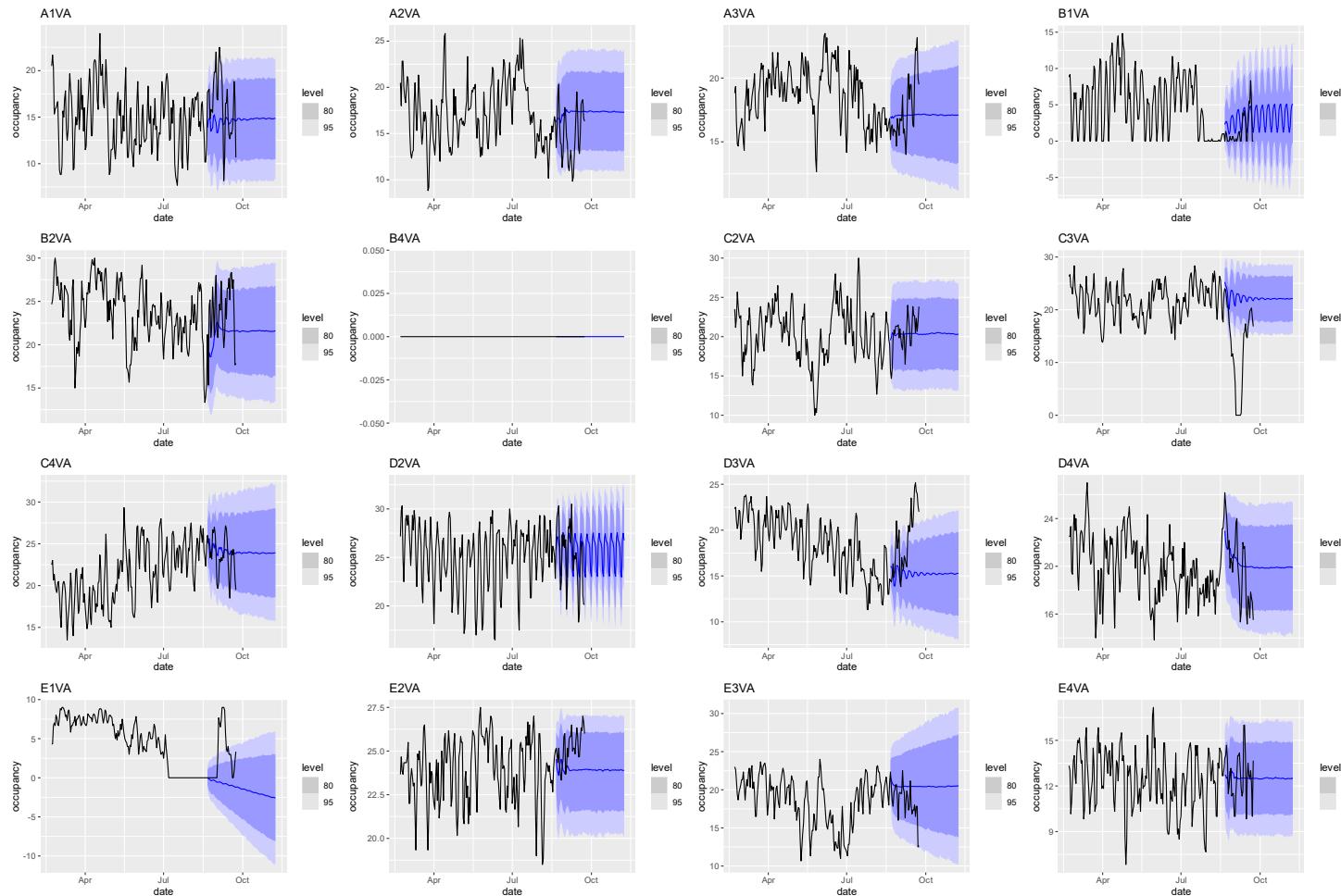


Figure 3.2: Time series used for opportunity costs 2018 outbreak



Chapter 4: Perioperative bridging of Vitamin K antagonist treatment in patients with atrial fibrillation: only a very small group of patients benefits

Table 4.1: R packages used

Package name	Reference
Base R	¹
Ggplot2	²
Dplyr	³
Mc2d	⁴
Forcats	⁵
Readxl	⁶
Extrafont	⁷
Multiplot	⁸

Table 4.2: stroke and bleeding incidence

Stroke incidence (/100 patient years)		Reference
Score	CHA ₂ D _{S_2} -VASc/CHADS ₂	9-11
0	0.2/0.6	
1	0.6/3	
2	2.2/4.2	
3	3.2/7.1	
4	4.8/11.1	
5	7.2/12.5	
6	9.7/13	
7	11.2/NA	
8	10.8/NA	
9	12.23/NA	
Pre-procedural bleeding incidence (/100 patient years)		9
Low risk (HAS-BLED 0 - 2)	1.34	
High risk (HAS-BLED 3 - 7)	2.78	
Post-procedural bleeding rate		

(/30 days, non-bridging)		
Base	0.36%	12,13

CHADS₂: congestive heart failure, hypertension, age, diabetes and stroke, transient ischemic attack or thromboembolism; CHA₂DS₂-VASc: congestive heart failure, hypertension, age, diabetes, stroke, transient ischemic attack or thromboembolism, vascular disease, age and sex; HAS-BLED:
Hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs/alcohol

Table 4.3: Risk and odds ratios

Stroke risk		Distribution	Reference
Patient status	OR		
INR<1.15	1	Fixed	^{14,15}
1.15<INR<1.85	Function: -1.24*INR+2.4	Fixed	^{14,15}
INR>1.85	0.14	Fixed	^{14,15}
Post-procedural	3	PERT (λ : 4; min: 1; max: 5)	Assumed
Additional bleeding risk	RR		
RR bridging	2.4	Lognormal (1.3 - 5)	¹²
OR HAS-BLED >2	11.9	Lognormal (5.6 - 24.9)	¹³

CI: Confidence Interval; HAS-BLED: score used to assess the bleeding risk; INR: International Normalized Ratio; OR: Odds Ratio; RR: Risk Ratio;

Table 4.4: Prevalence of atrial fibrillation

Sex	Age category (years)	Prevalence	Distribution (95% CI)	References
Women	55-59	1.7%	Lognormal (0.7% - 4%)	¹⁶
	60-64	1.3%	Lognormal (0.6% - 2.7%)	¹⁶
	65-69	2.7%	Lognormal (1.8% - 4.2%)	¹⁶
	70-74	5.1%	Lognormal (3.8% - 6.9%)	¹⁶
	75-80	9.6%	Lognormal (7.6% - 11.9%)	¹⁶
	80-84	12.2%	Lognormal (9.7% - 15.1%)	¹⁶
Men	55-59	1.3%	Lognormal (0.4% - 3.6%)	¹⁶
	60-64	1.9%	Lognormal (1% - 4%)	¹⁶
	65-69	5.5%	Lognormal (4% - 8%)	¹⁶
	70-74	7.3%	Lognormal (6% - 10%)	¹⁶

	75-80	12.5%	Lognormal (10% - 16%)	¹⁶
	80-84	16.1%	Lognormal (12% - 20%)	¹⁶

CI: Confidence Interval

Table 4.5: Mortality AF patients

Stroke classification	Deaths per person year	Distribution (95% CI)	References
mRS <=3	0.009	Normal (0.006 - 0.012)	¹⁷
mRS >3	0.055	Normal (0.037 - 0.072)	¹⁷

CI: Confidence Interval; mRS: modified Rankin Scale;

Table 4.6: Calculated life expectancy

Sex	Age category (years)	Life expectancy (years)			
		No comorbidities ¹⁸	Atrial fibrillation (95% CI)	Post mild stroke (95% CI)	Post severe stroke (95% CI)
Women	55-59	28.3	28.2 (28.1 - 28.2)	22.4 (21.1 - 24)	11.1 (9.3 - 13.8)
	60-64	23.9	23.4 (23.0 - 23.6)	19.3 (18.4 - 20.1)	10.3 (8.7 - 12.4)
	65-69	19.7	19.3 (19.1 - 19.4)	16.4 (15.7 - 17.1)	9.4 (8.1 - 11.2)
	70-74	15.7	15.3 (15.2 - 15.4)	13.4 (13 - 13.9)	8.3 (7.3 - 9.7)
	75-80	11.9	11.6 (11.5 - 11.6)	10.5 (10.2 - 10.8)	7.1 (6.3 - 8.1)
	80-84	8.5	8.2 (8.1 - 8.2)	7.6 (7.5 - 7.7)	5.6 (5.2 - 6.2)
Men	55-59	25.4	25.1 (24.7 - 25.3)	20.4 (19.4 - 21.5)	10.6 (8.9 - 12.9)
	60-64	21.1	20.7 (20.4 - 20.9)	17.4 (16.7 - 18.1)	9.7 (8.3 - 11.6)
	65-69	17.1	16.8 (16.7 - 16.9)	14.6 (14 - 15.1)	8.8 (7.6 - 10.3)

	70-74	13.4	13.1 (13 - 13.1)	11.7 (11.4 - 12.1)	7.6 (6.7 - 8.8)
	75-80	10	9.8 (9.8 - 9.8)	9 (8.8 - 9.2)	6.4 (5.7 - 7.2)
	80-84	7.1	6.9 (6.8 - 6.9)	6.5 (6.4 - 6.5)	5 (4.6 - 5.4)

CI: Confidence Interval

Table 4.7: Utilities

Health state	Value	Percentage of bleeding/stro ke events	Distribution	Reference
Baseline (atrial fibrillation patients)	0.774	-	Fixed	¹⁹
Post-bleeding	Identical to baseline	100%		
Post mild stroke	0.727	57%	Beta (α : 40; β : 15)	²⁰⁻²²
Post severe stroke	0.49	29%	Beta (α : 4.2; β : 4.4)	²⁰⁻²²
Death	0	14%	Fixed	²⁰

References

1. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
2. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. 2017.
3. Wickham H, Francois R, Henry L, Müller K. *dplyr: A Grammar of Data Manipulation*. 2017.
4. Pouillot R, Delignette-Muller M-L. Evaluating variability and uncertainty in microbial quantitative risk assessment using two R packages. *Int J Food Microbiol* 2010;142:330–40.
5. Wickham H. *forcats: Tools for Working with Categorical Variables (Factors)*. 2017.
6. Wickham H, Bryan J. *readxl: Read Excel Files*. 2017.
7. Chang W. *extrafont: Tools for using fonts*. 2014.
8. Chang W. *R graphics cookbook*. First edition. Beijing Cambridge Farnham Köln Sebastopol Tokyo: O'Reilly; 2013.
9. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500–10.
10. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70.
11. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–72.
12. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med* 2015;373:823–33.
13. Omran H, Bauersachs R, Rübenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. *Thromb Haemost* 2012;108:65–73.
14. Pappas MA, Barnes GD, Vijan S. Personalizing Bridging Anticoagulation in Patients with Nonvalvular Atrial Fibrillation—a Microsimulation Analysis. *J Gen Intern Med* 2017;32:464–70.
15. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltssova N, et al. Should Patient Characteristics Influence Target Anticoagulation Intensity for Stroke Prevention in Nonvalvular Atrial Fibrillation? *Circ Cardiovasc Qual Outcomes* 2009;2:297–304.
16. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746–51.

17. Chiu H-T, Wang Y-H, Jeng J-S, Chen B-B, Pan S-L. Effect of Functional Status on Survival in Patients With Stroke: Is Independent Ambulation a Key Determinant? *Arch Phys Med Rehabil* 2012;93:527–31.
18. Statistics Netherlands. CBS StatLine. Statline. <http://statline.cbs.nl/Statweb/> (4 September 2018)
19. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. *Med Decis Making* 2006;26:410–20.
20. Rost NS, Bottle A, Lee J-M, Randall M, Middleton S, Shaw L, et al. Stroke Severity Is a Crucial Predictor of Outcome: An International Prospective Validation Study. *J Am Heart Assoc* 2016;5:e002433.
21. Hallan S, Åsberg A, Indredavik B, Widerøe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. *J Intern Med* 1999;246:309–16.
22. Kleintjens J, Li X, Simoens S, Thijs V, Goethals M, Rietzschel ER, et al. Cost-Effectiveness of Rivaroxaban Versus Warfarin for Stroke Prevention in Atrial Fibrillation in the Belgian Healthcare Setting. *PharmacoEconomics* 2013;31:909–18.

Figure 4.1 - Stroke and bleeding outcomes in the simulation

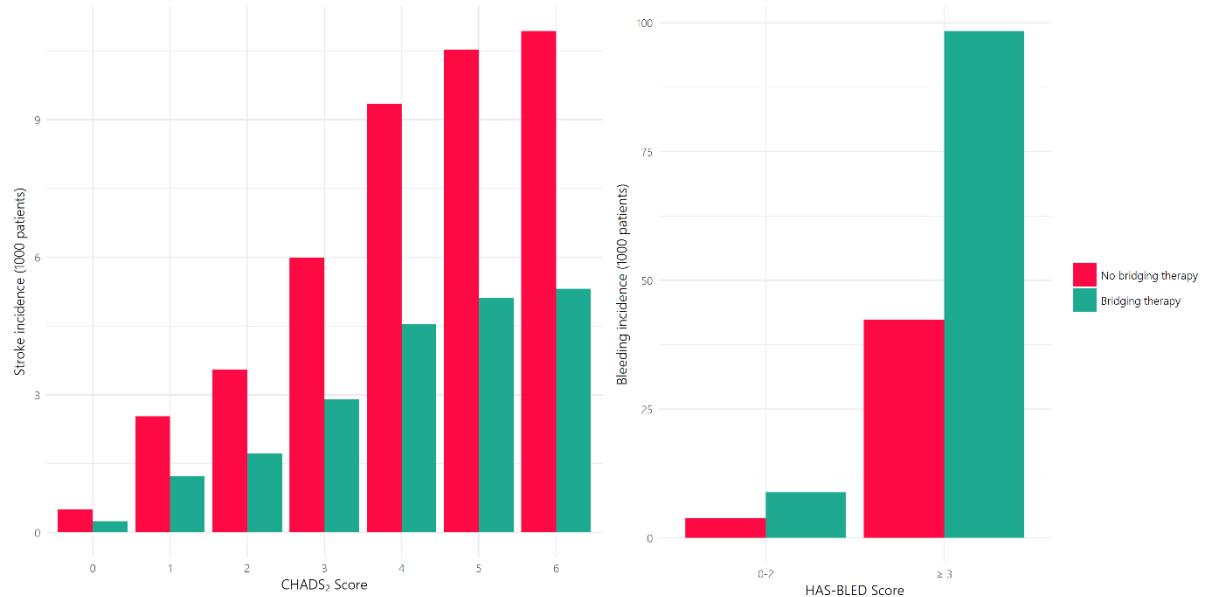


Figure 4.2 - results Monte Carlo simulation, by CHA₂DS₂-VASC score for women

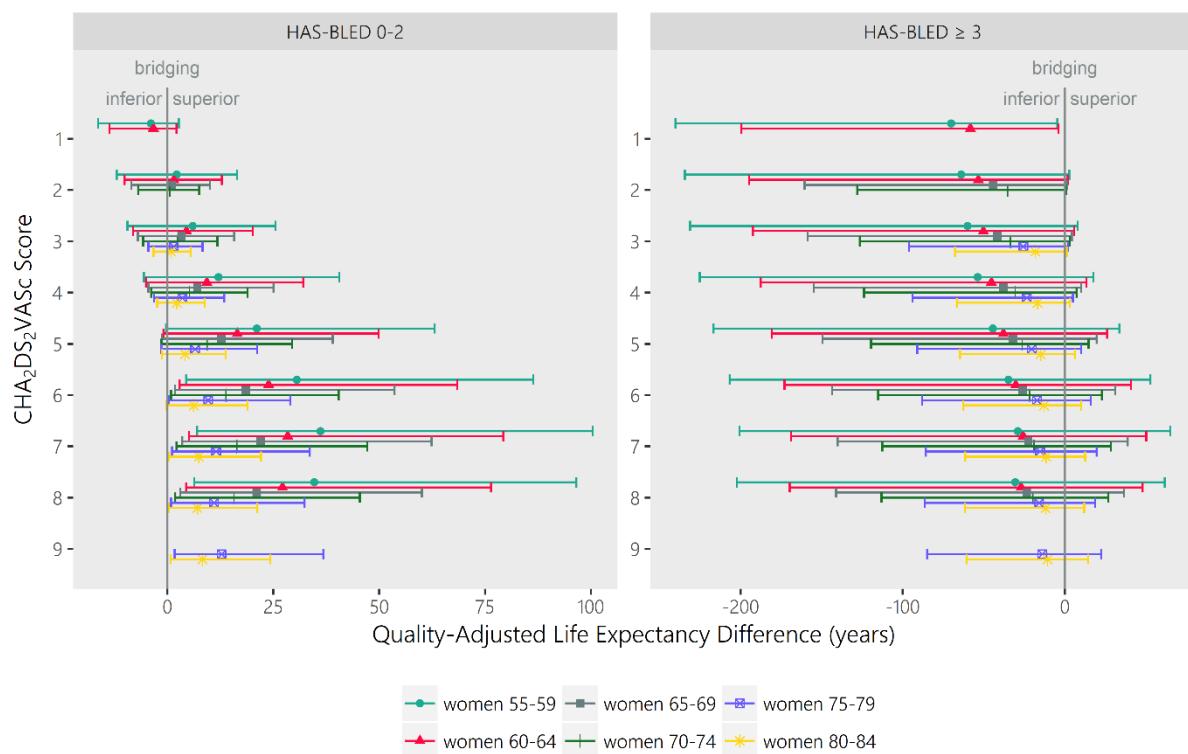


Figure 4.3 - results Monte Carlo simulation, by CHA₂DS₂-VASC score for men

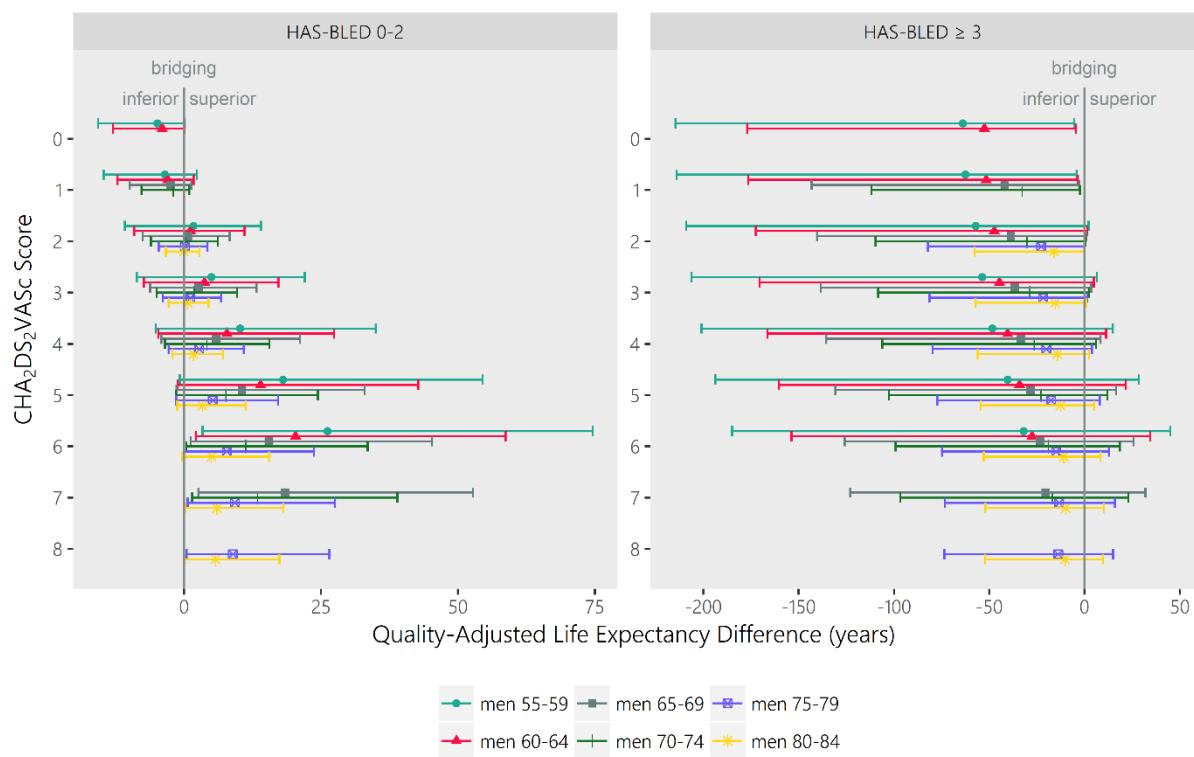


Figure 4.4 - results Monte Carlo simulation, by CHADS₂ score for women

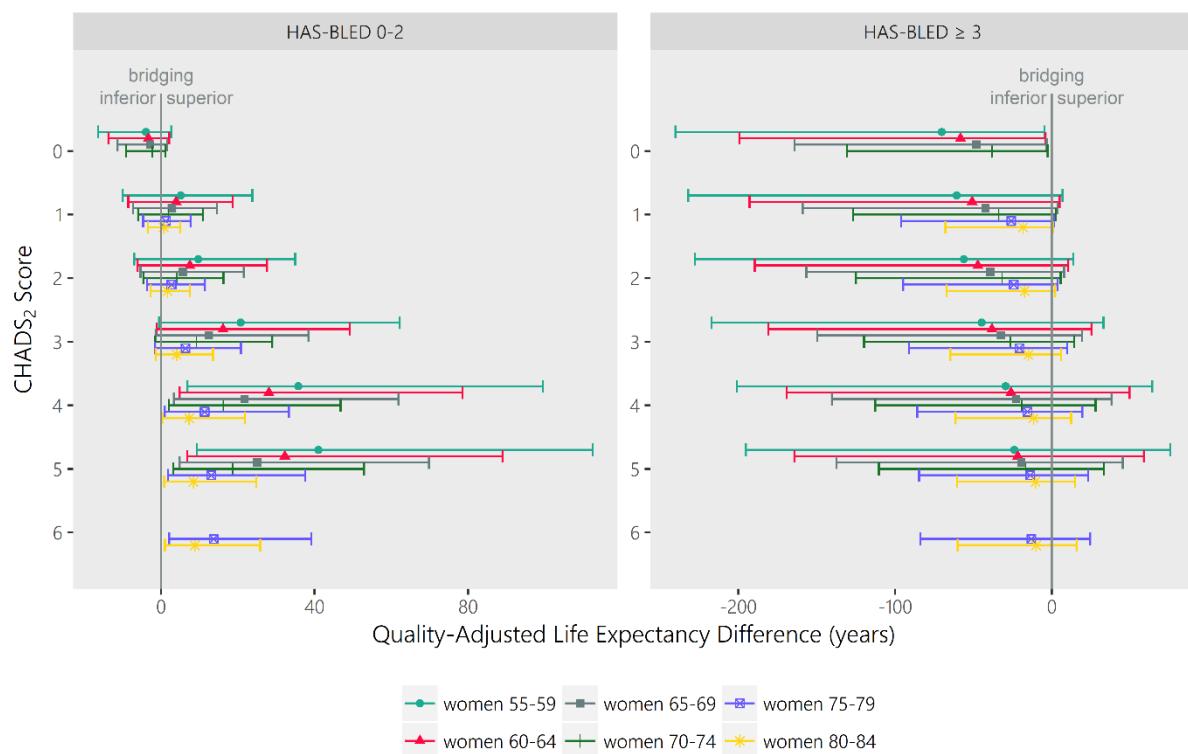


Figure 4.5 - results Monte Carlo simulation, by CHADS₂ score for men

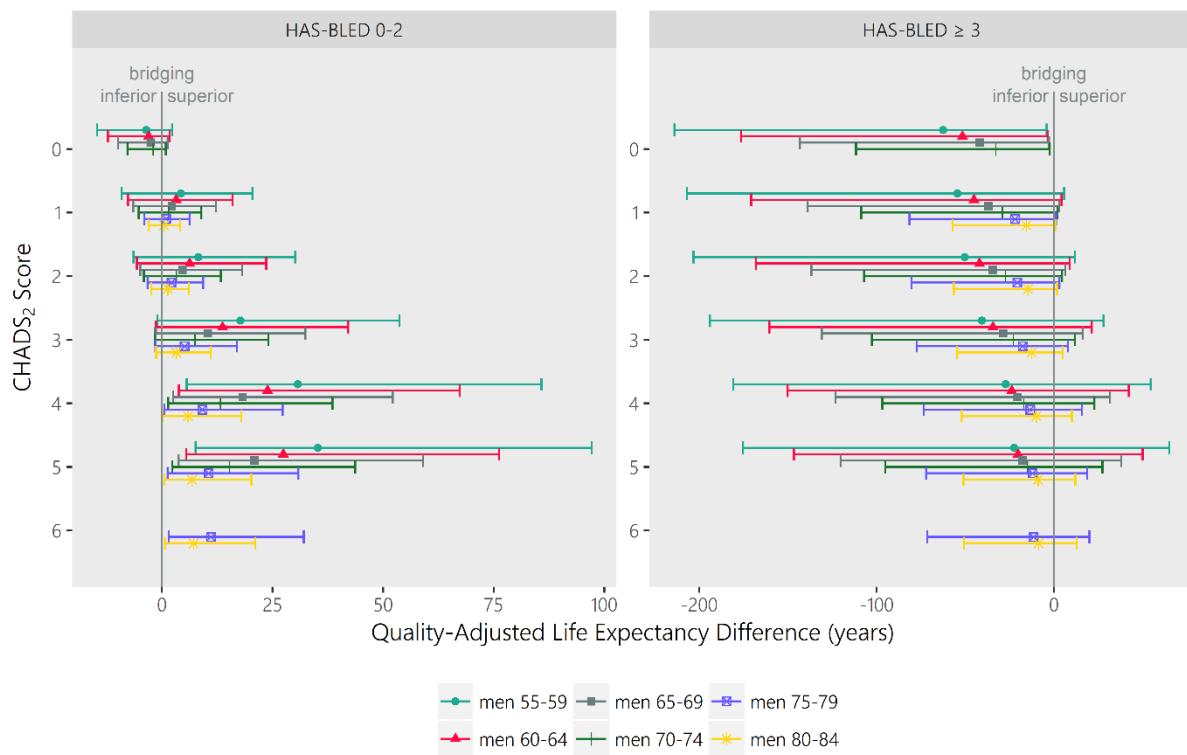
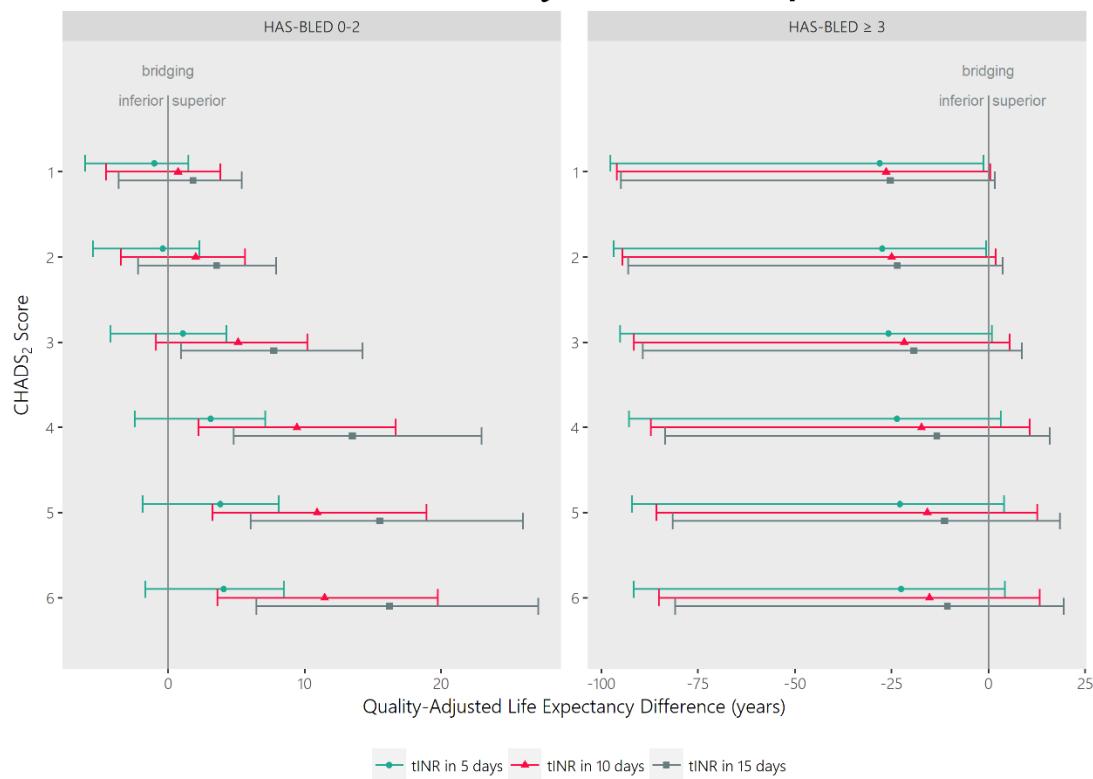
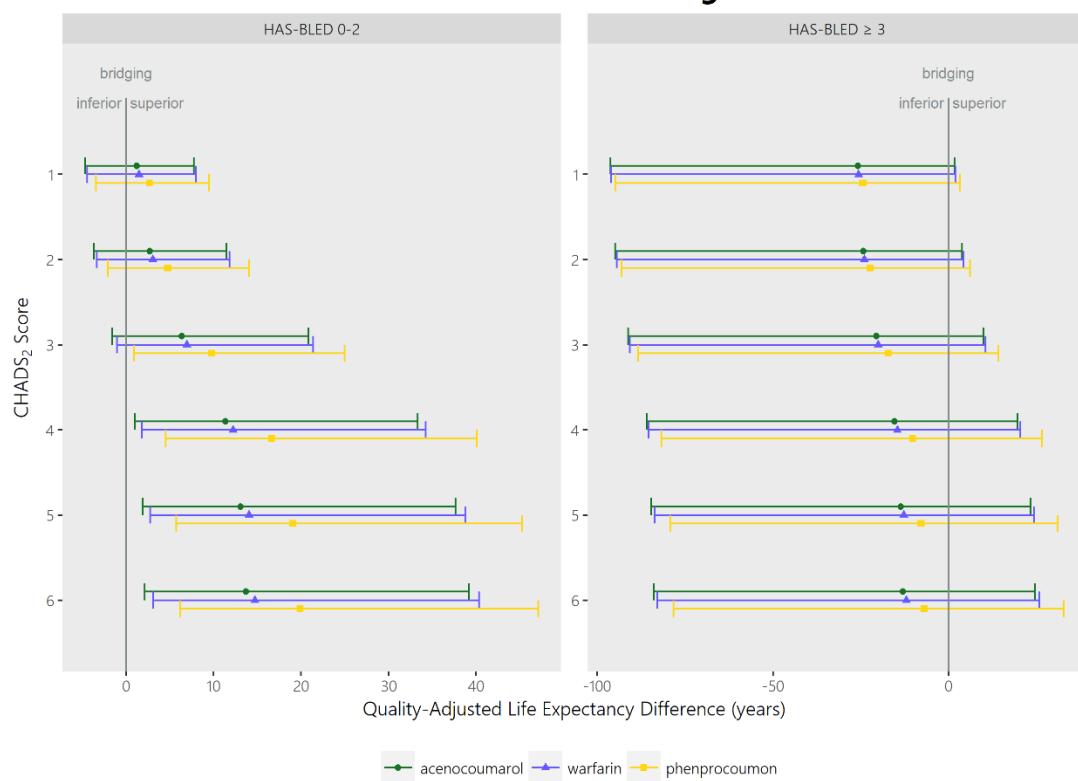


Figure 4.6 - Effect of various vitamin K antagonists and time to reach therapeutic INR on quality-adjusted life expectancy difference of bridging

Effect of number of days to reach therapeutic INR



Different vitamin K antagonists



Chapter 5: Economic analyses of respiratory tract infection diagnostics: a systematic review

Table 5.1 - Search syntax

Syntax used in Scopus	Syntax used in PubMed	Syntax used in Web of Science
(TITLE-ABS-KEY (pharmacoeconomic*)	(infectious	TS=(((“bacterial infection”
OR TITLE-ABS-KEY(cost- effectiveness)	OR “bacterial infection” OR “viral infection”	OR “viral infection” OR antibiotic*
OR TITLE-ABS-KEY(“economic evaluation”)	OR antibiotic*	OR antimicrobial
OR TITLE-ABS-KEY(“health technology assessment”))	OR antimicrobial) AND (“diagnostic”	OR infectious) AND (“diagnostics”
AND (TITLE-ABS-KEY(antibiotic*)	OR “diagnostics”	OR “diagnostic”
OR TITLE-ABS-KEY(infectious)	OR “test”	OR “test”
OR TITLE-ABS-KEY(“bacterial infection”)	OR “tests” OR “testing”	OR “tests” OR “testing”)
OR TITLE-ABS-KEY(“viral infection”))	AND (“2000/01/01”[Date - Publication]: “2020/05/31”[Date - Publication])	AND (pharmacoeconomic*
AND (TITLE-ABS-KEY(“diagnostic”)	AND (pharmacoeconomic*	OR cost-effectiveness
OR TITLE-ABS- KEY(“diagnostics”)	OR “cost-effectiveness”	OR "economic evaluation"
OR TITLE-ABS-KEY(“test”)	OR "economic evaluation"	OR “health technology assessment”)))
OR TITLE-ABS-KEY(“tests”)	OR “health technology	Period of time: 2000-2020
OR TITLE-ABS-KEY(“testing”))	assessment”)	
AND PUBYEAR > 1999		
AND PUBDATETXT < June 2020		

Table 5.2 - Key characteristics of included studies

Author (year)	Country/countries	Type of economic evaluation	Setting	Population	Perspective	Compared strategies	Time horizon	Inclusion of stochasticity	Inclusion of AMR
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Trial-based analyses

Böhmer (2002)	Germany	CEA	Hospital	Patients hospitalized with community-acquired pneumonia in the internal medicin department	Healthcare centre's perspective	Current practice; Inquaro, a computer system to aid in diagnosing community-acquired pneumonia patients	Hospital admission	No	No
Dinh (2018)	France	CEA	Emergency department	Patients who consulted for community-acquired pneumonia in emergency departments	Healthcare centre's perspective	Pneumococcal urinary antigen test; usual care	Not reported	No	Yes
Jha (2016)	South Africa	CEA	Laboratory	Patients with (clinically) suspected TB	Healthcare payer's perspective	Sputum smear microscopy alone; TBDx automated microscopy alone; TBDx automated microscopy, with confirmation of low positive results by Xpert MTB/RIF; TBDx automated microscopy,	Not reported	Yes	Yes

						with confirmation of all positive results by Xpert MTB/RIF; Xpert MTB/RIF performed on all specimens			
Naidoo (2016)	South Africa	CEA	Laboratory	Patients with presumptive TB	Laboratory perspective	A smear/culture-based algorithm; an Xpert-based algorithm	Not reported	No	Yes
Nicholson (2014)	UK	CEA	Hospital	People presenting to medical admissions units, or any ward accepting acute medical admissions, with an acute exacerbation of chronic cardiopulmonary illness of \leq 168 hours' (7 days') duration or an acute cardiopulmonary illness of \leq 7 days' duration	Healthcare centre's perspective	POCTs for influenza A and B and pneumococcal infection; RT-PCR tests for influenza A and B and RSV A and B; and conventional culture for these pathogens.	28 days	No	No

Oppong (2013)	Norway and Sweden	CEA	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.	Healthcare centre's perspective	Rapid test, POC CRP.	28 days	No	No
Oppong (2018)	Belgium, United Kingdom, Netherlands, Poland and Spain	CEA	Primary care	Patients presenting with respiratory tract infections in primary care, from Belgium, the Netherlands, Poland, Spain and the UK (England and Wales).	Healthcare payer's perspective	CRP; communication skills; CRP and communication skills combined; usual care	28 days	Yes	Yes
Pooran (2019)	South Africa, Zambia,	CEA	Primary care	Patients with presumptive TB	Healthcare provider's perspective	Same-day smear microscopy; POC Xpert	Not reported	Yes	No

	Zimbabwe, Tanzania									
Stankiewicz (2003)	USA	CEA	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	Healthcare centre's perspective	Subjective-based diagnosis; diagnosed with a screening CT scan.	Not reported	No	No	
Van Rie (2013)	South Africa	CEA	Primary care	individuals with prolonged (>2 weeks) cough and/or other TB symptoms, presenting at a primary care clinic	Not specified	Smear plus culture; Xpert	Not reported	No	No	

Wang (2019)	China	CEA	Hospital	Pulmonary and extrapulmonary TB suspect patients	Not reported	Single vs. repeated Xpert assay	Not reported	No	Yes
Yakhelef (2014)	Kenya	CEA	Hospital	Patients with a cough of at least 2 weeks and two negative smears	Healthcare centre's perspective	Conventional diagnostic algorithm (based on clinical findings, radiological features and an antibiotic trial); culture-based algorithm that uses TLA and LJ cultures in addition to the conventional algorithm	Not reported	No	No

Decision trees

Abimbola (2012)	Resource-limited countries in sub-Saharan Africa	CEA	Primary care	A group of patients eligible for antiretroviral therapy based on the presence of clinical illness and/or a CD4 cell	Health system perspective	Current practice (symptom screening, sputum smear microscopy, and chest radiography); culture as recommended by WHO guidelines (2007); the	182 days	Yes	No
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				count of <200 cells/microliter.		WHO algorithm as updated in 2011 and is based on the Xpert MTB/RIF test.			
Ang (2015)	Singapore	CEA	Hospital	Patients visiting an eye centre with signs suggestive of TB uveitis	Not specified	TST only; IGRA following a positive TST; IGRA only; TST and IGRA simultaneously	30 years	Yes	No
Behnamfar (2020)	Iran	CEA	Hospital	All the hospitalized patients between the years 2011 and 2015	Healthcare payer's perspective	Treatment for all; no treatment; treatment based on the rapid test for a streptococcal antigen; treatment based on the culture test result; treatment based on RTA plus culture; treatment based on the RTA result,	Not reported	Yes	No

						and in the case of a negative result, culturing.			
Bertran (2000)	Spain	CEA	Primary care, Hospital	Patients with CAP, less than 65 years old, without hospital admission criteria; Patients with AECB due to respiratory infection.	Healthcare centre's perspective	Simple chest x-ray and a blood count; empirical antibiotics	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	No	No
Bonnet (2010)	Kenya	CEA	Primary care/urban health clinic	TB-suspected patients (cough of at least 2 weeks)	Health service provider's perspective	Bleach smear (B) and direct smear (D) (under microscope) in various combinations and orders:	Not reported	No	No

						D1+D2; B1; B1+B2; D1+B1; B1+D2; D1+B2; D1+B1+D2; D1+D2+B2; D1+B1+B2; B1+D2+B2			
Cals (2011)	The Netherlands	CEA	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	Healthcare payer's perspective	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	28 days	No	No
Cowan (2017)	United States	CEA	Hospital	Inpatients placed in airborne infection isolation for	Healthcare centre's perspective	1 Xpert on an unconcentrated sputum sample; 1 Xpert on a concentrated sample; 2	Not reported	Yes	No

				presumptive pulmonary TB.		Xperts on concentrated sputum samples; 2 smears; and 3 smears			
de Bock (2001)	The Netherlands	CEA	Primary care	Patients presenting with Acute sinusitis in primary care	Healthcare centre's perspective	Wait and see; selective prescription; empirical antibiotics; ultrasound assessment; radiographic assessment	7 days	No	No
Dugas (2013)	USA	CUA	Emergency department	Patients presenting with symptoms of an acute respiratory infection at risk or potentially having influenza-related complications.	Societal perspective	Treat none; treat based on provider judgement; treat based on a PCR-based rapid test; treat all	Lifetime horizon	Yes	No

Durski (2013)	Uganda	CEA	Hospital	HIV-infected adults with suspected central nervous system infections	Healthcare centre's perspective	Comprehensive testing; stepwise testing; minimalist testing	Not reported	No	No
Giraldez-Garcia (2011)	Spain	CEA	Primary care	Patients between the ages of 2 and 14 years who consult with a primary care physician due to AP symptoms.	Healthcare payer's perspective	Treat all; clinical scoring; rapid testing; culture; rapid test + culture; clinical scoring + rapid test.	1 year	No	No
Gonzalez-Canudas (2011)	Mexico	CEA, BIA	Primary care	Patients admitted with suspected ILI	Healthcare centre's perspective	PCR; diagnosis with influenza RDT + clinical data	Not reported	Yes	No
Harris (2011)	South Africa	CEA	Primary care	Ambulatory HIV-infected patients in South Africa	Healthcare payer's perspective	33 diagnostic options, involving combinations of specimen collection methods (oral washes induced and expectorated	1 year	No	No

						sputum and bronchoalveolar lavage); PCR or clinical diagnosis with chest x-ray alone			
Herráez (2017)	Spain	CEA	Hospital	Patients with suspected TB	Healthcare centre's perspective	Routine TB diagnosis; XPERT	Not reported	Yes	No
Holmes (2018)	Wales, UK	CEA	Primary care	ARTI for >12 h where the antibiotic decision is unclear	Healthcare payer's perspective	Current standard of care; antibiotic prescribing conditional on POC CRP testing.	28 days	Yes	Yes
Lathia (2018)	Canada	CMA	Pharmacy	Patients with sore throat	Healthcare payer's perspective	Current standard of care; strep throat POC testing	Not reported	No	No
Lavelle (2012)	USA	CEA	Primary care	Unvaccinated children coming to a physician's office with age-	Societal perspective	No antiviral treatment; rapid testing for influenza, followed by oseltamivir if	1 year	Yes	Yes

				appropriate symptoms of uncomplicated ILI		results are positive; empiric oseltamivir treatment			
Maizia (2011)	France	CEA	Primary care	Adults (16 years and older) and children (up to 15 years old).	Healthcare payer's perspective	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.	Not reported	No	No
Mewes (2019)	USA	CEA	Hospital, ICU	Patients with suspected sepsis on the ICU and patients hospitalized with LRTI.	Societal perspective, Healthcare centre's perspective	Standard care; PCT-guided care	The length of the hospital stay	Yes	Yes

Michaelidis (2013)	USA	CEA	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.	Health care system perspective	Procalcitonin-guided antibiotic therapy; usual care.	ARTI treatment episode as the time horizon	Yes	Yes
Nelson (2015)	USA	CEA	Emergency department	Children presenting with ILI	Healthcare centre's perspective	Rapid multiplex PCR; traditional PCR; direct-fluorescent antibody staining; 4: rapid antigen tests.	Lifetime horizon	Yes	No
Neuner (2003)	USA	CEA	Primary care	Adults in the general U.S. population.	Societal perspective	Observation without testing or treatment; empirical treatment with penicillin; throat culture using a two-plate selective	1 year	Yes	No

						culture technique; OIA followed by culture to confirm negative OIA test results; OIA alone.			
Oostenbrink (2002)	The Netherlands	CUA	Hospital, Pediatric Emergency Department	Children (1 month to 15 years) visiting the paediatric emergency department of a hospital with meningeal signs	Societal perspective	Practice a lumbar puncture, based on the characteristics of the patient's history, physical examination and serum CRP; do not practice this	15 years	No	No
Ost (2003)	United States	CEA	ICU	Immunocompetent patients in the intensive care unit	Healthcare centre's perspective	Empiric treatment only; quantitative nonprotected endotracheal cultures; bronchoscopy; nonbronchoscopic mini-BAL	28 days	No	Yes

Perone (2007)	Switzerland	CEA	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.	Healthcare centre's perspective	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.	Not reported	No	No
Pinto (2016)	Brazil	CEA	Primary care	Presumptive TB patients undergoing an initial consultation	National TB programmes perspective	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); SSM testing of two samples was	Not reported	Yes	No

						replaced by Xpert testing of one sputum sample			
Rodriguez-Martinez (2019)	Colombia	CEA	Hospital	Patients 12 months of age and younger who were admitted for acute bronchiolitis	Healthcare centre's perspective	"good practice", which included adherence to diagnosis guidelines (including: hemogram, C-reactive protein, procalcitonin, chest radiography, and tests for detection of respiratory viruses); "bad practice"	1.5 years	Yes	No
Rothberg (2003)-1	USA	CUA	Physician's office	Unvaccinated, healthy, working adults aged 20-50, presenting with influenza-like illness during the influenza season	Societal perspective	No diagnostic test; Directigen (influenza A/B); FLU OIA; QuickVue; ZstatFlu	5 days	No	No

Rothberg (2003)-2	USA	CUA	Primary care	Persons aged >65 years, presenting with influenza symptoms during the influenza season	Societal perspective	Current care; Quickvue	Lifetime horizon	Yes	No
Rothberg (2005)	USA	CEA	Primary care	Healthy children at ages 2, 7 and 15 years	Societal perspective	Quickvue; ZstatFlu	Lifetime horizon	Yes	No
Schuetz (2015)	USA	CEA, BIA	Hospital	The patient population in this study is patients with suspected ARIinfection diagnoses seen in one of three settings: inpatient hospitalsetting (not in the intensive care unit - ICU); hospital ICU; outpatient clinic or ED	Healthcare payer's perspective	PCT testing and monitoring; usual care	30 days	No	Yes

				based on the meta-analysis data					
Schwarzinger (2003)	USA	CBA	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	Societal perspective	No zanamivir; test with zanamivir; systematic zanamivir	Duration of influenza-like illness	No	No
Shah (2013)	Uganda	CEA	Primary care, Hospital	HIV-infected individuals presenting with signs/symptoms of active TB disease	Healthcare payer's perspective	ZN smear-microscopy testing of two sputa; same as 1 plus one urine sample for point-of-care LF-LAM testing; Xpert on one sputum (rifampin resistance is confirmed with conventional culture and DST for all patients);	Lifetime horizon	No	No

						same as 3 plus one urine sample for point-of-care LF-LAM testing			
Shen (2016)	China	CEA	Primary care	Children aged 18 years or below with ILI, had symptoms and signs compatible with influenza.	Healthcare payer's perspective	No antiviral therapy; 2: post influenza RDT treatment; 3: empiric treatment	Not reported	No	No
Siddiqui (2008)	UK	CEA	Primary care	Patients presenting with ILI	Healthcare payer's perspective	Do not treat with antiviral drugs; treat all patients with antiviral drugs; test then treat those who test positive	Not reported	Yes	No
Smith (2002)	USA	CEA	Not reported	32-year old patients with typical influenza symptoms and a temperature 37.8°C during an influenza	Societal perspective, Healthcare	No antiviral testing or treatment; oseltamivir/zanamivir treatment without testing; empiric rimantadine;	Single episode of illness	Yes	No

				season. Other age categories in sensitivity analysis.	payer's perspective	empiric amantadine; test-treat oseltamivir/zanamivir; 6: test-treat rimantadine; 7: test-treat amantadine			
Stojanovic (2017)	China	BIA	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 ICU; (3) outpatient clinic or emergency department (ED).	Healthcare centre's perspective	Usual care; PCT testing and monitoring	30 days	No	Yes

Takwoingi (2019)	United Kingdom	CUA	Hospital	Adults presenting with suspected active TB	Healthcare payer's perspective	QFT-GIT; TSPOT.TB; reference standard (minimum set of tests defined by the NICE guideline, verified by a panel of blinded clinicians)	60 days	Yes	No
Tillekeratne (2019)	Sri Lanka	CEA	Emergency department	ILI patients	Societal perspective	Influenza clinical prediction tool; targeted rapid influenza testing; universal rapid influenza testing	An ILI treatment episode	Yes	Yes
Van Howe (2006)	USA	CUA	Primary care	Children and adolescents presenting with pharyngitis.	Societal perspective	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	Not reported	Yes	No

						positive rapid tests and those with positive throat cultures after negative rapid tests; use a clinical scoring measure to determine the diagnosis/treatment strategy.			
Vassall (2011)	India, South Africa, Uganda	CEA	Not reported	Individuals suspected of having TB	Healthcare payer's perspective	Two sputum microscopy, followed by clinical diagnosis that might include chest Xray and antibiotic trial; Xpert after two negative smear examinationss; Xpert instead of smear examination	Not reported	Yes	Yes

Walusimbi (2016)	Uganda	CEA	Primary care	The study population comprised adult HIV-infected patients older than 18 years, with presumptive active pulmonary TB	Healthcare centre's perspective	MODS assay; Xpert MTB/Rif test.	Not reported	No	No
Xie (2017)	Canada	CEA	Hospital	Hospitalized community acquired pneumoniae	Healthcare centre's perspective	BinaxNow-SP and culture; culture alone	3 days	Yes	No
You (2012)	China (Hong Kong)	CEA	Hospital	Adult patients hospitalized for severe respiratory infection, suspected of influenza	Healthcare provider	Immunofluorescence assay; PCR testing; empirical antiviral treatment plus PCR, to later continue or discontinue treatment based on test result; empirical antiviral treatment	Lifetime horizon	Yes	No

You (2015)	Hong Kong (China)	CEA	Hospital	Patients hospitalized for suspected active pulmonary TB	Healthcare provider's perspective	Conventional approach; smear plus Xpert (for smear-negative); Xpert	Not stated (appears to be 1 year)	Yes	No
You (2017)	China (Hong Kong)	CEA	Primary care	Elderly patients with ILI	Healthcare provider	Clinical judgement without testing; rapid molecular POCT	Lifetime horizon	Yes	No

Markov models

Balk (2001)	Not reported	CEA	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	Societal perspective	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)	14 days	No	Yes
Hunter (2015)	England	CEA	Primary care	Cohorts of 100 hypothetical patients with RTI	Healthcare payer's perspective	Current GP practice; Three strategies of CRP testing: 1) GP plus CRP; 2) Practice	3 years	No	No

						nurse plus CRP; 3) GP plus CRP and communicating training			
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Dynamic models

Langley (2014)	Tanzania	CEA	Diagnostic centre	Patients with presumptive TB - different algorithms for patients with and without HIV.	Healthcare payer's perspective	ZN microscopy; LED fluorescence microscopy; same-day LED fluorescence microscopy; full Xpert rollout; Xpert for known HIV+ cases; Xpert for HIV+ cases with additional HIV screening; Xpert for smear-negative and known HIV+ cases; Xpert for smear-negative and HIV+ cases with additional HIV testing	10 years	Yes	Yes
Mears (2016)	England	CEA	Multiple interacting components (laboratory,	Population of England, taking into consideration the age	Public sector perspective	National TB strain typing service	20 years	No	No

			public health and clinical services)	distribution of the population and medium TB incidence					
Menzies (2012)	Botswana, Lesotho, Namibia, South Africa, and Swaziland	CEA	Health facility	General population (with dynamic model). For TB diagnosis patients presenting to a health facility with suspected TB	Healthcare payer's perspective	Current diagnostic algorithms; implementing Xpert in accordance with current WHO recommendations	20 years	Yes	Yes
Nshimyumukiza (2016)	Canada	CEA	Outpatient clinic or emergency department	Quebec (Canada) population	Societal perspective	Current care; potential rapid POC test	1 year	Yes	No

Sohn (2019)	India	CEA	District TB and microscopy center	Patients presenting to care for TB diagnosis	Healthcare system perspective	Centralized Xpert; decentralized Xpert	10 years	Yes	Yes
Suen (2015)	India	CEA	Public sector clinics and private clinics	Individuals are followed from birth to death, TB suspects for TB diagnosis	Societal perspective	current standard of care; Xpert for DST; Xpert for initial diagnoses and DST in public clinics; PPM; PPM combined with GeneXpert for DST; PPM combined with GeneXpert for initial diagnoses and DST in public clinics	Lifetime horizon	Yes	Yes
Wikman (2017)	Mozambique	CUA	Primary care	TB suspects	Healthcare provider's perspective	SSM, base case; Xpert replacing SSM; Xpert after smear-negative SSM; MODS as a replacement; MODS as an add-on for smear-negative SSM	90 years	Yes	No

Other

Bogdanova (2019)	Russian federation	CMA	A centre dedicated to the diagnosis and treatment of TB	All the patients diagnosed with MDR-TB	Societal perspective, Healthcare system perspective	LPA-based diagnostic algorithm (smear positive (SSm+) and for smear negative(SSm-) culture confirmed TB patients by Bactec MGIT or LJ; conventional culture-based algorithm (LJ-for SSm- and SSm+ patients and BacTAlert-for SSm+patients).	TB treatment duration	No	Yes
Lee (2019)	India	CEA	Primary care, Hospital	Adult, HIV-negative patients with presumptive/pulmonary TB	Health system perspective	Sputum smear microscopy; Xpert; Truenat; Truenat POC	Lifetime horizon	Yes	Yes
Oostenbrink (2003)	The Netherlands	CMA	Hospital	360 children from one month up to fifteen years of age visiting the emergency department of a hospital with	Healthcare centre's perspective	Diagnostic decision rule, based on a clinical score and a CSF score for lumbar puncture and empirical	Not reported	No	No

				meningeal signs between 1988 and 1998		treatment for bacterial meningitis; current practice (a low threshold to perform a lumbar puncture, and empirical treatment)			
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ARTI (acute respiratory tract infection); CD (quadruple differentiation); CE (cost-effectiveness); CEA (cost-effectiveness analysis); CEAC (cost-effectiveness acceptability curve); CMA (cost-minimization analysis); CRP (C-reactive protein); CSF (cell count in cerebrospinal fluid); CT (computed tomography); CUA (cost-utility analysis); DALY (disability-adjusted life years); DSA (deterministic sensitivity analysis); DST (drug-susceptibility testing); ED (emergency department); GP (general practitioner); ICER (icer incremental cost effectiveness ratio); ICU (intensive care unit); IGRA (interferon-gamma release assay); ILI (influenza-like illness); LF-LAM (lateral flow urine lipoarabinomannan assay); LJ (Lowenstein-Jensen); LPA (line probe assays); LRTI (lower respiratory tract infection); Mini-BAL (mini-bronchoalveolar lavage); MODS (microscopic observation drug susceptibility); NICE (National Institute for Health and Care Excellence); OIA (optical immune assay); PCR (polymerase chain reaction); POCT (point-of-care test); PSA (probabilistic sensitivity analysis); QALY (quality-adjusted life years); RDT (rapid diagnostic test); RSV (respiratory syncytial virus); RT (reverse transcriptase); SSM (sputum smear microscopy); TB (tuberculosis); TLA (thin-layer agar); WHO (World Health Organization); ZN (Ziehl-Neelsen)

Table 5.3 - Key methods used in included studies

Author (year)	ICER	Currency (year)	Inclusion of stochasticity	Reporting of uncertainty	Main findings	Cost-effectiveness verdict	CHEERS score
Trial-based analyses							
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)	NA	No	DSA	Improvements were found for the patients (fewer infusions, faster symptom resolution and a shorted length-of-stay)	Cost-saving	11
Dinh (2018)	As only 7 PUA tests led to appropriate antimicrobial modification, we deemed that	NA	No	DSA	The test should be used only for patients with probable CAP	Cost-saving	13

	the potential cost savings, if the test had not been used, would have been 26,244 € during 3 years, that is 8748 € per year.						
Jha (2016)	Main outcome reported: \$1280 per incremental TB diagnosis, TBDx automated microscopy	US dollars (2015)	Yes	Table of DSA, Tornado diagram, 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	14
Naidoo (2016)	\$6274 per additional MDR-TB case diagnosed	US dollars (2013)	No	-	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	-	16

					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.		
Nicholson (2014)	734717 per QALY	Pound Sterling (2007)	No	DSA, Table of DSA, PSA, CE plane, CEAC	The total costs and QALYs of each diagnostic strategy were similar, 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.	Cost-effective	16

Oppong (2013)	€112,7 / antibiotic prescription saved	Euros (2007)	No	CEAC	Patients receiving POCCRP did not have significantly different measures of recovery or outcomes compared to patients not receiving this test.	Cost-effective, reduces the rate of antibiotic prescribing.	17
Oppong (2018)	Communication skills was associated with an ICER of €68.08 per percentage reduction in antibiotic prescribing when compared with usual care. The ICER for CRP compared with communication skills was €176.53 and the ICER for the combined intervention compared with CRP was €338.89	Euros (2016)	Yes	DSA, PSA, CE plane, CEAC	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	15
Pooran (2019)	Incremental costs per clinical outcome: diagnosed by index test: 4186; starting treatment: 1464; starting treatment same	US dollars (2014)	Yes	Tornado diagram, CEAC	Point-of-care Xpert is likely to be cost-effective in settings willing to pay at least \$4500 per treatment initiation or	Cost-effective	14

	day: 561; completing treatment: 1211; improved morbidity: 1918				\$3800 per treatment completion among culture-positive patients		
Stankiewicz (2003)	147 per patient	NA	No	NA	With screening CT scanning, patients are diagnosed more accurately, according to whether they have disease or not. This is important because the current subjective method of diagnosis of chronic rhinosinusitis is inaccurate.	Cost-saving	10
Van Rie (2013)	Cost savings of \$3.28 per valid Xpert result	US dollars (2010)	No	-	The cost per Xpert was only US\$1.88 higher than the cost for smear 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-saving	14

					cost per case diagnosed was similar for both strategies (US\$266 vs. US\$260).		
Wang (2019)	Pulmonary: 467.72; extrapulmonary: 291.87 per additional TB diagnosis	Not reported	No	Not reported	The cost-effectiveness analysis showed that the incremental cost of performing a second Xpert was very high for the smear-positive TB patients	Not cost-effective	12
Yakhelef (2014)	Varying between €452-€3121 per case depending on exact algorithm used	Euros (2009)	No	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 depends on the government/community's willingness to pay for it.	culture-based algorithm may be hard to afford for resource-limited countries	15
Decision trees							

Abimbola (2012)	culture: \$60,430/death averted; Xpert: dominated	US dollars (2010)	Yes	Tornado diagram, 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	16
Ang (2015)	TSt: \$3611/QALY; IGRA: dominated; TST and IGRA: 11506/QALY (using TST followed by IGRA as reference)	Singapore dollars (2010)	Yes	Table of DSA, Tornado diagram, One- way sensitivity analysis, 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	14
Behnamfar (2020)	RTA + culture: 0.007564; RTA: 0.048541; Culture: 0.049706	Not reported	Yes	Tornado diagram	The most effective mean observed quality-adjusted life days was the	Cost-effective	14

	(unit: costs /quality-adjusted life day)				simultaneous diagnostic treatment of RTA and culture; the highest amount of saving (monetary cost) was detected in RTA before treatment.		
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, ranging 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)	No	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	9

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)	No	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 due to its effectiveness and low ICER compared to B1.	Cost-effective	14
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. Communication was superior to usual care costs or savings/antibiotic prescription saved	Euros (Unclear. 2010)	No	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 implement the communication skills training.	Cost-effective	15

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)	Yes	Tornado diagram, Two-way 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	15
de Bock (2001)	Clinical assessment: DFL 515.59; Ultrasound assessment: DFL 5745.38; Radiographic assessment: DFL 3164.98; Antibiotics: DFL 881.67 costs or savings/patient	Dutch Florins (year NA)	No	DSA, One-way sensitivity analysis, Two-way sensitivity analysis	The costs for curing one additional patient were DFL516 when antibiotics were selectively prescribed and DFL882 when antibiotics were prescribed immediately	Cost-effective	14
Dugas (2013)	PCR: \$1389/QALY; treat all: \$6246/QALY; treat none:	US dollars (2011)	Yes	Tornado diagram, CEAC	Assuming a \$50,000 per quality-adjusted life-year willingness-to-pay	Cost-effective	18

	dominated (all compared to provider judgement)				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.		
Durski (2013)	133 per additional correct diagnosis	US dollars, South African Rand (2013)	No	DSA	Through strategically choosing the order and type of testing coupled with disease prevalence rates, algorithms can deliver more care more efficiently.	Cost-effective	16
Giraldez-Garcia (2011)	Only rapid test: 51.22; clinical scoring + rapid test: 50.72 (Costs per patient cured without complications and no adverse reaction to penicillin)	Not reported	No	One-way sensitivity analysis, Two-way sensitivity analysis	The “clinical scoring + rapid test” strategy was the most cost-effective of the six strategies analysed	Cost-effective	15

Gonzalez-Canudas (2011)	\$12.60 saved each suspected case	US dollars (2009)	Yes	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	11
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	No	DSA	Three metrics are relevant: proportion of PCP patients successfully treated, proportion of well persons unnecessarily treated, and the total diagnostic and treatment cost per life-year gained.	Cost-effective	15
Herráez (2017)	€2960/QALY	Euros (2016)	Yes	Table of DSA, Tornado diagram, PSA, CEAC	The implementation of a molecular microbiological technique in the diagnosis of TB extremely cost-effective compared to the usual method. Its introduction into the	Cost-effective	13

					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.		
Holmes (2018)	In patients with symptoms of ARTI and based on routine practice, the ICERs of CRP testing were £19,705 per quality-adjusted-life-year (QALY) gained and £16.07 per antibiotic prescription avoided	Pound Sterling (2016)	Yes	DSA, Table of DSA, PSA, CE plane, CEAC	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	17
Lathia (2018)	-18.66 (province AB); -14.86 (province BC); -12.78 (province NS); -12.47 (province ON); -24.36	Not reported	No	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	Cost-saving	12

	(province SK) costs or savings /patient				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.		
Lavelle (2012)	\$25,900 to \$71,200/QALY, depending on age, compared with the no oseltamivir treatment strategy	US dollars (2008)	Yes	Table of DSA, One-way sensitivity analysis, CEAC	This analysis demonstrates that when seasonal influenza viruses are circulating in the 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.	Cost-effective	17
Maizia (2011)	970 in children and at 903 in adults cost per suppurative complication avoided	Euros (2008)	No	DSA, Tornado diagram	The use of RDT was the most cost-effective strategy from the insurance perspective private US, while the use	Cost-effective	13

					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.		
Mewes (2019)	The incremental savings per antibiotic day avoided were -\$584 for the PCT group	US dollars (2017)	Yes	DSA, Tornado diagram	Using a Procalcitonin-algorithm to guide antibiotic use in sepsis and hospitalised lower respiratory tract infection patients is expected to generate cost-savings to the hospital and lower rates of antibiotic resistance and C.difficile infections.	Cost-effective	16

Michaelidis (2013)	149 / antibiotic prescription saved	US dollars (2012)	Yes	PSA, CEAC	Procalcitonin testing is unlikely to be preferred over usual care when costs alone are considered, but is likely to be 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.	Cost-effective	16
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)	Yes	One-way sensitivity analysis, 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	15
Neuner (2003)	Culture strategy: 0.2668 quality-adjusted life-day lost and an average cost of \$6.66 per patient	US dollars (2000)	Yes	DSA, PSA	Although the other four strategies had similar effectiveness (all resulted in about 0.27 lost QALY), culture was the least expensive strategy.	Cost-effective	15

Oostenbrink (2002)	€401,965 per QALY (<i>Streptococcus pneumoniae</i>) and €22,635 per QALY (<i>Neisseria meningitidis</i>)	Euros (2001)	No	DSA	Minimizing lumbar punctures and empirical treatments using a diagnostic decision rule, without missing a single case of meningitis, was a dominant strategy to actual practice.	Cost-effective, not generalizable for vaccination strategies.	17
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;	NA	No	DSA, Two-way sensitivity analysis, Three-way (or more) sensitivity analysis graph, PSA	From the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was three antibiotics with mini-BAL.	Cost-effective	14

	Empiric-dominated; Three antibiotics: Empiric + mini-BAL=NA; Empiric + ETT asp-dominated; Empiric + FOB=1375978; Empiric= Dominated						
Perone (2007)	\$15.30 (rapid test strategy) per patient	Not reported	No	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 greater than or equal to two.	Cost-effective	11
Pinto (2016)	\$943 per additional TB diagnosis; US\$356 per additional TB diagnosis with bacteriological confirmation	US dollars (2014)	Yes	Table of DSA, Tornado diagram, Two-way sensitivity analysis, PSA:	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.	-	15

				uncertainty ranges	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.		
Rodriguez-Martinez (2019)	"Good practice" was dominant	US dollars, Colombian pesos (COP) (2015)	Yes	DSA, Tornado diagram	Compared with lack of "good practice," the utilization of "good practice" in the diagnosis and management of patients with bronchiolitis was associated with both fewer patients readmitted within 10 days of post discharge (0.88 vs 0.99 on average per patient) and lower costs (US\$1529.3 versus \$1709.1 average)	Cost-effective	14

					cost per patient), thus leading to dominance		
Rothberg (2003) - 1	All testing strategies are dominated by empiric treatment with amantadine	US dollars (2001)	No	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	15
Rothberg (2003) - 2	Amantadine treatment only: \$1129/QALY; test-treat oseltamivir: \$5025/QALY, empiric oseltamivir: \$10,296/QALY, other test-treat combinations (extended) dominated	US dollars (2001)	Yes	One-way sensitivity analysis, Two-way sensitivity analysis, PSA	Under most circumstances, antiviral therapy is reasonably cost-effective and within the range of other widely accepted interventions for older adults. 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	14

Rothberg (2005)	Antiviral therapy: \$800 - \$1800/QALY; testing strategies were dominated in most scenarios	US dollars (2003)	Yes	One-way sensitivity analysis, PSA	During local influenza outbreaks, children with 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.	Testing not cost-effective - empirical treatment is cost-effective	14
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)	No	DSA, One-way sensitivity analysis	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	14

Schwarzinger (2003)	test: \$14.40 for 0.65 averted influenza days; empiric treatment: \$29.80 for 0.81 averted influenza day (1)	US dollars (1999)	No	Table of DSA, One-way sensitivity analysis	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	16
Shah (2013)	ZN microscopy + urine sample testing: \$33/DALY; Xpert on one sputum: \$58/DALY; Xpert on one sputum + urine sample testing: \$57/DALY (ZN microscopy as reference)	US dollars (2013)	No	One-way sensitivity analysis, 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	16

Shen (2016)	32,810/QALY	Chinese yuan (no year)	No	Tornado diagram, 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.	Not cost-effective	13
Siddiqui (2008)	For stockpiling: £1900 and £13700/QALY for the 1918 and 1957/69 scenarios; test-treat £31000 and £228000/QALY	Pound Sterling (2004)	Yes	Tornado diagram, One-way sensitivity analysis, 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-effective strategy would be to increase the stockpile of AV drugs.	Not cost-effective	14
Smith (2002)	Empiric amantadine: \$9.06 per illness day avoided; empiric oseltamivir: \$198 per illness day avoided; other strategies (extended) dominated	US dollars (2000)	Yes	Tornado diagram, 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.	"Economically reasonable"	12

					Rapid testing was, for the most part, more costly and less effective than treatment without testing.		
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	Chinese yuan (2015)	No	DSA	Our results demonstrate substantial savings associated with the use of PCT to guide antibiotic treatment of ARI across common China treatment settings.	Cost-saving	17
Takwoingi (2019)	Varying from 6640 to 22010 /QALY	Not reported	Yes	CE plane, CEAC	The use of current IGRA tests for ruling out active TB would be unlikely to be considered cost-effective if a QALY were to be valued at £20,000 or £30,000. There are cost savings, but	Not cost-effective	16

					the health detriment is large because of the delay in diagnosing active TB.		
Tillekeratne (2019)	The incremental cost per antibiotic prescription avoided with clinical prediction versus standard care was US\$3.0, which was lower than the base-case estimate of the cost of antimicrobial resistance per ILI antibiotic prescription (US\$12.5)	US dollars (2014)	Yes	DSA, PSA	Standard care was less expensive than other strategies across all parameter values in one-way sensitivity analyses. To obtain a cost-effectiveness ratio lower than US\$12.5 with targeted testing versus standard care, the test price must be <US\$2.6. At a higher threshold of US\$28.7, the test price must be <US\$7.7.	Cost-saving	16
Van Howe (2006)	\$32,132.01 rapid antigen testing had the best cost-utility. It dominated both "treat all" and "rapid test + culture" strategies	US dollars (2003)	Yes	Table of DSA, Tornado diagram, 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.	Cost-effective	15

Vassall (2011)	Xpert after two negative smear examinations: India: \$55/DALY, South Africa: \$110/DALY, Uganda: \$41/DALY; Xpert instead of smear examination: India: \$68/DALY, South Africa: \$138/DALY, Uganda: \$37/DALY	US dollars (2010)	Yes	Table of DSA, One-way sensitivity analysis, 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	16
Walusimbi (2016)	MODS: \$34 per TB patient diagnosed; Xpert: \$71 per TB patient diagnosed	US dollars (2014)	No	Table of DSA, Tornado diagram	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	16

Xie (2017)	Incremental cost per patient 36 dollars. Incremental costs per case correctly classified 582 dollars	Canadian dollars (year unknown)	Yes	DSA	An overall increase in diagnostic accuracy of 6.2% due to the addition of BinaxNOW-SP.	Cost-effective	13
You (2012)	Empirical treatment dominates testing	US dollars (2011)	Yes	Two-way sensitivity analysis, 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 ‘PCR guided treatment’ approach would be cost-effective at a low prevalence of less than 2.5%.	Not cost-effective	16
You (2015)	\$99/QALY	US dollars (2014)	Yes	One-way sensitivity analysis, CEAC	Using a simple sputum test of Xpert at initial assessment was the most cost-effective option	Cost-effective	12

You (2017)	\$29582/QALY	US dollars (2017)	Yes	Table of DSA, Tornado diagram, cost- effectiveness plane, CEAC	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.	Cost-effective	15
Markov models							
Balk (2001)	34.0 costs/symptom free day (in a mild scenario)	US dollars (year NA)	No	DSA, Table of DSA, One-way sensitivity analysis	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	15
Hunter (2015)	The two strategies result in 0.13 additional QALYs per 100 patients and costs 42 pounds less per 100 patients for the GP plus	Pound Sterling (2012)	No	DSA, PSA, CE plane, CEAC	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 the test is outweighed by cost savings and QALY increment	Cost-effective	18

	CRP strategy and 680 pounds less for the nurse plus CRP strategy				associated with a reduction in infections in the long run.		
Dynamic models							
Langley (2014)	LED microscopy: \$29/DALY; same-day LED microscopy: \$45/DALY; full Xpert: \$169/DALY; others dominated	US dollars (2011)	Yes	Table of DSA, Tornado diagram, PSA, CEAC, 95% credible intervals	We have assessed the effect of several promising TB diagnostic options that are being considered by many national TB 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	17
Mears (2016)	£95,628/QALY (LTBI detecting increase from 3% to 4%); £54,539/QALY (LTBI detecting increase from 3% to 13%); cost-	Pound sterling (unknown year)	No	Table of DSA, One-way sensitivity analysis	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	Not cost-effective	17

	saving if diagnostic delay was reduced with 1 week				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.		
Menzies (2012)	\$784/DALY; \$810/life-year saved	US dollars (2011)	Yes	Table of DSA, Tornado diagram, 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 to absorb these changes.	-	16

Nshimyumukiza (2016)	\$7573 saved /100,000 person years and 1.92 life-years saved /100,000 person years	Canadian dollars (2011-2012)	Yes	Tornado diagram, 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.	Cost-effective	16
Sohn (2019)	3161 /DALY	US dollars (2015)	Yes	One-way sensitivity analysis, CEAC	Provided that decentralized testing can be performed with equal quality as centralized testing, the costs and LTFU incurred by using a hub-and-spoke system are likely to justify the increased costs of decentralized testing, except in settings where testing volumes is low.	Not clear	16
Suen (2015)	PPM: \$72/QALY; PPM + Xpert: 145/QALY; PPM + Xpert in	US dollars (2013)	Yes	CEAC, partly PSA (on the simultaneous	Our results illustrate that there is no silver bullet for combating the TB epidemic – introducing rapid and	Cost-effective	16

	public clinics: 1104/QALY (others dominated)			effect of uncertainty about the quality of life lost due to TB and the costs of care)	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.		
Wikman (2017)	SM + MODS: \$5648/DALY; MODS: \$5375/DALY; SM + Xpert: \$346/DALY; Xpert: \$122/DALY	US dollars (2013)	Yes	Tornado diagram, PSA, CE plane	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 strategy or MODS implementation. However, the degree of uncertainty is high.	Cost-effective	15
Other							

Bogdanova (2019)	SSm+ LPA-based diagnostics reduced the costs by 4.5 times compared to LJ and by 2.5 times compared to BacTAlert liquid culture	US dollars (2014)	No	DSA	TB diagnostic algorithms incorporating LPA method proved to be both more clinically effective and less expensive due to reduction in the number of hospital days to the correct MDR-TB diagnosis and treatment initiation	Cost-saving	15
Lee (2019)	Truenat POC: 210 /LYG, which dominated all other strategies	US dollars (2017)	Yes	DSA, Two-way sensitivity analysis	Truenat, when replacing smear microscopy and used at point-of-care, increases the number of TB cases correctly detected and linked to care by 590 per 10,000 individuals with presumptive TB. It also increases life expectancy by nearly 0.4 years and is cost-effective	Cost-effective	17
Oostenbrink (2003)	Total costs current practice €2.976; total costs decision rule €2.684	Euros (2001)	No	DSA	The decision rule reduced total costs by 292 euros per patient, 33 euros in the diagnostic phase and 259 euros in	Cost-saving	14

					the treatment course. The application of the decision rule reduced the number of patients hospitalized.	
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ARTI (acute respiratory tract infection); CA (cost-analysis); CD (quadruple differentiation); CE (cost-effectiveness); CEA (cost-effectiveness analysis); CEAC (cost-effectiveness acceptability curve); CMA (cost-minimization analysis); CRP (C-reactive protein); CSF (cell count in cerebrospinal fluid); CT (computed tomography); CUA (cost-utility analysis); DALY (disability-adjusted life years); DSA (deterministic sensitivity analysis); DST (drug-susceptibility testing); ED (emergency department); GP (general practitioner); ICER (incremental cost effectiveness ratio); ICU (intensive care unit); IGRA (interferon-gamma release assay); ILI (influenza-like illness); LF-LAM (lateral flow urine lipoarabinomannan assay); LJ (Lowenstein-Jensen); LPA (line probe assays); LRTI (lower respiratory tract infection); Mini-BAL (mini-bronchoalveolar lavage); MODS (microscopic observation drug susceptibility); NICE (National Institute for Health and Care Excellence); OIA (optical immune assay); PCR (polymerase chain reaction); POCT (point-of-care test); PSA (probabilistic sensitivity analysis); QALY (quality-adjusted life years); RDT (rapid diagnostic test); RSV (respiratory syncytial virus); RT (reverse transcriptase); SSM (sputum smear microscopy); TB (tuberculosis); TLA (thin-layer agar); WHO (World Health Organization); ZN (Ziehl-Neelsen)

File 5.1 - Data extraction items

- General
 - Title
 - First author
 - Year published
 - Disease area
 - Specific pathogens
 - Objective
- Introduction
 - Research question(s)
 - Word used to describe “diagnostic strategy” in research question
 - Explicit statement on the context of the study
 - Explanation of relevance for health policy and practise decision
 - Country
- Methodology
 - Is the model used based on a previously-published model?
 - Target population and subgroups
 - Setting
 - Study perspective
 - Interventions or strategies being compared (diagnostics)
 - Treatment options included in the analysis
 - Time horizon
 - Is a time framework and reasoning provided by the authors
 - Discount rate for base case (health outcomes)
 - Discount rate for base case (economic outcomes)
 - Study type
 - Reported clinical outcomes
 - Measurement of effectiveness
 - 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
 - Are the resource and cost estimations explained in the article
 - Costs of diagnostic method
 - Costs of treatment options
 - Currency/currencies reported
 - Currency year used
 - What are the methods used to convert to a common currency
 - Type of model
 - Is the model stochastic or deterministic
 - Description of model
 - Software used to program the model and statistical analyses
 - Is the model design thoroughly described in the article

- Is antibiotic resistance included in the model
 - If yes, how is antibiotic resistance included
- Results
 - Incremental costs and outcomes
 - Unit of incremental costs and outcomes
 - Is the same common currency used as in the methods
 - How is the uncertainty reported
 - For the DSA, which ranges of values are used
 - For the PSA, how many replications are used
 - Have subgroup analyses been performed
- Discussion
 - Main findings
 - Limitations
 - Specific limitations/gaps in the assessment of diagnostics
 - Generalisability
 - Have the results been linked to current knowledge
 - What is the main conclusion or conclusions
 - If reported, which willingness-to-pay threshold(s) was/were used
 - Specific advantages of the modelling technique discussed in the article
 - Specific disadvantages of the modelling technique discussed in the article
- Other
 - Source of funding
 - Is a statement on the conflict-of-interest present

Chapter 7: the opportunity of point-of-care diagnostics in general practice: modelling the effects on antimicrobial resistance

Table 7.1 - Undiscounted costs

Cost type	Current standard-of-care	Incremental costs conservative scenario	Incremental costs uncertain scenario
antibiotics	€1,031,870 (€853,496 - €1,231,761)	-€196,510 (-€393,191 - €9,879)	-€197,375 (-€389,453 - €14,205)
consults	€6,079,643 (€5,464,075 - €6,800,547)	€0 (-€248 - €248)	€0 (-€248 - €248)
diagnostics	€236,757 (€195,815 - €285,837)	€1,550,974 (€1,387,462 - €1,739,797)	€775,928 (€684,646 - €881,291)
total	€7,345,854 (€6,599,496 - €8,212,296)	€1,354,946 (€1,108,864 - €1,625,343)	€576,952 (€374,786 - €818,117)

Table 7.2 - Total costs

Country	Cost category	Year	Current standard-of-care	Incremental costs conservative scenario	Incremental costs uncertain scenario
Netherlands	antibiotics	2020	€98,927 [€80,748 - €121,655]	-€6,970 [-€14,309 - €452)	-€7,037 [-€14,180 - €577)
Netherlands	antibiotics	2021	€100,085 [€81,806 - €121,925)	-€14,078 [-€28,685 - €801)	-€14,197 [-€28,568 - €1,328)
Netherlands	antibiotics	2022	€100,946 [€82,426 - €122,625)	-€21,309 [-€42,891 - €1,267)	-€21,584 [-€42,683 - €1,776)
Netherlands	antibiotics	2023	€101,740 [€83,423 - €124,198)	-€21,391 [-€43,341 - €1,225)	-€21,652 [-€43,498 - €1,771)
Netherlands	antibiotics	2024	€102,598 [€83,511 - €124,812)	-€21,604 [-€43,501 - €965)	-€21,826 [-€43,291 - €1,735)
Netherlands	antibiotics	2025	€103,779 [€85,151 - €126,518)	-€21,806 [-€44,372 - €1,068)	-€22,020 [-€43,983 - €1,686)
Netherlands	antibiotics	2026	€104,483 [€85,915 - €128,356)	-€22,128 [-€44,151 - €1,136)	-€22,167 [-€43,549 - €1,477)
Netherlands	antibiotics	2027	€105,302 [€86,371 - €127,343)	-€22,279 [-€44,574 - €1,313)	-€22,407 [-€44,522 - €1,394)
Netherlands	antibiotics	2028	€106,292 [€87,245 - €128,584)	-€22,343 [-€44,654 - €1,021)	-€22,594 [-€44,502 - €1,565)
Netherlands	antibiotics	2029	€107,190 [€88,346 - €130,770)	-€22,577 [-€45,641 - €1,207)	-€22,763 [-€45,222 - €1,695)

Country	Cost category	Year	Current standard-of-care	Incremental costs conservative scenario	Incremental costs uncertain scenario
Netherlands	consults	2020	€589,836 [€523,098 - €677,554]	€0 [€0 - €0)	€0 [€0 - €0)
Netherlands	consults	2021	€594,327 [€526,071 - €682,186)	€0 [€0 - €0)	€0 [€0 - €0)
Netherlands	consults	2022	€597,545 [€532,024 - €680,660)	€0 [-€70.73 - €70.73)	€0 [-€70.73 - €70.73)
Netherlands	consults	2023	€600,445 [€533,424 - €688,881)	€0 [-€70.73 - €70.73)	€0 [-€70.73 - €70.73)
Netherlands	consults	2024	€604,636 [€536,219 - €687,741)	€0 [-€70.73 - €70.73)	€0 [-€70.73 - €70.73)
Netherlands	consults	2025	€608,031 [€539,366 - €694,777)	€0 [-€70.73 - €70.73)	€0 [-€70.73 - €70.73)
Netherlands	consults	2026	€610,242 [€546,297 - €711,726)	€0 [-€70.73 - €70.73)	€0 [-€70.73 - €70.73)
Netherlands	consults	2027	€615,211 [€548,700 - €705,861)	€0 [-€35.37 - €35.37)	€0 [-€35.37 - €35.37)
Netherlands	consults	2028	€617,987 [€548,700 - €705,491)	€0 [-€35.37 - €35.37)	€0 [-€35.37 - €35.37)
Netherlands	consults	2029	€622,107 [€553,037 - €711,327)	€0 [-€35.37 - €35.37)	€0 [-€35.37 - €35.37)

Country	Cost category	Year	Current standard-of-care	Incremental costs conservative scenario	Incremental costs uncertain scenario
Netherlands	diagnostics	2020	€23,017 [€18,821 - €28,431)	€55,762 [€49,064 - €64,111)	€27,861 [€24,205 - €32,437)
Netherlands	diagnostics	2021	€23,129 [€18,947 - €28,710)	€112,351 [€99,170 - €129,228)	€56,196 [€48,689 - €65,231)
Netherlands	diagnostics	2022	€23,336 [€19,126 - €28,427)	€168,888 [€149,326 - €194,352)	€84,487 [€73,912 - €97,618)
Netherlands	diagnostics	2023	€23,412 [€18,987 - €28,758)	€169,828 [€150,441 - €195,466)	€84,839 [€74,115 - €98,778)
Netherlands	diagnostics	2024	€23,578 [€19,244 - €29,050)	€171,038 [€151,430 - €195,176)	€85,529 [€74,784 - €98,473)
Netherlands	diagnostics	2025	€23,776 [€19,423 - €29,235)	€172,132 [€152,445 - €198,415)	€86,038 [€75,054 - €99,662)
Netherlands	diagnostics	2026	€23,807 [€19,645 - €29,303)	€172,619 [€154,322 - €201,320)	€86,298 [€75,544 - €101,611)
Netherlands	diagnostics	2027	€23,997 [€19,606 - €29,461)	€173,965 [€153,753 - €200,665)	€86,912 [€75,855 - €100,968)
Netherlands	diagnostics	2028	€24,145 [€19,693 - €29,617)	€174,836 [€154,598 - €200,623)	€87,614 [€76,582 - €101,425)
Netherlands	diagnostics	2029	€24,245 [€19,846 - €29,853)	€175,895 [€155,536 - €202,182)	€88,005 [€76,484 - €102,273)

Country	Cost category	Year	Current standard-of-care	Incremental costs conservative scenario	Incremental costs uncertain scenario
Netherlands	total	2020	€711,678 [€631,498 - €819,865]	€48,833 [€39,813 - €59,371)	€20,774 [€13,272 - €29,781)
Netherlands	total	2021	€717,041 [€634,380 - €823,261)	€98,161 [€80,443 - €119,990)	€41,904 [€27,104 - €60,114)
Netherlands	total	2022	€721,508 [€640,555 - €821,419)	€147,685 [€120,819 - €179,305)	€62,911 [€40,637 - €89,973)
Netherlands	total	2023	€725,564 [€642,850 - €834,457)	€148,541 [€121,078 - €181,563)	€63,193 [€40,494 - €91,189)
Netherlands	total	2024	€730,940 [€645,972 - €835,152)	€149,624 [€120,408 - €181,958)	€63,656 [€41,563 - €89,975)
Netherlands	total	2025	€735,248 [€653,697 - €844,661)	€150,481 [€121,781 - €184,809)	€64,130 [€40,880 - €90,766)
Netherlands	total	2026	€738,955 [€658,911 - €857,975)	€151,379 [€122,515 - €185,395)	€64,276 [€41,212 - €93,208)
Netherlands	total	2027	€745,136 [€662,878 - €853,358)	€152,371 [€123,449 - €185,219)	€64,802 [€41,729 - €92,113)
Netherlands	total	2028	€748,365 [€663,752 - €854,892)	€152,693 [€123,909 - €186,273)	€65,158 [€41,730 - €93,102)
Netherlands	total	2029	€753,571 [€667,230 - €860,840)	€153,625 [€124,108 - €185,946)	€65,272 [€41,760 - €93,877)

Table 7.3 – Annual antibiotic consumption

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Amoxicillin/clavulanic acid	2020	3297 (1396 - 6174)	3108 (1670 - 5187)	3118 (1669 - 5260)
Netherlands	Amoxicillin/clavulanic acid	2021	3350 (1449 - 6332)	2898 (1606 - 4725)	2888 (1596 - 4882)
Netherlands	Amoxicillin/clavulanic acid	2022	3350 (1375 - 6353)	2662 (1091 - 5072)	2646 (1186 - 5145)
Netherlands	Amoxicillin/clavulanic acid	2023	3370 (1438 - 6374)	2656 (1102 - 5114)	2656 (1176 - 5271)
Netherlands	Amoxicillin/clavulanic acid	2024	3412 (1428 - 6594)	2698 (1112 - 5124)	2678 (1155 - 5334)
Netherlands	Amoxicillin/clavulanic acid	2025	3454 (1480 - 6636)	2740 (1134 - 5229)	2709 (1176 - 5344)
Netherlands	Amoxicillin/clavulanic acid	2026	3486 (1448 - 6678)	2730 (1124 - 5250)	2751 (1208 - 5419)
Netherlands	Amoxicillin/clavulanic acid	2027	3518 (1501 - 6720)	2762 (1102 - 5367)	2782 (1218 - 5366)
Netherlands	Amoxicillin/clavulanic acid	2028	3560 (1460 - 6552)	2788 (1124 - 5272)	2793 (1228 - 5502)

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Amoxicillin/clavulanic acid	2029	3580 (1522 - 6815)	2835 (1144 - 5292)	2824 (1239 - 5492)
Netherlands	Broad-spectrum penicillins	2020	37406 (29894 - 46778)	34786 (28728 - 42433)	34766 (28811 - 42842)
Netherlands	Broad-spectrum penicillins	2021	37674 (30208 - 47484)	32424 (26438 - 39932)	32487 (26533 - 40173)
Netherlands	Broad-spectrum penicillins	2022	38084 (30260 - 47859)	30104 (22994 - 38946)	30046 (23476 - 39407)
Netherlands	Broad-spectrum penicillins	2023	38398 (30491 - 48196)	30408 (23089 - 39470)	30324 (23551 - 39376)
Netherlands	Broad-spectrum penicillins	2024	38756 (30990 - 48575)	30660 (23329 - 39419)	30644 (23708 - 39820)
Netherlands	Broad-spectrum penicillins	2025	39070 (31195 - 48837)	30912 (23488 - 39902)	30812 (23886 - 40113)
Netherlands	Broad-spectrum penicillins	2026	39501 (31499 - 49162)	31174 (23654 - 40059)	31180 (24212 - 40826)
Netherlands	Broad-spectrum penicillins	2027	39806 (31626 - 49529)	31490 (23772 - 40868)	31426 (24475 - 40951)
Netherlands	Broad-spectrum penicillins	2028	39989 (32056 - 49729)	31794 (24233 - 40961)	31647 (24664 - 41118)

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Broad-spectrum penicillins	2029	40462 (32389 - 50959)	32036 (24191 - 41509)	31804 (24863 - 41638)
Netherlands	Narrow-spectrum penicillins	2020	3752 (1512 - 7561)	3528 (1890 - 6314)	3570 (1778 - 6315)
Netherlands	Narrow-spectrum penicillins	2021	3822 (1526 - 7672)	3346 (1736 - 5699)	3304 (1722 - 5810)
Netherlands	Narrow-spectrum penicillins	2022	3822 (1498 - 7756)	3038 (1176 - 6328)	2996 (1162 - 5978)
Netherlands	Narrow-spectrum penicillins	2023	3843 (1540 - 7770)	3066 (1204 - 6328)	3052 (1134 - 6105)
Netherlands	Narrow-spectrum penicillins	2024	3871 (1568 - 7896)	3122 (1204 - 6300)	3080 (1134 - 6146)
Netherlands	Narrow-spectrum penicillins	2025	3906 (1582 - 7883)	3136 (1218 - 6357)	3122 (1162 - 6216)
Netherlands	Narrow-spectrum penicillins	2026	3983 (1638 - 7981)	3185 (1232 - 6552)	3122 (1106 - 6412)
Netherlands	Narrow-spectrum penicillins	2027	3976 (1582 - 7994)	3206 (1190 - 6482)	3150 (1176 - 6300)
Netherlands	Narrow-spectrum penicillins	2028	4011 (1624 - 8316)	3192 (1246 - 6608)	3164 (1162 - 6384)

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Narrow-spectrum penicillins	2029	4046 (1652 - 8303)	3206 (1260 - 6735)	3178 (1204 - 6440)
Netherlands	Macrolides/lincosamides	2020	619 (176 - 1447)	598 (252 - 1184)	590 (248 - 1188)
Netherlands	Macrolides/lincosamides	2021	630 (173 - 1462)	558 (241 - 1062)	551 (238 - 1069)
Netherlands	Macrolides/lincosamides	2022	630 (184 - 1476)	497 (155 - 1174)	493 (148 - 1196)
Netherlands	Macrolides/lincosamides	2023	637 (176 - 1483)	504 (158 - 1217)	490 (140 - 1192)
Netherlands	Macrolides/lincosamides	2024	644 (191 - 1505)	508 (166 - 1217)	500 (144 - 1217)
Netherlands	Macrolides/lincosamides	2025	644 (191 - 1501)	518 (158 - 1206)	504 (151 - 1224)
Netherlands	Macrolides/lincosamides	2026	652 (191 - 1530)	518 (162 - 1199)	504 (144 - 1224)
Netherlands	Macrolides/lincosamides	2027	666 (198 - 1509)	520 (169 - 1217)	515 (155 - 1246)
Netherlands	Macrolides/lincosamides	2028	664 (191 - 1530)	529 (162 - 1224)	513 (148 - 1264)

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Macrolides/lincosamides	2029	666 (194 - 1555)	531 (166 - 1242)	522 (151 - 1253)
Netherlands	Quinolones	2020	158 (10 - 864)	168 (19 - 629)	170 (19 - 662)
Netherlands	Quinolones	2021	163 (10 - 878)	158 (19 - 534)	168 (19 - 566)
Netherlands	Quinolones	2022	168 (10 - 874)	120 (5 - 669)	130 (10 - 672)
Netherlands	Quinolones	2023	163 (10 - 882)	120 (5 - 662)	130 (10 - 682)
Netherlands	Quinolones	2024	163 (10 - 907)	120 (5 - 654)	134 (5 - 678)
Netherlands	Quinolones	2025	173 (10 - 883)	125 (5 - 679)	134 (5 - 696)
Netherlands	Quinolones	2026	168 (10 - 921)	120 (5 - 677)	134 (10 - 720)
Netherlands	Quinolones	2027	175 (10 - 932)	130 (5 - 696)	134 (5 - 696)
Netherlands	Quinolones	2028	173 (10 - 923)	125 (8 - 699)	134 (8 - 702)

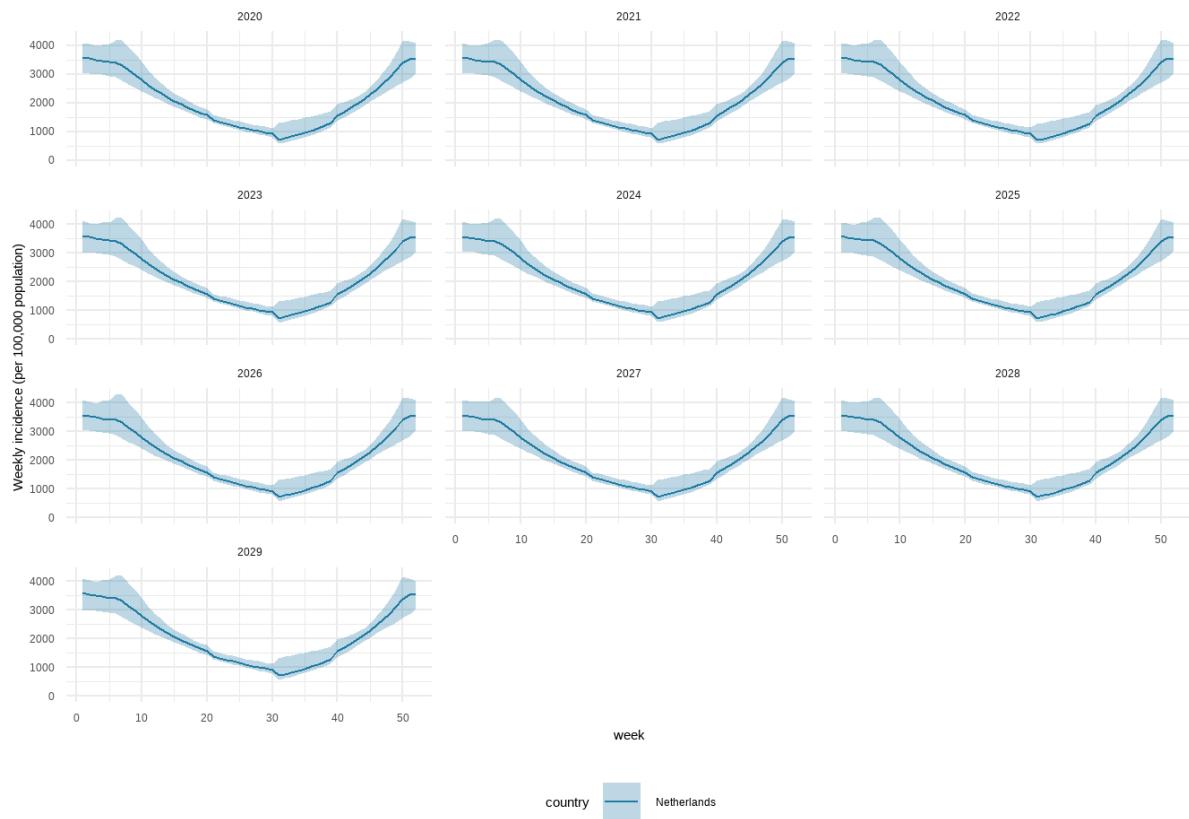
Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Quinolones	2029	178 (10 - 922)	125 (5 - 691)	134 (10 - 716)
Netherlands	Tetracyclines	2020	7441 (5019 - 10640)	6951 (5061 - 9373)	6937 (5047 - 9451)
Netherlands	Tetracyclines	2021	7525 (5026 - 10710)	6528 (4816 - 8701)	6503 (4711 - 8883)
Netherlands	Tetracyclines	2022	7602 (5110 - 10710)	6006 (3913 - 8716)	5978 (4039 - 8918)
Netherlands	Tetracyclines	2023	7648 (5187 - 10822)	6076 (4011 - 8828)	6072 (3997 - 8940)
Netherlands	Tetracyclines	2024	7690 (5292 - 10934)	6132 (4011 - 8800)	6125 (3997 - 9011)
Netherlands	Tetracyclines	2025	7784 (5271 - 11054)	6195 (4081 - 9031)	6153 (4074 - 9198)
Netherlands	Tetracyclines	2026	7882 (5367 - 11180)	6272 (4130 - 9108)	6216 (4108 - 9353)
Netherlands	Tetracyclines	2027	7931 (5389 - 11200)	6314 (4151 - 9199)	6265 (4158 - 9310)
Netherlands	Tetracyclines	2028	7994 (5390 - 11340)	6370 (4102 - 9185)	6307 (4130 - 9352)

Country	Antibiotic class	Year	Current standard-of-care	Conservative scenario	Uncertain scenario
Netherlands	Tetracyclines	2029	8046 (5425 - 11431)	6440 (4220 - 9289)	6363 (4186 - 9471)

Figure 7.1 – demographic projections



Figure 7.2 - Incidence projections



Chapter 9: Cost-effectiveness of Sacubitril/valsartan in Germany: An Application of the Efficiency Frontier

Table 9.1 - transition probabilities used in the Markov model

Transition	Probability (monthly)	References
Outpatient - death (cardiovascular)	0.0089	1
Background mortality		2
Age 55-59	0.00041	
Age 60-64	0.00064	
Age 65-69	0.00090	
Age 70-74	0.0015	
Age 75-79	0.0021	
Age ≥ 80	0.0020	
Mortality during ward hospitalization		3
Age 50-73	0.037	
Age 74-80	0.074	
Age 81-85	0.10	
Age ≥ 86	0.20	
Mortality during ICU hospitalization	0.11	4
Hospitalization		5
Month 1	0.012	
Month 100	0.0086	
Month 200	0.0082	
Month 300	0.0080	
Rehospitalization	Enalapril and candesartan: 0.199 Sacubitril/valsartan: 0.088 Placebo: 0.251	6 6 7

Table 9.2 - Treatment Effects, including uncertainty used for probabilistic sensitivity analysis

Treatment effects	Risk ratio [95% CI]	Distribution	References
Sacubitriil/valsartan (relative to enalapril)	All-cause Mortality: 0.84 [0.76-0.93]	Lognormal	1
	Hospitalization: 0.77 [0.67-0.89]	Lognormal	5
	ICU admission: 0.82 [0.72-0.94]	Lognormal	5
Placebo (relative to enalapril)	All-cause Mortality: 1.18 [1.03-1.33]	Lognormal	8
	Hospitalization: 1.56 [1.37-1.82]	Lognormal	8
	ICU admission: 1		Assumed
Candesartan (relative to placebo)	Mortality: 0.87 [0.74-1.03]	Lognormal	9
	Hospitalization: 0.68 [0.57-0.81]	Lognormal	9
	ICU admission: 1		Assumed

Table 9.3 – average direct and indirect relative risks

Hospitalization risk

	Placebo	Enalapril	Candesartan	SacubitriI/valsartan
Placebo	-	0.85 ⁸	0.87 ⁹	0.72*
Enalapril	1.18 ⁸	-	1.02*	0.84 ¹
Candesartan	1.15 ⁹	0.98*	-	0.83*
SacubitriI/valsartan	1.39*	1.19 ¹	1.21*	-

*indirect comparison

Mortality

	Placebo	Enalapril	Candesartan	SacubitriI/valsartan
Placebo	-	0.64 ⁸	0.68 ⁹	0.51*
Enalapril	1.56 ⁸	-	1.07*	0.77 ¹
Candesartan	1.47 ⁹	0.94*	-	0.75*
SacubitriI/valsartan	1.96*	1.30 ¹	1.33*	-

*indirect comparison

Table 9.4 - cost input parameters

Description	Monthly costs (2018 euros)	Reference
Enalapril treatment	€9.07^	10
Sacubitril/valsartan treatment	€199.8*	11
Candesartan treatment	€8.46^	10
Other CHF drugs† treatment	€12.36	1,10
Costs of outpatient CHF care (general practitioner and cardiologist)	€7.87	12,13
Hospitalization length of stay	Additional costs: general ward ICU (2018 euros)	14,15
0 days	€794.01	
1 day	€2420.18 €3543.58	
2 days	€3550.52 €5013.72	
3 days	€4200.63 €6483.85	
4 days	€4850.75 €7953.99	
5 days	€5500.87 €9424.12	
6 days	€5500.87 €10894.26	
>6 days	€5500.87 €10894.26	

[^]scenario analysis for €3 per day is included; *scenario analyses for €3 and €10 per day are included; †hydrochlorothiazide, digoxin, spironolactone and metoprolol, using the usage data from PARADIGM-HF and German reference pricing

CHF: Chronic Heart Failure; ICU: Intensive Care Unit; LOS: length of stay

Table 9.5 - scenario analyses

Scenario	ICER (sacubitril/valsartan vs. enalapril, /QALY)	ICER (enalapril vs. placebo, /QALY)	ICER (candesartan vs. placebo, /QALY)
Base case	€19,300	Dominating	Dominating
0% discounting rate	€17,000	Dominating	Dominating
5% discounting rate	€20,900	Dominating	Dominating
€3 per day for sacubitril/valsartan	€7,600	Dominating	Dominating
€10 per day for sacubitril/valsartan	€30,000	Dominating	Dominating
€1 per day for enalapril and candesartan	€17,400	€900	€1,200
No extrapolation of effects beyond 42 months	€17,000	Dominating	Dominating
Starting age: 55 years	€19,600	Dominating	Dominating
Starting age: 75 years	€18,800	Dominating	Dominating

ICER values rounded to the nearest hundreds of euros

ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year

Table 9.6 - Length of Stay in Hospital

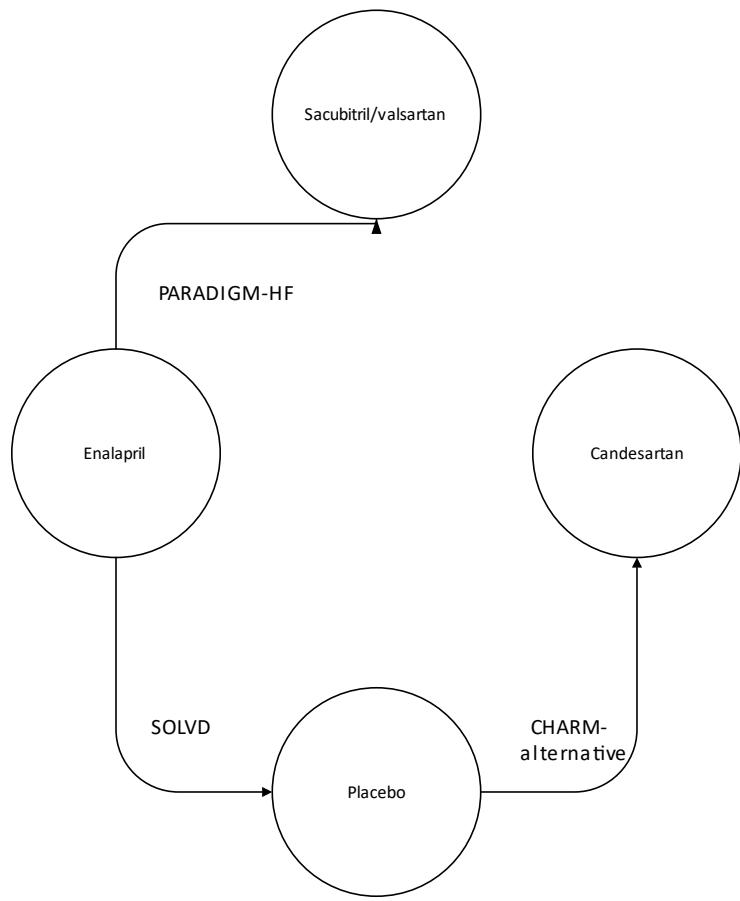
Group	Mean LOS	Standard error, LOS	Distribution	Source
Enalapril (normal ward)	9.7	9.5	Gamma	¹
Sacubitril/valsartan (normal ward)	10.8	17.5	Gamma	¹
Both enalapril and Sacubitril/valsartan (ICU, number of days in ICU)	3.3	1.2	Gamma	²
Both enalapril and Sacubitril/valsartan (ICU, number of days in normal ward)	16	5.1	Gamma	²

LOS: Length Of Stay

ICU: Intensive Care Unit

1. Packer M, McMurray JJV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. 2015;131(1):54-61. doi:10.1161/CIRCULATIONAHA.114.013748
2. van Vliet M, Verburg IWM, van den Boogaard M, et al. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. *Intensive Care Med*. 2014;40(9):1275-1284. doi:10.1007/s00134-014-3373-x

Figure 9.1 - flowchart of included trials

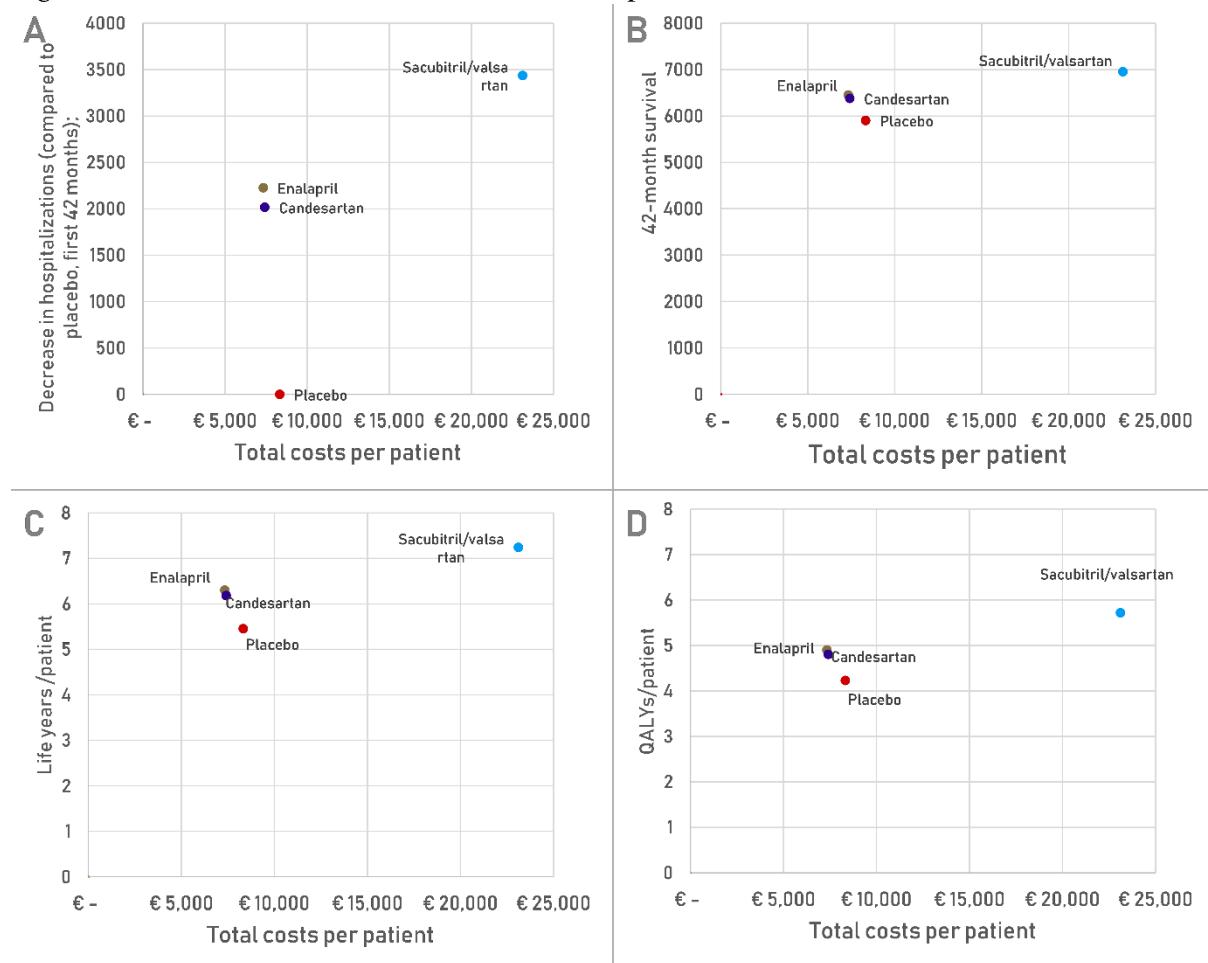


SOLVD: Studies Of Left Ventricular Dysfunction⁸

CHARM-alternative: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Alternative⁹

PARADIGM-HF: Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial¹

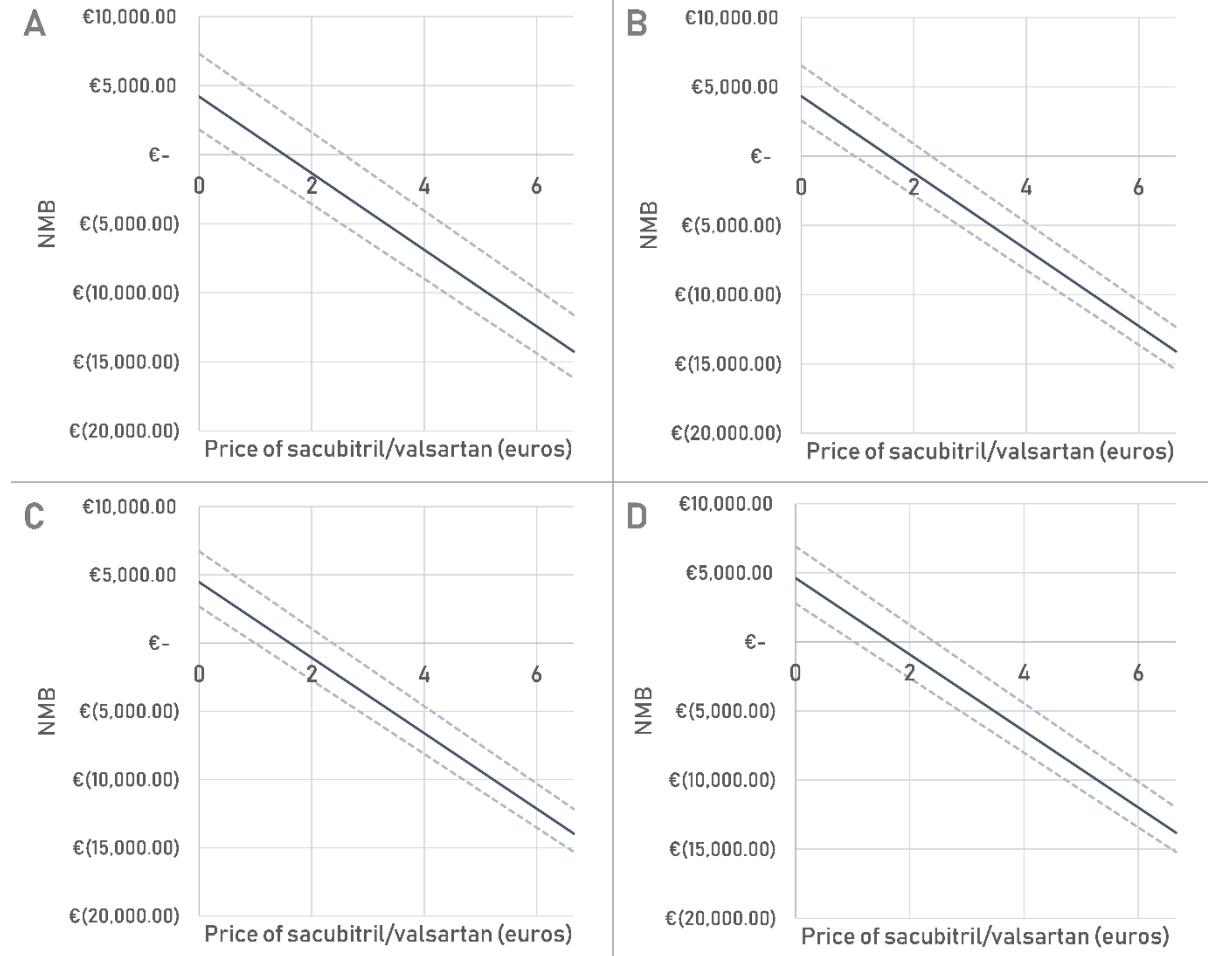
Figure 9.2 - base-case inverted cost-effectiveness planes for various outcomes



A: Decrease in hospitalizations (compared to placebo, first 42 months); B: 42-month survival;
C: Average total life years; D: Average total QALYs

QALY: Quality-adjusted life year

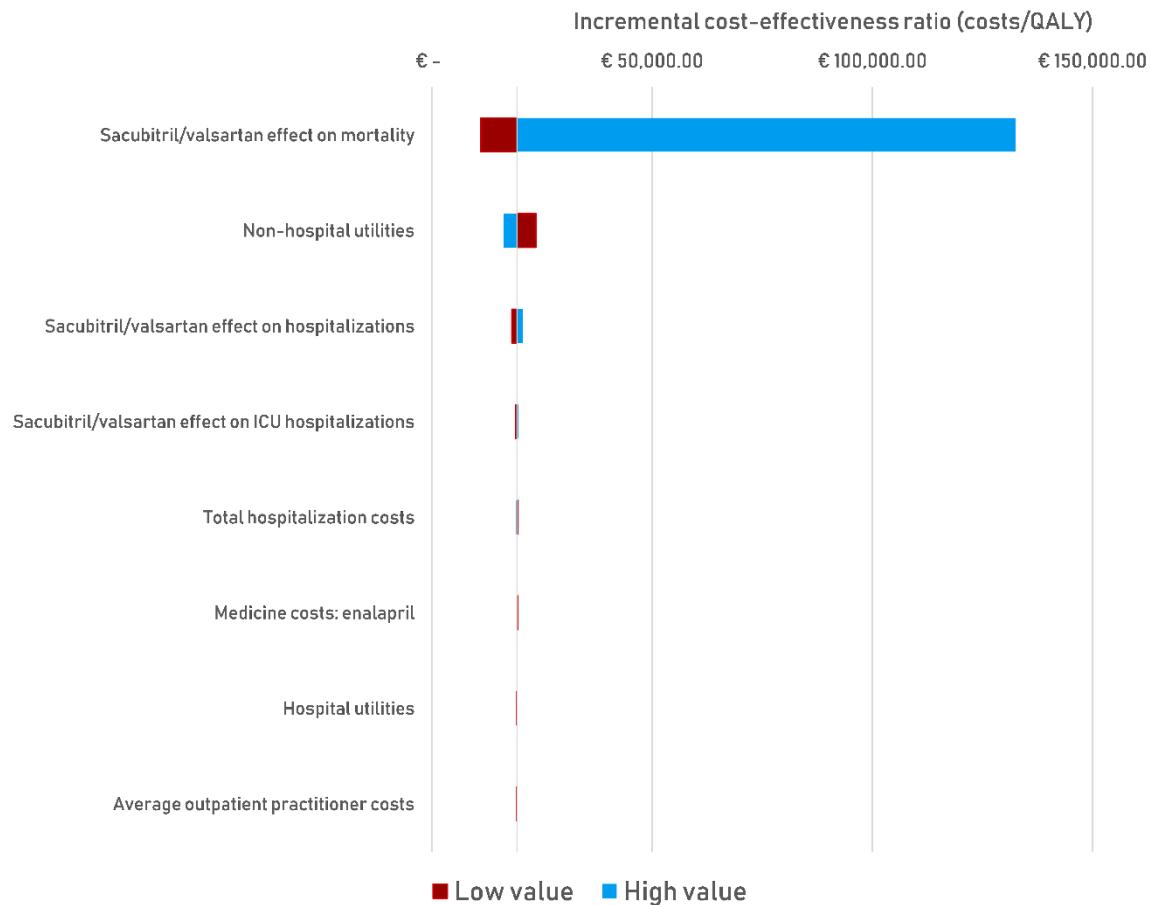
Figure 9.3 - NMB for a range of daily prices of sacubitril/valsartan the various outcomes, including the interquartile range (dotted line)



A: Decrease in hospitalizations (compared to placebo, first 42 months); B: 42-month survival; C: Average total life years; D: Average total QALYs

NMB: Net Monetary Benefit

Figure 9.4 - tornado diagram of the univariate sensitivity analysis of the ICER of sacubitril/valsartan compared to enalapril



QALY: Quality-Adjusted Life Year

ICU: Intensive Care Unit

File 9.1 – Excel model

<https://www.valueinhealthjournal.com/cms/10.1016/j.jval.2016.10.015/attachment/263e9b68-12f0-4d6e-bae5-0e3f7beefacd/mmc1.zip>

File 9.2 – AdViSHE form

<https://www.valueinhealthjournal.com/cms/10.1016/j.jval.2016.10.015/attachment/7b2fd7bd-3f17-4718-a904-5f3d73f94334/mmc3.pdf>

File 9.3 – CHEERS checklist

<https://www.valueinhealthjournal.com/cms/10.1016/j.jval.2016.10.015/attachment/fdc602cd-b5be-4dd3-9529-620e2dfd5282/mmc4.pdf>

References

1. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
2. Statistisches Bundesamt. Gestorbene: Deutschland, Jahre, Todesursachen, Altersgruppen. Destatis. https://www-genesis.destatis.de/genesis/online;jsessionid=9954CD4EB335B7C6302EF2B91455B386.tomcat_GO_1_1?operation=previous&levelindex=2&levelid=1505205518177&step=2. Accessed September 12, 2017.
3. Corrao G, Ghirardi A, Ibrahim B, Merlini L, Maggioni AP. Short- and long-term mortality and hospital readmissions among patients with new hospitalization for heart failure: A population-based investigation from Italy. *Int J Cardiol.* 2015;181:81-87. doi:10.1016/j.ijcard.2014.12.004
4. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J.* 2005;149(2):209-216. doi:10.1016/j.ahj.2004.08.005
5. Packer M, McMurray JJV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation.* 2015;131(1):54-61. doi:10.1161/CIRCULATIONAHA.114.013748
6. Desai AS, Claggett BL, Packer M, et al. Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization. *J Am Coll Cardiol.* 2016;68(3):241-248. doi:10.1016/j.jacc.2016.04.047
7. Luzier AB, Forrest A, Adelman M, Hawari FI, Schentag JJ, Izzo JL. Impact of angiotensin-converting enzyme inhibitor underdosing on rehospitalization rates in congestive heart failure. *Am J Cardiol.* 1998;82(4):465-469. doi:10.1016/S0002-9149(98)00361-0
8. The SOLVD Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. *N Engl J Med.* 1991;325(5):293-302. doi:10.1056/NEJM199108013250501
9. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *The Lancet.* 2003;362(9386):772-776. doi:10.1016/S0140-6736(03)14284-5
10. Deutsches Intitut für Medizinische Dokumentation und Information. ABDA Festbetragsrecherche. DIMDI. <https://portal.dimdi.de/festbetragsrecherche/>. Accessed August 24, 2018.

11. Gemeinsamer Bundesausschuss. *Zusammenfassende Dokumentation über eine Änderung der Arzneimittel Anlage XII Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGBV - Sacubitril/Valsartan*. Berlin: Gemeinsame Bundesausschuss; 2016. https://www.g-ba.de/downloads/40-268-4037/2016-06-16_AM-RL-XII_Sacubitril_Valsartan_D-207_ZD.pdf. Accessed July 19, 2018.
12. Hendricks V, Schmidt S, Vogt A, et al. Case Management Program for Patients With Chronic Heart Failure. *Dtsch Arztebl Int*. 2014;111(15):264-270. doi:10.3238/ärztebl.2014.0264
13. Neumann A, Mostardt S, Biermann J, et al. Cost-effectiveness and cost-utility of a structured collaborative disease management in the Interdisciplinary Network for Heart Failure (INH) study. *Clin Res Cardiol*. 2015;104(4):304-309. doi:10.1007/s00392-014-0781-4
14. Institut für das Entgeltsystem im Krankenhaus. Fallpauschalen Katalog 2018. https://www.g-drg.de/G-DRG-System_2018/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2018. Published November 24, 2017. Accessed September 4, 2018.
15. GKV-Spitzenverband. Landesbasisfallwerte. <https://www.gkv-spitzenverband.de/krankenversicherung/krankenhaeuser/budgetverhandlungen/landesbasisfallwerte/landesbasisfallwerte.jsp>. Accessed September 4, 2018.