

Modalities of group A streptococcal prevention and treatment and their economic justification

Supplementary Methods and Tables

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Supplementary Methods

Medline and Web of Science

(TI=("group a strep*" OR "Strep* pyogenes" OR pharyngitis OR "sore throat" OR *tonsillitis OR impetigo OR pyoderma OR "skin infection" OR "skin sore" OR "soft tissue" OR cellulitis or erysipelas OR "scarlet fever" OR (rheumatic AND (heart or fever)) OR glomerulonephritis) OR (TI=(sepsis OR septic*emia OR septic OR bacter*emia OR "toxic shock" or fasciitis OR osteomyelitis OR pneumonia OR meningitis) AND TS=(pyogenes or "group A strept*"))) AND

(TS=(cost-benefit OR benefit-cost OR cost-effective* OR cost-minimization OR cost-minimisation OR cost-utility or "cost of illness" OR "return on investment" OR "budget impact" or budget) OR TI=(cost* or economic))

EMBASE

("group a strep*" or "strep* pyogenes" or pharyngitis or "sore throat" or tonsillitis or impetigo or pyoderma or "skin infection" or "skin sore" or "soft tissue" or cellulitis or erysipelas or "scarlet fever" or (rheumatic and (heart or fever)) or glomerulonephritis).ti. or ((sepsis or septic*emia or septic or bacter*emia or "toxic shock" or fasciitis or osteomyelitis or pneumonia or meningitis).ti. and (pyogenes or "group a strep*").mp.) AND

((("cost benefit" or "benefit cost" or "cost effective*" or "cost minimi*ation" or "cost utility" or "cost of illness" or "return on investment" or "budget-impact" or budget).mp. or cost*.ti. or economic.ti.)

Supplementary Table 1. Studies stratified by prevention category

Study ID	Country/region	Primordial prevention	Primary Prevention		Secondary prevention		Tertiary prevention	Secondary prevention	
		Prevent infection	Reduce duration of illness	Prevent ARF/other	Prevent recurrent ARF	Prevent clinical/severe RHD	Prevent death	Prevent recurrent tonsillitis	Prevent recurrent cellulitis
Cannon, 2018 ¹⁷	Australia	Vaccination							
Burns, 2018 ¹⁸	UK		Pharyngitis Rx						
Bura, 2017 ¹⁹	Poland		Pharyngitis diagnostics						
Kose, 2016 ²⁰	Turkey		Pharyngitis diagnostics						
Nakhoul, 2013 ²³	USA		Pharyngitis diagnostics						
Humair, 2006 ²¹	Switzerland		Pharyngitis diagnostics						
Portier, 2001 ²²	France		Pharyngitis diagnostics						
Anusha, 2019 ²⁵	India		Impetigo Rx						
Alonso, 2008 ²⁴	Cuba		Impetigo Rx						
Ibrahim, 2019 ³⁰	Australia		Cellulitis; setting						
Li, 2018 ³¹	USA		Cellulitis; management						
Kameshwar, 2016 ³²	Australia		Cellulitis; setting						
Yarbrough, 2015 ³³	USA		Cellulitis; management						
Brugha, 2012 ³⁴	UK		Cellulitis; setting						
Vinken, 2003 ²⁷	USA		Cellulitis Rx						
Vinken, 2001 ²⁶	UK		Cellulitis Rx						
Lodise, 2019 ²⁸	USA		SSTI Rx						
Teeres, 2008 ²⁹	Spain		SSTI Rx						
Fraser, 2020 ⁴¹	UK		Pharyngitis diagnostics	Pharyngitis diagnostics					

Study ID	Country/region	Primordial prevention	Primary Prevention		Secondary prevention		Tertiary prevention	Secondary prevention	
		Prevent infection	Reduce duration of illness	Prevent ARF/other	Prevent recurrent ARF	Prevent clinical/severe RHD	Prevent death	Prevent recurrent tonsillitis	Prevent recurrent cellulitis
Behnamfar, 2019 ³⁸	Iran		Pharyngitis diagnostics	Pharyngitis diagnostics					
Little, 2014 ³⁹	UK		Pharyngitis diagnostics	Pharyngitis diagnostics (excl. ARF)					
Klepser, 2012 ³⁷	USA		Pharyngitis diagnostics	Pharyngitis diagnostics					
Van Howe, 2006 ³⁶	USA		Pharyngitis diagnostics	Pharyngitis diagnostics					
Neuner, 2003 ³⁵	USA		Pharyngitis diagnostics	Pharyngitis diagnostics					
Irlam, 2013 ⁴³	South Africa			Pharyngitis diagnostics					
Maizia, 2012 ⁴⁶	France			Pharyngitis diagnostics					
Giraldez-Garcia, 2011 ⁴⁵	Spain			Pharyngitis diagnostics					
King, 2002 ⁴²	USA			Pharyngitis diagnostics after genetic testing					
Ehrlich, 2002 ⁴⁴	USA			Pharyngitis diagnostics					
Watkins, 2015 ⁴⁸	Cuba			Pharyngitis Rx rates	SP adherence				
Nordet, 2008 ⁴⁷	Cuba			Pharyngitis Rx rates	SP adherence				
Watkins, 2016 ⁴⁹	African nations			Pharyngitis Rx rates	SP coverage		Access to surgery		
Soudarssanane, 2007 ⁵²	India			Treat	SP		Surgery		

Study ID	Country/region	Primordial prevention	Primary Prevention		Secondary prevention		Tertiary prevention	Secondary prevention	
		Prevent infection	Reduce duration of illness	Prevent ARF/other	Prevent recurrent ARF	Prevent clinical/severe RHD	Prevent death	Prevent recurrent tonsillitis	Prevent recurrent cellulitis
Coates, 2021 ⁵¹	African Union			Pharyngitis Rx rates ; CDR	SP coverage & adherence	SP (echo after 1 st ARF), family planning	Surgery, Heart failure management		
Manji, 2013 ⁵⁰	Developing country (e.g., in sub-Saharan Africa)			Test and treat or prophylaxis for all		Routine echo with SP			
Oetzel, 2019 ⁵³	New Zealand				SP adherence				
Ubels, 2020 ⁵⁵	Brazil					SP coverage (echo screening)			
Roberts, 2017 ⁵⁴	Australia					SP coverage (echo screening)			
Zachariah, 2015 ⁵⁶	Australia					SP coverage (echo screening)			
Uy, 2021 ⁵⁷	India						Surgery		
Osternmann, 2021 ⁶⁰	Germany							SilAto-5-90 adjuvant treatment	
Wilson, 2012 ⁵⁹	UK							Surgery	
Bhattacharyya, 2002 ⁵⁸	USA							Surgery	
Mason, 2014 ⁶¹	UK								Prophylaxis

ARF, acute rheumatic fever; RHD, rheumatic heart disease; Rx, pharmacological treatment; SP, secondary prophylaxis

Supplementary Table 2. Primordial prevention strategies for disease related to Strep A

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Cannon, 2018 ¹⁷	Prevention of incident Strep A infection (or clinical disease) and associated sequelae A. Vaccination B. No vaccination	Australia; Infants, 5yo children, and 65yo adults (55yo non-Indigenous Australian adults)	Model-based cost-utility analysis; health sector perspective	Assumed	• Reduce incidence of Strep A diseases • Reduce deaths • Reduce disability-adjusted life-years, comprising acute infection, long-term morbidity, and mortality	• Inpatient admissions • Emergency department episodes • General and specialist consultations • Pharmacy • Outpatient diagnostics • Patient transfers	Cost of childhood vaccination below AU\$260-289 for non-Indigenous Australians and AU\$897-920 for Indigenous Australians would have a favourable ICER from a health sector perspective.

ICER, incremental cost-effectiveness ratio

Supplementary Table 3. Primary prevention strategies for disease related to Strep A - treat acute disease

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Pharyngitis							
Burns, 2018 ¹⁸	Reduce duration of sore throat A. A single dose of 10mg oral dexamethasone B. Placebo	UK; adults 18-70 years with acute sore throat and painful swallowing	Trial-based CUA; healthcare services payer perspective	Trial	Improve QALYs based on the EuroQol-five dimensions-five levels (EQ-5D-5L) index.	• Intervention • Visits and telephone calls to the GP • Visits and telephone calls to nurses • Out-of-hours calls and visits • Pharmacy visits • Calls to helpline • Accident and emergency visits • Medication, including prescribed antimicrobials (delayed) and over-the-counter medications	Insufficient evidence to conclude that dexamethasone was cost-effective
Bura, 2017 ¹⁹	Appropriate treatment of pharyngitis A. RADT B. Culture C. Clinical score 3-4 D. RADT on clinical score = 2-3 and treat on clinical score = 4	Poland; adult patients aged 18–44 years	Trial-based CEA; perspective not stated	Trial	Improve appropriate antibiotic treatment rates	• Symptomatic treatment • RADT • Culture • Antibiotic course	RADT for all patients and treat positive cases had the lowest cost per appropriate treatment
Kose, 2016 ²⁰	Appropriate treatment of pharyngitis	Turkey; patients 3–14 years old who had been	Trial-based CEA; perspective not stated	Trial	Improve appropriate Antibiotic treatment rates	• Antibiotics • RADT	Antibiotic cost and total treatment cost

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	(including choice of antibiotic) A. RADT B. Empirical treatment	diagnosed with pharyngitis and who had not received antibiotics for 7 days before inclusion.					per patient was lower for routine RADT compared to routine empirical treatment
Nakhoul, 2013 ²³	Appropriate treatment of pharyngitis A. DNA backup after false RADT B. No Backup after false RADT	USA; all patients aged 18 years and older visiting a generalist physician with a diagnosis of acute pharyngitis	Post-hoc CEA of an observational trial; perspective not stated	Trial	Correction of false-negative RADT	DNA probe	The additional expense of routine backup testing by DNA probe in adults is not justified
Humair, 2006 ²¹	Appropriate treatment of pharyngitis A. Symptomatic treatment B. RADT all C. RADT on clinical score = 2-3) and empirical treatment on clinical score = 4 D. Empirical Treatment on clinical score = 3-4 E. Culture all	Switzerland; adult patients older than 15 years with pharyngitis and least 2 of 4 Centor criteria	Trial-based CEA; perspective not stated	Trial	Improve appropriate antibiotic treatment rates	• RADT • Culture • Antibiotics	Routine RADT had the lowest cost-effectiveness ratio
Portier, 2001 ²²	Appropriate treatment of pharyngitis	France; treatment of	Trial-based CBA;	Trial	Reduce net cost	• Symptomatic treatment • Antibiotics	The mean total treatment cost

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	A. RADT all B. No RADT	pharyngitis in adults (> 25 years of age). Patients presenting with rhinopharyngitis or pharyngitis not suggesting a streptococcal etiology were excluded	perspective not stated			• Complementary exams • Consult • RADT • Leave days	per episode of pharyngitis was lower for routine RADT compared to usual practice
Impetigo							
Anusha, 2019 ²⁵	Impetigo treatment A. Fusidic acid B. Mupirocin	India; impetigo patients aged 1-30 years	Trial-based CEA; perspective not stated	Trial	Improve cure rate	Treatment drug	Fusidic acid is cost-effective compared to mupirocin
Alfonso, 2008 ²⁴	Impetigo treatment A. Ozonized oil B. Mupirocin cream	Cuba; impetigo patients aged <15 years	Trial-based CEA; perspective not stated	Trial	Improve cure rate	Treatment drug	Ozonized oil is more effective and less costly than mupirocin cream
Cellulitis							
Ibrahim, 2019 ³⁰	Reduce treatment failure rate and improve QALYs. A. Intravenous ceftriaxone at home B. Intravenous flucloxacillin in hospital	Australia; Children aged 6 months to 18 years who had presented to an emergency department (ED) with moderate or severe uncomplicated cellulitis	Trial-based CUA and CEA; Healthcare and family perspectives	Trial	• Reduce treatment failure • Improve QALYs (from the Child Health Utility 9D (CHU9D) questionnaire)	Healthcare-related: • Salaries • Admission process • ED • Pathology • Pharmacy • Other • Transport Family:	Intravenous ceftriaxone at home was more effective and less costly from both perspectives

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
						• Absence from paid and from unpaid work • Expenses during treatment	
Li, 2018 ³¹	Reduce cellulitis misdiagnosis A. Early dermatology consultation B. Usual care	USA; patients presenting to an emergency department with an initial diagnosis of cellulitis	Model-based CBA; perspective not stated	Trial and literature	Reduce: • Antibiotic consumption • Inpatient length of stay • Complications	• Dermatology services • Inpatient days	Net cost savings for early dermatology consultation
Kameshwar, 2016 ³²	Reduce duration of treatment for lower-limb cellulitis A. Transfer to hospital in the home (HITH) B. Usual (inpatient) care	Australia; patients admitted for lower-limb cellulitis for 24 or more hours	Trial-based CBA; institutional perspective	Trial	• Reduce duration of treatment	• Direct patient costs (medical, nursing and allied health wages, ward consumables, theatre costs, drugs, anaesthetics, pathology and imaging) • Overheads (utilities, cleaning, medical records, finance, administration, security, information technology and engineering)	Duration of treatment was longer for HTIH compared to inpatient management but costs were statistically similar
Yarbrough, 2015 ³³	Reduce unnecessary treatment for cellulitis	USA; cellulitis patients 18 years or older admitted to the	Trial-based CEA; perspective not stated	Trial	• Reduce antibiotic consumption	• Pharmacy • Laboratory • Imaging • Facility	The evidence-based care pathway was

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	A. Evidence-based care pathway B. Usual care	emergency department or hospital			• Reduce diagnostic tests • Reduce 30-day readmission rate		less costly for similar effect
Brugha, 2012 ³⁴	Prevent complications of preseptal cellulitis A. IV antibiotic treatment by ambulatory care B. IV antibiotic treatment by inpatient care	UK; children <16 years presenting to Emergency Department with signs and symptoms of preseptal cellulitis	Trial-based CBA; perspective not stated	Trial	• Reduced duration of treatment	• Inpatient admission • High complexity ED attendance	Ambulatory treatment is less costly for a similar duration of treatment
Vinken, 2003 ²⁷	Successful empiric treatment of cellulitis (given methicillin resistant S aureus) A. IV oxacillin (with an option to switch to oral dicloxacillin) B. IV vancomycin C. IV linezolid (with an option to switch to oral).	USA; patients hospitalised for cellulitis	Model-based CMA; hospital perspective	Literature	• Treatment success	• Antibiotic course • Ward stay • Intensive care	Linezolid is likely to be less costly compared with vancomycin at all resistance rates and with oxacillin when the risk of infection with methicillin-resistant pathogens is greater than 18.7%
Vinken, 2001 ²⁶	Successful empiric treatment of cellulitis (given	UK; patients hospitalised for cellulitis	Model-based CMA; hospital perspective	Literature	• Treatment success	• Antibiotic course • Day treatment • Day stay	Initiating treatment with linezolid was more effective

Disease/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	methicillin resistant S aureus) A. Initiate treatment with IV linezolid B. Standard care					• General ward stay • Intensive care unit stay	and less costly than with flucloxacillin
Skin and soft tissue infections (SSTIs)							
Lodise, 2019 ²⁸	SSTI treatment success in outpatient settings A. Single dose oritavancin B. Multidose vancomycin	USA; patients who were >18 years old and treated in an outpatient setting with oritavancin or vancomycin	Retrospective trial-based CEA; perspective not stated	Trial	• lower 30-day hospital admission rates	• Inpatient admission • ED visits • Outpatient medical services • Outpatient pharmacy prescription costs	Oritavancin had a statistically similar cost to vancomycin but was more effective
Terres, 2008 ²⁹	Cost-minimisation of SSTIs treatment A. Tigecycline (100 mg initially, followed by 50 mg IV every 12 hours) B. Vancomycin plus aztreonam (1000/2000 mg IV every 12 hours)	Spain; adult patients hospitalised with complicated SSTI	Retrospective trial-based CMA; national health system perspective	Trial	• NA	• Inpatient admission and readmission • Ward days • Intensive care unit hours • Antibiotic treatment • Pathology and diagnostic tests	Treating complicated skin and soft tissue infections with tigecycline is cheaper than with vancomycin plus aztreonam

GP, general practice; RADT, rapid antigen detection test; ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; CMA, cost-minimisation analysis; QALYs, quality-adjusted life-years; IV, intravenous; CDR, clinical decision rule

Supplementary Table 4. Primary prevention strategies for disease related to Strep A - treat infection and prevent ARF or other sequelae

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Fraser, 2020 ⁴¹	Reduce duration of illness and risk of complications A. CDR + RADT (several manufacturers) B. CDR (usual care)	UK; people aged ≥ 5 years presenting with sore throat and a FeverPAIN score of 4 or 5 points or a Centor score of 3 or 4 points	Model-based CUA (stratified by age, children or adults); NHS/Personal Social Services perspective	Systematic review and meta-analyses	• QALDs, comprising treated and untreated infection, penicillin-induced rash, Quincke, penicillin-induced anaphylaxis (sepsis), and ARF.	• GP consultation • Antibiotics • Pain relief (paracetamol) • Throat culture • Admission for sepsis, abscess, or ARF • RADT (cost of test plus GP time)	Usual care
Behnamfar, 2019 ³⁸	Reduce duration of illness and risk of complications A. Treat all B. Treat none C. RADT D. Culture E. RADT + culture all F. RADT + culture -ve RADT	Iran; people presenting to a primary healthcare clinic with pharyngitis	Model-based CUA and CBA; perspective unclear.	Not reported (values nor source)	• QALDs, comprising PTA, anaphylaxis, adverse reaction, ARF, untreated GAS, and death	• PTA, anaphylaxis, adverse reaction, 'acute renal failure', APSGN	RADT all
Little, 2014 ³⁹	Reduce duration of illness and risk of quinsy and other complications (excl. ARF) A. CDR (FeverPAIN); score <2 = no rx, score 2-3=delayed	UK; aged ≥ 3 years and acute sore throat	Trial-based CEA and CUA with modelled long-term outcomes; National Health	Trial	• 'Symptom severity score' • QALYs, based on EQ5D scores measured during the trial	• Visit to GP • GP home visit • Per minute of GP time • Visit to NP • Antibiotic course and prescribing cost • Visit to A&E	CDR is less costly and more effective

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	rx; score 4+ = immediate rx. B. Usual care (delayed rx; fill script if symptoms worsen or persist after 3-5 days) C. RADT if CDR 3+ (delayed rx if CDR=2)		Services perspective			Overnight hospital stay	
Klepser, 2012 ³⁷	Reduce duration of illness and risk of complications A. Physician observation B. physician treatment of all C. physician throat culture D. physician RADT, and throat culture on negative RADT E. physician RADT only F. nurse practitioner in a walk-in clinic performing an RADT on all patients G. Pharmacist RADT on all patients (and dispensing antibiotics)	USA; adults seeking treatment for pharyngitis	Model-based CUA; perspective not stated	Literature	QALDs, comprising duration of illness, penicillin-induced rash, anaphylaxis, quinsy, uncomplicated ARF, RHD, and death	- RADT - Calling in prescription - Culture - Penicillin - Penicillin-induced rash - Anaphylaxis - Uncomplicated ARF - GP visit - Walk-in clinic visit - Pharmacist visit	Strep A treatment provided by a pharmacist was the most cost-effective treatment

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Van Howe, 2006 ³⁶	Reduce duration of illness and risk of complications A. Treat none B. Treat all C. RADT D. Culture E. RADT then culture F. Clinical decision rule	USA; children presenting with pharyngitis	Model-based CUA; societal and payer perspectives	Literature	• QALDs, comprising quinsy, ARF, death, penicillin reaction, duration of illness	• Quinsy • Penicillin • Cephalosporin • ARF • Culture • Death • Penicillin reaction • RHD • Follow-up telephone call • Parental wages	Societal: throat culture based on Medicaid rates; RADT based on private insurance rates Payer: treat none
Neuner, 2003 ³⁵	Reduce duration of illness and risk of complications A: Observation without testing or treatment B: Empirical treatment with penicillin C: Throat culture D: RADT followed by culture to confirm negative test E: RADT alone.	USA; adults presenting with pharyngitis	Model-based CUA; <i>societal</i> perspective	Literature	• QALDs, comprising duration of illness, penicillin-induced rash and anaphylaxis, quinsy, uncomplicated ARF, RHD, and death.	• Tests (point-of-care and throat culture) • Culture result notification • Calling in a prescription • Penicillin • Penicillin-induced rash • Anaphylaxis • PTA • ARF	Culture least costly and most effective

GP, general practice; RADT, rapid antigen detection test; ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; QALYs, quality-adjusted life-years; QALDs, quality-adjusted life-days

Supplementary Table 5. Primary prevention strategies for disease related to Strep A – prevent ARF or other sequelae.

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Irlam, 2013 ⁴³	Prevent ARF and RHD A. Treat all B. Culture C. CDR D. CDR & culture -ve E. Treat none	South Africa; children between the ages of 3 to 15 years who present to an urban primary care clinic with a complaint of sore throat and no history of ARF	Model-based CUA; societal perspective	Literature	QALYs, comprising ARF, RHD without surgery, RHD post-surgery, ARF, anaphylaxis, quinsy, and rash	• Outpatient visit at primary care clinic + out of pocket • penicillin-induced rash and anaphylaxis • Throat culture • Outpatient visit at hospital • Quinsy • ARF • Secondary prophylaxis • RHD	Treat those with a CDR score of 2+ is cost-effective (US\$ 136 per QALY)
Maizia, 2012 ⁴⁶	Prevent suppurative complications (not explicitly defined) A. Observation only [no treatment] B. CDR C. RADT D. Culture E. CDR ≥ 2 , then RADT F. RADT + culture -ve G. Treat all	France; children and adults presenting to primary clinics	Model-based CEA; health insurance perspective	Literature	Risk of suppurative complications	• Medical consultation • RADT • Culture • Antibiotic • Serious allergic reactions	The use of the RADT alone had the best cost-effectiveness ratio in both adults and children: 970 Euros in children and at 903 Euros in adults per suppurative complication avoided.
Giraldez-Garcia, 2011 ⁴⁵	Prevent complications A. Treat all B. CDR C. RADT	Spain; patients between the ages of 2 and 14 years who consult with a primary care physician due to	Model-based CEA; Spanish National	Literature	• Suppurative complications • ARF • Unnecessary treatments	• GP visit • Phone call • RADT • Culture • Penicillin	CDR + RADT was cost-effective in preventing complications (from Strep A or penicillin)

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	D. Culture E. RADT + culture F. CDR + RADT	pharyngitis symptoms	Health Service perspective		• Allergic reactions • Deaths	• Azithromycin • Reaction • Suppurative complications • ARF	compared to culture
King, 2002 ⁴²	Prevent ARF A. Screen all children at birth for genetic susceptibility to RF and provide monthly or daily antibiotic prophylaxis in susceptible, otherwise usual care B. Usual care for all	USA; 2000 birth cohort	Model-based CUA; societal perspective	Assumed	QALYs	• Genetic testing • Prophylaxis • Pharyngitis management • ARF admission and long-term management • Heart failure-related care • Endocarditis • Surgery	Genetic testing was cost-effective compared to usual care
Ehrlich, 2002 ⁴⁴	Prevent ARF A. Treat none B. Treat all C. RADT D. Culture E. RADT + culture	USA; paediatric population aged 5 to 17 presenting with sore throat	Model-based CEA; societal perspective	Literature	• RHD • ARF • Suppurative complications	• Culture • Antibiotic treatment and reaction • Suppurative complications • ARF	RADT was cost-effective

GP, general practice; RADT, rapid antigen detection test; ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; CMA, cost-minimisation analysis; QALYs, quality-adjusted life-years; CDR, clinical decision rule

Supplementary Table 6. Primary prevention strategies for disease related to Strep A with evaluation of secondary and/or tertiary prevention as independent or combined strategies

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Watkins, 2015 ⁴⁸	Prevent incident ARF/RHD and worsening or prevalent RHD A. Intervention - Improve health-seeking behaviours for sore throat patient adherence to penicillin prophylaxis B. Do nothing	Cuba; children aged 5 – 24 years	Post-hoc CUA of a population-wide program	Literature (Nordet, 2008)	DALYs	• Hospitalisation • Long-term prophylaxis and specialist care • Prevention program	The intervention was net cost-saving and more effective than usual care
Nordet, 2008 ⁴⁷	Prevent incident ARF/RHD and worsening or prevalent RHD A. Do nothing B. Improve health-seeking behaviours for sore throat patient adherence to penicillin prophylaxis	Cuba; school children	Post-hoc CEA of a population-wide program	Analysis of population-level data	• Incidence of ARF and RHD • Prevalence of ARF and RHD	• Total cost of ARF and RHD care • Intervention	The cost of care for ARF/RHD significantly reduced for a relatively minor cost for the intervention
Watkins, 2016 ⁴⁹	Prevent incident ARF and RHD Scaling up: A. Primary prevention	African nations; population aged 5-25 years	Model-based CUA; health system perspective	Literature and assumptions	DALYs	• ARF hospitalisation • Remission • RHD • Cardiovascular complications • Interventions	Primary prevention is cost saving (comparator not stated) Secondary preventions is cost effective

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
	(pharyngitis treatment rate) B. Secondary prevention (prophylaxis compliance rates) C. Heart valve surgery						(comparator not stated)
Soudarssanane, 2007 ⁵²	Prevent incident ARF and RHD A. Primary prevention B. Secondary prevention C. Tertiary prevention	India; people aged 5-15 years	Model-based CBA; government and community perspectives	Assumed	• Productivity from improved life expectancy • Reduced costs of upstream prevention strategies	Primary prevention • GP consultation • Throat culture • Patient travel • Pain relievers • Antibiotics • Indirect costs Secondary prevention • Hospital admission • Lost wages • Diagnostic services • Antibiotics • Pain relievers • Prophylaxis (9 years) • Patient travel • Specialist follow up • Community cost • Social cost (school failures) • Incidental costs Tertiary prevention	Primary prevention and secondary prevention resulted in positive net benefits, and primary prevention had the highest net benefit amount

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
						• Surgery • Post-surgery care • Lost wages • Patient travel • Specialist follow up • Cost of not implementing secondary prevention • Rheumatic fever admissions and management • Incidental costs	
Coates, 2021 ⁵¹	Prevent incident ARF/RHD and worsening or prevalent RHD	African Union; population between 2021 and 2030	Model-based CBA; health system perspective	Literature	Monetary value of reduced morbidity and mortality	Primary prevention • Public health campaign • Outpatient consultation • Antibiotics • Provider education and evaluation • Community health worker training, equipment, and administrative costs Secondary prevention • Outpatient visit • Antibiotics	Scale up of secondary prevention and secondary and tertiary care interventions resulted in a positive net benefit, and was negative for primary prevention

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
						• Patient transport • Echocardiography evaluation • Provider education and evaluation • Public health campaign • Handheld ultrasound equipment • Training • Other supplies Tertiary prevention • Heart failure management (tradeable and non-tradeable costs) • Handheld ultrasound equipment • INR machine • Training • Other supplies • Valve surgery • Patient transport • Post-surgical management (tradeable and non-tradeable costs) Other • ARF admission	

Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Manji, 2013 ⁵⁰	Prevent incident ARF and/or RHD A. Culture (50% seek treatment) and treatment B. Antibiotic prophylaxis for all regardless of clinical history C. Echo and SP D. Do nothing	Developing country (e.g., in sub-Saharan Africa); people between 5 and 21 years-old for intervention, 5-70 years for modelled outcomes	Model-based CUA; perspective not stated	Literature and assumptions	QALYs, comprising Strep throat, antibiotic side effects, RHD	• Throat swab • Lab analysis of swab • Wage for swab • Antibiotics • Ab side effects • Ab prophylaxis • Echocardiography • Wage for cardiography • Echo machine Direct and indirect costs of RHD	ECHO is cost-effective compared to doing nothing; strategies A and B are not cost-effective compared to echo.

GP, general practice; RADT, rapid antigen detection test; ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; CMA, cost-minimisation analysis; QALYs, quality-adjusted life-years; IV, intravenous; CDR, clinical decision rule

Supplementary Table 7. Secondary and tertiary prevention strategies for disease related to Strep A

Category/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
Secondary prevention							
Oetzel, 2019 ⁵³	Improve patient compliance to secondary prophylaxis A. Incentives for adherence B. Usual care	New Zealand; patients on prophylaxis management	Trial-based CEA; public provider perspective	Trial	Improved adherence (recommended schedule of BPG injections)	• Incentives • BPG injections • Follow up phone calls	ICER subject to decision maker's acceptability threshold
Ubels, 2020 ⁵⁵	Prevent worsening of RHD A. Routine screening B. Usual care	Brazil; 11-year-old children	Model-based CUA; public perspective	Assumed	Reduce DALYs	• Screening • RHD treatment • Surgery	Screening is cost-effective compared to usual care
Roberts, 2017 ⁵⁴	Prevent worsening of RHD A. Routine screening B. Usual care	Australia; remote Indigenous children aged 5 to 12 years	Model-based CUA; health sector perspective	Assumed	Reduce: • RHD severity at diagnosis • Heart failures • Surgeries • Deaths • DALYs, comprising acute infection, long-term sequelae, and death	• ARF and RHD diagnosis and long term management • Surgery • Screening	Cost-effective is cost-effective compared to usual care if RHD can be detected ≥ 2 years earlier by screening
Zachariah, 2015 ⁵⁶	Prevent worsening of RHD A. Routine screening B. Usual care	Australia; 11-year-old children	Model-based CUA; societal perspective	Assumed	Improved QALYs	• Screening • Primary care for subclinical RHD • RHD diagnosis and long term management	Screening is likely less costly and more effective compared to usual care

Category/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes
						• Surgery • Management post-valve surgery • Lost wages	
Tertiary							
Uy, 2021 ⁵⁷	Prevent worsening of heart disease or death A. Valve repair B. Mechanical valve replacement (MVR-M) C. Bioprosthetic valve replacement (MVR-B) D. Usual care (mix of A-C)	India; patients aged 20 years and older with rheumatic mitral valve disease	Model-based CUA; public payer perspective	Literature	• Reduced reoperations • Reduced cardiovascular complications • Improved QALYs	• Surgery • Post-surgery management • Cardiovascular complications	Repair was less costly and more effective than usual care and MVR-M. The ICER for MVR-B compared to repair was cost-effective at a threshold of India's per-capita gross domestic product

ICER, incremental cost-effectiveness ratio; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; QALYs, quality-adjusted life-years; DALYs, disability-adjusted life-years

Supplementary Table 8. Secondary prevention strategies for disease related to Strep A – prevent recurrences of diseases other than ARF

Category/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes/ recommendations
Osternmann, 2021 ⁶⁰	Prevent recurrent throat infections A. SilAtro-5-90 adjuvant therapy B. Usual care	Germany; patients with suspected moderate recurrent tonsillitis	Model-based CEA; societal perspective	Literature	Averted throat infections	• SilAtro-5-90 • Tonsillectomy • Antibiotics • GP • Productivity loss • Career time • Travel time	Adolescents/Adults >12-years-old: ICER subject to decision maker's acceptability threshold Children <= 6-12-years-old: adjuvant therapy is less costly and more effective than usual care
Wilson, 2012 ⁵⁹	Prevent recurrent pharyngitis A. Tonsillectomy B. Medical therapy	UK; children aged 4 to 15 years with recurrent sore throats	Trial-based CEA; perspective not stated	Trial	• Reduced recurrent sore throat and associated treatment • Improved quality of life (PedsQL Pediatric Quality of Life inventory score)	<i>Not reported</i>	"..., tonsillectomy can save up to 8 sore throats at a reasonable cost..."
Bhattacharyy, 2002 ⁵⁸	Tonsillectomy	USA; adults with chronic tonsillitis	(retrospective) Trial-based CEA; perspective not stated	Trial	• Improved quality of life (Glasgow Benefit Inventory) Reduced: • Antibiotic consumption	• Physician consultations • Antibiotics • Productivity loss • Tonsillectomy	Tonsillectomy "...results in significant improvement in quality of life, decreases health-care utilization, and diminishes the economic burden of chronic tonsillitis"

Category/Study	Intervention aim and strategies	Country; target population	Study design	Evidence of effectiveness	Benefits	Costs	Outcomes/ recommendations
					• Productivity loss • Physician consultations		
Mason, 2014 ⁶¹	Prevent recurrent cellulitis (of the leg)	UK	Multi trial-based CUA; public health and societal perspectives	Trials	• Reduction in recurrent infections • Improved QALYs (EuroQoL EQ-5D-3L)	• GP consultation • Nurse visits • Inpatient stays • Outpatient visits • Days of work • Antibiotics	“Antibiotic prophylaxis reduces cellulitis recurrence by nearly a third but is not associated with a significant increase in costs.”

GP, General Practice; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

Supplementary Table 9. Checklist for assessing economic evaluations.⁶²

[illegible]

Neuner, 2003 ³⁵	1	1	1	1	1	1	1	1	1	1	10
Irlam, 2013 ⁴³	1	1	1	1	1	1	1	1	1	1	10
Maizia, 2012 ⁴⁶	1	1	1	1	1	1	1	1	1	1	10
Giraldez-Garcia, 2011 ⁴⁵	1	1	1	1	1	1	1	1	1	1	10
King, 2002 ⁴²	1	1	0	1	1	1	1	1	1	0	8
Ehrlich, 2002 ⁴⁴	1	1	0	1	1	1	1	1	1	1	9
Watkins, 2015 ⁴⁸	1	1	0	1	1	1	1	1	1	1	9
Nordet, 2008 ⁴⁷	0	0	0	0	0	0	0	0	0	0	0
Watkins, 2016 ⁴⁹	1	1	1	1	0	0	1	1	1	1	8
Soudarssanane, 2007 ⁵²	0	1	0	0	1	0	0	1	0	0	3
Coates, 2021 ⁵¹	1	1	0	1	1	1	1	0	1	1	8
Manji, 2013 ⁵⁰	0	0	0	0	1	0	1	1	1	0	4
Oetzel, 2019 ⁵³	0	0	1	0	1	1	1	1	0	1	6
Ubels, 2020 ⁵⁵	1	1	0	1	1	1	1	1	1	1	9
Roberts, 2017 ⁵⁴	1	1	0	1	1	1	1	1	1	1	9
Zachariah, 2015 ⁵⁶	1	1	0	1	1	0	1	1	1	0	7
Uy, 2021 ⁵⁷	1	1	1	1	1	1	1	1	1	1	10
Osternmann, 2021 ⁶⁰	1	1	1	1	1	1	1	1	1	1	10
Wilson, 2012 ⁵⁹	0	1	1	0	1	1	1	1	1	1	8
Bhattacharyya, 2002 ⁵⁸	0	1	1	0	1	1	1	0	1	1	7
Mason, 2014 ⁶¹	1	1	1	1	1	1	1	1	1	1	10
Number (%) of evaluations with full criteria	26 (59%)	40 (91%)	32 (73%)	26 (59%)	39 (89%)	33 (75%)	42 (95%)	29 (66%)	35 (80%)	30 (68%)	

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