

Supplementary Material

Porto APM *et al.* Promise vs. Proof in Digital Interventions for Antimicrobial Stewardship: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Appendix 1. Search Strategy

Pubmed

Date: August 22nd, 2025

No date of publication or Language restriction

("digital tool"[Title/Abstract] OR "Computer"[Title/Abstract] OR "Mobile"[Title/Abstract] OR "Electronic"[Title/Abstract] OR "eHealth"[Title/Abstract] OR "Telemedicine"[Title/Abstract]) AND ("Antimicrobial Stewardship"[All Fields] OR "Antibiotic Stewardship"[All Fields] OR "stewardship antibiotic"[All Fields] OR "stewardship antimicrobial"[All Fields])

Records: 1179 results

BVS / LILACS

Date: August 22nd, 2025

No date of publication or Language restriction

("digital tool" OR computer OR mobile OR electronic OR ehealth OR telemedicine) AND ("Antimicrobial Stewardship" OR "Antibiotic Stewardship" OR "Stewardship, Antibiotic" OR "Stewardship, Antimicrobial") AND instance:"lilacsplus"

Records: 41 results

Scopus

Date: August 22nd, 2025

No date of publication or Language restriction

(TITLE-ABS-KEY ("digital tool" OR Computer OR Mobile OR Electronic OR eHealth OR Telemedicine) AND TITLE-ABS-KEY ("Antimicrobial Stewardship" OR "Antibiotic Stewardship" OR "Stewardship, Antibiotic" OR "Stewardship, Antimicrobial"))

Records: 2024 results

Embase

Date: August 22nd, 2025

No date of publication or Language restriction

('digital tool':ti,ab,kw OR computer:ti,ab,kw OR mobile:ti,ab,kw OR electronic:ti,ab,kw OR ehealth:ti,ab,kw OR telemedicine:ti,ab,kw) AND ('antimicrobial stewardship':ti,ab,kw OR 'antibiotic stewardship':ti,ab,kw OR 'stewardship, antibiotic':ti,ab,kw OR 'stewardship, antimicrobial':ti,ab,kw)

Records: 2042 results

Appendix 2. Primary outcomes definition according to the included studies for the meta-analysis

Appropriateness of antibiotic prescribing

Helou (2025): appropriate antibiotic therapy (AAT) described as adequate selection of drug, route and dose of antibiotic treatments in concordance with local guidelines at the patient level as described before according to a previous study (Schuts EC, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847e56. [https://doi.org/10.1016/s1473-3099\(16\)00065-7](https://doi.org/10.1016/s1473-3099(16)00065-7)).

Williams (2023): the primary outcome was exclusive guideline-concordant antibiotic prescribing during the first 24 hours of care. Concordance was pre-specified and emphasized use of narrow-spectrum antibiotics. Withholding antibiotics was presumed to be concordant because childhood pneumonia is frequently viral,^{4,27} and clinicians were considered highly unlikely to withhold antibiotics in those with suspected bacterial pneumonia.

Rutten (2022): the primary study outcome was the percentage of antibiotic prescriptions for suspected UTI that were appropriate (yes/no), that is, prescribed in compliance with the treatment advice generated by the decision tool.

Antibiotic prescription

Williams (2023): antibiotic prescription per ED encounter during the first 24 hours of care.

Van der Maat (2020): antibiotic prescription at ED discharge (yes/no)

Nelson (2022): the proportion of children prescribed an antibiotic by the treating physician.

Gulliford (2019): antibiotic prescription rate per respiratory tract infection consultation

Rutten (2022): total antibiotic prescribing

Table S1. Summary of all randomized clinical trials evaluating digital interventions for antimicrobial stewardship

Author, year	Country	Setting	Patient population	Digital tool studied	Infection site	Control group	Multimodal strategy	Primary Outcomes	Secondary Outcomes	Follow-up assessment	Sample size
Helou, 2025	Netherlands, Sweden, Switzerland	Tertiary hospitals	Adult (≥18 years)	Mobile smartphone application / Clinical Decision Support System (CDSS)	Unspecified	Standard care with conventional access to antibiotic guidelines via: website, PDF files, printed booklets	Alone	Appropriate antibiotic therapy (AAT) rate	Length of stay (LOS); mortality 30 days; ICU admission; readmission within 30 days; Medication-specific usage patterns; user analytics of the app; AAT assessed by user analytics	16 months	1,566
Gohil, 2024	USA	Community hospitals	Adult (≥18 years)	Computerized Provider Order Entry (CPOE) bundle with real-time prompts recommending empiric standard-spectrum antibiotics	Urinary tract infection	Routine stewardship (education + coaching calls) without CPOE prompts; patient-specific risk estimates calculated but not displayed	Multimodal (Real-time CPOE prompts for MDRO risk <10%; patient-specific risk estimates; educational materials; feedback reports; coaching calls; site visits & webinars	Empiric extended-spectrum antibiotic days of therapy (first 3 hospitalization days)	Vancomycin days of therapy; antipseudomonal days of therapy; days to antibiotic escalation; days to ICU transfer; length of stay in days	15 months	55,412
Gohil, 2024	USA	Community hospitals	Adult (≥18 years)	Computerized Provider Order Entry (CPOE) bundle with real-time prompts recommending empiric standard-spectrum antibiotics	Respiratory tract infections	Routine stewardship (education + coaching calls) without CPOE prompts; patient-specific risk estimates calculated but not displayed	Multimodal (Real-time CPOE prompts for MDRO risk <10%; patient-specific risk estimates; educational materials; feedback reports; coaching calls; site visits & webinars	Empiric extended-spectrum antibiotic days of therapy (first 3 hospitalization days)	Vancomycin days of therapy; antipseudomonal days of therapy; days to antibiotic escalation; days to ICU transfer; length of stay in days	15 months	44,780

Williams, 2023	USA	Pediatric emergency departments	Pediatric (6 months to < 18 years)	EHR-based antibiotic CDS in the ED	Respiratory tract infections	Standard care with access to local guidelines, but no CDS tool	Multimodal (EHR screening for pneumonia, CDS alerts with tailored regimens, education sessions, emails, and ED clinician champions)	Exclusive guideline-concordant antibiotic prescribing within the first 24 hours of care	Any guideline-concordant prescribing (24 h and entire encounter); safety (time to first antibiotic, LOS, delayed ICU transfer, 3- and 7-day revisits, 30-day mortality)	First 24 h of care, entire encounter, 3- and 7-day post-discharge revisits, and 30-day mortality	1,027
Van der Maat, 2020	Netherlands	Emergency departments	Pediatric (1 to 60 months)	Feverkidstool: Online digital calculator that stratifies fever-related infection risk using temperature, CRP, and clinical appearance, requiring manual access by clinicians before treatment decisions	Respiratory tract infections	Standard care (without CDS tool)	Bimodal (Fevkidstool + education)	Overall antibiotic prescription (binary); Strategy failure: antibiotic use + hospitalization + oxygen dependency or fever up to day 7 + complications	Compliance (intention-to-treat + per-protocol analyses); number of complications	Primary outcome at ED discharge; Strategy failure assessed at day 7 follow-up	999
Nelson, 2022	Bangladesh and Mali	Government hospitals and healthcare facilities	Pediatric (2 to 59 months)	Smartphone-based electronic Clinical Decision Support (eCDS) with Diarrheal Etiology Prediction (DEP) algorithm	Acute diarrhea	eCDS without DEP algorithm (standard smartphone eCDS); no algorithm-based prediction support	Alone	Proportion of children prescribed antibiotics	Diarrheal symptom resolution at 10 days post-discharge	Baseline (enrollment); 4-week intervention period; 10 days post-discharge follow-up	941
Rutten, 2022	Netherlands	Nursing Homes	Older adults NH residents (mean age 86 years)	An electronic health record (EHR)-integrated decision tool, based on a previously developed decision tool for the	Urinary tract infection	Standard care	Multimodal (CDS tool + supportive interventions: interactive training session proprovided by	Percentage of antibiotic prescriptions for suspected UTI that were appropriate (in compliance with the	Changes in treatment decision (ie, antibiotic start after initial withholding antibiotics); complications (side effects, renal	3, 7, and 21 days later in the intervention group; 7 and 21	212

				treatment of suspected UTI in frail older adults			the research team, pocket-cards, and an information leaflet to hand out to residents)	treatment advice generated by the decision tool)	impairment, and pyelonephritis/urosepsis); UTI-related hospitalization; mortality during follow-up, and pre-post study changes in total antibiotic prescribing	days later in the control group	
Ridgway, 2021	USA	Univeristy hospitals (Healthsystem)	Adult (≥18 years)	Electronic Clinical Decision Support system (CDSS) (Weighted Incidence Syndromic Combination Antibigram (WISCA))	Urinary tract infection; abdominal biliary infection; nonpurulent cellulitis; community acquired pneumonia; aspiration pneumonia, and nursing home-associated pneumonia.	Standard care with audit and feedback recorded in EHR but not communicated to providers unless the antibiotic regimen posed a clinical threat; no active prospective feedback intervention	Multimodal (EHR-based CDS tool + guideline-based empiric regimens + prospective audit and feedback by ASP physicians	Hospital length of stay (LOS)	30-day readmission; 30-day mortality; Antibiotic charges; Clostridioides difficile infection acquisition within 180 days; Multidrug-resistant gram-negative organism (MDRO) acquisition within 180 days	In-hospital, 30-day, and 180-day follow-up	6,849
Gulliford, 2019	United Kingdom	Primary care	General population	Clinical Practice Research Datalink (CPRD) integrated decision support	Respiratory tract infections	Standard care (usual prescribing practices; access to routine resources)	Multimodal (Webinar + Monthly data reports + Decision support tools (not specified if mobile/web)	Antibiotic prescription rate for RTI per 1,000 patient-years (12 months)	RTI consultation rate; Proportion of RTI consultations with antibiotics prescribed; Total antibiotic-prescribing rate; Subgroups of RTI; Health-care costs	12 months	626,625

Broussard, 2025 ¹	USA	Outpatient pediatric primary care clinics	Pediatric (3 months to <21 years)	An HER SSTI order panel with default, pre-populated guideline-concordant antibiotic durations and weight-based dosing	Skin and soft tissue infections	Control EHR SSTI order panel listing the same antibiotics but without any suggested durations or pre-populated dosing	Educational sessions on SSTI treatment guidelines + SSTI EHR order panel with default durations and weight-based dosing + visual reminders near workstations + reminder email about panel use	Inappropriately long antibiotic prescriptions rate for SSTIs (guidelines-based cutoffs)	Change in trajectories (pre- vs post-panel) of long prescription; rates over time; odds of long prescriptions; frequency of order panel use	12 months	1,123
Yan, 2020 ²	USA	Direct-to-Patient Telemedicine	General population	HER-integrated Audit & Feedback via Online Personalized Dashboard (web-based)	Respiratory tract infections	Standard Care (Education Only)	Education + Online feedback dashboard with: Practice Summary (aggregate rates), Individual clinician rates + Digital Monthly personalized dashboard	Antibiotic prescription rates for URI, bronchitis, sinusitis, pharyngitis;	Diagnostic shifting: proportion of visits coded as sinusitis/pharyngitis (potentially antibiotic-appropriate vs inappropriate conditions)	6 months	24,843

¹ Not included for quantitative synthesis (reason for exclusion: assessed different outcomes from those described in the protocol)

² Not included for quantitative synthesis (reason for exclusion: missing critical data)

Table S2. GRADE Summary of Findings from Randomized Clinical Trials on Digital Interventions for Antimicrobial Stewardship

Outcome	Relative effect (95% CI) ^a	No. of studies	Certainty of evidence ^b	Comment
Appropriateness of antibiotic prescription	RR 0.99 (0.93 – 1.05)	3 RCTs	⊕○○○ Very low	Certainty reduced due to serious risks of bias in study design, inconsistency in the direction of effects across the three trials, and significant imprecision due to the small cumulative sample size.
Antibiotic prescription	RR 0.98 (0.88 – 1.09)	5 RCTs	⊕○○○ Very low	Certainty downgraded for risk of bias (predominantly deviations from intended interventions), serious inconsistency (substantial heterogeneity, $I^2=71\%$, with effects in opposite directions), imprecision (pooled CI crossing the null), and suspected publication bias (only five studies).
30-day mortality	RR 0.91 (0.77 – 1.09)	3 RCTs	⊕○○○ Very low	Certainty downgraded for risk of bias (concerns in deviations from intended interventions, including one high-risk trial), imprecision (pooled CI crossing the null), and suspected publication bias (only three studies).
30-day hospital readmission	RR 0.95 (0.79 – 1.14)	3 RCTs	⊕○○○ Very low	Certainty downgraded for risk of bias (including one high-risk trial, primarily due to deviations from intended interventions), inconsistency (heterogeneity and opposing point estimates across two studies), imprecision (pooled CI crossing the null), and suspected publication bias (only two studies).
Length of hospital stay (LOS)	MD 0.17 (-0.01 – 0.35)	3 RCTs	⊕○○○ Very low	Certainty downgraded for risk of bias (including one high-risk trial), serious inconsistency (substantial heterogeneity, $I^2=74\%$, with effects in opposite directions), imprecision (pooled CI crossing the null), and suspected publication bias (only three studies).

Abbreviations: RCTs, randomized controlled trials.

^a RR (Relative Risk) or MD (Mean Difference) with 95% confidence interval obtained in the meta-analyses.

^b GRADE Working Group grades of evidence: High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low. Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate. Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high. Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high. *Substantially different = a large enough difference that it might affect a decision.

Appendix 3. PRISMA 2020 for Abstracts Checklist

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

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

Appendix 4. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	28-61
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	77-96
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	97-105
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	130-142
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	115-118
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	119-128; Supplementary material (Appendix 1)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	142-145
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	147-154
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	155-161; Supplementary material (Appendix 2)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplementary material (Table S1)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	163-165

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	171-177
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	130-142; Supplementary material (Table S1)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	159-161; 201-205
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supplementary material (Table S1); 247-287
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	171-177; 281-283
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	247-254
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	284-287 Supplementary material (Table S2);
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	208-245;
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	182-187; 208-245; 201-202
Study characteristics	17	Cite each included study and present its characteristics.	186-187; Supplementary material (Table S1);
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	247-251

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	256-281
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	247-251; 256-281
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	256-281
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	284-287; Supplementary material (Table S2);
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	292-321
	23b	Discuss any limitations of the evidence included in the review.	322-340
	23c	Discuss any limitations of the review processes used.	340-345
	23d	Discuss implications of the results for practice, policy, and future research.	346-393
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	112-113
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	112-113
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	396-403
Competing interests	26	Declare any competing interests of review authors.	406-408; ICMJE form
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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