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Quality indicators for hospital antimicrobial stewardship programmes: a systematic review.

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Background

Measuring the quality and effectiveness of antimicrobial stewardship (AMS) programmes with quality indicators (QIs) is an area of increasing interest. We conducted a systematic review to identify QIs of AMS programmes in the hospital setting and critically appraise their methodological quality.

Methods

We searched the Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL, Scopus/web of science databases and the grey literature for studies which defined and/or described the development process and characteristics of the QIs developed. The Appraisal of Indicators through Research and Evaluation (AIRE) instrument was used to critically appraise the methodological quality of the QI sets.

Results

We identified 16 studies of QI sets consisting of 229 QIs. The QI sets addressed a broad range of areas of AMS in the hospital setting and consisted of 75% process indicators, 24% structural indicators and 1% outcome indicators. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified.

Conclusion

The QIs identified in this study focused on process and structural indicators with few outcome indicators developed, a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS. Testing of the QIs in practice is an essential methodological element of the QI development process and should be included in the QI development study or as planned validation work.

Introduction

Antimicrobial resistance (AMR) is a major threat to public health contributing to increasing rates of illness, death and significant economic costs.[1 2] Antimicrobial stewardship (AMS) programmes have been implemented to address the escalating threat to human health posed by AMR. AMS aims to optimise antimicrobial use in order to maximise the probabilities of clinical cure or prevention of infection while minimising unintended consequences such as toxicity and the selection of pathogenic organisms (e.g. *Clostridioides difficile*).[3] AMS is an important element of patient safety and a widely applied quality improvement initiative.[4] Implementation guidelines for AMS programmes place a strong emphasis on improving the quality of antimicrobial use[5] and evaluation of AMS programmes, but do not identify specific indicators of performance.[6]

Measuring the quality of healthcare can be achieved by using quality indicators (QIs). QIs are defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care provided'.[7] QIs can measure the quality of care by examining the structures, processes, and outcomes of care.[8 9] This acknowledges that good structures increase the likelihood of good processes, and good processes increase the likelihood of good outcomes.[8]

To ensure QIs provide accurate measures of quality, they must adhere to certain quality requirements. QIs should be evidence based,[10] but in situations where scientific evidence is lacking, QIs can be defined by an expert panel of professionals using consensus techniques such as the Delphi technique or RAND/UCLA (Research and Development Corporation) (University of California, Los Angeles) appropriateness method.[11] The systematic method of combining scientific evidence and expert opinion is the most rigorous method to develop QIs as it provides face and content validity.[12] Furthermore QIs should be tested during their development[12] to demonstrate they are acceptable to users (those being assessed and their assessors), feasible to measure, reliable and reproducible,

sensitive to change and validated so as to ensure that they will produce consistent and credible measures of the quality of care.[9 13]

Cost savings were among the initial incentives for hospitals to implement AMS programmes.[14] However, this is injudicious because factors such as antimicrobial patent expiry, drug shortages and the increasing prevalence of multi-drug resistant organisms requiring the use of more expensive agents, all of which are beyond the control of an AMS programme. Thus cost savings alone is an unreliable indicator of performance [15] and makes a further case for measures to demonstrate the clinical and economic values of AMS programmes.[16] Measuring the effectiveness of AMS programmes is thus important and is an area of increasing interest.[17]

The purpose of this systematic review is to identify existing QIs of AMS programmes in the hospital setting, describe the methodological approaches used in their development, differentiate between the types of indicators (structure, process or outcome), and critically appraise the methodological quality of the identified QI sets using the Appraisal of Indicators through Research and Evaluation (AIRE) instrument.

Methods

This study was conducted and reported according to the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA).[18]

Search strategy

An initial search for other systematic reviews of QIs for AMS programmes in hospitals identified two existing reviews.[19 20] However, neither study undertook a quality assessment of the methodological development of the QIs sets identified.

The search strategy aimed to identify publications concerning the development, testing or implementation of indicators of the quality of AMS programmes and antimicrobial prescribing. The Cochrane Library, PubMed, MEDLINE, EMBASE, CINAHL and Scopus/web of science databases were searched. A manual search of the grey literature, including conference proceedings, reports and thesis, was also conducted to find information regarding QI development initiatives which were not published in peer-reviewed journals. The reference lists of full text articles identified were screened to find other relevant studies. No language restrictions were imposed on the search algorithms. Searches were limited to studies of humans. The search period ran from the inception of the databases to the 1/12/2019 and the search was repeated on the 26/9/2020. The search terms were:

Anti-infective agents [MeSH] OR Antibiotic prophylaxis [MeSH] OR Antibiotic* [tiab] OR Antimicrobial*[tiab] OR Anti microbial*[tiab] OR Anti infective*[tiab] OR Antiinfective*[tiab] OR Antibacterial*[tiab] OR Anti bacterial*[tiab]	AND	Quality indicators, health care [MeSH] OR Quality indicator*[tiab] OR Quality measure*[tiab] OR Quality metric*[tiab] OR Quality criteria[tiab] OR Qualitative measure*[tiab] OR Quality improvement [ti]

Inclusion criteria and study selection

Studies were eligible for inclusion if they met the following criteria:

1. The study defines and/or describes the development process and characteristics of the QIs developed.
2. The identified QIs are applicable to adult patients in the hospital setting and related to the overall assessment of AMS programmes or the assessment of AMS related to specific clinical indications (e.g. sepsis, Community Acquired Pneumonia (CAP), Urinary Tract Infections (UTIs)) or settings (e.g. ICU).
3. Where the set of QIs were updated the publication describing the updated QIs was selected for inclusion.

Exclusion Criteria

1. Editorials, letters to the editor, comments, and narrative case reports.
2. Publications describing the application of existing QIs in clinical practice or reviews of sets of QIs.

Following completion of the database searches, the identified references were entered into a bibliographical database and duplicates removed. The title and abstracts of these references were screened for relevance (keywords in the title, abstract or study subject headings) by one reviewer (FOR). The resulting abstracts were included for full text review by two reviewers (FOR and AF) independently, according to inclusion criteria, and any disagreements resolved by consensus. If no consensus could be reached a third reviewer (FS) was consulted. The reference lists of the selected publications were then screened for other relevant studies that had not been identified in the electronic database searches.

Data extraction

A data extraction form was designed and used to extract relevant information about the QIs from the included articles (Supplementary data SD1).

Categorising and grouping of the extracted QIs

The QIs extracted were categorised as structural, process or outcome QIs, classified by theme within each category and where there was conceptual, or content overlap in the description of the QI they were grouped together as agreed on by all authors.

Critical appraisal

The AIRE instrument[21] was used to appraise the methodological quality of the QI sets included in this study. It is a validated instrument which has been designed to assess the quality of QIs.[22] It addresses four quality domains of a QI and consists of 20 items which are applied to each completed set of QIs. Three domains address the methodological quality of QIs and were used in this review: 'Stakeholder involvement', 'Scientific evidence' and 'Additional evidence, formulation and usage'. The fourth domain: 'purpose, relevance and organisational context' reflect the relevance of the QIs within a particular context rather than methodological quality so was not used in this review. Table 1 contains the AIRE domains and items applied in this study. Each item consists of a statement which is scored according to a 4-point Likert scale (1 'strongly disagree or no information provided' to 4 'strongly agree'(confident that the criterion has been fulfilled)). Scores for each domain were calculated by summing up the scores for each individual item in a category and standardising the total as a percentage of the maximum possible score for the domain. The AIRE instrument was completed by two reviewers independently (FOR and AF or FS) for each complete QI set rather than for each QI individually as most studies gave general information for the QI sets concerning development and supporting evidence. (Further details about the AIRE instrument and its scoring system are contained in Supplementary data SD2). The scores for each domain are independent and should not be aggregated into a single total quality score. The standardised scores for each domain

range from 0% to 100%, with a score of 50% or higher indicating a higher methodological quality for each domain of the instrument.[21]

Inter-rater reliability between reviewers

The inter-rater reliability between the three reviewers was assessed by comparing the individual scores per AIRE item for two separate publications included in this study by calculating the weighted Cohen's Kappa. The inter-rater reliability between (FOR and AF) and (FOR and FS) amounted to 0.69 and 0.73 respectively. (Supplementary data SD3). A Cohen's Kappa of between 0.61 and 0.80 is considered substantial agreement.

Results

Search results

The PRISMA flow diagram of the study selection process and reasons for exclusion is seen in Figure 1. The systematic literature search identified 4833 potentially relevant studies. Following screening of titles and abstracts, 85 potentially relevant studies were selected for full-text screening. Six additional studies were included in the full text screening after reference screening of the selected publications. 75 studies were excluded and 16 publications of QI sets were included in this review.

Study characteristics

Table 2 presents an overview of the studies included in this review. Most included studies originated from Europe (11) followed by the UK (2), the USA (1) and Indonesia (1), one further study involved an assessment of USA and European hospitals.

The most common study design used in QI development involved a combination of a literature review (8) or review of clinical evidence and/or clinical guidelines (4), and, a consensus process [RAND modified Delphi (7), modified Delphi (2), RAND/UCLA appropriateness (2) or Delphi (1)] involving national or international multi-disciplinary expert panels. Other techniques included: a literature review and consensus, a multi-disciplinary team consensus, a national target for *Clostridioides difficile* and a national working group evidence base review.

The 16 QI sets addressed a broad range of areas of AMS in the hospital setting. These included 7 sets of QIs to address specific infections [CAP, COPD, UTI, Sepsis, *Clostridioides difficile* infection (CDI)], one set of generic QIs to assess antibiotic use in the treatment of all bacterial infections in hospital, 4 sets for specific hospital settings (e.g. ICU, High Dependency Unit (HDU)) and 4 sets of broader QIs to evaluate AMS programmes or hospital antimicrobial prescribing or to compare hospital AMS programmes.

Stakeholder involvement

The most common stakeholders involved in the QI development process were infectious diseases specialists, medical microbiologists, hospital pharmacists and physicians/clinicians. Their expertise was supplemented by various specialist depending on the QIs to be developed (i.e. ICU care involved intensivists, CAP & COPD QIs involved respiratory physicians, UTI QIs- urologists, nephrologists and a gynaecologist). One study reported the participation of patients, payers and policy makers. Five studies reported general details of the stakeholder participants (i.e. multi-disciplinary team or expert group, medical professionals) rather than specific details.

Quality indicators

A total of 229 QIs were extracted from the 16 included studies and the full list is available as supplementary data SD4. QIs were grouped together and duplicates removed where there was conceptual or content overlap and several QIs were extracted from multiple publications. Table 3 contains a description of each unique QI, categorisation of the QI as a structural, process or outcome indicators, classification of QIs by theme within each category, and identification of the studies in which they appeared.

Structural Indicators

55 structural QIs (55/229, 24%) were derived from six studies which aimed to provide a quality assessment of the organisational framework, multi-disciplinary expertise, resources, and supportive activities required to implement an AMS programme. QIs with conceptual or content overlap were grouped together and were classified by themes which were developed and agreed on by all authors. The themes identified were: (1) AMS governance, leadership and accountability [3 indicators, 4 studies], (2) AMS expertise and resources [4 indicators, 3 studies], (3) AMS policies and programmes to improve prescribing [6 indicators, 4 studies], (4) Antimicrobial guidelines [4 indicators, 6 studies], (5) AMS education [1 indicator, 3 studies] and (6) Microbiology laboratory standards, antimicrobial resistance surveillance and feedback [3 indicators, 3 studies].

Process Indicators

172 process indicators (172/229, 75%) were derived from fifteen studies which aimed to assess the general clinical management of all infections, or specific infections, or patient populations. QIs with conceptual or content overlap were grouped together and were classified into four themes: (1) Infection diagnostics [4 indicators, 9 studies], (2) Pharmacy-supported interventions [7 indicators, 8 studies], (3) Elements of good antimicrobial prescribing practice [12 indicators, 12 studies] and (4) Indicators for specific infectious conditions/settings [54 indicators, 10 studies].

Outcome Indicators

Two outcome indicators (2/229, 1%) were identified, recommending the monitoring of clinical outcomes of patients receiving antibiotics and the monitoring of the rate of nosocomial CDI.

Methodological quality

Table 4 presents the results of the critical appraisal of the methodological quality of the 16 QI sets assessed with the AIRE instrument. There was a wide variation in the information and level of detail presented describing the methodological characteristics of the QI sets identified and this was reflected in the AIRE instrument domain scores. Most of the indicator sets achieved a score of 50% or higher indicating a high methodological quality in the first AIRE domain of 'stakeholder involvement'. The 10 studies with a high 'stakeholder involvement' domain score detailed the constituent stakeholders involved in the QI development process which ranged from medical opinion leaders[32] to broad multidisciplinary groups.[37] Studies considered of lower methodological quality for this domain did not include sufficient information within the publications regarding the relevant stakeholders' involvement in the QI development process. Most studies had a low score for the AIRE item within this domain of 'the indicator has been formally endorsed' with only one study providing this information (QI set endorsed and used by the European Centre for Disease Prevention and Control).[30]

The 'scientific evidence' domain of the QI development process was well reported and most studies (12) were considered of high methodological quality. Four studies were considered of low quality as

they received low or no score due to the absence of information regarding the search methods, evidence base, or the evidence-based appraisal techniques applied to develop the QI sets.

The lowest overall methodological quality was seen in the 'additional evidence, formulation, usage' domain where only 7 studies scored greater than 50%. The AIRE items within this domain which were allocated the lowest scores were 'a strategy for risk adjustment has been considered and described', 'the indicator has sufficient discriminative power' and 'specific instructions for presenting and interpreting the indicator results are provided'. Only 8 studies included information regarding the piloting of indicators in practice.

Five QI sets were considered to have a high methodological quality in all three AIRE domains [24 26 27 28 29] and only one QI set had scores of less than 50% across all three AIRE domains.[38]

Discussion

This is the first systematic review to provide an overview and critical appraisal of the methodological quality of QIs for AMS in the hospital setting. A total of 229 QIs were identified from sixteen studies. Process indicators accounted for 75% of the extracted QIs and focused on the clinical management of infections. Structural indicators accounted for 24% of the extracted QIs focussing on the organisational requirements of AMS programmes, and 1% of the extracted QIs assessed outcomes of care. The findings of the critical appraisal of QIs using the AIRE instrument indicate considerable variation in the methodological quality and applicability of the QI sets developed.

Most studies involved a comprehensive QI development process consisting of an appraisal of the evidence-base followed by an expert panel consensus process. There was some variability in the constituents of stakeholders involved in the development of QI sets and several studies did not provide details of the participants of the expert group. The involvement of a diverse range of stakeholders strengthens the results of the consensus process, and enhances the credibility and acceptability of the QIs.[39] Patient participation as members of the expert panel of key stakeholders in the QI development is often overlooked[40] but is of increasing importance.[41] Future studies should ensure the inclusion of a broad range of relevant stakeholders including patients, who all have an interest in the QIs to be developed.

Process indicators for AMS programmes accounted for 75% of the indicators identified. They focused on the general clinical management of infection and antibiotic treatment along with more specific indicators for infectious processes such as sepsis, CAP, COPD and UTIs. Process indicators offer hospitals the ability to assess the core competencies of antimicrobial prescribing[42] and the opportunity to adapt education and training of prescribers based on the findings. The high proportion of AMS process indicators may be related to the findings that process interventions are considered the most effective AMS strategies to improve antimicrobial prescribing in hospital.[3]

Structural indicators for AMS programmes accounted for 24% of the indicators identified. They focused on the organisational requirements and necessity for a core multi-disciplinary AMS team of infectious diseases specialists, microbiologists and pharmacists providing leadership and expertise to implement and support a multi-faceted AMS programme. AMS programmes are resource intensive which influences the variability in the implementation of hospital AMS programmes worldwide.[43] Core elements for AMS programme[44] have been developed which can be adapted depending on the resources available in different countries and hospitals. Structural indicators offer the opportunity to measure the implementation of the proposed core elements and for benchmarking of performance between hospitals, within countries and across jurisdictions and to identify outliers.

The low number of outcome indicators identified is reflective of the ongoing challenges of AMS programmes to accurately measure and demonstrate their impact on patient outcomes.[17 45] Expert panels developing quality measures consider outcome measures important[17 46] but are often reluctant to include such measures in QI sets due to the need for risk adjustment for confounding factors.[47] These include changes in the hospital setting such as the patterns of bacterial prevalence, patient demographics, patient case-mix, and infection control interventions and their intensity, all of which can influence AMR and antimicrobial prescribing. Other barriers include concerns that overall clinical outcomes (such as mortality) may be insensitive to changes as a result of interventions such as intravenous to oral switching, and perceived feasibility issues with other outcome measures.[46] In such situations where there is a difficulty in developing an accurate case-mix adjustment system for outcome indicators then alternative strategies may be more effective at measuring the quality of care.

Process and structural indicators can act as direct measures of the quality of healthcare, where a link has been demonstrated between a given process and outcome.[48] They are relatively easy to measure as the information is accessible from medical records or other hospital sources. They usually assess a clearly defined patient population and thus there is less need for risk adjustment.

The availability of such measures and their practicality means they can be used as alternative outcome measures as they are easier to interpret and more sensitive to changes in the quality of care.[48] The AMS process indicators (use of empiric antimicrobial therapy according to guidelines, de-escalation of therapy, intravenous to oral switching, therapeutic drug monitoring) and structural indicators (use of a list of restricted antibiotics and bedside consultation (especially in *Staphylococcus aureus* bacteraemia)) have demonstrated significant benefit to clinical outcomes, adverse events and costs.[49] The process measure of documented indications for antimicrobial prescriptions has also shown a positive influence on patient outcomes.[50] Furthermore a recent study of UK hospitals has evaluated the impact of AMS process and structural indicators (similar to those extracted in this study) on antimicrobial prescribing as an outcome measure and shown promising results.[45]

A further possible approach for the development of outcome measures may be to consider using indirect evidence for the success of a process indicator as an outcome. Process indicators such as de-escalation of therapy, or, IV to oral switching, could be used to assess an outcome such as 'not showing harm' where such indicators could decrease the likelihood of catheter-related infections/events without demonstrating an impact on more traditional outcomes such as mortality or AMR rates.[49]

The development of future QIs must address the lack of outcome indicators currently available while acknowledging the difficulties in their development such as risk adjustment and case-mix, along with the multitude of other factors which can influence AMR. The potential use of AMS process and structural indicators with a direct link to outcomes should also be explored further as surrogate AMS outcome measure.[45]

The methodological requirements for the development of QIs are well established.[9 12] Most studies concentrated on the development of the QIs and were considered of high methodological quality in the 'stakeholder involvement' and 'scientific evidence' domains. However, studies scored poorly in

the 'additional evidence, formulation, usage' domain due to limited reporting of information about validation and piloting of the QIs in practice or testing of the clinimetric characteristics. Such practice testing prior to wider usage of QIs is essential[40] as the validation and clinimetric testing of QIs is important to demonstrate the applicability and implementability of QI sets in practice, in different settings and to demonstrate the robustness of the indicators. The studies which were considered of the highest methodological quality scored well in all three AIRE domains and recognised the need to test indicators in the setting where they are intended for use.[24 26-29]

Several studies, which were considered of high methodological quality in the first two AIRE domains had low scores in the third domain.[23 30 31 36 37] Some studies acknowledged the need for piloting and clinimetric testing of their QIs prior to use on a wider scale. [27 30 31 35 37] The QIs from two studies[27 37] have undergone subsequent clinimetric testing.[51 52] This resulted in one QI set reducing the 11 initial QIs to 7, based on applicability[51] and of 33 QIs assessed reduced to 18 process indicators considered suitable to identify processes with a greater need for improvement within an AMS programme.[52] This supports the findings seen in other studies which have shown that 10-20% of developed QIs are not measurable in practice.[53] The implementability, applicability and feasibility testing of indicator measurements are important considerations and should be conducted as part of the development process but also in new settings where the QIs are to be potentially applied. Potential users need to know if they will be able to retrieve the data to assess the QI from sources such as medical records and this may vary between countries and sometimes within clinical settings.[28 30 51]

Point prevalence surveys are one of the most frequently used methods to assess the quality of antimicrobial prescribing in the hospital setting[54] and have been used to test QIs sets.[51 52] They are a particularly useful method of assessing the impact of process indicators on patient care and outcomes[55] in practice so future QI development studies should consider if new process QI sets can be incorporated and applied in point prevalence surveys.

Strengths and limitations of this study

This is the first systematic review of the QIs for AMS programmes which has included a critical appraisal of the methodological quality of the QI sets, a strength of this study.

The selection of articles, data extraction and quality assessment with the AIRE assessment tool was conducted by two reviewers independently and showed good inter-rater reliability which increases the overall reliability of the results. This review included QIs assessing specific infectious conditions as well as broader QIs of AMS programmes so provides a comprehensive overview of AMS programme QIs.

We may have missed some QI sets which have not been published in an article or report. However, it is unlikely that validated and reliable QI sets for AMS have not been published in peer-reviewed literature.

The AIRE instrument used in this study to assess the methodological quality of studies mainly focusses on the QI development process and scores are allocated based on the information contained within the published article. Unfortunately, the process of developing QIs was not always reported in detail in studies and this resulted in some studies being assigned lower scores for these criteria. As a result of this limitation the methodological quality of the QIs identified in this article may have been underestimated by using the AIRE instrument. There were, however, some studies which acknowledged the need to conduct piloting and clinimetric testing of their indicators so the low scores in these situations were accurate. A further limitation of this study was that we relied solely on the information contained within the published article.

Conclusions

This review provides an overview and critical appraisal of the methodological quality of QIs of AMS programmes. The study highlights the continuing need for transparent, valid and feasible QIs. Studies to date have focused on process and structural indicators with few outcome indicators developed, a major deficiency in this area. Future research should focus on the development of outcome indicators or the use of process or structural indicators linked to outcomes to assess AMS.

Testing of the QIs in practice should be an essential element of the QI development process and should be included in the QI development study or as planned validation work.

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Transparency declarations

Nothing to declare

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505 **Table 1 AIRE domains and items[21]**

AIRE domain	AIRE items
Stakeholder involvement	1. The group developing the indicator includes individuals from relevant professional groups
	2. Considering the purpose of the indicator, all relevant stakeholders have been involved at some stage of the development process
	3. The indicator has been formally endorsed
Scientific evidence	4. Systematic methods were used to search for scientific evidence
	5. The indicator is based on recommendations from an evidence-based guideline or studies published in peer-reviewed scientific journals
	6. The supporting evidence has been critically appraised
Additional evidence, formulation, usage	7. The numerator and denominator are described in detail
	8. The target patient population of the indicator is defined clearly
	9. A strategy for risk adjustment has been considered and described ('case-mix adjustment')
	10. The indicator measures what it is intended to measure (validity)
	11. The indicator measures accurately and consistently (reliability)
	12. The indicator has sufficient discriminative power
	13. The indicator has been piloted in practice
	14. The efforts needed for data collection have been considered
	15. Specific instructions for presenting and interpreting the indicator results are provided

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507 **Table 2. Characteristics of the AMS quality indicator sets**

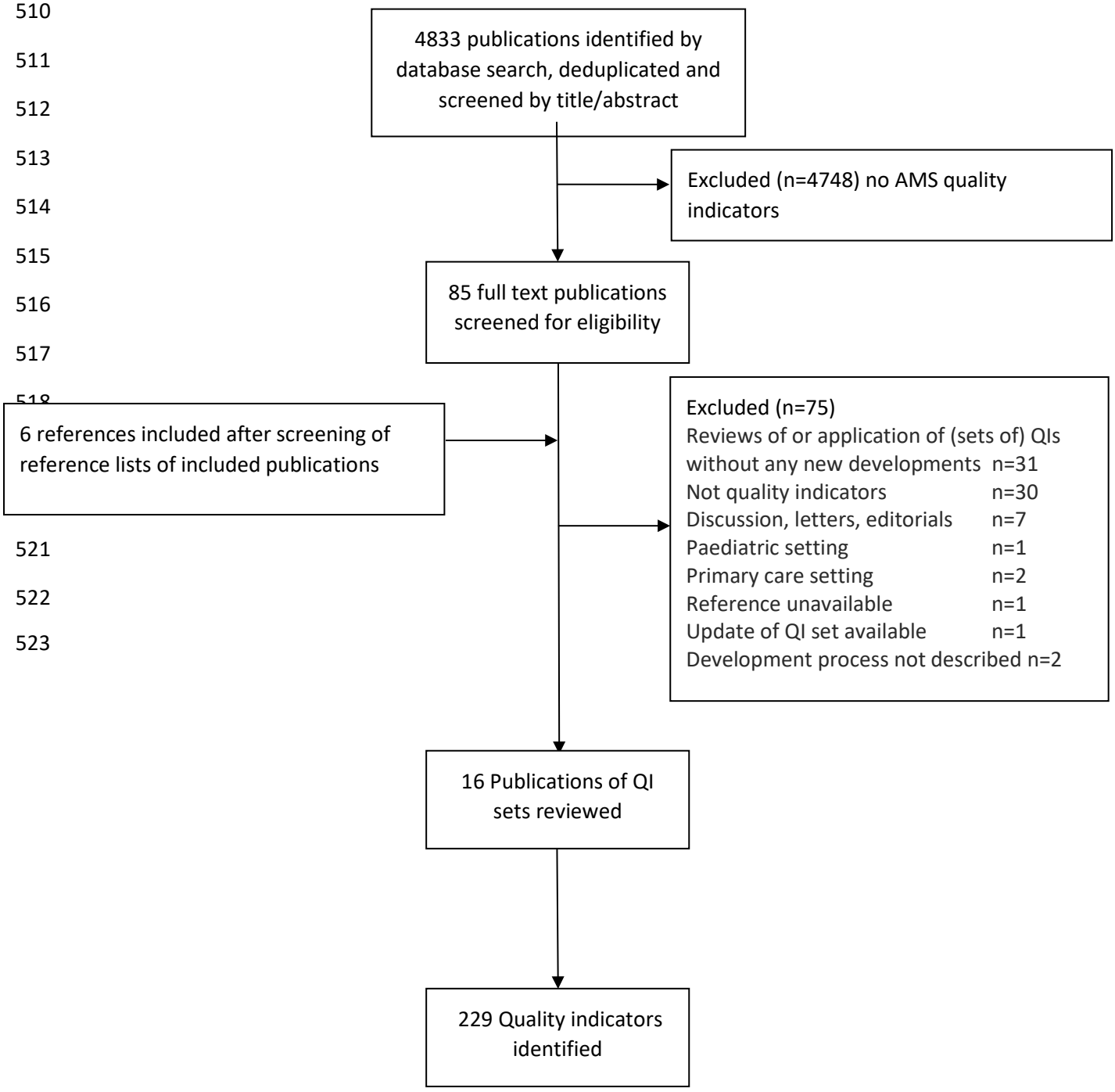
Author, year, location	Aim/focus	Study description	Stakeholder involvement	Number of AMS indicators per type
Berenholtz [23] 2007, USA	Sepsis care	Interdisciplinary panel literature review and a modified Delphi procedure with a multi-disciplinary expert panel from multiple hospitals	Physicians, nurses and pharmacist with expertise in sepsis, critical care and infectious diseases (ID), and experts in developing quality measures	Process:6 Structural:0
Buyle[24] 2013, Europe	Structural indicators to evaluate AMS programmes	Literature review and consensus process with a 13-member multi-disciplinary panel from multiple (4) countries	5 ID specialists, 2 clinical microbiologists, 3 hospital pharmacists, 3 quality of health-care experts	Process:0 Structural:10
Coll[25] 2012, UK	AMS in a high dependency unit	Multi-disciplinary team agreement, reference to the evidence base, national strategy and local policy	Multi-disciplinary team	Process: 30 Structural:0
Farida[26] 2015, Indonesia	Development of QIs for the antimicrobial management of CAP	QI development based on a previous study and guideline review followed by a 2 step Delphi procedure with an 18-member national multi-disciplinary expert panel	10 internists, 3 internist-pulmonologists, 2 pharmacists, 3 clinical microbiologists	Process:6 Structural:0
Thern[27] 2014, Europe	Hospital antimicrobial prescribing quality indicators	Literature review and RAND/UCLA appropriateness consensus with a multi-disciplinary expert panel from multiple hospitals	Clinicians, hospital pharmacists, microbiologists, infection control doctors	Process:21 Structural:21
Hermanides[28] 2008, Europe	QIs for the antibiotic treatment of complicated UTIs	Evidence based guidelines used in a 3-step modified Delphi approach with a 13-member multi-disciplinary expert panel from multiple hospitals	2 Medical microbiologists, 4 ID specialists, 2 hospital pharmacists, 2 urologists, 2 nephrologists, 1 gynaecologist	Process:13 Structural:0

Kallen[29] 2018, Europe	QIs for appropriate antibiotic use in the ICU	Literature review and four round modified RAND Delphi procedure with a 15-member multi-disciplinary expert panel of Dutch experts	3 anaesthesiologists-intensivists, 3 internist-intensivists, 1 intensivist-infectious diseases physician, 3 internists-ID physicians, 2 clinical microbiologists, 3 clinical pharmacists	Process:3 Structural:1 (1 quality metric)
Monnier[30] 2018, Europe	QIs for responsible inpatient antibiotic use	Systematic literature review and a four step RAND modified Delphi method with a 25-member international multi-disciplinary expert panel	Medical community (15) public health and patients (12); antibiotic R&D (14); and payers, policymakers, governments and regulators (11).	Process:35 Structural:14 Outcome:2
Pollack[31] 2016, USA & Europe	QIs to assess and compare AMS programmes among US and EU hospitals	Literature review followed by Modified Delphi process using RAND/UCLA appropriateness method with a 20-member multi-disciplinary multinational expert panel	Clinical medicine, pharmacy, public health	Process:10 Structural:7
Schouten[32] 2005, Europe	Measurement of the quality of antibiotic use in CAP & COPD	Literature and guideline review and a four step modified Delphi procedure with 11-member medical opinion leader expert panel from multiple hospitals	Medical microbiology, ID, respiratory medicine, quality of care medicine	Process:15 Structural:0
Schouten[33] 2012, Europe	QI bundle for ICU antimicrobial use	Literature search followed by a 2 round RAND modified Delphi method with 11 member multi-disciplinary expert panel from 6 EU countries	11 member multi-disciplinary expert panel	Process: 6 Structural:0
Sneddon[34] 2012, UK	QIs to support a 50% reduction in CDI and improve prescribing practice	Development and implementation of QIs based on national CDI target reduction	Scottish Antimicrobial Prescribing Group	Process:2 Structural:0

Ten Oever[35] 2019, Europe	QIs for the management of *Staphylococcus Aureus* bacteraemia	Systematic literature review followed by a RAND modified Delphi procedure with an international expert panel of medical professionals	Medical professionals (MD)	Process:11 Structural:0
Van den Bosch[36] 2014, Europe	QIs for antimicrobial treatment in adults with sepsis	QIs from national sepsis guidelines followed by a RAND modified Delphi consensus with a 14-member multi-disciplinary expert panel from multiple hospitals	4 ID physicians, 2 medical microbiologists, 2 hospital pharmacists, 3 intensive care specialists, two haematologists, 1 general surgeon	Process:5 Structural:0
Van den Bosch[37] 2015, Europe	QIs to measure appropriate antimicrobial use in hospitalised adults	Literature review followed by a RAND modified Delphi consensus with a 17-member international multi-disciplinary expert panel	5 medical microbiologists, 4 ID specialists, 2 clinical hospital pharmacists, 2 general surgeons, 2 pulmonologists, and 2 gynaecologists	Process: 9 Structural:2
Vera[38] 2014, Europe	QIs for antimicrobial use in critically ill (ICU) patients	Selection of QIs proposed by Spanish working group of Infectious Diseases followed by validity and reliability confirmation and review of supporting evidence	Spanish working group of Infectious Diseases	Process:10 Structural:0

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Figure 1: PRISMA flow diagram of literature search



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Table 3. Quality indicators

Indicator	Source (s), Reference(s)	Description of the indicator
Structural Indicators by theme		
AMS governance, leadership and accountability	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014 Thern 2014, Monnier 2018, Pollack 2016	Establish a multi-disciplinary AMS committee that meets regularly. AMS representation and membership of the hospitals drugs and therapeutic committee. Strategic report submitted to D&T and hospital management including quantitative objectives and selected performance indicators.
AMS multi-disciplinary expertise and resources	Buyle 2013, Pollack 2016 Monnier 2018 Pollack 2016 Pollack 2016	Dedicated physician and pharmacist resources to provide AMS advice (and AMS leadership). Antibiotics from the antibiotic formulary should not be out of stock at the health care facility. Salary support for dedicated time for antimicrobial stewardship activities. Information technology capability to support the needs of the AMS activities.
AMS policies and programmes to improve antimicrobial prescribing	Buyle 2013, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016 Thern 2014, Monnier 2018, Pollack 2016 Buyle 2013, Thern 2014, Pollack 2016 Thern 2014 Monnier 2018	AMS programme should be in place (including reports, objectives, performance indicators). Audit and feedback to prescribers of antimicrobial consumption and prescribing practices (including indications, surgical prophylaxis choice and duration). Restricted antimicrobials requiring approval. Regular AMS ward rounds and availability of expert consultation advice. Written recommendation for parenteral-to-oral switch antimicrobial therapy. Prophylactic antibiotics should be added to a pre-operative checklist.

	Pollack 2016	Policy that requires prescribers to document an indication in the medical record or during order entry for all antimicrobial prescriptions.
Antimicrobial guidelines	Buyle 2013, Thern 2014, Monnier 2018, Pollack 2016, Van der Bosch 2014, Van der Bosch 2015 Buyle 2013, Thern 2014 Buyle 2013, Thern 2014, Monnier 2018 Thern 2014	Antimicrobial guidelines (correspond to national guideline but should be adapted based on local resistance patterns and updated biannually). Surgical antimicrobial policy. Antimicrobial formulary. Electronically available guideline/ decision making aids.
AMS education	Buyle 2013, Thern 2014, Monnier 2018	AMS prescriber education provided.
Microbiology laboratory standards, antimicrobial resistance surveillance and feedback	Thern 2014 Thern 2014, Monnier 2018 Thern 2014, Monnier 2018, Pollack 2016	Written in-house preanalytical requirements for microbiologic samples (including rejection criteria). Use of selected antibiograms (adapted according to local guidelines). Reporting of AMR resistance rates, C.*difficile* incidence, nosocomial sepsis/bactaremia rates for clinical isolates available annually (and for specific services).
Process indicators by theme		
Infection diagnostics	Coll 2012, Thern 2014, Hermanides 2008, Kallen 2018, Monnier 2018, Schouten 2005, Schouten 2012, Van der Bosch 2014, Van der Bosch 2015, Farida 2015 Coll 2012, Monnier 2018 Monnier 2018 Monnier 2018	Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken (sputum, urine,etc). The results of bacteriological sensitivity(s) is documented. Microbiological investigations should be performed according to guidelines. Clinical and laboratory sepsis parameters should be documented in the medical records when prescribing antibiotics.
Pharmacy-supported interventions	Coll 2012, Monnier 2018 Coll 2012, Monnier 2018 Monnier 2018	Allergy status and documentation. Interaction management with concurrent medication. Contra-indications should be taken into account when prescribing antibiotics.

	Coll 2012, Kallen 2018, Monnier 2018, Ten Oever 2019, Van der Bosch 2015 Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Ten Oever 2019, Van der Bosch 2015 Thern 2014 Monnier 2018	Therapeutic drug monitoring of vancomycin and gentamicin is conducted correctly and documented. Monitoring and adjustment of antimicrobial treatment for renal impairment. Oral administration of drugs with high bioavailability. The dosage regimen of antibiotics with an increased risk of toxicity (such as vancomycin or gentamicin) should be managed according to guidelines.
Important elements of good antimicrobial prescribing practice	Coll 2012, Thern 2014, Hermanides 2008, Monnier 2018, Schouten 2005, Schouten 2012, Ten Oever 2019, Van der Bosch 2014, Van der Bosch 2015 Coll 2012, Hermanides 2008, Schouten 2012, Sneddon 2012 Farida 2015, Monnier 2018, Schouten 2005, Van der Bosch 2015 Coll 2012, Monnier 2018, Schouten 2012 Coll 2012, Hermanides 2008, Monnier 2018, Schouten 2005, Schouten 2012, Van der Bosch 2014, Van der Bosch 2015 Monnier 2018, Schouten 2005, Farida 2015 Monnier 2018, Van der Bosch 2015 Coll 2012, Hermanides 2008, Monnier 2018, Schouten 2012 Monnier 2018, Van der Bosch 2015 Monnier 2018	Empiric systemic antimicrobial therapy should be compliant/prescribed according to local policy guidelines (choice, route, dosage). Documentation of an antimicrobial plan including indication for prescribing, intended duration of treatment. Prompt administration of antimicrobial within 4 hours of presentation. Antimicrobial treatment is reviewed according to clinical response and/or sensitivities. Empiric systemic antimicrobial therapy should be changed to pathogen-directed therapy if culture results become available. Prompt switching from intravenous route of administration to oral when clinically appropriate. Duration of antibiotic therapy should be compliant with guidelines. Antibiotic therapy should be discontinued based on the lack of clinical evidence of infection. Antimicrobial treatment is discontinued on completion of the documented course. Antibiotic prescriptions that deviate from guidelines should be justified.

	Van der Bosch 2015	Prescribed antibiotics should actually be administered to the patients. The maximum duration of empirical systemic antibiotic treatment should be seven days.
Specific infectious conditions/settings		
Surgical antimicrobial prophylaxis (SAP)	Thern 2014, Monnier 2018, Sneddon 2012	SAP (drug and dosage): administered according to local guidelines. SAP administered within 1 hour before incision. SAP discontinued with 1 day (24 hours).
Community acquired pneumonia	Schouten 2005, Farida 2015	Prescribe antibiotic therapy for exacerbations only when indicated. Optimal duration of antibiotic therapy from 5-7 days.
Chronic obstructive pulmonary disease	Schouten 2005	Prescribe antibiotic therapy for exacerbations only when indicated. Optimal duration of antibiotic therapy from 5-7 days.
Hospital acquired pneumonia	Thern 2014	Duration of therapy no longer than 10 days.
Urinary tract infections	Thern 2014 Hermanides 2008	Documentation of positive urine culture. Duration of pyelonephritis therapy not longer than 10 days (patients on general ward). Oral antimicrobial drugs initiated not later than day 5 (pyelonephritis, patients on normal wards only). No antimicrobials for asymptomatic, catheter-associated bacteriuria. Selective use of fluoroquinolones (only as oral or in beta-lactam allergy/anaphylaxis). Duration of treatment for at least 10 days (in accordance with national guideline). Prescription of treatment for men in accordance with national guidelines. Start iv antibiotics in pregnant women with pyelonephritis. Do not prescribe antibiotic prophylaxis to patients with a urinary catheter in place.

		Change urinary catheter within 24 hours of initiation of antibiotic treatment. Consider all diabetic patients with cystitis as having a complicated UTI and treat with empiric treatment according to national guidelines.
Blood stream infections (BSI) *Staphylococcus Aureus* BSI	Thern 2014 Ten Oever 2019	Additional monitoring-Heart ultrasound (TEE) within 10 days. Collection of follow-up blood cultures 4-7 days after collection of first positive blood culture. Follow-up blood cultures after initiation of antimicrobial therapy should be done regardless of clinical evolution. Collection of repeat blood cultures should be performed until first negative blood culture. Initial antibiotic therapy should be administered intravenously in patients with SAB. Initial therapy should be intravenous (flu)cloxacillin (or nafcillin or oxacillin) or cefazolin in the case of methicillin-susceptible strains in patients with SAB. Antibiotic therapy should be initiated within 24 h after first positive blood culture. Appropriate treatment should be adapted within the first 24 h after a methicillin susceptibility result is available, if so required. Appropriate duration of intravenous antibiotic treatment should be at least 14 days for uncomplicated SAB. Appropriate duration of intravenous antibiotic treatment should be at least 28 days for SAB complicated by metastatic abscesses or deep foci of infection. Intravenous-to-oral switch should not be performed in uncomplicated SAB after 48–72 h.

		Intravenous-to-oral switch should not be performed in complicated SAB after 48–72 h. Other management aspects: Infectious disease specialist consultation should be performed in patients with SAB. SAB should be documented in the medical discharge summary.
Multi drug resistant infection management	Thern 2014	Infection and/or colonization by multidrug- resistant (MDR) organisms explicitly listed on discharge summary.
Sepsis	Monnier 2018, Van der Bosch 2014 Berenholtz 2007	Antimicrobial therapy in adult patients with sepsis should be started intravenously. Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock. Vancomycin prescribing-% of sepsis patients with unidentified organism received vancomycin within 24 hours of identification. Median time to vancomycin following sepsis diagnosis. % of patients with sepsis and an unidentified organism who received a recommended broad spectrum antibiotic within 24 hours of sepsis diagnosis. Median time to broad spectrum antibiotic initiation following sepsis diagnosis. % of patients with sepsis who had 2 sets of blood cultures collected within 24 hours following sepsis identification. % of patients with sepsis and an organism other than MRSA or MRSE (metacillin-resistant staphylococcus epidermis) who had vancomycin discontinued within 96 hours of diagnosis.
ICU	Kallen 2018	Perform surveillance cultures if selective digestive or oropharyngeal decontamination is applied at the ICU .

	Vera 2014	Biannual face-to-face meetings between ICU and microbiology staff in which local resistance rates are discussed. **Antimicrobial use in the intensive care unit Formula**: Total number of days of use of antimicrobial agent /Total number of days of ICU patients ×100. **Non-empirical antimicrobial use Formula**: Total antimicrobials used to treat infections in a directed manner /Total of antimicrobials used to treat infections ×100. **Changes in antimicrobials used as treatment Formula:** Total number of antimicrobials changed to another antimicrobial / Total of antimicrobials used to treat infections × 100. **Days without antimicrobial use in ICU Formula:** Total number of ICU days without antimicrobials / Total number of days of ICU patients × 100. **Days free of antimicrobials in patients on antimicrobial treatment Formula**: Number of days free of antimicrobials in patients on antimicrobial treatment / Total days in ICU of patients on antimicrobial treatment × 100 . **Number of days of antimicrobials for surgical prophylaxis Formula**: Number of days of use of antimicrobials for surgical prophylaxis / Total number of patients with surgical prophylaxis treatment × 100. **Inappropriate empirical antimicrobial treatment Formula:** Total number of inappropriate empirical antimicrobials / Total number of empirical antimicrobials used to treat infections × 100. **Empirical antimicrobials changed because they are inadequate Formula:** Number of empirical

		antimicrobials changed because they are inadequate Total number of empirical antimicrobials used to treat infections × 100. **Empirical antimicrobial changed for de-escalation Formula:** Number of empirical antimicrobials changed by adjustment or de-escalation Total number of empirical antimicrobials used to treat infections × 100. **Patients with severe sepsis/septic shock treated with antimicrobials in the first three hours Formula:** Number of patients with severe sepsis/septic shock, treated with antimicrobials in the first 3 hours / Total number of patients with severe sepsis/septic shock × 100.
Outcome indicators by theme		
Clinical outcome	Monnier 2018	Clinical outcomes of patients receiving antibiotics should be monitored at the health care facility. Rates of nosocomial *Clostridioides difficile* should be monitored at the health care facility.

Table 4. Critical appraisal of the publications using the AIRE instrument

Publication	Aire Items																	
	Stakeholder involvement			Domain score	Scientific methods			Domain score	Additional evidence, formulation, usage									Domain score
	1	2	3		4	5	6		7	8	9	10	11	12	13	14	15	
Berenholtz[23] 2007	4,4	4,4	1,1	**67%**	3,2	4,4	3,3	**72%**	4,4	4,4	3,3	1,1	1,1	3,3	1,1	3,3	1,1	**44%**
Buyle[24] 2013	4,4	4,4	1,1	**67%**	2,3	4,4	2,1	**56%**	1,1	4,3	1,3	2,1	2,1	3,3	4,4	4,3	3,3	**52%**
Coll[25] 2012	3,3	3,3	1,1	**44%**	1,2	4,4	2,1	**44%**	1,1	4,4	1,1	2,1	2,1	3,2	4,4	1,1	4,4	**43%**
Farida[26] 2015	4,4	4,4	1,1	**67%**	3,3	4,4	4,4	**89%**	1,1	4,4	1,2	4,4	4,4	3,3	4,4	4,4	1,1	**65%**
Thern[27] 2014	4,3	4,3	1,1	**56%**	3,3	4,3	1,1	**50%**	1,1	4,3	1,2	3,3	3,3	1,2	4,4	4,4	1,1	**50%**
Hermanides[28] 2008	4,4	4,4	1,1	**67%**	3,2	4,4	4,4	**83%**	1,1	4,4	4,4	4,4	4,4	4,3	4,4	4,4	1,1	**76%**
Kallen[29] 2018	4,4	4,4	1,1	**67%**	4,4	4,4	1,1	**83%**	4,4	4,4	3,4	4,4	3,3	3,3	1,1	4,4	4,4	**80%**
Monnier[30] 2018	4,4	4,4	3,3	**89%**	4,4	4,4	1,1	**67%**	1,1	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**11%**

Pollack[31] 2016	4,4	4,4	1,1	**67%**	4,4	4,4	2,2	**78%**	3,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	1,1	**28%**
Schouten[32] 2005	2,2	3,3	1,1	**39%**	4,4	4,4	4,3	**94%**	2,2	4,4	4,4	4,4	4,4	4,4	4,4	4,4	1,1	**83%**
Schouten[33] 2012	2,2	1,1	1,1	**11%**	1,1	2,2	1,1	**11%**	2,2	4,4	1,1	3,3	1,1	1,1	4,4	4,3	1,1	**43%**
Sneddon[34] 2012	2,2	1,1	1,1	**11%**	1,1	1,1	1,1	**0%**	4,3	4,4	1,1	4,1	4,4	1,1	4,4	2,2	4,4	**61%**
Ten Oever[35] 2019	3,3	3,3	1,1	**44%**	4,4	4,4	4,4	**100%**	2,2	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**15%**
Van den Bosch[36] 2014	4,3	4,4	1,1	**61%**	1,1	4,3	3,3	**50%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**22%**
Van den Bosch [37] 2015	4,3	4,4	1,1	**61%**	3,4	4,4	4,4	**94%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	1,1	1,1	**22%**
Vera[38] 2014	1,1	1,1	1,1	**0%**	1,1	1,1	1,1	**0%**	4,4	4,4	1,1	1,1	1,1	1,1	1,1	3,3	3,3	**37%**