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A systematic review of the global seasonality of infections caused by Acinetobacter species in hospitalized patients

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Key Words:	Acinetobacter baumannii, Seasonality, Season, Climate, Healthcare associated infection, Epidemiology
Abstract:	Background: Acinetobacter is a leading multidrug resistant pathogen in hospitals worldwide that has been seen to exhibit periodic surges during summer months. However, winter peaks and lack of seasonality have also been noted. Objectives: To systematically collate and examine the evidence describing seasonal patterns in the incidence of Acinetobacter infection in hospitalized patients. Data sources: MEDLINE/Ovid, EMBASE, Scopus and Web of Science. Study eligibility criteria: Longitudinal observational studies investigating seasonal variation in the incidence of Acinetobacter infection. Participants: Patients receiving hospital care. Interventions: Routine hospital care. Methods: Systematic review with narrative evidence synthesis structured around clinical and methodological heterogeneity and internal validity of retrieved studies, seasonal patterns and risk factors detected, and stated hypotheses of mechanisms underlying seasonality. To examine consistency in reported seasonal patterns across different conditions, monthly incidence data were extracted, standardised, weighted and presented graphically. Results: Twenty-five studies reporting 37006 cases of Acinetobacter infection or colonization during 1954 months of follow-up were reviewed. Standardised monthly incidence data pooled across studies exhibited a global seasonal pattern with an incidence peak in summer/warmer months and a trough in winter/colder months. This seasonal pattern remained consistent under different weighting schemes accounting for study size, length of follow-up and overall quality assessment rating. Seasonality persisted in different clinical settings and for different types and sources of infection. Nine studies provided consistent evidence of temperature-associated variation in Acinetobacter incidence, while there were controversial findings regarding other environmental variables. No study detected patient-related or clinical practice-related seasonal

	variation in Acinetobacter incidence. Conclusions: Despite substantial clinical and methodological heterogeneity in retrieved studies, a consistent global seasonal pattern in Acinetobacter infection incidence was evident in this review. This merits attention when designing or evaluating infection control interventions in hospitals. Future research should focus on elucidating driving mechanisms underlying the observed seasonality.

Systematic Review

A systematic review of the global seasonality of infections caused by *Acinetobacter* species in hospitalized patients

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ABSTRACT

Background: *Acinetobacter* is a leading multidrug resistant pathogen in hospitals worldwide that has been seen to exhibit periodic surges during summer months. However, winter peaks and lack of seasonality have also been noted.

Objectives: To systematically collate and examine the evidence describing seasonal patterns in the incidence of *Acinetobacter* infection in hospitalized patients.

Data sources: MEDLINE/Ovid, EMBASE, Scopus and Web of Science.

Study eligibility criteria: Longitudinal observational studies investigating seasonal variation in the incidence of *Acinetobacter* infection.

Participants: Patients receiving hospital care.

Interventions: Routine hospital care.

Methods: Systematic review with narrative evidence synthesis structured around clinical and methodological heterogeneity and internal validity of retrieved studies, seasonal patterns and risk factors detected, and stated hypotheses of mechanisms underlying seasonality. To examine consistency in reported seasonal patterns across different conditions, monthly incidence data were extracted, standardised, weighted and presented graphically.

Results: Twenty-five studies reporting 37006 cases of *Acinetobacter* infection or colonization during 1954 months of follow-up were reviewed. Standardised monthly incidence data pooled across studies exhibited a global seasonal pattern with an incidence peak in summer/warmer months and a trough in winter/colder months. This

seasonal pattern remained consistent under different weighting schemes accounting for study size, length of follow-up and overall quality assessment rating. Seasonality persisted in different clinical settings and for different types and sources of infection. Nine studies provided consistent evidence of temperature-associated variation in *Acinetobacter* incidence, while there were controversial findings regarding other environmental variables. No study detected patient-related or clinical practice-related seasonal variation in *Acinetobacter* incidence.

Conclusions: Despite substantial clinical and methodological heterogeneity in retrieved studies, a consistent global seasonal pattern in *Acinetobacter* infection incidence was evident in this review. This merits attention when designing or evaluating infection control interventions in hospitals. Future research should focus on elucidating driving mechanisms underlying the observed seasonality.

Key words:

Acinetobacter baumannii; Seasonality; Season; Climate; Healthcare associated infection; Epidemiology.

Introduction

Acinetobacter species, particularly *Acinetobacter baumannii* is a leading multidrug resistant microorganism in hospitals worldwide causing severe nosocomial infections such as bloodstream infections and ventilator-associated pneumonia [1–3]. The abilities of the organism to survive in inanimate environments for long times, rapidly develop antibiotic resistance and spread clonally potentiate the persistence and transmission of the species in healthcare settings [3,4]. *Acinetobacter* is also one of the first nosocomial pathogens that has been reported to exhibit periodic peaks in its incidence during the summer or warmer months [5]. However, opposite seasonal occurrence with peaks during winter and lack of seasonality have also been reported [6,7]. The reasons for this variability remain poorly understood [8].

This study aims to systematically collate and evaluate the existing evidence describing seasonal patterns in the incidence of *Acinetobacter* infection in hospitalized patients. Moreover, factors found to be associated with seasonal variation and hypotheses of mechanisms underlying seasonality were recorded. Methods used to assess seasonality, internal validity and clinical heterogeneity of retrieved studies were examined.

Methods

This systematic review is PROSPERO-registered (registration number: CRD42018114547) and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9].

Search strategy

MEDLINE/Ovid, EMBASE, Scopus and Web of Science were searched up until 23 October 2018 for longitudinal observational studies investigating seasonal variation in the incidence of infections caused by *Acinetobacter* spp. in hospital settings. The search was restricted to research articles written in English and published in peer-reviewed journals. Different combinations of the keywords "*Acinetobacter*", "*Acinetobacter baumannii*", "*Acinetobacter infections*", "seasonal pattern" and "season*" were used to retrieve the articles (detailed in Supplementary Appendix A). Manual checking of reference lists and citation tracking of included papers in Scopus and Web of Science were performed.

Screening and eligibility

Duplicate records were removed using the Mendeley reference managing software. A two-step screening process for eligibility was undertaken. First, one author (AGK) excluded ineligible studies by screening titles and abstracts. Then, both authors reviewed independently the full texts of potentially eligible studies for inclusion in the review. Disagreements were resolved through discussion and consensus. Eligibility was

assessed by applying the PICOS (population, intervention, comparators/controls, outcomes and study design) question format [9], as follows:

- Population: Patients receiving hospital care.
- Intervention: Experimental studies and outbreak reports were excluded from the review because of possible interference that interventions might have on transmission dynamics of *Acinetobacter* spp in routine care settings.
- Comparators/controls: Presence of a control group was not a requirement for study inclusion.
- Outcomes: The outcome of interest was the incidence (expressed as count, proportion or rate) of hospital-acquired or community-acquired infection, at any site, that was caused by *Acinetobacter* species in hospitalized patients. Studies not distinguishing colonization from infection were included.
- Study design: Observational longitudinal studies reporting the incidence of *Acinetobacter* spp. infections, with at least 12 consecutive months of follow-up to cover all seasons, were included.

Studies that did not fulfil the eligibility criteria were excluded and reasons stated (Supplementary Appendix B).

Data extraction

Information extracted from retrieved studies included: identification data (first author, title and year of publication); study design, length of follow-up; geographical location and data source; type or specialty of patients; total number of infections;

source of infection (community- or hospital- acquired); type/site of infection; and member of the *Acinetobacter* species. Additionally, factors found to be associated with and factors found not to be associated with seasonal variation, and hypotheses on mechanisms of seasonality (argued for or against by the authors) were recorded. Where available, monthly or quarterly incidence counts, proportions or rates of *Acinetobacter* infection were extracted. Data presented in graphical format were retrieved using Plot Digitizer version 2.6.6 (http://plotdigitizer.sourceforge.net/). Data were summarized in a Google spreadsheet by one author (AGK) and crosschecked by the other author (EIK).

Evidence synthesis

Findings were summarised in a narrative synthesis structured around clinical heterogeneity, methodological characteristics and quality assessment of retrieved studies, seasonal patterns detected, risk factors and hypotheses of mechanisms underlying seasonality. To describe and assess consistency in reported seasonal patterns, monthly infection incidence data were standardised using z-scores on a study-by-study basis to bring different units of measurement into one common scale across studies. Data from studies in the southern hemisphere were adjusted by six months. The average of standardised monthly incidence data across all studies was then plotted. Different weighting schemes were used to account for length of follow-up, study size and overall quality rating. Stratified graphs of standardized data were used to examine consistency in seasonality for different types and sources of infection and between different clinical settings.

Quality appraisal

Internal validity of each study was assessed by one author (EIK) based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [10]. Appendix C details how this assessment was carried out. We also assessed methodological heterogeneity in relation to whether studies were performed with the specific objective of assessing seasonality, what their scale and coverage were, and which statistical methods were used to assess seasonality. For the latter, the statistical method was classified into one of four distinct types [11]: (a) graphical inspection of incidence data over time; (b) direct comparison of incidence between discrete calendar periods; (c) geometrical model assuming a sinusoidal cyclic pattern, and (d) generalised linear and/or time series regression model.

Results

Setting and clinical heterogeneity of retrieved studies

The search identified 294 non-duplicate publications, of which 25 met the eligibility criteria and were reviewed (Figure 1). Main characteristics of the studies are summarised in Table I. The studies were published from 1979 to 2018 and 15 (60%) appeared over the last 10 years. Most studies (n=18; 72%) were conducted in countries in the Northern Hemisphere (8 in North America, 6 in Europe and 4 in Asia), and only a quarter (n=6; 24%) were in the Southern Hemisphere (5 in Brazil and 1 in Australia). One

study was multi-national and included countries in both North and South America. Most (n=19; 76%) were performed at a single institution, while 6 (24%) were multi-centre studies. The majority of studies (n=20; 80%) were conducted hospital-wide, while a fifth of the investigations (n=5; 20%) were restricted in ICUs. There was no age restriction in 11 (44%) studies, 3 (12%) studies examined only adult patients and 11 (44%) studies did not report patient demographics.

Overall, 37006 cases of *Acinetobacter* infection during 1954 months of follow-up were reported. Colonization was not distinguished from infection in 11 (44%) reports, while 13 (52%) studies reported infection only and 1 (4%) study examined colonization only. Hospital-acquired cases were not distinguished from community-onset cases in 12 (48%) occasions, while 10 (40%) studies examined hospital-acquired cases only, 1 (4%) included community-onset cases only and 2 (8%) studies contrasted between hospital-acquired and community-onset cases. In relation to infection type, 13 studies (52%) reported all types of infections combined, while 11 (44%) studies looked at bacteraemia only and 1 (4%) investigated pneumonia only.

Methodological characteristics and quality assessment

Retrieved studies were case-series (16/25; 64%) or cohort studies (9/25; 36%) that examined longitudinally the incidence of *Acinetobacter* infection based on routine clinical cultures. Most studies collected data retrospectively (n=15; 60%). There were 15 (60%) studies performed with the specific objective of assessing seasonality and the remaining 10 studies (40%) assessed seasonal occurrence as a secondary objective. To

assess seasonality, the authors relied mostly on graphical inspections of disease incidence over time (n=9; 36%) or direct comparison of incidence data between discrete calendar periods (n=11; 44%). One study used a geometrical model and 4 (16%) studies utilized a generalised linear model. Using the Quality Assessment Tool for Observational Studies, the average quality score of included studies was 79% (SD 13.8%; range 45%-100%) and only 4 studies (16%) obtained a rating below 70% (Table C2, supplementary Appendix C**).**

Global seasonal patterns

Seasonal variation in *Acinetobacter* infections was reported in 18/25 (72%) studies; whereas 4 (16%) concluded absence of seasonality and 3 (12%) studies were inconclusive. Seasonality was concluded in 13 of the 15 (87%) studies that assessed it as a primary objective and in 5 of the 10 studies (50%) that looked at seasonality as a secondary objective.

All but four studies [8,12–14] reported monthly incidence data in tables and/or graphs and we extracted 27 series of monthly incidence data from 21/25 (84%) studies (Table II). Extracted monthly incidence of *Acinetobacter* infections peaked in the summer in 12/21 (57.1%) studies, spring in 2/21 (9.5%) studies, autumn in 2/21 (9.5%) studies, and in the winter in 1/21 (4.8%) study. Differential seasonal variation was noted in 4/21 (19%) studies in relation to source of infection (summer peak for community-onset infections vs. winter peak for hospital-acquired infections) [15], antimicrobial resistance (summer peak for non-MDR isolates vs. winter peak for MDR) [7], clinical

setting (summer peak in wards vs. autumn peak in ICUs) [16], or location (winter peak in Latin America vs autumn peak in Canada and USA) [17].

When monthly incidence data were standardised and pooled across studies, a clear seasonal pattern in *Acinetobacter* incidence with a peak in summer/warmer months and a trough in winter/colder months was evident. This remained consistent under different weights to account for length of follow-up, number of infections and quality rating of the studies (Figure 2, panel a). The same seasonal pattern persisted when we examined pooled standardised data in relation to seasonality objective (primary v. secondary), clinical setting (hospital-wide v. ICU), continent where the studies were performed, infection origin (hospital-acquired v. community-onset), infection type (any infection v. bacteraemia only), infection status (colonization or infection v. infection only), and *Acinetobacter* group (Figure 2, panels b-h).

Factors associated with seasonal variation

Ten (40%) studies examined the relation to weather parameters (ambient temperature, relative humidity and precipitation or rainfall) [7,8,12,13,15,18–22]. Three of these additionally looked at or controlled for patient-related risk factors and/or clinical practice indicators [12,21,22]. To this end, most studies (7/10; 70%) relied on multivariable generalized linear models (Poisson [8,13,19,20], negative binomial [22] or logistic [12,21] regression), while the remaining 3 studies used bivariate correlation coefficients [7,15,18].

All nine studies that examined ambient temperature found a positive association with *Acinetobacter* incidence [7,8,12,13,15,19–22]. Of note, one study was conducted exclusively in ICUs [22] and another found that temperature-associated variation in *Acinetobacter* infections persisted in the subgroup of patients admitted to ICUs [21], which were units with climate control. In contrast, of the 5 studies examining relative humidity, 4 did not find an association with *Acinetobacter* incidence [8,13,19,21] and 1 noted a negative association [12]. Results were more variable regarding precipitation, which was examined in 3 studies and was seen to exhibit negative [8], positive [18] or no correlation [19] with *Acinetobacter* incidence.

All three studies that examined patient-related and/or clinical practice-related risk factors noted lack of association with *Acinetobacter* incidence. Factors studied were patient age and sex [12], ICU admission [12,21], Charslon comorbidity index [21], length of stay or time at risk [12,22], device utilization indices [22], size and type of ICU or hospital [22], and number of pathogens isolated in the previous month [22]. In addition, *Acinetobacter* occurrence was measured as an incidence density rate in 4 studies, using patient-days [22–24] or device-days [25] in the denominator thereby controlling for fluctuations in admissions, length of stay and intensity of device use. Moreover, one study examined the molecular heterogeneity of isolates and established that the seasonal increase in *A. baumannii* was not due to clonal dissemination of a single strain [26].

Hypotheses of underlying mechanisms

Reviewed studies considered several explanatory hypotheses of mechanisms underlying the seasonality of *Acinetobacter* infections. Several authors raised the possibility of community-associated origins related to increased bacterial growth [15,19,27] and/or survival in environmental reservoirs [8,12,13,21] outside the hospital setting in higher temperatures. These, in turn, was hypothesized to lead to increased colonization of humans and increased inflow of *Acinetobacter* carried by patients and healthcare workers into hospitals during warmer months [8,12,13,19].

The possibility that higher temperatures may modulate the virulence of *Acinetobacter* via regulating the lipid A moiety of lipopolysaccharide in its outer membrane, thereby contributing to increases in infection occurrence in warmer periods, was also considered [19]. Others suggested that increased ambient temperature may promote a biofilm "bloom" of *Acinetobacter* species in hospital tap water which, similarly to *Pseudomonas aeruginosa*, may be related to increased isolation from standing tap water in patient rooms and higher fecal carriage of healthy adults during the summer months [20,25]. Another suggestion was that the photoperiod (dark-light cycles) and not temperature per se might contribute to seasonality because host susceptibility may depend on the photoperiod and mediated by the length of daily melatonin pulse and a range of other physiologic parameters [22].

Stated hypotheses also acknowledged a potential role of non-weather-related seasonal factors including understaffing due to summer vacations that may lead to higher workload and/or lower adherence to infection control measures [8,27], intern

inexperience with infection control methods and obtaining clinical cultures at different frequencies in summer [19].

Discussion

Our evidence synthesis suggests that the incidence of *Acinetobacter* infection in hospitalised patients is characterised by a global seasonal pattern with a peak in summer/warmer months and a trough in winter/colder months. In our descriptive graphical assessment, the seasonal pattern remained robust when we gave more weight to studies with greater follow-up times (as repetition over several years is more likely to reflect true seasonality), those with larger effective sample size (which avoid potential masking of temporal patterns because of recording few infections) or those with higher quality ratings. Moreover, the same seasonal pattern was seen irrespective of whether the studies addressed seasonality as primary or secondary objective, whether infection onset was hospital-associated or community-associated, whether the investigation was performed in ICUs or hospital-wide, whether reporting was restricted to infections or included colonizations, and whether studies reported *A. baumannii* or other members of the species. Therefore, the phenomenon of seasonality in the occurrence of *Acinetobacter* infection in hospitalized patients appears to be a robust finding that merits attention when designing or evaluating strategies for infection prevention and control in hospitals.

This global seasonal pattern does not seem to relate simply to seasonal variation in admission times or hospital crowding or susceptibility of the patient population, and our results show that the mechanisms underlying seasonality remain largely obscure. We identified consistent evidence of temperature-associated variation in *Acinetobacter* incidence in all studies that examined this possibility by incorporating measurements of ambient temperature in their analysis [7,8,12,13,15,19–22]; whereas we noted inconsistent findings regarding other weather parameters. Consequently, temperature-driven considerations pointing mostly to community-associated origins of the seasonal surges in *Acinetobacter* infections within hospitals were most dominant in forming hypotheses on mechanisms for seasonality in reviewed studies.

The most common causal hypothesis proposed that higher temperature promotes bacterial growth, environmental reservoirs, virulence and/or biofilm formation in *Acinetobacter* outside healthcare settings, which somehow increase the inflow of carriers into hospitals. This hypothesis is supported by increasing evidence that traits such as antibiotic resistance, biofilm formation and twitching motility can be thermoregulated in *Acinetobacter* [28,29]. The organism also adapts rapidly to temperature shift (from room temperature to 37ºC) and to availability of nutrients (from starvation to food availability), conditions easily found in new patients [30]. The community-associated (rather than healthcare-associated) origins of the increased incidence of *Acinetobacter* during summer or warmer months is supported by our finding of a persisting seasonal pattern when we looked at data from studies performed solely in ICUs, where climate conditions are largely artificial and stable. An investigation

in 73 German ICUs revealed temperature-associated variation in *Acinetobacter* incidence despite that 83% of the units were air-conditioned during the entire study period [22]. The hypothesis of community-associated origins may be supported further by observations of polyclonal increase in *Acinetobacter* in summer/warmer months; however, we identified only one study that provided relevant evidence by examining the molecular heterogeneity of the isolates [26].

On the other hand, strictly community origins of incidence peaks in *Acinetobacter* infections are difficult to justify in light of our findings. We were able to extract 27 series of monthly data from reviewed studies, which produced a similar seasonal pattern irrespective of whether the origin of infections was associated with the community (n=3), the hospital (n=11) or a mixture of the two (n=13). Moreover, *Acinetobacter* is characterised by multidrug resistance, which is highly clonal in nature and a proxy of nosocomial origin. Only two studies attempted to examine seasonal variation in relation to the antimicrobial susceptibility of *Acinetobacter* isolates and produced conflicting results. In a single-centre study in the USA, significantly more non-MDR *A. baumannii* cases were identified in warm months than in cold months, but a similar pattern was not observed for MDR cases [7]. In contrast, a single-centre in Brazil noted a stronger association of temperature with imipenem-resistant than with imipenem-susceptible strains of *A. baumannii* [8]. The possibility of differential variation depending on antimicrobial susceptibility should be addressed in future studies. Future research should also consider competing explanations based on non-weather-related seasonal factors such as understaffing associated with summer vacations, changes in

adherence to isolation precautions, or obtaining clinical cultures at different frequencies in summer. Empirical evidence for such associations is limited but appears to suggest that understaffing and bed occupancy rates correlate with the spread of hospital-acquired infections [31]. Therefore, different mechanisms might explain the seasonal flow of *Acinetobacter* inside and outside the hospital and future explanatory studies should emphasize on clearly distinguishing between hospital-acquired and community-acquired cases.

We did not identify different seasonality between studies that included all types of infections combined and those that included *Acinetobacter* bacteraemia only. However, the current literature has not examined other infection types and we cannot exclude the possibility that seasonal variation might depend on the site of infection. It is not unreasonable, for example, to expect that pneumonias might peak during the colder months. Similarly, we did not identify differences between studies that examined colonization in conjunction with infection and those that examined infection only. However, only one study assessed colonization only and we cannot exclude the possibility of a difference in seasonal variation between *Acinetobacter* infections and colonizations. This would provide further insight into potential mechanisms underlying seasonality [32]. A time lag between seasonal peaks in colonization compared to infection would support the role of seasonal factors on *Acinetobacter* transmission and colonization. Seasonality in infection but not colonization would indicate that seasonal factors somehow affect host susceptibility to progression from colonization to infection [32]. These scenarios require validation in future studies.

In common with other reviews of the seasonality of infectious diseases [11,32,33], we identified that the bulk of the literature on the topic lacks robust statistical methodology. Graphical inspection or direct numerical comparison of *Acinetobacter* incidence over discrete calendar seasons were dominant approaches in assessing seasonality. However, aggregation of cases by calendar season may result in loss of information if infection occurrences have other periodicity (e.g. biannual) [11,33]. Direct comparison between discrete time intervals is limited by the inability to compare more than two intervals at once [11]. The geometrical model is outperformed by Poisson regression when estimating the magnitude of seasonal variation [34]. Therefore, time-series regression models should be preferred when studying the seasonality of infectious diseases [11,33]. However, appropriate regression modelling was utilized in only 4 (16%) of reviewed studies and this should be kept in mind when interpreting results from individual studies.

The potential for publication bias should be considered because 40% of the reviewed studies were not performed with the primary objective of assessing seasonality. We should thus assess the possibility of a bias towards reporting results whenever seasonality was observed and not reporting them when no such seasonal variation was seen [32]. Our findings oppose this possibility because seasonality was reported in the great majority (13/15; 87%) of studies that assessed it as a primary objective, compared with half (5/10; 50%) of those that included seasonality as a non-specific objective. Moreover, the seasonal pattern in *Acinetobacter* incidence remained consistent when we examined pooled standardised data in relation to seasonality

objective (primary v. secondary) and persisted under different data weights accounting for study size and overall quality rating.

Individual studies reported *Acinetobacter* incidence with different metrics and we utilized z-scores to standardize the data across studies. This enabled us to examine consistency or robustness of the same seasonal pattern under different conditions by graphically comparing standardized data pooled across distinct subgroups. However, standardization masks the amplitude between the peak and the trough in disease incidence. Moreover, we did not attempt to estimate the magnitude or intensity of the seasonal effect that may vary substantially in different settings. Therefore, our analysis supports global consistency in the seasonal pattern of *Acinetobacter*, not a global magnitude of the seasonal effect. Another important consideration in interpreting our findings is that most data come from North America and Europe – regions with temperate climate and similar income level and health care infrastructure. Fewer studies were from tropical or sub-tropical zones in the southern hemisphere, almost all South American studies were done in Brazil and there was no data from Africa, which is a considerable gap in available information from those regions.

Conclusions

This systematic assessment of the literature suggests that the occurrence of *Acinetobacter* infections in hospitalised patients is characterised by a robust global seasonal pattern with an incidence peak in summer/warmer months and an incidence

trough in winter/colder months. This merits attention when designing or evaluating strategies for infection prevention and control in hospitals. We hope that our evaluation of the current evidence will prompt future investigations into the seasonality of *Acinetobacter* infections to elucidate the mechanisms underlying the phenomenon.

Transparency declaration

The authors report no conflicts of interest. No external funding was received for this work.

Supplementary data

Appendix A. Search strategy

Appendix B. Excluded studies with reasons

Appendix C. Critical appraisal of the quality of reviewed studies

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Table I Characteristics of studies included in the review

Study	Location	Data source	Design*	Data Collection	Duration (mm/yyyy)	Follow-up (months)	No. of cases**	Seasonality objective	Method	Quality rating (%) $
Caldeira et al, 2015 [12]	Sao Paulo, Brazil	1 teaching hospital (450 beds)	Case-series	Retr.	01/2005 - 12/2010	72	177	Primary	Comp.	82
Christie et al, 1995 [26]	Connecticut , USA	1 tertiary-care hospital (770 beds)	Case-series	Pros.	01/1990 - 12/1992	36	320	Primary	Comp.	82
da Silveira et al, 2018 [8]	Sao Paulo, Brazil	1 teaching hospital (335 beds)	Case-series	Retr.	01/2006 - 12/2017	144	1207	Primary	GLM/TS	91
Davis et al, 2014 [18]	Darwin , Australia	1 tertiary referral hospital (350 beds)	Case-series	Pros.	01/1997 - 12/2012	192	41	Secondary	Gmodel	82
Eber et al, 2011 [19]	All USA	The Surveillance Network, 132 hospitals	Cohort	Pros.	01/1999 - 09/2006	93	7618	Primary	GLM/TS	100
Fillaux et al, 2006 [27]	Toulouse, France	1 university hospital (1000 beds)	Case-series	Retr.	01/2000 - 12/2003	48	791	Secondary	Comp.	73
Fortaleza et al, 2014 [13]	Sao Paulo, Brazil	1 teaching hospital (450 beds)	Case-series	Retr.	01/2005 - 12/2010	72	177	Primary	GLM/TS	91
Fukuta et al, 2012 [7]	Pittsburg, USA	1 university hospital	Case-series	Retr.	05/2000 - 04/2011	132	1476	Primary	Comp.	73
Gales et al, 2001 [17]	Canada, USA, Argentina, Chile, Colombia, Mexico, Brazil, Venezuela	46 sentinel hospitals (28 in the USA, 8 in Canada, 10 in Latin America)	Case-series	Pros.	01/1997 - 12/1999	36	261	Primary	Graph	73
Gerner-Smidt, 1987 [35]	Odense, Denmark	1 ICU (12 beds)	Cohort	Retr.	01/1984 - 12/1985	24	111	Secondary	Comp.	73
Iqbal Hossain et al, 1998 [36]	Dhaka, Bangladesh	International Centre for Diarrhoeal Disease Research	Cohort	Retr.	01/1994 - 12/1994	12	138	Secondary	Comp.	45
Kim et al, 2018 [15]	Gyeonggido, Korea	1 community hospital (742 beds)	Case-series	Retr.	01/2006 - 12/2015	120	3520	Primary	Comp.	82
Kolonitsiou et al, 2017 [14]	Patra, Greece	1 university hospital (770 beds)	Cohort	Retr.	01/2011 - 12/2013	36	151	Primary	Comp.	73
Lastoria et al, 2014 [23]	Sao Paulo, Brazil	1 teaching hospital (450 beds),	Cohort	Retr.	01/2005 - 12/2010	72	na	Secondary	Graph	55
McDonald et al, 1999 [25]	All USA	National Nosocomial Infections Surveillance	Cohort	Pros.	01/1987 - 12/1996	120	3447	Primary	Comp.	82

		System, ICU patients in 253 hospitals								
Morfin-Otero et al, 2013 [37]	Guadalajara, Mexico	1 tertiary care teaching hospital (1,000 beds)	Case-series	Retr.	01/1999 - 12/2011	156	3680	Secondary	Graph	73
Papadimitriou-Olivgeris et al, 2017 [24]	Patra, Greece	1 university hospital, ICU (13 beds)	Cohort	Retr.	01/2010 - 12/2015	72	129	Secondary	Graph	73
Perencevich et al, 2008 [20]	Maryland, USA	1 tertiary care hospital (669 beds)	Cohort	Pros.	01/1998 - 12/2005	96	1444	Primary	GLM/TS	100
Porter et al, 2013 [38]	Nakhon Phanom & Sa Kaeo, Thailand	20 hospitals	Case-series	Pros.	05/2005 - 12/2008	44	72	Secondary	Graph	64
Retailliau et al, 1979 [39]	All USA	National Nosocomial Infections System, 81 hospitals	Case-series	Pros.	07/1974	54	1372	Primary	Graph	91
Rodrigues et al, 2019 [21]	Sao Paulo, Brazil	1 teaching hospital (450 beds)	Case-series	Retr.	07/2012	48	116	Primary	Comp.	91
Schwab et al, 2014 [22]	All Germany	SARI Surveillance System, 73 ICUs in 41 hospitals	Cohort	Pros.	01/2001	144	3067	Primary	Comp.	100
Seifert et al, 1994 [40]	Cologne, Germany	4 ICUs in a university hospital (800 beds)	Case-series	Pros.	01/1991	12	189	Secondary	Graph	64
Siau et al, 1996 [16]	Hong-Kong	1 tertiary care hospital (1350 beds)	Case-series	Retr.	01/1990	59	7475	Primary	Graph	91
Smego, 1985 [41]	West Virginia, USA	1 university hospital (450 beds)	Case-series	Retr.	01/1979	60	27	Secondary	Graph	73

ICU, intensive care unit; Retr., retrospective; Pros., prospective; Comp., direct comparison of incidence frequencies between discrete calendar periods; Graph, graphical inspections of incidence frequency over time; Gmodel, geometrical model; GLM/TS, generalised linear model or time series regression.

* With regard to assessing seasonality, longitudinal studies with strictly-outcome based sampling (i.e. only patients infected or colonized by *Acinetobacter*) were labelled “case series”. Longitudinal studies that sampled from the pool of hospitalized patients were labelled “cohort” studies.

** Overall number of infections or colonizations recorded during the study period.

$ Based on the percentage of fulfilled applicable criteria in accordance with the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [10]

Table II Monthly incidence of *Acinetobacter* infection (27 data series) retrieved from 21 studies

Study	Incidence measure	Sub-group	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Peak Season[$]
Christie et al, 1995 [26]	Avg monthly proportion (%) of inpatients with BSI by *A. baumannii* *	-	6.5	6.5	4.7	4.7	4.7	14.6	14.6	14.6	7.7	7.7	7.7	6.5	Summer
Davis et al, 2014 [18]	Cumulative monthly count of community-onset pneumonias caused by *Acinetobacter* spp.*	-	6	3	5	3	2	2	0	0	3	4	2	11	Summer
Eber et al, 2011 [19]	Avg monthly number of BSIs by *Acinetobacter* spp.*	-	0.5	0.46	0.51	0.49	0.62	0.64	0.79	0.675	0.78	0.725	0.62	0.57	Autumn
Fillaux et al, 2006 [27]	Avg monthly proportion (%) of *A. baumannii* clinical isolates	-	10.7	7.2	5.5	4.7	6.4	6.0	8.5	11.8	11.3	10.2	9.6	8.0	Autumn
Fukuta et al, 2012 [7]	Cumulative monthly count of *Acinetobacter* spp isolates*	Not MDR MDR	32 108	26 62	30 69	36 64	39 64	47 40	97 62	121 55	100 49	63 64	47 63	54 84	Summer Winter
Gales et al, 2001 [17]	Cumulative monthly count of BSIs due to Acinetobacter spp.*	Canada & USA Latin America	12 11	11 13	1 6	8 9	5 6	12 11	15 15	8 17	11 7	20 16	9 13	13 11	Autumn Winter
Gerner-Smidt, 1987 [35]	Avg quarterly proportion (%) of *A. calcoaceticus* colonizations over all ICU admissions	-	6.4	6.4	6.4	6.2	6.2	6.2	7.0	7.0	7.0	5.4	5.4	5.4	Summer
Iqbal Hossain et al, 1998 [36]	Monthly proportion (%) of inpatients with BSI by *Acinetobacter* spp.	-	2.8	2.8	2.8	2.3	2.3	2.3	2.4	2.4	2.4	1.3	1.3	1.3	Spring
Kim et al, 2018 [15]	Avg monthly proportion of *Acinetobacter* spp. clinical isolates per 1,000 patients	COI HAI	9.9 10.7	11.2 7.9	9.1 9	11.3 8.9	10.5 8.9	11 8.4	12.2 8.7	18.1 9.2	14.6 11.1	9.9 9	10.6 8.5	7.6 12.6	Summer Winter
Lastoria et al, 2014 [23]	Avg monthly rate of BSI by *A. baumannii* per 10,000 patient-days *	-	2.40	2.61	1.44	2.19	3.24	5.08	1.79	1.92	2.40	2.03	2.60	1.75	Winter
McDonald et al, 1999 [25]	Avg monthly rate of infections per 10,000 patient-days in ICU*	*A. baumannii* *Acinetobacter spp.*	4.15 0.53	4.68 0.29	3.63 0.86	3.71 1.17	3.22 1.13	4.77 1.12	6.09 1.60	7.08 1.29	6.29 1.51	5.48 1.19	4.74 1.06	4.03 0.94	Summer Summer
Morfin-Otero et al, 2013 [37]	Avg. monthly count of *A. baumannii* clinical isolates*	-	246.3	246.3	246.3	340.7	340.7	340.7	341.3	341.3	341.3	298.3	298.3	298.3	Summer

Papadimitriou-Olivgeris et al, 2017 [24]	Avg monthly rate of BSI by *A. baumannii* per 1,000 ICU-days*	-	7.74	3.54	3.63	5.13	5.6	8.73	2.35	9.26	3.77	4.91	3.14	3.51	Summer
Perencevich et al, 2008 [20]	Cumulative monthly count of *A. baumannii* clinical isolates*	-	114	100	108	112	111	131	128	162	128	127	114	111	Summer
Porter et al, 2013 [38]	Cumulative monthly count of patients with BSI by *Acinetobacter* spp.*	HAI COI	5 0	3 1	7 3	4 4	2 0	4 8	4 5	5 3	3 4	1 0	2 1	0 3	Spring Spring
Retailliau et al, 1979 [39]	Avg. monthly count of infections by *A. calcoaceticus**	-	27.5	23.9	23.6	28.4	31.1	32.5	46.9	49.9	37.6	37.4	26.4	22.6	Summer
Rodrigues et al, 2019 [21]	Avg monthly count of hospital-acquired BSIs by *A. baumannii*	-	10.7	10.7	10.7	10.7	10.7	7.0	7.0	7.0	10.3	10.3	10.3	10.7	Summer
Schwab et al, 2014 [22]	Avg monthly rate of *A. baumannii* clinical isolates per 1,000 patient-days in ICU*	-	1.05	1.39	1.44	1.36	1.40	1.61	2.07	1.76	1.43	1.49	1.25	1.15	Summer
Seifert et al, 1994 [40]	Monthly count of ICU patients with clinical culture positive for *A. baumannii* *	-	24	14	14	11	19	22	13	16	15	16	13	12	Summer
Siau et al, 1996 [16]	Cumulative monthly count of *Acinetobacter* clinical isolates *	ICU patients Ward patients	194 518	176 491	172 567	155 594	172 614	166 657	230 810	186 792	197 757	209 745	300 685	178 519	Autumn Summer
Smego, 1985 [41]	Cumulative monthly count of patients with blood culture positive for *A. calcoaceticus* *	-	3	1	3	2	0	4	7	1	3	1	1	1	Summer

Avg, average; BSI, bloodstream infection; ICU, intensive-care unit; MDR, multi-drug resistant; COI, community onset infection; HAI, hospital-acquired infection.

* Data extracted from graph(s).

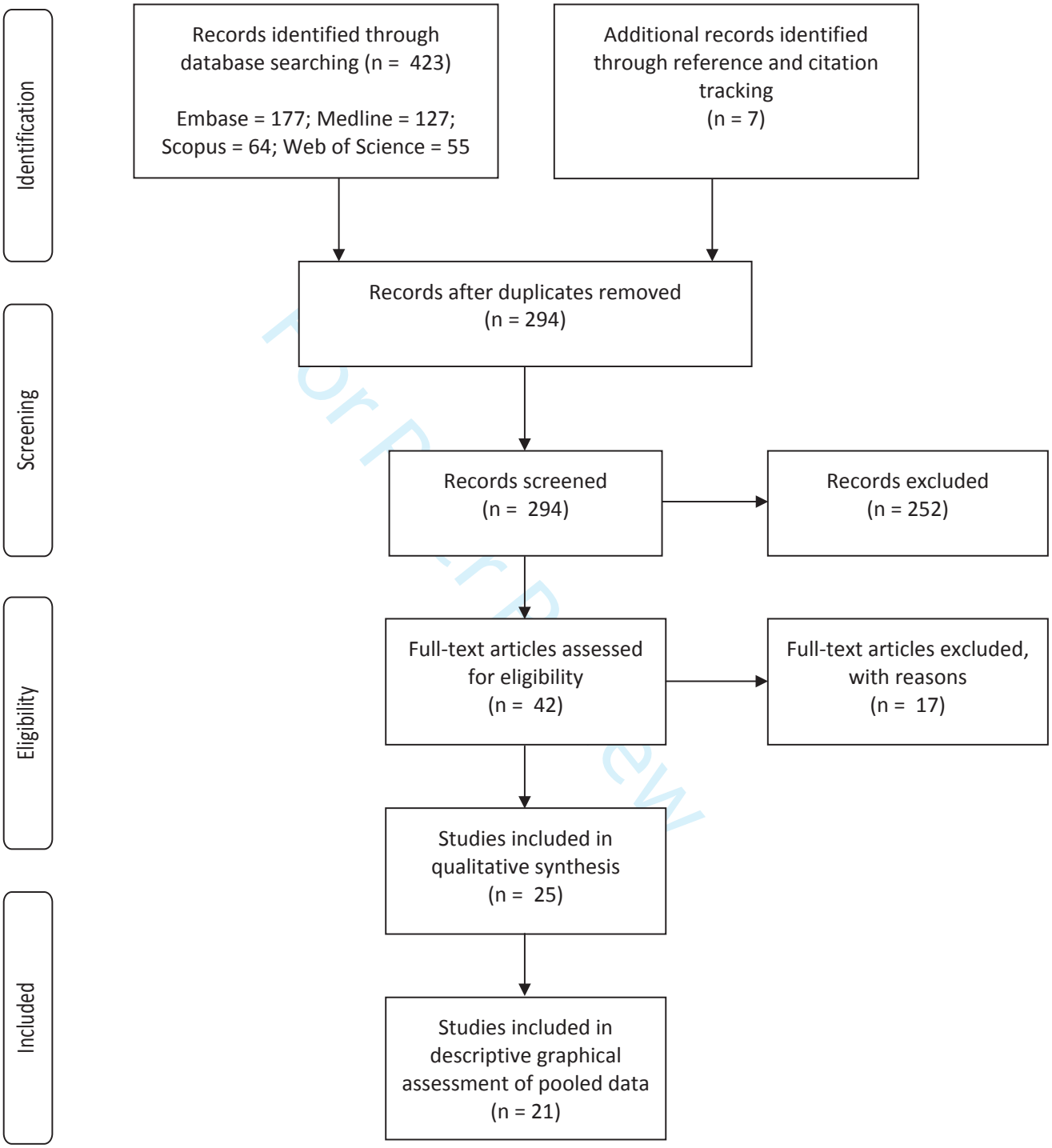
$ Peak season was defined as the season for which the sum of monthly incidence data was highest. Season are reported in accordance to hemisphere (e.g., summer is defined as June–August in the northern hemisphere and December–February in the southern hemisphere).

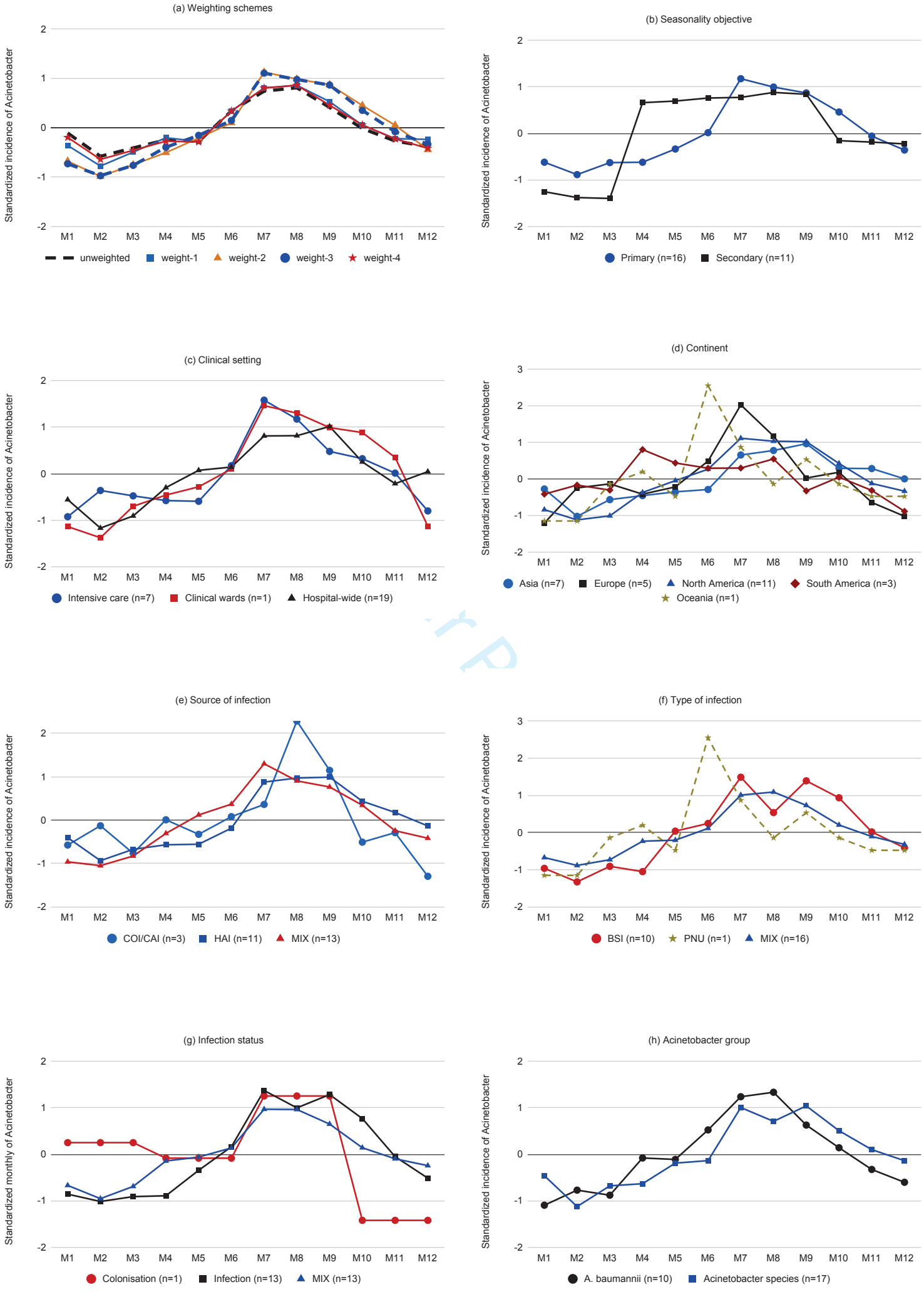
FIGURE CAPTIONS

Figure 1. PRISMA flow diagram of the literature search conducted on 23rd October 2018 to identify longitudinal epidemiological studies investigating seasonal variation in the incidence of infection caused by *Acinetobacter* species in hospitalized patients.

Figure 2. Graphical assessment of monthly incidence of *Acinetobacter* infection in hospitalized patients using 27 data series retrieved from 21 studies. Data were adjusted by six months in data series from the southern hemisphere (i.e. January = M7). Panel (a) weighting schemes were based on follow-up time (weight-1), overall number of infections (weight-2), composite product of follow-up time and number of infections (weight-3) and overall quality rating of each study (weight-4). The composite weight-3 was used in panels (b)-(h). n, number of data series; BSI, bloodstream infection; PNU, pneumonia; COI/CAI, community-onset or community-acquired infection; HAI, hospital-acquired infection; MIX, not distinguishing between different types.

Figure 1.




(a) Weighting schemes
Standardized incidence of Acinetobacter
unweighted
weight-1
weight-2
weight-3
weight-4
(b) Seasonality objective
Primary (n=16)
Secondary (n=11)
(c) Clinical setting
Intensive care (n=7)
Clinical wards (n=1)
Hospital-wide (n=19)
(d) Continent
Asia (n=7)
Europe (n=5)
North America (n=11)
South America (n=3)
Oceania (n=1)
(e) Source of infection
COI/CAI (n=3)
HAI (n=11)
MIX (n=13)
(f) Type of infection
BSI (n=10)
PNU (n=1)
MIX (n=16)
(g) Infection status
Standardized monthly of Acinetobacter
Colonisation (n=1)
Infection (n=13)
MIX (n=13)
(h) Acinetobacter group
A. baumannii (n=10)
Acinetobacter species (n=17)
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12

Supplementary Data

Appendix A. Search strategy

Database: **EMBASE**
Host: **OVID**
Data Parameters: **<1974 to 2018 October 23>**
Date Searched**: OCTOBER 23rd, 2018**
Hits: **177**

#	Searches	Results
1	season*.mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq]	193001
2	Acinetobacter baumannii.mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq]	13453
3	"Acinetobacter".mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq]	26443
4	Acinetobacter infections.mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq]	310
5	seasonal pattern.mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq]	2941
6	1 or 5 (193001)	193001
7	2 or 3 or 4	26443
8	6 and 7	**177**

Database: **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)**
Host: **OVID**
Data Parameters: **<1946 to October 23, 2018>**
Date Searched**: OCTOBER 23rd, 2018**
Hits: **127**

#	Searches	Results
1	Acinetobacter baumannii.mp. or *Acinetobacter/ or *Acinetobacter baumannii/ or *Acinetobacter Infections/	10108
2	"Acinetobacter".mp. or ACINETOBACTER BAUMANNII/ or ACINETOBACTER/ or ACINETOBACTER CALCOACETICUS/ or ACINETOBACTER INFECTIONS/	15974
3	seasons.mp. or SEASONS/	112894
4	SEASONS/ or season*.mp. (	189938
5	Seasons/ or seasonal pattern.mp.	98375
6	1 or 2	15974
7	3 or 4 or 5	189938
8	6 and 7	**127**

Database: **SCOPUS**
Data Parameters: **<from inception to October 23, 2018>**
Date Searched**: OCTOBER 23rd, 2018**
Hits: **64**

#	Searches	Results
	(TITLE-ABS-KEY((ACINETOBACTER AND BAUMANNII) OR (ACINETOBACTER) OR (ACINETOBACTER AND INFECTIONS)) OR TITLE-ABS-KEY (*ACINETOBACTER*)) AND (TITLE-ABS-KEY (SEASONS) OR (*SEASON)) AND NOT INDEX (MEDLINE) AND (LIMIT-TO (LANGUAGE,"ENGLISH")) AND (LIMIT-TO (EXACTKEYWORD,"ACINETOBACTER") OR LIMIT-TO (EXACTKEYWORD,"HUMAN") OR LIMIT-TO (EXACTKEYWORD, "HUMANS") OR LIMIT-TO (EXACTKEYWORD,"ACINETOBACTER BAUMANNII"))	**64**

Database: **WEB OF SCIENCE**
Data Parameters: **<from inception to October 23, 2018>**
Date Searched**: OCTOBER 23rd, 2018**
Hits: **55**

#	Searches	Results
1	TI=(ACINETOBACTER BAUMANNII/OR ACINETOBACTER/ OR ACINETOBACTER INFECTIONS) Timespan=All years Search language=English	14,779
2	TS=(ACINETOBACTER) Timespan=All years Search language=English	38,321
3	TI=(SEASON*/OR SEASONAL PATTERN) Timespan=All years Search language=English	193,548
4	#2 OR#1 Timespan=All years Search language=English	38,321
5	#4 AND #3 Timespan=All years Search language=English	**55**

Appendix B. Excluded studies with reasons

Study identification	Title	DOI	Reason for exclusion
Adams D et al., 2011	Investigation and management of an *A. Baumannii* outbreak in ICU	10.12968/bjon.2011.20.3.140	Outbreak report
Al Masoudi et al., 2013	Incidence and prevalence of *Acinetobacter baumannii* in king fahd general hospital, Saudi Arabia	ISSN:1097-8135	Less than 12 months follow-up
Brahmi et al., 2007	Epidemiology and risk factors for colonization and infection by *Acinetobacter baumannii* in an ICU in Tunisia, where this pathogen is endemic	10.1007/s10156-007-0557-0	Outbreak report
Chu YW et al	Skin carriage of Acinetobacters in Hong Kong	jcm.asm.org/content/37/9/2962	Not reporting the incidence of *Acinetobacter* spp. infection or colonization.
Freeman et al., 2009	Emerging evidence for seasonality of gram-negative bacterial infections	10.1086/597506	Commentary article. Not a longitudinal observational study. Not reporting the incidence of *Acinetobacter* spp. infection or colonization.
Herruzo et al., 2004	Two consecutive outbreaks of *Acinetobacter baumannii* 1-a in a burn Intensive Care Unit for adults	10.1016/j.burns.2004.01.008	Outbreak report
Hurley et al., 2016	Worldwide variation in incidence of *Acinetobacter* associated ventilator associated pneumonia: a meta-regression.	10.1186/s12879-016-1921-4	Not a longitudinal observational study. Not reporting the incidence of *Acinetobacter* spp. infection or colonization.
Mc Donald et al., 1998	Outbreak of *Acinetobacter* spp. bloodstream infections in a nursery associated with contaminated aerosols and air conditioners.	10.1097/00006454-199808000-00011	Outbreak report
Munoz-Price et al., 2008	*Acinetobacter* infection	10.1056/NEJMra070741	Literature review. Not a longitudinal observational study
Ramphal et al	*Acinetobacter calcoaceticus* variety *anitratus*: An increasing nosocomial problem.	10.1097/00000441-197901000-00007	Could not retrieve full text
Schloesser et al., 1990	An Outbreak of *Acinetobacter calcoaceticus* Infection in a Neonatal Care Unit	10.1007/BF01643394	Outbreak report
Schwab et al., 2009	Summer season in the incidence of Gram-negative bacteria in ICUs	NA	Conference abstract for which the published paper has been included in the review.
Seifert et al., 1995	Nosocomial bacteremia due to *Acinetobacter baumannii*: Clinical features, epidemiology, and predictors of mortality	10.1097/00005792-199511000-00004	Not reporting the incidence of *Acinetobacter* spp. infection or colonization.

Smith et al., 1979	Seasonal incidence of *Acinetobacter* infection	10.1093/infdis/140.2.275	Commentary. Not a longitudinal observational study.
Wisplinghoff et al., 2000	Nosocomial Bloodstream Infections Caused by *Acinetobacter* Species in United States Hospitals: Clinical Features, Molecular Epidemiology, and Antimicrobial Susceptibility	10.1086/314040	Not reporting the incidence of *Acinetobacter* spp. infection or colonization.
Yallew et al., 2016	Point prevalence of hospital-acquired infections in two teaching hospitals of Amhara region in Ethiopia	10.2147/DHPS.S107344	Not longitudinal, less than 12 months follow-up
Zhang et al., 2014	Epidemiological investigation on respiratory diseases in 1300 children, in Jinan, Shandong	cma.j.issn.0254-6450.2014.11.022	Not in English language

Appendix C. Critical appraisal of the quality of reviewed studies

Critical appraisal of study quality was based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. We utilized 11 of 14 criteria that were applicable in the context of this review as shown in Table C1. All criteria were applied in accordance with the guidelines developed by the authors of the tool with the additional considerations and/or modifications shown in Table C1. A summary of our quality appraisal of reviewed studies is presented in Table C2. To obtain a crude sense of overall study quality, we calculated the percentage of fully fulfilled criteria for each study (i.e. percentage of "yes" responses to applicable criteria).

Table C1. Criteria in the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and modifications in the current review

No.	Criterion	Modification or additional consideration
Q1.	Was the research question or objective in this paper clearly stated?	Assessed in relation to seasonality objective. Set to "Yes" only in studies that had a specific primary objective of assessing seasonal variation in the incidence of *Acinetobacter* infection.
Q2.	Was the study population clearly specified and defined?	Set to "Yes" in studies that included a clear statement or description of their target population irrespective of whether a summary presentation of patient demographics was presented or not. An example of a clear statement for the target population would be "Inpatients with a clinical culture positive for *A. baumannii* collected after day 3 of hospital admission."
Q3.	Was the participation rate of eligible persons at least 50%?	Set to "No" only when there were legitimate reasons to expect that the study methodology or implementation would lead to exclusion of a substantial proportion of eligible patients in the target population.
Q4.	Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	-

Q5.	Was a sample size justification, power description, or variance and effect estimates provided?	Set to "Yes" if any of the following applied: (a) clear justification of sample size in accordance with the tool guidelines, or (b) large effective sample size of at least 10 cases per month of follow up, or (c) reported low p-values for differences or trends (e.g. in Edward's test for seasonality).
Q6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	The exposure of interest was taken to be calendar season or any other discrete time period. The outcome of interest was the occurrence of *Acinetobacter* infection. All studies examined the association between exposure and outcome longitudinally. Therefore, Criterion **Q6 was not applicable** in this review.
Q7.	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Eligibility criteria required at least 12 months of follow-up, so that at least a single comparison between seasons could be performed. Obviously, studies with repetition over several years would be more likely to detect true seasonality. Criterion Q7 was set to "Yes" for studies having at least 2 years of follow-up (i.e. at least two repetitions).
Q8.	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	The exposure of interest was taken to be calendar season or any other discrete time period. Therefore, Criterion **Q8 was not applicable** in this review.
Q9.	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	-
Q10.	Was the exposure(s) assessed more than once over time?	Set to "No" for studies having less than 1 year of follow-up and for those that performed 2-group comparisons of incidence data (e.g. summer v. winter). It was set to "Yes" when the data were examined longitudinally for at least 2 years of follow-up and a formal assessment of seasonality was included.
Q11.	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	-
Q12.	Were the outcome assessors blinded to the exposure status of participants?	**Q12 was not applicable** in this review.
Q13.	Was loss to follow-up after baseline 20% or less?	None of the studies reported loss to follow-up. Criterion Q13 was set to "No" only when there were legitimate reasons to expect that the study methodology or implementation would lead to substantial losses to follow-up.
Q14.	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	This criterion was set to "Yes" for studies that utilised regression models to adjust for variation in climate parameters and/or other risk factors.

Table C2. Summary of the critical appraisal of the quality of reviewed studies

Study	Q1	Q2	Q3	Q4	Q5	Q7	Q9	Q10	Q11	Q13	Q14	"Y" count	"Y" percent (%)
Caldeira et al, 2015	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	9	82
Christie et al, 1995	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9	82
da Silveira et al, 2018	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10	91
Davis et al, 2014	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	9	82
Eber et al, 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
Fillaux et al, 2006	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	8	73
Fortaleza et al, 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10	91
Fukuta et al, 2012	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	8	73
Gales et al, 2001	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	8	73
Gerner-Smidt, 1987	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	8	73
Iqbal Hossain et al, 1998	N	CD	CD	Y	Y	N	Y	N	Y	Y	N	5	45
Kim et al, 2018	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9	82
Kolonitsiou et al, 2017	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	8	73
Lastoria et al, 2014	N	Y	Y	Y	N	Y	N	N	Y	Y	N	6	55
McDonald et al, 1999	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	9	82
Morfin-Otero et al, 2013	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	8	73
Papadimitriou-Olivgeris et al, 2017	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	8	73
Perencevich et al, 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
Porter et al, 2013	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	7	64
Retailliau et al, 1979	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10	91
Rodrigues et al, 2019	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	10	91
Schwab et al, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
Seifert et al, 1994	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	7	64
Siau et al, 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	10	91
Smego, 1985	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	8	73

Y, Yes; N, No; CD, cannot determine.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 (lines 72-76)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5 (lines 81-83)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6 (lines 97-118)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 (lines 85-94)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (lines 85-94) + Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6 (lines 97-118)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7 (lines 120-131) + Appendices B, C
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7 (lines 120-131) + Appendix C
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8 (lines 141-151)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7 (lines 134-145)

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7 (lines 134-145)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8 (lines 147-157)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 (lines 162-163), + Figure 1 + Appendix B
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8,9 (lines 164-182) + Table I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10 (lines 184-196) + Appendix C
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	(a) Tables I and II, Figure 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11 + Figure 2 (descriptive analysis of data pooled across subgroups)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, 10 + Appendix C, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14 – 17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19-20

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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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