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Worldwide variation in *Pseudomonas* associated ventilator associated pneumonia. A meta-regression

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ABSTRACT

Purpose: The objective here is to define the extent and possible reasons for geographic variation in *Pseudomonas aeruginosa* associated with Ventilator Associated Pneumonia (VAP).

Methods: A random effects meta-regression model of *Pseudomonas* associated VAP incidence within the published literature was undertaken incorporating group level factors such trauma admission, year of publication and use of bronchoscopic sampling towards VAP diagnosis.

Results: Pseudomonas associated VAP incidence was reported in 162 studies from seven worldwide regions published over 30 years. The highest incidence is among reports from the Middle East and Mediterranean being respectively 6.8; 5.2–9.0 (mean; 95% CI) and 6.9; 5.4–8.8 per 1000 mechanical ventilation (MV) days, versus that from North American ICU's (3.7; 2.3–5.9). In a meta-regression model, the variation in the incidence of *Pseudomonas* associated VAP was not significantly associated with bronchoscopic sampling in the diagnosis of VAP ($p = 0.12$) nor with admission to a trauma ICU ($p = 0.13$).

Conclusion: Pseudomonas associated VAP incidence among reports from six geographic regions worldwide varies by less than twofold with some decline by year of publication. Trauma ICU admission is a significant factor underlying variations in incidence of VAP overall but not *Pseudomonas* associated VAP.

1. Background

Ventilator associated pneumonia (VAP) in association with *Pseudomonas aeruginosa* occurs in intensive care units (ICU) worldwide [references in appendix]. *Pseudomonas aeruginosa* accounted for 24% of bronchoscopically documented cases of VAP in a series drawn predominantly from centres in Europe and The United States of America [1].

Pseudomonas aeruginosa has great clinical importance in part due to the potential for antimicrobial resistance issues with which it is associated. The attributable mortality in association with ventilator associated pneumonia may depend on the infecting organism [2,3]. There may be a specific mortality risk for VAP in association with *Pseudomonas aeruginosa* [4,5]. Among a large European wide study of sepsis in ICU patients, the only microorganism independently associated with increased mortality rates was *Pseudomonas* species [6].

There is a seasonal influence on hospital-acquired infections with gram-negative bacteria including *Pseudomonas aeruginosa* [7,8]. Within 132 US hospitals, blood stream infections with *Pseudomonas aeruginosa* were 28% higher in summer months compared to winter months adjusted for long-term trends [7]. That a seasonal variation exists raises the possibility that an important worldwide variation in *Pseudomonas* associated VAP may also exist as appears to be the case for *Acinetobacter* associated VAP [9].

This worldwide variation has been studied previously [10-16]. However, the degree to which any variation may be explainable by study related factors, such as the use of bronchoscopic techniques for VAP diagnosis [17], admission for trauma [18] versus other risk factors [19] is uncertain. The objective here is to define and attempt to model the extent of geographic variation within the published literature using meta-regression methods.

2. Methods

The literature search and analytic approach used here is as described previously [9,20]. In brief, an electronic search of PubMed, The Cochrane database and Google Scholar for systematic reviews containing potentially eligible studies was undertaken using the following search terms; "ventilator associated pneumonia", "mechanical ventilation", "intensive care unit" and "*Pseudomonas*." These systematic reviews were used as a starting point to find relevant original studies. The inclusion criteria were as follows; a listing of *Pseudomonas* among the VAP isolates, reporting in the English language and reports for which a VAP

Abbreviations: ICU, Intensive Care Unit; MV, Mechanical Ventilation; MVD, mechanical ventilation days; VAP, Ventilator associated pneumonia.

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incidence could be estimated using either the number of mechanical ventilation days (MVD) or the number of patients receiving prolonged mechanical ventilation as the denominator.

Randomized controlled trials designed to evaluate interventions to prevent specifically either ventilator associated pneumonia or *Pseudomonas* associated colonization were excluded. However, studies that were undertaken within the context of process improvement for the purpose of general infection prevention were retained in the model and designated ‘intervention period’ studies. Studies that were limited to restricted patient populations such as pediatric, burns or heatmo-oncology ICU's were excluded.

The *Pseudomonas* associated VAP is the number of patients with VAP having a *Pseudomonas* species isolated from respiratory sampling. Where necessary, this number was derived as the number of patients with VAP multiplied by the proportion of VAP isolates that were *Pseudomonas* species. This approximation allows for VAP patients with multiple isolates. In addition, the following group level variables were extracted where available; the overall incidence of VAP per 1000 mechanically ventilated days; whether the mode of diagnosis of VAP required bronchoscopic sampling; whether the ICU was a trauma ICU (defined as either a trauma identified subgroup or >50% of patient admissions to the ICU being for trauma); and whether the mode of reporting of *Pseudomonas* infection was specified as *Pseudomonas aeruginosa* versus more generally as *Pseudomonas species*.

The assignment of countries to near neighbour groupings was solely determined in relation to geographic proximity without regard to political, economic or other considerations.

A meta-regression model of *Pseudomonas* associated VAP was undertaken. The weight in this model is the inverse of the study variance. Because heterogeneity across estimates both within and between regions is to be expected, a random effects method was used. The following group level predictor variables were included in the regression model; the region from where the study originated; whether bronchoscopic sampling was used in the diagnosis of VAP; trauma ICU admission; and year of publication. All factors were entered into the regression models without any pre-selection step. For the purpose of the meta-regression models, the groups from multinational studies and those from studies that were ungrouped were collapsed into a single group.

2.1. Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional file.

3. Results

The search found 162 studies extracted from 138 publications published over a period spanning 3 decades [references in appendix]. Of the 138 publications found, 54 had been cited within one of nine systematic reviews identified by the search [21-29] and 84 had been sourced elsewhere (e-Fig. 1). The studies are detailed in the e-Appendix (e-Tables 1–6). The studies were classified by geographic region as detailed in Table 1. There were 20 multinational ICU surveys which were derived from ICU's that had been anonymized by originating country in these publications (e-Table 1).

The period of study ranged from 1 to 150 months. Eleven studies may have been subject to seasonal variation in *Pseudomonas* incidence as the period of study in each was <12 months. Twenty-two studies reported for trauma ICU's or trauma populations. While none of the studies were undertaken in the context of an apparent outbreak, there were eleven studies undertaken in the context of an infection control intervention with results before and after the infection control intervention.

For twelve studies, the *Pseudomonas* associated with VAP was reported as *Pseudomonas* without speciation. In all other instances, the *Pseudomonas* was reported specifically as *Pseudomonas aeruginosa*.

The individual study results for each of the seven regions are shown in e-Fig. 2 – e-Fig. 7 and all together in Fig. 1. Over all 162 groups, the summary incidence of VAP was 21.8 (19.7–24.3) per 1000 MVD (e-Fig. 8) and 17.7 (14.6–21.1) per 100 patients (e-Fig. 9). The summary *Pseudomonas* associated VAP incidence was 5.0 (4.3–5.6) per 1000 MVD (Fig. 1) and 3.93 (3.1–5.1) per 100 patients (e-Fig. 10).

The overall VAP incidence did not significantly vary across the six region categories ($p = 0.36$; Table 1). The *Pseudomonas* associated VAP incidence was highest among reports from ICU's in the Middle East and the Mediterranean (mean; 95% confidence interval; 6.9 5.2–9.0 per 1000 mechanical ventilation days and 6.8; 5.2–9.1, respectively) versus reports from Northern Europe (4.3; 3.2–5.7) and North American ICU's (3.7; 2.3–5.9) (Table 1). There was a decline in the incidence of *Pseudomonas* associated VAP incidence over the thirty years (Fig. 2).

Meta-regression models of VAP incidence overall and also *Pseudomonas* associated VAP incidence per thousand MV days are presented in Table 2. In the meta-regression model for VAP incidence overall, origin from a trauma ICU but not mode of diagnosis using bronchoscopic sampling were significant correlates (Table 2). In the meta-regression model for *Pseudomonas* associated VAP incidence, neither mode of diagnosis using bronchoscopic sampling nor origin from a trauma ICU were significant correlates (Table 2). In the regression model for *Pseudomonas* associated VAP incidence, origin from a North American ICU but no other region was a significant correlate. Origin from a study subject to an intervention period was not a significant factor in either model.

The meta-regression model for *Pseudomonas* associated VAP incidence was subjected to sensitivity tests as follows. The model was repeated excluding the eleven studies that potentially may have been subject to seasonal variation. The model was also repeated excluding those studies for which the mode of reporting of *Pseudomonas* infection was as *Pseudomonas species*. The results of these meta-regression models gave similar findings (data not shown).

4. Discussion

This is a survey of the incidence of *Pseudomonas* associated VAP among published studies using meta-analysis to model the variation in incidence worldwide. It reveals a limited degree of variation in incidence among six broad multinational regions together with the influence of a limited number of group level factors.

Of note, variation in incidence of VAP overall across six regions of this survey is >30%. Moreover, the current survey includes 99 of 101 studies that were included within a survey of *Acinetobacter* associated VAP incidence and there are several contrasting findings [9]. Within these 99 studies there is a greater than five-fold variation in *Acinetobacter* associated VAP incidence with the highest incidence occurring in studies from the Middle East. In contrast to the findings of the previous survey of *Acinetobacter* associated VAP incidence [9], the worldwide distribution of *Pseudomonas* associated VAP shows less variation between the worldwide regions.

This survey also examined a small number of factors that might be explanatory towards the variations in world-wide incidence that were found. In this regard, neither the mode of diagnosis nor admission for trauma were significant correlates in meta-regression models of *Pseudomonas* associated VAP. By contrast, trauma but not mode of diagnosis were significant correlates in meta-regression models of *Acinetobacter* associated VAP incidence [9].

Also of note here is that the size and the statistical significance of the correlates in meta-regression models of the incidence of VAP overall and the model of *Pseudomonas* associated VAP were similar.

The findings here were robust to tests of sensitivity to exclusion of studies that may have been subject to seasonal influences and studies

Table 1
Characteristics of studies[a].

	Multinational & ungrouped[b]	Europe[c]	Mediterranean[d]	Asia[e]	Middle East[f]	Central & South America[g]	USA/Canada[h]
Sources [ref]	e-Table 1 [1–5, 135–138]	e-Table 2 [6–49]	e-Table 3 [49–78]	e-Table 4 [49, 79–89]	e-Table 4 [90–101]	e-Table 5 [49, 102–110]	e-Table 5 [49, 111–134]
Number of groups	20	46	30	15	13	11	27
MV for >48 h for <75%[i]	0	1	3	0	0	1	1
Trauma ICUs[j]	1	5	7	0	2	0	7
Bronchoscopic sampling[k]	2	28	17	1	2	3	11
Intervention period[l]	1	2	2	2	1	1	2
Study publication year (range)	1987–2015	1988–2018	1987–2015	2003–2016	1990–2017	1995–2014	1986–2014
Numbers of patients per study group; median (IQR)	850; 382–2238	496; 221–1004	184; 103–322	482; 333–1076	448; 100–1716	278; 233–508	340; 223–521
Duration of MV (days); median (IQR)	7; 5–9	11; 8–13	8; 7–12	9; 6–9	9; 7–10	9; 7–11	6; 5–10
VAP incidence;							
Per 1000 MV days							
Mean[m]	25.0	18.4	25.5	21.3	26.2	20.2	21.9
95% CI	20.7–30.3	14.9–23.6	20–32.5	16.7–26.8	20.3–33.4	14.2–30.0	17.3–28.2
Pseudomonas aeruginosa VAP incidence[i]							
Per 1000 MV days							
Mean[n]	5.8	4.5	6.9	4.4	6.8	4.2	3.7
95% CI	4.5–7.5	3.2–5.7	5.4–8.8	2.9–6.6	5.2–9.0	2.9–5.9	2.3–5.9

[a] Abbreviations; ICU, Intensive care unit; MV; Mechanical ventilation; NA not applicable; VAP ventilator associated pneumonia; IQR, interquartile range.
[b] Ungrouped includes Australia and South Africa.
[c] Europe includes France, Germany, United Kingdom, Switzerland, Sweden, Iceland, and Poland.
[d] Mediterranean includes Spain, Italy, Greece and Tunisia.
[e] Asia includes China, India, Pakistan and Bangladesh.
[f] Middle East includes Turkey, Iraq, Lebanon and Saudi Arabia.
[g] Central & South America includes Argentina, Brazil, Chile, Colombia, Cuba and Guatemala.
[h] Northern America includes USA and Canada.
[i] Studies for which <75% of patients were reported to receive >48 h of mechanical ventilation.
[j] Trauma ICU defined as an ICU with >50% of patient admissions for trauma.
[k] Bronchoscopic versus tracheal sampling towards the diagnosis of VAP.
[l] Number of groups that were studied during an infection control intervention.
[m] Mean VAP incidence (per 1000 MV days) was not significantly different between the six geographic regions; $p = 0.42$.
[n] Mean *Pseudomonas* VAP incidence (per 1000 MV days) was significantly different between the six geographic regions; $p = 0.018$.

that had reported isolates as *Pseudomonas species* rather than *Pseudomonas aeruginosa.*

The findings here reinforce and further characterize previous observations in three multi-national surveys [13-16]. Rello et al. surveyed four sites in Paris, Barcelona, Montevideo, and Seville and likewise found less variation between the sites in *Pseudomonas* associated VAP than was the case for *Acinetobacter* associated VAP [16]. A prospective 24 month four-site survey [13] of 55 ICUs of 46 hospitals in Argentina, Brazil, Colombia, India, Mexico, Morocco, Peru, and Turkey. This anonymized survey found that there was much less variation in *Pseudomonas* associated VAP than was the case for *Acinetobacter* associated VAP. This survey found an overall rate of VAP of 24.1 per 1000 MV days with *Pseudomonas* species accounting for between 13 and 53% of VAP isolates among the eight anonymized countries [13].

Kollef et al. prospectively surveyed *P. aeruginosa* ventilator-associated pneumonia among 1873 mechanically ventilated patients in 56 ICU's from 11 countries in the following four-regions; Europe, United States, Latin America and the Asia-pacific region [15]. This survey

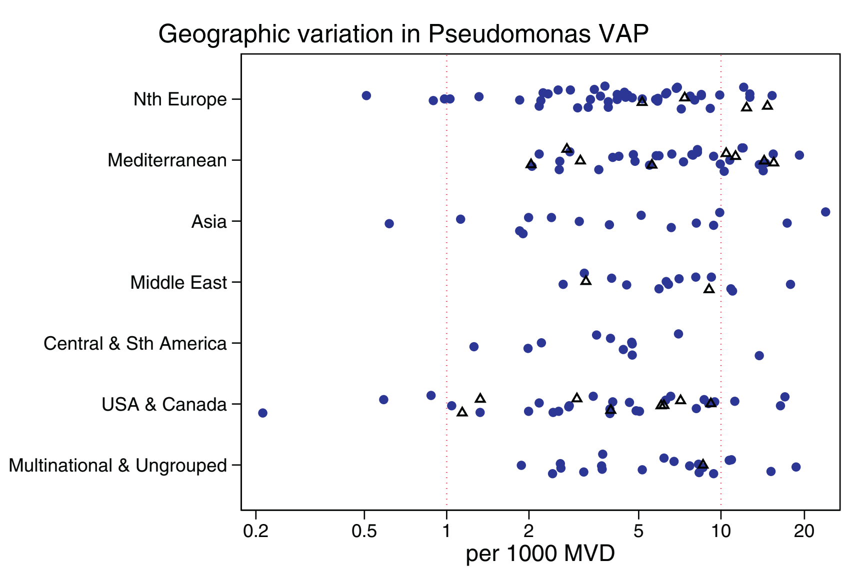

Fig. 1. A scatter plot of *Pseudomonas* VAP incidence (per 1000 MV days) among published studies in seven geographic regions with rates for studies reporting from trauma ICU's (open triangles) versus other ICU's (closed symbols). Note logarithmic scale of incidence). The vertical lines are for reference at incidence rates of 1 and 10 per 1000 MV days.

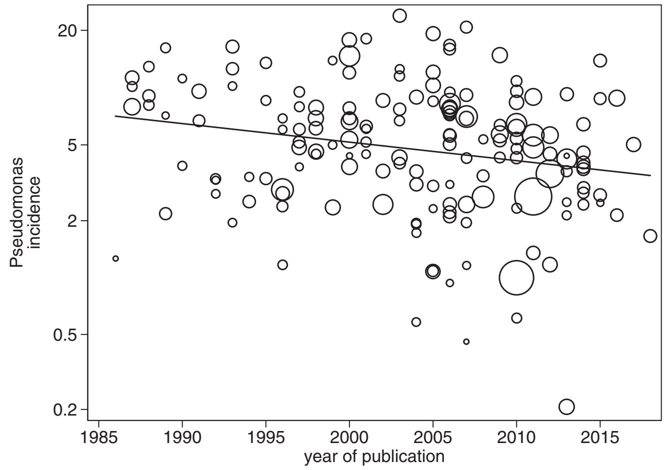

Fig. 2. A scatter plot of *Pseudomonas* VAP incidence (per 1000 MV days) versus year of study publication together with a linear regression ($p = 0.002$). The symbol size is proportional to the inverse of the study variance. Note logarithmic scale of incidence.

[15] found that there was no significant variation in incidence in *P. aeruginosa* ventilator-associated pneumonia despite there being a significant variation in incidence in incidence of ventilator-associated pneumonia overall. The incidence of VAP overall and *P. aeruginosa* ventilator-associated pneumonia among all 56 ICU's was 293/1873 (15.6%) and 76/1873 (4.1%), respectively. This compares to incidence proportions found here being 17.7 (14.6–21.1) and 3.9 (3.1–5.1) per 100 patients, respectively.

However, the extent to which any possible variation in VAP microbiology between regions is explainable by group level factors is difficult to establish in studies that are either short term or single center. Indeed, the findings here that neither bronchoscopic sampling towards VAP diagnosis nor admissions for trauma are significant group level factors towards *Pseudomonas* ventilator-associated pneumonia are in contrast to patient level findings reported from single center studies [17,18].

Seasonal variation is an important consideration in surveillance [7,8]. However, seasonal variation is unlikely to be an important factor towards explaining the variation seen worldwide. In contrast to multi-country incidence studies, which tend to be a snap shot over typically less than six months, most of the studies here extended over more than twelve months.

The advantage of a literature survey is that published data is readily available and the meta-regression methods for analysing these types of data are established. Here a random effects methods is used as previously [9]. By using these methods, the precision associated with each individual study estimate is incorporated in the derivation of both the overall summary estimate and in the derivation of the meta-regression model. Moreover, in contrast to a fixed effects model, a random effect meta-regression model will generate more conservative summary estimates (i.e. wider 95% confidence limits) as the method incorporates both within and between study variability. In this way, comparisons to address questions of study specific and contextual influences that would not be apparent within a single center study are enabled [20].

There are several limitations to this literature-based study. It is not a systematic review. The searched could have been broadened to include nosocomial pneumonia, although this would have risked the specificity of the findings for pneumonia acquired in the ICU. The analysis is limited to English language articles. This is a major limitation of any attempt to define the world-wide incidence and regional variation. The number of non-English language articles is difficult to estimate. Of interest, there are two English language articles that summarize a substantial Chinese language literature [27,28]. The incidence of overall VAP among 195 Chinese studies is 23.8 (95% CI; 20.6–27.2) per 1000 MVD. Whilst a comparable incidence density for *Pseudomonas* associated VAP was not available, *Pseudomonas aeruginosa* accounts for 19.4% of VAP isolates among 28 Chinese studies [28].

A decline in *Pseudomonas* species associated VAP over three decades is noted (Fig. 2). The clinical significance of this is unclear given the likely substantial changes in standards of care over this period.

Further limitations are that this is an analysis at the group level and is unable to take account of patient specific risk factors for *Pseudomonas* species associated VAP. This literature search specifically excluded from the analysis controlled studies designed to evaluate interventions to prevent specifically either VAP overall or *Pseudomonas* associated VAP. Whilst there is a potential for a contextual effect in the presence of such an intervention within an ICU on the incidence of VAP overall [30], the overall contextual effect of prevention interventions on Pseudomonas as a proportion of VAP isolates is unclear [30,31].

Another patient specific risk factor is the duration of mechanical ventilation for each patient and this was not able to be explored at the

Table 2
Log *Pseudomonas* incidence per thousand MV days; meta-regression models[a].

Factor[b]	Overall VAP			*Pseudomonas aeruginosa* VAP		
	Coefficient[c]	95% CI	p	Coefficient[c]	95% CI	p
Multinational & ungrouped studies (reference group)	+3.63	+3.17 − +4.11		+2.44	+1.90 − +2.98	
Geographic region						
Northern Europe	−0.30	−0.66 − +0.05	0.09	−0.21	−0.62 − +0.19	0.31
Mediterranean	−0.03	−0.41 − +0.36	0.90	+0.09	−0.35 − +0.54	0.68
Asia	−0.18	−0.61 − +0.24	0.40	−0.10	−0.58 − +0.39	0.70
Middle East	+0.04	−0.40 − +0.48	0.86	+0.21	−0.29 − +0.71	0.42
Central & South America	+0.01	−0.46 − +0.47	0.97	−0.22	−0.77 − +0.33	0.43
USA & Canada	−0.35	−0.74 − +0.04	0.08	−0.53	−0.98 − −0.08	0.02
Trauma[d]	+0.37	+0.08 − +0.66	0.014	+0.26	−0.08 − +0.61	0.13
Year of publication[e]	−0.016	−0.03 − −0.002	0.024	−0.03	−0.04 − −0.01	0.002
Mode of diagnosis[f]	−0.13	−0.35 − +0.09	0.25	−0.20	−0.46 − +0.05	0.12
Intervention period[g]	−0.36	−0.74 − +0.03	0.07	−0.33	−0.78 − +0.12	0.15

[a] This table displays the results of a meta-regression analysis for log *Pseudomonas* incidence per thousand MV days.
[b] Repeating the meta-regression analysis for log *Pseudomonas* incidence after excluding groups from studies of duration <12 months and potentially subject to seasonal influences did not change the overall findings (data not shown).
[c] The co-efficient for trauma represents the increment in log for an ICU having a majority of admissions for trauma.
[d] The co-efficient for year of publication represents the linear increment in log for each year after 1980.
[e] For sampling using bronchoscopic versus tracheal sampling.
[f] Studies undertaken during an infection control intervention.
[g] Interpretation. The reference group is the Multinational * ungrouped studies and this coefficient equals the difference in log from 0 (a log equal to 0 equates to a rate of 1. The other coefficients represent the difference in log for groups positive for that factor versus the reference group.

group level of analysis. Not all studies included here limited patient inclusion to those receiving prolonged mechanical ventilation. The median duration of mechanical ventilation before the finding of *Pseudomonas* is significantly longer than the median duration for most other isolates [32]. There was no evidence that surveys undertaken during infection control interventions gave different summary results here. However, the methodology used here is not appropriate for the evaluation of the effectiveness of infection control interventions.

As with any multi-national survey, a range of definitions exist with various key end points in the literature, for example the diagnosis of VAP. Hence, working definitions were used here to achieve standardisation among the studies included here. The working definition of trauma ICU, based on majority of admission type, may not correspond to how the units classified themselves. The classification of studies into those that did versus did not use bronchoscopic sampling towards VAP diagnosis was also a working definition. The most common mode of reporting was as *Pseudomonas aeruginosa.* Excluding studies reporting as *Pseudomonas* species did not make any difference to the findings.

The grouping of countries into near neighbour groupings is somewhat arbitrary. Country and even regional groupings could be confounded by other variables such as infection control practices, prevalence of antibiotic use and standards of care for patients receiving mechanical ventilation that have not been able to be considered in the analysis here. Indeed even the imperative to publish may differ in different countries. The influence of publication bias is difficult to estimate.

5. Conclusion

Pseudomonas associated VAP incidence among reports from six geographic regions worldwide varies by less than twofold with some decline by year of publication. Trauma ICU admission is a significant factor underlying variations in incidence of VAP overall but not *Pseudomonas* associated VAP. This variation is not explainable by variations in incidence of VAP overall. Nor is it explainable by year of publication or the use of bronchoscopic sampling towards VAP diagnosis as group level variables. Admissions for trauma is a significant factor underlying variations in incidence of VAP overall but not *Pseudomonas* associated VAP.

Ethics approval and consent to participate

Being an analysis of published work, ethics committee review of this study was not required.

Consent to publish

The author (JH) approved its submission for publication and is the guarantor for this article.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the additional file.

Competing interest

The author declares that he has no conflict of interest.

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Disclosure of potential conflicts of interest

The author declares that he has no conflict of interest.

Author contribution

The author (JH) undertook the literature search, data analysis, manuscript preparation and approved its submission for publication.

Appendix A. Supplementary data

Supplementary data, listing the study data, references and additional figures, to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.02.001.

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