The global prevalence and trend of human intestinal carriage of ESBL-producing *E. coli* in the community

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Running Title: The global faecal carriage of ESBL *E. coli* in the community

Abstract

Objectives

Intestinal colonisation by ESBL *Escherichia coli* and its association with community-acquired MDR infections is of great concern. This review determined the worldwide prevalence of human faecal ESBL *E. coli* carriage and its trend in the community over the past two decades.

Methods

A systematic literature search was conducted using PubMed, EMBASE and Google Scholar to retrieve articles published between 1st January 2000 to 13th February 2020 that contained data on the prevalence of faecal carriage of ESBL *E. coli* among healthy individuals. A cumulative (for the whole period) meta-analysis was used to estimate the global and regional pooled prevalence rates. Articles were grouped into study periods of three years and subgroup meta-analyses were undertaken to examine the global pooled prevalence over time.

Results

Sixty-two articles covering 29,872 healthy persons were included in this meta-analysis. The cumulative (2003-2018) global pooled prevalence of ESBL *E. coli* intestinal carriage in the community was 16.5% (95% CI: 14.3–18.7%, P<0.001). The pooled prevalence showed an upward trend, increasing from 2.6% (95% CI: 1.6-4.0) in 2003-2005 to 21.1% (95% CI: 15.8-27.0%) in 2015-2018. Over the whole period, the highest carriage rate was observed in South-East Asia (27%, 95% CI: 2.9–51.3%), while the lowest occurred in Europe (6.0%, 95% CI: 4.6–7.5%).

Conclusion

Globally, an eight-fold increase in the intestinal carriage of ESBL *E. coli* in the community occurred over the past two decades. Prevention of its spread may require new therapeutic and public health strategies.

Introduction

The gut microbiota is a reservoir of antimicrobial resistance genes [1]. Among Enterobacteriaceae, *Escherichia* coli is becoming a major storehouse of ESBL genes which impart resistance to a number of β-lactam antibiotics [2–4].

E. coli, a gram-negative facultative anaerobe [5,6] whose primary habitat is the distal intestines of humans and animals, [7,8] is the most common cause of urinary tract infections [9] and urosepsis in humans [10]. Acquisition of drug resistance genes by *E. coli* makes the treatment of these infections difficult. For example, ESBL-producing *E. coli* are resistant to many β-lactam antibiotics, including penicillins, aztreonam and most cephalosporins [11]. ESBL *E. coli* can emerge in the human or animal gut following the use of antibiotics [12,13]. Since *E. coli* are generally transmitted through the faecal-oral route, [14] MDR forms of ESBL *E. coli* are transmissible through contact with humans, animals or the environment, or ingestion of contaminated food or water [15–19]. In fact, 60% of community-acquired ESBL *E. coli* was attributable to human-to-human transmission, whereas food accounted for about 20% [20].

The intestinal carriage of ESBL *E. coli* is usually asymptomatic and persistent [21]. However, many studies have shown the association of the faecal carriage with ESBL *E. coli* infections [22–25]. Unlike infections with β-lactam-sensitive *E. coli*, ESBL *E. coli* infections have poor clinical outcomes. For instance, the mortality rate of ESBL *E. coli* sepsis (60%) is three times higher than for β-lactam-sensitive strains (20%) [26].

Two systematic reviews on ESBL Enterobacteriaceae in 2011 and 2016 showed a steady increase in the worldwide community prevalence [27,28]. Faecal ESBL *E. coli* carriage, in particular, has become a global pandemic which can lead to widespread infections with limited therapeutic options [28]. Understanding the current status of this MDR bacterium is critical for developing effective methods for its control, including the prevention of its transmission and decolonisation of carriers. The 2016 review [27] covered Enterobacteriaceae in general, but did not provide specific details on ESBL *E. coli*. The meta-analysis presented here highlights the global prevalence and evolution of faecal ESBL *E. coli* carriage in healthy individuals over the past two decades.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist (Table S1) [29].

Data sources and search terms

A systematic literature search was conducted in PUBMED, EMBASE and Google Scholar to retrieve relevant articles published from 1st January 2000 to 13th February 2020. We used four groups of search terms: (1) *Escherichia coli* OR *E. coli,* (2) extended spectrum β-lactamase OR ESBL, (3) faecal OR faeces OR stool OR intestinal OR gastrointestinal tract, and (4) community OR community-acquired. These groups of search terms were then connected by the Boolean operator "AND" to find papers that contain the terms anywhere in the article. The search retrieved 122, 173, and 280 articles indexed in PubMed, EMBASE and Google scholar, respectively, for further screening (Figure 1). Two authors (Y. B., W. B.) screened titles and abstracts to select studies. Another author (A. B) was involved in reaching a consensus for discrepancies.

Study selection: inclusion and exclusion criteria

Studies that reported the prevalence of ESBL *E. coli* carriage among healthy individuals of any age group were eligible. A healthy individual was defined as an asymptomatic person who lived in the community or visited a hospital only for a routine wellness check-up, antenatal care, vaccination, pre-international travel screening or for transrectal biopsy screening for prostate cancer. We excluded studies that reported faecal ESBL *E. coli* prevalence among hospital outpatients, admitted patients, residents of aged care facilities, and household contacts of colonised individuals, as well as studies that analysed non-faecal samples or involved only non-human study subjects. Our analysis included original articles written in English, and excluded reviews, retrospective and case-control studies, and conference abstracts. In addition, we only included studies that confirmed ESBL production with at least the double-disk synergy test (DDST) or PCR and excluded those studies that relied solely on antibiotic susceptibility testing. Studies that determined the faecal carriage of ESBL Enterobacteriaceae, but did not perform bacterial species identification or did not specify the total number of ESBL *E. coli* positive persons, were excluded (Figure 1).

Data extraction and quality control

The main outcome of interest was the prevalence of gastrointestinal colonisation by ESBL *E. coli* in healthy individuals. The prevalence was obtained by dividing the total number of confirmed ESBL *E. coli* positive individuals by the total number of individuals screened via stool testing. For each research article, year of study, study design, nature of study participants, method of ESBL confirmation and study location (country and WHO region[30]) were recorded and shown in a spreadsheet (Table S2). For studies that took more than a year (e.g. 2012-2013) the approximate mean (2013) was taken as the "year of study".

The methodological quality of each study was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Heart, Lung, and Blood Institute of the NIH [31] (Table S3).

Figure 1 here

Data Analysis

A random-effects meta-analysis using the DerSimonian and Laird method [32] was performed to obtain a pooled prevalence and estimate the global trend of faecal ESBL *E. coli* carriage. Subgroup meta-analyses were performed by grouping studies using the WHO regions [30] and three-year intervals of study period. The Freeman-Tukey arcsine methodology [33] was used to stabilise the variance of raw proportions, and no studies with 0% or 100% proportions were excluded [34]. The I-squared (I^2) statistic was the measure of heterogeneity, [32] and probability values less than 0.05 at 95% CI were considered significant. The presence of publication bias was assessed using Egger's regression test [35]. The meta-analysis was performed using OpenMeta (Analyst) [36]. GraphPad Prism (Version 8.0.2, San Diego, California, USA) was used to create linear regression plots and bar graphs.

Results

Study characteristics and quality assessment

Of the 575 relevant articles produced by the search, 62 were included in our meta-analysis (Figure 1). They comprised 20 prospective and 42 cross-sectional studies deemed to be of fair to good quality. The characteristics and quality assessment of the selected studies are presented in Table S2.

Prevalence of faecal ESBL *E. coli* carriage in the community

The 62 studies covered a total of 29,872 healthy individuals from the six WHO regions. This gave a global pooled prevalence of ESBL *E. coli* intestinal carriage in the community of 16.5% (95% CI: 14.3–18.7%) (Figure 2). The highest carriage rates occurred in South-East Asia (27%, 95% CI: 2.9–51.3%), followed by Western Pacific (24.5%, 95% CI: 17.6–31.4%), Africa (21.4%, 95% CI: 12.7–30.1%) and Eastern Mediterranean (20.6%, 95% CI: 10.2–30.1%). The lowest pooled prevalence was reported from European studies (6.0%, 95% CI: 4.6–7.5%) (Figure 2 and Table S2).

Looking at the country level, the highest community prevalence was reported from Tanzania (76.3%), followed by Vietnam (75.1%), Laos (70.2%), China (58.5%), Thailand (56.1%), Egypt (45.1%) and Lebanon (38.5%). Australia (with a prevalence of 1.9%) and the USA (at a carriage rate of up to 3.5%), were among countries with the lowest prevalence (Figure S1, Table S2).

Figure 2 here

Global trend in prevalence of human intestinal ESBL *E. coli* carriage

The results of subgroup meta-analyses performed by dividing the study period into three-year intervals are shown in Figure S2. The pooled prevalence increased steadily from 2.6% (95% CI: 1.6-4.0%) in 2003-2005 to 21.1% (95% CI: 15.8-27.0%) in 2015-2018, representing an average increase of 1.2% per year (Figure 3A and Figure S2). Similarly, an estimated projection from linear regression analysis revealed a 1.5% yearly increase, with an estimated global prevalence of just under 30% in 2020 (P=0.021) (Figure 3B).

Figure 3 here

Discussion

We studied the intestinal carriage of MDR ESBL *E. coli* among healthy people as it has very significant clinical and public health implications [37,38]. Healthy carriers may develop serious urinary, intraabdominal or blood-stream infections at some point in their lifetime [22]. Mortality rates following ESBL *E. coli* infections are generally high, [26] and last-resort carbapenems are the only reliable treatment options [38]. Even mild urinary tract infections have a tendency to become recurrent, leading to increased morbidity [39,40]. From a public health perspective, human-to-human transmission of ESBL *E. coli* and its extensive spread throughout the world is a great concern [37]. Clonal and plasmid-mediated spread are responsible for the increasing global incidence of MDR *E. coli*, as seen, for example, with the pandemic *E. coli* ST131 clone and the $bla_{\text{CTX-M}}$ plasmid [37,41]. Furthermore, the possible horizontal transfer of ESBL genes to other flora within the human gut is another concern [21].

Using a 15-year pooled prevalence, this study found that at least one-sixth (16.5%) of the world's population is colonised by ESBL *E. coli*. Subgroup meta-analysis by every three years of study period showed an increasing trend with a much higher carriage rate in recent years. For example, the pooled prevalence for the period 2015-2018 was 21.1% (95% CI: 15.8-27.0%). This is almost a three-fold increase when compared to the pooled prevalence of 10 years earlier (7.8% (95% CI: 2.2-13.3%) in 2006-2008), and an eight-fold increase from 2003-2005 (2.6% (95% CI: 1.6-4.0%)). The global pooled prevalence in our study is higher than that reported by Karanika *et al.,* who found a 14% global pooled prevalence for the intestinal carriage of ESBL Enterobacteriaceae (*E. coli*, *K. pneumonia*, etc.) among healthy people [27]. However, Karanika *et al.* considered studies conducted between 1978 and 2015, missing 2015-2018 which, as our analysis showed, was a period of further increase in prevalence. A study by Woerther *et al.* also showed an increasing trend of ESBL Enterobacteriaceae between 2002 and 2011 in each of the six WHO regions [30].

By WHO region, [30] the pooled prevalence was highest in South-East Asia whereas Europe and the Americas had the lowest carriage. These relative estimates concurred with the ones presented by Karanika *et al.,* who showed the highest prevalence rate in South-East Asia (46%, 95% CI: 29–63%) and the lowest prevalence rates in the Americas (North (2%, 95% CI: 0-5%) and South (3%, 95% CI: 0-7%)) and Europe (central (3%, 95% CI: 1-5%), northern (4%, 95% CI: 2-6%), southern (6%, 95% CI: 1-12%)) [27]. Differences in the regional carriage rates compared with our study are most likely due to variation in the study periods and methods (inclusion and exclusion criteria). For instance, our study determined carriage rates specific for ESBL *E. coli* and we included only those confirmed by at least DDST or PCR.

There could be several explanations for the successful worldwide spread of ESBL *E. coli*. The first, and most likely, is a high transmission rate as seen in the rates of ESBL *E. coli* colonisation among travellers. A Swiss study recruited 170 Swiss travellers to South Asia (India, Bhutan, Nepal, and Sri Lanka) who initially had negative ESBL *E. coli* upon pre-travel stool screening. Surprisingly, on return, 118/170 (70%) of these travellers were found to have been colonised with ESBL *E. coli* (86% among travellers to India) [42]. A Danish study also reported a more than 90% colonisation rate among travellers to India [43]. Second, the faecal titre of ESBL *E. coli* was high among colonised humans (10^2-10^8 colony-forming unit (cfu)/gram of stool) [44] and animals (10^3-10^7 cfu/gram of stool) [45,46]. This high faecal ESBL *E. coli* titre among carriers could relate to the documented high rate of human-to-human transmission related with poor post-toilet hygiene. Hence, effective feco-oral transmission seems the main driving factor for the increasing worldwide prevalence.

Our findings suggest that the presence of MDR gram-negative ESBL *E. coli* is dramatically increasing outside the hospital setting. This is concerning, given the risk of persistent intestinal carriage,[21] as well as the possible horizontal transfer of ESBL genes to other flora within the human gut [47–49]. In addition, because ESBL *E. coli* are resistant to most of the available

antibiotics, our findings signal that the world could be heading to the worst phase of a "post-antibiotic era", where common infections that used to be easily treated will no longer respond to currently existing medications. Since *E. coli* is a common cause of urinary tract infections, sepsis and neonatal meningitis, increasing prevalence of ESBL *E. coli* has significant clinical implications, with an anticipated increase in morbidity and mortality. With antimicrobial resistance projected to become the number one killer of humans by 2050,[50] ESBL *E. coli* could become one of the main culprits. The WHO's global antimicrobial resistance surveillance system (GLASS) has already been monitoring the resistance profile of *E. coli* from blood and urine samples obtained during routine clinical care since 2015 [51]. However, since ESBL *E. coli* is no longer restricted to the hospital setting, and given the high community carriage shown by our results, we believe control strategies by WHO and other organisations would be better informed by including monitoring of faecal carriage of ESBL *E. coli* among healthy individuals.

A strength of this review is in following a strict inclusion criterion on the method of ESBL *E. coli* detection. In addition, we used subgroup meta-analysis to show the temporal pattern. It is important to note, however, that the study also had several limitations. First, it determined the pooled prevalence in each WHO region, [30] that may lead to an over- or underestimation of the prevalence for certain member countries and the findings need careful interpretation. For example, a 9.9% pooled prevalence in the Americas was mainly contributed by the high carriage rate in the South Americas, not the USA. Second, there was a limited number of studies in certain locations, such as Africa, South−East Asia, North America, and Australia. This might have overestimated or underestimated the prevalence in these areas. Third, the review only considered articles published in English, and relevant data published in other languages may have been missed. Finally, the varying time periods of studies from different WHO regions [30] might have under- or overestimated the regional cumulative prevalence and the global trend.

Conclusion

The intestinal carriage of MDR ESBL *E. coli* showed a high and increasing prevalence among healthy individuals worldwide. Based on the findings, we recommend that the WHO and other institutions should consider a community stool ESBL *E. coli* surveillance scheme and implement preventive measures to address its community spread.

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Transparency declarations

None to declare.

Data sharing

All data is available in the manuscript or the supplementary materials.

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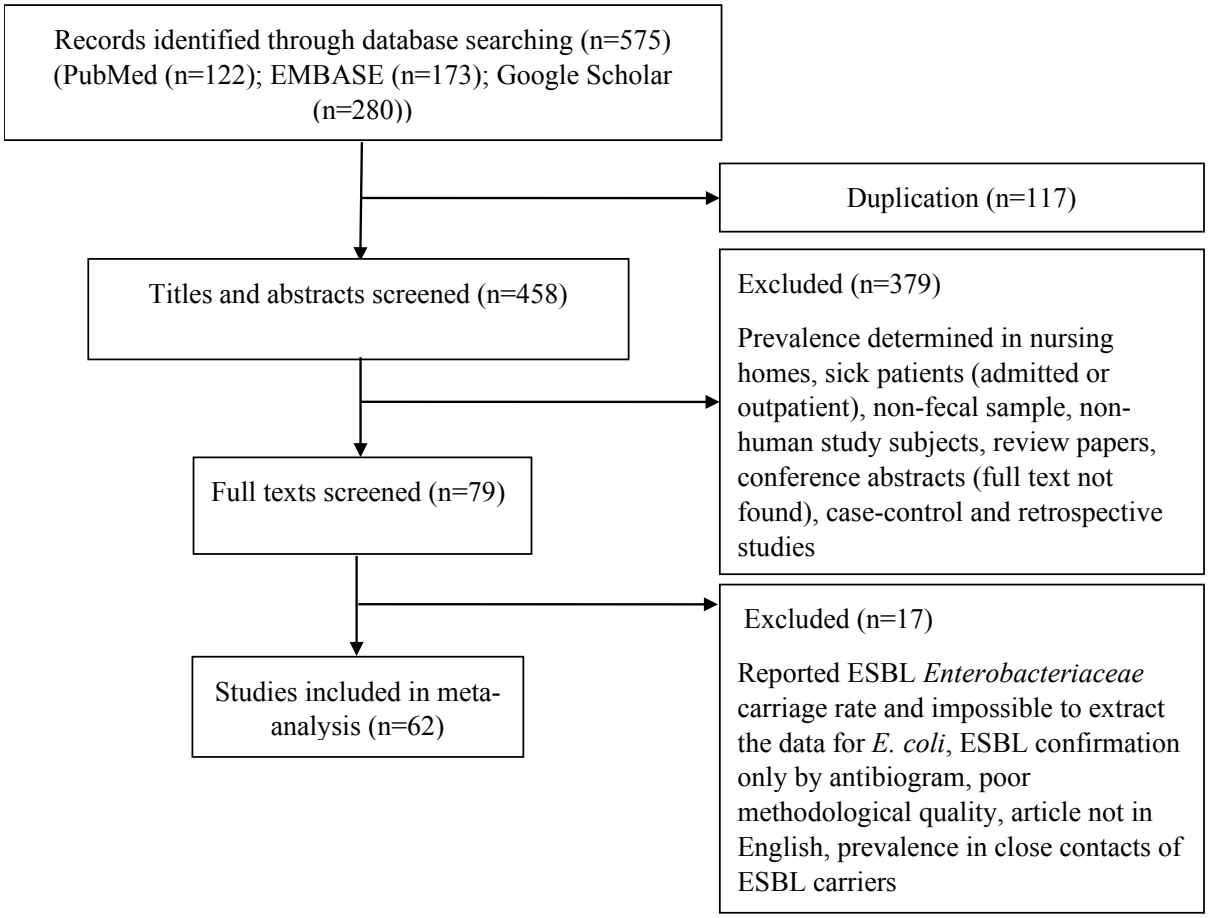

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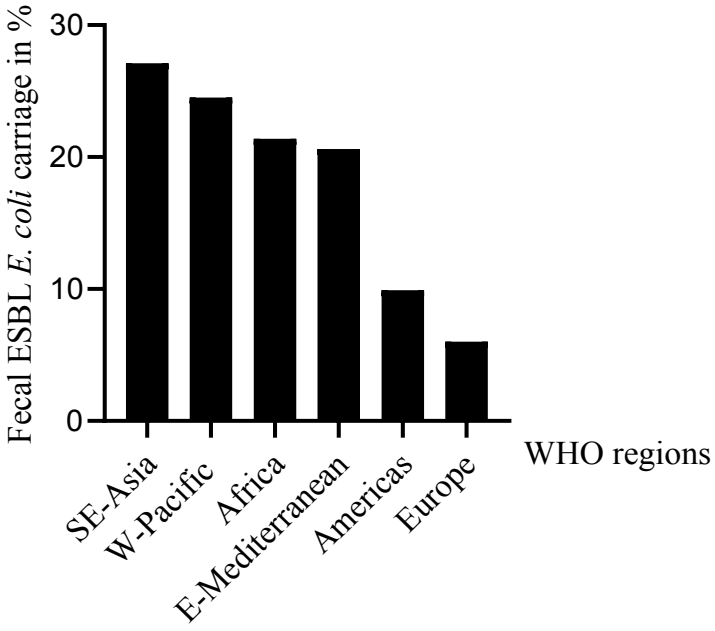
552 Figure 1: Flow chart showing selection of articles for meta-analysis.



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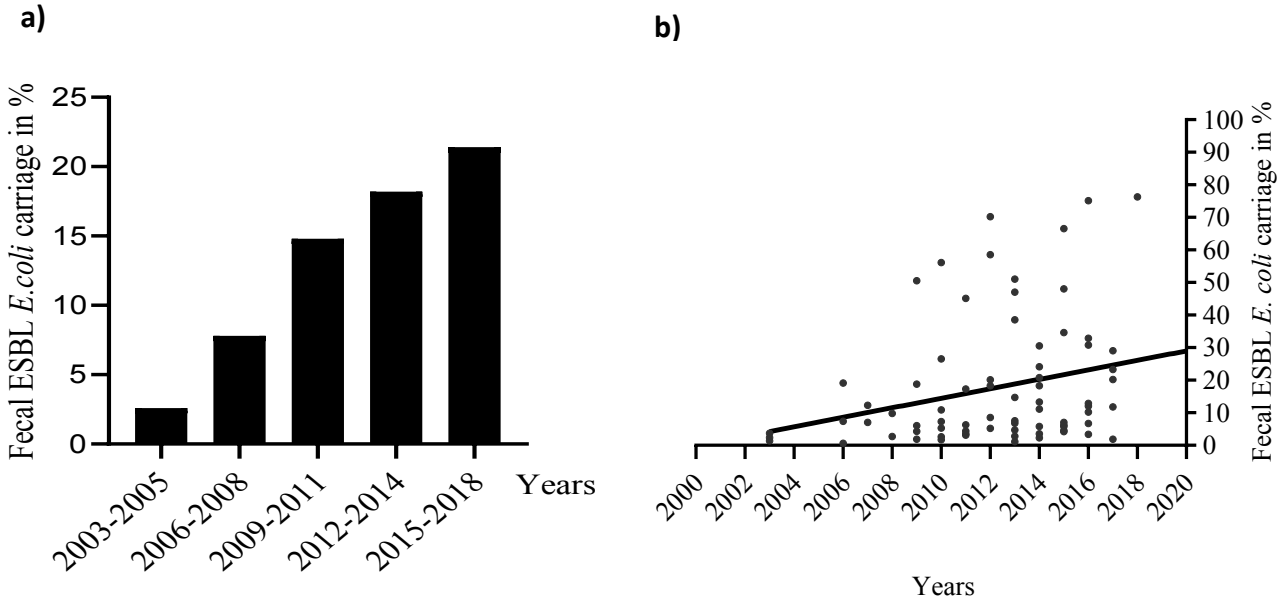
554 Figure 2: Pooled prevalence of intestinal ESBL *E. coli* carriage among healthy individuals in
555 six WHO regions [30]. E-Mediterranean: Eastern Mediterranean; SE-Asia: South-East Asia; W-
556 Pacific: Western pacific region.



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558 Figure 3: Global trend in faecal ESBL *E. coli* carriage among healthy individuals. (**a**) Pooled
559 prevalence showing a clear increase from one three-year interval to another. (**b**) A simple linear
560 regression plot depicting the trend of carriage (1.5% rise per year, P=0.021).

561 **Annexes**

562 **Figure S1:**Forest plot showing subgroup meta-analysis of studies stratified by the six WHO
563 regions[30]. Abbreviations: *E. coli, Escherichia coli*; ES, effect size; ESBL, extended spectrum
564 B-lactamase.

565 **Figure S2:** Forest plot showing subgroup meta-analysis of studies stratified by three-year
566 interval of study period. Abbreviations: *E. coli, Escherichia coli*; ES, effect size; ESBL,
567 extended spectrum B-lactamase.

568 **Table S1:** PRISMA Checklist

569 **Table S2:** Summary table of the 62 articles that contain data on the prevalence of faecal
570 ESBL *E. coli* carriage among healthy persons worldwide, 2000-2020.

571 **Table S3:** Quality assessment criteria for the eligible studies

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Studies	Estimate	(95% C.I.)		ESBL-E/Total
Moubareck *et al.,* 2005 (Lebanon)[52]	0.024	(0.008,	0.039)	9/382
Kader and Kamath, 2009 (Saudi Arabia)[53]	0.123	(0.094,	0.151)	62/505
Rahman and El−Sherif, 2011 (Egypt)[54]	0.451	(0.412,	0.490)	285/632
Barguigua *et al.,* 2015 (Morocco)[55]	0.011	(−0.010,	0.032)	1/93
Hijazi *et al.,* 2016 (Lebanon)[56]	0.385	(0.296,	0.473)	45/117
Elkersh *et al.,* 2015(Saudi Arabia)[57]	0.147	(0.090,	0.203)	22/150
Sana *et al.,* 2016 (Tunisia)[58]	0.067	(0.019,	0.114)	7/105
Hashemizadeh *et al.,* 2018 (Iran)[59]	0.480	(0.382,	0.578)	48/100
Subgroup Eastern Mediterranean (I^2=98.77 %, P=0.000)	**0.206**	**(0.102,**	**0.310)**	**479/2084**
Valverde *et al.,* 2004 (Spain)[60]	0.037	(0.001,	0.073)	4/108
Guibout *et al.,* 2008 (France)[61]	0.006	(−0.002,	0.015)	2/322
Guimaraes*et al.,* 2009 (Portugal)[62]	0.027	(−0.003,	0.057)	3/112
Tigen *et al.,* 2014 (Turkey)[63]	0.188	(0.149,	0.226)	75/400
Janvier *et al.,* 2011 (France)[64]	0.043	(0.025,	0.061)	22/512
Kaarme *et al.,* 2013 (Sweden)[65]	0.026	(0.008,	0.043)	8/313
Valenza *et al.,* 2013 (Germany)[66]	0.063	(0.055,	0.071)	211/3344
Chanoine *et al.,* 2012 (France)[67]	0.061	(0.036,	0.086)	21/345
Meyer *et al.,* 2012 (Germany)[68]	0.035	(0.011,	0.058)	8/231
Kuenzli *et al.,* 2014 (Switzerland)[42]	0.028	(0.004,	0.052)	5/179
Ny *et al.,* 2016 (Sweden)[2]	0.047	(0.038,	0.056)	101/2134
Lubbert *et al.,* 2015 (Germany)[69]	0.068	(0.034,	0.103)	14/205
Ebrahimi *et al.,* 2016 (Hungary)[70]	0.023	(0.013,	0.034)	18/779
Bunt *et al.,* 2019 (Netherlands)[71]	0.042	(0.036,	0.048)	174/4177
Ulstad *et al.,* 2016 (Norway)[72]	0.045	(0.022,	0.069)	14/308
Ramila *et al.,* 2018 (Spain)[73]	0.070	(0.052,	0.087)	57/815
Kaarme *et al.,* 2018 (Sweden)[74]	0.129	(0.093,	0.165)	43/334
Dall *et al.,* 2019 (Denmark)[43]	0.120	(0.030,	0.210)	6/50
Ruh *et al.,* 2019 (Cyprus)[75]	0.202	(0.167,	0.237)	101/500
Subgroup Europe (I^2=93.71 %, P=0.000)	**0.060**	**(0.046,**	**0.075)**	**887/15168**
Mathai *et al.,* 2014 (India)[76]	0.191	(0.119,	0.263)	22/115
Luvsansharav *et al.,* 2012 (Thailand)[77]	0.561	(0.514,	0.609)	234/417
Babu *et al.,* 2016 (India)[78]	0.265	(0.212,	0.319)	69/260
Maharjan *et al.,* 2018 (Nepal)[79]	0.067	(0.045,	0.088)	34/510
Subgroup South−East Asia (I^2=99.16 %, P=0.000)	**0.271**	**(0.029,**	**0.513)**	**359/1302**
Tian *et al.,* 2008 (China)[80]	0.070	(0.040,	0.101)	19/270
Li *et al.,* 2011 (China)[81]	0.505	(0.411,	0.598)	55/109
Kennedy & Collignon, 2010 (Australia)[82]	0.019	(−0.007,	0.045)	2/106
Qin *et al.,* 2013 (China)[83]	0.073	(−0.007,	0.153)	3/41
Nakane *et al.,* 2016 (Japan)[84]	0.031	(0.024,	0.039)	70/2230
Atterby *et al.,* 2019 (Cambodia)[85]	0.173	(0.130,	0.215)	53/307
Zhou *et al.,* 205 (China)[86]	0.585	(0.517,	0.653)	117/200
Nakamura *et al.,* 2016 (Japan)[87]	0.085	(0.060,	0.109)	42/496
Nakayama *et al.,* 2015 (Laos)[88]	0.702	(0.583,	0.821)	40/57
Nakayama *et al.,* 2015 (Vietnam)[88]	0.470	(0.400,	0.539)	93/198
Joo *et al.,* 2018 (South Korea)[89]	0.183	(0.111,	0.256)	20/109
Sadahira *et al.,* 2017 (Japan)[90]	0.133	(0.107,	0.159)	85/640
Kamei *et al.,* 2017 (Japan)[91]	0.058	(0.035,	0.082)	22/379
Ni *et al.,* 2016 (China)[92]	0.305	(0.283,	0.327)	528/1732
Nhi *et al.,* 2018 (Vietnam)[93]	0.751	(0.713,	0.789)	374/498
Wu *et al.,* 2019 (Taiwan)[94]	0.019	(0.009,	0.029)	14/724
Mo *et al.,* 2019 (Singapore)[95]	0.233	(0.185,	0.280)	71/305
Higa *et al.,* 2018 (Japan)[96]	0.118	(0.079,	0.157)	31/263
Subgroup Western Pacific Region (I^2=99.33 %, P=0.000)	**0.245**	**(0.176,**	**0.314)**	**1639/8664**
Lonchel *et al.,* 2012 (Cameroon)[97]	0.060	(0.022,	0.098)	9/150
Mshana *et al.,* 2016 (Tanzania)[98]	0.111	(0.077,	0.144)	37/334
Ouedraogo *et al.,* 2016 (Burkina Faso)[99]	0.208	(0.129,	0.287)	21/101
Kurz *et al.,* 2017 (Rwanda)[4]	0.241	(0.197,	0.285)	87/361
Herindrainy *et al.,* 2018 (Madagascar)[100]	0.102	(0.066,	0.138)	28/275
Akinduti *et al.,* 2018 (Nigeria)[101]	0.034	(0.017,	0.052)	14/406
Mahamat *et al.,* 2019 (Chad)[102]	0.290	(0.201,	0.379)	29/100
Budel *et al.,* 2019 (Tanzania)[103]	0.763	(0.654,	0.871)	45/59
Subgroup Africa (I^2=97.33 %, P=0.000)	**0.214**	**(0.127,**	**0.301)**	**270/1786**
Woerther et al.,2013(Guyana)[104]	0.053	(0.017,	0.089)	8/151
Weisenberget al, 2012 (USA)[105]	0.017	(−0.016,	0.049)	1/60
Cortes−Cortes *et al.,* 2017 (Mexico)[106]	0.183	(0.085,	0.281)	11/60
Islam *et al.,* 2019 (USA)[107]	0.035	(0.019,	0.050)	18/519
Araque, 2018 (Venezuela)[108]	0.346	(0.241,	0.452)	27/78
Subgroup Americas (I^2=90.79 %, P=0.000)	**0.099**	**(0.041,**	**0.157)**	**65/868**
Overall (I^2=98.61 %, P=0.000)	**0.165**	**(0.143,**	**0.187)**	**3699/29872**

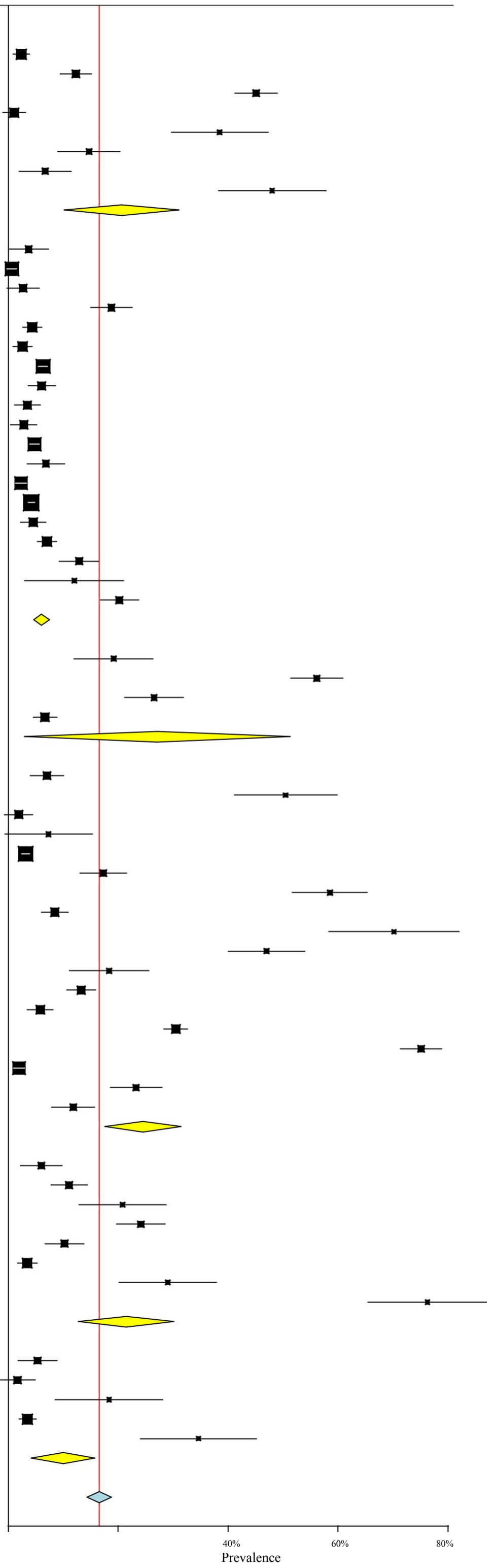

Figure S1: Forest plot showing subgroup meta-analysis of studies stratified by the six WHO regions(32). Abbreviations: *E. coli, Escherichia coli*; ES, effect size; ESBL, extended spectrum B-lactamase; ESBL-E, ESBL *E. coli*.

Studies	Estimate	(95% C.I.)		ESBL E. coli + Total screened
Moubareck *et al.,* 2005 (Lebanon)	0.024	(0.008,	0.039)	9/382
Valverde *et al.,* 2004 (Spain)	0.037	(0.001,	0.073)	4/108
Subgroup 2003−2005 (I^2=0 %, P=0.495)	**0.026**	**(0.012,**	**0.040)**	**13/490**
Guibout *et al.,* 2008 (France)	0.006	(−0.002,	0.015)	2/322
Mathai *et al.,* 2014 (India)	0.191	(0.119,	0.263)	22/115
Kader and Kamath, 2009 (Saudi Arabia)	0.123	(0.094,	0.151)	62/505
Tian *et al.,* 2008 (China)	0.070	(0.040,	0.101)	19/270
Guimaraes *et al.,* 2009 (Portugal)	0.027	(−0.003,	0.057)	3/112
Subgroup 2006−2008 (I^2=95.64 %, P=0.000)	**0.078**	**(0.022,**	**0.133)**	**108/1324**
Lonchel *et al.,* 2012 (Cameroon)	0.060	(0.022,	0.098)	9/150
Tigen *et al.,* 2014 (Turkey)	0.188	(0.149,	0.226)	75/400
Janvier *et al.,* 2011 (France)	0.043	(0.025,	0.061)	22/512
Li *et al.,* 2011 (China)	0.505	(0.411,	0.598)	55/109
Kennedy & Collignon, 2010 (Australia)	0.019	(−0.007,	0.045)	2/106
Woerther et al.,2013(Guyana)	0.053	(0.017,	0.089)	8/151
Weisenberget al, 2012 (USA)	0.017	(−0.016,	0.049)	1/60
Kaarme *et al.,* 2013 (Sweden)	0.026	(0.008,	0.043)	8/313
Luvsansharav *et al.,* 2012 (Thailand)	0.561	(0.514,	0.609)	234/417
Babu *et al.,* 2016 (India)	0.265	(0.212,	0.319)	69/260
Qin *et al.,* 2013 (China)	0.073	(−0.007,	0.153)	3/41
Rahman and El−Sherif, 2011 (Egypt)	0.451	(0.412,	0.490)	285/632
Valenza *et al.,* 2013 (Germany)	0.063	(0.055,	0.071)	211/3344
Chanoine *et al.,* 2012 (France)	0.061	(0.036,	0.086)	21/345
Meyer *et al.,* 2012 (Germany)	0.035	(0.011,	0.058)	8/231
Nakane *et al.,* 2016 (Japan)	0.031	(0.024,	0.039)	70/2230
Atterby *et al.,* 2019 (Cambodia)	0.173	(0.130,	0.215)	53/307
Subgroup 2009−2011 (I^2=98.58 %, P=0.000)	**0.148**	**(0.106,**	**0.190)**	**1134/9608**
Cortes−Cortes *et al.,* 2017 (Mexico)	0.183	(0.085,	0.281)	11/60
Zhou *et al.,* 205 (China)	0.585	(0.517,	0.653)	117/200
Nakamura *et al.,* 2016 (Japan)	0.085	(0.060,	0.109)	42/496
Nakayama *et al.,* 2015 (Laos)	0.702	(0.583,	0.821)	40/57
Barguigua *et al.,* 2015 (Morocco)	0.011	(−0.010,	0.032)	1/93
Hijazi *et al.,* 2016 (Lebanon)	0.385	(0.296,	0.473)	45/117
Elkersh *et al.,* 2015(Saudi Arabia)	0.147	(0.090,	0.203)	22/150
Sana *et al.,* 2016 (Tunisia)	0.067	(0.019,	0.114)	7/105
Kuenzli *et al.,* 2014 (Switzerland)	0.028	(0.004,	0.052)	5/179
Ny *et al.,* 2016 (Sweden)	0.047	(0.038,	0.056)	101/2134
Lubbert *et al.,* 2015 (Germany)	0.068	(0.034,	0.103)	14/205
Nakayama *et al.,* 2015 (Vietnam)	0.470	(0.400,	0.539)	93/198
Mshana *et al.,* 2016 (Tanzania)	0.111	(0.077,	0.144)	37/334
Ouedraogo *et al.,* 2016 (Burkina Faso)	0.208	(0.129,	0.287)	21/101
Kurz *et al.,* 2017 (Rwanda)	0.241	(0.197,	0.285)	87/361
Islam *et al.,* 2019 (USA)	0.035	(0.019,	0.050)	18/519
Ebrahimi *et al.,* 2016 (Hungary)	0.023	(0.013,	0.034)	18/779
Joo *et al.,* 2018 (South Korea)	0.183	(0.111,	0.256)	20/109
Sadahira *et al.,* 2017 (Japan)	0.133	(0.107,	0.159)	85/640
Kamei *et al.,* 2017 (Japan)	0.058	(0.035,	0.082)	22/379
Ni *et al.,* 2016 (China)	0.305	(0.283,	0.327)	528/1732
Subgroup 2012−2014 (I^2=98.38 %, P=0.000)	**0.182**	**(0.139,**	**0.225)**	**1334/8948**
Araque, 2018 (Venezuela)	0.346	(0.241,	0.452)	27/78
Hashemizadeh *et al.,* 2018 (Iran)	0.480	(0.382,	0.578)	48/100
Bunt *et al.,* 2019 (Netherlands)	0.042	(0.036,	0.048)	174/4177
Ulstad *et al.,* 2016 (Norway)	0.045	(0.022,	0.069)	14/308
Ramila *et al.,* 2018 (Spain)	0.070	(0.052,	0.087)	57/815
Herindrainy *et al.,* 2018 (Madagascar)	0.102	(0.066,	0.138)	28/275
Akinduti *et al.,* 2018 (Nigeria)	0.034	(0.017,	0.052)	14/406
Maharjan *et al.,* 2018 (Nepal)	0.067	(0.045,	0.088)	34/510
Kaarme *et al.,* 2018 (Sweden)	0.129	(0.093,	0.165)	43/334
Dall *et al.,* 2019 (Denmark)	0.120	(0.030,	0.210)	6/50
Nhi *et al.,* 2018 (Vietnam)	0.751	(0.713,	0.789)	374/498
Mahamat *et al.,* 2019 (Chad)	0.290	(0.201,	0.379)	29/100
Ruh *et al.,* 2019 (Cyprus)	0.202	(0.167,	0.237)	101/500
Wu *et al.,* 2019 (Taiwan)	0.019	(0.009,	0.029)	14/724
Mo *et al.,* 2019 (Singapore)	0.233	(0.185,	0.280)	71/305
Higa *et al.,* 2018 (Japan)	0.118	(0.079,	0.157)	31/263
Budel *et al.,* 2019 (Tanzania)	0.763	(0.654,	0.871)	45/59
Subgroup 2015−2018 (I^2=99.12 %, P=0.000)	**0.214**	**(0.158,**	**0.270)**	**1110/9502**
Overall (I^2=98.61 %, P=0.000)	**0.165**	**(0.143,**	**0.187)**	**3699/29872**

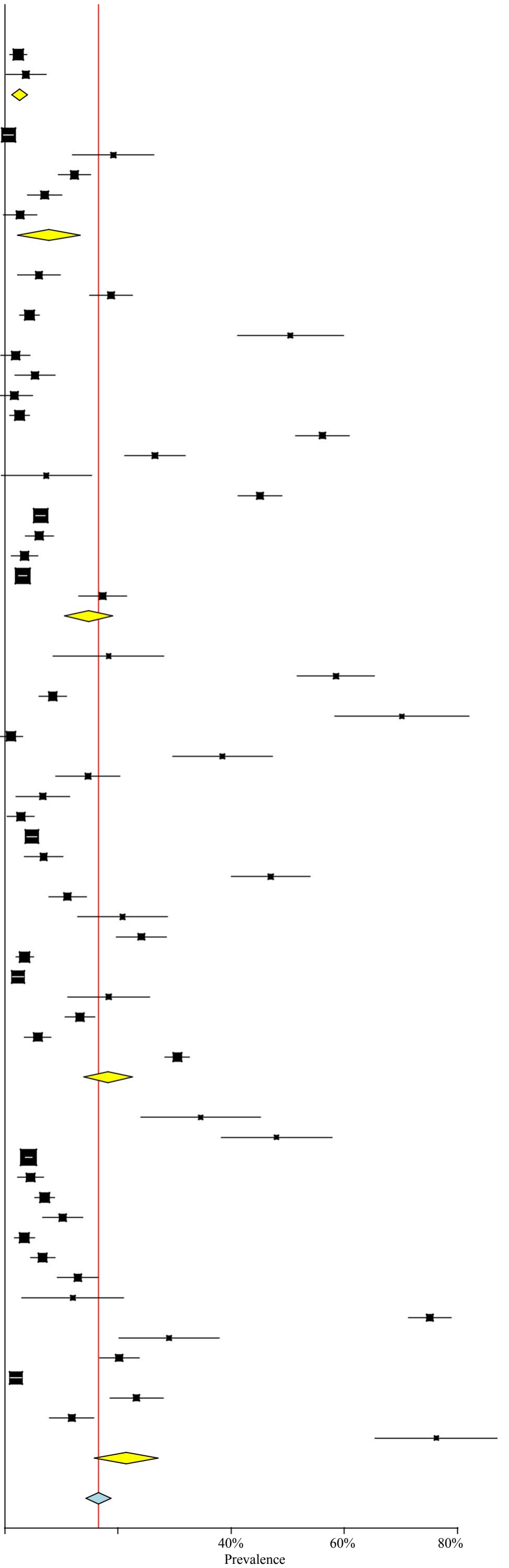

Figure S2: Forest plot showing subgroup meta-analysis of studies stratified by three-year interval of study period. Abbreviations: E. coli, Escherichia coli; ES, effect size; ESBL, extended spectrum B-lactamase.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	page 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.	pages 1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	page 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	page 3
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.	–
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.	pages 4-5
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.	pages 3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Pages 3-6
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).	page 4
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.	Pages 4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4
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.	page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	pages 5-6
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.	page 5-6

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).	pages 5-6
Section/topic	**#**	**Checklist item**	**Reported on page #**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	pages 5-6
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.	page 6, Figure 1
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.	page 6, Table S2
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).	page 6
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.	pages 6-8, Figures 2 and 3, Supplementary Figures 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-8, Supplementary Figures 1 and 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Pages 6-8, Supplementary Figures 1 and 2
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).	pages 8-12

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).	page 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	pp 11-12
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.	12

Table S1: PRISMA Checklist

WHO area	Country	Year of study	Study design	Study participants (All healthy individuals-community setting)	Total number of individuals screened (stool sample)	Number of ESBL *E. coli* positive individuals among screened	Faecal ESBL *E. coli* carriage rate in (%)	Method of ESBL detection (stool sample) Screening, confirmatory	Quality score
AFRICA	Herindrainy *et al.,* 2018 (Madagascar)	2015-2016	Prospective cohort	Healthy pregnant women	275	28	10.2%	CHROMagar ESBL (France), DDST	Good
	Mshana *et al.,* 2016 (Tanzania)	2014	Cross-sectional	Healthy community residents	334	37	11.1%	CHROMagar ESBL (France), VITEK-2 system, PCR	Good
	Oue´draogo *et al.,* 2016 (Burkina Faso)	2014	Cross-sectional	healthy volunteers	101	21	20.8%	bioMe´rieux ESBL agar plates (France), DDST, PCR	Good
	Lonchel *et al.,* 2012 (Cameroon)	2009	Cross-sectional	healthy students	150	9	6%	Drigalski and MacConkey with cefotaxime (1.5 mg/L) and ceftazidime (2 mg/L), DDST, PCR	Good
	Kurz *et al.,* 2017 (Rwanda)	2014	Prospective cohort	caregivers of patients recruited within 48 h of admission	361	87	24.1%	CHROMagar-ESBL Mast Diagnostica (Germany), ESBL-AmpC-Detection Test Mast Diagnostica	Good
	Mahamat *et al.,* 2019 (Chad)	2017	Cross-sectional	health staff and university students	100	29	29.0%	BioMérieux ESBL agar plates (	Good

								France), double-disc synergy test, PCR	
	Bu¨del *et al.,* 2019 (Tanzania)	2018	Cross-sectional	hotel employees in Zanzibar	59	45	76.3%	BioMe´rieux ChromID ESBL (France), PCR	Good
	Akinduti *et al.,* 2018 (Nigeria)	2016	Cross-sectional	community residents	406	14	3.4%	starch-iodide paperacidometric method,double disc method, PCR	Fair
AMERICAS	Woerther et al.,2013(Guyana)	2010	Cross-sectional	healthy adults	151	8	5.3%	Chemunex ESBL plates (France), DDST, PCR	Good
	Islam *et al.,* 2019 (USA)	2013-2015	Prospective cohort	Children in well-child visits	519	18	3.5%	ESBL CHROMagar plates (France), DDST	Good
	Araque, 2018 (Venezuela)	2015	Cross-sectional	healthy children	78	27	34.6%	MacConkey agar plates with cefotaxime (2 mg/L), VITEK 2 system,PCR	Good
	Weisenberg et al, 2012 (USA)	2009-2010	Prospective cohort	Healthy individuals pre-travel	60	1	1.7%	MacConkey with cefpodoxime (4ug /ml), DDST, PCR	Good
	Cort´es-Cort´es *et al.,* 2017 (Mexico)	2012	Cross-sectional	healthy volunteers (age range 15–60 years)	60	11	18%	disk containig lactamaseinhibitr +PCR	Fair
SOUTH-EASTASIA	Luvsansharav *et al.,* 2012 (Thailand)	2010	Cross-sectional	Healthy individuals in rural Thailand	417	234	56.1%	MacConkey with cefotaxime 2 mg /ml, DDST, PCR	Good
	Babu *et al.,* 2016 (India)	2011-2013	Prospective cohort	healthy individuals/health check-up	260	69	26.5%	MacConkey with 1ug/ml ceftazidime, PCR	Good
	Mathai *et al.,* 2014 (India)	2005-2007	Cross-sectional	Healthy Volunteers	115	22	19.1%	MacConkey with Ceftazidime (2ug/ul), DDST, PCR	Good
	Maharjan *et al.,* 2018 (Nepal)	2016	Cross-sectional	healthy adults (health science students)	510	34	6.7%	DDST, PCR	Good
EUROPE	Kaarme *et al.,* 2013 (Sweden)	2010	Prospective cohort	Healthy preschool children	313	8	2.6%	Luria-Bertani broth (USA) with cefpodoxime (5ug/mL), double disc approximation, PCR	Good

	Kaarme *et al.,* 2018 (Sweden)	2016	Prospective cohort	healthy preschool children	334	43	12.9%	Luria-Bertani broth (USA) with cefpodoxime (5ug/mL), double disc approximation, PCR	Good
	Kuenzli *et al.,* 2014 (Switzerland)	2012-2013	Prospective cohort	Pretravel for all age groups	179	5	2.8	BioMérieux chromID® ESBL (France), Vitek-2® system, PCR	Good
	Dall *et al.,* 2019 (Denmark)	2014-2017	Prospective cohort	Pre-travel screening for adults	50	6	12%	BioMe´rieux ChromID ESBL (France), ESBL + AmpC Screen Kit (Rosco, Denmark)	Good
	Valenza *et al.,* 2013 (Germany)	2009-2012	Prospective cohort	Healthy individuals living in the community	3344	211	6.3%	MacConkey agar with 1mg/L cefotaxime, DDST, PCR	Good
	Ruh *et al.,* 2019 (Cyprus)	2017	Cross-sectional	Healthy volunteers (health check-up)	500	101	20.2%	MacConkey agar with cefotaxime and ceftazidime 1mg/L, DDST	Good
	Ny *et al.,* 2016 (Sweden)	2012-2013	Cross-sectional	Volunteers in the community	2134	101	4.7%	CHROMoriental-agar plate supplemented with 3 mg/L cefpodoxime+ PCR	Good
	Ebrahimi *et al.,* 2016 (Hungary)	2013-2014	Cross-sectional	Healthy individuals screened for employment purposes	779	18	2.3%	EMB with 2 mg/L cefotaxime, DDST, PCR	Good
	Chanoine *et al.,* 2012 (France)	2011	Cross-sectional	healthy subjects living in the Paris area	345	21	6%	Biomerieux chromogenic ESBL agar plates (France), DDST, PCR	Good
	Guibout *et al.,* 2008 (France)	2006	Cross-sectional	healthy subjects living in the Paris area	322	2	0.6%	Drigalski agar plates with 0.5mg/L cefotaxime, PCR	Good
	Valverde *et al.,* 2004 (Spain)	2003	Cross-sectional	Healthy volunteers	108	4	3.7%	MacConkey (cefotaxime or ceftazidime 1ug/ml), DDST, PCR	Good

	Lübbert *et al.,* 2015 (Germany)	2013	Prospective cohort	Pre-travel screening for adults	205	14	6.8%	BioMérieux CHROMagarTM ESBL (Paris, France), Etest (bioMérieux, Marcy l'Etoile, France), PCR	Good
	Bunt *et al.,* 2019 (Netherlands)	2014-2016	Cross-sectional	community residents	4177	174	4.2%	MacConkey agar with 1 mg/L cefotaxime, PCR	Good
	Ulstad *et al.,* 2016 (Norway)	2014-2016	Cross-sectional	Healthy Norwegians (general practitioners)	308	14	4.5%	MacConkey agar plates with cefotaxime (1 mg/L), Total ESBL + AmpC Confirm kit (Rosco Diagnostica, Denmark), PCR	Good
	Tigen *et al.,* 2014 (Turkey)	2008-2010	prospective cohort	Men with undergoing transrectal biopsy of prostate (all had sterile urine)	400	75	19%	MacConkey with 1 mg/mL cefotaxime or 1mg/mL ceftazidime, Modified combined disk method, PCR	Good
	Meyer *et al.,* 2012 (Germany)	2011	Cross-sectional	healthy volunteers (physicians and nurses)	231	8	3.5%	ChromID ESBL screening, VITEK 2 system.	Good
	Guimara˜es *et al.,* 2009 (Portugal)	2007-2008	Cross-sectional	healthy children	112	3	2.7%	Levine agar plates with 2mg/L cefotaxime, DDST, PCR	Good
	Rámila *et al.,* 2018 (Spain)	2014-2015	Cross-sectional	Pregnant women at time of delivery	815	57	7%	combination disk test on Mueller Hinton with and without 250 mg/L cloxacillin, PCR	Fair
	Janvier *et al.,* 2011 (France)	2009	prospective cohort	Asymptomatic soldiers	512	22	4.3%	DDST, PCR	Good
Eastern Mediterranean	Rahman and El-Sherif, 2011 (Egypt)	2010-2011	Cross-sectional	Asymptomatic individuals attending check-up clinic	632	285	45.1%	MacConkey with 1ug/ml of cefotaxime, DDST	Good

	Hashemizadeh *et al.,* 2018 (Iran)	2014-2015	Cross-sectional	Health volunteers	100	48	48%	DDST, PCR	Good
	BARGUIGUA *et al.,* 2015 (Morocco)	2013	Cross-sectional	healthy humans in community	93	1	1.1%	MacConkey (cefotaxime or ceftazidime 1mg/L), DDST	Good
	Kader and Kamath, 2009 (Saudi Arabia)	2006-2007	Cross-sectional	healthy individuals attending pre-employment check up	505	62	12.3%	MacConkey (cefotaxime or ceftazidime 1ug/ml), DDST	Good
	Moubareck *et al.,* 2005 (Lebanon)	2003	Prospective cohort	Healthy subjects	382	9	2.4%	DDST, PCR	Good
	Hijazi *et al.,* 2016 (Lebanon)	2013	Cross-sectional	healthy infants (1-12 month)	117	45	38.5%	DDST, PCR	Good
	Elkersh *et al.,* 2015 (Saudi Arabia)	2012-2013	Cross-sectional	Healthy neonates ≤7 days	150	22	14.7%	Disc diffusion(screening), DDST	Good
	Sana *et al.,* 2016 (Tunisia)	2013	Cross-sectional	healthy children at school	105	7	6.60%	cefotaxime (2µg/ml), DDST, PCR	Fair
	Joo *et al.,* 2018 (South Korea)	2014	cross sectional	Healthy Korean adults	109	20	18.3%	PCR	Good
	Tian *et al.,* 2008 (China)	2007 *	Cross-sectional	Elderly people with age more than 65 in the community	270	19	7%	EMB with 1ug cefotaxime, VITEK 2 system (bioMérieux, Marcy l'Etoile, France), PCR	Good
	Sadahira *et al.,* 2017 (Japan)	2013-2015	Prospective cohort	Men prior to transrectal biopsy	640	85	13.3%	ChromAgar/ESBL plates- Kanto Chemical (Tokyo, Japan)	Good
	Kamei *et al.,* 2017 (Japan)	2013-2015	Prospective cohort	Men prior to transrectal biopsy	379	22	5.9%	chromID ESBL (Sysmex-bio-Merieux, Tokyo, Japan), PCR	Good
	Zhou *et al.,* 205 (China)	2012	Cross-sectional	healthy asymptomatic adults (Pre-employment)	200	117	58.5%	ChromID ESBL agar (bioMe´rieux, Marcy l'Etoile, France), DDST, PCR	Good
	Qin *et al.,* 2013 (China)	2008-2011	Prospective cohort	Healthy Volunteers	41	3	7%	ESBL scre, Disk diffusion, PCR	Good

	Wu *et al.,* 2019 (Taiwan)	2016-2017	Cross-sectional	Healthy Volunteers	724	14	1.9%	CHROMagar™, ESBL plate (CHROMagar Paris, France), PCR	Good
	Mo *et al.,* 2019 (Singapore)	2016-2017	Cross-sectional	healthy community-dwelling individuals	305	71	23.3%	CHROMagar ESBL((bioMérieux), whole genome sequencing of all ESBL positive E. coli	Good
	Higa *et al.,* 2018 (Japan)	2017	Cross-sectional	healthy community-dwelling individuals	263	31	11.8%	Mackonckey with 2ug/ml cefotaxime, DDST	Good
	Nhi *et al.,* 2018 (Vietnam)	2016	prospective cohort	healthy children (urban)	498	374	75%	MacConkey with ceftriaxone 6mg/L, PCR	Good
	Nakane *et al.,* 2016 (Japan)	2010-2011	Cross-sectional	Healthy food handlers	2230	70	3.1%	DDST, PCR	Good
	Nakamura *et al.,* 2016 (Japan)	2011-2012	prospective cohort	Health individuals working at food supply centers	496	42	8.5%	MacConkey with 1 mg/L cefotaxime or 1 mg/L ceftazidime, DDST, PCR	Good
	Ni *et al.,* 2011 (China)	2009	Cross-sectional	Healthy subjects attending annual P/E	109	55	50.5%	MacConkey with 1 mg/L cefotaxime or 1 mg/L ceftazidime, PCR	Good
	Atterby *et al.,* 2019 (Cambodia)	2011	Cross-sectional	Persons from 10 households in 10 villages of Cambodia	307	53	17%	chromID OXA-48 (BioMérieux), chromID CARBA (BioMérieux) and C3GR CHROMag), PCR	Good
	Kennedy & Collignon, 2010 (Australia)	2008-2009	Prospective cohort	Healthy individuals pre-travel	106	2	1.9%	chro mID ESBL (bioMérieux, France), PCR	Good
	Nakayama *et al.,* 2015 (Laos)	2012	Cross-sectional	community residents	57	40	70.2%	MacConkey with 2 mg/L cefotaxime, DDST, PCR	Good
	Nakayama *et al.,* 2015 (Vietnam)	2013	Cross sectional	community residents	198	93	47%	MacConkey with 1 mg/L cefotaxime, DDST, PCR	Good

	Ni *et al.,* 2016 (China)	2014	Cross sectional	healthy individuals in six communities /check-up	1732	528	30.5%	MacConkey with 4 µg/ml cefotaxime, CHROMagar ESBL plates (Mei xiang, China), PCR	Fair

Table S2: Summary table of the 62 articles that contain data on the prevalence of faecal ESBL *E. coli* carriage among healthy persons worldwide, 2000-2020.

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. 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)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			

13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials: YB
Rater #2 initials: WB
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Table S3: Quality assessment criteria for the eligible studies