Chapter 12

Evaluating Meta-Analysis Research of *Escherichia coli*

Noel Pabalan, Eloisa Singian, Lani Tabangay and Hamdi Jarjanazi

Additional information is available at the end of the chapter

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Abstract

This chapter summarizes the progress in *Escherichia coli* research that used the meta-analysis approach. Using systematic searches for *E. coli* literature, we tracked meta-analysis publications and analyzed them based on a number of parameters. These included subject/topic (epidemiology, clinical/intervention/prevention and environmental), geographical region (the Americas, Europe and Australasia) and clinical syndrome (enteric, renal, and sepsis/meningitis). These parameters were plotted in terms of time span to obtain a sense of dynamic change or its absence through the years since the turn of the twentieth century. In terms of region, topic and syndrome, highest meta-analysis productivity was attributed to the Americas, clinical/intervention/prevention and enteric, all of which took place in the last 5 years (2011–2016). Over the combined time span of 16 years, the Americas significantly dominated meta-analysis outputs when compared to Europe and Australasia (P = 0.003). In conclusion, our findings facilitate awareness of the progress in this field wherein the studied parameters were analyzed for patterns over time and differential rates of publication productivity.

Keywords: *Escherichia coli*, meta-analysis

1. Introduction

Published researches on *Escherichia coli* (*E. coli*) have increased in number since the turn of the twentieth century. A search of *E. coli* publications in PubMed reveals an output value of 339,415 (as of July 16, 2016) which when narrowed to *E. coli* in title only, the number is still substantial (96,594). Majority of the *E. coli* publications are primary studies which when addressing the same issue, most often produce contradictory results [1]. Thus when primary studies are reviewed (usually in the narrative style), these contradictions hinder meaningful integration of results. A more systematic way to integrate primary study findings is the use of meta-analysis.

1.1. Meta-analysis defined

Meta-analysis is defined as a statistical analysis of primary study results for the purpose of integrating the findings into a summary effect [2]. Considered at the top of the hierarchy of evidence [3], it is a logically formal and objective technique as well as quantitative mode of summarizing research findings in order to identify genuine associations [1, 4]. Meta-analysis is categorized under the rubric of a systematic review, a process that entails gathering all completed published studies from the primary literature specific to a targeted research question [5]. Meta-analysis opens the possibility to accurately estimate the overall outcome measure, with increased statistical power, than is possible using only a single study [6]. Historical application of meta-analysis in *E. coli* research is relatively extensive as it has addressed key research questions. These include epidemiology, prevention, intervention issues and environmental concerns.

1.2. Importance of meta-analysis

The importance of meta-analysis is best appreciated when compared to the primary study. First, meta-analysis is cheaper, but not necessarily easier to do. Primary studies on the other hand are more expensive and logistically problematic, especially when large [1, 7]. Second, primary studies often do not have enough statistical power to assess relationships between risks (interventions) and outcomes. Being most useful when individual studies are too small to yield valid conclusions, meta-analysis increases power, reduces risk of error and facilitates exploratory analysis to generate hypotheses for future research [8]. The reason for performing a meta-analysis has to do with sample sizes of the studies, when they are large but results conflict, or when they are small, but their positive findings are not consistent [9]. The meta-analysis approach enables its findings to unmask large-scale patterns not obvious in primary studies [10, 11]. This then results in greater statistical precision meriting higher confidence. Thus, meta-analysis findings facilitate more efficient transfer of knowledge from researcher to clinician enabling analyses of important patient subgroups, delineation of high risk factors for infection enough for information to be useful for public health advice in risk for infection. Consequently, meta-analysis lends rigor to better assist health authorities in directing therapeutic decisions to target populations, urgency for health education and control measures [1]. Indeed, in the public health domain, a number of difficult issues that had been repeatedly studied were either resolved or clarified by the application of meta-analysis techniques [12]. This has led some government guidelines to recommend meta-analysis as the preferred method of summarizing evidence of effectiveness and safety of health technologies in the face of multiple study results [13].

1.3. Performing meta-analysis

1.3.1. Literature search and data abstraction

A publishable meta-analysis should have enough primary studies that address a common topic. The published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommends that a full electronic search strategy for at least one major

database be presented [14], although such an approach is considered insufficient by some [15]. Still a typical search strategy should involve electronic retrieval of all available literature, which includes databases such as PubMed using Medline (http://www.ncbi.nlm.nih.gov/pubmed), ScienceDirect (www.sciencedirect.com), Institute of Scientific Information (ISI) Web of Knowledge (http://www.isiwebofknowledge.com) and Google Scholar (http://scholar.google.com). For greater precision in this step, additional measures to exhaustively identify eligible studies include manual searching of relevant journals, references lists and personal contact with researchers.

1.3.2. Summary effect analysis

Meta-analyses report findings in terms of effect sizes, which provide information about the magnitude of change. The forest plot typifies presentation of meta-analysis results, which are generated by software such as Stata®, Review Manager and Comprehensive Meta-analysis®. The forest plot example [16] in **Figure 1** was generated from Review Manager (Cochrane Collaboration, Oxford, England). The plot is composed of five columns, the leftmost with qualitative data (study, named by last name of first author) and the remaining four with quantitative data. Between columns three and four is the actual forest plot with a solid vertical line (labeled 1 on the x-axis) which corresponds to the null effect. The area to the left of the vertical line indicates decreased risk and to its right increased risk. The two leftmost columns show the raw data (cases/controls) from which the odds ratios (OR) and 95% confidence intervals (CI) (rightmost column) are calculated. The OR and 95% CI express the study-specific findings (there are 18 of them), and a single summary effect that systematically combines the 18 ORs. Significance of the study-specific and summary effects is visually determined when

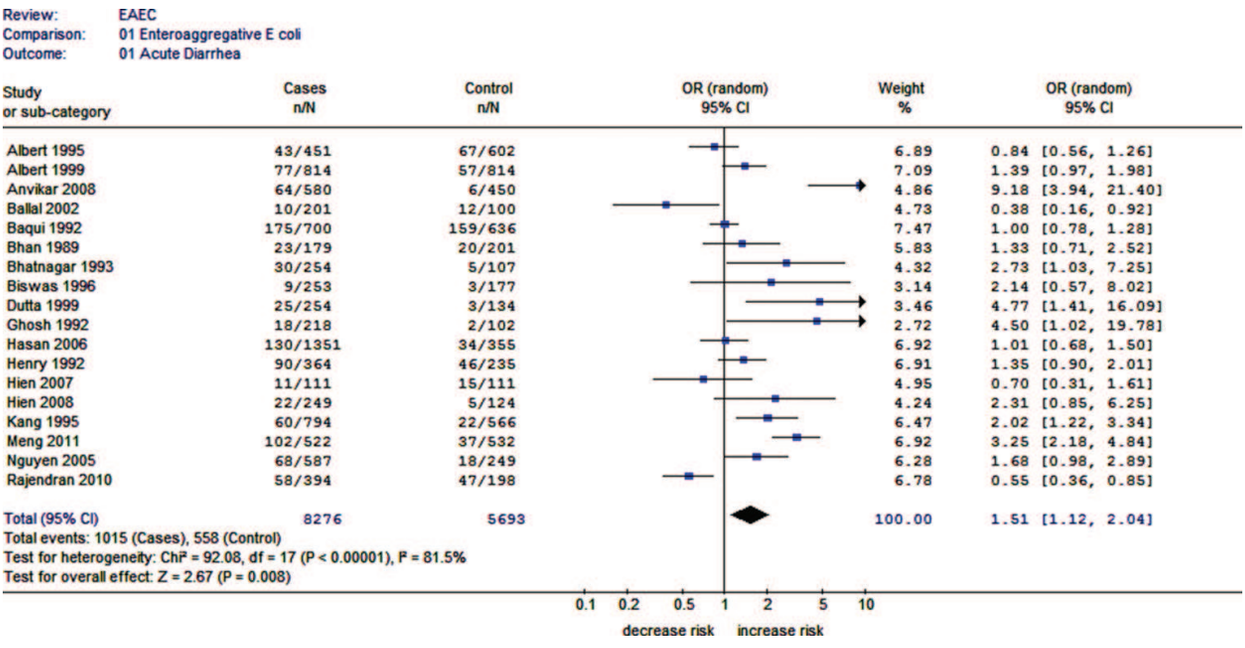

Figure 1. Forest plot for the overall effect of EAEC on acute diarrhea among South-Asian children [16]. EAEC: enteroaggregative *E. coli*; n: affected number; N: total number; OR: odds ratio; CI: confidence interval; df: degree of freedom; I^2: measure of variability between studies; P: P value.

the lines associated with the squares and the diamond (♦) touch the vertical line (labeled 1). If the vertical line is touched, the interpretation is non-significant, otherwise it is significant. Numerically, each 95% CI, expressed as decimal, will either pass 1 (non-significant) or not (significant). For significance of the summary effect (♦), this is also determined by the tests generated by the software, results of which are found at the bottom left of the forest plot. The test for overall effect, represented here by the Z-test and its corresponding P value, is 0.008 indicating significance. This graph has been much more explained in detail in two previous papers [1, 16].

1.3.3. Modifier analyses

Standard meta-analysis comprises a set of features that include a summary effect (expressed in various types of statistical metrics). Not being the endpoint, the summary or pooled effect needs to be tested further to ensure rigor of this methodology. An armory of statistical techniques is available to test the stability of this effect. These techniques include subgroup, outlier and sensitivity analyses, collectively known as modifiers. First, modifier analysis could take the forms of subgrouping by categories such as geography, gender and ethnicity. From these categories, one could delineate similar or contrasting effects between the subgroups, along with the precision or lack of it as indicated by the CI. Second, pooled effects could be influenced by outlying studies, and these are determined by the Galbraith plot method [17]. Omission of such studies followed by re-analysis generates one of the two results affecting the original pooled effect: (i) unaltered, indicating stability and (ii) altered in terms of direction of association which indicates instability. In addition, outlier treatment could affect heterogeneity (see below). Finally, summary effects are tested for robustness with sensitivity analysis wherein the studies are serially omitted followed by recalculation to determine deviation or resistance of the pooled effect from the original [18].

1.4. Biases in meta-analysis

Despite the appeal of meta-analysis, it is only as good as the studies used to create it dependent on the experience of the researcher performing it [19]. As in primary studies, meta-analysis is not immune to biases, but the good thing about these limitations is its transparency in admitting their presence. Furthermore, the meta-analysis protocol contains inherent statistical mechanisms to adjust and minimize these biases.

1.4.1. Heterogeneity

Heterogeneity in a broad sense involves clinical, methodological, biological and epidemiological issues and is often topic specific [20]. In this section, we examine statistical heterogeneity, which in the meta-analytical context, is defined as statistical dissimilarity across various studies [1]. Adjusting for heterogeneity involves appropriate use of analysis models. This involves use of the random-effects model [2], which assumes variability across populations usually resulting in a wider CI [21]. However, when component studies in a meta-analysis are similar to each other, this indicates absence of heterogeneity; then, the fixed-effects method of analysis [22] is applied based on the assumption that associations are the same across studies

and recognizing that the collection of eligible literature is not heterogeneous. Heterogeneity is statistically estimated using a chi-square–based Q test [23] and quantified with the I^2 metric, which shows what proportion of the total variation across studies is beyond chance [24]. Values of I^2 lie between 0 and 100% where a value >75% may be considered substantially heterogeneous [24]. Heterogeneous results warrant investigation into its sources, either through meta-regression [25] or outlier treatment [17]. The former focuses on covariates and the latter is graphically assessed with the Galbraith plot [17], which is used to detect outlying studies. Exclusion of outliers followed by recalculation either reduces or removes heterogeneity of the original findings.

1.4.2. Publication bias

Publication bias [26] occurs when significant findings receive priority in published literature over those whose results are non-significant [18]. This bias is evaluated graphically with the funnel plot (**Figure 2A**). The points with small studies scattered along the length of the x-axis but still centered on the OR estimates from large, more precise studies. This figure shows a symmetrical distribution indicating absence of bias. In contrast, **Figure 2B** shows a simulated funnel plot indicating presence of publication bias, which shows an asymmetrical distribution of the points [1]. The subjectivity in interpreting the funnel plot is overcome with objective statistical tests for publication bias, the Egger's regression asymmetry [21] and Begg's and Mazumdar's rank correlation [27] tests.

1.5. *Escherichia coli*

In this section, we discuss *E. coli* studies as is relevant to the topics addressed by meta-analysis. Meta-analyses have covered *E. coli* topics that included environmental factors such as water quality, clinical aspects, which include intervention/prevention approaches and epidemiological issues which address prevalence factors. *E. coli* is the predominant facultative anaerobe of the human colonic flora that inhabit the gastrointestinal tracts of humans and warm-blooded

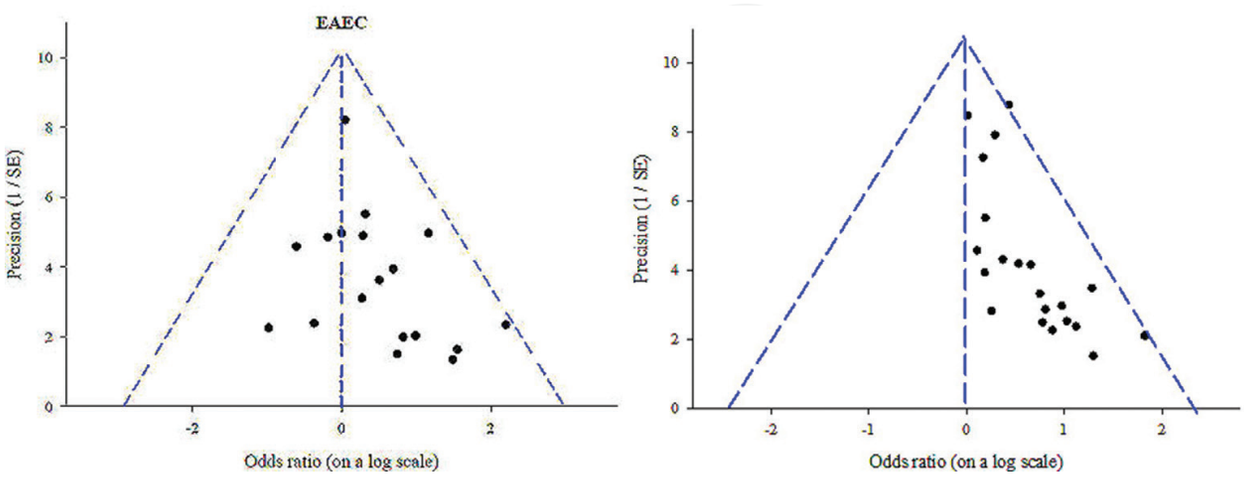

Figure 2. Funnel plot showing absence (A) and presence (B) of publication bias [1]. EAEC: enteroaggregative *E. coli*; SE: standard error; (B) is a simulated funnel plot [1].

animals, as well as one of the most important pathogens [28]. Occupying the mucous layer of the mammalian colon, *E. coli* colonizes this area in infants within hours of life, and thereafter, it usually remains harmlessly confined to the intestinal lumen [29]. As commensal, *E. coli* lives in a mutually beneficial association with hosts and rarely causes disease. Thus, *E. coli* is part of the protective microbial community in the intestine and is essential for general health. The conditions where *E. coli* strains cause disease are among immunocompromised hosts or where the normal gastrointestinal barriers are violated [30]. Infections due to pathogenic *E. coli* may be limited to the mucosal surfaces or can disseminate throughout the body. This spread throughout the body includes the digestive, renal and nervous systems [28, 29, 31]. We use these systems appear in our survey of meta-analysis publications on *E. coli* to track the evolvement and progress in this field.

1.6. Methods used in the survey

To obtain a sense of outputs in *E. coli* meta-analyses, we performed a systematic search of meta-analysis publications using the keywords, "meta-analysis" and "*E. coli*" in PubMed using Medline, Google Scholar and Science Direct in the title/abstract box. If the title did not explicitly indicate the above keywords, we read the abstracts and/or full-text article to determine its study design. Nevertheless, we excluded systematic reviews without the meta-analysis aspect in the article. For articles to be included, meta-analysis and/or *E. coli* should be in the title. If only meta-analysis was in the title, we read the text to determine if the role of *E. coli* was central or marginal. Central role meant that *E. coli* was the focus of the paper. If *E. coli* was among the foci of the paper, findings for *E. coli* should be statistically significant. If otherwise, the paper was relegated to marginal status. We defined marginal as *E. coli* being grouped with other bacteria and/or that *E. coli* findings were non-significant or unassociated with the outcome.

Figure 3 is a flowchart of our literature search of meta-analyses on *E. coli*. Of the 202 citations, 130 were excluded because they were not meta-analyses nor reviews nor about *E. coli*. In addition, many were duplicates of those already found in PubMed. Of the remaining 72 records, 45 had *E. coli* and/or meta-analysis in the title and the other 27 did not. These 27 were then assessed further by reading the full text from which we excluded 14 marginal papers leaving 13 central articles for inclusion in the analysis. These 13 with the 45 titled papers gave a total of 58 articles which we evaluated based on three parameters: (i) subject [epidemiology (EPI), clinical intervention/prevention (CIP), and environmental (ENV)]; (ii) time span (2000–2004, 2005–2010 and 2011–2016) and (iii) region (the Americas, Europe and Australasia). The number of publications was assessed using these parameters. Of the 58 papers, 15 articles could not be categorized into clinical syndromes because they addressed unrelated issues such as water, sanitizing and contamination. The remaining 43 papers were categorized by syndrome wherein the articles were either enteric (ENT), renal (REN), sepsis (SEP) or a combination of these three (MUL for multiple). From these parameters, we generated publication output rates in the following plots: (i) topic spread through time (**Figure 4**); (ii) topic standardized by number of countries per region through time (**Figure 5**); (iii) region through time wherein both were standardized by the number of countries per region (**Figure 6**) and number of years

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per time span (**Figure 7**), respectively and (iv) clinical syndrome wherein both were standardized by the number of countries per region (**Figure 8**) and number of years per time span (**Figure 9**), respectively. Visual differences between the parameters were further analyzed statistically.

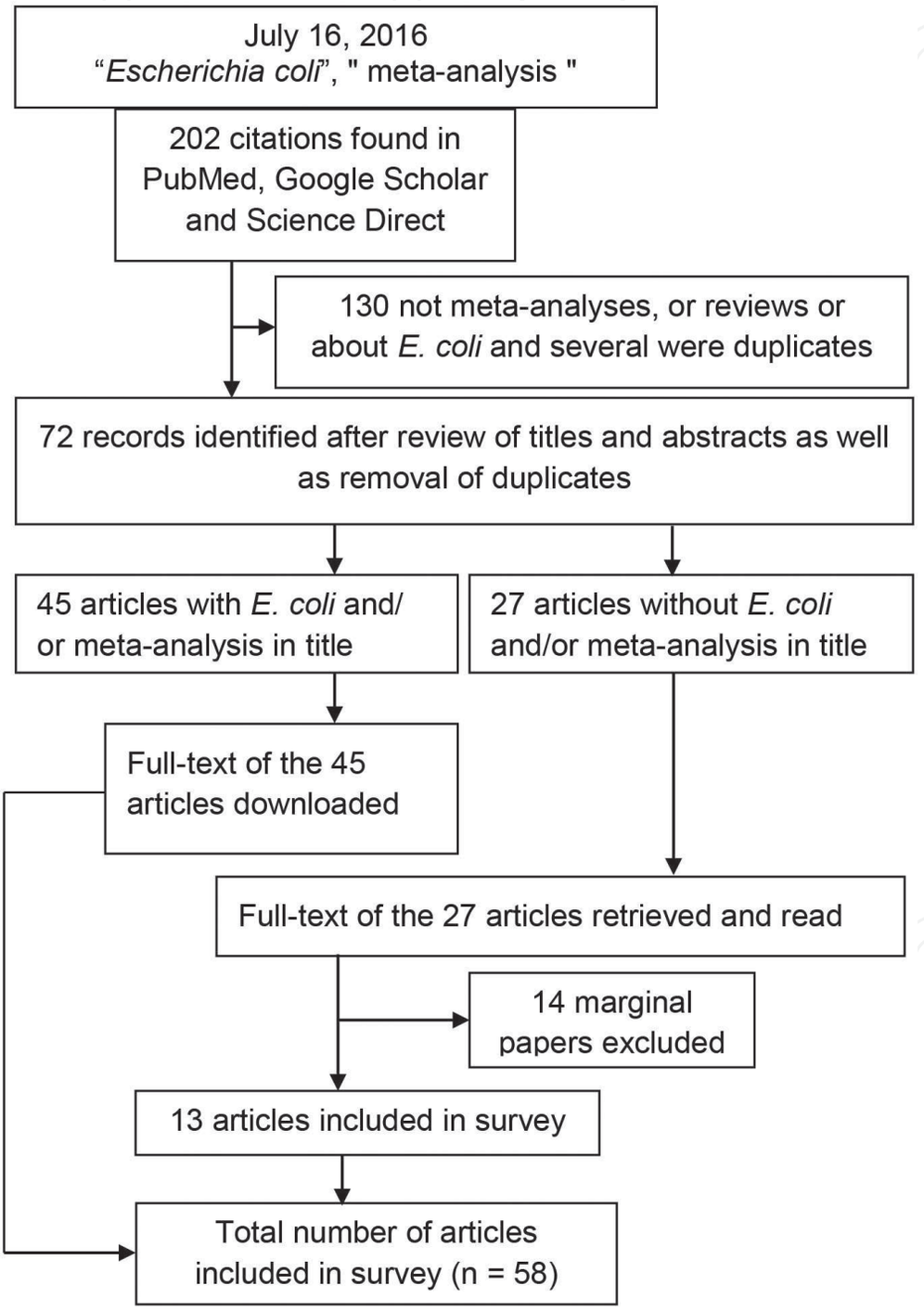

Figure 3. Flowchart of selection of studies for inclusion in the systematic survey.

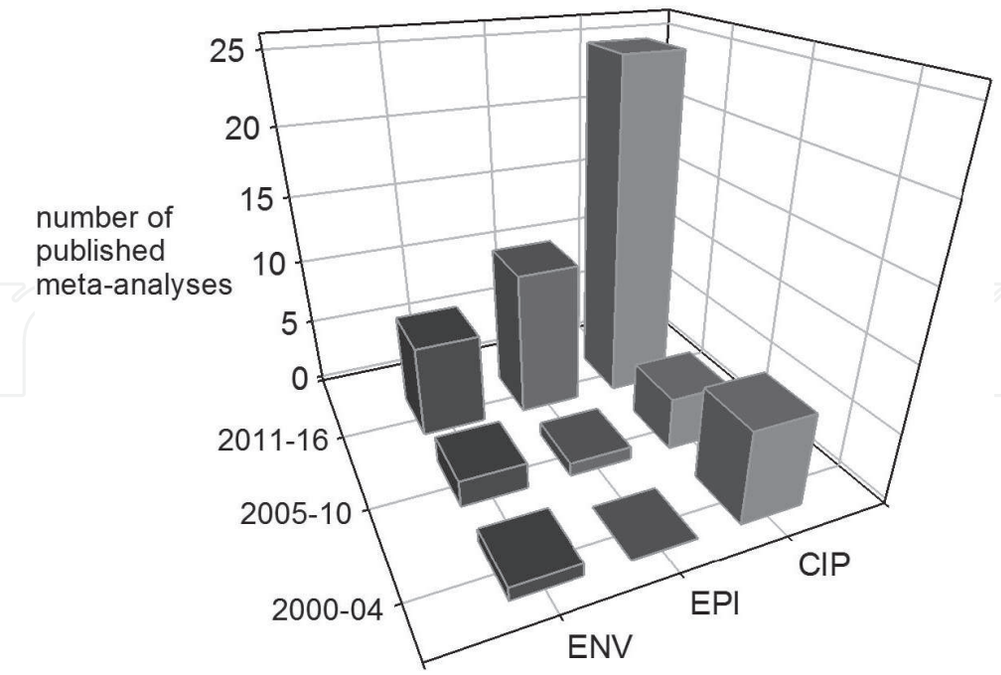

Figure 4. Meta-analysis publication outputs in *E. coli* research by topic. ENV: environmental; EPI: epidemiological; CIP: clinical/intervention/prevention.

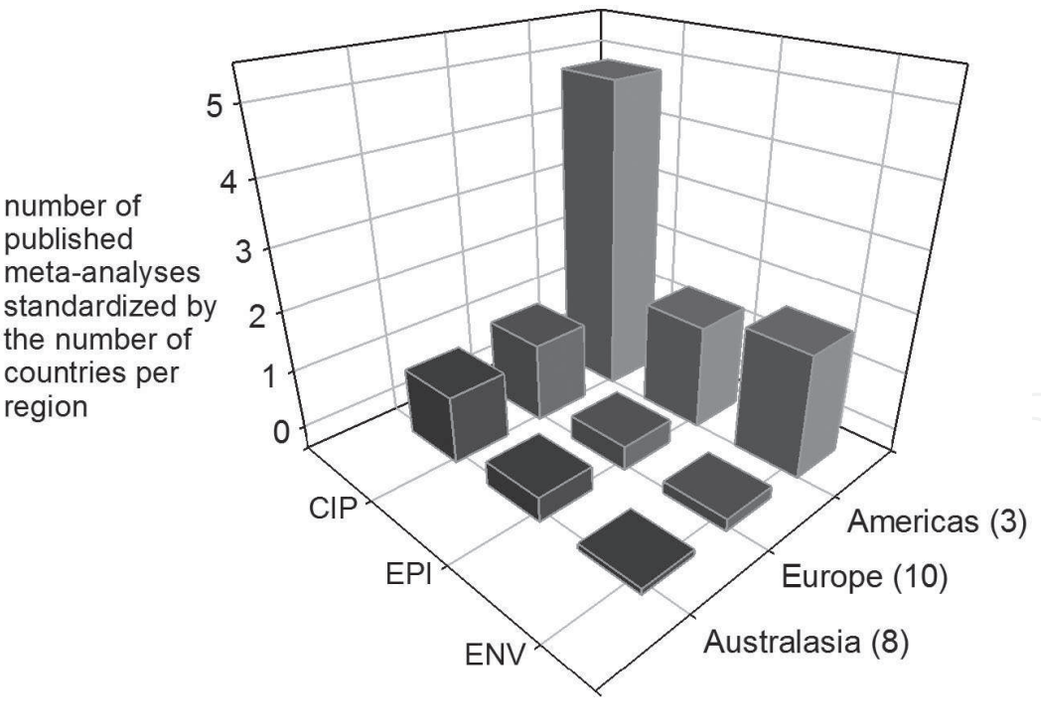

Figure 5. Meta-analysis publication outputs in *E. coli* research of three major world regions categorized by topic. Values in the Y-axis indicate number of meta-analyses divided by the number of countries per region. Numbers in parentheses indicate number of countries comprising the region; ENV: environmental; EPI: epidemiological; CIP: clinical/intervention/prevention.

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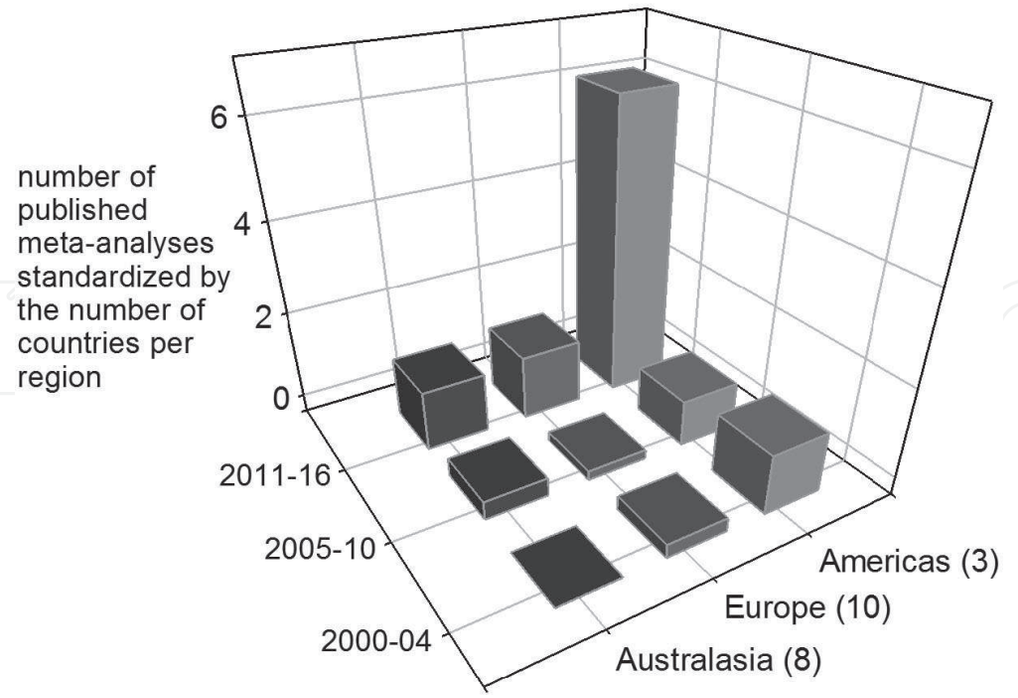

Figure 6. Meta-analysis publication outputs in *E. coli* research standardized by the number of countries per region. Numbers in parentheses indicate number of countries comprising the region.

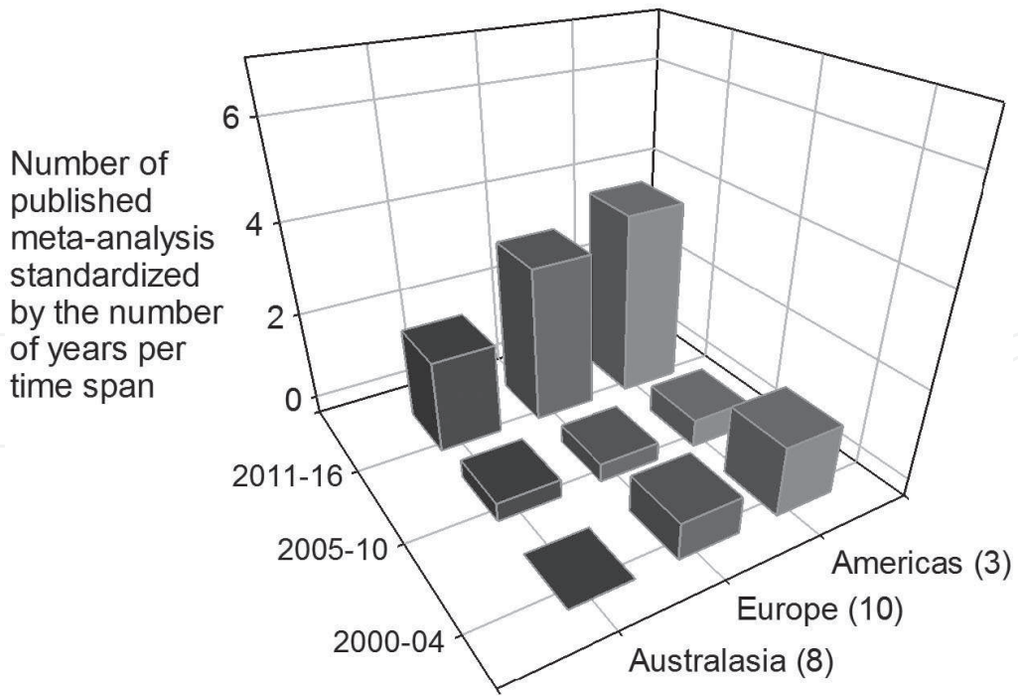

Figure 7. Meta-analysis publication outputs in *E. coli* research standardized by the number of years per time span. Numbers in parentheses indicate number of countries comprising the region.

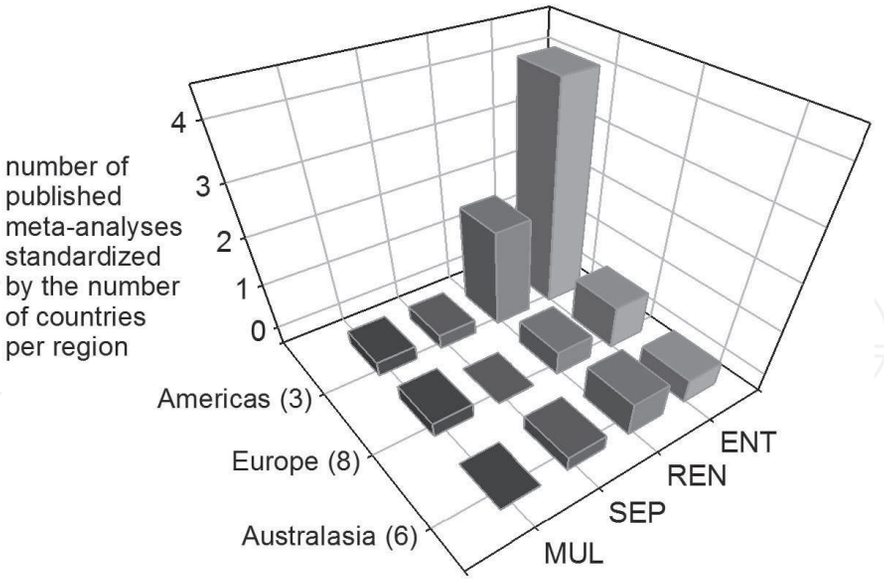

Figure 8. Meta-analysis publication outputs in *E. coli* research by clinical syndrome standardized by the number of countries per region. Numbers in parentheses indicate number of countries comprising the region; MUL: multiple; SEP: sepsis; REN: renal; ENT: enteric.

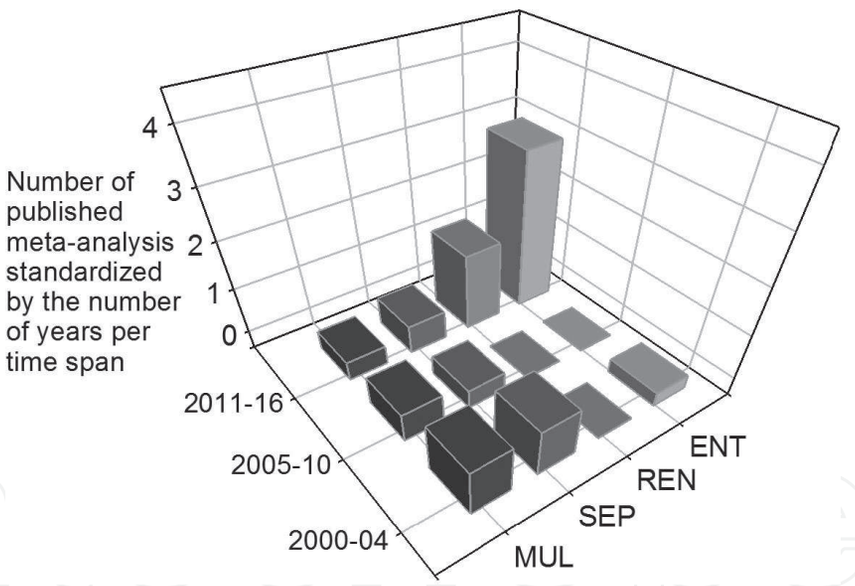

Figure 9. Meta-analysis publication outputs in *E. coli* research by clinical syndrome standardized by the number of years per time span. MUL: multiple; SEP: sepsis; REN: renal; ENT: enteric.

2. Main body

2.1. Review of *E. coli* meta-analyses based on topics

E. coli is responsible for a good number of hospital-acquired and community-acquired infections more than any other single bacterial species. In a wider context, it is responsible for a great deal of infant morbidity and mortality due to its action as a pathogen in the bowel [32].

Studies of *E. coli* in the ENV context have not been well undertaken compared to CIP studies. ENV studies of this pathogen in the meta-analysis context have involved water, which addressed quality [33, 34], contamination [35] and treatment issues [36]. Yet, the importance of this environmental factor related to *E. coli* pathogenicity is relevant to particular regions of the world especially the developing countries. Fecal pollution of natural waters has been increasingly important, and the consequences of discharge of untreated sewage into river estuaries and the sea have been extensively studied [32]. To a lesser degree, soil research has been undertaken to a magnitude that warranted meta-analysis treatment [37]. In general, strategies for prevention and control of the spread of *E. coli* should include access to safe water, good handling practices to reduce the risk of food contamination, sanitation measures, public education and vaccination [38, 39]. *E. coli* in the context of epidemiology as approached from a meta-analysis perspective involves prevalence issues [40, 41] and reviews epidemic potential [42, 43] of this pathogen as well as being a causative factor in diarrheal illness [44]. Given the variety of epidemiological areas of *E. coli* research warranting meta-analysis, it provides a fertile base of future undertakings in this area. Clinical topics addressed with the meta-analysis approach vary depending on subjects involved. These topics provide a sense of the number of primary studies in areas such as infection, treatment and prevention.

2.2. Review of *E. coli* meta-analyses based on clinical syndromes

Enteric/diarrheal diseases involve intestinal pathogens that are spread through the fecal-oral route by ingestion of contaminated food or water [45]. These pathogens termed diarrheagenic *E. coli* (DEC) are differentiated, among others, on the basis of distinct clinical and pathogenic features (pathotypes) [29]. The five pathotypes of DEC are enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), enterohemorrhagic *E. coli* (EHEC) and enteroinvasive *E. coli* (EIEC). In addition, Shiga Toxin-producing *E. coli* (STEC) are foodborne pathogens that cause human infections acquired through fecal-oral contact with contaminated human and animal feces [46]. Urinary tract infection (UTI) is the most common extra-intestinal *E. coli* infection caused by uropathogenic *E. coli* which when isolated, the condition generally responds rapidly to antibiotic therapy. Sequelae from UTI could complicate pregnancy and target pre-school age children rendering the possibility of chronic renal damage [32]. Related to the renal system is verocytotoxin-producing *E. coli* (VTEC) infection, which could result in hemolytic uremic syndrome; this occurs in up to 15% of cases [47]. An increasingly common cause of extra-intestinal infections is the pathotype responsible for meningitis and sepsis/meningitis-associated *E. coli* [32]. The included meta-analyses here addressed issues with *E. coli* strains such as STEC, VTEC, ETEC and EAEC [16, 40, 44, 47–51]. Two of these strains were addressed with antibiotics [47, 49]. Resistance to antibiotics was the subject of five studies [52–56]. Associations of antibiotics with infection were addressed in seven articles [57–63]. The topics of *E. coli* associations with water were addressed in 10 papers [33–37, 64–69]. There were three papers on *E. coli* shedding in cattle [70–72]. Immunology topics were the focus in three papers [73–75]. Although most meta-analyses included here addressed enteric *E. coli* infections, there are papers that addressed renal infections [53, 54, 76] with a fairly good number of *E. coli* meta-analyses and UTI performed in various contexts such as epidemiology [42, 55], intervention [52, 54] and prevention [73]. Meta-analyses of *E. coli* in the context of sepsis/meningitis have so far been confined to mice and infants [58, 77].

2.3. *E. coli* meta-analyses involving non-human animals and plants

Our collection of *E. coli* meta-analyses involved non-human animals and plants, mainly farm animals. These included poultry [78], cattle [41, 69–72, 79–81] and pigs [61, 82]. Non-farm animals where *E. coli* studies have been meta-analyzed were mice [77]. Farmed non-animals where *E. coli* research has been meta-analyzed included fresh-produce studies [68, 83]. *E. coli* infection among pets and wild animals has produced primary studies [32] but not enough of their numbers warranted meta-analysis.

2.4. Assessing *E. coli* meta-analyses by topic

Figure 4 shows the results of *E. coli* meta-analysis productivity in span of 16 years (grouped into three time spans) and across three topics. Between 2000 and 2004, CIP outputs dominated those of EPI and ENV, but between 2005 and 2010, outputs from all three topics were more or less similar. Between 2011 and 2016, CIP outputs dwarfed those of the other two, although EPI outputs were slightly more than those of ENV. The combined data of 16 years between the topics showed non-significant higher CIP outputs than EPI and ENV [one-way analysis of variance (ANOVA): $P = 0.08$].

2.5. Assessing *E. coli* meta-analyses by topic and region

Figure 5 graphs the number of published *E. coli* meta-analyses ordered by topic from the three world regions. Published outputs from the Americas were higher across the topics than Europe and Australasia, but when regionally combined, the higher American productivity was not significant (one-way ANOVA: $P = 0.62$). However, when ordered by topic and analyzed by one-way ANOVA and the Holm-Sidak post-test, CIP productivity was significantly higher than EPI ($P = 0.005$) and ENV ($P = 0.003$) but not between EPI and ENV ($P = 0.63$).

2.6. Assessing *E. coli* meta-analyses by region

Figure 6 shows the number of published meta-analyses which was standardized by region. This figure shows low meta-analysis outputs in the years 2000–2010 from Europe and Australasia compared to the moderate American outputs in the same period. The last 5 years (2011–2016) showed high American output compared to the moderate number of publications from Europe and Australasia. **Figure 7** shows meta-analysis productivity of the three regions standardized by year. Per year output of published meta-analyses on *E. coli* in the first 4 years of the twentieth century was zero for Australasia but moderate for Europe and the Americas. This productivity declined in the following 4 years (2005–2010) for all regions then shot back up to good productivity in between 2011 and 2016. Thus, comparing **Figures 6** and **7**, we observed higher meta-analysis productivity in the Americas per region than that per year. Between 2011 and 2016, Europe and Australasia had higher meta-analysis productivity when standardized by year than that by region. The unadjusted values from **Figures 6** and **7** were subjected to statistical comparison (one-way ANOVA, Holm-Sidak post-test) that combined the data of 16 years. Results showed significantly higher number of published outputs from the Americas than Europe ($P = 0.003$) and Australasia ($P = 0.002$) but not between the latter two ($P = 0.89$).

2.7. Assessing *E. coli* meta-analyses by clinical syndrome

Figure 8 shows the standardized number of meta-analyses from the three regions categorized under the four syndromes. This graph shows American predominance in ENT and REN meta-analysis research compared to the two other regions. Between these two syndromes, ENT had more than twice the output compared to REN. SEP and MUL outputs were flat from all regions. **Figure 9** shows minimal output of REN and ENT meta-analyses between 2000 and 2010 compared to SEP and MUL researches, which were considerably higher in the same time span. Between 2011 and 2016, REN and ENT outputs were up to three times higher than SEP and MUL meta-analyses. The unadjusted values from **Figure 9** of the combined data of 16 years showed non-significant associations between the syndromes over time (one-way ANOVA: $P = 0.20$).

2.8. Summary of *E. coli* meta-analysis publication outputs

Based on the three topics analyzed, increase of CIP meta-analyses indicates *a priori* increase in the number of primary studies (which are requisite to meta-analysis) in a span of 16 years. This increase has probably to do with focus on treating *E. coli* infections given the infrastructure in laboratories that enable such researches. **Table 1** shows that in terms of region, leadership of the Americas, specifically the USA in *E. coli* meta-analysis research seem to have been unchallenged since the turn of the twentieth century. Even when *E. coli* publication outputs were low between 2000 and 2010, the Americas still dominated over Europe and Australasia. This domination is best interpreted in three contexts: (i) only three countries comprise the Americas compared to 10 and eight for the other two regions (**Figure 4** and **Table 1**). (ii) **Table 1** shows the USA output in meta-analysis to be twice that of Canada and eight times that of Brazil. (iii) USA meta-analysis output is four times those of Netherlands and Australia, which both lead Europe and Australasia, respectively (**Table 1**). Given the concentration of developing countries in the Asian region where *E. coli* research would be most useful, such outputs are comparatively low and maybe warrant priority in future research of this pathogen. Our findings suggest that the region with the capabilities to undertake such researches result in higher publication outputs. In terms of outputs per year, Australasia and Europe appear to be catching up in productivity in the last 5 years. Summing the pattern of the graphs (**Figures 4–9**), meta-analysis outputs were highest for CIP, the Americas and ENT, all between 2011 and 2016 where this time span was involved. The lowest meta-analysis outputs were concentrated between 2000 and 2004, specifically in the ENV topic and the Australasian region. The year 2000 showed one published meta-analysis on *E. coli* [75] and none before that.

2.9. Limitations and strengths

One limitation of this undertaking was that we confined our survey to published *E. coli* research from standard databases. There might have been meta-analyses done in government and university settings on *E. coli* but were not included in the databases we searched on. Another limitation is non-inclusion of gray literature in our survey, which by its nature has not been published. However, one strength is that this chapter gave a sense of the direction of

	Europe	N	Americas	N	Australasia	N
1	Netherlands	4	USA	16	Australia	4
2	UK	3	Canada	8	China	3
3	Denmark	2	Brazil	2	Japan	1
4	Germany	4	Total	**26**	Iran	1
5	Poland	1			Pakistan	1
6	Italy	6			Bangladesh	1
7	Sweden	1			Turkey	1
8	Greece	1			Philippines	1
9	France	1			Total	**13**
10	Ireland	1				
11	Portugal	1				
12	Slovenia	1				
	Total	**26**				

N: number of published articles; UK: United Kingdom; USA: United States of America.

Table 1. Countries comprising each of the three world regions and published outputs of *E. coli* research resulting from literature searches in PubMed, Science Direct and Google Scholar.

E. coli research based on previous publications. Because we used parameters such as region, year, topic and clinical syndrome, this provided some measure of direction as to how *E. coli* research was conducted and what areas in this discipline need focusing in the future.

2.10. Conclusions

E. coli meta-analyses in this survey varied in many aspects, not only in geography but also in the topic and syndrome. Most salient was variability in the outcomes and approaches. For outcomes, they ranged from presence to absence of associations and effectivity or absence of treatment. The point of these outcomes is the exposition of magnitude where influence of factors may be great or minimal; all these having been statistically treated. For approaches, subjects range from humans to non-human animals and even plants (fresh produce). This survey of meta-analysis publications indicates areas of discipline that were emphasized and those that were not. *E. coli* research outputs, as in other biomedical disciplines, are increasing at an exponential rate. Because of the critical importance of *E. coli* research findings across populations and geographical regions, objective evaluation of these primary studies may facilitate decision making that impacts upon public health policy. Clinicians, researchers and demographers in this field would likely benefit from the use and interpretation of meta-analysis. The survey in this review delineates a relatively high use of meta-analysis in *E. coli* research in the Americas, where the USA most specifically continues to assert its capability in utilizing outputs from primary *E. coli* studies since the turn of the twentieth century. Of note, the recent years also showed increasing use of *E. coli* meta-analyses from Europe and Australasia. Not

only do primary studies addressing the same issue had conflicting results, they also varied in geography, methodology, and sample size-leading to perceived controversy or uncertainty about the pathogenic nature of this organism. Application of systematic statistical approaches allowed confirmation that many strains of *E. coli* cause endpoint diseases. Similar meta-analysis in the larger sphere of microbiology may have the ability to advance our understanding of other emerging and established pathogens.

Of the three *E. coli* topics this chapter has covered, ENV studies have garnered the least attention over the last 16 years compared to EPI and CIP. Even less in magnitude are genetic/genomic issues which were barely covered in this chapter given the paucity of primary studies on this topic. If the past is any guide to future prospects, then it would be judicious to forego what is fashionable in research and begin addressing issues that impact upon the lives of those affected/infected with *E. coli*. The tide of geopolitical forces has given rise to mass migration and exponential increase in world population at the cost of environmental degradation. These global features define regions most susceptible to the ravages of *E. coli* infection. Thus, it seems most suited to emphasize the future in *E. coli* research along these scales in order of priority, ENV, EPI and CIP. However, this is not to de-prioritize the genomic/proteomic approaches as it forms the foundation upon which *E. coli* research achieves milestones. The future of genomic epidemiology is detailed in Eppinger and Cebula's paper where they focus on the EHEC serotype [84].

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Appendices and nomenclatures

E. coli	*Escherichia coli*
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ISI	Institute of Scientific Information
OR	Odds ratio
CI	Confidence interval
CIP	Clinical/intervention/preventive
EPI	Epidemiological
ENV	Environmental
ENT	Enteric or diarrheal
REN	Renal; which includes the term uremic

SEP	Sepsis/meningitis
MUL	Multiple; has the combination of ENT, ENV and/or REN
DEC	Diarrheagenic *E. coli*
EHEC	Enterohemorrhagic *E. coli*
ETEC	Enterotoxigenic *E. coli*
EPEC	Enteropathogenic *E. coli*
EAEC	Enteroaggregative *E. coli*
EIEC	Enteroinvasive *E. coli*
STEC	Shiga toxin-producing *E. coli*
UTI	Urinary tract infection
VTEC	Verocytotoxin-producing *E. coli*
ANOVA	Analysis of variance

Author details

Noel Pabalan[1]*, Eloisa Singian[2], Lani Tabangay[3] and Hamdi Jarjanazi[4]

*Address all correspondence to: npabalan@alumni.yorku.ca

1 Center for Research and Development, Angeles University Foundation, Angeles City, Philippines

2 Department of Medical Technology, College of Allied Medical Professions, Angeles University Foundation, Angeles City, Philippines

3 Department of Biology, Angeles University Foundation, Angeles City, Philippines

4 Environmental Monitoring and Reporting Branch, Ontario Ministry of the Environment and Climate Change, Toronto, ON, Canada

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