

Estimating the proportion of hemolytic uremic syndrome cases in Shiga toxin-producing
Escherichia coli cases – A systematic review and proportional meta-analysis

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The work entailed in this thesis is content which I authored, with the exception of the following content. Part of the research in this thesis was commissioned and paid for by the World Health Organization (WHO), specifically all methods for the systematic literature search and extraction, and the extracted data. Copyright in the original work on which these elements are based belongs to WHO. I have been given permission to publish these elements in this thesis. I alone am responsible for the views expressed in this publication and they do not necessarily represent the views, decisions, or policies of WHO.

This thesis was based on a publicly available PROSPERO protocol, [CRD42023485066](https://www.crd42023485066). The PROSPERO protocol was developed by myself and Dr. Shannon Majowicz, with input from Dr. Zahid Butt, Dr. Mark Oremus, and key contacts from WHO. Jackie Stapleton of the University of Waterloo assisted in developing search strategies by advising on database specifications and search strategy revisions. Dr. Shannon Majowicz provided search terms for the literature searches, including non-English terms which were provided by WHO colleagues.

Dr. Shannon Majowicz and I developed an instructional manual that outlined for the team members how to conduct each screening step. Together with Dr. Shannon Majowicz, I trained second screeners from our research group (in no specific order): Antonela Ilic, Ashvini Gulasingam, Jacob Hammond and Kanika Sarwal. I screened all studies in title and abstract and full text screening alongside the second screeners and Dr. Shannon Majowicz to resolve conflicts. I carried out the data extraction of the thesis based on a [standard data extraction template](#) from WHO, that Dr. Shannon Majowicz and I adapted with significant input from Carlotta Di Bari of Sciensano, the animal health and food security agency of Belgium.

I carried out study quality assessment by selecting critical appraisal tools, modifying these tools, training Kanika Sarwal as a graduate research assistant to conduct all the assessments, and reviewing her assessments for completeness and accuracy before finalizing them.

Abstract

Background: Shiga-toxin producing *Escherichia coli* (STEC) infection is a foodborne zoonotic infection causing a range of diseases, permanent injury and even death. STEC has been linked to large epidemics globally. While STEC can affect different organs of the human host, the kidneys are the primary site of pathological injury during infection. Hemolytic uremic syndrome (HUS) is a common sequela affecting the kidneys and can affect certain subpopulations disproportionately. This thesis aimed to estimate the cumulative incidence of HUS among symptomatic STEC cases, based on available data.

Methods: I conducted a systematic review and meta-analysis to determine the overall and stratified cumulative incidence of HUS. I searched PubMed, Web of Science, Ovid® Embase and Scopus for published literature, followed by five grey literature databases, which were Google Scholar, INASP Journals Online project, OAIster, GreyGuide, and WHO IRIS. The inclusion criteria were human populations of all sociodemographic factors, as either confirmed or probable cases of symptomatic STEC infection. HUS was the condition of interest. Eligible records published in English, between 1 January 1990 and 14 January 2024 from all geographical regions were included. A second screener and I independently identified and included eligible studies in the systematic review. I extracted summary-level data on study information, STEC cases and HUS cases from included studies. A second reviewer and I assessed study quality of included records using tools by the Joanna Briggs Institute. To estimate the pooled cumulative incidence of HUS, I performed a random-effects meta-analysis for single proportions. To estimate the stratified cumulative incidence, I used subgroup analyses and meta-regression models for age, sex, STEC characteristics and study characteristics.

Results: I identified 4,906 records from the literature searches, of which 269 studies (comprising 189,350 STEC cases aged 0 – 98 years) from 28 countries were included. The

pooled cumulative incidence of HUS was 8.22% (95% CI, 7.82 – 8.61). In subgroup analyses, the cumulative incidence of HUS was highest among children aged between 0 and 4 years at 17.82% (95% CI, 14.57 – 21.07) and among female STEC cases at 13.03% (95% CI, 11.04 – 15.02). STEC O157 and co-infections with multiple serotypes were the most common serogroups among included studies. By study year, the highest cumulative incidence of HUS occurred between 2010 to 2014 at 14.79% (95% CI, 12.74 – 16.84). By study regions, the highest cumulative incidence of HUS was from the WHO European Region at 12.66% (95% CI, 11.47 – 13.85). The included studies were mostly high- quality studies. Age, sex, STEC serogroup, STEC genes, study year range and WHO Regions were significant predictors of cumulative incidence of HUS.

Conclusion: The proportion of STEC cases that progress to HUS is relatively low. However, STEC cases are underestimated, and these proportions may overrepresent the true cumulative incidence estimates of the population. Some subpopulations had higher HUS incidence estimates, with age, sex, infecting STEC serogroup, STEC genes, study year range and region being significant predictors of STEC-HUS development. Thereby, these findings support current knowledge of STEC-HUS, provide important insights into STEC-HUS epidemiology, and can be used by clinical specialists and other stakeholders in research, policymaking and clinical guidance.

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“Education is the most powerful weapon which you can use to change the world”

Nelson Mandela

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List of Abbreviations

A/E	Attaching-and-effacing
BC CDC	British Columbia Centre for Disease Control
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CoCoPop	Condition, context, and population
Cr.I.	Credible interval
CRAN	Comprehensive R Archive Network
DNA	Deoxyribonucleic acid
e-mail	Electronic mail
e.g.	exempli gratia
EAEC	Enteraggregative <i>Escherichia coli</i>
EHEC	Enterohemorrhagic <i>Escherichia coli</i>
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
ESRD	End stage renal disease
<i>et al.</i>	et alia
FERG	Foodborne Disease Burden Epidemiology Reference Group
FoodNet	The Foodborne Diseases Active Surveillance Network
GFR	Glomerular filtration rate
GRA	Graduate research assistant
HUS	Hemolytic uremic syndrome
i.e.	id est
JBI	Joanna Briggs Institute
LAMP	Loop-mediated isothermal amplification
LPS	Lipopolysaccharide
MLVA	Multilocus variable number tandem repeat analysis
NAAT	Nucleic acid amplification tests
NESSS	National Enhanced Surveillance System for STEC
p-value	probability value
PCR	Polymerase chain reaction
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism
PDF	Portable document format
PFGE	Pulsed-field gel electrophoresis
pH	Potential of hydrogen
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
SMAC	Sorbitol-MacConkey agar
spp.	species (pl.)
STEC	Shiga Toxin-Producing <i>Escherichia coli</i>
Stx	Shiga toxin
<i>stx</i>	Shiga toxin gene
UI	Uncertainty interval
USA	United States of America
USD	United States Dollar
VCA	Vero cell cytotoxicity neutralization assay
VTEC	Verotoxin-producing <i>Escherichia coli</i>
WGS	Whole genome sequencing
WHO	World Health Organization
κ	kappa

1. Background

1.1. Burden of foodborne infection and disease

Foodborne diseases represent an important cause of morbidity and mortality worldwide, accounting for approximately 2 billion illnesses and more than 1 million deaths (Kirk *et al.*, 2015). The World Bank evaluated the economic burden of foodborne diseases to be USD 95.2 billion as the total productivity loss in low- and middle-income countries annually, and USD 15 billion as the annual cost of treating foodborne illnesses (The World Bank, 2018). Foodborne infectious diseases occur by (1) ingestion of pathogens via contaminated food, and (2) ingestion of toxins released by toxigenic pathogens or environmental hazards (Bintsis, 2017). The scientific literature suggests that certain subpopulations may be at an elevated risk of infection and disease by foodborne pathogens. The subpopulations are young children, immunocompromised persons, elderly people (> 65 years) and individuals in shared living conditions or spaces (California Department of Public Health, 2024a; The World Bank, 2018; Bintsis, 2017; Kirk *et al.*, 2015).

Many foodborne bacteria, viruses, protozoa and fungi have been identified and studied in research. Important foodborne pathogens include norovirus, rotavirus, *Salmonella* spp., *Shigella* spp., *Escherichia coli*, *Vibrio cholerae*, *Listeria monocytogenes*, and *Campylobacter jejuni* (Kirk *et al.*, 2015). While foodborne infections can lead to common treatable ailments, like emesis, abdominal pain, and diarrhea, these infections can also cause multisystemic diseases, organ dysfunction, and even death (Bintsis, 2017). The unpredictable outcomes of foodborne infections render them important in public health contexts. Shiga toxin-producing *Escherichia coli* (STEC) is one such bacterium noted for its association with multisystemic organ injuries (Liu *et al.*, 2022; Quiñones *et al.*, 2012).

1.2. *Escherichia coli* – Friend or foe?

Escherichia coli is the predominant facultative anaerobe of the human colon microbiome and forms a genetically heterogenous group of typically non-infectious bacteria (Liu *et al.*, 2022; Hunt,

2010). While *E. coli* may be considered beneficial symbiotic bacteria in humans, the bacteria have also genetically acquired the potential to cause a diverse range of clinical manifestations such as bloody diarrhea and hemorrhagic colitis (Liu *et al.*, 2022; Quiñones *et al.*, 2012).

1.3. Shiga toxin-producing *Escherichia coli*

STEC represents one pathogenic *E. coli* associated with both human and animal diseases. STEC has been recognized by alternate nomenclature as well, including verotoxigenic *E. coli* (VTEC) and Enterohemorrhagic *E. coli* (EHEC) (Melton-Celsa *et al.*, 2012; Paton and Paton, 1998). The estimated infective dose of STEC is as low as 100 bacteria, rendering STEC a highly contagious pathogen (Terajima *et al.*, 2017). The extremely low infective dose may be attributed to acid resistance of STEC and its ensuing ability to survive the gastric environment (Terajima *et al.*, 2017; Hunt, 2010).

1.3.1. Transmission of STEC infection

Ruminants, such as cattle and sheep, are the primary reservoirs of STEC (Bagel and Sergentet, 2022). STEC infections are largely considered foodborne infections (Martin and Beutin, 2011), and worldwide outbreaks of STEC have been attributed to a variety of contaminated foods, including but not limited to raw milk cheeses (Minary *et al.*, 2022), leafy greens (Butt *et al.*, 2021; Waltenburg *et al.*, 2021; Bottichio *et al.*, 2020), fruits (Chan *et al.*, 2023), vegetables (Marder *et al.*, 2023), dairy (Hirose *et al.*, 2023; Jenkins *et al.*, 2022), meat (Ostroff *et al.*, 1990), and meat products (Byrne *et al.*, 2020). A systematic review by Kintz *et al.* (2017) examined the most common transmission routes of STEC infection and identified the consumption of undercooked meat as the most important risk factor for STEC infection.

However, ruminant carriers can also transmit the bacteria to humans without foodborne routes (Bagel and Sergentet, 2022). Frequent transmission routes identified by Kintz *et al.* (2017) have also been implicated in STEC outbreaks. These routes include visits to animal farms and

petting zoos (Ferraro *et al.*, 2023; Goode *et al.*, 2009), contact with ruminants and manure (Nichols *et al.*, 2021), consumption of contaminated drinking water (McCall *et al.*, 2010), contact with recreational water (Vanden Esschert *et al.*, 2020), travel (Devaux *et al.*, 2015) and direct contact transmission (e.g., communal household with cases) (Slutsker *et al.*, 1998).

1.3.2. Microbiological characteristics and pathogenesis of STEC

1.3.2.1. Microbiological characteristics of STEC

STEC are rod-shaped, Gram-negative bacteria of the *Enterobacteriaceae* family. STEC is mainly characterized by the production of a toxin (Stx) called Shiga toxin 1 (Stx1), which was first isolated from *Shigella dysenteriae* serotype 1 (Furchtgott *et al.*, 2011; Keusch *et al.*, 1998). Stx2 is the other Stx produced by STEC. The Stx toxins are encoded by *stx* genes (Keusch *et al.*, 1998). Although the Stx2 is immunologically distinct to Stx1, Stx2 is highly homologous to Stx1, such that the two toxins are 70% similar in terms of amino acid levels (Melton-Celsa *et al.*, 2012). The Stx1 and Stx2 toxins also exert the same mode of action (Melton-Celsa *et al.*, 2012). The two toxins have related toxins, like Stx1a and Stx2a, which are crucial to host pathogenesis. Other recognized STEC virulence factors are enterohemolysin (e.g., encoded by the *ehlyA* gene), intimin (encoded by the *eae* gene) and adhesins (Kawano *et al.*, 2008).

1.3.2.2. Classification of serotypes

Serotyping of STEC and *E. coli* utilizes antigens on the bacterial surface, namely somatic (O), flagellar (H) and capsular polysaccharide antigens (K) (Stenutz *et al.*, 2006). O antigens are a highly variable bacterial component, owing to biochemical and structural differences of the O antigen. These differences, in turn, give rise to various clones of STEC, which are also classified according to the O antigen. For example, a highly virulent serogroup of STEC is STEC O157 (Liu *et al.*, 2020).

A common classification scheme implemented for STEC categorization is immunological serotyping by combinations of 174 somatic surface antigens (O-antigens) and 53 flagellum antigens (H-antigens) (Amézquita-López *et al.*, 2018). Thereby, more than 400 different serotypes of STEC have been identified. Furthermore, certain serotypes are grouped into seropathotypes based on frequencies of serotype detection and disease severity. The seropathotype categories range from seropathotype A for relatively high incidence and severe disease to seropathotype E for no human illness. A few serotypes in the seropathotypes A and B include O157:H7, O157:NM, O126:H11, O103:H2, O111:NM, O121:H19, and O145:NM (Amézquita-López *et al.*, 2018).

1.3.2.3. Geographical distribution of serotypes

STEC serotypes are distributed geographically. The STEC O104:H4 serotype has emerged as a highly virulent serotype and has been linked to large outbreaks in Europe (Delmas *et al.*, 2014; King *et al.*, 2012; Colic *et al.*, 2011; Frank *et al.*, 2011). The highest incidence of hemolytic uremic syndrome (HUS) due to STEC has been recorded in Argentina, where STEC-HUS is an endemic disease (Alconcher *et al.*, 2024). The highly virulent *E. coli* O157 serotype is prevalent in Argentina (Alconcher *et al.*, 2021).

1.3.2.4. STEC pathogenesis in human hosts

To cause illness, STEC first enters the human host through contaminated food or alternate routes described earlier (Melton-Celsa *et al.*, 2012). If STEC survives the gastric pH, the bacteria will remain in the host's gut and release Stx toxins to exert both localized and systemic effects (Paton and Paton, 1998). Thereby, STEC initiates the colonization of intestinal mucosa, while also competing with other intestinal bacteria (Melton-Celsa *et al.*, 2012; Paton and Paton, 1998).

STEC achieves pathogenesis through virulence factors, like the outer membrane adherence protein known as intimin, and bacterial processes, such as the attaching-and-effacing (A/E) lesion

(Farfan and Torres, 2012; Paton and Paton, 1998). The Stx toxins released by STEC enter intestinal epithelial cells and are translocated to enter the bloodstream. Ergo, STEC infection may manifest as asymptomatic infections, may cause common intestinal symptoms (e.g., abdominal pains), or may result in severe illnesses (e.g., kidney injury) or even death (Melton-Celsa *et al.*, 2012). It is noteworthy that certain virulence factors of STEC, especially the Stx2, have been associated with more severe illness, such as HUS (Neupane *et al.*, 2011; Ostroff *et al.*, 1989). The degree of Stx translocation, especially Stx2, across intestinal epithelia is an important driver of pathogenesis in humans (Tran *et al.*, 2018).

1.3.3. Detection and diagnosis of STEC

The diagnosis of STEC infection is important particularly in surveillance, such as to detect confirmed cases for public health action (Slayton *et al.* 2013). STEC detection includes culture or agar plating (biochemical detection), immunological tests, molecular tests, and cell-based assays (Parsons *et al.*, 2016).

The culture on sorbitol-MacConkey agar (SMAC) is a frequently used method for the O157 serotype (Parsons *et al.*, 2016; March *et al.*, 1986). There is no culture medium which can detect all STEC serotypes (Parsons *et al.*, 2016). However, all STEC serotypes produce Stx toxins (Boone *et al.*, 2016). Hence, simultaneous testing of Stx toxins or genes along with culture of human samples is recommended by public health organizations, such as the British Columbia Centre for Disease Control (BC CDC) and the Centers for Disease Control and Prevention (CDC) (Allen *et al.*, 2013; Gould *et al.*, 2009a).

One immunological method is enzyme-linked immunosorbent assays (ELISAs). ELISAs detect virulence factors, like Stx1 and the anti-lipopolysaccharide (LPS) antibody. ELISAs can be used to analyze fecal samples and cultures from humans (Fomsgaard and Dinesen, 1987). The severity of human disease may depend on the Stx toxins released by the infecting STEC bacteria, as described in Section 1.3.2 (Boone *et al.*, 2016). A range of enzyme immunoassays (EIAs) are

known to successfully detect Stx, like optical immunoassays and microwell immunoassays (Boone *et al.*, 2016; Teel *et al.*, 2007).

In addition, molecular methods have been developed to detect and differentiate serotypes. The genes encoding bacterial components and toxins (e.g. *stx*, *eae*, *aggR*) and antimicrobial resistance can be detected in human samples (e.g., fecal samples) using molecular methods such as nucleic acid amplification tests (NAATs) (Carroll *et al.*, 2021; Gentle *et al.*, 2020). Real-time polymerase chain reaction (PCR) and multiplex PCR detect and differentiate *stx* genes (Jääskeläinen *et al.*, 2023). Loop-mediated isothermal amplification (LAMP) is another NAAT that uses specifically-designed primers and polymerase enzymes to target STEC genes (Wang *et al.*, 2012). Restriction fragment length polymorphism (PCR-RFLP) is a deoxyribonucleic acid (DNA) fingerprinting method based on the diversity of the STEC nucleotide sequence. PCR-RFLP differentiates STEC rapidly, using minimal instrumentation (Sugimoto *et al.*, 2011). While STEC can be classified based on serotypes, additional typing determines the relatedness of isolates by serotype. This typing can be achieved by pulsed-field gel electrophoresis (PFGE) (Jaros *et al.*, 2015). To enhance the resolution of STEC typing, PFGE can also be used in conjunction with another molecular test known as multilocus variable number tandem repeat analysis (MLVA) (Parsons *et al.*, 2016). MLVA has been recognized consistently for its superior discriminatory power in clusters of STEC cases (Byrne *et al.*, 2014). Whole genome sequencing (WGS) is considered a minimalistic process in STEC typing (Chattaway *et al.*, 2016).

The Vero cell cytotoxicity neutralization assay (VCA) is reported sparsely in epidemiological research. However, the method is recognized as a reference or gold standard for Stx detection, owing to its picogram-level analytical sensitivity (Silva *et al.*, 2019; Boone *et al.*, 2016). The Vero cells are derived from African green monkey kidney cells. These cells are highly sensitive to Stx, as Vero cells contain high concentrations of eukaryotic receptors for Stx (Gb3 and Gb4) (Gould *et al.*, 2009a). The latex agglutination test uses antibody detection against bacterial components, like the LPS, and is recommended with another method (e.g., ELISA) (Rastawicki *et al.*, 2017).

1.3.4. Utility of STEC diagnostics and public health surveillance

1.3.4.1. Evolution of STEC diagnostics

As seen in Section 1.3.3, a multitude of diagnostic tools can detect and differentiate STEC, with some tools used more extensively in public health. Section 1.3.3 also illustrates the evolution of STEC diagnostics through time with the advent of more sophisticated technologies, offering improved detection and differentiation of STEC. There is evidence of culture techniques being used in STEC detection even before the 1980s (Coombes, Gilmour and Goodman, 2011). The use of molecular and immunological tests for STEC has been described in scientific literature from the 1990s, to coincide with the introduction of these methods (Acheson *et al.*, 1990; Pollard *et al.*, 1990).

1.3.4.2. Assessing the performance of diagnostics

In epidemiology and medicine, the performance of diagnostics is evaluated using measures such as sensitivity, specificity, and positive and negative predictive values (Safari *et al.*, 2015; Drake and Levine, 2005). The sensitivity is the probability of a positive test result in a patient with the illness and can be determined by the proportion of cases identified correctly as diseased (true positive cases) (Baratloo *et al.*, 2015; Drake and Levine, 2005). The specificity is the probability of a negative diagnostic test in a patient free of the disease and can be determined by the proportion of cases correctly identified as healthy cases (true negative cases) (Baratloo *et al.*, 2015; Drake and Levine, 2005).

A systematic review and meta-analysis by Tarr *et al.* (2020) compared the performance of EIA and PCR in STEC detection. The authors indicated that PCR tests (pooled sensitivity: 1.00; 95% CI, 0.904–1.00) performed better in comparison to EIAs (pooled sensitivity: 0.681; 95% CI 0.571–0.773), with no meaningful loss of specificity. Therefore, it is important to consider the sensitivity and specificity of the diagnostic methods.

Standard culture methods may not routinely detect non-O157 serotypes (Cukrovany *et al.*, 2024). As indicated in Section 1.3.3., SMAC is largely for STEC O157. However, an increasing shift towards other detection methods, like EIAs and molecular methods, began since the 1990s (Hoefer *et al.*, 2011). Therefore, STEC infections have likely been underestimated until recently with the use of more accurate detection methods (Cukrovany *et al.*, 2024). As a result, STEC epidemiology may vary over time and by STEC detection methods. The differences may need to be addressed in epidemiological analyses (Majowicz *et al.*, 2014; Majowicz *et al.*, 2010).

1.3.4.3. Shortcomings in surveillance systems

Non-O157 serotypes are underdiagnosed, even in countries such as Germany, where health authorities recommend the detection of non-O157 serotypes (Kuehne *et al.*, 2016). The largest recorded outbreak of STEC-HUS occurred in Germany in the summer of 2011 (Frank *et al.*, 2011). STEC surveillance in many countries does not account for non-O157 infections compared to O157 infections (Kuehne *et al.*, 2016). Therefore, the reporting of non-O157 serotypes and associated illness is inadequate in epidemiology. In addition, the notifiable surveillance systems only detect and report a fraction of the true numbers of illnesses occurring in a population (Kuehne *et al.*, 2016).

An example of this shortcoming is health surveillance systems in the United Kingdom. Since the 1980s, STEC-HUS outbreaks in England have been predominantly traced to STEC O157:H7 (Jenkins *et al.*, 2020; Byrne *et al.*, 2015). Therefore, laboratory methods largely relied on cefixime-tellurite SMAC agar, a selective medium for STEC O157. The dependence on STEC O157-specific detection methods undermined the surveillance of other serotypes (Butt *et al.*, 2021). However, the marked increase in detecting non-O157 STEC since 2013 in England, has led to an understanding that non-O157 STEC serotypes can also cause debilitating illnesses, such as HUS (Jenkins *et al.*, 2020).

Industrialized countries (e.g., the United States, the United Kingdom) have more robust surveillance systems to detect STEC compared to developing regions with limited resources. These robust systems enable prompt and efficient management and mitigation of infection transmission (Caprioli *et al.*, 2014).

1.3.4.4. Population factors affecting surveillance

In addition to the role of diagnostics, the severity of illness and health-seeking behaviours can inadvertently bias and underestimate STEC cases and associated illness in a given population (e.g., preferential ascertainment bias) (Lipsitch *et al.*, 2015). As described in Section 1.3.2, STEC infections manifest variably, even leading to death.

For infections like STEC, with varied clinical outcomes, persons with severe symptoms (e.g., bloody diarrhea) likely seek medical care (Lipsitch *et al.*, 2015). Therefore, these severe cases are captured in surveillance databases relative to asymptomatic STEC infections or STEC cases with mild or general symptoms. This phenomenon is particularly true during infection outbreaks when health systems are overwhelmed by burgeoning case numbers (Lipsitch *et al.*, 2015).

1.4. Sequelae following STEC infection

The mean incubation period of STEC ranges from 3.5 to 8.1 days (Awofisayo-Okuyelu *et al.*, 2019). As Stx toxins enter the bloodstream, STEC can cause diseases affecting multiple organs, even culminating in death. These diseases include hemorrhagic colitis, HUS, renal failure, colonic strictures, cholelithiasis, coma, epileptic seizures, cardiac ischemia, rhythm disorders, cardiac arrest and diabetes mellitus (Joseph *et al.*, 2020; Schuppner *et al.*, 2016; Suri *et al.*, 2009).

However, the kidneys are known to be the primary site of long-term damage after STEC infection (Spinale *et al.*, 2013). The kidney and bloodstream have specific cells, like endothelial cells and cells modulating filtration and fluid balance, which are targets for Stx toxins. Afterwards, these cells undergo processes such as cellular inflammation and apoptosis (Obrig and Karpman, 2012).

1.5. Hemolytic uremic syndrome

HUS is one of the most well-described STEC-related sequelae in the scientific literature. HUS is the most important etiology of acute kidney injury in children (Liu *et al.*, 2022). The disease was first described in 1955 by Gasser *et al.* and was historically known as Gasser's syndrome (Gasser *et al.*, 1995; Petrova, 1970).

HUS is a systemic group of diseases, primarily characterized by a triad of physiological processes due to toxin-mediated injury to vascular endothelia by STEC. The triad, referred to as thrombotic microangiopathy, occurs in three simultaneous reactions: (1) destruction of red blood cells, (2) low platelet count and (3) acute kidney failure. The pathological lesion of thrombotic microangiopathy mainly affects the kidneys (Michael *et al.*, 2022).

The highest incidence of HUS cases in children aged < 5 years was reported in Argentina, at 10.4 and 12.2 cases/100,000 children < 5 years of age, in 2001 and 2002, respectively (Rivas *et al.*, 2006). In Argentina, HUS is the main cause of acute renal failure in children and the second leading cause of chronic renal failure and renal transplantation in children (Monteverde *et al.*, 2023; Rivero *et al.*, 2010). While the burden of foodborne infections is largest in developing regions (Kirk *et al.*, 2015), the effects of STEC and STEC-HUS are observed globally. For example, STEC-HUS is considered the most common cause of renal failure in children in the United States and the United Kingdom (Gould *et al.*, 2009b; Lynn *et al.*, 2005).

Currently, no targeted treatments are available for HUS, and disease management centres on treating symptoms. In addition, patients seeking medical care or hospitalized patients for STEC-HUS have generally developed organ injuries already (Liu *et al.*, 2022; Walsh and Johnson, 2019).

1.6. Risk factors for STEC infection and HUS

1.6.1. Miscellaneous risk factors for STEC infection

Known risk factors for STEC infection are travel (mainly international travel), contact with ill persons (mainly diarrheal illness and children < 5 years with diarrheal illness), contact with farm

animals (e.g., calves, chickens, cows, goats, horses, pigs, sheep, horse feed, animal manure), agritourism (e.g., visits to petting zoos or farms), the female sex, attending childcare, occupational exposures (e.g., handling livestock, working in meat processing plants or abattoirs), consuming contaminated food, eating at a restaurant, consuming untreated drinking water (e.g., from a lake, spring, well), camping, regular contact with farming environments, contact with recreational water (e.g., swimming pool, swimming in lakes), contact with soil and certain medications (e.g., antibiotics, stomach-acid reducing medicines) (Marder *et al.*, 2023; Augustin *et al.*, 2021; Frank *et al.*, 2011; Rivas *et al.*, 2008).

1.6.2. Food-related risk factors for STEC infection

Contaminated food is the primary vehicle of STEC transmission to humans (Erickson and Doyle, 2007). Food contamination is highest during three phases in the food production chain, which are the field, initial processing, and in the kitchen (Luna-Guevara *et al.*, 2019; Ailes *et al.*, 2008). Food products such as meat, dairy, fish, and exotic fruits (e.g., kiwi, mango) are considered risk factors for STEC infection (Marder *et al.*, 2023). More specifically, the following meat items are associated with sporadic STEC infections and STEC outbreaks: ground beef, undercooked beef, meatballs, ham, salami, hamburgers, hotdogs, donner kebab, tartare, barbecued meats, processed meats, meat-based ready-to-eat items, cold/deli meats, minced meat, sausage rolls, corned beef, bacon, raw spreadable sausage, pre-cooked meat, and poultry. The consumption of dairy products, such as unpasteurized milk, raw milk, farm-prepared ice cream, formula milk, and raw milk cheeses, has been linked to STEC infection (Marder *et al.*, 2023; Augustin *et al.*, 2021).

STEC outbreaks have also been linked to fruits and vegetables, such as lettuce, iceberg lettuce, romaine lettuce, fresh herbs, spinach, tomatoes, and raspberries (Marder *et al.*, 2023). The most common vegetable sources are sprouts and green leafy vegetables (Luna-Guevara *et al.*, 2019). The contamination of leafy greens can occur directly via animal shedding and indirectly through irrigation, runoff, manure, soil, and sewage (Marshall *et al.*, 2020; Luna-Guevara *et al.*, 2019). In the

United States and Canada, ground beef is the leading source of foodborne STEC O157 outbreaks, followed by leafy greens (Marshall *et al.*, 2020).

Food preparation and hygiene practices related to STEC infection have been described in the literature. These practices include poor handwashing, no handwashing after contact with soil, manure or animals, consuming raw meat, consuming undercooked food, eating from a restaurant, and no handwashing in food preparation (Rivas *et al.*, 2008). Apart from localized outbreaks, STEC outbreaks can cross international borders due to the increased globalization of food manufacturing and the supply chain (Ingle *et al.*, 2019).

1.6.3. Risk factors for HUS development

A few risk factors for HUS are younger ages, prolonged oliguria (low urine output), neurological involvement, increased leukocytosis, genetic predisposition and STEC infection (Wong *et al.*, 2012; Taranta *et al.*, 2009). However, most research on risk factors has investigated the role of STEC infection in HUS development (Wong *et al.*, 2012).

1.7. Epidemiology of STEC and STEC-HUS

The STEC O157 serogroup, especially the O157:H7 serotype, represents a highly virulent form of STEC. STEC O157:H7 is often the main cause of the most severe outbreaks of STEC and HUS (Etcheverría and Padola, 2013). STEC O157:H7 first garnered recognition as the likely pathogen in two outbreaks of gastrointestinal illness in Michigan and Oregon in the United States in 1982 (Riley *et al.*, 1983). STEC O157:H7 was isolated from 9 of 12 samples and had only been detected previously in a sporadic case of hemorrhagic colitis in 1975 in California, United States (Riley *et al.*, 1983). Thereafter, STEC has been implicated in numerous outbreaks of gastrointestinal diseases worldwide (Vasant *et al.*, 2017; Launderers *et al.*, 2016; Frank *et al.*, 2011; Michino *et al.*, 1999).

Table 1. Characteristics of patients, STEC and study setting associated with numbers of STEC cases that develop HUS

Predictive risk factor	General findings from literature
Age	STEC infection and renal sequelae (e.g., HUS) have been known to affect children more, especially children < 5 years. The risk of STEC infection is also high for older ages (> 65 years) (Lisboa <i>et al.</i> , 2019; Byrne <i>et al.</i> , 2015; Gould <i>et al.</i> , 2009b). However, there are also research reports on adults being primarily affected by STEC infection and sequelae (Frank <i>et al.</i> , 2011).
Sex	There have been reports of higher cases of STEC and HUS in females in comparison to males since the 1990s (Bell <i>et al.</i> , 1997; Ostroff <i>et al.</i> , 1990) and during important outbreaks in the 2000s as well (Frank <i>et al.</i> , 2011).
Country	STEC-associated sequelae have been investigated in all WHO Regions (Alakrea <i>et al.</i> , 2022; Gould <i>et al.</i> , 2013; Kumar <i>et al.</i> , 2012; Frank <i>et al.</i> , 2011; Ngbede, Jideani & Agbo, 2006; Elliott <i>et al.</i> , 2001). In general, foodborne illness is known to affect primarily developing regions (Kirk <i>et al.</i> , 2015). However, a large volume of published literature on STEC epidemiology are from the United States, the United Kingdom and the European Union. The largest number of cases of STEC-HUS cases hitherto occurred in Germany (Frank <i>et al.</i> , 2011). Additionally, there is a geographical variation in circulating serotypes based on epidemiological studies (Alconcher <i>et al.</i> , 2021; Delmas <i>et al.</i> , 2014; Frank <i>et al.</i> , 2011). STEC surveillance can also be impacted by country due to different surveillance systems in countries and availability of resources (Caprioli <i>et al.</i> , 2014).
Year	STEC has been attributed to outbreaks of gastrointestinal illness since the 1980s (Riley <i>et al.</i> , 1983). With the development of improved detection methods, the identification of different serotypes and the improvements in STEC surveillance, STEC epidemiology may change through time (Cukrovany <i>et al.</i> , 2024). The highest number of STEC-HUS cases hitherto occurred in 2011 (Frank <i>et al.</i> , 2011).

STEC serotype	Historically, STEC O157:H7 has been implicated in outbreaks and renal sequelae, such as HUS. STEC O157:H7 has also been the target serotype in STEC diagnostics over time (Cukrovany <i>et al.</i> , 2024). However, the largest outbreak of STEC-HUS was attributed to STEC O104:H4 (Frank <i>et al.</i> , 2011).
STEC genes and toxins	The <i>stx2</i> gene has been attributed to severe outcomes of STEC infection and development of HUS (Byrne, Adams and Jenkins, 2020; Luna-Gierke <i>et al.</i> , 2014; Kawano <i>et al.</i> , 2008).
STEC detection methods	Historically, STEC detection has focused on culture-based methods, especially to detect STEC O157:H7 (Cukrovany <i>et al.</i> , 2024). However, there has been an increased reporting of other STEC serotypes (e.g., STEC O104:H4) with the introduction of other detection methods, such as PCR and sequencing; These molecular methods offer more accurate differentiation of STEC.
Study setting or design	STEC is detected by various epidemiological systems, such as passive surveillance (e.g., British Paediatric Surveillance Unit) (Byrne <i>et al.</i> , 2023), active surveillance (e.g., FoodNet) (Gould <i>et al.</i> , 2013), and outbreak reports (Frank <i>et al.</i> , 2011). Additionally, STEC transmission as case clusters may also skew the proportion of STEC infections leading to HUS. This concept is especially true for enclosed spaces like a family household, a children's day care or a restaurant. For example, an epidemic of STEC O118:H2-associated gastrointestinal illness in a Junior High School reported to the Minami Kaga Public Health Center, Japan in 1999 reported 0 HUS cases from 241 symptomatic STEC cases. The proportion of symptomatic STEC cases developing HUS in this particular outbreak was 0% (Hashimoto <i>et al.</i> , 1999). In a family cluster in eastern Slovakia, 3 cases of HUS occurred among 5 symptomatic STEC O157 cases, leading to a proportion of 60% of STEC cases that developed HUS (Liptakova <i>et al.</i> , 2004).

1.7.1. Epidemiology of STEC-HUS

The proportion of STEC cases developing HUS can range from 5 to 15%, depending on patient characteristics (e.g., age), infecting serotype, STEC virulence profile, and epidemiological context (Bruyand *et al.*, 2018). As typically observed with foodborne diseases, STEC and STEC-HUS primarily affect both younger ages (mostly < 5 years) and advanced ages (> 60 years) (Ylinen *et al.*, 2020; Sarcerdoti *et al.*, 2018; Byrne *et al.*, 2015; Gould *et al.*, 2009b). In addition, STEC and sequelae may affect females more than males (Sawyer *et al.*, 2021; Byrne *et al.*, 2015; Frank *et al.*, 2011; Gould *et al.*, 2009b).

While STEC encodes a myriad of virulence factors, the *stx2* gene is more frequently associated with HUS (Kawano *et al.*, 2008). As described in Section 1.7, STEC epidemiology may also be governed by infecting serotypes, with STEC O157:H7 being a highly virulent and prevalent serotype (Byrne *et al.*, 2015; Etcheverría and Padola, 2013). Table 1 summarizes the most well-described factors that may predict the number of STEC cases that develop HUS.

1.7.2. First estimations of STEC and related sequelae

Due to the dearth of data on foodborne illness, the World Health Organization (WHO) founded the Foodborne Disease Burden Epidemiology Reference Group (FERG) (World Health Organization, 2024; Kirk *et al.*, 2015). The FERG initiated the WHO Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases (Kirk *et al.*, 2015). The initiative summarized the global and regional disease burden of several important foodborne bacterial, protozoal (parasitic), and viral diseases for the first time in the scientific literature. The WHO Estimates also included data for STEC infection (Majowicz *et al.*, 2014). Kirk *et al.* (2015) estimated the disability-adjusted life years to be 26,827 (95% uncertainty interval [UI], 12,089–72,204), as the epidemiological indicator of overall disease burden.

The estimations for STEC infection and HUS for the WHO Estimates (Kirk *et al.*, 2015) were based on a systematic review by Majowicz *et al.* (2014). This systematic review summarized

the first estimates of the global incidence for STEC and related sequelae, using data circa 2010. Despite being an important cause of foodborne and multisystemic illness for decades, the global burden estimations had not explicitly accounted for STEC infection before this publication.

The authors estimated the annual number of STEC cases to be 2,801,000 acute infections (95% credible interval [Cr.I.], 1,710,000–15,227,000) worldwide. STEC led to 3,890 HUS cases (95% Cr.I., 2,400–6,700), supporting the importance of STEC as a foodborne pathogen (Majowicz *et al.*, 2014). The systematic review also found that STEC infection occurs worldwide. However, the highest numbers of STEC cases were from the WHO South-East Asia Region and WHO Western Pacific Region (Majowicz *et al.*, 2014).

To estimate the proportion of STEC cases developing HUS, the authors used surveillance data from the United States from the Foodborne Diseases Active Surveillance Network (FoodNet) between 2000 to 2010 (Majowicz *et al.*, 2014; Gould *et al.*, 2013). The systematic review estimated the incidence of STEC and HUS by the serogroup classification of STEC O157 and non-O157 STEC. The highest proportion of HUS following STEC infection was reported for STEC O157 at 0.823% in comparison to non-STEC O157 at 0.025% (Majowicz *et al.*, 2014). The values were estimated as described below:

$$\begin{aligned}
 \text{Proportion of HUS among O157 cases} &= \frac{\text{number of HUS cases}^1 \times \text{underreporting multiplier of } 2^2}{\text{number of O157 cases}^1 \times \text{underreporting multiplier for total notified O157 cases}^2} \\
 &= \frac{83 \times 2}{773 \times 26.1} \\
 &= 0.823\% \\
 \text{Proportion of HUS among non-O157 cases} &= \frac{\text{number of HUS cases}^1 \times \text{underreporting multiplier of } 2^2}{\text{number of non-O157 cases}^1 \times \text{underreporting multiplier for total notified non-O157 cases}^2} \\
 &= \frac{4 \times 2}{301 \times 106.8}
 \end{aligned}$$

¹ Case numbers from FoodNet surveillance data between 2008 - 2009 by Gould *et al.* (2013)

² STEC-specific multipliers published by Mead *et al.* (1999) using surveillance data

$$= 0.025\%$$

1.7.3. Epidemiology of STEC and STEC-HUS since 2010

Since 2010, the highest number of STEC-HUS cases ever recorded came from a STEC O104:H4 outbreak in Germany from May to July 2011 (Frank *et al.*, 2011). This outbreak, linked to contaminated sprouts, led to 845 STEC-HUS cases among 3,816 STEC cases (i.e., 22% of STEC cases), which was a comparatively higher proportion compared to previous outbreaks. In addition, the causative pathogen was STEC O104:H4 rather than STEC O157:H7. Another interesting observation was that 88% of HUS cases were in adults (i.e. > 17 years) in contrast to the general trend of higher HUS morbidity in children (Frank *et al.*, 2011).

In 2011, an outbreak of STEC O157 occurred in Yamagata Prefecture, Japan linked to two varieties of rice cakes produced by a local manufacturer (Nabae *et al.*, 2013). The STEC outbreak led to 142 confirmed cases, 136 suspected cases, 26 asymptomatic cases, and 25 secondary cases. An analysis of 278 suspected and confirmed cases indicated higher STEC cases among females compared to males (55.4%). In addition, 1.8% (n = 5) of the 278 cases developed HUS (Nabae *et al.*, 2013).

From 2014 to 2018, the East and South-east regions of England were affected by recurrent outbreaks of STEC O55:H7 (Sawyer *et al.*, 2021). The outbreak led to 43 confirmed and 3 probable cases of STEC O55:H7, with 54% (n = 25) of these cases developing HUS.

In April 2018, an outbreak of STEC O157 and STEC O61 was linked to romaine lettuce in the United States. The outbreak recorded 240 STEC cases from 37 states and 28 HUS cases (Bottichio *et al.*, 2020). The proportion of HUS cases was an approximate two-fold increase from the previous STEC O157:H7 outbreak examined by FoodNet (Gould *et al.*, 2009b).

The first nationwide outbreak of STEC O26:H11 in the United Kingdom occurred in October 2019 and was traced to foodborne origins of pre-packaged sandwiches. However, no HUS cases were recorded among 32 confirmed STEC cases (Butt *et al.*, 2021). An outbreak of the

same serotype in France from April to September 2019 was linked to raw cow milk cheese. This outbreak led to 20 HUS cases³ (Minary *et al.*, 2022).

1.8. Cumulative incidence of HUS as a data gap

The previous sections suggest limitations and data gaps in research on STEC epidemiology, such as shortcomings in STEC surveillance and outdated data. The estimated proportions of STEC cases that develop HUS provided by Majowicz *et al.* (2014) and Kirk *et al.* (2015) were based on data circa 2010. Given the considerable number of reports published since then, these estimates may no longer reflect the current proportion of STEC cases that develop HUS. In addition, the proportion of STEC cases that develop HUS may vary based on characteristics of the study population, STEC, and study design (Table 1).

The proportion of STEC cases that developed HUS was based solely on data from one country, the United States (Gould *et al.*, 2013). The epidemiological research also suggests that STEC-HUS may disproportionately affect females more than males (Bell *et al.*, 1997; Ostroff *et al.*, 1990). The stratified estimates reported by Majowicz *et al.* (2014) and Kirk *et al.* (2015) did not include sex-stratified data on proportions of HUS following STEC, and serotype classification was limited to two categories, namely O157 and non-O157. No data were available on the proportions of HUS by different serotypes, given the important role of serotype on the clinical course of infection (Majowicz *et al.*, 2014).

1.9. Rationale of thesis

A systematic review is yet to be conducted to estimate the proportion of STEC cases that develop HUS. Such a systematic review would address the data gaps and limitations in Section 1.8. Therefore, estimates for cumulative incidence of HUS among symptomatic STEC cases currently persist as data gaps. As seen in Section 1.7.1, individual studies report higher frequencies of HUS in certain groups (Frank *et al.*, 2011; Loos *et al.*, 2012). However, these studies have not been systematically selected and synthesized to investigate any differences in the number of HUS cases

³ Number of STEC cases has not been reported by Minary *et al.* (2022) and other articles related to this outbreak

following STEC infection. Thereby, the stratification of incidence estimates by potential risk factors such as age, sex, serotype and STEC virulence profile (e.g., genes), will expand our knowledge about STEC infection.

To bridge these gaps, a systematic review on the cumulative incidence of HUS among STEC cases, is important to provide novel insight on STEC-related renal sequelae. This thesis was a systematic review and proportional meta-analysis undertaken to estimate the cumulative incidence of HUS following STEC infection.

2. Aims

The overarching aim of this thesis was to estimate the cumulative incidence of HUS among people with symptomatic STEC infection. The cumulative incidence is the number of incident HUS cases, expressed as a proportion of symptomatic STEC cases, i.e. the number of persons at-risk of developing HUS.

The specific objectives were:

1. To estimate the cumulative incidence of HUS in the 1-2 months following STEC infection, among people with symptomatic STEC infection
2. To stratify the estimate by age, sex, serogroup, STEC genes, STEC toxins, study year, WHO Regions, study setting, laboratory methods, and study quality, where possible

3. Methods

Scope of thesis

This systematic review was part of a larger systematic review on sequelae of STEC infection (PROSPERO CRD42023485066) that was commissioned by WHO (Principal Investigator: Dr. Shannon Majowicz) to support the WHO FERG initiative (Majowicz *et al.*, 2023; World Health Organization, 2022a). The initiative aims to report on the updated global estimates of foodborne disease burden and to devise public health action for 2025 (World Health Organization, 2022a).

The dataset which I used for the thesis, consisted of preliminary data for the commissioned systematic review. I extracted these data from included articles with verification for 27 included articles by my thesis supervisor during training of extractors, i.e. myself and a graduate research assistant (GRA). From this dataset, I used data only from the English-language records and data on HUS. Therefore, I have described methods only on including English language records and HUS as a sequela.

3.1. Development of review protocol

The current systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020, described by Page *et al.* (2021) (Appendix 1). I designed an initial review protocol based on the WHO concept note, which is a publicly available document describing the summary, methods, and logistics of the FERG initiative (World Health Organization, 2022b). I also used feedback from my thesis proposal, input from experts, and additional readings (Schwarzer and Rücker, 2022; Barker *et al.*, 2021; Borges Migliavaca *et al.*, 2020) to design the protocol.

Thereafter, my thesis supervisor and I revised the protocol based on feedback from the thesis committee and WHO contacts. The review protocol was prospectively registered in the International

Prospective Register of Systematic Reviews (PROSPERO) during the literature search stage (CRD42023485066) (Majowicz *et al.*, 2023) on 3 December 2023.

3.2. Conduct of systematic review

I conducted this systematic review as the lead reviewer (see: [Statement of Contributions](#)), alongside a team of trained second reviewers and experts on systematic reviews and epidemiology. The review team adhered to an instructional manual, which was continually trialled and revised during team training. I used Covidence (Covidence, Australia) to manage the systematic review.

3.3. Eligibility criteria

Table 2 lists the eligibility criteria for inclusion and exclusion of records in the systematic review. These criteria were based primarily on methodological guidance developed by Munn *et al.* (2015) from the Joanna Briggs Institute (JBI), called the CoCoPop mnemonic (condition, context, and population).

The review included published scientific papers and research studies, except for pre-prints, conference proceedings and abstracts. From grey literature, we included reports (annual, research, project), working papers, government documents, national surveillance data, white papers and unpublished scientific literature.

3.4. Information sources

The literature sources were selected based on expert advice issued by the WHO (2022b). I searched the following four bibliographical databases: PubMed, Web of Science, Ovid® Embase and Scopus. I searched the following five grey literature databases: GreyGuide (formerly SIGLE, OpenSIGLE, OpenGrey), Google Scholar, INASP Journals Online project, OAIster, WHO Library (WHO IRIS).

Table 2. Eligibility criteria to screen articles in systematic review to estimate cumulative incidence of HUS among STEC cases, 1990-2024

Element	Inclusion criteria	Exclusion criteria
Population	Human populations of all ages, sexes, ethnicities, and sociodemographic factors STEC ^a cases were defined as one or more of the following: - Symptomatic cases of STEC in humans - Confirmed or probable cases with laboratory-confirmed infection, or epidemiological link to a laboratory-confirmed case - Confirmed or probable cases of STEC infections without reported clinical and/or laboratory information	- Only on urinary tract infections associated with STEC in humans - Only on asymptomatic infections of STEC in humans - Studies on animals, foods, or environmental samples - <i>In vitro</i> studies - Studies on the management or treatment of STEC infection or HUS - Laboratory studies about isolating, diagnosing, or characterizing STEC
Condition	STEC cases that developed HUS	
Context	Study designs: - Observational studies: Case series, case-control studies, cross-sectional studies, cohort studies - Surveillance reports - Outbreak reports Geographical region: All geographical regions Time period: 1990 - 2024 Setting: Community-based and facility-based reporting	Study designs: - Case reports - Systematic reviews (used in citation tracking) - Narrative and scoping reviews - Randomized controlled trials, clinical trials - Abstracts, conference proceedings, preprints - Commentaries, letters - Book chapters - Studies without new information (e.g., duplicates) - Studies where the full text is not accessible

^a STEC may also be referred to as VTEC, EHEC, *E. coli* O157 and alternate nomenclature with variants (e.g., EHEC O157)

3.5. Search strategy

The design of search strategies encompassed a series of methods to ensure a balance of sensitivity and specificity in searches and to maximize recall of eligible studies. The complete list of search strategies is documented in Appendix 2, including links to each information source except for Ovid® Embase. Ovid® Embase was accessed by an institutional subscription held by the University of Waterloo.

I initiated the process by designing a search term table using tools provided by the Liaison Librarian of the School of Public Health Sciences, University of Waterloo. The search term table contained thesaurus terms for the main concepts of the research aims, namely (1) STEC, (2) HUS and (3) measures. I also used search terms from the previous systematic review on STEC epidemiology (Majowicz *et al.*, 2014) (Dr. Shannon Majowicz, e-mail communication to Udani De Silva, June 2023).

Using these search strategies as a basis, I constructed original search strategies based on the eligibility criteria and research questions of my thesis. For example, I did not use “bloody diarrhea”, “hemorrhagic colitis” and “thrombotic thrombocytopenic purpura” as search terms although the terms were in search strategies of the systematic review by Majowicz *et al.* (2014). I continuously consulted with the Liaison Librarian throughout the development and refinement of the search strategies. For instance, I considered including “Gasser’s syndrome” in addition to HUS but considered the term redundant. We tested different versions of the search strategy for PubMed by ensuring that key eligible studies (e.g., Frank *et al.* (2011)) were included in the search recall. Thereafter, I customized each search strategy to individual specifications of the databases.

I conducted the literature searches with a publication date range of 1 January 1990 to the present year. I did not apply filters for geographical regions and languages. I applied filters to remove unpublished literature (e.g., conference proceedings, pre-prints, publications only with abstracts) and to focus on ‘Human’ as ‘Species’.

The search results of the following databases were combined into a single database in Zotero (Corporation for Digital Scholarship, USA): PubMed, Web of Science, Ovid® Embase, Scopus, OAIster, WHO IRIS. The individual records from these databases were de-duplicated using both Zotero and Covidence (automatically upon import) to ensure maximum de-duplication. I stored the collection of records awaiting title and abstract screening on Covidence. The search results of Google Scholar, GreyGuide and INASP Journals Online were stored as Portable Document Formats (PDFs) for manual screening, as described in Section 3.6.1.

3.6. Selection process

Together with my thesis supervisor, I trained a team of second screeners during title and abstract screening and full-text screening according to the instructional manual. To ensure consistent screening, the second screeners and I independently screened titles and abstracts of 100 records from the systematic review in a separate Covidence project to calculate interrater reliability using a kappa (κ) coefficient (McHugh, 2012). The training allowed screeners to become accustomed to the process. My thesis supervisor and I corrected errors in the screening process and instructional manual following training at both screening stages. Thereafter, I calculated the κ coefficient for interrater reliability using a built-in Covidence function. I considered a high reviewer agreement to be a κ value higher than 0.60 during training based on guidelines by McHugh (2012). I also liaised with Covidence Support to confirm whether reviewer agreement was sufficient (Julie Brown, e-mail communication to Udani De Silva, March 2024).

Thereafter, the review team and I screened records independently in both title and abstract and full text screening stages. We adhered to the instructional manual with additional guidance issued to screeners when needed. After training sessions and during the screening process, the screeners informed me and my thesis supervisor of their questions, which we answered only if they maintained blinded screening

3.6.1. Title and abstract screening

We adopted two different approaches to screen titles and abstracts, either via (1) Covidence or (2) manual screening for databases that did not facilitate exports of literature searches. In the first approach, a blinded second screener and I assessed each record on Covidence according to the instructional manual, with a third screener to resolve conflicts.

In the second approach, I de-duplicated and screened search results from Google Scholar, INASP Journals Online and GreyGuide manually outside of Covidence. Due to the large search recall from the Google Scholar searches (Appendix 2), I limited the search results to 100 records from each of the six search strategies. I screened records from Google Scholar as a single screener. To do this, I firstly calculated reviewer agreement in dual-screening records ($n = 14$) from Google Scholar searches by my thesis supervisor and myself before single screening, to ensure consistency. I screened the records from INASP Journals Online alongside my thesis supervisor as a second screener. To maximize the identification of eligible studies, I conducted backward citation tracking (reference list screening) of systematic reviews and included articles (after full text screening) and contacted WHO experts to refer additional studies to me.

3.6.2. Full text screening

All eligible records from title and abstract screening, including those from manual screening outside Covidence, were advanced into full text review on Covidence. To ensure consistent dual-screening, I retrieved PDFs of records awaiting full text review via Covidence automation, open-source bibliographical databases (e.g., PubMed), OMNI, interlibrary loans through the University of Waterloo Library, correspondence with article authors, and professional networks. Thereafter, a second screener and I independently assessed the eligibility of records for review inclusion, with a third screener to resolve conflicts. We categorized the excluded articles from full text review on Covidence by predefined exclusion reasons based on the eligibility criteria. I have listed and

detailed the exclusion reasons in Appendix 3. All included records were advanced from full text review to data extraction.

3.7. Data collection and items

The data extraction template used in the systematic review was based on a standard data extraction form issued by the WHO (2022b). During the pilot step, I developed an initial draft form to include other variables (e.g., sex, serotype) unique to this systematic review based on the research questions and PROSPERO protocol (Majowicz *et al.*, 2023). Then, my thesis supervisor and I used two key studies (Gould *et al.*, 2013; Frank *et al.*, 2011) from the included records to further revise the form. After reviewing literature on STEC-HUS epidemiology, we selected important determinants for HUS development from STEC infection as predictor variables in data extraction. All predictor variables were categorical variables.

After several discussions with my thesis supervisor and Carlotta Di Bari at Sciensano, we developed a codebook of variables for this systematic review. We adhered to instructions from WHO and Sciensano to ensure the data from the articles were entered into the extraction form exactly as they were and according to instructions for consistency. I was trained by my thesis supervisor and Carlotta Di Bari in regular meetings and email correspondence. Then, I would be given instructions and have questions on extracted studies clarified. Thereby, my thesis supervisor, as a second extractor, verified data, which I had extracted from 27 included articles, during training sessions. Thereafter, I extracted data from each included article as a single extractor into Microsoft Excel spreadsheets, to generate the final dataset for the systematic review.

3.8. Study risk of bias assessment

I used the Critical Appraisal Tools for risk of bias assessments, specifically the Checklists for Analytical cross sectional studies, Case control studies, Prevalence studies, Case series, and Cohort studies, by the Joanna Briggs Institute (2020). The pre-defined categories for study designs

in this systematic review were ‘Outbreak report’, ‘Cross-sectional study’, ‘Active surveillance’, ‘Passive surveillance’, ‘Cohort study’, ‘Case series’, ‘Modelling study’ and ‘Other’. The category of ‘Other’ included case-control study, cluster, and chart review, as study designs. To create assessment forms, I used Microsoft Excel spreadsheets to enter the exact checklist items from each JBI Tool, as shown in Appendix 7. Then, I adapted these items to the systematic review by entering descriptions for each checklist item specific to the systematic review.

JBI Critical Appraisal Tools are available for cross-sectional studies, case-control studies, case series and cohort studies. I adapted the JBI Checklists for case series and prevalence to also be used for outbreak reports, clusters, chart reviews, and surveillance studies. By definition, case series are descriptions of patient characteristics and outcomes during defined timeframes (Torres-Duque, Patino & Ferreira, 2020). As outbreaks, cluster reports, and chart reviews are similar to case series by definition.

Currently, there are no risk of bias tools for surveillance reports. By definition, public health surveillance systems encompass the continual collection, analysis, and dissemination of data to monitor and improve population health (Chiolero & Buckeridge, 2020). While the focus of this systematic review is incidence and not prevalence, the JBI Tool for Prevalence studies was deemed appropriate, because the included studies used data from surveillance systems, which store all cases from inception to the present as prevalent cases. Therefore, I adapted the JBI Tool for Prevalence to permit study quality assessment for surveillance studies.

This way, I created three spreadsheets for case series, prevalence studies, and case-control studies. To pilot the spreadsheets, I used three studies each for the case series and prevalence spreadsheets and one study for the case-control spreadsheet, as there were only eight case-control studies. I used these studies to revise the descriptions under each checklist item in the pilot step.

I trained a GRA using ten studies each for the Case series and Prevalence spreadsheets to ensure that we reached the same consensus. I described how to use the case-control spreadsheet with the study from the pilot step. I instructed the GRA to read the full-length PDFs of the articles,

supplementary material, and additional readings (e.g., statistical methods, study design). The GRA answered all checklist items in the spreadsheets as ‘Yes’, ‘No’, ‘Unclear’ or ‘Not applicable’. Likewise, the GRA completed study quality assessments for all included studies. I verified their assessments as a second reviewer. Afterwards, I used pre-set calculations with the ‘IF’ function, on Microsoft Excel to assign study quality ratings according to the following criteria on the PROSPERO protocol (Table 3):

Table 3. Final study quality ratings for each included study based on numbers of Checklist items answered ‘Yes’ in study quality assessment

Quality rating	Criteria
HIGH	$\geq 75\%$ questions answered ‘Yes’
MODERATE	50 – 74% questions answered ‘Yes’
LOW	$< 50\%$ questions answered ‘Yes’

3.9. Synthesis methods

I conducted all data analyses using Microsoft Excel (Microsoft, USA) and R v.4.4.0 (The R Foundation for Statistical Computing, Austria). I performed data cleaning on the original dataset by combining data to produce single rows for studies, carrying out any data checks and corrections, deleting rows of duplicated data, and deleting unneeded columns and rows from the dataset. During data checks (especially for complex studies with a lot of data), I checked whether counts of STEC and HUS cases were complete, whether stratified data were complete or whether as many data entries were complete as possible. To correct these errors, I would re-assess the corresponding full text of the article on Covidence and rectify any errors. To ensure completeness of data entry, I used the Microsoft Excel ‘COUNT’ functions to ensure that every entry for STEC cases had a corresponding value for HUS cases. I did not perform descriptive analyses (e.g., chi-squared test), as the predictors had been pre-determined to be included in any analyses regardless of any associations. I summarized all included studies in a table, using Study ID, Study synopsis, number of STEC cases, and number of HUS cases. I visualized all included studies using a forest plot for overall cumulative incidence, with case numbers and proportions for individual studies.

I based the R code on statistical methods and programming language described by Wang (2023), which were specific to proportional meta-analyses, with supplemental information by The Comprehensive R Archive Network (CRAN) (no date) (<https://cran.r-project.org/>). I used the R packages, ‘meta’, and ‘metafor’, the R functions of *escalc*, *rma*, *metaprop*, and *forest* for the unstratified meta-analysis and subgroup analyses, and the R functions of *escalc*, *rma*, and *metareg* for meta-regression. All proportional meta-analyses, subgroup analyses and meta-regressions conformed to inverse-variance, random-effects meta-analyses of the conventional method by DerSimonian and Laird (1986) for single proportions, without transformations.

I estimated the overall cumulative incidence of HUS among symptomatic STEC infections (including heterogeneity) using a pooled proportional meta-analysis. Thereafter, I investigated between-study variance and statistical heterogeneity using summary statistics from the unstratified meta-analysis (e.g., I^2 , τ^2), subgroup analyses for each categorical variable, univariable meta-regression models and multivariable meta-regression.

The pre-defined predictor variables for subgroup analyses and meta-regression models were all categorical variables. The variables were age, sex, STEC serogroup, STEC genes, STEC toxins, year range of data, WHO Region (<https://www.who.int/countries>), study settings and STEC detection methods (Majowicz *et al.*, 2023). The categories for these predictors are in Table 4. The subgroup analyses and univariable meta-regression were done by examining one predictor per analysis. The multivariable meta-regression model included all the predictors in Table 4.

Table 4. Categories of each predictor variable for subgroup analyses and meta-regression based on published literature and PROSPERO protocol

Predictor	Categories
Age	0 – 4 years 5 – 19 years ≥ 20 years
Sex	Male Female
STEC serogroups ^a	Co-infections; O-nontypeable; non-O157; O103; O104; O111; O113; O117; O118; O121; O128; O145; O146; O15; O156; O157; O174; O26; O28; O41; O45; O5; O50; O55; O69; O70; O76; O8; O80; O88; O91; Other; Ungroupable; Unknown; Unspecified non-O157; Untypeable

	Co-infections: Multiple STEC serogroups detected (Note: The study may also give case numbers stratified by some or all STEC serogroups) O-nontypeable: STEC with O antigens Non-O157: Studies list specific non-O157 serogroups as a serogroup breakdown Other: Studies define serogroups as 'Other' without additional information Ungroupable: Studies define serogroups as 'Ungroupable' without additional information Unknown: Studies define serogroup as 'Unknown' without additional information Unspecified non-O157: Studies define serogroups only as 'non-O157' without a breakdown of all non-O157 serogroups detected Untypeable: Studies define serogroups only as 'Untypeable' without additional information
STEC genes ^a	<i>stx1</i> or subtypes only <i>stx2</i> or subtypes only <i>stx1</i> + <i>stx2</i> <i>stx1</i> + Other genes <i>stx2</i> + Other genes <i>stx1</i> + <i>stx2</i> + Other genes Other genes
STEC toxins ^a	Stx1 or subtypes only Stx2 or subtypes only Stx1 + Stx2 Stx1 + Stx2 + Hemolysin
Year range	1990-1994; 1995-1999; 2000-2004; 2005-2009; 2010-2014; 2015-2019; 2020-2024
WHO Region	African Region Eastern Mediterranean Region European Region Region of the Americas South-East Asia Region Western Pacific Region
Study setting	Outbreak - general community (single) Outbreak - facility or event Outbreak - general community (multiple or dispersed) Non-outbreak - disease surveillance/registry (unadjusted) Non-outbreak - surveillance, adjusted Non-outbreak - health facility Cluster – family Cluster - facility Cluster - other Non-public health Other

STEC detection methods ^a	Culture only Molecular only Culture + Molecular + Other Culture + Molecular Culture + Other Molecular + Other Other
Study quality	Low Moderate High

^a Mutually exclusive subgroups in the variable

3.10. Protocol deviations

I altered a few methods from relevant sections of the PROSPERO protocol while conducting the systematic review. I had specified to include articles published between 1 January 1990 to November 2023 in the PROSPERO protocol. However, I used the date, on which I conducted the literature search, for end dates (Appendix 2). I did not conduct updated literature searches following the initial searches.

I stratified the cumulative incidence of HUS by more variables in addition to age, sex, country, year, and STEC serotype, which had already been specified in the PROSPERO protocol. Ultimately, I stratified the estimates by age, sex, STEC serogroup, STEC genes, STEC toxins, year, WHO Region, study setting, STEC detection methods, and study quality. For the stratified estimates, I used STEC serogroups instead of STEC serotypes, because too many serotypes existed for categorization. Similarly, I categorized each included article by the WHO Regions (<https://www.who.int/countries>) instead of country, to minimize categories. An initial analysis revealed that too many country categories existed, and some categories would have only one included article, which was not appropriate for meta-analyses (Wang, 2023). I did not conduct tests for publication bias, as Wang (2023) does not recommend assessing publication bias using conventional methods in proportional meta-analyses.

4. Results

4.1. Summary of literature searches and screening

The searches of the four bibliographical databases collectively retrieved 3,704 records, and the searches of the five grey literature databases retrieved 1,202 records. Collectively, 4,906 records were retrieved solely via database searches. I proceeded to title and abstract and full text screening after high reviewer agreement in training. The κ coefficients described in Section 3.6 for training second screeners and Section 3.6.1 for Google Scholar have been described in Table 5.

Table 5. Kappa (κ) coefficients for dual-screening reviewer agreement in screener training and Google Scholar screening

Section in Methods	κ coefficient
3.6. Selection process Title and abstract screening of 100 records by thesis author and second screeners during training	0.64 – 0.91
3.6.1. Title and abstract screening Title and abstract screening of 14 records from Google Scholar search recall by thesis author and thesis supervisor	0.10 ^a

^a κ value does not account for screening of duplicates by myself and my thesis supervisor, reducing original number of records to screen from 60 records to 14 records

After removing 1,593 duplicates and screening 2,667 titles and abstracts, the second screeners and I advanced 1,005 records to full text review. After screening 646 titles and abstracts from INASP Journals Online and Google Scholar in manual screening, I advanced 27 records for full text review. Additionally, I retrieved 57 records via backward citation tracking and 8 records via experts for full text review.

In summary, the second screeners and I advanced 1,067 records to full text review. After full text review, the second screeners and I included 269 records in the systematic review and meta-analysis. The entire review process has been described in Figure 1 and detailed in Appendix 3.

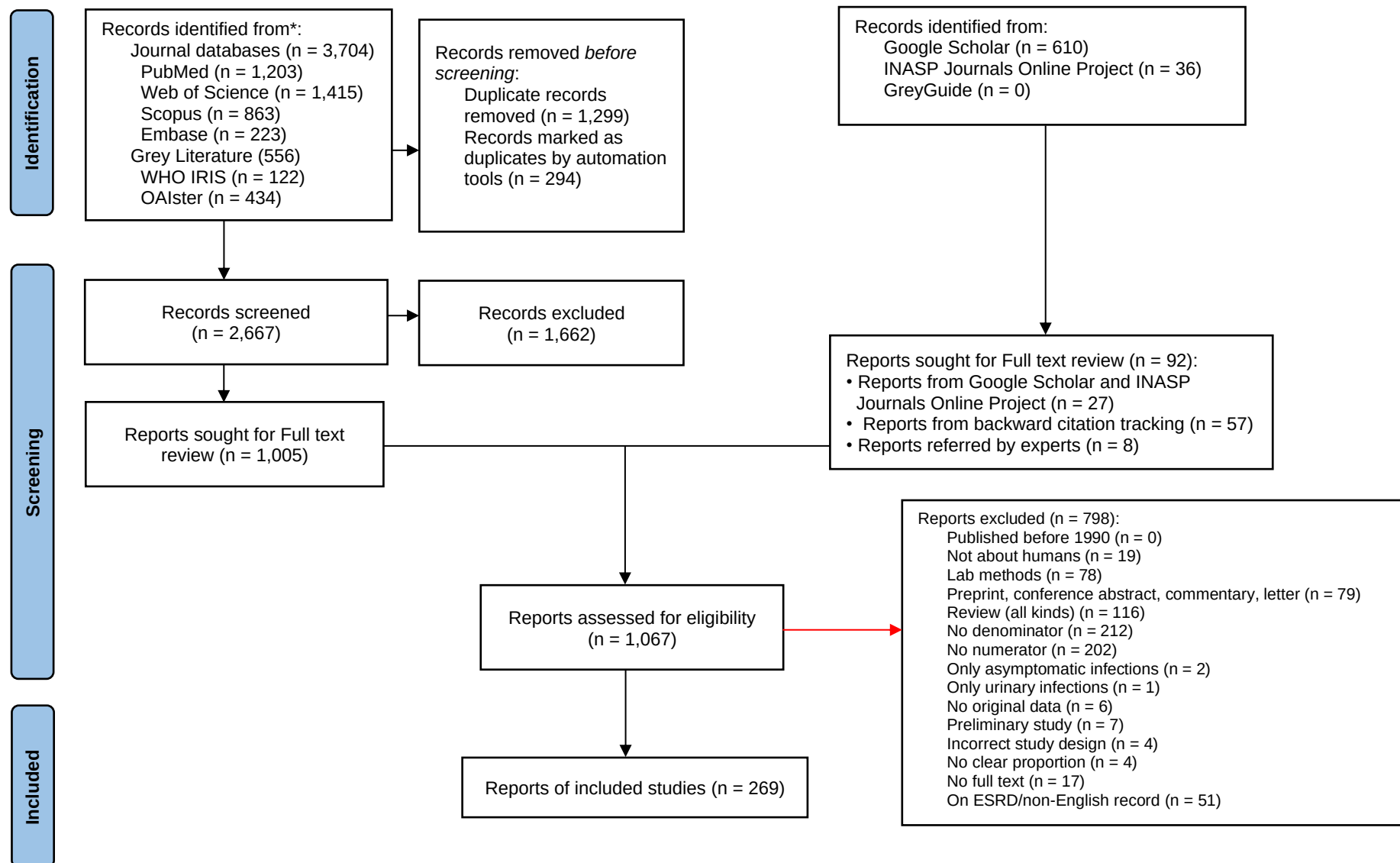


Figure 1. PRISMA Flow Diagram 2020 documenting systematic review of thesis

4.2. Description of included studies

I included 269 studies in the systematic review and meta-analysis following the completion of screening. All included studies are described in Table 6. Collectively, the systematic review included 189,350 STEC cases and 10,014 HUS cases. The lowest and highest sample sizes of STEC cases were 3 and 29,094, respectively. The lowest and highest numbers of HUS cases were 0 and 845, respectively. The ages of participants ranged between 0 years to 98 years.

A widespread geographical distribution was noted among the included studies, with most studies being from the WHO Region of the Americas and WHO European Region. The specific countries of origin for the included articles were Argentina (n=3), Australia (n=6), Belgium (n=5), Canada (n=15), Denmark (n=6), Finland (n=4), France (n=4), Germany (n=14), Israel (n=2), Italy (n=7), Japan (n=19), the Netherlands (n=2), Norway (n=6), Poland (n=2), Spain (n=2), Sweden (n=4), Switzerland (n=3), United Kingdom (n=59), and the United States (n=91). Further, one study each originated from Bosnia and Herzegovina, Brazil, Egypt, Hungary, Ireland, Republic of Korea, Romania, Slovakia, and Uruguay. An additional six studies included data from multiple countries.

Among the included studies, 21 studies were active surveillance studies, 19 studies were case series, 132 studies were outbreak reports, 81 studies were passive surveillance studies, 9 studies were case-control studies, 5 studies were cluster reports, 1 study was a retrospective chart review and 1 study was a combination of both passive and active surveillance.

4.3. Cumulative incidence of HUS among symptomatic STEC cases

All 269 studies presented numbers of STEC and HUS cases, mostly as count data or sometimes as proportions. The pooled estimate from the meta-analysis, for the cumulative incidence of HUS among symptomatic STEC cases was 8.22% (95% CI, 7.82 – 8.61) (Figure 2). The lowest and highest estimates from individual studies in the meta-analysis were 0% and 100%, respectively.

Table 6. Summary of the 269 included studies in this systematic review including STEC and HUS cases

#	Study ID	Country of data	Study synopsis	Number of cases of	
				STEC	HUS
1	Ackers 1998	United States of America	• STEC outbreak in Montana, USA during July 1995 • Age of participants ranged from 4-86 years	40	1
2	Ackman 1997	United States of America	• STEC outbreak in Dutchess County, New York, USA during 17-24 July 1994 • STEC outbreak was associated with swimming in a park lake • Age of participants ranged from 1-13 years	12	2
3	Acquaotta 2017	Italy	• Surveillance data in Lombardy Region, Italy from 2010-2013 • Age of participants ranged from 0-20 years	53	5
4	Adams 2019a	United Kingdom	• Surveillance data in England from 2011-2014 • Data on paediatric STEC and HUS cases identified in the Public Health England (PHE) National Enhanced Surveillance System for STEC (NESSS) and British Paediatric Surveillance Unit HUS surveillance • Age of participants ranged from 0-15 years	1059	207
5	Adams 2019b	United Kingdom	• Surveillance data in England of all symptomatic STEC cases with an enhanced surveillance questionnaire (ESQ) reported to NESSS between 1 January 2010 and 31 December 2015 • Data from the PHE NESSS	3972	154
6	Afza 2006	United Kingdom	• An outbreak of <i>E. coli</i> O157 in West Midlands, UK • Based at an elderly care home • Participants included residents and staff identified via case finding and routine surveillance • Cases in North Staffordshire among the community from General Practitioners, hospital clinical and microbiology staff • <i>E. coli</i> O157 infections since 1 July 2001	88	1
7	Ahn 2009	United States of America	• A time-space cluster in Missouri, USA • <i>E. coli</i> O157:H7 infection was identified by St Louis Children's Hospital (SLCH) physicians during 19-20 October 2007	5	2

			- Cluster was associated with contaminated deer sausage, a novel vehicle - Age of participants ranged from 3-33 years		
8	Akashi 1994	Japan	A large outbreak of <i>E. coli</i> O157 in a nursery school in Saitama, Japan from September to November 1990	121	20
9	Al-Jader 1999	United Kingdom	- An outbreak of <i>E. coli</i> O157 in a nursery in North Wales (possibly Bangor), UK caring for 104 infants and preschool age children - Age of participants ranged from 0-7 years - From 10 August to 30 September 1995	31	2
10	Alexander 1995	United States of America	- An outbreak of <i>E. coli</i> O157 in Washington and California, USA in 1994 - Linked to dry-cured salami purchased at a local grocery chain - Age of participants ranged from 1-77 years	20	1
11	Ardissino 2020	Italy	- Surveillance data from 63 pediatric units in ItalKid-HUS based in Northern Italy - a screening program of bloody diarrhea for STEC infection in children - During 2010 - 2019 - Participants were aged <20 years old has been developed - The referral pediatric population was 2.3 million people	214	34
12	Ardissino 2021	Italy	- Surveillance data during 2010-2019 from 63 pediatric units in ItalKid-HUS based in Northern Italy - a screening program of bloody diarrhea for STEC infection in children - Participants were aged <20 years old has been developed - Most common serotypes are O157, O26, O103, O111, O145, and O104 in study	214	34
13	Awofisayo-Okuyelu 2019	United Kingdom	- Outbreak-associated cases from England and Wales - During 2009 - 2016 - Data from PHE and NESSS	205	17
14	Bai 2021	Sweden	Surveillance data from Jönköping County, Sweden from diarrheal patients and individuals from April 2003-2017	184	5

15	Bell 1994	United States of America	• An outbreak in Greater Seattle area, USA linked to hamburgers at a fast-food chain (chain A) from 1 December 1992, through 28 February 1993 • Active surveillance for bloody diarrhea and <i>E. coli</i> O157:H7 infection through hospital emergency departments, infection control practitioners, and laboratories in the three counties forming the greater Seattle area • Age of participants ranged from 0-88 years	501	45
16	Bell 1997	United States of America	• A large outbreak of <i>E. coli</i> O157:H7 in Washington, USA linked to consumption of inadequately cooked hamburgers in restaurants of Chain A in Washington State • Occurred in January or February 1993 • Age of participants ranged from 0-15 years	278	37
17	Belongia 1991	United States of America	• An outbreak in a junior high school in Minnesota, USA during October 1988 • STEC-infected children were more likely than controls to have eaten heat-processed meat patties in the school cafeteria on a specific day • Age of participants ranged from 9-15 years	54	0
18	Bender 2004	United States of America	• FoodNet surveillance areas for laboratory confirmed infections entered into the CDC Public Health Laboratory Information System and compiled at the CDC • Laboratory-confirmed cases of <i>E. coli</i> O157 infection via routinely contacting each clinical laboratory in their surveillance areas • Data from 1996-1999	1734	91
19	Bennett-Wood 2004	Australia	• Hospital-based data from Melbourne, Australia during mid-February 1997 to mid-February 1998 • Two separate studies: ○ Study 1: Royal Children's Hospital, Melbourne, for 12 months from mid-February 1997	16	2

			○ Study 2 was undertaken for 12 months from in August 1998, and included specimens from both the Royal Children's Hospital and the Monash Medical Centre		
20	Bergmire-Sweat 2000	United States of America	● An outbreak in Texas, USA from Tarrant County Health Department, USA, Texas Department of Health and CDC via routine testing ● Data from 1999 ● Age of participants ranged from 12-53 years	58	2
21	Besser 1993	United States of America	● An outbreak of <i>E. coli</i> O157:H7 in Southeastern Massachusetts, USA due to fresh-pressed apple cider ● Illnesses occurring in Swansea, Somerset, or Fall River, Mass (subsequently referred to as the "Fall River area"), in October or November 1991 ● Age of participants ranged from 2-70 years	23	4
22	Beutin 1994	Germany	● Surveillance data from 10 of the 16 Federal States of Germany ● STEC detection based on verotoxins ● Data from 1985-1992 ● Age of participants ranged from 0-74 years	42	6
23	Beutin 1998	Germany	● Surveillance data from Germany from 37 private, hospital, and public health laboratories from rural and urban areas of Germany ● Data from 1996 ● Age of participants ranged from 0-72 years	89	4
24	Beutin 2002	Germany	● All cases were from sent to the Robert Koch Institute based from Bavaria, North Rhine Westfalia (NRW), Mecklenburg-Pomerania (MVP), Berlin, Lower Saxony, Schleswig-Holstein, Bremen, Hesse, Thuringia, Rheinland-Pfalz, Baden Wurtemberg, Brandenburg, Hamburg and Saxony (14 federal states), Germany ● Data from 1996	168	15
25	Bokete 1993	United States of America	Bacterial cultures from the microbiology laboratory of the Children's Hospital and Medical Center between 15 January 1991, and 10 January 1991 in Seattle, USA	18	0

26	Bottichio 2020	United States of America	• PulseNet, the national molecular subtyping network for foodborne disease surveillance from 37 states • A large multistate outbreak of <i>E. coli</i> O157 (and O61) infections, linked to romaine lettuce from the Yuma growing region • Between 13 March 2018 and 22 August 2018 • Age of participants ranged from 1-93 years	240	28
27	Bradley 2012	United States of America	• An outbreak of <i>E. coli</i> in rural Oklahoma, USA associated with a buffet style restaurant, during 10 and 24 August 2008 • Age of participants ranged from 0-89 years	341	25
28	Braeye 2014	Belgium	• A case-control study detecting <i>E. coli</i> O157:H7 in North-East Limburg region, Belgium region from 30 May 2012 until 14 June 2012 • Age of participants ranged from 6-84 years	24	5
29	Brandal 2015	Norway	Surveillance data from Norway STEC during 1992-2006, obtained from Norwegian Surveillance System for Communicable Diseases (MSIS) at the Norwegian Institute of Public Health (NIPH)	513	57
30	Brewster 1994	United Kingdom	An outbreak of <i>E. coli</i> O157 in south-east Scotland, UK during 1992	5	1
31	Brigotti 2019	Italy	• Surveillance data from Northern Italy from pediatric patients presenting with STEC-linked bloody diarrhea • Age of participants ranged from 0-15 years • During 2010 – 2015	20	3
32	Brooks 2004	United States of America	• An outbreak in Texas, USA during mid-June 1999 based on the Texas Department of Health • Linked to a cheerleading camp held 9–11 June 1999 among patients with gastroenteritis, including bloody diarrhea • Age of participants ranged from 12-53 years	55	2
33	Brooks 2005	United States of America	• Data from STEC isolated from state public health laboratories to the CDC's reference laboratory • Data between 1983 and 2002	940	21
34	Brown 2012	United States of America	• An outbreak in Colorado, USA beginning on or after 24 May 2010	41	0

			• The largest reported outbreak of laboratory-confirmed O26:H11 infection in the United States • The largest reported non-O157 STEC outbreak in a US childcare center		
35	Bruce 1996	United States of America	• An outbreak in Clark County, Washington, USA during August 1999 • Age of participants ranged from 0-39 years	37	3
36	Buteau 2000	Canada	• Culture-proved, sporadic <i>E. coli</i> O157:H7 infections treated at Sainte-Justine Hospital, Montreal, Quebec, Canada • The medical charts of children <18 years old between 15 June 1987, and 1 December 1997 reviewed	369	72
37	Butt 2021a	United Kingdom	• Small outbreak in Scotland and England with ongoing transmission of <i>E. coli</i> O157:H7 PT21/28 harbouring <i>stx2a/stx2c</i> in 2019 • Age of participants ranged from 1-46 years	7	0
38	Butt 2021b	United Kingdom	• <i>E. coli</i> O26:H11 <i>stx1/eae</i> infections in Scotland, England and Wales, UK in 2019 • Age of participants ranged from 3-77 years	26	0
39	Butt 2022	United Kingdom	Symptomatic cases of <i>E. coli</i> O157 during 2009-2014 and 2015-2019 in England, UK	7598	323
40	Buven 2012	Belgium	Surveillance data from Universitair Ziekenhuis Brussel and six hospitals in Brussels-Capital Region (BCR), Belgium during the years 2008 to 2010	136	5
41	Byrne 2014	United Kingdom	• An outbreak in England, UK due to non-O157 STEC isolates between 1 January 2009 and 31 December 2013 • Data from the Gastrointestinal Bacteria Reference Unit (GBRU)	74	18
42	Byrne 2015	United Kingdom	• Surveillance data from England, UK based NESSS and PHE data during 2009-2012 • ESQs available and symptomatic infection	3359	215
43	Byrne 2016	United Kingdom	• An outbreak across England and Scotland, UK in 2014	20	1

			• Data from NESSS, which collects standardized demographic, clinical, and exposure data on all cases of STEC reported in England using ESQs • Age of participants ranged from 12-62 years		
44	Byrne 2020a	United Kingdom	• Surveillance data from England, UK on all <i>E. coli</i> O157:H7 cases in England reported from January 1, 2009, through December 31, 2019 • Data from patients with ESQs and WGS on isolates based on NESSS	3131	86
45	Byrne 2020b	United Kingdom	• An outbreak across England and Scotland, UK based on data from NESSS, during 28 September 2017 to 23 November 2017 • Age of participants ranged from 1-65 years	12	4
46	Cadwagan 2002	United Kingdom	• Data on <i>E. coli</i> O157 cases from the Aberdeen Royal Infirmary in North East Scotland, UK collecting microbiologically-confirmed cases of <i>E. coli</i> infection during 1997 to 2000 • Age of participants ranged from 16-93 years	32	6
47	Cai 1998	United States of America	• <i>E. coli</i> O157:H7 cases across 16 counties of north Central Wisconsin, USA • Data from 1991 - 1997 • Retrospective review of cases and case finding via Wisconsin health services to identify cases any outbreak cases • Age of participants ranged from 0-86 years	66	2
48	Caroll 2019	United Kingdom	Surveillance data from Southeast England, UK from 1 November 2013 to 31 March 2017 in an area served by the Ashford and Horsham Health Protection Teams of PHE	548	1
49	CDC 2007	United States of America	• A multistate outbreak across the US linked to eating frozen pizza that contained pepperoni and was produced by the General Mills Company • Cases from Illinois, Kentucky, Missouri, New York, Ohio, Pennsylvania, South Dakota, Tennessee, Virginia and Wisconsin in the US • Cases became ill between 20 July 2007 10 October 2007	21	4

			• Age of participants ranged from 1-65 years		
50	CDC 2009	United States of America	• A multistate outbreak across California, Connecticut, Massachusetts, Maryland, Maine, New Hampshire, New York, and Vermont, USA • First reported illness began on 17 September 2009, and the last began on 6 November 2009 • Age of participants ranged from 1-88 years	26	5
51	CDC 2010a	United States of America	• A multistate outbreak during 2009 across California, Colorado, Florida, Hawaii, Iowa, Indiana, Kansas, Michigan, Minnesota, Nevada, Ohio, Oklahoma, South Dakota, Tennessee, Utah, and Washington, USA • Cases detected using DNA fingerprint or PFGE pattern reported from 13 states • Age of participants ranged from 14-87 years	21	1
52	CDC 2010b	United States of America	• An outbreak across Arizona, California, Colorado, New Mexico and Nevada, USA with case finding via PulseNet surveillance during 2010 • Age of participants ranged from 1-85 years	38	1
53	Chalmers 1999	United Kingdom	Surveillance data from all five health authority areas in Wales, UK during 1990	353	17
54	Cimolai 1994	Canada	• Patients were treated at a pediatric hospital in British Columbia, Canada during 1984-1989 • <i>E. coli</i> strains were confirmed by BC CDC or the Enteric Reference laboratory for Disease Control Ottawa for <i>E. coli</i> O157:H7	118	28
55	Clark 1997	United Kingdom	An outbreak in northwest England, UK linked VTEC O157 infection in East Lancashire and neighbouring areas of Yorkshire between 1 November and 22 December 1996	6	1
56	Cody 1999	Canada and the United States of America	• An outbreak of <i>E. coli</i> O157:H7 across Western US, including California, Colorado, Washington and British Columbia, Canada	70	14

			• A small cluster of <i>E. coli</i> O157:H7 infections epidemiologically linked to a particular brand (brand A) of unpasteurized apple juice during Fall 1996 • Age of participants ranged from 1-46 years		
57	Coia 1998	United Kingdom	• An outbreak across Scotland (Health boards of residence: Grampian, Lothian, Lanarkshire, Tayside, Greater Glasgow, Ayrshire & Arran, Fife, Dumfries & Galloway, Argyll & Clyde, Borders, Forth Valley, Orkney, Highland, Shetland, Western Isles), UK over an 18-month period from 1 July 1992 to 31 December 1993 • Age of participants ranged from 0-87 years	138	21
58	Crampin 1999	United Kingdom	• An outbreak in Somerset, Southwest England, UK linked to VTEC O157 that was associated with attendance at the Glastonbury Music Festival at the end of June 1997 • The open-air music festival held in Somerset, South West England, is attended by around 80,000 people	8	1
59	Crump 2002	United States of America	• An outbreak across five counties in eastern Pennsylvania (including Montgomery County) and one county in New Jersey, USA • Most cases were visitors to a popular petting farm (traditionally a dairy farm) • Data from 2000 • Age of participants ranged from 1-52 years	51	8
60	Curran 2017	United States of America	• An outbreak in Washington State, USA after 27 April 2015 • <i>E. coli</i> O157:H7 infections were associated with a possible outbreak to a dairy education event held in a barn 20–24 April during school field trips • Age of participants ranged from 0-47 years	60	6
61	Davies 2005	United States of America	An outbreak in North Carolina and Florida, USA based on data from North Carolina Division of Public Health, Florida Department of Health Bureau of Laboratories and Arizona Department of Health Services during 2004-2005	104	22

62	Davis 1993	United States of America	• A multistate outbreak across Washington, Idaho, California and Las Vegas, USA based on state health department • Linked to consumption of hamburgers from a restaurant chain • Data from 1992 - 1993 • Age of participants ranged from 0-83 years	583	41
63	Dedic-Ljubovic 2009	Bosnia and Herzegovina	• Children with acute diarrhoeal diseases, admitted to the paediatric clinic at the University of Sarajevo in Bosnia and Herzegovina • Data from 2007 - 2008 • Age of participants ranged from 0-10 years	85	2
64	Den Ouden 2023	United Kingdom	• Surveillance data from England (most cases resided in the North of England), UK referred to the GBRU and UK Health Security Agency (UKHSA) • Data from 2015 - 2022	40	7
65	Desai 2013	United Kingdom	• An outbreak likely London, England at a primary school in 2006 • Cases were positive for <i>E. coli</i> O157 and were symptomatic • Age of participants ranged from 1-11 years	22	1
66	Devaux 2015	Germany	Multinational outbreak of <i>E. coli</i> O104 in 2011, based on data from European Centre for Disease Prevention and Control (ECDC) for European Union outbreak investigation	98	37
67	Diallo 2011	United States of America	An outbreak in Northeastern Oklahoma (Tulsa and neighboring counties), USA during October 1999 linked to <i>E. coli</i> O157:H7	16	3
68	Diercke 2014	Germany	• A cluster of <i>E. coli</i> O104:H4 in Lower Saxony and Bavaria, Germany • Linked to a family birthday party on 28 May 2011 in a community centre in the south of Lower Saxony party during a large <i>E. coli</i> O104:H4 outbreak in Germany	23	4
69	Doyle 2004	Australia	Surveillance data on screening of stool samples for STEC toxin genes, <i>stx1</i> and <i>stx2</i> between January 1999 and December 2002 in South Australia and Hunter Health Area of New South Wales, Australia	143	5
70	Dundas 2001	United Kingdom	• An outbreak in central Scotland, UK due to <i>E. coli</i> O157:H7 based on the Information Statistics Division of the National Health Service in Scotland	345	34

			• Cases occurred from 20 November 1996 through 16 December 1996 • Linked to a retail source in which cooked meats were cross-contaminated		
71	Espié 2006	France	• A family cluster in the district of Vosges, France around 4 June 2004 via routine surveillance for HUS • Source of infection was fresh unpasteurized goats' cheese, produced by an independent producer • Age of participants ranged from 0-14 years	3	2
72	Ethelberg 2004	Denmark	• Surveillance data in Denmark based on clinical specimens used in analysis for bacterial gastrointestinal pathogens are submitted to the Statens Serum Institut (SSI) or to 1 of 10 regional clinical microbiologic laboratories • Data from 1 January 1997 to 1 May 2003 • Population of Denmark was 5.4 million	343	21
73	Falup-Pecurariu 2019	Romania	• Surveillance data from Braşov (in central part of Romania), Romania collected in parallel to the 2016-HUS epidemic in southern Romania (in January–February 2016) • Stool samples from 1 March 2016 to 31 December 2016 • Other pathogens also detected	46	11
74	Ferguson 2005	United States of America	• An outbreak in Minnesota and Colorado, USA in 2003 in Minnesota • Both outbreaks were linked to alfalfa seeds from a single seed distributor • Age of participants ranged from 10-64 years	20	0
75	Frank 2011	Germany	• The highest number of HUS cases in a STEC outbreak in record • The outbreak occurred throughout Germany from 1 May through 4 July 2011 due to <i>E. coli</i> O104:H4	3816	845
76	Freedman 2017	Canada	• A retrospective case series in Alberta, Canada from 1 June 2014, and 31 October 2014 • Patient population was children < 19 years	78	10

77	Friesema 2015	Netherlands	Surveillance data on O157 and non-O157 cases during 2008–2012	208	17
78	Frost 1994	United States of America	• An outbreak in Virginia, USA during the July 17-30 session at a rural camp in 1994 • Camp attendees engaged in activities like frequent overnight trips during which meals were cooked over a campfire • Age of participants ranged from 9-22 years	20	1
79	Fukushima 1999	Japan	• A large outbreak of hemorrhagic colitis in Sakai City among elementary schools in 1996 • The study analyzed clinical experiences in the Sakai City Hospital	12680	12
80	Furukawa 2018	Japan	• An outbreak in Kanagawa, Japan, in October 2016 due to <i>E. coli</i> O157:H7 • Cases identification through the notification system under the Infectious Diseases Control Law • Age of participants ranged from 1-79 years	61	4
81	Gallagher 2013	United States of America	An outbreak in Cook County, Illinois, USA during 2 February 2009 due to <i>E. coli</i> O157:H7 infections among children who attended the same childcare center	18	1
82	Gaulin 2015	Canada	• An outbreak in Province of Quebec, Canada on 19 December 2013 due to confirmed <i>E. coli</i> O157:H7 by the Bureau de Surveillance et de Vigie (BSV) at the Ministry of Health and Social Services • Linked to consuming tartare at a restaurant • Age of participants ranged from 17-43 years	7	1
83	Germinario 2016	Italy	• An outbreak in Apulia region, Italy, including outbreak investigation and case-control study, between 4 June and 9 August 2013 • Considered the largest outbreak of STEC-associated HUS ever observed in Italy • Age of participants ranged from 0-6 years	20	20
84	Gobin 2018	United Kingdom	• An outbreak in England, Scotland, Wales and Northern Ireland, UK including outbreak investigation and case-control study from May 2016	163	9

			• Epidemiological and environmental investigations indicated a possible link to salad vegetables consumed at catering premises (e.g., restaurants or cafés) • Age of participants ranged from 1-98 years		
85	Goh 2002	United Kingdom	• An outbreak in North Cumbria, England including outbreak investigation and case-control study around 1 March 1999 due to <i>E. coli</i> O157 • Age of participants ranged from 0-85 years	61	3
86	Gould 2009	United States of America	• Surveillance data from Connecticut, Georgia, Maryland, Minnesota, Oregon, and Tennessee, and selected counties in California and New York, USA based on FoodNet • Data from 2000 - 2006 • FoodNet is a collaborative project among the Centers for Disease Control and Prevention, participating state health departments, the US Department of Agriculture, and the US Food and Drug Administration, with a catchment area in 2006 of ~45 million Persons	3464	218
87	Gould 2013	United States of America	• Surveillance data based on active, population-based surveillance from Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee, and selected counties in California, Colorado, and New York, USA • Data from 2008 – 2009	1074	87
88	Grant 2008	United States of America	• A multistate outbreak investigation, involving 26 states initiated on 14 September, including a case-control study • Cases detected from Utah and New Mexico, USA during 1 August 2006–1 October 2006	23	7
89	Guh 2010	United States of America	• An outbreak of <i>E. coli</i> infections connected with raw milk consumption, during June to July 2008 • Age of participants ranged from 0-81 years	14	3
90	Hadler 2011	United States of America	• Surveillance data from Connecticut, USA based on a decade of surveillance for STEC, as 1 January 2000 through 31 December 2009	663	46

			• All <i>E. coli</i> O157 isolates and stool-inoculated broths testing positive for Shiga toxins identified by clinical laboratories state-wide • Isolates submitted to the Department of Public Health (DPH) Laboratory for confirmation and further testing		
91	Hadler 2018	United States of America	• Surveillance data from states of Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and selected counties in California, Colorado, and New York, USA • Data from 2010 - 2014 • FoodNet staff conduct active population-based surveillance for laboratory-confirmed cases of STEC, including O157 and non-O157 serogroups, and HUS	5234	308
92	Hamilton 2019	Ireland	• Data from national Irish Computerized Infectious Disease Reporting (CIDR) system during the years 2013–2015 • The dataset consisted of all symptomatic STEC infections registered on CIDR as ‘Confirmed’	1397	71
93	Hashimoto 1999	Japan	An outbreak in Komatsu, Japan linked to diarrheal illness at R Junior High School between 8 July and 21 July 1996	241	0
94	Hassan 2019	United States of America	• A multistate outbreak across 12 states in the US during January-April 2017 linked to <i>E. coli</i> O157:H7 • Age of participants ranged from 1-70 years	32	9
95	Haugum 2014	Norway	• Surveillance data from Trondheim, Norway during 1996-2011 • STEC infection is notifiable to the MSIS at the NIPH	118	11
96	Hedican 2009	United States of America	• Data were collected through 2 sentinel surveillance sites in Minnesota, USA during 2000–2006 ○ Site 1 was the laboratory for a large Minneapolis-St. Paul metropolitan area health maintenance organization ○ Site 2 was a hospital laboratory serving a small city and rural area that is thriving in agriculture and food production, especially dairy • Age of participants ranged from 0-88 years	206	7
97	Heiman 2015	United States of America	• <i>E. coli</i> O157 outbreaks in the USA from the Foodborne Disease Outbreak Surveillance System (FDOSS) for outbreaks during	4928	299

			2003–2012, the Waterborne Disease Outbreak Surveillance System (WBDOSS) for outbreaks during 2003–2010 (data were not available after 2010) and the National Outbreak Reporting System (NORS) for outbreaks facilitated by transmission between persons, animal contact, environmental contamination, or with an unknown transmission mode during 2009–2012 • Collaboration also linked to the Centers for Disease Control and Prevention of person-to-person and animal contact–associated outbreaks during 2003–2008		
98	Heo 2023	Republic of Korea	• A large outbreak in Gyeonggi-do, South Korea during June 2020, occurred at a preschool A in Gyeonggi-do • Age of participants ranged from 3-5 years	85	15
99	Hilborn 1999	United States of America	• A multistate outbreak in Connecticut and Illinois, USA during June 1996 linked to <i>E. coli</i> O157:H7 infections • Linked to eating mesclun lettuce (a mixture of small red and green leaf lettuces) distributed by a single producer • Age of participants ranged from 2-87 years	43	3
100	Hilborn 2000	United States of America	• An outbreak in New Haven County (most cases) and 2 other counties, Connecticut, USA in October 1996 • The Connecticut DPH responded to the report of an unusual number of <i>E. coli</i> O157:H7 infections among residents of New Haven County • Linked to drinking a single brand of unpasteurized apple cider	14	5
101	Hildebrand 1996	United Kingdom	• An outbreak in southwest London, England during July 1993 • Data collected via the Consultant in Communicable Disease Control (CCDC) for a health authority in southwest London	7	3
102	Hiruta 2000	Japan	An outbreak in Japan in a nursey (children and staff) linked to <i>E. coli</i> O26 infections in 1997	27	0
103	Holton 1999	Canada	• Surveillance data across five Canadian cities: Vancouver (British Columbia), Edmonton (Alberta), Calgary (Alberta), Quebec City (Quebec) and Halifax (Nova Scotia) in 1991 • Data only from cases from case-control study	100	4

			• Case identification by <i>E. coli</i> O157:H7 infection reported to one health unit or one public health laboratory in the five cities from 4 June until 19 September 1991 • Age of participants ranged from 1-87 years		
104	Honish 2005	Canada	• A case series in Edmonton, Alberta, Canada based on <i>E. coli</i> O157:H7 by the Alberta Provincial Laboratory of Public Health (Microbiology) in 2002 • Age of participants ranged from 1-73 years	13	2
105	Honish 2017	Canada	• An outbreak in Alberta, Canada linked to <i>E. coli</i> O157:H7 • Linked to pork consumption in Asian-style restaurants, across multiple cities • Age of participants ranged from 1-82 years	119	6
106	Huppertz 1996	Germany	• Surveillance data in 1994 from Wurzburg, Germany, including all children and adolescents < 16 years of age • Cases were hospitalized in either of the two children's hospitals	13	1
107	Ihekweazu 2012	United Kingdom	• An outbreak in 2009 in Southeast England, UK, also considered the largest documented outbreak of <i>E. coli</i> O157 infection linked to animal contact in England and Wales at the time • Age of participants ranged from 0-36 years	78	17
108	Iwata 2019	Japan	• A retrospective cohort study and interrupted time-series analysis to assess the impact of banning raw beef liver at restaurants • Data from 2008 – 2017	21150	717
109	Jaakkonen 2017	Finland	• An outbreak in Turku (Turku University Hospital), Finland from June 2012 linked to a farm considered a historical tourist sight with 1950s methods in raising cattle and sheep • The farm frequently offers theme visits especially for families and organizing events	6	4
110	Jackson 2000	United States of America	• A series of 4 outbreaks in Washington and Oregon, USA from March through August 1993, linked to <i>E. coli</i> O157:H7 • The outbreaks occurred at 4 separate Oregon (3 outbreaks) and Washington (1 outbreak)	93	0

			• Linked to steak and salad bar restaurants affiliated with a single national chain • Age of participants ranged from 3-87 years		
111	Jalava 2011	Finland	Surveillance data from the National Infectious Disease Register (NIDR) in Finland between 1997 and 2006	74	21
112	Januszkiewicz 2012	Poland	• A family cluster in Gizycko, northeastern Poland from a household outbreak with a suspected epidemiological link to the large outbreak in Germany in 2011 • Age of participants ranged from 7-68 years	3	1
113	Januszkiewicz 2015	Poland	Surveillance data from human infections reported to the National Institute of Public Health during 1997 to 2014	9	2
114	Jay 2004	United States of America	• An outbreak in California, Nevada, and Arizona, USA with illness onsets during 5–17 November 1999 • Included 2 sequential case-control to identify risk factors • Age of participants ranged from 2-75 years	13	3
115	Jenkins 2022	United Kingdom	• An outbreak in South Yorkshire region, England, UK with illness onset from 1 October 2019 to 31 March 2020 • An Incident Management Team (IMT) investigated the outbreak • Linked to door-step delivery of milk from the same dairy farm • Data based on UKHSA GBRU for confirmation and typing	21	3
116	Jensen 2006	Denmark	• The Danish VTEC reference laboratory at SSI during January and February 2004 • Includes an investigation of this first general outbreak of VTEC infection in Denmark • Age of participants ranged from 1-60 years	25	0
117	Jones 1996	United Kingdom	• An outbreak in village in Fife, Scotland • Attributed to stream water into which treated sewage discharged contaminated the public water supply • Infections occurred between 6 March 1995 and 24 March 1995 inclusive	6	2

118	Kaindama 2021	United Kingdom	- An outbreak in 2017 in England, UK based on national Gastrointestinal Pathogens Unit Department (GIPU) at PHE linked to <i>E. coli</i> O157:H7 - Age of participants ranged from 6-45 years	4	1
119	Kamitsuji 2008	Japan	Surveillance data from Japan with <i>E. coli</i> cases detected as confirmed via culture or significant antibody titers	26	13
120	Kanayama 2015	Japan	- Surveillance data based on outbreaks, including those associated with childcare facilities, through the National Epidemiological Surveillance of Infectious Diseases (NESID) system from each Local Public Health Centers (LPHCs) - During 2010 – 2013 - Age of participants ranged from 0-88 years	1035	4
121	Käppeli 2011a	Switzerland	Surveillance data using non-O157 strains obtained from the Swiss National Centre for Enteropathogenic Bacteria, during 2000–2009	95	38
122	Käppeli 2011b	Switzerland	STEC strains sent to the National Centre for Enteropathogenic Bacteria (NENT) from 2000 to 2009	44	13
123	Keene 1997	United States of America	- An outbreak in three counties (Multnomah, Washington, and Clackamas), Portland, USA linked to <i>E. coli</i> O157:H7 - Cases review: Symptom onsets from January 1992 through June 1994 among residents of the three counties - Age of participants ranged from 1-73 years	173	0
124	King 2009	France	- An outbreak in 2005 in southwest (Gironde and Pyrenees-Atlantiques/six neighboring administrative districts) France linked to <i>E. coli</i> O157:H7 - Case identified via active case finding by hospitals, laboratories, paediatricians and general practitioners in the affected administrative districts and surrounding districts in southwest France - Age of participants ranged from 1-98 years	69	17
125	King 2012	France	An outbreak near Bordeaux, southwest France, including a retrospective cohort study, during 2011	24	7

126	Klein 2002	United States of America	• Prospective cohort study in Seattle, USA across 2 sites: the Children's Hospital and Regional Medical Center Emergency Department • Data from 1998 - 2001 • Includes O157:H7 and non-O157:H7 cases • Age of participants ranged from 1-17 years	39	5
127	Krogvold 2011	Norway	• A nationwide outbreak with data from all five university-hospitals in Norway, from 30 January to 13 March 2006 • Age of participants ranged from 1-8 years	16	10
128	Lahti 2002	Finland	• Surveillance data for Finland's new NIDR, consisting of linked mandatory laboratory and physician notification data, was established at the National Public Health Institute • During 1994 • Age of participants ranged from 2-17 years	3	2
129	Laidler 2013	United States of America	• An outbreak in Oregon, USA due to <i>E. coli</i> O157 during 2011 • Age of participants ranged from 4-85 years	15	4
130	Laine 2005	United States of America	• An outbreak in Minnesota, USA due to <i>E. coli</i> O157 infection in 2003 • A history of consuming brand A steaks in the 7 days prior to onset of illness, and had a brand A steak that tested positive for O157 with the outbreak-associated PFGE subtype • Age of participants ranged from 5-59 years	6	1
131	Lathrop 2009	United States of America	• Population-based active surveillance from New Mexico, USA from clinical laboratories from 2004 to 2007 • The surveillance was performed as part of FoodNet	111	5
132	Launders 2013	United Kingdom	• An outbreak due to <i>E. coli</i> O157 in England and Wales, UK during 30 August and 19 September 2013 • Epidemiological data from NESSS and then sent to the Gastrointestinal Bacteria Reference Unit for further characterization	18	0
133	Launders 2016a	United Kingdom	An outbreak in Scotland, England and Wales, UK from December 2010 to 2 August 2011 linked to <i>E. coli</i> O157	252	2

134	Launders 2016b	United Kingdom	• Surveillance data from England, UK due to <i>E. coli</i> O157 infection • Data from 2009 - 2012 • Data from local PHE Centres in England and NESSS • Bacterial cultures of <i>E. coli</i> O157 were then sent for confirmation at the PHE GBRU	3323	172
135	Lerman 1992	Israel	• A cluster of four cases of <i>E. coli</i> O157:NM infection in 1990, among infants aged under 1 year • Occurred at the same day-care class in a small communal settlement (kibbutz)	3	0
136	Lin 2021	Canada and the United States of America	• A retrospective review of medical records in the USA and Canada between 1 January 2011 and 31 December 2015 • Participating sites were members of the Pediatric Emergency Medicine Collaborative Research Committee (PEMCRC) and/or Pediatric Emergency Research Canada (PERC) • Age of study participants were < 18 years	927	167
137	Liptakova 2004	Slovakia	A family outbreak in eastern Slovakia due to <i>E. coli</i> O157 infection	5	3
138	Lisboa 2019	Canada	A review of the public health database for cases of <i>E. coli</i> O157 infections in Alberta, Canada during period 2009 to 2016	762	39
139	Locking 2011	United Kingdom	• Surveillance data from Scotland, UK based on Health Protection Scotland in close collaboration with the Scottish <i>E. coli</i> O157/VTEC Reference Laboratory (Edinburgh, Scotland), established enhanced surveillance of <i>E. coli</i> O157 • During 1999 – 2008	2026	196
140	Loconsole 2020	Italy	• A STEC infection symptom-based surveillance system for the pediatric population was established in Apulia, Southern Italy in June 2018 • Surveillance captured both residents and non-residents of Apulia between 22nd June 2018 and 21st August 2019 • Age of participants ranged from 0-14 years	87	5
141	Lopez 2012	Argentina	• Surveillance data from Buenos Aires, Santa Fe, Mar del Plata, La Plata, Parana, Cordoba, and Bahía Blanca in Argentina during 2006	93	8

			Cases were both male and female and were aged between 6 months and 15 years, presenting with watery diarrhea or bloody diarrhea		
142	Luna 2018	United States of America	- An outbreak of <i>E. coli</i> O157:H7 in Arizona-Utah Border, USA linked to animal manure in mid-2017 - Age of participants ranged from 1-28 years	12	4
143	Luna-Gierke 2014	United States of America	- Multiple outbreaks in USA during July 2000 - Identified mode of transformation: Food, vehicle/animal and water-based punch - Queries of the Waterborne Disease Outbreak Surveillance System for outbreaks during 1971–2010, the Foodborne Disease Outbreak Surveillance System (FDOSS) for outbreaks during 1973–2010, and NORS for outbreaks transmitted by contact with animals or persons or by unknown mode during 2009–2010	121	11
144	MacDonald 1996	United Kingdom	- Surveillance data from Grampian region, Scotland during September 1987 to December 1988 - Diarrhoeal stools with blood or stools from patients with a history of bloody diarrhoea were examined for <i>E. coli</i> O157 sent to the Regional Laboratory were examined for <i>E. coli</i> O157	75	8
145	Mag 2010	Hungary	- Surveillance data from National Reference Laboratory (NRL) for Enteric Aerob Bacteria - The retrospective study was to characterise all human verotoxin-producing <i>E. coli</i> strains isolated in Hungary from 2000 to 2006	33	2
146	Marshall 2020	United States of America	- Five-solved STEC outbreaks linked to contaminated food - All possible multistate outbreaks linked to <i>Salmonella</i>, STEC and <i>L. monocytogenes</i> infections identified and reported to ORPB during the 2016 reporting period were included in this analysis	106	5
147	Matussek 2015	Sweden	- Surveillance data from County of Jönköping, Sweden - All routine diarrheal stool culture specimens from patients younger than 10 years of age from 1 May 2003 through April 2013	191	7
148	McDonnell 1997	United Kingdom	A cluster outbreak in southern counties of England (Dorchester/Weymouth (Dorset)), England, UK	23	2

			• Two outbreaks of VTEC O157 infection in the summer of 1995 • Age of participants ranged from 1-79 years		
149	McFarland 2017	United Kingdom	• An outbreak associated to residence/visits to Dorset in southwest England from July 2014 to September 2015 • Only symptomatic STEC cases • Age of participants ranged from 0-69 years	21	13
150	McKee 2020	Canada and the United States of America	• 38 care pediatric emergency departments (EDs) in 21 US states and 6 Canadian provinces • All children <18 years of age who had STEC detected in their stools between 1 January 2011 and 31 December 2015 • Multicentre analysis: Children's Hospital of Colorado, Primary Children's Hospital Utah, Alberta Children's Hospital, Children's Hospitals and Clinics Minnesota, Seattle Children's Hospital, Cincinnati Children's Hospital, Washington University - St. Louis, Texas Children's Hospital, Nationwide Children's Hospital, Stollery Children's Hospital, Children's Hospital of Pittsburgh, Norton Children's Hospital, The Hospital for Sick Children, Lurie Children's Hospital of Chicago, Children's Hospital of Western Ontario, Boston Children's Hospital, The Children's Hospital of Winnipeg, Montreal Children's Hospital, Children's of Alabama, Children's Medical Center of Dallas, British Columbia Children's Hospital, Children's Hospital of Eastern Ontario, CS Mott Children's Hospital, Arkansas Children's Hospital, Centre Hospitalier Universitaire Sainte-Justine, The Children's Hospital (Oklahoma), McMaster Children's Hospital, Children's Hospital of Wisconsin, Children's Hospital of Philadelphia, Vanderbilt Children's Hospital, Rady Children's Hospital – San Diego, Children's Healthcare of Atlanta at Egleston Hospital, Jacobi Medical Center, Joseph M. Sanzari Children's Hospital, Janeway Children's Health and Rehabilitation Centre, Children's Hospital at Montefiore, Johns Hopkins Children's Center, University of Minnesota Masonic Children's Hospital	886	126

151	McPherson 2009	Australia	• OzFoodNet data from 2003 to 2007 from South Australia, Victoria, New South Wales, Western Australia, Queensland (constituting 6 of 8) states and territories in Australia • OzFoodNet conducted a case-control study of patients infected with serogroup O157 and all other (non-O157) serogroups • A case-control study of sporadic STEC infection from July 2003 through April 2007 in 6 of the 8 states and territories in Australia	113	8
152	McPherson 2011	Australia	• Surveillance data from Australia from 2003 to 2006 • Interviews with patients with a sporadic STEC infection in South Australia to determine the costs due to STEC infection • Age of participants ranged from 1-94 years	46	2
153	Mead 1997	United States of America	• Surveillance data from New Jersey, USA during 1994 • A survey of 20 laboratories that had reported at least one isolate of <i>E. coli</i> O157:H7, to identify different risk factors • Telephone interviews using questionnaire divided into two sections: (1) about food, drink and any recreational exposures to <i>E. coli</i>, and (2) interview of the primary food preparer in each household • Age of participants ranged from 0-78 years	23	2
154	Milne 1999	United Kingdom	• An outbreak in England in 1997 among children infected with <i>E. coli</i> via direct contact with farm animals • Age of participants ranged from 4-7 years	3	2
155	Moran-Gilad 2017	Israel	• An outbreak in a rural community (Kibbutz) in Southern Israel in the same nursery at the local day-care centre in 2016 • The outbreak during 25–27 April 2016 due to admission to the regional hospital of two young infants with HUS	14	3
156	Morgan 1993	United Kingdom	• An outbreak in 1991 in Northwest England, UK among children linked consuming the same brand of yogurt of different flavors produced by a local dairy • Age of participants ranged from 1-56 years	16	5
157	Mota 2010	Uruguay	• Surveillance data from Montevideo and other cities of Uruguay among pediatric patients during 2001 to 2008	3	2

			• Detection of pathogens resulting in bloody diarrhea in multiple health care centers		
158	Nabae 2013	Japan	• A series of outbreak clusters in Yamagata Prefecture, Japan in 2011 • Cluster were among pupils and staff at a nursery, festival participants, child sports team members, and college student club members • Age of participants ranged from 1-94 years	278	5
159	Naseer 2017	Norway	• Surveillance data from NRL for Enteropathogenic Bacteria from 1992 to 2012 • Clinical and epidemiological information of cases corresponding to the selected STEC isolates were retrieved from the MSIS database • Age of participants ranged from 0-97 years	333	31
160	Neil 2012	United States of America	• Surveillance data from PulseNet as a collaboration with State and local public health officials and the Centers for Disease Control and Prevention (CDC) during 2009 • Initiated as a multistate investigation of the outbreak • Based on data from Arizona, California, Colorado, Connecticut, Delaware, Georgia, Iowa, Illinois, Kentucky, Massachusetts, Maryland, Maine, Minnesota, Missouri, Montana, North Carolina, New Hampshire, New Jersey, Nevada, New York, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Virginia, Washington, and Wisconsin • Age of participants ranged from 2-65 years	57	10
161	Nichols 2021	United States of America	• An outbreak in southeastern Connecticut, USA in 2016 • Connecticut DPH laboratory conducted testing and data were shared with PulseNet • The collaboration facilitated characterization of STEC O157 isolated from people, animals, or the farm environment • The outbreak was linked to goat dairy farm in southeastern Connecticut • Age of participants ranged from 0-50 years	50	3

162	NIID 2020	Japan	Surveillance data during 2019 collected by local public health centres and reported to the NESID system	2511	78
163	Nishimura 2012	United States of America	Surveillance data from Connecticut, USA as Connecticut FoodNet from January 2006 to May 2010	106	20
164	Novello 1999	United States of America	An outbreak in 2019 of <i>E. coli</i> and <i>Campylobacter</i> in New York among attendees of the Washington Fair	116	12
165	Nüesch-Inderbinen 2018	Switzerland	• Surveillance data collected as clinical data from cases from May to December 2017 via all diagnostic laboratories • Stx-positive clinical samples collected by the Swiss National Reference Centre for Enteropathogenic Bacteria and <i>Listeria</i> (NENT) for culture and further strain characterization	94	7
166	O'Donnell 2002	United Kingdom	An outbreak of VTEC O157 in Ireland linked to a creche in 1998	11	0
167	Olesen 2005	Denmark	• Surveillance data during a 5-year period from April 1997 to April 2002 • All stool samples from patients after recent travel or continuous episodes of diarrhoea • Data from hospitals and general practitioners across 6 of the 16 Danish counties consecutively examined for pathogens including diarrhoeagenic <i>E. coli</i> • Age of participants ranged from 2-60 years	20	0
168	Olsen 2002	United States of America	• A multistate outbreak across 15 states, including Alpine and Wyoming in 1998 • A cohort study of cases from out-of-state families and all residents of Alpine • Dates of illness onset ranged from June 25 to July 27 for patients with culture-confirmed infection and June 22 to July 30 for patients with culture-negative stools	157	4
169	Oporto 2019	Spain	• Surveillance data from Basque Country, northern Spain • Stool samples from inpatients and outpatients of all ages sent to the Microbiology Service of Hospital Universitario Donostia • Between January 2014 and December 2016	29094	2

			Cases presented symptoms of gastrointestinal disease and were screened for STEC		
170	Orr 1994	Canada	- An outbreak in 6 Inuit communities in the Canadian Northwest Territories, Canada - From 4 June to 31 October 1991 - Across the settlements of Arviat, Baker Lake, Rankin Inlet, Whale Cove, Chesterfield Inlet and Sanikiluaq	521	22
171	Ota 2019	Japan	- An outbreak in Oita Prefecture in 2005 in western Japan via an institute for adults and children with intellectual disabilities - Age of participants ranged from 6-59 years	14	2
172	OzFoodNet 2021	Australia	- Surveillance data from the OzFoodNet network covering all Australian states and territories via National Notifiable Diseases Surveillance System (NNDSS) - Data from 2013 - 2015 - Age of participants ranged from 0-91 years	431	30
173	Pavia 1990	United States of America	An outbreak in Utah, USA from Utah State Training school, between 8 July and 10 July	16	5
174	Pebody 1999	Spain	- An outbreak in Corralejo on Fuerteventura, the Canary Islands in 1997 - Island is a popular tourist destination and the outbreak was among European tourists to the Islands - Age of participants ranged from 0-77 years	15	3
175	Pederson 2018	Denmark	Surveillance data from Southern Denmark from two laboratories from 2011 to 2014	209	9
176	Pereboom 2018	United States of America	- A family cluster in Staffordshire, England during 2017 - Linked to person-person transmission of <i>E. coli</i> by a shared inflatable home paddling pool	3	2
177	Persson 2007	Denmark	Data from 1 January 1997 to 28 October 2003 from the Danish National STEC cohort	241	20
178	Phan 2001	United States of America	Surveillance data from Connecticut residents with a culture-confirmed case of STEC infection between February 1 2000 and January 31 2001	90	10

			• Age of participants ranged from 1-90 years		
179	Phan 2007	United States of America	• Surveillance data from Connecticut, USA via Connecticut Department of Public Health • Analysis of results of confirmatory testing conducted in the state laboratory during 2000-2005	403	25
180	PHLS 1993	United Kingdom	• An outbreak cluster in SW Thames Region, England in 1993 • Isolates confirmed by the Laboratory of Enteric Pathogens (LEP) at the Public Health Laboratory Service (PHLS) Central Public Health Laboratory	5	3
181	Piérard 1990	Belgium	• Akademisch Ziekenhuis, Vrije Universiteit Brussel, Laarbeeklaan, Brussels, Belgium • Fecal samples submitted for culture between April 1987 and September 1988 • Detection on sorbitol MacConkey agar • Age of participants ranged from 0-79 years	14	
182	Piérard 1997	Belgium	• Surveillance data from Brussels, Belgium during October 1990 to December 1995 • Fecal samples submitted for routine culture to the laboratory of the Akademisch Ziekenhuis of the Vrije Universiteit, Brussels (AZ-VUB) and VTEX screening by PCR • Age of participants ranged from 0-91 years	139	4
183	Piérard 1999	Belgium	• A case-control study of sporadic cases of VTEC infection • To determine risk factors for VTEC infections in Belgium • Age of participants ranged from 0-76 years	36	5
184	Piercefield 2010	United States of America	• An outbreak from Oklahoma, USA due to bloody diarrhea among attendees of an independently owned, country buffet-style restaurant in Oklahoma • Causative agent was suspected to be <i>E. coli</i> O111:NM • Restaurant exposure for all related cases occurred during 10 August 2008, to 24 August 2008	72	26

			• Restaurant exposure dates for persons with confirmed O111 infections ranged from 15 August 2008 to 24 August 2008 • Age of participants ranged from 1-88 years		
185	Preußel 2013	Germany	• Surveillance data from Germany national reporting database on infectious diseases, hosted by the Robert Koch Institute (RKI), Germany federal level public health institute • During 2004 to 2011	8400	627
186	Proctor 2000	United States of America	• Surveillance data from Wisconsin, USA after which HUS became reportable in 2000 • All laboratory-confirmed <i>E. coli</i> cases from 1992 to 1999	1333	63
187	Raffaelli 2007	United States of America	• An outbreak in Bronx, New York, USA via Bronx childcare center • Suspected cases of STEC included childcare attendees or staff members with a diarrheal illness after 1 June 2004 • <i>E. coli</i> O157:H7 was identified as the causative agent	45	2
188	Rangel 2005	United States of America	All outbreaks of <i>E. coli</i> in the USA reported to the CDC by telephone, outbreak report, or the routine surveillance system, from 1982-2002	8598	354
189	Rechel 2011	United Kingdom	• A cluster of <i>E. coli</i> O157 among families in Norfolk and Lincolnshire (neighbouring counties), England, UK • Five families in the neighbouring counties of Norfolk and Lincolnshire in April and May 2007	12	1
190	Reida 1994	Germany	• An outbreak in a daycare centre in Northern Germany, linked to <i>E. coli</i> O157: H7 in 1992 • Age of participants ranged from 1-6 years	39	3
191	Rivas 2023	Argentina	• Surveillance data from Buenos Aires, La Pampa, Mendoza, Neuquén, Río Negro and Santa Fe provinces, and Buenos Aires City, Argentina among STEC-positive bloody diarrhea (BD) cases • Between 10 October 2018 and 30 June 2019 in seven tertiary-care hospitals (Reference Sites) • Acute BD: A prospective multicenter surveillance study of pediatric patients with acute BD (first cohort) conducted in 18 hospitals that treat patients with less complex illnesses (referral units) in these cities	29	4

			• HUS cohort: A second cohort of HUS cases aged 1-9 years, known to be infected with STEC in the same hospitals during the study interval		
192	Rivero 2010	Argentina	• Cities of Tandil and its surroundings, Bahia Blanca, Moron (Province of Buenos Aires) and Rio Cuarto (Province of Cordoba), Argentina • Children up to 6 years old with acute diarrhea attending public or private healthcare institutions in the cities of Tandil, Bahia Blanca, Moron and Rio Cuarto • Between December 2002 and April 2009	44	16
193	Roberts 2000	United Kingdom	• An outbreak in a rural community west of Edinburgh, Scotland, UK in 1994 • Study objective was to assess the economic and social impact of outbreak	69	10
194	Robinson 2014	United States of America	• Surveillance data from Minnesota, USA during 2001–2010 • Patients identified through routine disease surveillance conducted at the Minnesota Department of Health (MDH)	12	1
195	Rodrigue 1995	United States of America	• An outbreak linked to a graduation banquet at a university in Wisconsin, USA • The study was done in late May and early June 1988 by use of a standard questionnaire requesting information on foods consumed and clinical symptoms	61	0
196	Rodwell 2022	United Kingdom	• Surveillance data from England, Scotland and Wales, UK • Time frames for isolate detection from each country were as follows: ○ Cases from England and Wales were identified from 2015 to 2021 ○ Cases from Scotland were detected between 2004 and 2021 ○ Cases from Northern Ireland were detected from 2018 to 2021 ○ STEC isolates from Ireland were referred to the UKHSA for WGS from 2016 to 2018	156	14

197	Rodwell 2023	United Kingdom	• Surveillance data from England, UK from Gastrointestinal Bacteria Reference Unit (GBRU), UKHSA for confirmation and typing • Data from 2014 - 2021 • Stool samples from hospitalised patients and community-acquired gastrointestinal infections	459	40
198	Rounds 2012	United States of America	An outbreak in a high school in Minnesota, USA around 1 December 2010 to the MDH	29	0
199	Rowe 1991	Canada	• Surveillance data from Ottawa, Ontario and Western Quebec, Canada: The Children's Hospital of Eastern Ontario and two general hospitals in adjacent Western Quebec • 4-year retrospective cohort study using a representative group of children presenting to hospital with <i>E. coli</i> O157:H7 gastroenteritis and a cohort of age-matched children with <i>Campylobacter jejuni</i> gastroenteritis for comparison • During 1985 to 1988 • Age of participants ranged from 0-17 years	72	6
200	Rowe 1994	Canada	• An outbreak in Arviat (formerly Eskimo Point - an Inuit community), western border of Hudson Bay, northern Canada • First stool isolate of <i>E. coli</i> O157:H7 from an adult in Arviat confirmed in mid- June 1991 • Epidemic continued until mid-October 1991 • Included a case-control study • Age of participants ranged from 0-15 years	38	19
201	Rowe 1998	Canada	• Surveillance data coordinated by the Canadian Pediatric Kidney Disease Research Centre, including Alberta and other provinces • From 1 June 1991 to 31 March 1994 • Children < 15 years of age either with (1) HUS associated with gastrointestinal symptoms or (2) gastroenteritis and evidence of <i>E. coli</i> O157 infection in cultures of stool submitted to the microbiology laboratories of one of the participating hospitals or provincial laboratories across Canada	739	157

202	Rowell 2016	United Kingdom	• An outbreak from a Lambing Live event in the North West of England, UK in April 2014 • Linked to <i>E. coli</i> O157 via an animal petting event	30	5
203	Sartz 2008	Sweden	• An outbreak in Skania, southern Sweden • During the period of 15 September to 5 November 2002 • Traced to consumption of fermented sausage • Aim was to describe the microbiological and epidemiological investigation that led to identification of a specific outbreak-related <i>E. coli</i> O157:H7 strain • Age of participants ranged from 2-75 years	38	12
204	Sato 2022	Japan	• An outbreak in Niigata Prefecture (which includes Niigata City and four neighboring municipalities), Japan linked to <i>E. coli</i> O157 • Gastrointestinal illness such as diarrhea, bloody stool, and abdominal pain with date of onset from 1 October 2017 to 12 November 2017	29	4
205	Sawyer 2021	United Kingdom	• An investigation of recurrent outbreaks in England, UK during the period 2014–2018 • Linked to <i>E. coli</i> O55:H7 • Age of participants ranged from 0-69 years	36	25
206	Sayed 2005	Egypt	• Health records from Assiut Children University Hospital, Assiut, Egypt from children with acute diarrhea during October 2003 to September 2004 • Age of participants ranged from 0-69 years	20	8
207	Scavia 2018	Italy	• An outbreak in central Italy, which is a densely populated urban area), considered at lower risk for HUS • Attendees or workers at nursery since 7 May 2015 • A family contact of ill nursery attendees with positive stool test for <i>E. coli</i> O26, by culture, real-time PCR or Vero-cell assay • Age of participants ranged from 1-5 years	7	1
208	Schaffzin 2012	United States of America	Two outbreaks in New York, USA: 1. Outbreak 1: 28 September 2004	265	0

			Infection-control personnel at a local community hospital notified local health officials of 4 hospitalizations due to diarrhoeal illness 2. Outbreak 2: 8 September 2005 The New York State Department of Correctional Services (NYSDOCS) notified an outbreak of bloody diarrhea among inmates at a NYSDOCS correctional facility		
209	Scharlach 2013	Germany	• A cluster in district of Cuxhaven, Lower Saxoy, Northern Germany occurring at a 70th birthday on 7 May 2011 with 84 attendants • Age of participants ranged from 30-78 years	11	2
210	Schimmer 2008	Norway	• An outbreak between 20 February and 7 April 2006 in Norway with the outbreak strain of <i>E. coli</i> O103 • Initiated with NIPH from an academic hospital in Oslo, Norway on 20–21 February 2006 • Age of participants ranged from 1-18 years	16	10
211	Schindler 2014	United States of America	• Surveillance data from St. Louis Children's Hospital with STEC detection in stool and rectal swab specimens submitted to the hospital microbiology lab, from 2001-2011 • Age of participants ranged from 0-18 years	100	16
212	Sharapov 2016	United States of America	• A multistate outbreak across 27 states in the US in 2006 linked to <i>E. coli</i> O157:H7 • CDC notified public health officials in all states about the outbreak via the Health Alert Network • State public health laboratories used PFGE analyses on clinical isolates of <i>E. coli</i> O157:H7 and submitted results to the national database (PulseNet) at CDC • State investigators notified CDC of case reports	200	39
213	Sharp 1994	United Kingdom	• Surveillance data from Peterhead, north-east coast of Scotland • Between January 1989 and August 1991 • <i>E. coli</i> O157 was detected via microbiological services were provided by the Regional Laboratory, City Hospital, Aberdeen • Age of participants ranged from 1-62 years	12	3

214	Shefer 1996	United States of America	• A cluster in San Diego county, USA linked to <i>E. coli</i> O157:H7 • From mid-November 1992 through mid-January 1993 • Case identification via the San Diego County Department of Health Services • Age of participants ranged from 1-58 years	34	7
215	Shillam 2002	United States of America	An outbreak in Colorado and six other states (California, Iowa, Michigan, South Dakota, Washington, and Wyoming), USA during 17 - 30 June 2002	28	5
216	Slayton 2013	United States of America	• A multistate outbreak in Arizona, Arkansas, Georgia, Illinois, Indiana, Kansas, Kentucky, Minnesota, Missouri, and Nebraska, USA • Illness onset dates ranging from October 9 through November 7, 2011 • State and local public health officials in the St. Louis metropolitan area identified laboratory-confirmed cases of <i>E. coli</i> O157 • Local health care providers were encouraged through the health alert to test for STEC in diarrheal cases • PulseNet to identify cases matching PFGE pattern of the outbreak strain submitted to public health laboratories outside metropolitan area • Age of participants ranged from 1-94 years	47	3
217	Slutsker 1998	United States of America	• 2-year multicentre case-control study across 10 sites throughout the United States from 1990 to 1992 • Ten hospitals were enrolled such that at least 1 were from each of the four census divisions of the USA • Causative agent identified as <i>E. coli</i> O157:H7 • Information via several sources, including hospital charts, laboratory records, and telephone interviews • Age of participants ranged from 0-87 years	93	7
218	Smith 2012	United States of America	Surveillance data from Minnesota, USA from 1996 to 2002, linked to <i>E. coli</i> O157	1417	76

219	Soborg 2013	Denmark	• An outbreak in Central Copenhagen Hospital notified by SSI, Denmark linked to <i>E. coli</i> O157 • Date of disease onset ranged from 18 September to 28 October 2012 • Age of participants ranged from 3-68 years	11	8
220	Söderström 2008	Sweden	• An outbreak in west coast of Sweden, began from summer of 2005 • Collaborative investigation by the Departments of Communicable Disease Control in Vastra Gotaland and Halland, local Environmental Health Protection Boards, the hospital laboratories, and the Swedish Institute for Infectious Disease Control • Age of participants ranged from 0-90 years	128	11
221	Sodha 2011	Canada and the United States of America	• A multinational outbreak across New Jersey, New York, Pennsylvania, Delaware and South Carolina, USA and Ontario, Canada • From 2006 to 2007 • As routine surveillance, isolates of <i>E. coli</i> O157 from clinical laboratories with human specimens are submitted to state public health laboratories for PFGE subtyping during December 2006 to January 2007 • Age of participants ranged from 4-61 years	80	7
222	Soysal 2016	France	Surveillance data using all <i>E. coli</i> O80:H2 isolates received during January 2005 to October 2014 by the Centre National de Référence Associé <i>Escherichia coli</i> in Paris, France	53	48
223	Spano 2021	Brazil	• An outbreak in Vila Velha, Espírito Santo State, Brazil due to gastroenteritis occurred from 15 March to 7 April 2019 • Occurring in daycare center in southeastern Brazil involving children, staff, and family members	14	3
224	Stevenson 1996	United Kingdom	• Surveillance data during 2015 from Sunderland, UK • Cases of <i>E. coli</i> infection reported by the local hospital submitted to consultant in communicable disease control in Sunderland	14	2

			• Illnesses were bloody diarrhoea, abdominal pain, vomiting, HUS, or thrombotic purpura, with onset between 13 July 1995 and 14 August 1995 • Age of participants ranged from 2-89 years		
225	Swerdlow 1992	United States of America	An outbreak in Cabool, rural southern Missouri within Burdine Township, USA, between 14 and 29 December 1989	243	2
226	Tack 2021	United States of America	Surveillance data in the United States, examining all STEC outbreaks from 2010-2017, including O157 and non-O157 outbreaks	4769	303
227	Tajiri 2015	Japan	• Surveillance data from Japan during 1997 to 2013 • All children diagnosed with an STEC infection, from 7 institutes that, constituting the Japanese Study Group for Pediatric Gastrointestinal Infectious Diseases	118	64
228	Takeda 1998	Japan	• A retrospective nationwide survey of EHEC infection diagnosed in 1996 • Via questionnaires sent to 3,908 hospitals across Japan	1271	199
229	Talan 2001	United States of America	• Surveillance data from 11 urban, university-affiliated emergency departments, EMERGEncy ID NET in the USA • A prospective case series of consecutive pediatric and adult patients with bloody diarrhea from 1 July 1996 through 30 September 1998	10	0
230	Tarr 2018a	United States of America	Surveillance data from Washington, USA using culture-confirmed <i>E. coli</i> O157:H7 cases reported to the Washington State Department of Health (DOH) from 2005 through 2014	1118	76
231	Tarr 2018b	United States of America	• Surveillance data Washington, USA, as all culture-confirmed <i>E. coli</i> O157:H7 cases reported to the Washington State DOH from 2005 through 2015 • Passive surveillance to collect cases of hospitalized confirmed cases of <i>E. coli</i> O157:H7	433	161
232	Taylor 2013	United States of America	• A multistate outbreak in Michigan, Ohio, New York, Tennessee, and Pennsylvania, USA linked to <i>E. coli</i> O145 infection during 2010	31	3

			• Notification of clusters of diarrheal illnesses and/or non-O157 STEC infections by Michigan Department of Community Health (MDCH), Ohio Department of Health (ODH), and New York State Department of Health (NYSDH) • PulseNet was used for additional cases of STEC O145 infection • Age of participants ranged from 13-31 years		
233	Thomas 1993	United Kingdom	• Surveillance data as results of investigations performed by the Laboratory of Enteric Pathogens • To collect data on STEC infection in the UK during the period 1989-1991	1230	193
234	Thomas 1996	United Kingdom	Surveillance data from England and Wales, UK on VTEC infections from the Laboratory of Enteric Pathogens, Central Public Health Laboratory, between 1992 and 1994	1468	269
235	Treacy 2019	United Kingdom	• An outbreak of <i>E. coli</i> O157:H7 in Isle of Wight in the UK • A review of questionnaires from all cases who were either residents (n=5) of, or visitors to the Isle of Wight within the 7 days before symptom onset • Collaboration between PHE and NESSS • Cases reviewed to identify epidemiologically-linked cases to the Isle of Wight via notification nationally since early January 2017 • Age of participants ranged from 1-62 years	7	3
236	Trotz-Williams 2012	Canada	• An outbreak in Southwestern Ontario, Canada of cases of bloody diarrhoea following a four-day gathering that had ended four days earlier in 2011 • Age of participants ranged from 1-84 years	29	3
237	Tseng 2016	United States of America	• Surveillance data from Michigan, USA from the Michigan Disease Surveillance System (MDSS) during 2001-2012 • MDSS is a web-based surveillance system maintained by the Michigan Department of Health and Human Services (MDHHS) formerly known as the Michigan Department of Community Health	1334	26

238	Tserenpuntsag 2005	United States of America	• Surveillance data from New York, USA in 1998 and 1999 • Medical charts of hospitalized cases of <i>E. coli</i> O157:H7 to the New York State Department of Health's Communicable Disease Surveillance System (CDSS)	238	36
239	Ullrich 2013	Germany	• An outbreak in Northern Germany in 2011, due to hospitalizations with bloody or painful diarrhea induced by EHEC colitis • Linked to <i>E. coli</i> O104 outbreak	61	10
240	University of Washington 1996	Canada and the United States of America	• A multinational outbreak in British Columbia, Canada and several states in the USA, namely California, Colorado, and Washington, USA in 1996 • <i>E. coli</i> O157:H7 associated with illness after 30 September 1996 after consumption of Odwalla juice within 10 days before illness onset • Epidemiologically associated with drinking Odwalla brand unpasteurized apple juice or Odwalla juice mixtures containing apple juice from a coffee shop chain, grocery stores, or other locations • Age of participants ranged from 1-41 years	28	12
241	Vachon 2020	United States of America	Surveillance data from Indiana, USA on laboratory-confirmed STEC cases reported to the Indiana State Health Department (ISDH) from 2012 to 2018	784	46
242	van Duynhoven 2002	Netherlands	• Surveillance data via all laboratories in the Netherlands on positive results for <i>E. coli</i> O157 (either a presumptive isolate from a faecal sample or a positive serological test for <i>E. coli</i> O157 antibodies) to the local public health service • During 1999 – 2001 • Age of participants ranged from 1-84 years	82	12
243	Varma 2003	United States of America	• A cluster outbreak in Lorain County, Ohio, cluster due to <i>E. coli</i> infections in 2001 • Linked to attendance at the Lorain County Fair • Age of participants ranged from 1-64 years	23	2

244	Vasant 2017	Australia	• An outbreak in Brisbane, Queensland, Australia in 2013, associated with an annual agricultural show • Investigation by a multidisciplinary incident management team via an outbreak of STEC illness • Age of participants ranged from 1-77 years	57	0
245	Verma 2007	United Kingdom	• A cluster of <i>E. coli</i> O157 in Trafford, Manchester, England, UK in 2004 • Initiated by the Greater Manchester Health Protection Unit (GMHPU) via notification by local hospital microbiology laboratory of three possible isolates of • <i>E. coli</i> O157 in children from the Trafford area • Linked to swimming in the learners' pool of a local leisure centre on the morning of 5 September 2004 • Age of participants ranged from 0-34 years	8	2
246	Vishram 2021	United Kingdom	• Surveillance data from England, UK from 1 January 2014 to 31 December 2018 • <i>E. coli</i> O157 isolated at diagnostic laboratories from stool of hospitalized cases and community cases of gastrointestinal disease from the GBRU for confirmation and typing • Data from the NESSS	4324	190
247	Wahl 2011	Norway	• A cluster outbreak in city of Trondheim, Norway in daycare centre in September and October 2009 • Linked to <i>E. coli</i> O145:H28	16	0
248	Wall 1996	United Kingdom	• A total of 1,590 general outbreaks of infectious intestinal disease in England and Wales, from 1 January 1992 to 31 December 1994 • Via a surveillance system to document general outbreaks of infectious intestinal disease developed by the PHLS Communicable Disease Surveillance Centre (CDSC), introduced in 1992 • Collaboration among consultants in communicable • disease control	173	36

			Follows a recommendation by the Committee on the Microbiological Safety of Food		
249	Wang 2012	Canada	- Surveillance data from British Columbia, Canada from 2009 to 2011 - Age of participants ranged from 1-98 years	260	217
250	Warrner 1996	United States of America	- An outbreak in Illinois, USA during June 1995 to July 1995 with culture-confirmed <i>E. coli</i> O157:H7 infection - Initiated with Winnebago County Health Department in northern Illinois on 5 July 1995 - The Illinois DPH closed the swimming beach because of suspected transmission of infection through lake water ingestion during 24-25 June 1995 - Age of participants ranged from 2-12 years	12	3
251	Watahiki 2014	Japan	- An outbreak in three public health centers in Toyama Prefecture, public health institutes in Fukui Prefecture, Ishikawa Prefecture, Kanazawa City, and Yokohama City, Japan - Linked to a large EHEC outbreak in Japan in April and May 2011 - Linked to EHEC O111 and O157 cases	67	26
252	Watanabe 1999	Japan	- An outbreak in Oku City, Okayama Prefecture, Japan in May 1996, occurring in primary schools - Linked to EHEC O157:H7	138	2
253	Waters 1994	Canada	- Surveillance data from Alberta, Canada and Scotland during 1987 to 1991 - Rates of VTEC infection calculated base on the above data and age- and sex-specific population figures for 1990 as prepared by the Alberta Bureau of Statistics - Age of participants ranged from 0-96 years	1993	115
254	Wendel 2009	United States of America	- An outbreak in Wisconsin, USA due to <i>E. coli</i> O157: H7 from 1 August through 1 October 2006 - Age of participants ranged from 1-84 years	49	9

255	Wengenroth 2012	Germany	An outbreak in Hamburg, Germany, including a cohort of patients with confirmed EHEC infection treated in the Asklepios Clinic Barmbek during 2011	68	32
256	Werber 2002	Germany	• A multistate outbreak in 2000 reported by the NRL for <i>Salmonella</i> and Other Bacterial Enteric • Pathogens across different parts of Germany • Linked to <i>E. coli</i> O26:H11 strains that carried identical genotypic characteristic • The source of exposure was suspected to be a type of beef, known as “Seemerrolle”) • Age of participants ranged from 2-31 years	6	0
257	Werber 2007	Germany	• Laboratory-based sentinel surveillance system coordinated by the National Reference Center from 2001 to 2003 • From designated 14 German federal states between 1 April 2001 and 31 March 2003 • Age of participants ranged from 0-89 years	202	5
258	Werber 2008	United Kingdom	An outbreak of culture-confirmed <i>E. coli</i> O157 from 15 September through 1 November 2005 in the 3 most affected local authority areas in South Wales	134	8
259	Werber 2013	Denmark, France, Germany and Sweden	• Surveillance data from single cohorts each in Denmark, France, and Sweden and 3 cohorts in Germany • The 3 cohorts from Germany consisted of 10 groups that visited a particular restaurant (cohort 1) and 2 groups who stayed at a hotel over a weekend (cohort 2 and 3) • The cohorts of Denmark and Sweden (cohorts 4 and 5) were travel groups visiting the northern Germany outbreak area • The cohort from France were attendees to a children’s community center near Bordeaux, France (cohort 6)	119	26
260	Whitney 2015	United States of America	• Surveillance data from Connecticut, USA via FoodNet for all isolates of <i>Salmonella</i>, <i>E. coli</i> O157:H7 and Stx-positive broths • All incident cases of <i>Salmonella</i> and STEC infection with onset during 2000–2011	764	49

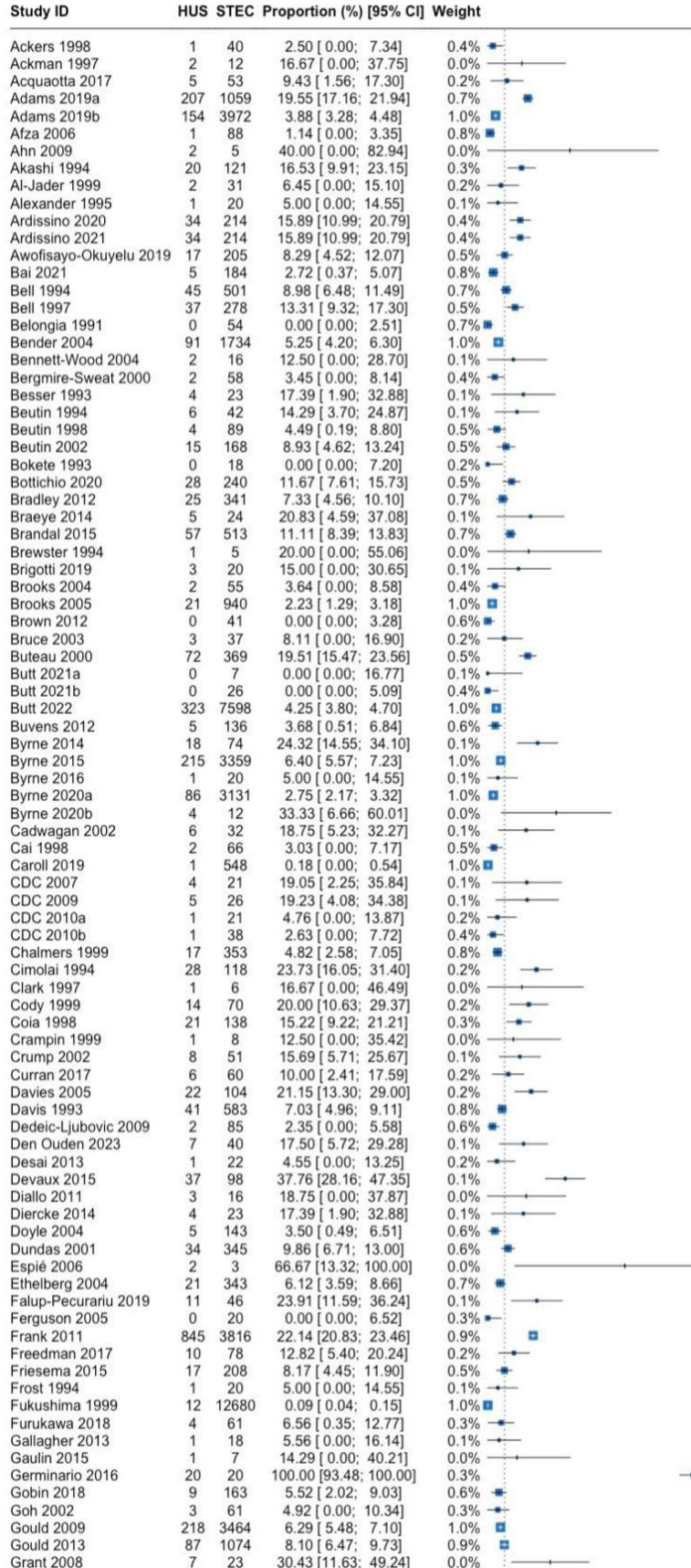
261	Willshaw 1994	United Kingdom	• An outbreak in a South Wales town, Wales, UK • Detected initially in 4 residents with 4 more reports from general practitioners • Symptom onset ranged from 15 August to 1 September 1993 • Linked to <i>E. coli</i> O157 • Age of participants ranged from 7-70 years	8	1
262	Wilson 2018	United Kingdom	• An outbreak in north-east of England, UK during July 2015 • The PHE Health Protection Team (HPT) in the north-east of England noted an increase in STEC O157 cases • Age of participants ranged from 6-89 years	15	7
263	Wong 2000	United States of America	Surveillance data from Washington, Oregon, Idaho, and Wyoming, USA due to <i>E. coli</i> O157:H7 infections between 1 April 1997 and 31 August 1999	71	10
264	Wong 2012	United States of America	• Surveillance data from Washington, Oregon, Idaho, and Wyoming, USA between April 1997 and October 2006 • A network of 47 cooperating laboratories in Washington, Oregon, Idaho, and Wyoming, USA Identification of children < 10 years of age • <i>E. coli</i> O157:H7 infections between 1 April 1997 and 31 August 1999	259	36
265	Wood 2001	United Kingdom	• An outbreak from patients attending Wishaw clinic, Scotland, UK linked to <i>E. coli</i> O157 infection • All the data relating to the patients monitored at the Wishaw clinic during the central Scotland outbreak have been validated and linked by the Information and Statistics Division of the NHS in Scotland	245	9
266	Yahata 2015	Japan	• An outbreak in Toyama, Fukui, Ishikawa, and Kanagawa prefectures, Japan during April to May 2011 due to <i>E. coli</i> O111 • Linked to a restaurant chain	86	34
267	Yahata 2018	Japan	• A multi-prefectural outbreak in Chiba, Saitama, Tokyo, Kanagawa and Okinawa prefectures, Japan, initiated from 14 November 2009 to 2 January 2010 linked to EHEC O157	21	0

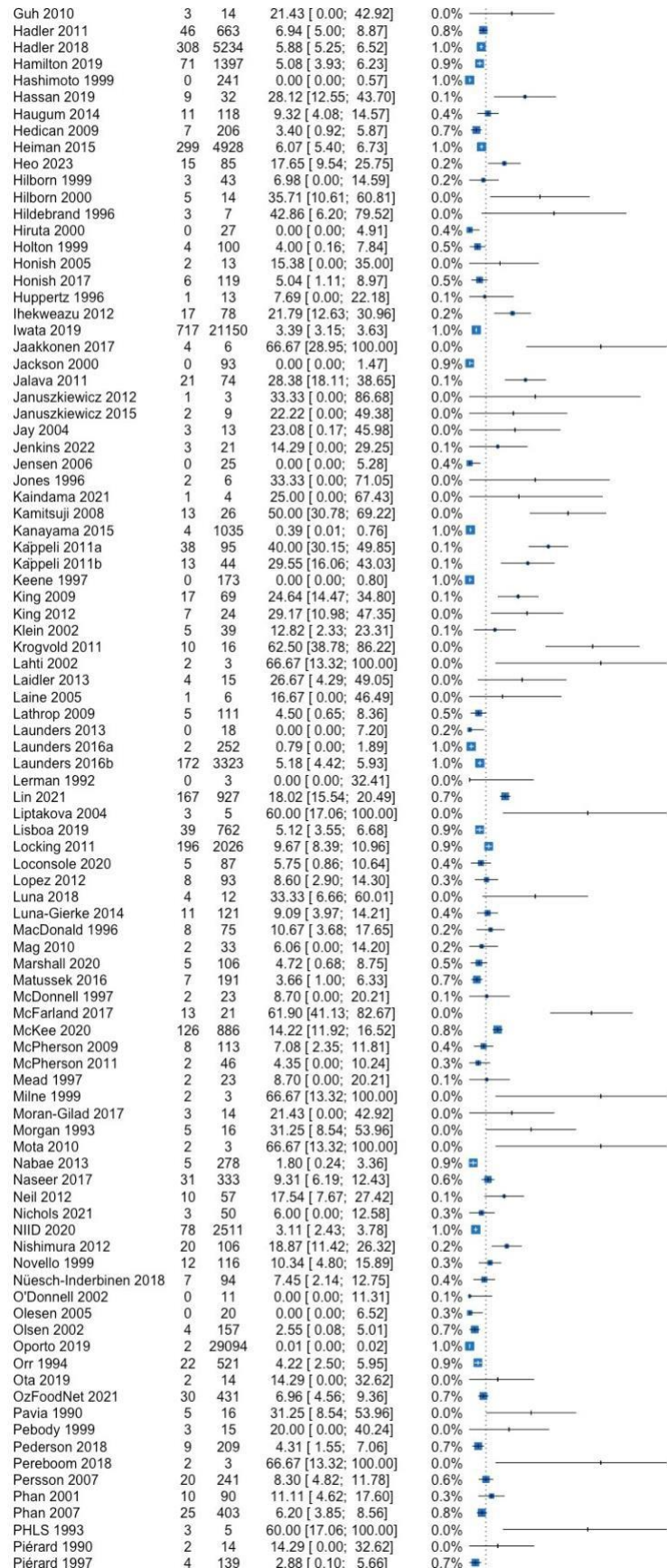
			• All cases had visited a Restaurant A branch serving Korean cuisine • Age of participants ranged from 12-48 years		
268	Yamamoto 2009	Japan	An outbreak of <i>E. coli</i> O157:H7 in Osaka, Japan in 1996	12021	182
269	Ylinen 2020	Finland	• Surveillance data from 2000 to 2016 across five University Hospitals • STEC findings from a total of 262 pediatric patients (< 17 years of age) to the NIDR, as required by the Finnish legislation	262	58

CDC: Centres for Disease Control and Prevention

NIID: National Institute of Infectious Diseases

PHLS: Public Health Laboratory Service





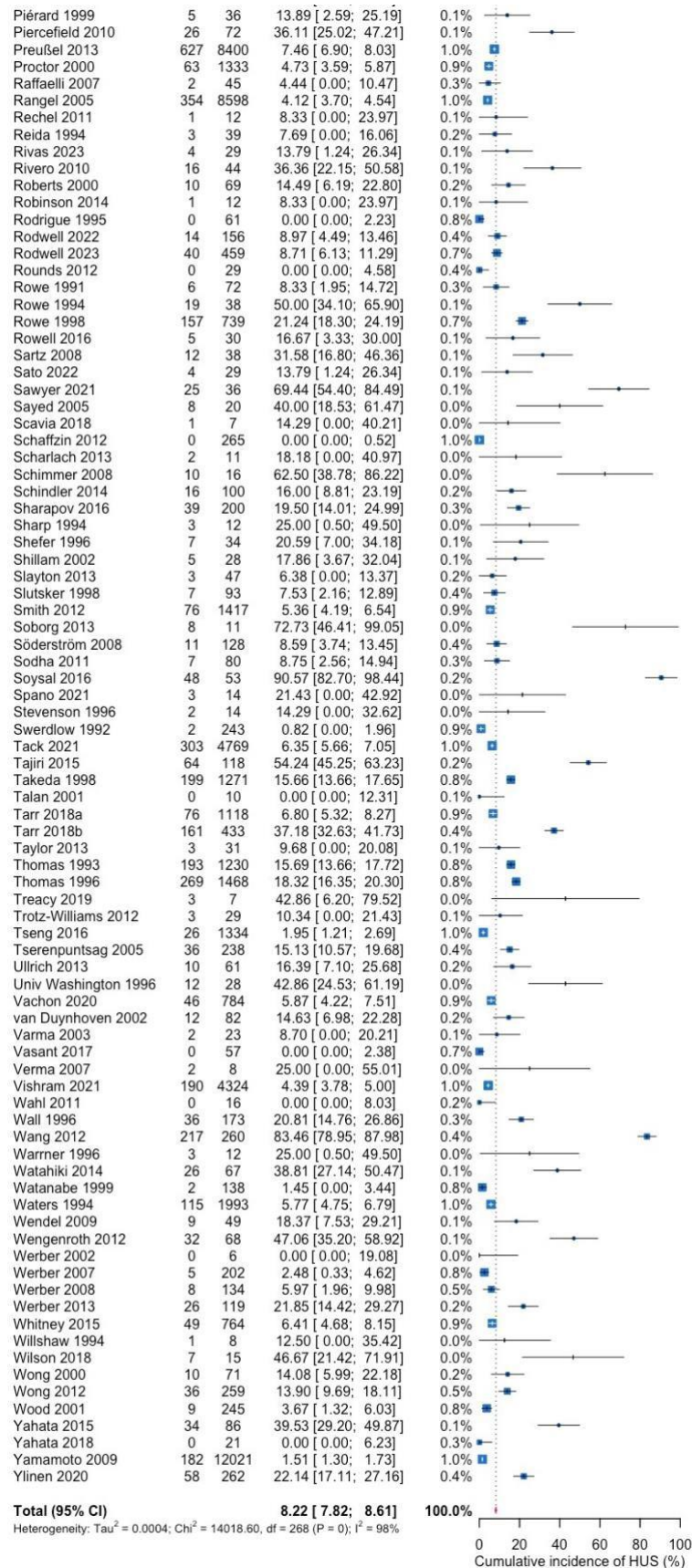


Figure 2. Cumulative incidence of HUS among symptomatic STEC cases, 1990 – 2024

4.4. Subgroup analyses of cumulative incidence of HUS

The stratified meta-analyses or subgroup analyses for each predictor are summarized in Table 7 and as forest plots in Appendix 6.

Table 7. Cumulative incidence (%) of HUS among symptomatic STEC cases stratified by pre- selected predictors in subgroup analyses

Predictor (n)	Cumulative incidence (%) (95% CI)
Age	
0 – 4 years (n = 23)	17.82 (14.57 – 21.07)
5 – 19 years (n = 18)	11.91 (8.73 – 15.09)
≥ 20 years (n = 12)	4.30 (2.36 – 6.24)
Sex	
Male (n = 41)	10.71 (8.95 – 12.48)
Female (n = 41)	13.03 (11.04 – 15.02)
STEC serogroup ^{a,b}	
O157 (n = 179)	8.73 (8.00 – 9.46)
Co-infections (n = 51)	9.41 (7.93 – 10.90)
O26 (n = 21)	11.25 (5.34 – 17.16)
O111 (n = 16)	8.80 (5.42 – 12.18)
Unspecified non-O157 (n = 19)	4.85 (2.67 – 7.02)
O104 (n = 9)	26.44 (20.10 – 32.79)
O103 (n = 11)	4.45 (1.14 – 7.77)
O117 (n = 3)	0 (0 – 3.64)
O145 (n = 8)	5.19 (2.16 – 8.21)
O146 (n = 2)	0 (0 – 1.16)
O121 (n = 5)	6.57 (1.11 – 12.03)
O91 (n = 2)	0 (0 – 1.22)
O128 (n = 2)	0 (0 – 2.05)
O55 (n = 3)	45.05 (7.26 – 82.85)
O5 (n = 2)	0 (0 – 34.50)
O76 (n = 2)	0 (0 – 34.50)
O45 (n = 4)	0 (0 – 0.85)
O113 (n = 2)	50 (0 – 100)
Other (n = 3)	6.10 (0 – 12.27)
Unknown (n = 3)	6.23 (0 – 13.76)
Ungroupable (n = 4)	4.85 (0 – 12.39)
STEC gene ^b	
<i>stx1</i> or subtypes only (n = 10)	0.15 (0 – 0.40)

<i>stx2</i> or subtypes only (n = 14)	9.19 (5.63 – 12.76)
<i>stx1</i> + <i>stx2</i> (n = 31)	8.04 (6.30 – 9.79)
<i>stx1</i> + Other genes (n = 5)	0.72 (0 – 3.30)
<i>stx2</i> + Other genes (n = 16)	35.32 (14.55 – 56.09)
<i>stx1</i> + <i>stx2</i> + Other genes (n = 29)	5.52 (4.35 – 6.69)
Other genes (n = 12)	14.11 (9.81 – 18.42)
STEC toxin ^{a, b}	
Stx1 or subtypes only (n = 3)	1.19 (0 – 3.58)
Stx2 or subtypes only (n = 10)	17.56 (10.22 – 24.91)
Stx1 + Stx2 (n = 18)	11.15 (8.22 – 14.09)
Year range of data ^a	
1990 – 1994 (n = 36)	10.96 (8.14 – 13.77)
1995 – 1999 (n = 39)	5.53 (4.48 – 6.58)
2000 – 2004 (n = 24)	6.79 (4.47 – 9.11)
2005 – 2009 (n = 32)	10.90 (8.53 – 13.27)
2010 – 2014 (n = 50)	14.79 (12.74 – 16.84)
2015 – 2019 (n = 31)	7.48 (5.75 – 9.22)
WHO Region ^a	
European Region (n = 126)	12.66 (11.47 – 13.85)
Region of the Americas (n = 116)	9.94 (8.82 – 11.05)
Western Pacific Region (n = 26)	5.01 (3.94 – 6.08)
Study setting ^a	
Outbreak – general community (single) (n = 57)	14.12 (11.91 – 16.32)
Outbreak – facility or event (n = 31)	7.88 (5.45 – 10.30)
Outbreak – general community (multiple/dispersed) (n = 47)	9.57 (7.96 – 11.18)
Non-outbreak – disease surveillance/registry (unadjusted) (n = 95)	10.37 (9.40 – 11.35)
Non-outbreak – surveillance, adjusted (n = 2)	5.63 (4.90 – 6.36)
Non-outbreak – health facility (n = 23)	14.80 (10.23 – 19.38)
Cluster – family (n = 6)	31.37 (11.95 – 50.80)
Cluster – facility (n = 3)	3.51 (0 – 15.56)
Cluster – other (n = 4)	25.42 (11.73 – 39.12)
STEC detection method ^b	
Culture only (n = 28)	9.57 (7.96 – 11.17)
Molecular only (n = 22)	7.88 (5.92 – 9.84)
Culture + Molecular + Other (n = 91)	14.44 (12.73 – 16.16)
Culture + Molecular (n = 70)	6.29 (5.30 – 7.29)
Culture + Other (n = 29)	16.30 (12.18 – 20.41)
Molecular + Other (n = 4)	31.33 (4.34 – 58.32)
Study quality rating	

Low (n = 2)	8.33 (7.93 – 8.74)
Moderate (n = 19)	8.98 (5.72 – 12.23)
High (n = 248)	4.84 (1.03 – 8.64)

n: Number of studies in subgroup

CI: Confidence interval

^a Predictor subgroups with only one study have been excluded

^b Mutually exclusive subgroups in the variable

4.4.1. Cumulative incidence by human characteristics

The subgroup meta-analyses for age (Appendix 6 – Figure A1) indicate that cumulative incidence of HUS among symptomatic STEC cases was 17.82% (95% CI, 14.57 – 21.07) in STEC cases aged 0 – 4 years, 11.91% (95% CI, 8.73 – 15.09%) in STEC cases aged 5 – 19 years and 4.30% (95% CI, 2.36 – 6.24) in STEC cases aged ≥ 20 years. The cumulative incidence of HUS among symptomatic STEC cases was 10.71% (95% CI, 8.95 – 12.48) among male STEC cases and 13.03% (95% CI, 11.04 – 15.02) among female STEC cases (Appendix 6 – Figure A2).

4.4.2. Cumulative incidence by STEC characteristics

According to the subgroup analysis (Appendix 6 – Figure A3), most published studies were on O157 infections (n = 179), followed by co-infections with multiple STEC serotypes (n = 61). The cumulative incidence of HUS among STEC O157 cases was estimated to be 8.73% (95% CI, 8.00 – 9.46), and among co-infections was estimated to be 9.41% (95% CI, 7.93 – 10.90). The gene-stratified meta-analysis (Appendix 6 – Figure A4) determined that the highest cumulative incidence was in the ‘stx2 + Other genes’ subgroup at 35.32% (95% CI, 14.55 – 56.09). The toxin-stratified meta-analysis (Appendix 6 – Figure A5) indicated the highest cumulative incidence in the ‘Stx2 or subtypes’ only subgroup at 17.56% (95% CI, 10.22 – 24.91).

4.4.3. Cumulative incidence by study design characteristics

Among the six categories of year ranges, the lowest cumulative incidence occurred in the 1995 to 1999 year range at 5.53% (95% CI, 4.48 – 6.58). The highest cumulative incidence was in the year range of 2010 – 2014 at 14.79% (95% CI, 12.74 – 16.84) (Appendix 6 – Figure A6).

A large geographical distribution was noted in the subgroup analysis (Appendix 6 – Figure A7) with countries from the WHO Region of the Americas, WHO European Region, WHO Western Pacific Region and WHO Eastern Mediterranean Region. Most studies originated either from the United States or the United Kingdom. The lowest cumulative incidence was estimated at 5.01% (95% CI, 3.94 – 6.08) from the Western Pacific Region. The highest cumulative incidence was from the European Region at 12.66% (95% CI, 11.47 – 13.85). Compared to other countries in the meta-analyses, high cumulative incidences were noted in countries within the WHO Region of the Americas and the WHO European Region.

In terms of study setting, most included studies focused on outbreaks in general communities or disease surveillance (Appendix 6 – Figure A8). The lowest cumulative incidence of HUS was in the subgroup of ‘Cluster – facility’, such as childcare facilities, nurseries, and restaurants. The estimate was 3.51% (95% CI, 0 – 15.56). The highest cumulative incidence was noted in the subgroup ‘Cluster – family’, at 31.37% (95% CI, 11.95 – 50.80).

Most studies used a combination of culture and molecular methods (Appendix 6 – Figure A9). The lowest cumulative incidence was in the ‘Culture + Molecular’ subgroup at 6.29% (95% CI, 5.30 – 7.29). The highest cumulative incidence was recorded in the ‘Molecular + Other’ subgroup at 31.33% (95% CI, 4.34 – 58.32).

In terms of study quality, approximately 92% of included studies were high-quality studies and the cumulative incidence was estimated to be 8.33% (95% CI, 7.93 – 8.74) in this subgroup. Only two

included studies were of low quality and produced the lowest estimate for cumulative incidence at 4.84% (95% CI, 1.03 – 8.64) (Appendix 6 – Figure A10).

4.5. Meta-regression

A series of univariable meta-regression models assessed the impact of these predictors on the cumulative incidence of HUS (Table 8). Among these predictors, age ($p < 0.0001$), sex ($p < 0.0001$), serogroup ($p < 0.0001$), STEC genes ($p < 0.0001$), year range of data ($p < 0.0001$), WHO Region ($p = 0.02$) and STEC detection methods ($p < 0.0001$) were statistically significant determinants of the incidence estimates.

Table 8. Univariable meta-regression analyses of factors potentially affecting study heterogeneity

Predictor variable	Co-efficient (95% CI)	p-value
Age (Reference: 0 – 4 years; n = 53)		
5 – 19 years	- 0.04 (-0.12 – 0.04)	0.31
≥ 20 years	- 0.09 (-0.18 – 0)	0.04 *
Sex (Reference: Female, n = 82)		
Male	-0.02 (-0.07 – 0.04)	0.57
Serogroup (Reference: Co-infections, n = 366) ^a		
O157	0 (-0.03 – 0.04)	0.75
O26	0 (-0.06 – 0.06)	0.95
O111	0 (-0.06 – 0.07)	0.89
non-O157	-0.09 (-0.30 – 0.11)	0.38
Unspecified non-O157	-0.03 (-0.09 – 0.03)	0.27
O104	0.15 (0.06 – 0.24)	< 0.001 ***
O103	-0.02 (-0.09 – 0.06)	0.67
O117	-0.09 (-0.21 – 0.04)	0.16
O145	-0.05 (-0.14 – 0.03)	0.20
O146	-0.10 (-0.25 – 0.05)	0.20
O121	-0.03 (-0.15 – 0.09)	0.66
O91	-0.09 (-0.25 – 0.08)	0.29
O128	-0.08 (-0.25 – 0.08)	0.33
O156	-0.03 (-0.33 – 0.27)	0.85
O55	0.41 (0.24 – 0.58)	<0.0001 ***
O15	0.01 (-0.37 – 0.39)	0.95
O70	0.01 (-0.37 – 0.39)	0.95
O174	0.01 (-0.37 – 0.39)	0.95
O5	0.08 (-0.29 – 0.46)	0.67

O41	0.05 (-0.42 – 0.52)	0.82
O76	0.08 (-0.29 – 0.46)	0.67
O88	0.05 (-0.42 – 0.52)	0.82
O45	-0.10 (-0.21 – 0)	0.06
O118	-0.11 (-0.32 – 0.09)	0.29
O113	0.39 (-0.06 – 0.84)	0.09
O80	0.79 (0.57 – 1.01)	< 0.0001 ***
O28	0.14 (-0.50 – 0.77)	0.67
O50	0.08 (-0.29 – 0.46)	0.67
O69	0.14 (-0.50 – 0.77)	0.67
O8	0.14 (-0.50 – 0.77)	0.68
Other	-0.04 (-0.16 – 0.09)	0.58
Unknown	-0.04 (-0.17 – 0.09)	0.57
Ungroupable	-0.04 (-0.17 – 0.08)	0.47
O-nontypeable	-0.05 (-0.31 – 0.21)	0.71
Untypeable	-0.09 (-0.30 – 0.13)	0.42
STEC genes (Reference: Other, n = 117) ^a		
<i>stx1</i> or subtypes only	-0.13 (-0.23 – -0.02)	0.02 *
<i>stx2</i> or subtypes only	-0.06 (-0.15 – 0.04)	0.28
<i>stx1</i> + <i>stx2</i>	-0.05 (-0.13 – 0.03)	0.25
<i>stx1</i> + <i>stx2</i> + Other genes	-0.05 (-0.13 – 0.04)	0.30
<i>stx1</i> + Other genes	-0.13 (-0.26 – 0)	0.06
<i>stx2</i> + Other genes	0.16 (0.06 – 0.29)	< 0.01 **
STEC toxins (Reference: Stx1 or subtypes only, n = 32) ^a		
Stx2 and subtypes only	0.14 (0 – 0.29)	0.04 *
Stx1 + Stx2	0.10 (-0.02 – 0.23)	0.11
Stx1 + Stx2 + Hemolysin	0.09 (-0.19 – 0.36)	0.54
Year range of data (Reference: 1990 – 1994, n = 213)		
1995 – 1999	-0.03 (-0.10 – 0.04)	0.44
2000 – 2004	-0.02 (-0.10 – 0.06)	0.65
2005 – 2009	0.01 (-0.06 – 0.08)	0.75
2010 – 2014	0.04 (-0.02 – 0.10)	0.23
2015 – 2019	0.03 (-0.05 – 0.10)	0.50
2020 – 2024	0.05 (-0.24 – 0.33)	0.75
Region (Reference: Eastern Mediterranean Region, n = 269)		
European Region	-0.24 (-0.58 – 0.11)	0.18
Region of the Americas	-0.28 (-0.63 – 0.07)	0.12
Western Pacific Region	-0.29 (-0.64 – 0.06)	0.11
Study design (Reference: Cluster – facility, n = 269)		
Outbreak – general community (single)	0.06 (-0.15 – 0.27)	0.55
Outbreak – facility or event	0 (-0.21 – 0.22)	0.95

Outbreak – general community (multiple/dispersed)	0.04 (-0.18 – 0.25)	0.74
Non-outbreak – disease surveillance/registry (unadjusted)	0.02 (-0.19 – 0.22)	0.89
Non-outbreak – surveillance, adjusted	-0.05 (-0.34 – 0.23)	0.71
Non-outbreak – health facility	0.05 (-0.16 – 0.27)	0.64
Cluster – family	0.19 (-0.08 – 0.46)	0.17
Cluster – other	0.18 (-0.11 – 0.46)	0.22
Other	-0.01 (-0.11 – 0.46)	0.93
STEC detection methods (Reference: Culture only, n = 244) ^a		
Molecular only	0 (0 – 0.34)	0.97
Culture + Molecular + Other	0.05 (-0.02 – 0.11)	0.15
Culture + Molecular	-0.03 (-0.09 – 0.04)	0.41
Culture + Other	0.05 (-0.03 – 0.13)	0.22
Molecular + Other	0.17 (0 – 0.33)	0.05 *
Study quality rating (Reference: High, n = 269)		
Low	-0.09 (-0.29 – 0.11)	0.39
Moderate	0 (-0.08 – 0.07)	0.94

n: Number of studies in analysis

CI: Confidence interval

p-value: Probability value

^a Mutually exclusive subgroups in the variable

* : Statistical significance at 0.05

** : Statistical significance at 0.01

*** : Statistical significance at 0.001

A multivariable meta-regression model with all predictors quantified the impact of the predictors on the cumulative incidence of HUS among symptomatic STEC cases (Table 9-10). This meta-regression included 711 data entries. The overall estimate of variance due to these covariates in the final model was substantial ($R^2 = 60.08\%$, $p < 0.001$). Approximately 60% of the difference in true effect sizes can be explained by all predictors included in the regression model. The random-effects multivariable meta-regression produced co-efficients to describe changes in cumulative incidence of HUS in subcategories (Table 10).

Table 9. Summary of multivariable meta-regression model including all predictors quantifying relationships among variables

Point estimate	0.31
Standard error	0.18
95% CI	-0.04 – 0.67
z-value	1.72
p-value	0.09

Table 10. Co-efficients in multivariable meta-regression analysis including all predictors

Predictor variable	Co-efficient (95% CI)	p-value
Age (Reference: No available data)		
0 – 4 years	0.05 (0.01 – 0.10)	< 0.005 *
5 – 19 years	0.03 (0 – 0.01)	0.13
≥ 20 years	-0.04 (-0.08 – 0.07)	0.13
Sex (Reference: No available data)		
Male	0.02 (-0.02 – 0.06)	0.28
Female	0.04 (0 – 0.08)	0.04 *
Serogroup (Reference: No available data) ^a		
O157	0 (-0.02 – 0.04)	0.61
Co-infections	0.01 (-0.02 – 0.05)	0.45
non-O157	0 (-0.10 – 0.08)	0.85
O-nontypeable	-0.02 (-0.26 – 0.23)	0.90
O103	0.02 (-0.05 – 0.09)	0.55
O104	0.05 (-0.03 – 0.14)	0.24
O111	0.06 (0.01 – 0.11)	0.02 *
O112	0.50 (0.07 – 0.92)	0.02 *
O113	0.31 (0 – 0.62)	0.05 *
O114	0.48 (0.09 – 0.87)	0.02 *
O115	0.10 (-0.18 – 0.37)	0.49
O116	0.26 (0.01 – 0.52)	0.04 *
O117	0.07 (-0.06 – 0.20)	0.29
O118	0.01 (-0.19 – 0.21)	0.93
O121	-0.04 (-0.16 – 0.07)	0.48
O128	0 (-0.27 – 0.26)	0.95
O145	-0.03 (-0.10 – 0.04)	0.43
O146	-0.05 (-0.25 – 0.14)	0.60
O15	0.05 (-0.33 – 0.42)	0.81
O156	0 (-0.28 – 0.29)	0.98
O158	0.04 (-0.19 – 0.28)	0.72
O174	0.05 (-0.33 – 0.42)	0.81
O26	0.03 (-0.03 – 0.08)	0.30
O28	0.21 (-0.42 – 0.84)	0.52
O41	0.09 (-0.37 – 0.55)	0.71
O45	-0.04 (-0.14 – 0.06)	0.43

O5	0.13 (-0.24 – 0.50)	0.49
O50	0.21 (-0.42 – 0.84)	0.52
O55	0.42 (0.32 – 0.53)	< 0.0001 ***
O69	0.21 (-0.42 – 0.84)	0.52
O70	0.05 (-0.33 – 0.42)	0.81
O76	0.13 (-0.24 – 0.50)	0.49
O8	0.21 (-0.42 – 0.84)	0.52
O80	0.83 (0.63 – 1.02)	< 0.0001 ***
O88	0.09 (-0.37 – 0.55)	0.71
O91	-0.02 (-0.27 – 0.23)	0.90
Other	0.03 (-0.08 – 0.15)	0.57
Ungroupable	0 (-0.11 – 0.11)	0.97
Unknown	-0.04 (-0.18 – 0.10)	0.57
Unspecified non-O157	-0.02 (-0.07 – 0.02)	0.30
Untypeable	-0.01 (-0.21 – 0.18)	0.88
STEC genes (Reference: No available data) ^a		
<i>stx1</i> or subtypes only	-0.06 (-0.13 – 0)	0.04 *
<i>stx2</i> or subtypes only	0 (-0.04 – 0.04)	0.95
<i>stx1</i> + <i>stx2</i>	0 (-0.02 – 0.04)	0.60
<i>stx1</i> + <i>stx2</i> + Other genes	0.01 (-0.03 – 0.04)	0.65
<i>stx1</i> + Other genes	-0.08 (-0.18 – 0.02)	0.11
<i>stx2</i> + Other genes	0.15 (0.09 – 0.22)	< 0.0001 ***
Other	0.04 (-0.01 – 0.09)	0.09
STEC toxins (Reference: No available data) ^a		
Stx1 or subtypes only	-0.02 (-0.13 – 0.09)	0.74
Stx2 or subtypes only	0.08 (0 – 0.16)	0.05
Stx1 + Stx2	0.05 (0 – 0.09)	0.05
Stx1 + Stx2 + Hemolysin	0.03 (-0.23 – 0.28)	0.84
Year range of data (Reference: No available data)		
1990 – 1994	0.01 (-0.03 – 0.04)	0.78
1995 – 1999	-0.01 (-0.04 – 0.03)	0.65
2000 – 2004	0 (-0.04 – 0.04)	0.95
2005 – 2009	0.04 (0 – 0.07)	0.03 *
2010 – 2014	-0.02 (-0.08 – 0.03)	0.44
2015 – 2019	0 (-0.03 – 0.04)	0.06
Region (Reference: No available data)		
European Region	-0.25 (-0.44 – -0.05)	0.02 *
Region of the Americas	-0.26 (-0.45 – -0.06)	0.01 *
Western Pacific Region	-0.28 (-0.48 – -0.08)	< 0.05 **
Study setting (Reference: Cluster – facility)		
Outbreak – general community (single)	0.02 (-0.12 – 0.15)	0.78
Outbreak – facility or event	-0.01 (-0.15 – 0.13)	0.88
Outbreak – general community (multiple/dispersed)	0.03 (-0.10 – 0.17)	0.64
Non-outbreak – disease surveillance (unadjusted)	-0.03 (-0.16 – 0.10)	0.67
Non-outbreak – surveillance, adjusted	-0.10 (-0.25 – 0.04)	0.17

Non-outbreak – health facility	0 (-0.13 – 0.15)	0.89
Cluster – family	0.07 (-0.12 – 0.27)	0.46
Cluster – other	0.16 (-0.08 – 0.40)	0.20
STEC detection methods (Reference: Culture only) ^a		
Molecular only	-0.01 (-0.06 – 0.04)	0.61
Culture + Molecular + Other	0 (-0.03 – 0.04)	0.80
Culture + Molecular	-0.02 (-0.06 – 0.02)	0.24
Culture + Other	0.03 (-0.01 – 0.07)	0.20
Molecular + Other	0 (-0.08 – 0.07)	0.92
Study quality rating (Reference: High)		
Low	-0.05 (-0.19 – 0.09)	0.51
Moderate	0.01 (-0.03 – 0.05)	0.49

CI: Confidence interval

p-value: Probability value

^a Mutually exclusive subgroups in the variable

* : Statistical significance at 0.05

** : Statistical significance at 0.01

*** : Statistical significance at 0.001

4.6. Study quality assessment

The results of the study quality assessment according to the JBI Tools, have been summarized in Tables 11-13. The majority of included studies (~ 92.2% of all included records) were of high quality. Of 269 studies, 248 (92.2%) included studies were rated as ‘High’ quality, 19 (7.0%) included studies were rated ‘Moderate’ quality and two (0.7%) included studies were rated ‘Low’ quality.

One of the two records classified as ‘Low’ quality was an active surveillance study in Germany (Beutin, Zimmermann and Gleier, 1998) and the second record was a passive surveillance study in Hungary (Mag *et al.*, 2010). The reasons for low quality in these studies were study length, study settings like case definitions and surveillance systems, and statistical analyses. Both studies do not give case definitions, clear descriptions of case ascertainment, and descriptive statistics of the study population. The full texts focus heavily on laboratory methods to characterize STEC infections.

Table 11. Results of study quality assessment for included studies in systematic review according to adapted JBI Critical Appraisal Tool for Case series

Study ID	Checklist Item in JBI Critical Appraisal Tool										N _Y	N _Y (%)	Rating
	1	2	3	4	5	6	7	8	9	10			
Ackers 1998	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	90.00	HIGH
Ackman 1997	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Afza 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Ahn 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Akashi 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Al-Jader 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Alexander 1995	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Bell 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Bell 1997	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Belongia 1991	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Bergmire-Sweat 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Besser 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Beutin 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Bottichio 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Braeye 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Brewster 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Brooks 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Brown 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Bruce 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Buteau 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Butt 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Butt 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Byrne 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Byrne 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Cadwagan 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
CDC 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
CDC 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH

CDC 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
CDC 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Cimolai 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Clark 1997	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Cody 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Crampin 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Crump 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Curran 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Davies 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Davis 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Univ of Washington 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Desai 2013	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	90.00	HIGH
Devaux 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Diallo 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Diercke 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Dundas 2001	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Espié 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Ferguson 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Frank 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Freedman 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Frost 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Fukushima 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Furukawa 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Gallagher 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Gaulin 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Germinario 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Gobin 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Goh 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Grant 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Guh 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Hashimoto 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Hassan 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Heo 2023	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH

Hilborn 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Hilborn 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Hildebrand 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Hiruta 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Honish 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Honish 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Huppertz 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Ihekweazu 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Jaakkonen 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Jackson 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Januszkiewicz 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Jay 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Jenkins 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Jensen 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Jones 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Keene 1997	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Kaindama 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
King 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
King 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Klein 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Krogvold 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Laidler 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Laine 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Launders 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Launders 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Lerman 1992	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Lin 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Liptakova 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Luna-Gierke 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Luna 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
McDonnell 1997	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
McFarland 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Milne 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH

Moran-Gilad 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Morgan 1993	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Nabae 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Neil 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Nichols 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Novello 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
O'Donnell 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Olsen 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Orr 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Ota2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Pavia 1990	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Pebody 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Pereboom 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Phan 2001	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Piercefield 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
PHLS 1993	Y	Y	Y	U	Y	N	N	Y	Y	N/A	6	60.00	MODERATE
Raffaelli 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Rechel 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Reida 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Roberts 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Rodrigue 1995	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Rounds 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Rowe 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Rowell 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Sartz 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Sato 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Sayed 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Scavia 2018	Y	Y	Y	Y	Y	Y	N	Y	Y	N	8	80.00	HIGH
Schaffzin 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Scharlach 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Schimmer 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Sharapov 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Shefer 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH

Shillam 2002	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9	90.00	HIGH
Slayton 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	9	90.00	HIGH
Soborg 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Söderström 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Sodha 2011	Y	Y	Y	Y	Y	Y	N	Y	Y	N/A	8	80.00	HIGH
Spano 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Stevenson 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Swerdlow 1992	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Talan 2001	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Taylor 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Treacy 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Trotz-Williams 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Ullrich 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Varma 2003	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Vasant 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Verma 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Wahl 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Wall 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Warrner 1996	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Watahiki 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Watanabe 1999	Y	Y	Y	Y	N	N	N	Y	Y	N/A	6	60.00	MODERATE
Wendel 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Wengenroth 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Werber 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Werber 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Willshaw 1994	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Wilson 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Wong 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Yahata 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Yahata 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	9	90.00	HIGH
Yamamoto 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH

Y: Yes N: No. U: Unclear N/A: Not applicable N_Y: Number of Checklist items answered 'Y' CDC: Centres for Disease Control and Prevention PHLS: Public Health Laboratory Service

Table 12. Results of study quality assessment for included studies in systematic review according to adapted JBI Critical Appraisal Tool for Prevalence

Study ID	Checklist Item in JBI Critical Appraisal Tool									N _Y	N _Y (%)	Rating
	1	2	3	4	5	6	7	8	9			
Acquaotta 2017	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Adams 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Adams 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	100.00	HIGH
Ardissino 2021	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Ardissino 2020	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Awofisayo-Okuyelu 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	100.00	HIGH
Bai 2021	Y	Y	N	Y	Y	Y	Y	Y	N/A	7	77.78	HIGH
Bender 2004	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Bennett-Wood 2004	Y	Y	Y	Y	N	Y	Y	N/A	N/A	6	66.67	MODERATE
Beutin 2002	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Beutin 1998	N	Y	N/A	N	N/A	Y	Y	N	N/A	3	33.33	LOW
Bokete 1993	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Bradley 2012	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Brandal 2015	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Brigotti 2019	Y	Y	Y	Y	Y	Y	Y	N	N/A	7	77.78	HIGH
Brooks 2005	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Butt 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	100.00	HIGH
Buven 2012	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Byrne 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	100.00	HIGH
Byrne 2020	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Byrne 2014	Y	Y	Y	Y	Y	Y	Y	N/A	Y	8	88.89	HIGH
Cai 1998	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Caroll 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Chalmers 1999	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Coia 1998	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Dedeic-Ljubovic 2009	Y	Y	Y	Y	N	Y	Y	N/A	N/A	6	66.67	MODERATE
Den Ouden 2023	Y	Y	N	Y	N	Y	Y	N/A	N/A	5	55.56	MODERATE
Doyle 2004	Y	Y	Y	N	N	Y	Y	N/A	N/A	5	55.56	MODERATE
Ethelberg 2004	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH

Falup-Pecurariu 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Gould 2009	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Gould 2013	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Hadler 2011	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Hadler 2018	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Hamilton 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Haugum 2014	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Hedican 2009	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Heiman 2015	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Iwata 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Jalava 2011	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Januszkiewicz 2015	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Kanayama 2015	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Käppeli 2011	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Käppeli 2011	Y	Y	Y	N	Y	Y	Y	N/A	N/A	6	66.67	MODERATE
Lahti 2002	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Lathrop 2009	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Launders 2016	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Lisboa 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Locking 2011	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Loconsole 2020	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Lopez 2012	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
MacDonald 1996	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Mag 2010	Y	Y	N/A	N	N	Y	Y	N/A	N/A	4	44.44	LOW
Marshall 2020	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Matussek 2016	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
McKee 2020	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
McPherson 2011	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Mota 2010	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	6	66.67	MODERATE
Naseer 2017	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
NIID 2020	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Nishimura 2012	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Nüesch-Inderbinnen 2018	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Olesen 2005	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Oporto 2019	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH

Pederson 2018	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Persson 2007	Y	Y	Y	N	Y	Y	Y	N/A	N/A	6	66.67	MODERATE
Phan 2007	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Piérard 1990	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	6	66.67	MODERATE
Piérard 1997	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Preußel 2013	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Proctor 2000	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Rangel 2005	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Rivas 2023	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Rivero 2010	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Robinson 2014	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Rodwell 2022	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Rodwell 2023	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Rowe 1998	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Sawyer 2021	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Schindler 2014	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Sharp 1994	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Smith 2012	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Soysal 2016	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Tack 2021	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Tajiri 2015	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Takeda 1998	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	100.00	HIGH
Tarr 2018	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Tarr 2018	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
The OzFoodNet Working Group 2021	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Thomas 1996	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Thomas1993	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Tseng 2016	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Tserenpuntsag 2005	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Vachon 2020	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
van Duynhoven 2002	Y	Y	Y	Y	Y	Y	Y	N/A	Y	8	88.89	HIGH
Vishram 2021	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	7	77.78	HIGH
Wang 2013	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Waters 1994	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH

Werber 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Werber 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Whitney 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Wong 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Wong 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH
Ylinen 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	8	88.89	HIGH

Y: Yes N: No. U: Unclear N/A: Not applicable N_Y: Number of Checklist items answered 'Y' NIID: National Institute of Infectious Diseases

Table 13. Results of study quality assessment for included studies in systematic review according to adapted JBI Critical Appraisal Tool for Case-control studies

Study ID	Checklist Item in JBI Critical Appraisal Tool										N _Y	N _Y (%)	Rating
	1	2	3	4	5	6	7	8	9	10			
Friesema 2015	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	9	90.00	HIGH
Holton 1999	Y	Y	U	Y	U	U	Y	U	Y	Y	6	60.00	MODERATE
Kamitsuji 2008	Y	Y	Y	Y	U	N	Y	Y	U	Y	7	70.00	MODERATE
McPherson 2009	Y	Y	Y	Y	Y	N	N	U	Y	Y	7	70.00	MODERATE
Mead 1997	Y	Y	Y	Y	Y	N	N	U	Y	Y	7	70.00	MODERATE
Piérard1999	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	9	90.00	HIGH
Rowe 1991	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100.00	HIGH
Slutsker 1998	Y	Y	Y	Y	Y	N	N	Y	Y	Y	8	80.00	HIGH

Y: Yes N: No. U: Unclear N/A: Not applicable N_Y: Number of Checklist items answered 'Y'

5. Discussion

5.1. Contribution of thesis

HUS is one of the most common and well-described sequelae of STEC infection (Bruyand *et al.*, 2018). The scientific literature provides a general understanding of HUS in the clinical course of STEC infection with regard to human characteristics, STEC characteristics, and study design. In terms of age, younger (< 5 years) and older (> 65 years) subpopulations are at a higher risk of STEC infection (California Department of Public Health, 2024a; Lisboa *et al.*, 2019; Byrne *et al.*, 2015; Gould *et al.*, 2009b). To the best of my knowledge, studies have not yet analyzed sex differences in STEC infections and STEC-HUS in meta-analyses. However, several outbreaks have reported higher cases of STEC and STEC-HUS among females (Bell *et al.*, 1997; Ostroff *et al.*, 1990). Certain STEC serogroups, such as STEC O157 and STEC O104, have been implicated in large outbreaks and higher virulence (Frank *et al.*, 2011; Bell *et al.*, 1997). The *stx2* gene has been associated with higher disease severity in STEC infection (Luna-Gierke *et al.*, 2014; Kawano *et al.*, 2008). STEC cases and HUS cases may vary by region, study year(s), STEC detection methods, and study setting due to various reasons detailed in previous sections (Table 1).

This systematic review is the first research effort to statistically combine all available data on STEC leading to HUS in a meta-analysis, which estimated the cumulative incidence of HUS among symptomatic STEC cases. It is also the first meta-analysis to investigate differences in the cumulative incidence of STEC-HUS cases by age, sex, STEC characteristics, and study characteristics. Thereby, this thesis contributes to epidemiological research on STEC infection and STEC-HUS.

The findings of the thesis will suggest which subpopulations are at a higher-than-average risk of developing STEC-HUS based on all available data. Public health professionals on a global scale will be able to use these data to inform clinical guidance, health surveillance, outbreak management, disease

management, and policymaking. As the thesis findings indicated higher cumulative incidence estimates among specific subpopulations, these subpopulations can be prioritized in future research and HUS management. The apparent data gaps by regions can also be addressed in future research and policies. For example, large STEC outbreaks can overwhelm health facilities (e.g., hospitals), laboratory services, and surveillance systems. Therefore, health systems can determine risk groups for resource allocation (e.g., subpopulations prioritized for medical care) and methods in outbreak management (e.g., risk based on serogroup). For decades, STEC O157 has been associated with a higher risk of HUS, large outbreaks, high virulence, and high pathogenicity (Etcheverría and Padola, 2013). STEC O157 has been targeted in laboratory methods for STEC and public health surveillance (Cukrovany *et al.*, 2024; Hoefer *et al.*, 2011). In recent years, STEC outbreaks have been linked to other serogroups (Frank *et al.*, 2011). This systematic review identified other STEC serogroups that could be important in surveillance and outbreaks. The results also elucidated the burden of STEC-HUS by region and uncovered data gaps by region.

5.2. STEC-HUS epidemiology

The cumulative incidence reported in the thesis is 8.22% (95% CI, 7.82 – 8.61) based on a meta-analysis of 269 individual records. This estimate is consistent with data from other research and organizational reports summarizing articles, that had not necessarily been selected and synthesized through a rigorous systematic review process (Table 14).

Table 14. Estimated proportions of STEC cases that develop HUS reported in other publications

Author(s)	Proportion of STEC cases developing HUS
Majowicz <i>et al.</i> (2014)	0.823% (for STEC O157) 0.025% (for non-O157)
Bruyand <i>et al.</i> (2018)	5 – 15%
Travert <i>et al.</i> (2021)	5 – 20%

Gould <i>et al.</i> (2009a)	8% (for STEC O157)
World Health Organization (2018)	up to 10%
European Centre for Disease Prevention and Control (no date)	8%
California Department of Public Health (2024b)	10%

The estimate of 8.22% is based only on published literature of reported data and ascertained cases. As with most foodborne infections, STEC infections are underestimated and the estimate of 8.22% may overrepresent the true incidence of HUS among STEC cases in the population (Meadows *et al.*, 2022; Gibbons *et al.*, 2014; Majowicz *et al.*, 2014). Collectively, case underestimation denotes under-ascertainment at the community level and underreporting at the healthcare level. Under-ascertainment occurs when cases do not seek healthcare and are not entered into surveillance systems as a result. While asymptomatic cases may not be aware of their infection, even symptomatic cases may not be recorded in routine surveillance, when symptoms are mild or common, or when the illness is self-limiting. Thus, underreported cases are cases, who seek health services but are not recorded in surveillance systems, due to underdiagnosis, misdiagnosis, and under-notification by data management errors (Gibbons *et al.*, 2014).

As described in Section 1.3.4., STEC cases may also be underestimated due to laboratory methods limited only to STEC O157 detection, limited knowledge of other serogroups and errors in surveillance (Noftall *et al.*, 2019; Chui *et al.*, 2018; Parsons *et al.*, 2016). Furthermore, STEC cases may be misdiagnosed because the clinical presentations of STEC infection and HUS are similar to other gastrointestinal infections, especially common symptoms like diarrhea and colitis. STEC infection and HUS may also be classified under umbrella terms (e.g., gastrointestinal disease, gastrointestinal infection, diarrhea) or as misdiagnoses (e.g., thrombocytopenic purpura) in research (McFarlane *et al.*, 2021).

Among the reports listed in Table 14, the systematic review by Majowicz *et al.* (2014) was the only epidemiological report that used multipliers to address STEC case underestimation. The estimate for STEC O157 in this thesis was 8.73% (Table 7). The corresponding estimate for STEC O157 reported by Majowicz *et al.* (2014) was 0.823%. Therefore, we may assume that the difference due to STEC case underestimation is approximately ten-fold. According to the individual included articles, statistical adjustment was insufficient, with only two of the 269 included studies having adjusted analyses using surveillance data (Hadler *et al.*, 2018; Hamilton and Cullinan, 2019) (Appendix 6 – Figure A8).

5.2.1. STEC-HUS epidemiology by human characteristics

Based on the age range of STEC cases in the pooled sample population (0 - 98 years), STEC and HUS can occur at any age for an individual. STEC-HUS occurred in all three age categories based on the stratified meta-analysis (Appendix 6 – Figure A1). Consistent with the general understanding of STEC-HUS, the highest cumulative incidence was among children aged 0 – 4 years at 17.82% (95% CI, 14.57 – 21.07) (Table 7). Additionally, univariable and multivariable meta-regressions adjusted for age indicated that cumulative incidence decreased as age increased from 0 – 4 years, 5 – 19 years and ≥ 20 years (Tables 8 and 10).

Currently, an underlying pathophysiology for the age difference has not been described in the literature. Children aged under 5 years have underdeveloped digestive systems and produce less gastric acid compared to adults (Sarker, Ahmed and Brüssow, 2017). Therefore, STEC may evade the bactericidal stomach conditions and may colonize gastrointestinal tracts more easily in young children. The glomerular filtration rate (GFR) is a common indicator of renal function. The GFR increases gradually from infancy and kidney development is completed only during adolescence (Arant, 1987). Thus, the higher incidence of STEC-HUS can also be attributed to immature renal systems and

insufficient renal function in young children. The immune systems of children may also still be in the development phase, unable to counteract STEC infections. For example, the adaptive immune response begins function at 2 years and completes development after age 10 years (Moraes-Pinto, Suano-Souza and Arandad, 2021).

This systematic review estimated the cumulative incidence of HUS to be 10.71% (95% CI, 8.95 – 12.48) among males and 13.03% (95% CI, 11.04 – 15.02) among females. As hypothesized in this thesis, STEC-HUS was higher among females. Several studies did not provide sex-stratified data for STEC and HUS cases. When sex-stratified data were provided in some included studies, STEC and HUS case numbers were given for only one sex and not both sexes. In such instances, I could not calculate the case numbers for the sex lacking data as a derivation using available data, given that participant response rates for demographic questionnaires may not always be 100%. Additionally, univariable and multivariable meta-regressions adjusted for sex indicated that cumulative incidence decreased in the male subgroup (Tables 8 and 10).

A systematic review of eight articles by Aldharman *et al.* (2023) on the prevalence and incidence of all HUS (not only STEC-HUS) found that females were marginally more likely to develop HUS than males. Typically, HUS frequencies are similar among both sexes during childhood, and HUS is higher among females in adulthood (Loirat and Frémeaux-Bacchi, 2011). The underlying cause for the higher HUS incidence among females has not been discovered or hypothesized in scientific literature (Loirat and Frémeaux-Bacchi, 2011). The clinical triad of physiological reactions leading to HUS includes low platelet count, microangiopathic hemolytic anemia, and acute kidney injury (Michael *et al.*, 2022). Microangiopathic hemolytic anemia occurs when red blood cells are destroyed due to the narrowing or blockage of small blood vessels (Morishita, 2015). The red blood cell counts, the amount of hemoglobin, and the concentration of iron in blood are lower in females compared to males, owing

to monthly blood loss during menstruation (Coad and Pedley, 2014; Murphy, 2014). Therefore, the hemolytic anemia related to HUS may be exacerbated in females due to the already low parameters.

5.2.2. STEC-HUS epidemiology by STEC characteristics

While much research on STEC-HUS has focused on STEC O157, this thesis identified other STEC serogroups linked to large HUS outbreaks. The main STEC serogroups included O111, O103, O104, and O26. However, the majority of included studies were on STEC O157 (Table 7). Many studies were also on co-infections with multiple STEC serogroups, including STEC O157 (Table 7). The cumulative incidence of HUS among STEC O157 cases was 8.73% (95% CI, 8.00 – 9.46). The cumulative incidence of HUS among STEC co-infections was 9.41% (95% CI, 7.93 – 10.90). The highest number of STEC-HUS cases ($n = 845$) was recorded during an epidemic of STEC O104:H4 in Germany in mid-2011 (Frank *et al.*, 2011). The cumulative incidence of HUS among STEC O104 cases was 26.44% (95% CI, 20.10 – 32.79) based on a subgroup analysis of nine studies.

STEC O157 is known to have higher virulence and can cause severe disease in humans. STEC O157 can thrive in various environments ranging from the animal reservoir to the farm environment (Kolodziejek, Minnich and Hovde, 2022). A few important virulence factors of STEC O157 are Stx2, STEC O157:H7 type 3 secretion system, products of locus of enterocyte effacement (a pathogenicity island), and products of the F-like plasmid pO157 (Kolodziejek, Minnich and Hovde, 2022; Lim, Yoon and Hovde, 2010). pO157 plasmid genes facilitate bacterial adherence to eukaryotic cells, colonization of cattle, and acid resistance (Lim, Yoon and Hovde, 2010).

Other research has also suggested that unique characteristics of STEC strains can contribute to large outbreaks and severe disease. For example, an investigation of the 2011 STEC O104:H4 outbreak strain found that the strain had a unique combination of virulence determinants (Haarmann *et al.*, 2018). This strain contained a prophage-encoded *stx* gene, the main virulence factor of

enterohemorrhagic STEC. Furthermore, this strain shared the highest DNA sequence similarity with enteroaggregative STEC (EAEC) and facilitates tight adherence to epithelial cells, which is characteristic of EAEC. Consequently, secretion of Stx toxins and EAEC characteristics can be linked to the unusually high virulence of this outbreak strain. The authors foreshadowed the emergence of more hypervirulent strains compared to previous years (Haarmann *et al.*, 2018).

Ingle *et al.* (2019) acknowledged that STEC outbreaks and surveillance have been documented extensively in North America and Europe with sparser research from the Southern hemisphere. The authors conducted the largest STEC analysis in the Southern hemisphere to describe major STEC lineages in Australia. The analysis determined that lineage II of the global STEC O157:H7 strain was the most prevalent strain in Australia and found mutations in the strains. The study supports the importance of STEC O157 as a virulent serogroup from around the world. The use of WGS has been relatively novel in STEC surveillance since its implementation over the past two decades. The research supported the use of genomics-based surveillance for STEC on the national level (Ingle *et al.*, 2019). Among STEC gene subgroups, the highest cumulative incidence of HUS was in the ‘*stx2* + Other’ subgroup estimated at 35.32% (95% CI, 14.55 – 56.09). The highest cumulative incidence of HUS was in the ‘Stx2 or subtypes’ subgroup among the toxin subgroups in this systematic review. The estimate for the subgroup was 17.56% (95% CI, 10.22 – 24.91 (Table 7, Appendix 6 - Figure A5). As previously described, the Stx2 toxin is an important driver of STEC pathogenesis in humans (Tran *et al.*, 2018). The findings of this systematic review support the higher propensity of HUS development due to the *stx2* genes and the Stx2 toxins.

5.2.3. STEC-HUS epidemiology by study characteristics

In general, surveillance and outbreak reports describe STEC and STEC-HUS by age, sex, and infecting serogroup. This thesis also analyzed STEC-HUS by important study characteristics, as these

characteristics can impact HUS case numbers following STEC infection. In this systematic review, most studies report data from years 2010 – 2014 with 50 included studies. The highest cumulative incidence of HUS based on study years was in the same year range at 14.79% (95% CI, 12.74 – 16.84).

The most apparent reason for the relatively high cumulative incidence in the 2010 – 2014 period was the STEC O104:H4 outbreak in Germany and Europe in 2011, also considered the largest outbreak of STEC-HUS ever recorded (Frank *et al.*, 2011). This outbreak resulted in 845 STEC-HUS cases (Frank *et al.*, 2011). Additionally, the globalization of the food supply, travel-related cases and large-scale publicization may have contributed to the higher estimate during this period. Contaminated food persists as the primary vehicle of STEC transmission to humans (Erickson and Doyle, 2007). Food chains follow the farm-to-fork/plate pattern and microbial contamination can occur across food supplies and cross international borders (Fung, Wang and Menon, 2018; Godfray *et al.*, 2010). Travel (especially international travel) has been consistently associated with STEC-related diarrhea and outbreaks (Ria *et al.*, 2024; Marder *et al.*, 2023; Alexander *et al.*, 2012). There was a marked increase in the number of included studies from the 2010 – 2014 year range, likely due to imported and travel-linked cases from inside and outside Europe (Devaux *et al.*, 2015; Alexander *et al.*, 2012; Januszkiewicz *et al.*, 2012; King *et al.*, 2012). The publicization of the outbreak may have increased awareness among the general population, increased vigilance in public health systems and increased disease surveillance. Schulz *et al.* (2014) analyzed the association of media coverage with the number of diarrheal cases presenting to the emergency room of a tertiary centre. In 2011, a minimum of 1,350 reports were broadcast during the outbreak on news channels in Germany compared to 0 reports in 2010. A clear positive association was observed between the frequency of television reports covering the outbreak and the rate of diarrheal patients in emergency rooms (Schulz *et al.*, 2014).

By WHO Regions of study publication, the cumulative incidence was highest in the WHO European Region at 12.66% (95% CI, 11.47 – 13.85), followed by the WHO Region of the Americas

at 9.94% (95% CI, 8.82 – 11.05) (Table 7, Appendix 6 - Figure A7). The higher estimates in these two WHO Regions are likely due to dedicated STEC surveillance systems in these WHO regions, which offer enhanced surveillance (e.g., PulseNet, FoodNet, NESSS). Another likely reason is circulating STEC serogroups with higher virulence such as STEC O157 and O104:H4 in these WHO Regions (Byrne *et al.*, 2023; Hoefler *et al.*, 2011; Gould *et al.*, 2009b).

The subgroup analysis for study settings reported the highest cumulative incidence of HUS (31.37%; 95% CI, 11.95 – 50.80) in the ‘Cluster – family’ subgroup. The result may be due to the communal living conditions often observed among family clusters, which increase the risk of STEC transmission in family households. The communal living conditions mean shared use of facilities (e.g., kitchens, latrines), similar hygiene practices, similar food practices (e.g., eating with hands in some cultures), and consumption of the same foods, all of which increase the risk of STEC transmission (Yeng *et al.*, 2020). The numbers of STEC cases (denominator) are considerably small in family clusters in comparison to other subgroups. Thus, the proportion of HUS among these STEC cases would be substantially higher. The cumulative incidence observed in family clusters is likely higher than facility clusters, as children in daycares, diners in restaurants or school students can still avert the same STEC exposure.

STEC detection methods described in the epidemiological literature evolved through time, coinciding with the advancement of diagnostics. As described in Section 1.3.3, public health units are recommended to detect Stx toxins and *stx* genes in conjunction with culture methods in STEC diagnosis (Gould *et al.*, 2009a). According to Table 7, most included articles, and thus, public health and surveillance systems follow the general recommendations. The use of only one laboratory method (e.g., only culture) is uncommon among included studies (Table 7). I found difficulty in classifying included studies by laboratory methods due to insufficient information. Hence, these data must be interpreted judiciously. STEC case detection would be higher with molecular methods. Therefore, we would observe a comparatively lower cumulative incidence for molecular methods

5.3. Study quality assessment

The study quality assessment tools and process focused on various components of study design. These components included eligibility criteria, study frame, STEC case definitions, STEC detection methods, HUS diagnosis, result reporting and statistical analysis (Joanna Briggs Institute, 2020). The majority of included studies (~ 92.2% of included studies) were rated as high quality (Tables 11-13). Therefore, the results presented in this thesis may be based on generally high-quality evidence. The two articles rated as 'Low' quality were focused primarily on laboratory methods for STEC, with minimal information on case identification in surveillance systems, demographics of the study sample and statistical analyses. In included articles rated as 'Moderate' quality, the studies would not have data for the checklist items or would not be described in sufficient detail for checklist items.

5.4. Study strengths

This thesis is the first systematic review to systematically search, identify, and synthesize data to estimate the cumulative incidence of HUS among symptomatic STEC cases. The hallmarks of high-quality systematic reviews include transparency and reproducibility (Chin *et al.*, 2022; Patel *et al.*, 2022). Therefore, I adopted specific tools and approaches to ensure rigorous completion of all review steps. I designed a review protocol based on the PRISMA 2020 Statement, the latest version of a widely used reporting guideline for systematic reviews (Page *et al.*, 2021). Thereby, I completed and clearly reported all possible steps of the systematic review process, to reduce reporting bias. I completed and included the PRISMA Checklist in the thesis (Appendix 1). I used tools and guidelines published by recognized health research institutes (e.g., the JBI), to conduct screening and study quality assessment (Joanna Briggs Institute, 2020; Munn *et al.*, 2015).

The protocol for this systematic review was designed in consultation with methods experts and registered in the PROSPERO database of systematic reviews, during the literature search phase (Majowicz *et al.*, 2023; Schiavo, 2019; Straus and Moher, 2010). I adhered to most methods in the

review protocol, and accurately described all deviations from the protocol in Section 3.10.

Grey literature constitutes unpublished research useful in systematic reviews to increase comprehensiveness, as some research may not be published in peer-reviewed journals and other traditionally academic formats. A few forms of grey literature are academic research (e.g., theses), conference proceedings, committee reports, research reports, governmental reports, and ongoing research (DeVito and Goldacre, 2019; Paez, 2017). In this systematic review, I searched several grey literature databases and included records in different formats, such as theses. To have comprehensive eligibility criteria, I designed these criteria using guidelines specific to prevalence systematic reviews (Munn *et al.*, 2015).

To design the literature search strategies, I used the search strings of a similar systematic review and consulted with the Liaison Librarian of the School of Public Health Sciences at the University of Waterloo. To promote transparency and reproducibility, I have provided all literature search strategies in Appendix 2 including search dates and numbers of hits. To manage the systematic review, I used Covidence, a web-based software specialized in health science systematic reviews with in-built features to ensure research rigour (Harrison *et al.*, 2020). The automated features of Covidence remove duplicate records, permit multiple reviewers, prevent study allocation to reviewers, enable blinded screening and store the same title, abstract and full-text record (Harrison *et al.*, 2020).

The involvement of multiple screeners is an important step and publishing standard for systematic reviews. Independent screening by two reviewers avoids errors that may lead to the exclusion of eligible articles from the systematic review (Polanin *et al.*, 2019; Stoll *et al.*, 2019; Waffenschmidt *et al.*, 2019). To ensure consistency, I trained reviewers using an instructional manual, which was revised if needed, after training. We followed checklist formats for screening in the instructional manual for consistency and straightforwardness. We initiated screening records after a high reviewer agreement during training, quantified by κ coefficients (McHugh, 2012).

5.5. Study limitations

This systematic review may be subject to certain limitations arising from the dependence on available literature to answer the research questions. Firstly, the cumulative incidence estimates were calculated using available data, which can reduce the validity and quality of the findings. Therefore, the thesis findings are lacking data from all geographical regions, and are indicative of biases (e.g., selection bias, reporting bias). Secondly, the estimates reported in this thesis overrepresent the true estimates of HUS among STEC cases in the general population. To handle underestimation of STEC cases, previous work on foodborne infections have used pathogen-specific underreporting multipliers, data from prospective population-based studies, and census data (Majowicz *et al.*, 2014; Majowicz *et al.*, 2010; Thomas *et al.*, 2006). To estimate the cumulative incidence of HUS, I could have used a sensitivity analysis to extrapolate the estimates of the proportional meta-analysis. However, I did not perform this analysis in the thesis, as the necessary data for the analyses were not available at the time. Thirdly, there was a clear lack of data from certain regions of the world, as seen in the subgroup analysis by WHO Region (Table 7, Appendix 6 – Figure A7). Considerably, fewer studies were published from the WHO Eastern Mediterranean Region and Western Pacific Region compared to the European Region and Region of the Americas. There were no studies from the WHO South-East Asia Region and WHO African Region, indicative of an important knowledge gap. The burden of foodborne illness is widespread and highest in developing countries, especially in Africa, South America and Asia (The World Bank, 2018; Kirk *et al.*, 2015). The cumulative incidence data in this thesis may not reflect the incidence of HUS from STEC infections in these regions.

Fourthly, I excluded 51 non-English language records from analyses in this thesis (Figure 1). According to Bahji *et al.* (2022), ~ 75% of published scientific articles are in the English language. The results in this thesis may be affected by language or selection bias, and further analyses could explore these excluded articles to assess the presence of bias (e.g., if these articles originate from WHO Regions with obvious data gaps) (Drucker, Fleming and Chan, 2016).

Fifthly, I did not synthesize some included studies in subgroup analyses and meta-regressions. For example, I only used categorical variables as predictors, including age. Therefore, I could not use age data or categories if they did not conform to the pre-specified age categories in the PROSPERO protocol. Likewise, some articles did not provide data for all variables (e.g., sex, STEC toxins). For example, some included studies would provide STEC and HUS cases by only one sex. Therefore, I would not synthesize these included studies in the subgroup analysis.

5.6. Scope for future research

This thesis provided important preliminary data on the cumulative incidence of STEC-HUS for epidemiological research to build upon in the future. While I analyzed several predictors in subgroup analyses and meta-regressions, future research can investigate other factors thought to predict the progression of STEC infection to the disease state of HUS. The use of antibiotics is one such factor due to contradicting research on the association of antibiotic treatment with HUS development. While some studies have found positive associations between antibiotic use and development of STEC-HUS (Kakoullis *et al.*, 2019; Freedman *et al.*, 2016; Wong *et al.*, 2012), some evidence suggests fosfomycin treatment early in STEC infection can protect against HUS (Mody *et al.*, 2021; Tajiri *et al.*, 2015; Ikeda *et al.*, 1999).

The extracted data will be used in the upcoming second round of estimations for Global and Regional Disease Burden by FERG (World Health Organization, 2024). The estimations will quantify STEC-HUS epidemiology using key parameters, address case underestimation and identify recurring data gaps (e.g., by geographical region) (Kirk *et al.*, 2015). Environmental temperatures, precipitation, and humidity are key factors governing the spread, reproduction, and survival of microorganisms (Dietrich *et al.*, 2023). Given the impending effects of climate change, the effects of environmental changes, such as heavy rainfall and increased flooding, on STEC transmission must be investigated in greater depth (Philipsborn *et al.*, 2016). For example, Acquavotta *et al.* (2017) discovered a temporal

relationship between STEC infection among children and the number, duration and frequency of heat waves. Likewise, Philipsborn *et al.* (2016) reported an 8% (95% CI, 5%–11%) increase in the incidence of diarrheagenic *E. coli* for each 1°C increase in mean monthly temperature.

5.7. Implications of findings

These findings support the existing knowledge on STEC leading to HUS and can be useful in knowledge translation for various stakeholders. In symptomatic STEC infections, more HUS cases are found among young children. Therefore, young children can be prioritized in HUS management and treatment in outbreak emergencies. While guidelines for STEC prevention are publicly available by health agencies (e.g., the Government of Canada, the CDC), this information might not reach the general public in the intended manner (Government of Canada, 2021; Centres for Disease Control and Prevention, 2024). Preventative measures can be targeted for risk groups. For example, parents of young children with diarrheal disease can be advised directly by their attending health professionals to limit their children's exposure to sources of STEC transmission in their communities (e.g., advising against recreational swimming, distribution of infographics).

The findings support using two laboratory methods in STEC diagnosis, detecting all serogroups in STEC diagnosis and developing laboratory methods and surveillance systems to accommodate the efficient management of STEC infections. Given that most well-documented outbreaks occurred in developed and industrialized countries, reporting bias appears to be evident in disease estimations (Ingle *et al.*, 2019). The Global Burden of Disease estimations by FERG indicated data gaps from developing regions, as also seen in this thesis (Kirk *et al.*, 2015). Therefore, international and national health agencies, governments and stakeholders can focus efforts on collecting and analyzing data from these regions. Additionally, governments and municipalities can enforce measures and action plans to protect people from STEC infection (e.g., legislation, intersectoral action).

Currently, the food industry employs measures such as quality audits and quality standards for

food safety. In light of recent controversies on food safety and the globalization of the food supply, the food industry must continue to develop new approaches and improve existing ones to ensure food safety and quality (Kotsanopoulos and Arvanitoyannis, 2017).

6. Conclusion

Foodborne infections can have detrimental impacts on human health, environmental health, the food industry and health administrative expenditure. STEC is a foodborne pathogen, associated with severe illness especially among young children, and large epidemics around the world. This thesis estimated the cumulative incidence of HUS among symptomatic STEC cases based on available data. At 8.22%, the estimate reported in the thesis was similar to proportions reported by other public health researchers and organizations. In accordance with other research, children aged under 5 years, the presence of the *stx2* gene and STEC O157 were attributed to a high cumulative incidence of HUS. In addition, age, sex, infecting serogroup, STEC genes, year range of data and WHO Region were strong predictors of HUS development following STEC infection.

However, the estimates reported in this thesis likely overestimate the true population parameter for the cumulative incidence of HUS among STEC cases, given that STEC case ascertainment has historically been low. In addition, these findings can be used by various stakeholders, like WHO, to determine disease burden estimations, devise strategies to address knowledge gaps especially in developing regions, improve and develop prevention strategies, and allocate resources for future research efforts. This thesis provides important insights on the epidemiology and management of STEC infection and HUS for health professionals. Future research can further investigate the differences in cumulative incidence of HUS in subpopulations and devise action plans to improve STEC and HUS surveillance.

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Appendices

Appendix 1: Completed PRISMA 2020 Checklist (Page *et al.*, 2021)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	i
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	v
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	18
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	23
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	136
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	25
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	27
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
		compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	27
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	29
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	29
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	29
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	29
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	29
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	34
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	36
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	90
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	78
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	90
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	78
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	81
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	101
	23b	Discuss any limitations of the evidence included in the review.	109

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	111
	23d	Discuss implications of the results for practice, policy, and future research.	113
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	21
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	21
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	32
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	iv
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix 2: Literature search documentation including search result numbers

SEARCH DOCUMENTATION - Journal

DATABASE 1: PubMed (Website: <https://pubmed.ncbi.nlm.nih.gov/advanced/>)

SEARCH DATE: 7 November 2023

OF HITS: 1,203

1	end-stage kidney disease OR ESKD OR end-stage renal disease OR ESRD OR dialysis	Text Word
2	haemolytic uraemic syndrome OR hemolytic uremic syndrome OR haemorrhagic colitis OR hemorrhagic colitis OR bloody diarrhoea OR bloody diarrhea OR thrombotic thrombocytopenic purpura OR thrombotic thrombocytopenic purpura	Text Word
3	Hemolytic-Uremic Syndrome	MeSH Terms
4	1 OR 2 OR 3	
5	Cytotoxin-producing Escherichia coli OR Cytotoxin-producing E. coli OR Cytotoxigenic Escherichia coli OR Cytotoxigenic E. coli	Text Word
6	STEC OR Shiga-toxin producing Escherichia coli OR Shiga-toxin producing E. coli OR Shiga-toxigenic Escherichia coli OR Shiga-toxigenic E. coli	Text Word
7	EHEC OR Enterohaemorrhagic Escherichia coli OR Enterohaemorrhagic E. coli OR Enterohemorrhagic Escherichia coli OR Enterohemorrhagic E. coli	Text Word
8	VTEC OR Verocytotoxin-producing Escherichia coli OR Verocytotoxin-producing E. coli OR Verotoxin-producing Escherichia coli OR Verotoxin-producing E. coli OR Verocytotoxigenic Escherichia coli OR Verocytotoxigenic E. coli OR Verotoxigenic Escherichia coli OR Verotoxigenic E. coli	Text Word

9	("Escherichia coli" OR "E.coli") AND (O157 OR O1 OR O2 OR O5 OR O6 OR O8 OR O15 OR O22 OR O26 OR O45 OR O48 OR O55 OR O76 OR O91 OR O98 OR O103 OR O104 OR O111 OR O113 OR O117 OR O118 OR O119 OR O121 OR O128 OR O145 OR O146 OR O150 OR O165 OR O174 OR OX3)	Text Word
10	Escherichia coli O157	MeSH Terms
11	Shiga toxigenic Escherichia coli	MeSH Terms
12	Enterohemorrhagic Escherichia coli	MeSH Terms
13	Shiga toxins	MeSH Terms
14	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	
15	Incidence OR Prevalence OR Proportion OR Proportions OR epidemiolog*	Text Word
16	epidemiology OR incidence OR prevalence OR morbidity	MeSH Terms
17	15 OR 16	
18	4 AND 14 AND 17	
19	#4 AND #14 AND #17 AND ((humans[Filter]) AND (1990:2023[pdat]))	
Filter: Results by year: 1990 – 2024, Species: Humans		

DATABASE 2: Web of Science (Website: <https://www.webofscience.com/wos/woscc/basic-search>)

SEARCH DATE: 7 November 2023

OF HITS: 1,415

1	Topic	"haemolytic uraemic syndrome" OR "hemolytic uremic syndrome" OR "haemorrhagic colitis" OR "hemorrhagic colitis" OR "bloody diarrhoea" OR "bloody diarrhea" OR "thrombotic thrombocytopenic purpura" OR "thrombotic thrombocytopenic purpura"
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2	Topic	"end-stage kidney disease" OR "ESKD" OR "end-stage renal disease" OR "ESRD" OR "dialysis"
3		1 OR 2
4	Topic	"Cytotoxin-producing Escherichia coli" OR "Cytotoxin-producing E. coli" OR "Cytotoxigenic Escherichia coli" OR "Cytotoxigenic E. coli"
5	Topic	"STEC" OR "Shiga-toxin producing Escherichia coli" OR "Shiga-toxin producing E. coli" OR "Shiga-toxigenic Escherichia coli" OR "Shiga-toxigenic E. coli"
6	Topic	"EHEC" OR "Enterohaemorrhagic Escherichia coli" OR "Enterohaemorrhagic E. coli" OR "Enterohemorrhagic Escherichia coli" OR "Enterohemorrhagic E. coli"
7	Topic	"VTEC" OR "Verocytotoxin-producing Escherichia coli" OR "Verocytotoxin-producing E. coli" OR "Verotoxin-producing Escherichia coli" OR "Verotoxin-producing E. coli" OR "Verocytotoxigenic Escherichia coli" OR "Verocytotoxigenic E. coli" OR "Verotoxigenic Escherichia coli" OR "Verotoxigenic E. coli"
8	Topic	("Escherichia coli" OR "E.coli") AND (O157 OR O1 OR O2 OR O5 OR O6 OR O8 OR O15 OR O22 OR O26 OR O45 OR O48 OR O55 OR O76 OR O91 OR O98 OR O103 OR O104 OR O111 OR O113 OR O117 OR O118 OR O119 OR O121 OR O128 OR O145 OR O146 OR O150 OR O165 OR O174 OR OX3)
9		4 OR 5 OR 6 OR 7 OR 8
10	Topic	"Incidence" OR "Prevalence" OR "Proportion" OR "Proportions" OR epidemiolog*
11		3 AND 9 AND 10
12		#3 AND #9 AND #10 and 2023 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 or 2013 or 2012 or 2011 or 2010 or 2009 or 2008 or 2007 or 2006 or 2005 or 2004 or 2003 or 2002 or 2001 or 2000 or 1999 or 1998 or 1997 or 1996 or 1995 or 1994 or 1993 or 1992 or 1991 or 1990 (Publication Years) and Article (Document Types)
Filter: Publication Years: 1990 – 2024, Document Types: Article		

DATABASE 3: Ovid® Embase

SEARCH DATE: 7 November 2023

OF HITS: 223

1	exp Shiga toxin producing Escherichia coli/
2	exp hemolytic uremic syndrome/di, ep [Diagnosis, Epidemiology]
3	exp bloody diarrhea/di, ep [Diagnosis, Epidemiology]
4	exp hemorrhagic colitis/di, ep [Diagnosis, Epidemiology]
5	exp end stage renal disease/di, ep [Diagnosis, Epidemiology]
6	2 OR 3 OR 4 OR 5
7	1 AND 6
8	limit 7 to "remove preprint records"
9	limit 8 to yr="1990 -Current"
10	limit 9 to human

DATABASE 4: Scopus (Website: <https://www.scopus.com/search/form.uri?display=basic> - basic)

SEARCH DATE: 7 November 2023

OF HITS: 863

1	TITLE-ABS-KEY	"haemolytic uraemic syndrome" OR "hemolytic uremic syndrome" OR "haemorrhagic colitis" OR "hemorrhagic colitis" OR "bloody diarrhoea" OR "bloody diarrhea" OR "thrombotic thrombocytopenic purpura" OR "thrombotic thrombocytopenic purpura"
2	TITLE-ABS-KEY	"end-stage kidney disease" OR "ESKD" OR "end-stage renal disease" OR "ESRD" OR "dialysis"
3		1 OR 2
4	TITLE-ABS-KEY	"Cytotoxin-producing Escherichia coli" OR "Cytotoxin-producing E. coli" OR "Cytotoxigenic Escherichia coli" OR "Cytotoxigenic E. coli"
5	TITLE-ABS-KEY	"STEC" OR "Shiga-toxin producing Escherichia coli" OR "Shiga-toxin producing E. coli" OR "Shiga-toxigenic Escherichia coli" OR "Shiga-toxigenic E. coli"
6	TITLE-ABS-KEY	"EHEC" OR "Enterohaemorrhagic Escherichia coli" OR "Enterohaemorrhagic E. coli" OR "Enterohemorrhagic Escherichia coli" OR "Enterohemorrhagic E. coli"
7	TITLE-ABS-KEY	"VTEC" OR "Verocytotoxin-producing Escherichia coli" OR "Verocytotoxin-producing E. coli" OR "Verotoxin-producing Escherichia coli" OR "Verotoxin-producing E. coli" OR "Verocytotoxigenic Escherichia coli" OR "Verocytotoxigenic E. coli" OR "Verotoxigenic Escherichia coli" OR "Verotoxigenic E. coli"
8	TITLE-ABS-KEY	("Escherichia coli" OR "E.coli") AND (O157 OR O1 OR O2 OR O5 OR O6 OR O8 OR O15 OR O22 OR O26 OR O45 OR O48 OR O55 OR O76 OR O91 OR O98 OR O103 OR O104 OR O111 OR O113 OR O117 OR O118 OR O119 OR O121 OR O128 OR O145 OR O146 OR O150 OR O165 OR O174 OR

		OX3)
9		4 OR 5 OR 6 OR 7 OR 8
10	TITLE-ABS-KEY	"Incidence" OR "Prevalence" OR "Proportion" OR "Proportions" OR epidemiolog*
11		3 AND 9 AND 10
Filters: Year range: 1990 – 2024, Document type: Article		

SEARCH DOCUMENTATION - Grey Literature and Supplementary Searches

DATABASE 5: Google Scholar (Website: <https://scholar.google.ca/>)

SEARCH DATE: 14 January 2024

LANGUAGE	SEARCH STRING	# of hits
Filters: 1990 – 2024 ; ‘Sort by relevance’		
English	“Shiga toxin-producing Escherichia coli” AND (“hemolytic uremic syndrome” OR “haemolytic-uremic syndrome”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 6,990
	“Verotoxin-producing Escherichia coli” AND (“hemolytic uremic syndrome” OR “haemolytic-uremic syndrome”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 2,590
	“E. coli O157” AND (“hemolytic uremic syndrome” OR “haemolytic-uremic syndrome”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 7,860
	“Shiga toxin-producing Escherichia coli” AND (“end stage renal disease” OR “ESRD”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 290
	“Verotoxin-producing Escherichia coli” AND (“end stage renal disease” OR “ESRD”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 86
	“E. coli O157” AND (“end stage renal disease” OR “ESRD”) AND “humans” AND (“epidemiology” OR “surveillance”)	~ 335

	TOTAL (Screened)	586
Spanish	“Escherichia coli productora de toxinas Shiga” AND “Síndrome urémico hemolítico” AND (“Humanos” OR “Humanas”) AND (“Epidemiología” OR “Vigilancia”)	11
	“Escherichia coli productora de toxinas Shiga” AND “Enfermedad renal terminal” AND (“Humanos” OR “Humanas”) AND (“Epidemiología” OR “Vigilancia”)	1
French	“E. coli producteur de Shigatoxines” AND “le syndrome hémolytique et urémique” AND (“Humains” OR “Humaines”) AND (“Épidémiologie” OR “Surveillance”)	2
	“E. coli producteur de Shigatoxines” AND “phase terminale de la maladie rénale” AND (“Humains” OR “Humaines”) AND (“Épidémiologie” OR “Surveillance”)	0
Russian	“Шига-токсин, продуцирующий E. coli” AND “Гемолитико-уремический синдром” AND “Люди” AND (“Эпидемиология” OR “Наблюдение”)	0
	“Шига-токсин, продуцирующий E. coli” AND “Терминальная стадия заболевания почек” AND “Люди” AND (“Эпидемиология” OR “Наблюдение”)	0
Chinese	“产志贺毒素大肠杆菌” AND “溶血性尿毒综合征” AND “人类” AND (“流行病学” OR “监视”)	10
	“产志贺毒素大肠杆菌” AND “终末期肾脏病” AND “人类” AND (“流行病学” OR “监视”)	0
Arabic	“الاشريشيا القولونية المنتجة لسموم الشيقا” AND “متلازمة انحلال الدم البولي (اليوريمي)” AND “البشر” AND (“علم الأوبئة” OR “مراقبة”)	0
	“الاشريشيا القولونية المنتجة لسموم الشيقا” AND “المرحلة النهائية لمرض الكلى” AND “البشر” AND (“علم الأوبئة” OR “مراقبة”)	0
TOTAL		610

DATABASE 6: GreyGuide (Website: <http://greyguiderep.isti.cnr.it/simplesearchloc.php>)

SEARCH DATE: 7 November 2023

LANGUAGE	SEARCH STRING	# of hits
English	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (hemolytic uremic syndrome OR HUS OR haemolytic-uremic syndrome) AND humans AND (epidemiology OR surveillance)	0
	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (end stage renal disease OR ESRD) AND humans AND (epidemiology OR surveillance)	0
Spanish	Escherichia coli productora de toxinas Shiga AND Síndrome urémico hemolítico AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
	Escherichia coli productora de toxinas Shiga AND Enfermedad renal terminal AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
French	E. coli producteur de Shigatoxines AND le syndrome hémolytique et urémique AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	0
	E. coli producteur de Shigatoxines AND phase terminale de la maladie rénale AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	0
Russian	Шига-токсин, продуцирующий E. coli AND Гемолитико-уремический синдром AND Люди AND (Эпидемиология OR Наблюдение)	0
	Шига-токсин, продуцирующий E. coli AND Терминальная стадия заболевания почек AND Люди AND (Эпидемиология OR Наблюдение)	0
Chinese	产志贺毒素大肠杆菌 AND 溶血性尿毒综合征 AND 人类 AND (流行病学 OR 监视)	0
	产志贺毒素大肠杆菌 AND 终末期肾脏病 AND 人类 AND (流行病学 OR 监视)	0
Arabic	(مراقبة علم الأوبئة) AND البشر AND متلازمة انحلال الدم البولي (اليوريمي) AND الاشرشيبيا القولونية المنتجة لسموم الشيفا	0
	(مراقبة علم الأوبئة) AND البشر AND المرحلة النهائية لمرض الكلى AND الاشرشيبيا القولونية المنتجة لسموم الشيفا	0
TOTAL		0

DATABASE 7: INASP Journals Online (Website <https://www.inasp.info/project/journals-online-project>)

- According to their website, the INASP Journals Online is a platform of 8 databases, namely:
 - African Journals Online (www.ajol.info)
 - Philippines Journals Online (Refer note below)
 - Vietnam Journals Online (www.vjol.info.vn)
 - Bangladesh Journals Online (www.banglajol.info)
 - Central America Journals Online (www.camjol.info)
 - Mongolia Journals Online (www.mongoliajol.info)
 - Nepal Journals Online (www.nepjol.info)
 - Sri Lanka Journals Online (www.sljol.info)
- Philippines Journals Online is an inactive database as of 21 November 2023.
- Sri Lanka Journals Online (www.sljol.info) is a collection of journals spanning a range of research fields. The following journals related to medicine, health, food, agriculture and child health were considered relevant for the review and were searched:
 - Anuradhapura Medical Journal (<https://amj.sljol.info/>)
 - Ceylon Journal of Medical Science (<https://cjms.sljol.info/>)
 - Ceylon Journal of Science (<https://cjs.sljol.info/>)
 - Ceylon Medical Journal (<https://cmj.sljol.info/>)
 - Galle Medical Journal (<https://gmj.sljol.info/>)
 - Jaffna Medical Journal (<https://jmj.sljol.info/>)
 - Journal of Food and Agriculture (<https://jfa.sljol.info/>)
 - Journal of Health Sciences and Innovative Research (<https://jhsir.sljol.info/>)
 - Journal of the Ceylon College of Physicians (<https://jccp.sljol.info/>)
 - Journal of the College of Community Physicians of Sri Lanka (<https://jccpsl.sljol.info/>)
 - Journal of the Postgraduate Institute of Medicine (<https://jpgim.sljol.info/>)
 - Sri Lanka Journal of Child Health (<https://sljch.sljol.info/>)
 - Sri Lanka Journal of Health Research (<https://sljhr.sljol.info/>)
 - Sri Lanka Journal of Medicine (<https://sljm.sljol.info/>)
 - Sri Lankan Journal of Health Sciences (<https://sljhs.sljol.info/>)
 - Sri Lankan Journal of Infectious Diseases (<https://sljid.sljol.info/>)

African Journals Online (www.ajol.info)		
SEARCH DATE: 24 December 2023		
LANGUAGE	SEARCH STRING	# of hits
English	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (hemolytic uremic syndrome OR HUS OR haemolytic-uremic syndrome) AND humans AND (epidemiology OR surveillance)	30
	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (end stage renal disease OR ESRD) AND humans AND (epidemiology OR surveillance)	4
Spanish	Escherichia coli productora de toxinas Shiga AND Síndrome urémico hemolítico AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
	Escherichia coli productora de toxinas Shiga AND Enfermedad renal terminal AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
French	E. coli producteur de Shigatoxines AND le syndrome hémolytique et urémique AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	2
	E. coli producteur de Shigatoxines AND phase terminale de la maladie rénale AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	0
Russian	Шига-токсин, продуцирующий E. coli AND Гемолитико-уремический синдром AND Люди AND (Эпидемиология OR Наблюдение)	0
	Шига-токсин, продуцирующий E. coli AND Терминальная стадия заболевания почек AND Люди AND (Эпидемиология OR Наблюдение)	0
Chinese	产志贺毒素大肠杆菌 AND 溶血性尿毒综合征 AND 人类 AND (流行病学 OR 监视)	0
	产志贺毒素大肠杆菌 AND 终末期肾脏病 AND 人类 AND (流行病学 OR 监视)	0
Arabic	(مراقبة OR علم الأوبئة) AND البشر AND متلازمة انحلال الدم البولي (اليوريمي) AND الاشريشيا القولونية المنتجة لسموم الشيقا	0
	(مراقبة OR علم الأوبئة) AND البشر AND المرحلة النهائية لمرض الكلى AND الاشريشيا القولونية المنتجة لسموم الشيقا	0
TOTAL		36

Vietnam Journals Online (www.vjol.info.vn) Bangladesh Journals Online (www.banglajol.info) Central America Journals Online (www.camjol.info) Mongolia Journals Online (www.mongolajol.info) Nepal Journals Online (www.nepjol.info) SEARCH DATE: 7 November 2023		
Sri Lanka Journals Online (www.sljol.info) SEARCH DATE: 19 November 2023		
LANGUAGE	SEARCH STRING	# of hits
English	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (hemolytic uremic syndrome OR HUS OR haemolytic-uremic syndrome) AND humans AND (epidemiology OR surveillance)	0
	(Shiga toxin-producing Escherichia coli OR verotoxin-producing Escherichia coli OR E. coli O157) AND (end stage renal disease OR ESRD) AND humans AND (epidemiology OR surveillance)	0
Spanish	Escherichia coli productora de toxinas Shiga AND Síndrome urémico hemolítico AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
	Escherichia coli productora de toxinas Shiga AND Enfermedad renal terminal AND (Humanos OR Humanas) AND (Epidemiología OR Vigilancia)	0
French	E. coli producteur de Shigatoxines AND le syndrome hémolytique et urémique AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	0
	E. coli producteur de Shigatoxines AND phase terminale de la maladie rénale AND (Humains OR Humaines) AND (Épidémiologie OR Surveillance)	0
Russian	Шига-токсин, продуцирующий E. coli AND Гемолитико-уремический синдром AND Люди AND (Эпидемиология OR Наблюдение)	0
	Шига-токсин, продуцирующий E. coli AND Терминальная стадия заболевания почек AND Люди AND (Эпидемиология OR Наблюдение)	0
Chinese	产志贺毒素大肠杆菌 AND 溶血性尿毒综合征 AND 人类 AND (流行病学 OR 监视)	0
	产志贺毒素大肠杆菌 AND 终末期肾脏病 AND 人类 AND (流行病学 OR 监视)	0
Arabic	(مراقبة OR علم الأوبئة) AND البشر AND متلازمة انحلال الدم البولي (اليوريمي) AND الاشرشيا القولونية المنتجة لسموم الشيقا	0
	(مراقبة OR علم الأوبئة) AND البشر AND المرحلة النهائية لمرض الكلى AND الاشرشيا القولونية المنتجة لسموم الشيقا	0
TOTAL		0

DATABASE 8: OAIster (Website: <https://oaister.on.worldcat.org/discovery>)

SEARCH DATE: 7 December 2023

LANGUAGE	SEARCH STRING	# of hits
Filter: 1990 – 2024 ; Excluded 'Format': Book, Computer file, Internet resource		
English	• kw:(Shiga toxin-producing Escherichia coli) AND kw:(Hemolytic uremic syndrome)	203
	• kw:(verotoxin-producing Escherichia coli) AND kw:(Hemolytic uremic syndrome)	15
	• kw:(O157) AND kw:(Hemolytic uremic syndrome)	191
	kw:(Shiga toxin-producing Escherichia coli) AND kw:(ESRD)	4
Spanish	• kw:(Escherichia coli productora de toxinas Shiga) AND kw:(Síndrome urémico hemolítico)	0
	• kw:(O157) AND kw:(Síndrome urémico hemolítico)	19
	kw:(Escherichia coli productora de toxinas Shiga) AND kw:(Enfermedad renal terminal)	0
French	• kw:(E. coli producteur de Shigatoxines) AND kw:(le syndrome hémolytique et urémique)	0
	• kw:(O157) AND kw:(le syndrome hémolytique et urémique)	1
	kw:(E. coli producteur de Shigatoxines) AND kw:(phase terminale de la maladie rénale)	0
Russian	• kw:(Шига-токсин, продуцирующий E. coli) AND kw:(Гемолитико-уремический синдром)	0
	• kw:(O157) AND kw:(Гемолитико-уремический синдром)	1
	kw:(Шига-токсин, продуцирующий E. coli) AND kw:(Терминальная стадия заболевания почек)	0
Chinese	• kw:(产志贺毒素大肠杆菌) AND kw:(溶血性尿毒综合征)	0
	• kw:(O157) AND kw:(溶血性尿毒综合征)	0
	kw:(产志贺毒素大肠杆菌) AND kw:(终末期肾脏病)	0
Arabic	• kw:(متلازمة انحلال الدم البولي (البوريمي) (الاشريشيا القولونية المنتجة لسموم الشيقا)	0
	• kw:(O157) AND kw:(متلازمة انحلال الدم البولي (البوريمي)	0
	المرحلة النهائية لمرض الكلى AND الاشريشيا القولونية المنتجة لسموم الشيقا	0
TOTAL		434

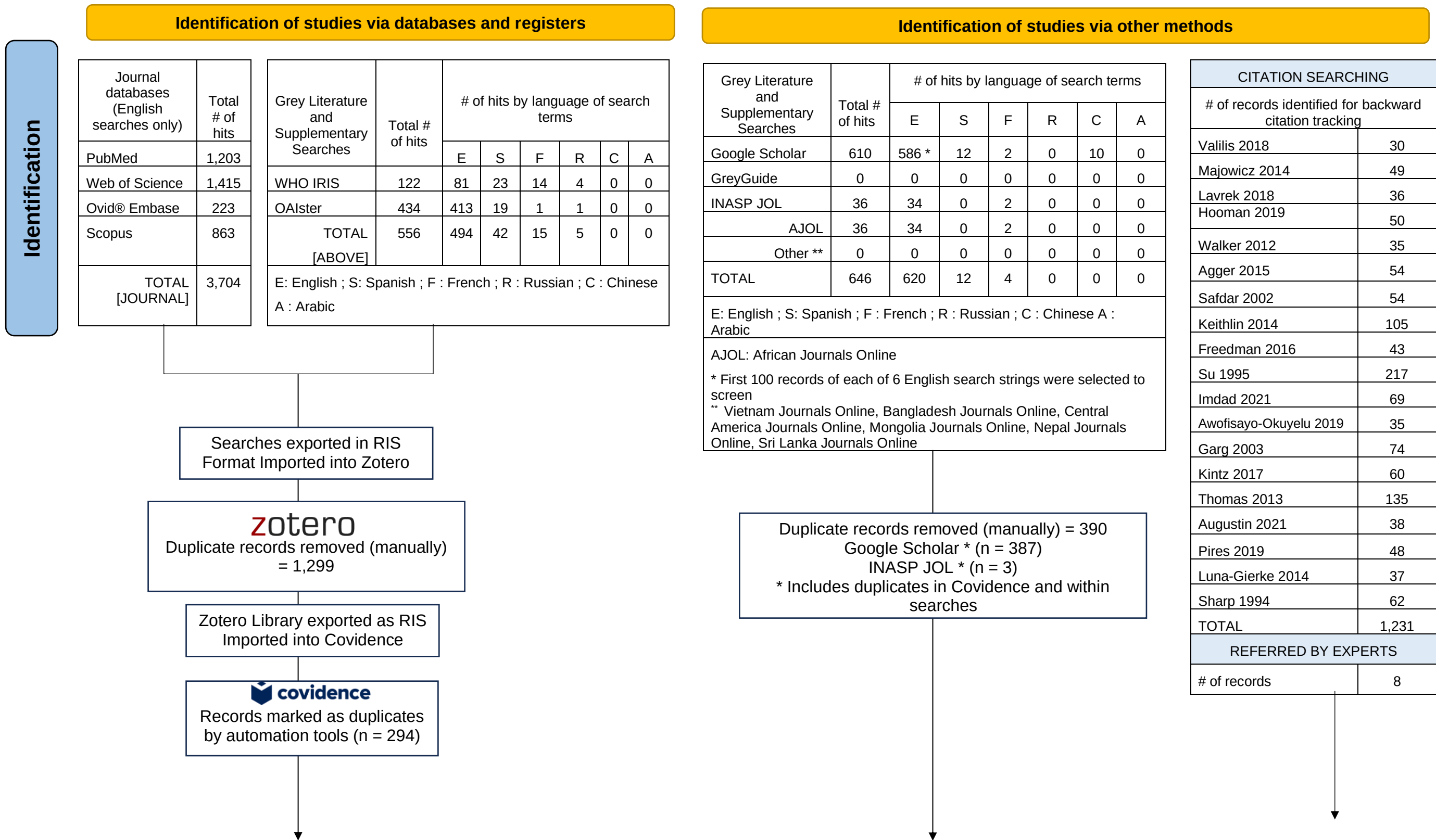
DATABASE 9: WHO IRIS (Website: <https://iris.who.int/>)

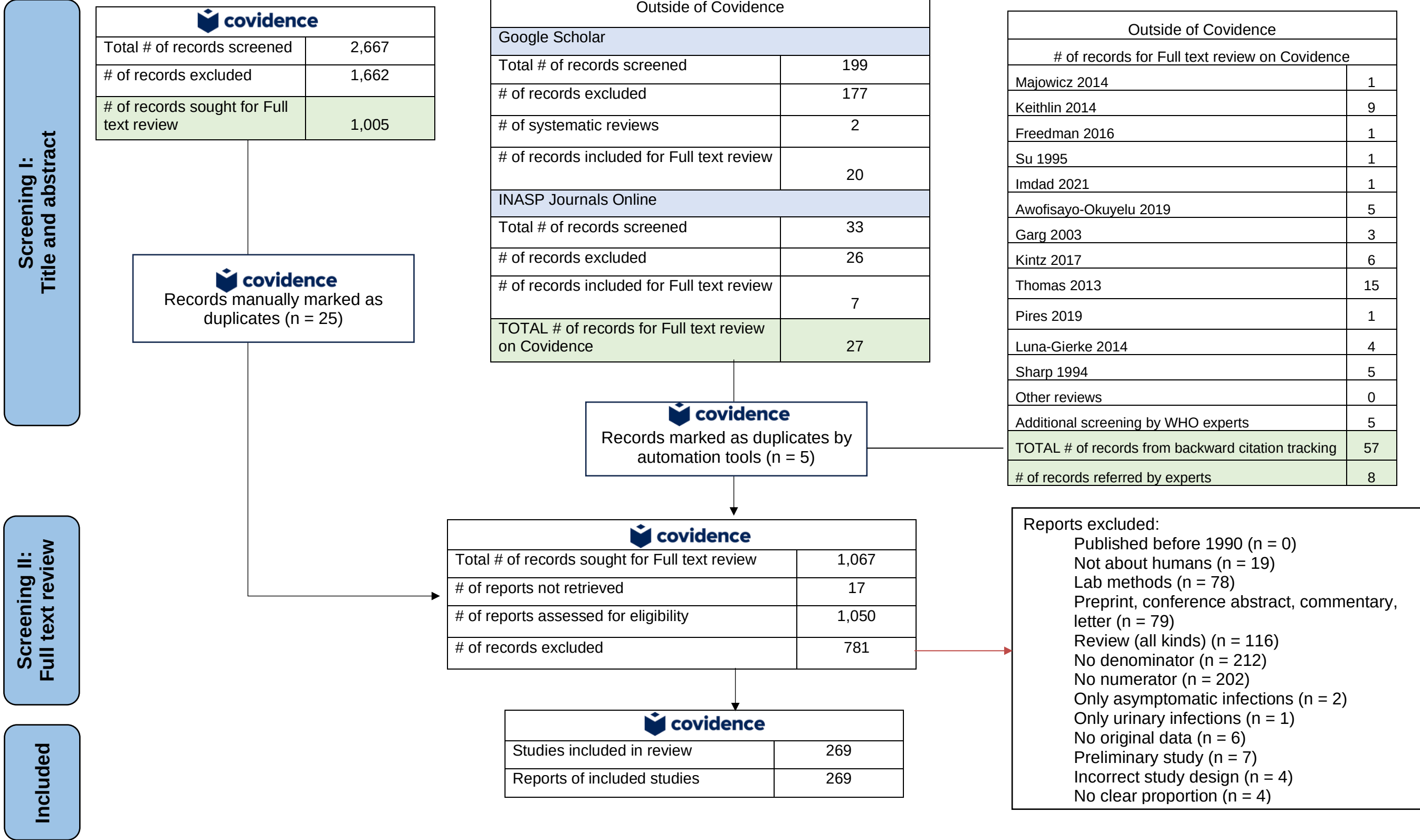
SEARCH DATE: 13 November 2023

LANGUAGE	SEARCH STRING	# of hits
Filters: Date issued: 1990 – 2024		
English	Shiga toxin-producing Escherichia coli AND HUS	64
	Shiga toxin-producing Escherichia coli AND ESRD	17
Spanish	Escherichia coli productora de toxinas Shiga AND Síndrome urémico hemolítico	4
	Escherichia coli productora de toxinas Shiga AND Enfermedad renal terminal	19
French	E. coli producteur de Shigatoxines AND le syndrome hémolytique et urémique	5
	E. coli producteur de Shigatoxines AND phase terminale de la maladie rénale	9
Russian	Шига-токсин, продуцирующий E. coli AND Гемолитико-уремический синдром	1
	Шига-токсин, продуцирующий E. coli AND Терминальная стадия заболевания почек	3
Chinese	产志贺毒素大肠杆菌 AND 溶血性尿毒综合征	0
	产志贺毒素大肠杆菌 AND 终末期肾脏病	0
Arabic	متلازمة انحلال الدم البولي (اليوريمي) AND الاشريشيا القولونية المنتجة لسموم الشيفا	0
	المرحلة النهائية لمرض الكلى AND الاشريشيا القولونية المنتجة لسموم الشيفا	0
TOTAL		122

Appendix 3: Descriptions of exclusion reasons at full text screening

Exclusion reason	Description
Published before 1990	The article has been published in 1989 or preceding years and is not eligible based on the time limit specified in the eligibility criteria
Not about humans	The article describes STEC in animals, biological samples of animals, food, water and environmental samples
Lab methods	The article describes the characterization of STEC using laboratory methods, including human samples (human isolates)
Preprint, conference abstract, commentary, letter	The article - is not peer-reviewed and indexed in a literature database - only has an abstract available as a conference proceeding - is a comment or letter to the editor and does not report on results of original research
Review (all kinds) – includes book chapters	- The article is a review published as a systematic review, meta-analysis, scoping review or narrative review - The record is an entire book or book chapter
No denominator (no STEC number)	The article - does not have data on symptomatic STEC cases - reports on detecting STEC cases within a sample of HUS cases
Only asymptomatic	The article only contains data on asymptomatic STEC cases and does not contain any data on symptomatic cases of STEC
Only urinary infections	The article only contains data on urinary tract infections associated with STEC infections
No numerator (no HUS)	The article does not report on number of HUS cases and describes other sequelae (e.g. only neurological complications)
No original data	The article does not report new data or data that had not been previously published (e.g. multiple reports published after a major outbreak)
Preliminary study	The article describes only initial findings from an outbreak or event and does not report on all data
Incorrect study design	The study design is not among the study designs enlisted in the inclusion criteria
No clear proportion	The article defines STEC and HUS according to inclusion criteria. However, the number of STEC cases developing HUS is unclear or cannot be determined
No full text	The article could not be retrieved from any method used to acquire full texts and PDFs
On ESRD	The article is only on ESRD as a sequela
Non-English record	The article is published in a language other than English





Appendix 5: List of included studies

1. Ackers, M. L., Mahon, B. E., Leahy, E., Goode, B., Damrow, T., Hayes, P. S., Bibb, W. F., Rice, D. H., Barrett, T. J., Hutwagner, L., Griffin, P. M., & Slutsker, L. (1998). An outbreak of *Escherichia coli* O157:H7 infections associated with leaf lettuce consumption. *J Infect Dis*, 177(6), 1588-1593.
2. Ackman, D., Marks, S., Mack, P., Caldwell, M., Root, T., & Birkhead, G. (1997). Swimming-associated haemorrhagic colitis due to *Escherichia coli* O157:H7 infection: evidence of prolonged contamination of a fresh water lake. *Epidemiol Infect*, 119(1), 1-8.
3. Acquavotta, F., Ardissino, G., Fratianni, S., & Perrone, M. (2017). Role of climate in the spread of shiga toxin-producing *Escherichia coli* infection among children. *Int J Biometeorol*, 61(9), 1647-1655.
4. Adams, N., Byrne, L., Rose, T., Adak, B., Jenkins, C., Charlett, A., Violato, M., O'Brien, S., Whitehead, M., Barr, B., Taylor-Robinson, D., & Hawker, J. (2019a). Sociodemographic and clinical risk factors for paediatric typical haemolytic uraemic syndrome: retrospective cohort study. *BMJ Paediatrics Open*, 3(1).
5. Adams, N. L., Byrne, L., Rose, T. C., Adak, G. K., Jenkins, C., Charlett, A., Violato, M., O'Brien, S. J., Whitehead, M. M., Barr, B., Taylor-Robinson, D. C., & Hawker, J. I. (2019b). Influence of socio-economic status on Shiga toxin-producing *Escherichia coli* (STEC) infection incidence, risk factors and clinical features. *Epidemiol Infect*, 147, e215.
6. Afza, M., Hawker, J., Thurston, H., Gunn, K., & Orendi, J. (2006). An outbreak of *Escherichia coli* O157 gastroenteritis in a care home for the elderly. *Epidemiol Infect*, 134(6), 1276-1281.
7. Ahn, C. K., Russo, A. J., Howell, K. R., Holt, N. J., Sellenrick, P. L., Rothbaum, R. J., Beck, A. M., Luebbering, L. J., & Tarr, P. I. (2009). Deer sausage: a newly identified vehicle of transmission of *Escherichia coli* O157:H7. *J Pediatr*, 155(4), 587-589.
8. Akashi, S., Joh, K., Tsuji, A., Ito, H., Hoshi, H., Hayakawa, T., Ihara, J., Abe, T., Hatori, M., & Mori, T. (1994). A severe outbreak of haemorrhagic colitis and haemolytic uraemic syndrome associated with *Escherichia coli* O157:H7 in Japan. *Eur J Pediatr*, 153(9), 650-655.
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Appendix 6: Forest plots of each predictor variable in subgroup analyses

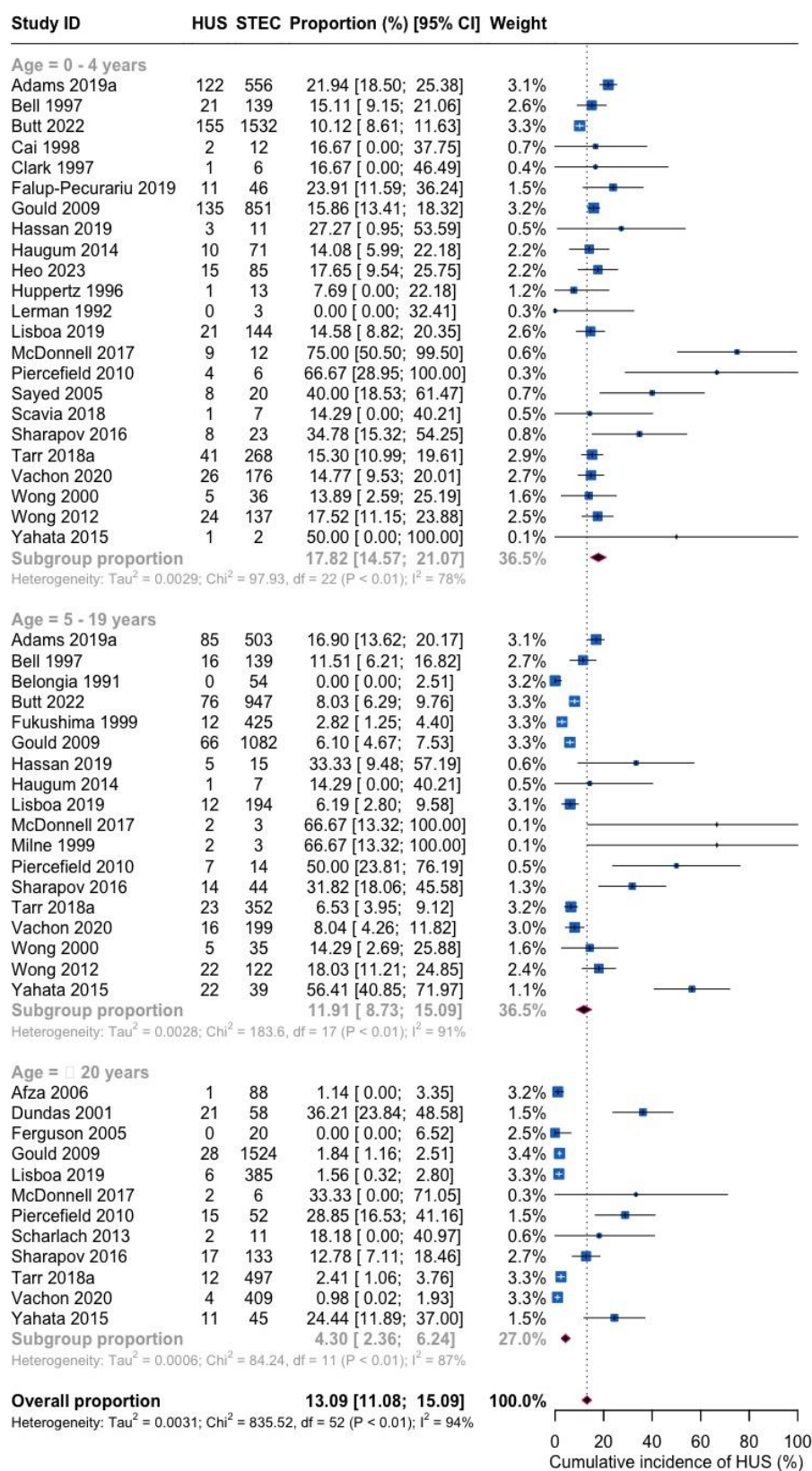


Figure A1. Cumulative incidence of HUS among symptomatic STEC cases by age

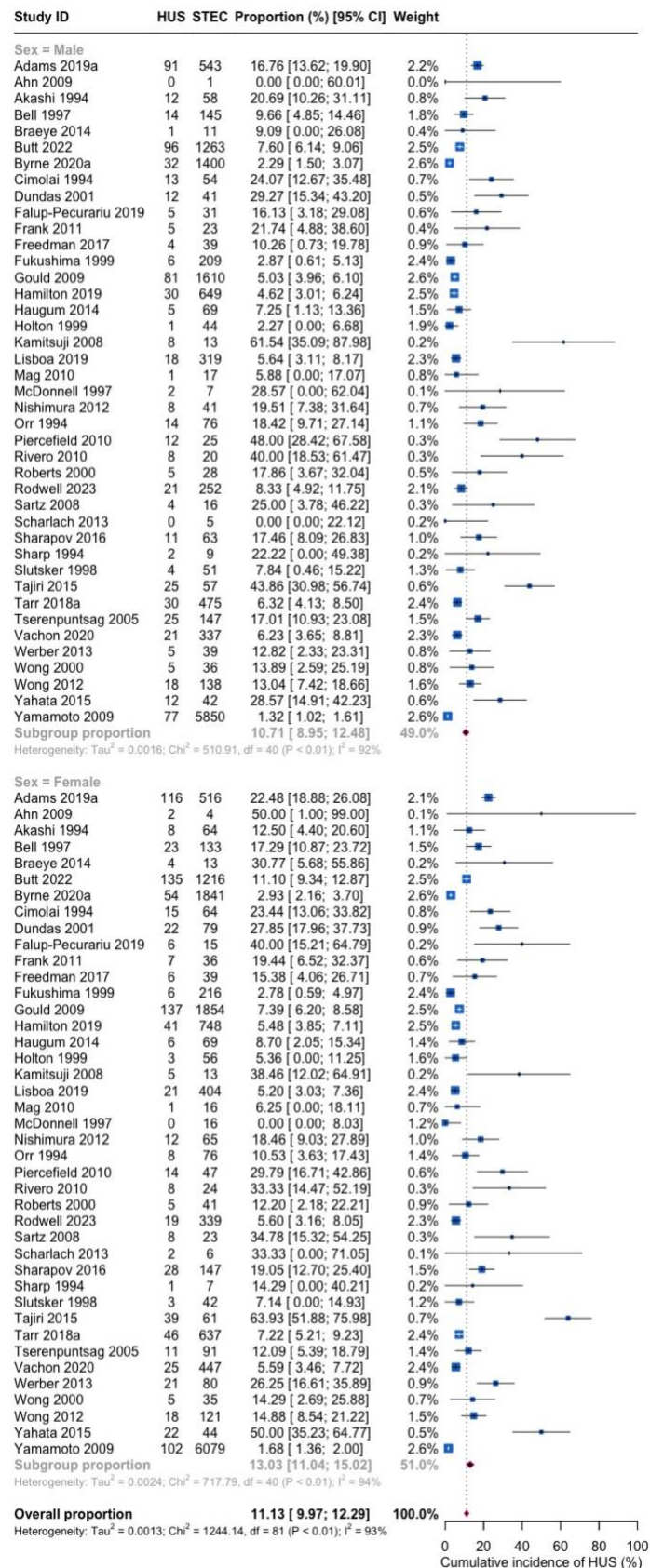
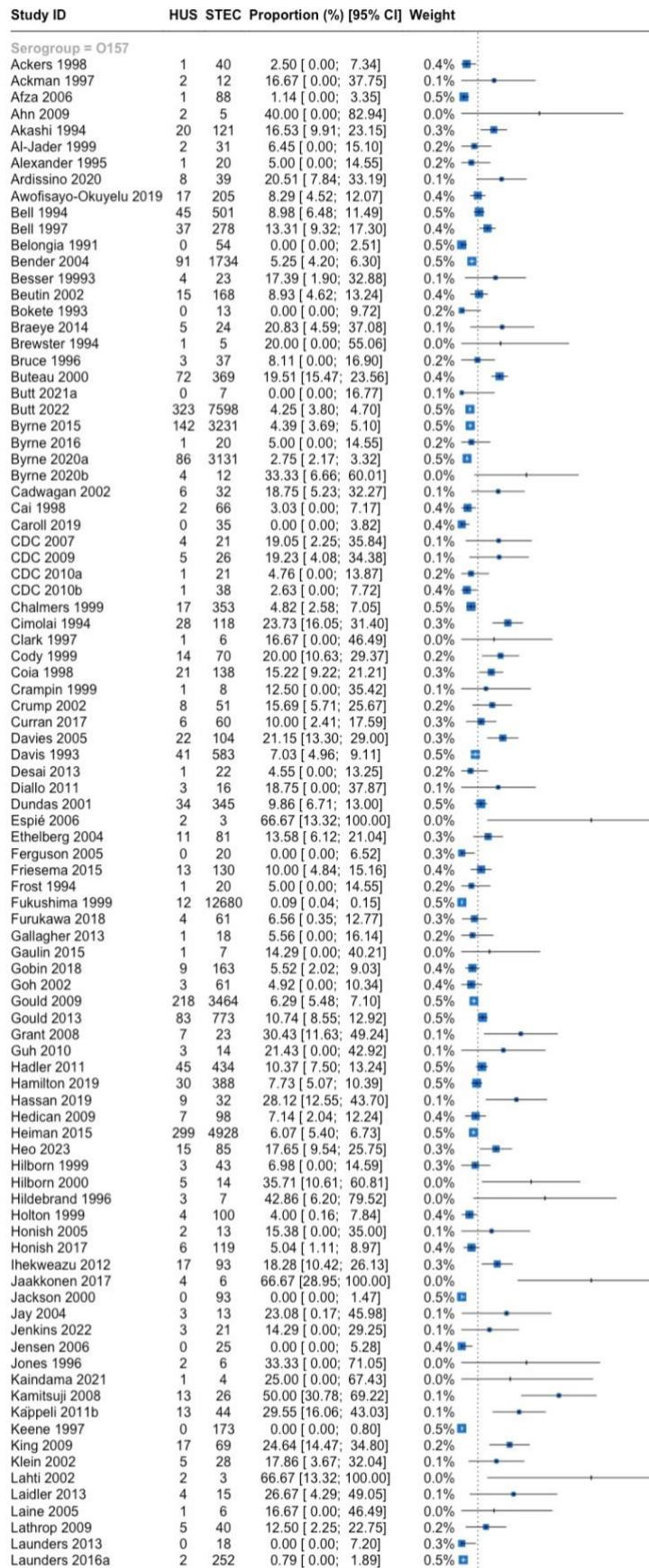
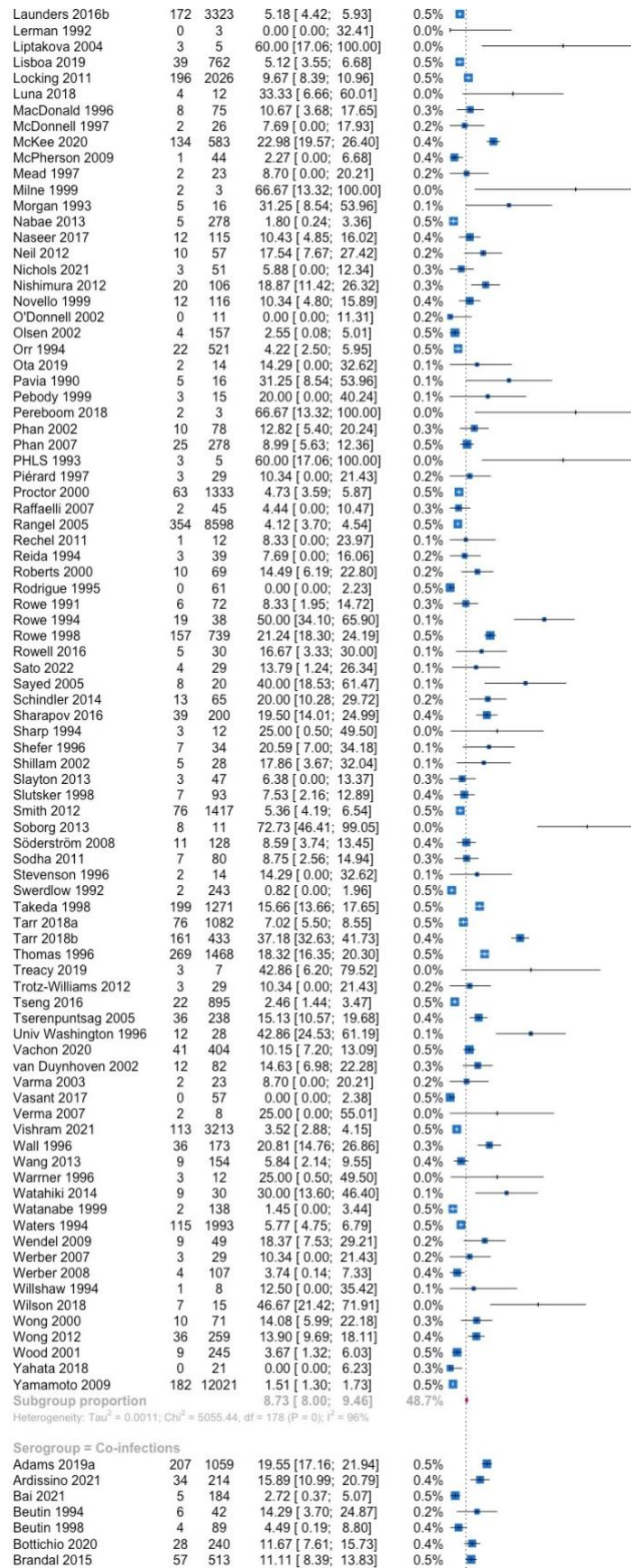
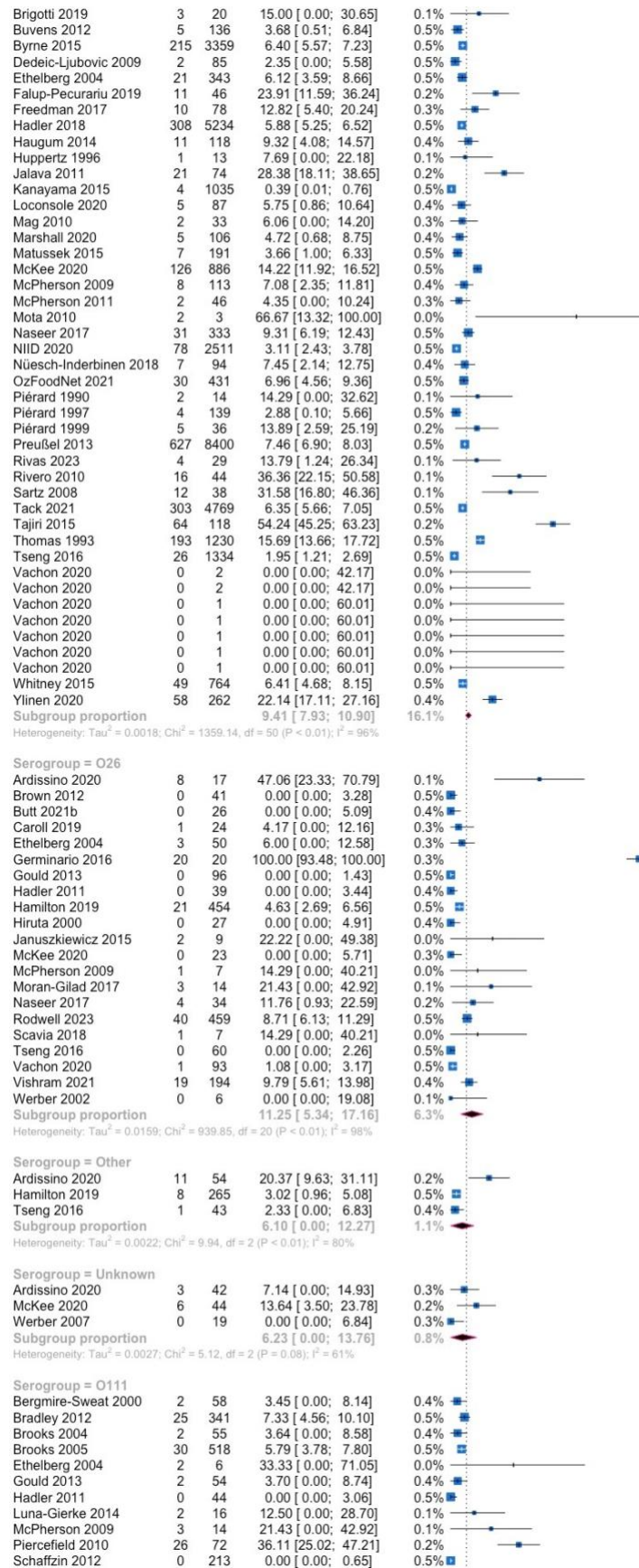
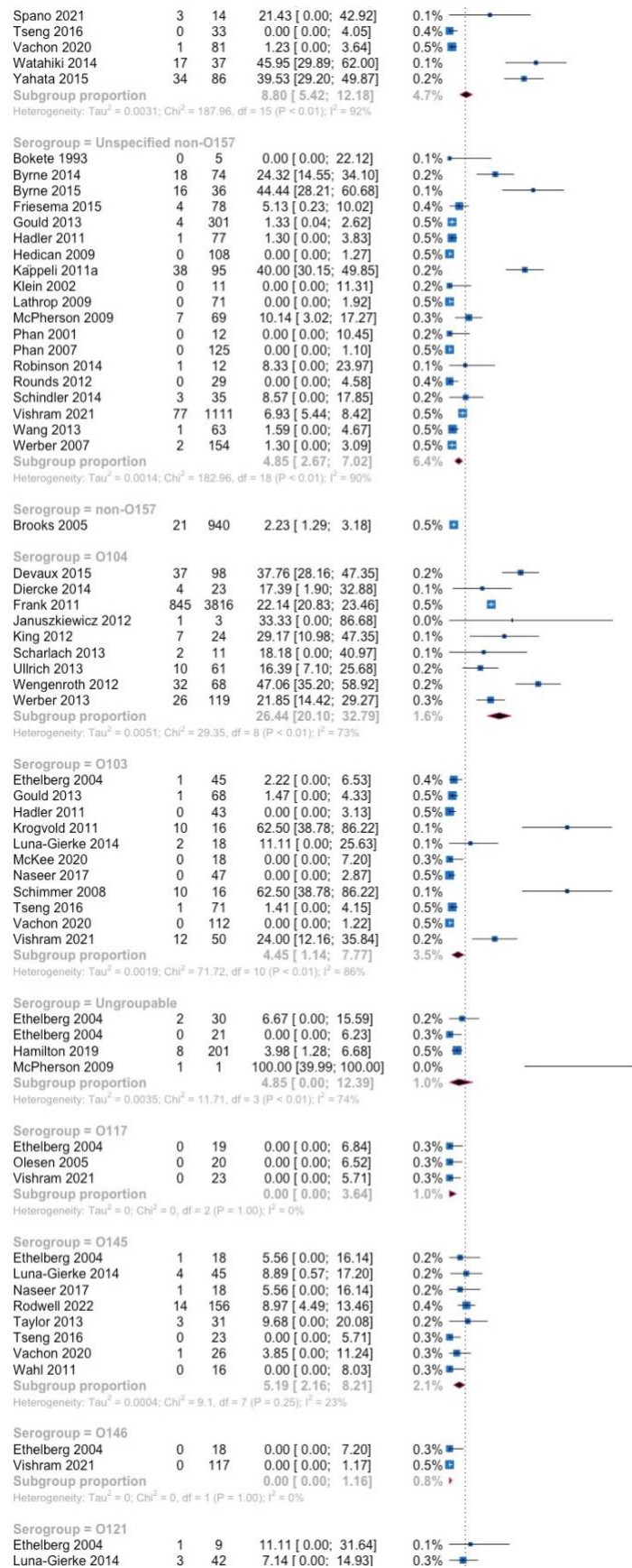


Figure A2. Cumulative incidence of HUS among symptomatic STEC cases by sex









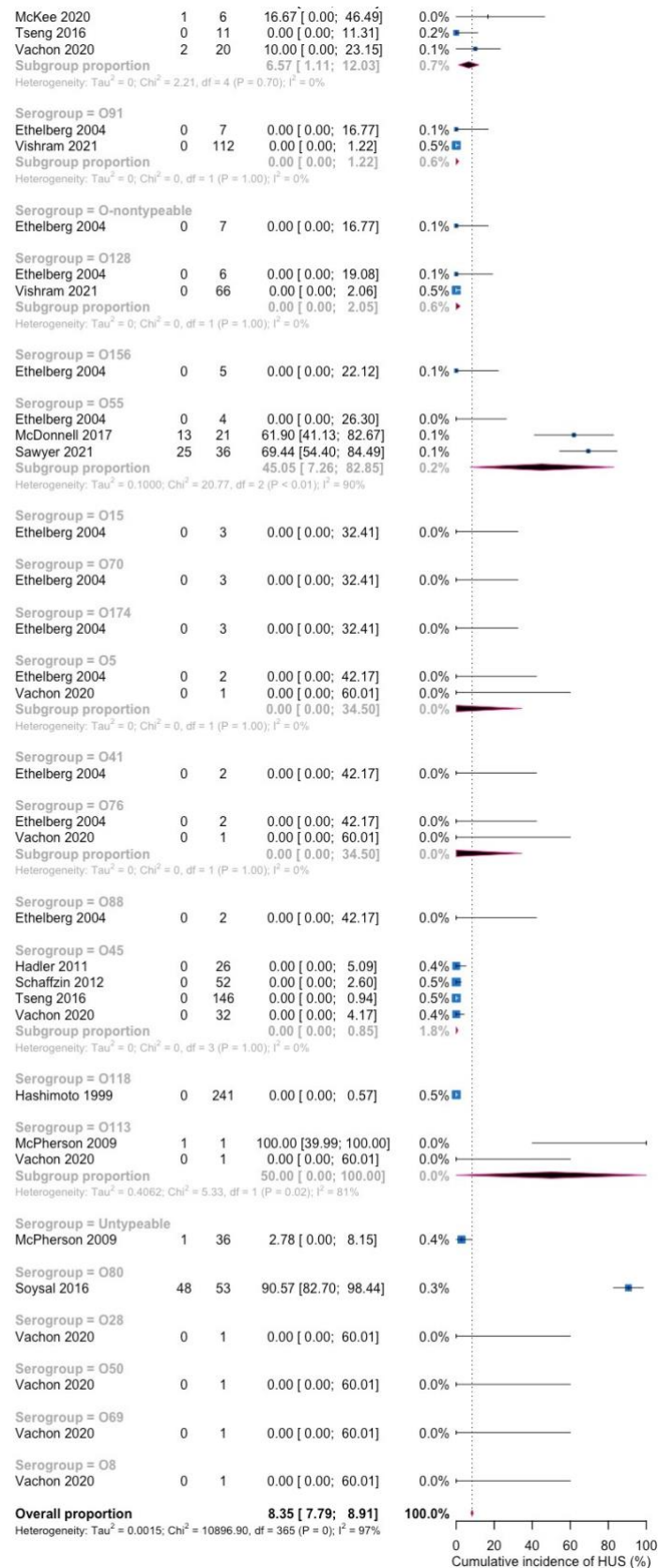
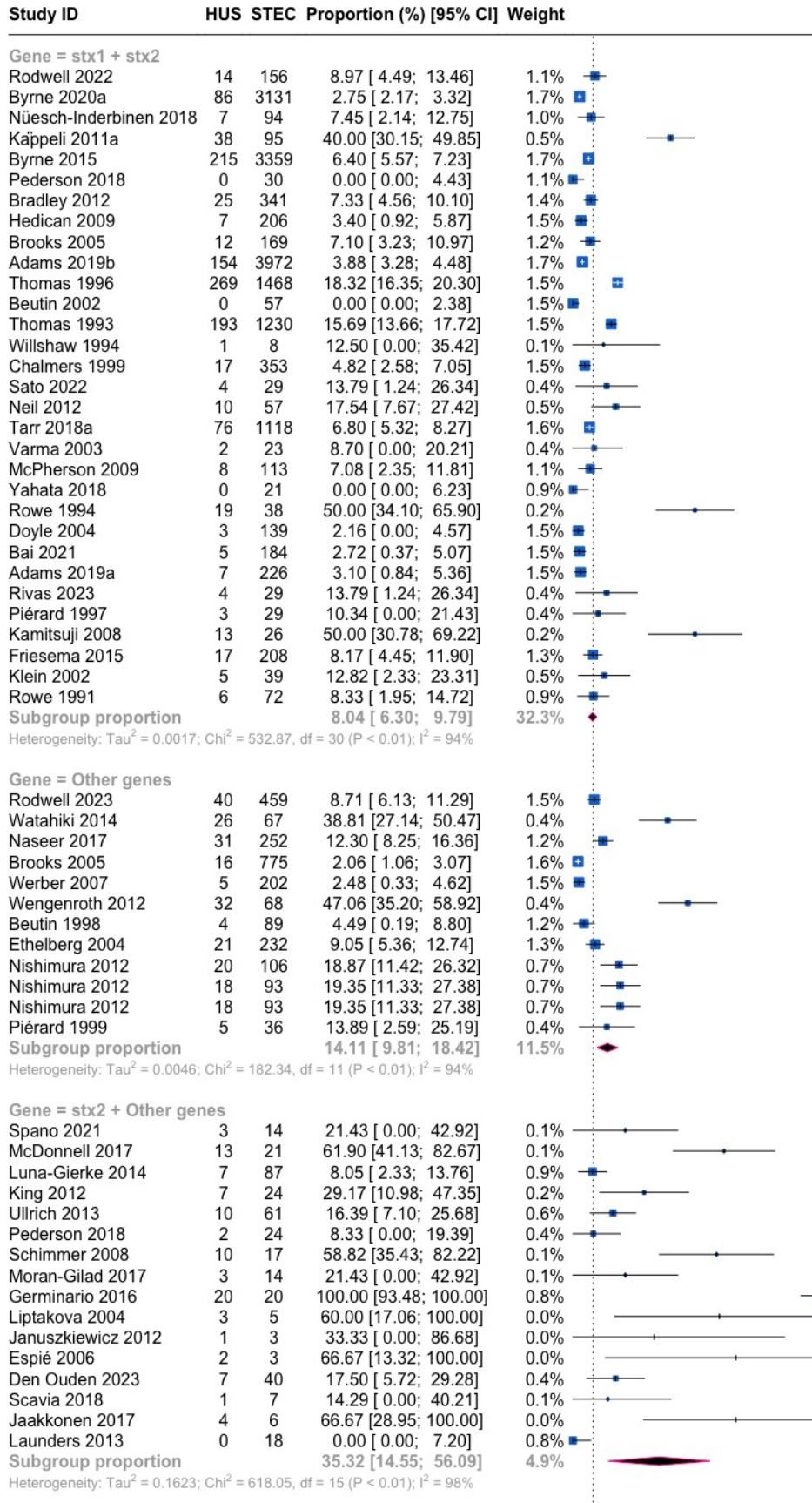


Figure A3. Cumulative incidence of HUS among symptomatic STEC cases by STEC serogroups



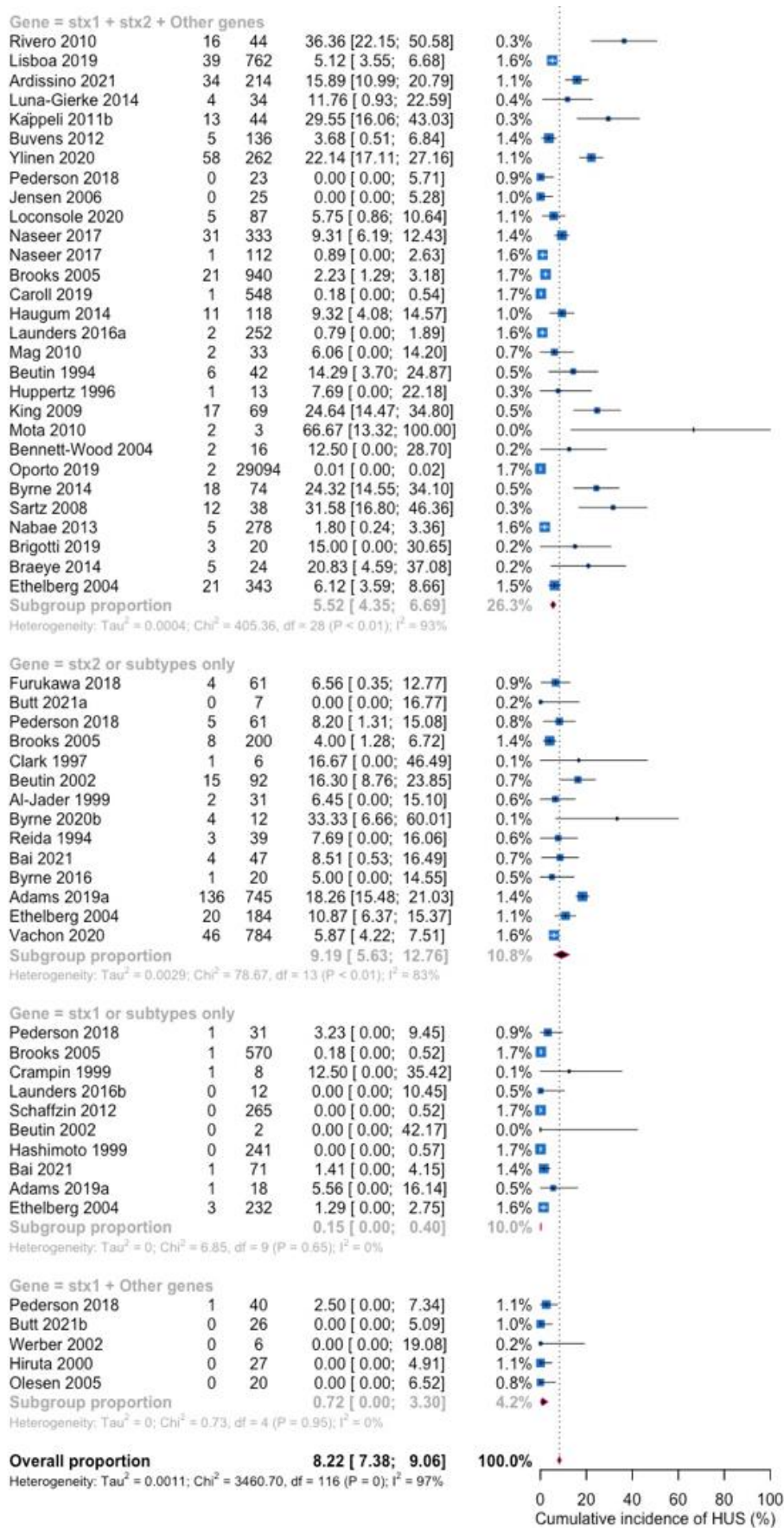


Figure A4. Cumulative incidence of HUS among symptomatic STEC cases by STEC genes

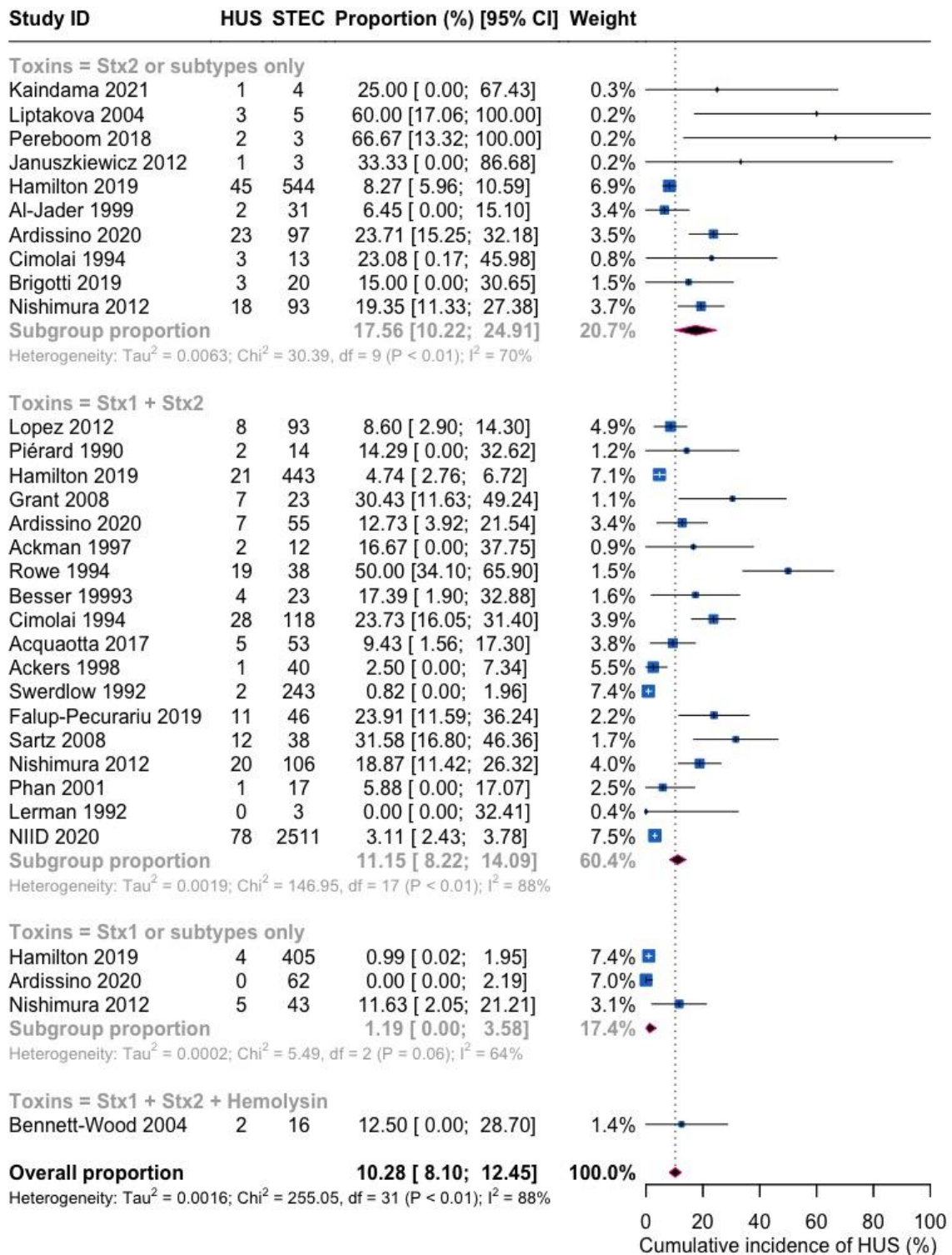
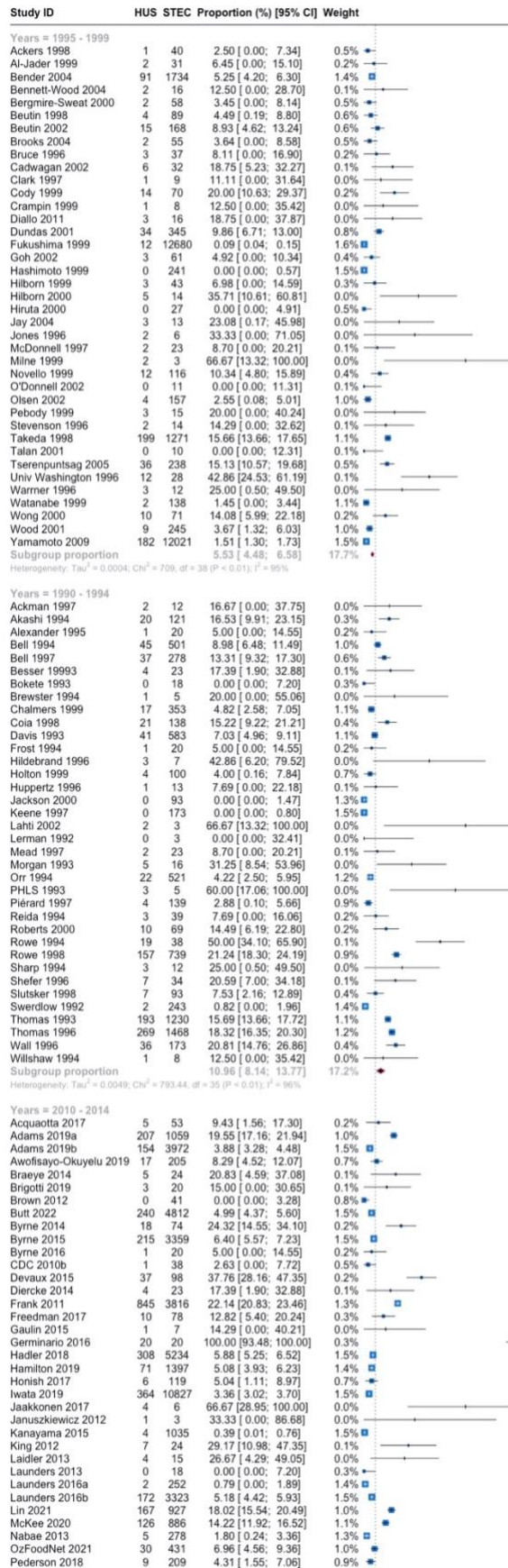


Figure A5. Cumulative incidence of HUS among symptomatic STEC cases by STEC toxins



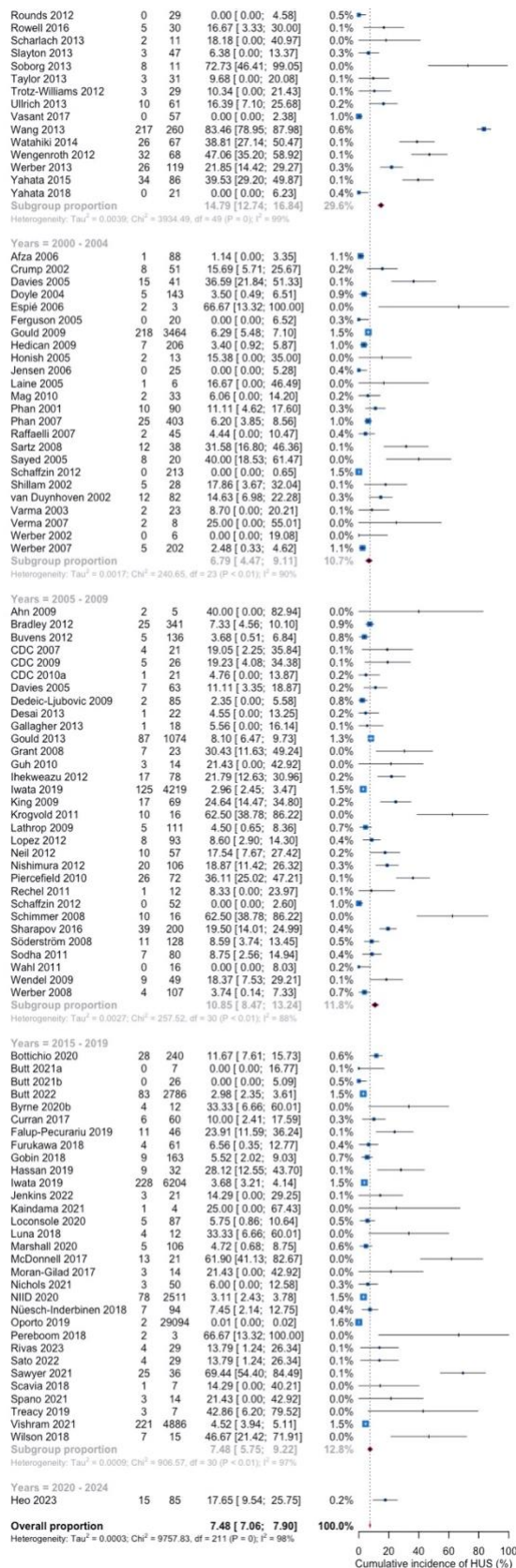
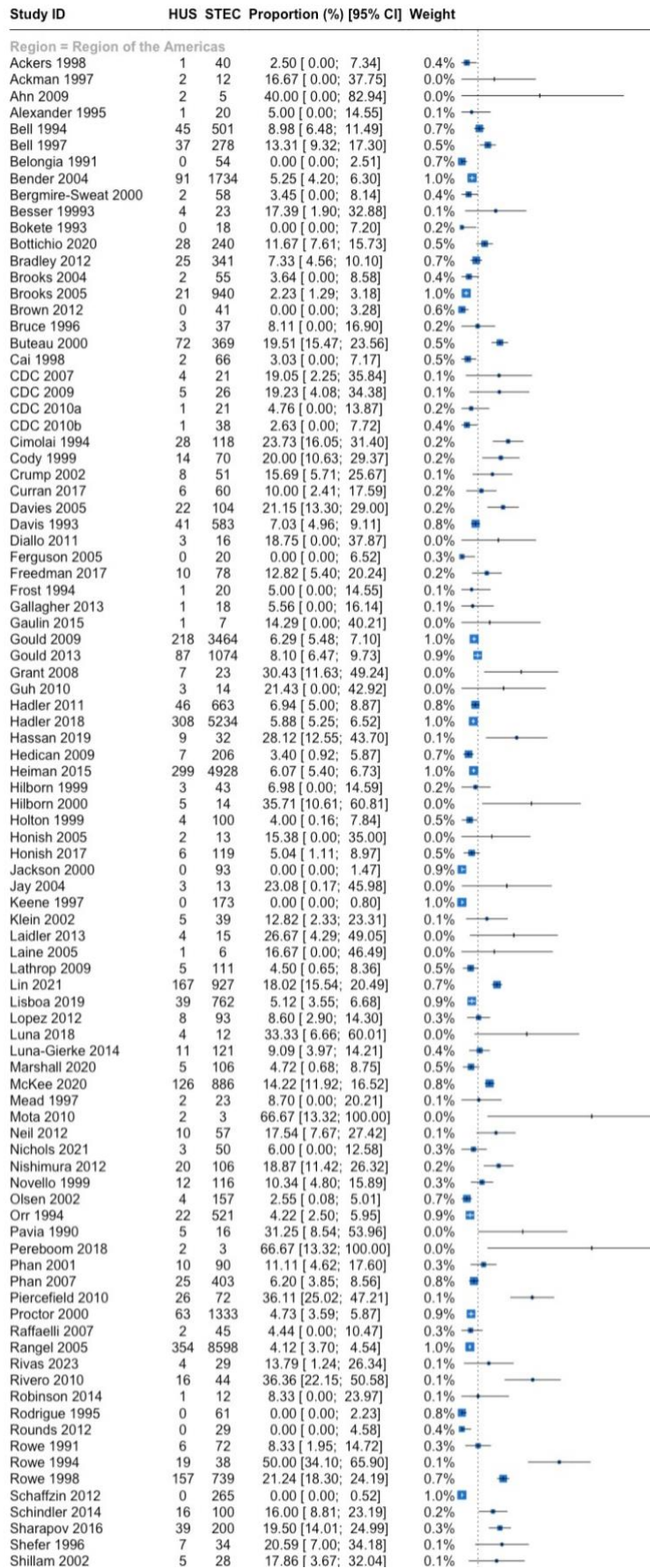
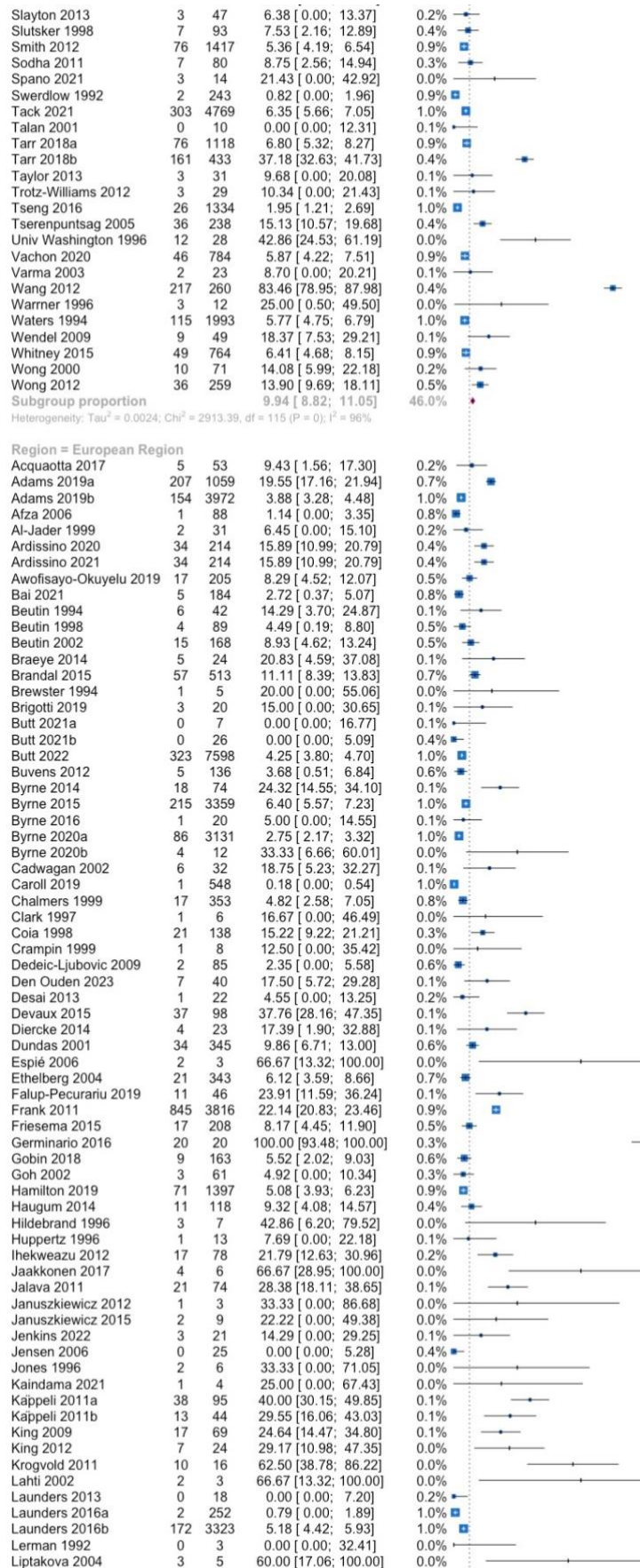


Figure A6. Cumulative incidence of HUS among symptomatic STEC cases by year range of data





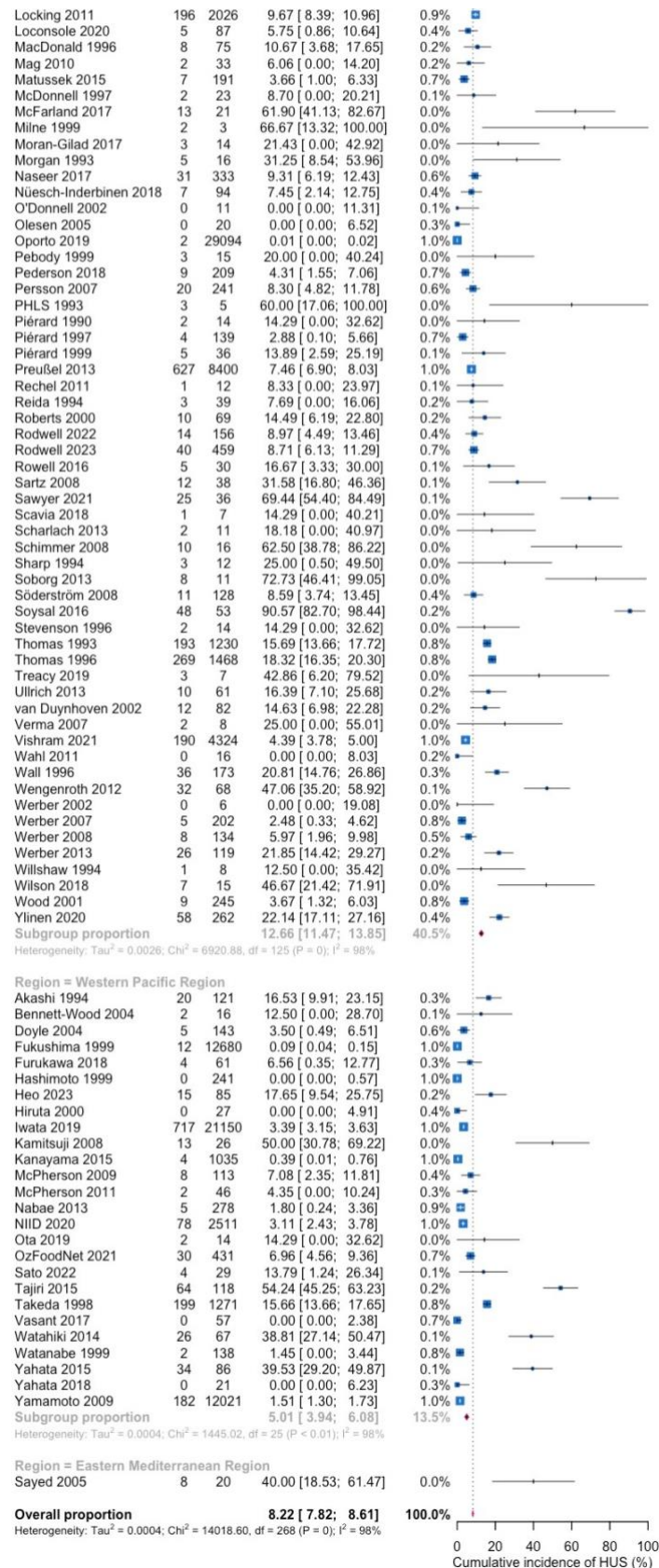
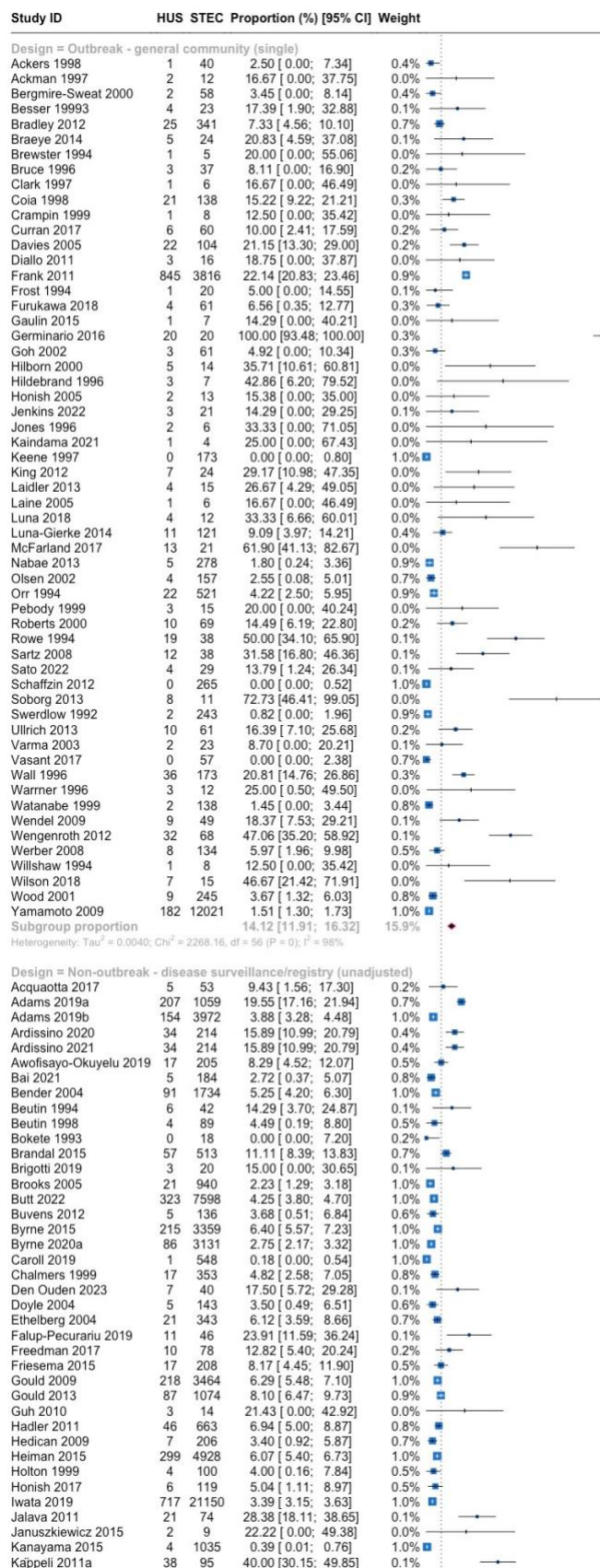
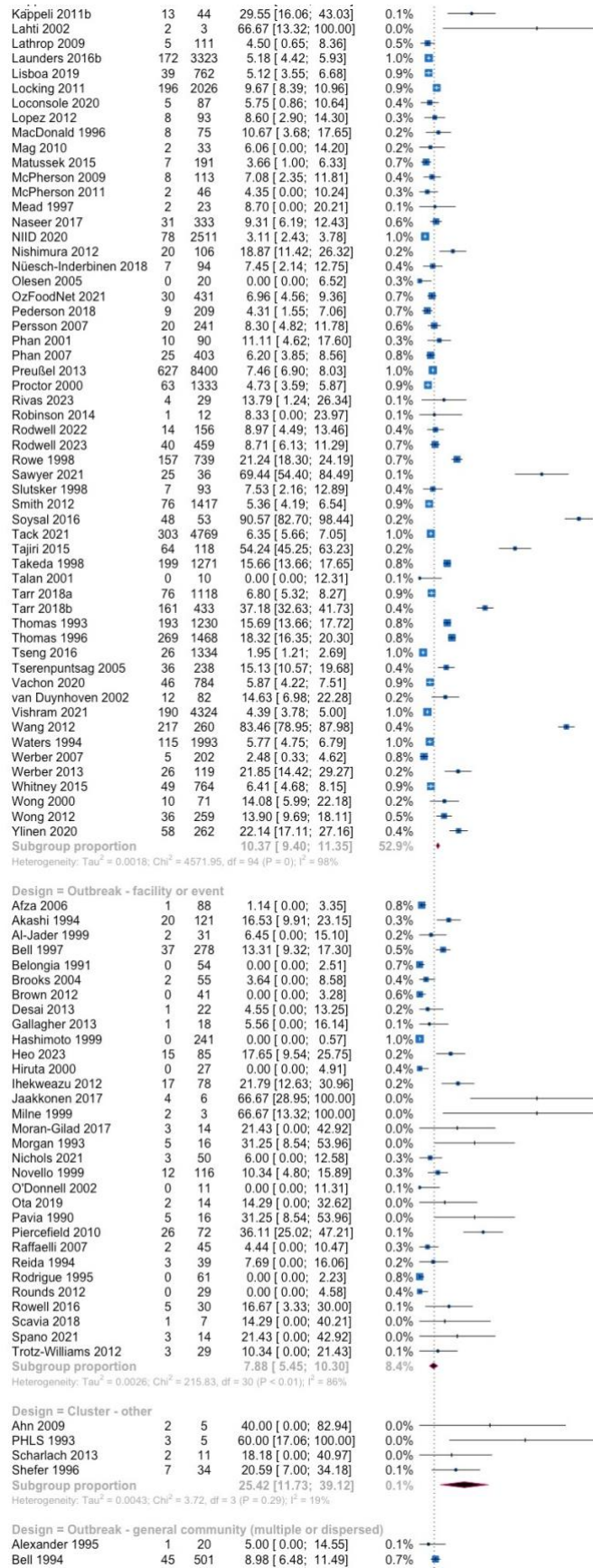


Figure A7. Cumulative incidence of HUS among symptomatic STEC cases by WHO Regions





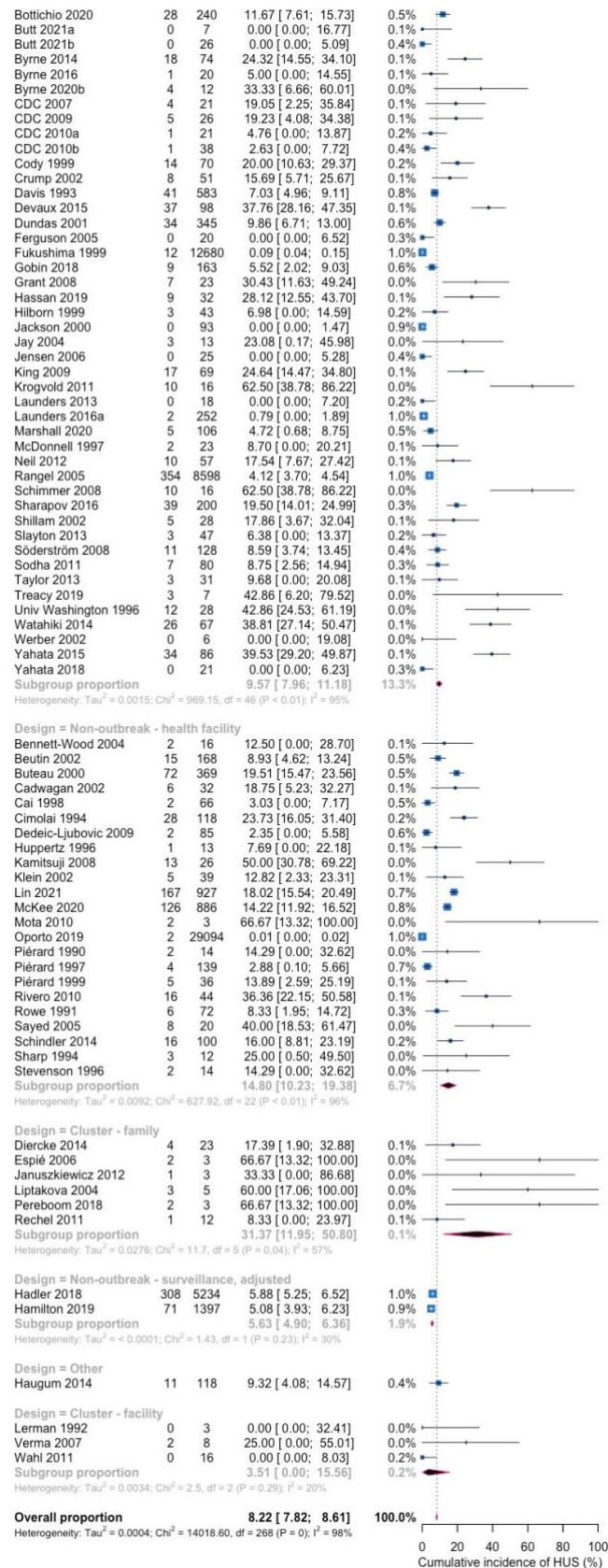
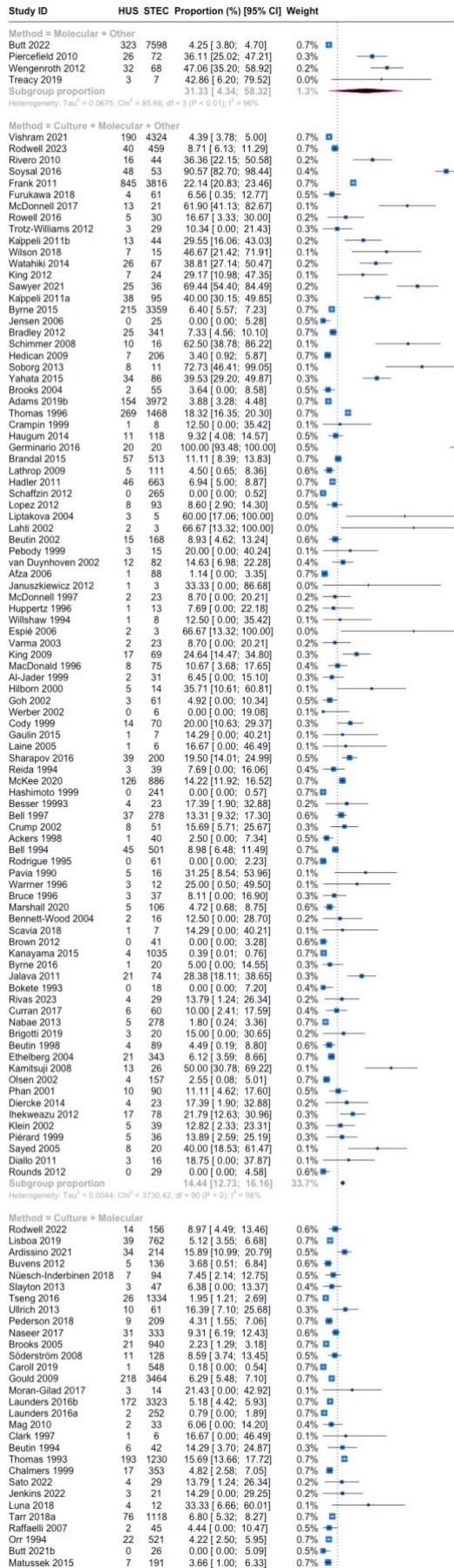


Figure A8. Cumulative incidence of HUS among symptomatic STEC cases by study setting



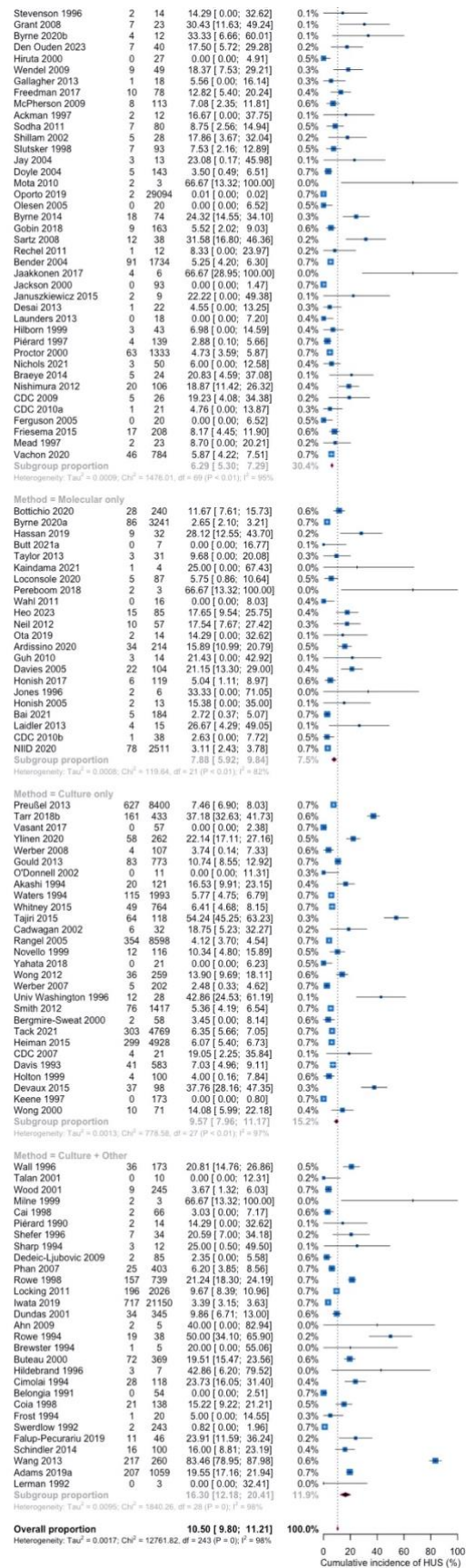
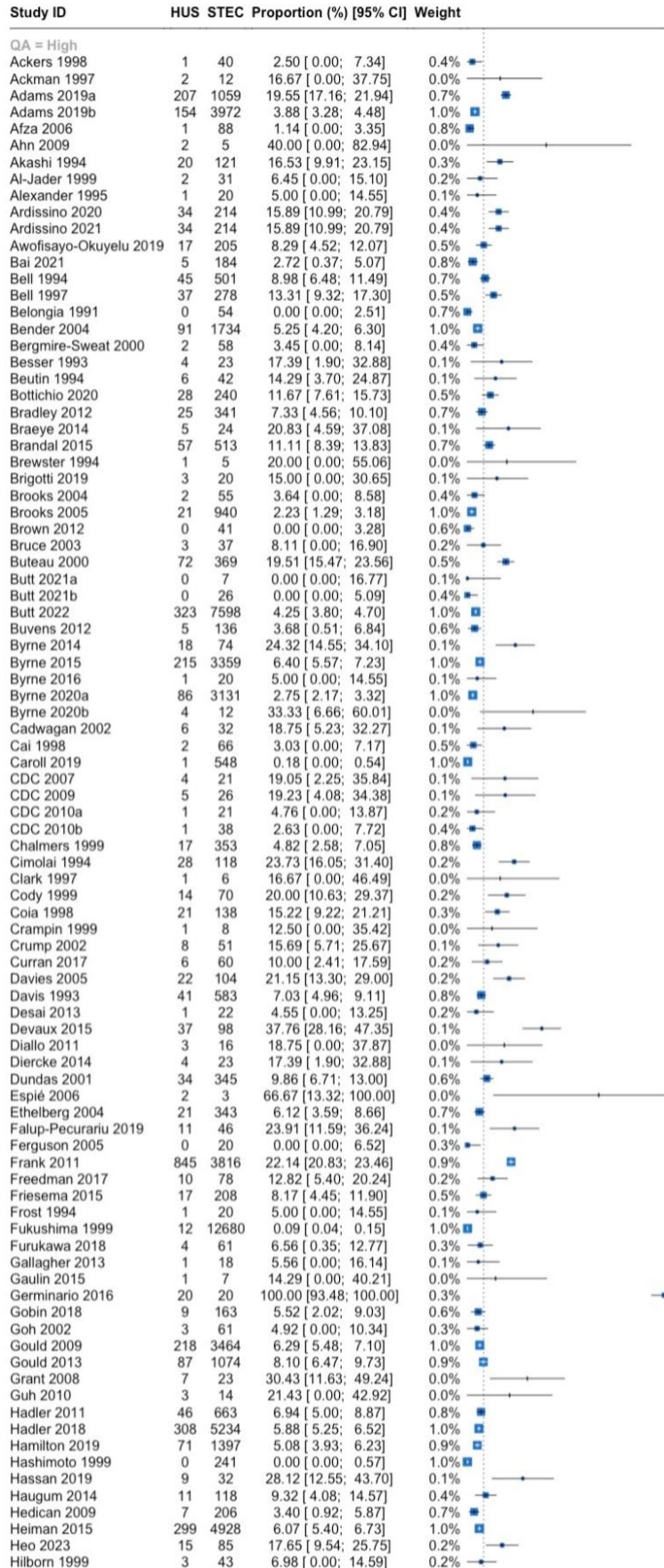
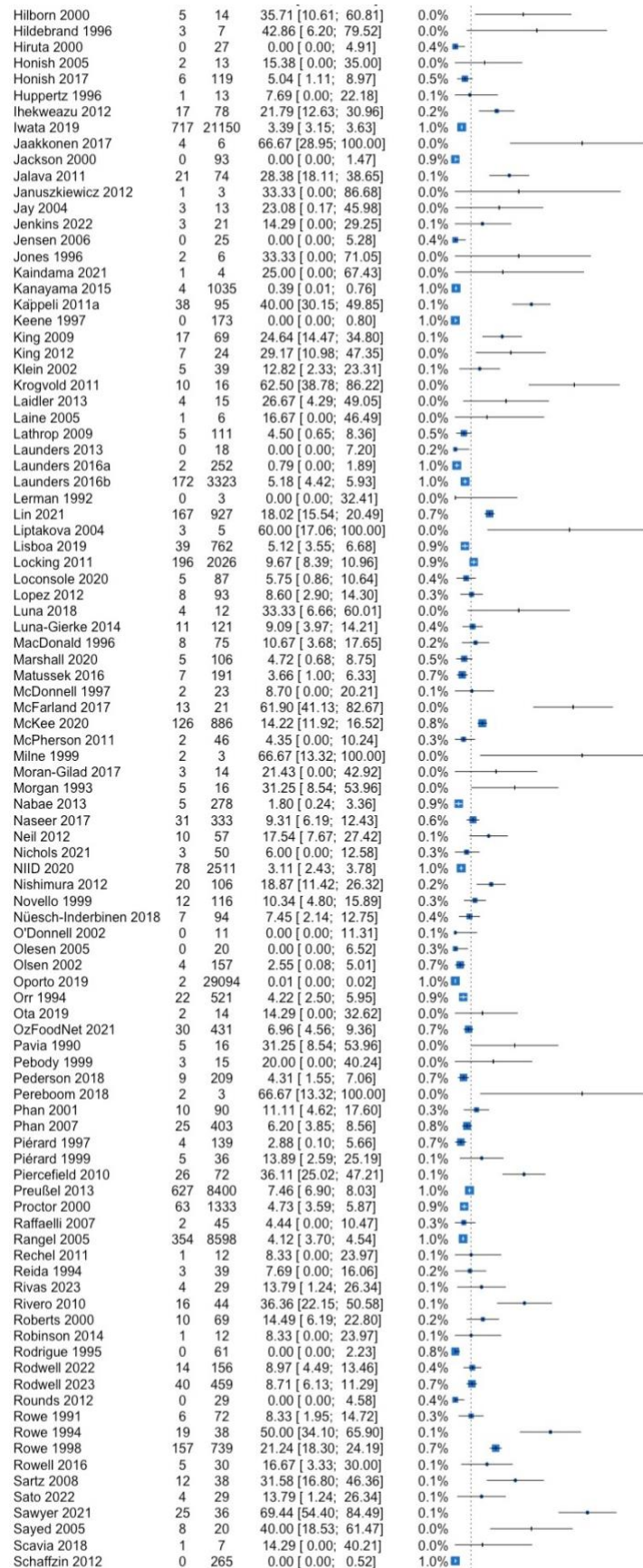


Figure A9. Cumulative incidence of HUS among symptomatic STEC cases by detection method





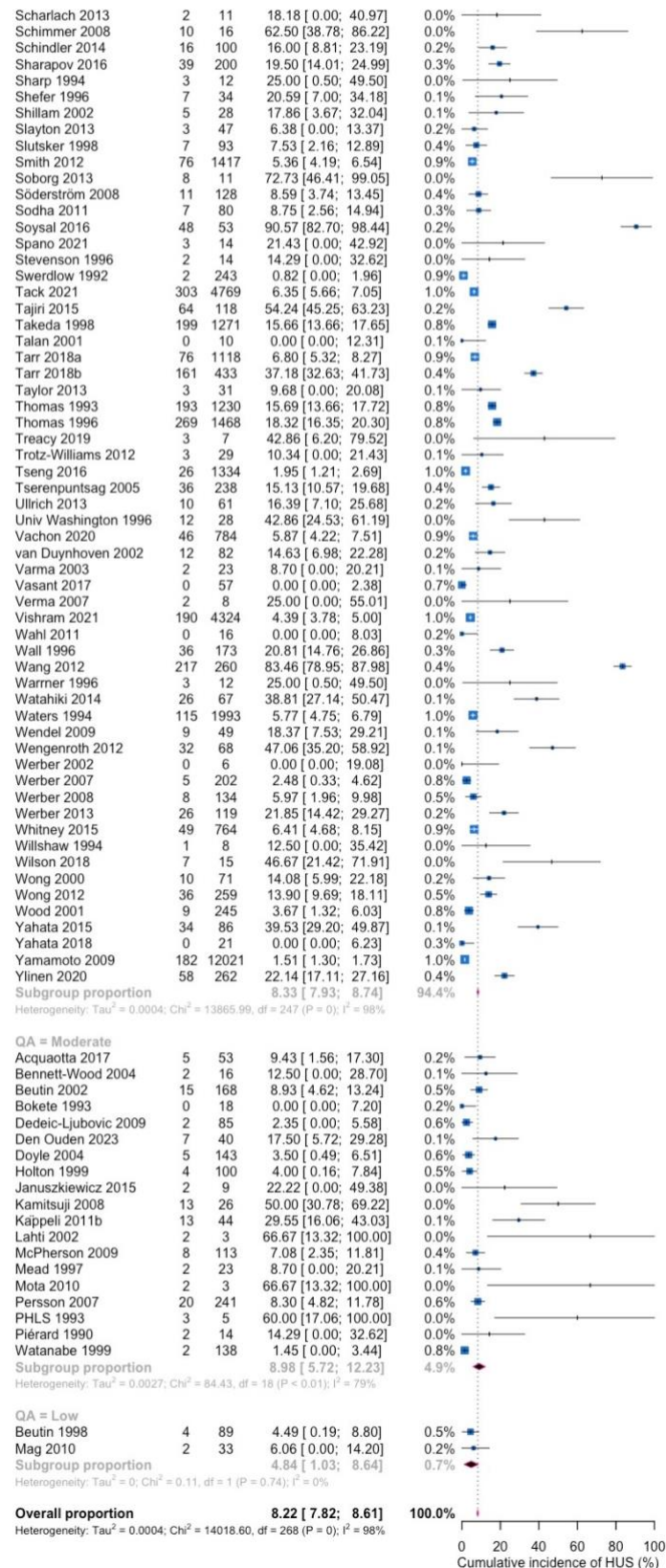


Figure A10. Cumulative incidence of HUS among symptomatic STEC cases by study quality ratings

Appendix 7: Checklist items in adapted JBI Critical Appraisal Tools

Checklist for Case series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Checklist for Prevalence

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Checklist for Case-control studies

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?