

An overview of diarrheagenic *Escherichia coli* in Iran: A systematic review and meta-analysis

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Background: Diarrheagenic *Escherichia coli* (DEC) is a common enteric pathogen that causes a wide spectrum of gastrointestinal infections, particularly in developing countries. This is a systematic review and meta-analysis to determine the prevalence of DEC in various geographical regions in Iran. **Materials and Methods:** English (PubMed, Web of Science, Scopus, Embase, Cochrane Library, and Google Scholar) and Persian (IranMedex, SID, Magiran, and Iran Doc) databases were comprehensively searched from January 1990 to April 2017. Study selection and data extraction were performed by two independent reviewers. After assessing heterogeneity among studies, a random effects model was applied to estimate pooled prevalence. Data analyses were done with the Stata software (version 12.0). This meta-analysis was registered with PROSPERO, number CRD42017070411. **Results:** A total of 73 studies with 18068 isolates were eligible for inclusion within the meta-analysis. The results of random effects model showed that the most prevalent DEC pathotypes were enterotoxigenic *E. coli* (ETEC) (16%; 95% confidence interval [CI]: 11%–23%), enteroaggregative *E. coli* (11%; 95% CI: 8%–15%), atypical enteropathogenic *E. coli* (EPEC) (11%; 95% CI: 8%–14%), Shiga toxin-producing *E. coli* (9%; 95% CI: 6%–13%), diffuse adherent *E. coli* (6%; 95% CI: 6%–12%), enteroinvasive *E. coli* (4%; 95% CI: 2%–6%), and typical EPEC (3%; 95% CI: 1%–5%). **Conclusion:** This study showed that DEC infections in the Iranian population have low frequency. Our data suggest that the ETEC pathotype can be regarded as one of the most important etiological agents of diarrhea in this country. However, the prevalence of DEC pathotypes is diverse in different regions of Iran.

Keywords: Diarrhea, *Escherichia coli*, Iran, meta-analysis, systematic review

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INTRODUCTION

Escherichia coli is a ubiquitous commensal inhabitant bacterium present in the gastrointestinal tracts of humans and animals, although some strains have acquired several putative virulence factors that enable it to adapt to new niches and cause a broad spectrum of infections.^[1,2] Pathogenic *E. coli* is one of the major causes of infectious diseases that span from the gastrointestinal tract to extraintestinal sites. Extraintestinal diseases include the urinary tract infection (UTI), septicemia, newborn meningitis,

central nervous system, and respiratory system infections.^[3,4]

Pathogenic *E. coli* agents of gastrointestinal infections are significant causes of sporadic outbreaks of diarrhea worldwide, especially in developing countries.^[5] Based on virulence factors and phenotypic traits, diarrheagenic *E. coli* (DEC) strains are generally classified into eight pathotypes: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC)/Shiga toxin-producing *E. coli* (STEC)/verotoxin-producing

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E. coli (VTEC), enteroaggregative *E. coli* (EAEC or EAaggEC), diffuse adherent *E. coli* (DAEC), and adherent-invasive *E. coli* (AIEC).^[6-8]

The prevalence of pathogenic *E. coli* which causes gastrointestinal infections has been reported in the literature from different regions of Iran; therefore, it is necessary to conduct a comprehensive analysis. This study presents a systematic review and meta-analysis of the literature on the DEC pathotypes in the Iranian population.

MATERIALS AND METHODS

Search strategy

This study is a systematic review and a meta-analysis study on original research articles that have been published in English or Persian which present the prevalence of DEC in Iran. The databases of PubMed, Web of Science, Scopus, Embase, Cochrane Library, Google Scholar, Iranmedex, SID, and Magiran were searched for studies published from January 1990 to April 2017. The following keywords or medical subject headings in titles or abstracts were used with the help of Boolean operators ("and" or "or"): "diarrheagenic *Escherichia coli*," "enterotoxigenic *Escherichia coli*," "ETEC," "enteropathogenic *Escherichia coli*," "EPEC," "enterohemorrhagic *Escherichia coli*," "EHEC," "enteroinvasive *Escherichia coli*," "EIEC," "enteroaggregative *Escherichia coli*," "EAEC," "shiga-toxigenic *Escherichia coli*," "shiga toxin-producing *Escherichia coli*," "STEC," "verotoxin-producing *Escherichia coli*," "verotoxigenic *Escherichia coli*," "VTEC," "Diffusely Adherent *Escherichia coli*," "DAEC," "Adherent-invasive *E. coli*," "AIEC," and "Iran." This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement with the PRISMA 2015 checklist. The planned systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42017070411.^[9]

Selection studies

To select studies, two authors scrutinized titles and abstracts of all studies returned by the search strategy. Then, they independently evaluated the full text of potentially relevant nonduplicated articles. Any disagreement was resolved by discussion between the two reviewers. When no agreement was reached, a third reviewer was consulted.

Eligibility criteria

The manual revision was conducted on all displayed articles, and the first levels of screening were based on information in the titles and/or abstracts. The final level was applied to the original publications. The included articles were confirmed by bacteriological standard methods for

identification of *E. coli* isolates (e.g., the biochemical API 20E identification system or conventional biochemical tests) and molecular method for the detection of DEC genes (e.g., PCR). Studies were excluded from the analysis that did not focus on the prevalence of DEC from human specimens in various region of Iran.

Data extraction

For all articles, the compiled information contains age (e.g., young children, adults, and the elderly), year of study, year of publication, place of study, the source of samples, number of cases analyzed, and the prevalence of *E. coli* pathotypes. The isolates were divided into five groups depending on the sample status: diarrheic, UTI, bloody diarrhea, healthy feces, and mixed (diarrheic and healthy). To assess the quality of each included study in the meta-analysis, we used the 22-item STROBE checklist (<https://strobestatement.org>). We categorized all studies in three categories in which obtained based on total score of checklists: >80% of the total score of checklists yes = high, 60%–80% of total score yes - medium, and <60% yes = low.

Statistical analysis

At the beginning of the analysis, we undertook an initial descriptive analysis for describing the essential characteristics of studies. Then, for each study, the prevalence (the number of current positive cases divided into a total number of the sample) and standard error were calculated. When the estimated prevalence for a study tends toward either 0% or 100%, the variance for that study moves toward zero, and as a result, its weight is overestimated in the meta-analysis. Therefore, we conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method.^[10] To investigate the influence of each individual study on the overall estimate, a sensitivity analysis was performed. Before the quantitative pooling of the results, heterogeneity among studies was assessed using the Cochran's Q-statistic ($P < 0.1$ as significant) and the I^2 index (25%, 50%, and 75% as low, moderate, and high heterogeneity; respectively).^[11] When heterogeneity was present, we used a random effects model (DerSimonian–Laird method); otherwise, we applied a fixed effects model (Mantel–Haenszel method) to estimate the pooled prevalence. The point prevalence of pathotypes and its 95% confidence interval (CI) were estimated for pooled effect size and each study. Forest plots illustrated the proportion of *E. coli* pathotypes, along with 95% CI. We used subgroup analysis to assess sources of heterogeneity using categorical variables as type of DEC, location which study performed, the source of sample and also using meta-regression for sample size of studies, quality of studies and year of study publication. The funnel plot (visual method) and

Egger's test ($P < 0.1$ as significant) were used to evaluate the possibility of publication bias among studies. In the case with significant publication bias, a nonparametric trim and fill method was performed to rectify the bias. All statistical analyses were conducted using Stata MP Software version 14.0 (Stata Corp, College Station, TX, USA) with metaprop command.

RESULTS

Study characteristics

In the initial database searches, 786 potential studies were identified. After the primary screening of titles and abstracts, 254 articles were selected for full-text search. Assessment of title and abstract resulted in the identification of 158 duplicate studies. Among them, 96 full-text articles were retrieved to check the eligibility, of which 73 were included. A total of 73 studies with 86 datasets (18068 isolates) were included in the final review and meta-analysis. Figure 1 presents the PRISMA flowchart, which describes the articles identified from the search strategy. These 86 data consisted of diarrhea samples (53), feces of healthy samples (13), acute diarrhea samples (9), UTI samples (6), bloody diarrhea samples (2), persistent diarrhea samples (1), and mixed (diarrheic and healthy feces) samples (1). The exclusion of articles based on the title and abstract of studies was mainly because of the following reasons: duplicated population groups, the articles were based on case report, assessment of specific methods on DEC pathotypes diagnosis, reported DEC pathotypes from animal and environmental samples, narrative reviews studies with inadequate data and generally, and studies that did not focus on the prevalence of even one of the DEC pathotypes from human samples in Iran. Table 1 presents a summary of the characteristics of the 86 included data.

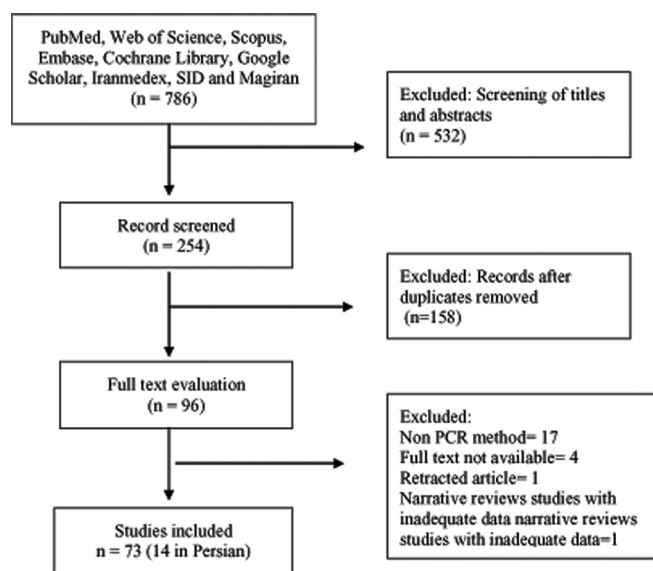


Figure 1: Flowchart of study selection

A description of the characteristics of each study, reporting the prevalence of DEC pathotypes in the Iranian population, is presented in "Appendix 1." Quality of study for five studies was moderate and for 68 studies was high; the results of subgroup analysis showed that the prevalence of DEC in the two groups (moderate and high quality) was statistically not significant ($P = 0.13$).

Sensitivity analysis

At first, the sensitivity analysis was conducted to evaluate whether individual studies influenced pooled prevalence. The result indicated that no study substantially influenced the pooled prevalence of pathotypes of DEC, which indicates that all studies need to be included for further research.

Heterogeneity

We performed a fixed effects model to estimate the pooled prevalence of pathotypes of DEC, 17.0% (95% CI: 16.9%–18.0%; $I^2 = 98.9$, $P < 0.001$). The results showed that there was substantial statistical heterogeneity among the effect size of studies. To assess the causes of the heterogeneity, five subgroup analyses were undertaken. The results showed that characteristics such as sample size, quality of studies, and year of publication are possible sources of heterogeneity [Table 1]; however, after using these variables in multiple meta-regression, the results indicated that sample size ($P = 0.031$) can be one of the causes of heterogeneity [Table 2]; so that, studies with small sample size were affected than studies with large sample [Figure 2].

Shiga toxin-producing *Escherichia coli*

The presence of STEC was examined in 9185 isolates in 38 publications. Overall, 953 of 9185 *E. coli* isolates were positive for the STEC pathotype. According to a random effects model ($I^2 = 95.14$, $P < 0.001$), the pooled prevalence was estimated to be 9% (95% CI: 6%–13%) [Table 1]. The

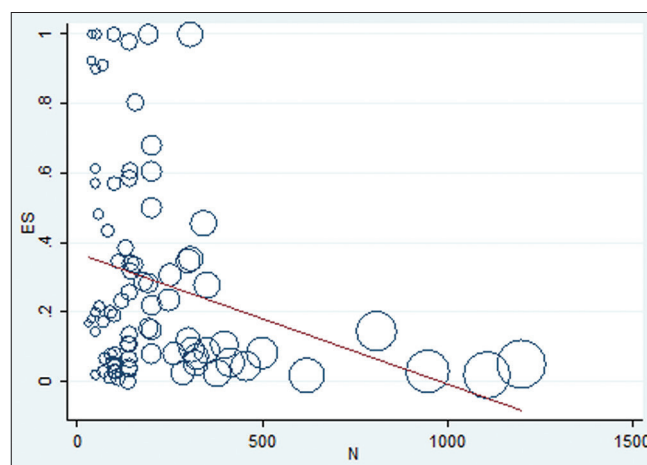


Figure 2: Relationship between sample size and effect size for included studies

Table 1: Subgroup meta-analysis and publication bias for diarrheagenic *Escherichia coli* pathotypes

| Characteristics | Subgroup | Number of study | Isolates positive | Isolates tested | Prevalence of pathotype (95% CI) | Heterogeneity | | Publication bias test | |
|---------------------|-------------|-----------------|-------------------|-----------------|----------------------------------|--------------------|--------|-----------------------|---------|
| | | | | | | I ² (%) | Q-test | Bias | Egger's |
| DEC pathotypes | STEC | 38 | 953 | 9185 | 9 (6-13) | 95.14 | <0.001 | 2.48 | 0.04 |
| | ETEC | 28 | 878 | 5669 | 16 (11-23) | 97.29 | <0.001 | 0.64 | 0.31 |
| | aEPEC | 38 | 923 | 9459 | 11 (8-14) | 95.91 | <0.001 | 1.97 | 0.002 |
| | tEPEC | 12 | 144 | 4240 | 3 (1-5) | 92.45 | <0.001 | 1.08 | 0.06 |
| | EAEC | 27 | 815 | 6526 | 11 (8-15) | 94.91 | <0.001 | 0.54 | 0.17 |
| | EIEC | 17 | 142 | 3184 | 4 (2-6) | 88.42 | <0.001 | 0.54 | 0.46 |
| | DAEC | 2 | 35 | 401 | 6 (6-12) | NES | NES | NES | NES |
| | AIEC | - | - | - | - | - | - | - | - |
| Type of sample | Diarrhea | 53 | 2398 | 12,234 | 19 (8-38) | 98.74 | <0.001 | 4.35 | 0.21 |
| | UTI | 6 | 104 | 866 | 7 (4-16) | 97.11 | <0.001 | 3.41 | 0.16 |
| | Stool | 13 | 329 | 2416 | 12 (7-21) | 97.99 | <0.001 | 2.12 | 0.77 |
| | Acute Dia | 9 | 959 | 2296 | 14 (5-31) | 99.56 | <0.001 | 2.57 | 0.435 |
| Quality of studies | High | 68 | 3692 | 17,426 | 11 (9.0, 14.0) | 96.97 | <0.001 | 5.11 | 0.021 |
| | Moderate | 5 | 179 | 642 | 19 (14.0, 31.0) | 89.77 | <0.001 | NES | NES |
| Year of publication | <2010 | 13 | 1191 | 5491 | 11 (8-14) | 98.5 | <0.001 | 4.82 | 0.055 |
| | 2010-2015 | 50 | 1912 | 10,095 | 3 (1-5) | 91.3 | <0.001 | 3.57 | 0.001 |
| | >2015 | 10 | 768 | 2482 | 11 (8-15) | 84.7 | <0.001 | 6.31 | 0.054 |
| Location* | Shiraz | 7 | 215 | 943 | 30 (0.8-58) | 98.32 | <0.001 | 2.21 | 0.69 |
| | Tabriz | 5 | 321 | 824 | 36 (12-65) | 90.11 | <0.001 | 7.17 | 0.02 |
| | Tehran | 31 | 1801 | 10,501 | 19 (11-28) | 98.45 | <0.001 | 2.45 | 0.47 |
| | Hamadan | 4 | 181 | 575 | 47 (17-78) | 81.01 | <0.001 | 3.68 | 0.02 |
| | Kerman | 6 | 278 | 1558 | 33 (12-58) | 98.61 | <0.001 | 1.70 | 0.52 |
| | Zanjan | 3 | 203 | 920 | 19 (13-27) | 73.70 | 0.003 | 2.96 | 0.74 |
| | Sample size | <100 | 23 | 589 | 1445 | 11 (7-25) | 98.17 | <0.001 | 8.13 |
| | 100-500 | 45 | 3046 | 11,940 | 9 (3-21) | 98.7 | <0.001 | 4.02 | 0.001 |
| | >500 | 5 | 236 | 4683 | 4 (2-9) | 88.7 | <0.001 | 3.0 | 0.031 |

*Cities which not included in analysis had not enough sample. *E. coli*=*Escherichia coli*; EPEC=Enteropathogenic *E. coli*; aEPEC=Atypical EPEC; tEPEC=Typical EPEC; ETEC=Enterotoxigenic *E. coli*; STEC=Shiga toxin-producing *E. coli*; EAEC=Enterococcal *E. coli*; EIEC=Enteroinvasive *E. coli*; DAEC=Diffuse adherent *E. coli*; AIEC=Adherent-invasive *E. coli*; UTI=Urinary tract infection; DEC=Diarrheagenic *E. coli*; CI=Confidence interval; NES=No enough sample size

Table 2: Results of multiple meta-regression to assess the source of heterogeneity

| Variables | Coefficient | SE | t | P |
|---------------------|-------------|--------|-------|-------|
| Sample size | -0.0004 | 0.0014 | -2.94 | 0.004 |
| Quality of studies | -0.002 | 0.003 | -0.70 | 0.484 |
| Year of publication | -0.006 | 0.003 | -0.62 | 0.540 |
| Location | -0.002 | 0.006 | -0.33 | 0.745 |

SE=Standard error

prevalence of STEC isolated from diarrheic samples was 21/43 (48.8%), from acute diarrheic samples was 9/43 (20.9%), from healthy stool samples was 6/43 (13.9%), from UTI samples was 3/43 (6.9%), from bloody diarrheic samples was 2/43 (4.6%), and from persistent diarrheic and mixed samples each one was 1/43 (2.3%). Based on previous reports from various regions in Iran, a high prevalence of the STEC pathotype of *E. coli* was detected in Shahrekord (central; 48.3%);^[12] central, western, and northern (44.5%);^[13] and Shiraz (south; 35.3%)^[14] [Appendix 1 and Figure 3].

Enterotoxigenic *Escherichia coli*

The presence of ETEC was investigated in 5669 isolates in 28 publications. A random effects model ($I^2 = 97.21$, $P < 0.001$)

showed that the pooled prevalence of ETEC was 16% (95% CI: 11%–23%) [Table 1]. The prevalence of ETEC in dependent of diarrheic sample status was 17/34 (50%) with 8/34 (23.5%) in acute diarrheic samples, 7/34 (20.6%) in healthy samples, 2/34 (5.9%) in UTI samples, and 1/34 (2.9%) in the persistent diarrheic sample. The highest report of the ETEC was 64.1%,^[15] 58.3%,^[16] and 46.4%^[17] of *E. coli* isolates from Kerman (south-east), Tehran and Sanandaj (capital and west), and Tabriz (north-west), respectively [Appendix 1 and Figure 3].

Enteropathogenic *Escherichia coli*

The presence of atypical EPEC (aEPEC) was investigated in 9459 isolates in 38 publications. In total, the pooled prevalence of aEPEC (923 out of 9459) based on a random effects model ($I^2 = 95.9$, $P < 0.001$) was estimated to be 11% (95% CI: 8%–14%) [Table 1]. aEPECs were found more often in diarrheic (25/44; 56.8%) samples than in acute diarrheic (10/44; 22.7%), feces of healthy (6/44; 13.6%), UTI (1/44; 2.3%), mixed (1/44; 2.3%), and persistent diarrheic (1/44; 2.3%) samples. The prevalence of aEPEC ranged from 0.00% among *E. coli* isolated from children (Tehran, capital)^[18] to 59.6% among *E. coli* isolated from acute diarrheic (Sanandaj, west).^[19] Egger's

test and funnel plot showed a significant publication bias for STEC (bias = 2.48, $P = 0.04$) and aEPEC (bias = 1.97, $P = 0.002$), but for other pathotypes, there was no publication bias [Appendix 1 and Figure 3].

The presence of typical EPEC (tEPEC) was examined in 4240 isolates in 12 publications. The results of a random effects mode showed that ($I^2 = 92.45$, $P < 0.001$) the pooled effect prevalence of tEPEC was estimated to be 3% (95% CI: 1%–5%) from 144 *E. coli* isolates which were positive for tEPEC pathotype [Table 1]. This pathotype was identified in diarrheic (10/14; 71.4%) samples than in the feces of healthy (3/14; 21.4%) and acute diarrhea (1/14; 7.1%) samples. The percentage of tEPEC is higher in Tehran (central; 21.5%)^[20] and Tehran, Ilam, and Mazandaran (central, west, and north of Iran; 14.2%)^[21] [Appendix 1 and Figure 3].

Enteroaggregative *Escherichia coli*

The presence of EAEC was investigated in 6526 isolates in 27 publications. The EAEC was present in 815 isolates. Based on a random effects model ($I^2 = 92.45$, $P < 0.001$), the pooled estimate of prevalence was obtained 11% (95% CI: 8%–15%) [Table 1]. The prevalence of EAEC in diarrheic samples was 42.8% (15/35), in healthy stool was 25.7% (9/35), in acute diarrhea was 20% (7/35), in UTI was 8.6% (3/35), and in persistent diarrhea was 2.8% (1/35). The percentages of EAEC vary with the geographical location of the patients: 28.3% in Tabriz,^[22] 25.6% in Zanjan,^[23] and 20% in Tehran^[24] [Appendix 1 and Figure 3].

Enteroinvasive *Escherichia coli*

The presence of EIEC was examined in 3184 isolates in 17 publications. A random effects model showed that the pooled prevalence of EIEC was 4% (95% CI: 2%–6%)

from 142 *E. coli* isolates which were positive for the EIEC pathotype [Table 1]. The prevalence of the EIEC pathotype isolated from diarrheic samples was 12/21 (57.1%), and it was 3/21 (14.3%) from acute diarrhea samples, 3/21 (14.3%) from healthy stool samples, 2/21 (9.5%) from UTI samples, and 1/21 (4.8%) from persistent diarrhea. EIEC was found in 22.2%, 14.3%, and 8.5% of the isolates in Sanandaj (west),^[19] Shiraz (south),^[25] and Tehran (central),^[26] respectively [Appendix 1 and Figure 3].

Diffusely adherent *Escherichia coli*

The presence of DAEC was evaluated in 401 isolates in two publications. To calculation of heterogeneity, there were not enough studies ($n = 2$). According to a fixed effects model, the pooled prevalence of DAEC was estimated at 6% (95% CI: 6%–12%) based on 35 isolates [Table 1]. DAEC was found more often in isolates from diarrheic isolates (29/35; 82.8%) as compared to isolates from UTI isolates (6/35; 17.1%). The prevalence of DAEC ranged from about 8% (Shiraz)^[27] to 9% (Tehran and Sanandaj)^[16] in Iran [Appendix 1 and Figure 3].

Adherent-invasive *Escherichia coli*

There are no data about the prevalence of the AIEC pathotype until April 2017 in Iran.

Publication bias

Funnel plot depicted for 73 studies. It seems that there is an asymmetric in funnel plot and small studies (smaller precision) trending to have large effect t size (prevalence) [Figure 4], this was cross-checked by Egger's regression test in which the results of this test confirm that a publication bias among studies ($t = 4.05$, $P < 0.001$). Furthermore, publication bias was assessed in each of subgroup using Egger's test; the results indicated that there was a considerable publication bias in some variables such as quality of studies, year of publication, and

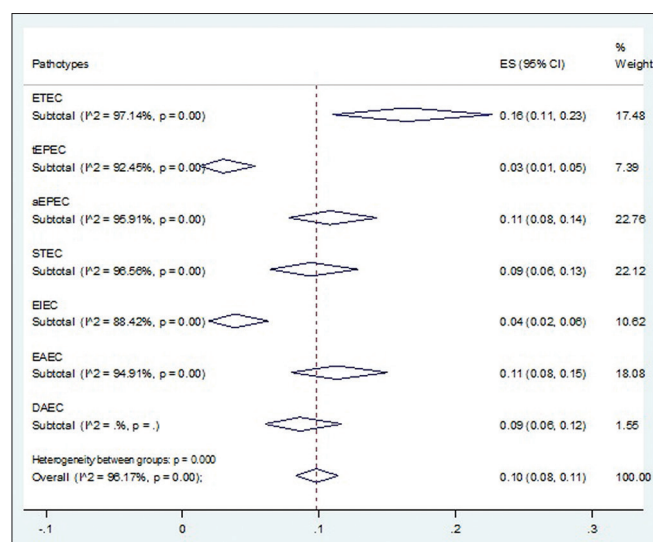


Figure 3: Forest plot of prevalence for seven pathotypes of diarrheogenic *Escherichia coli* in Iran. Diamonds indicate the 95% confidence interval for each pathotypes

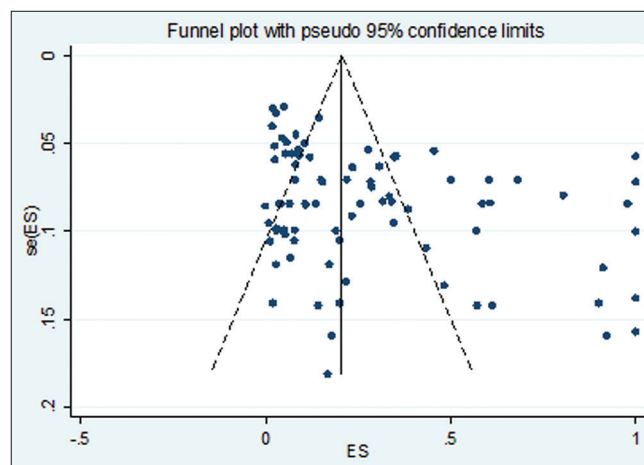


Figure 4: Funnel plot to display publication bias among 73 studies included in meta-analysis

sample size [Table 1]. A trim and fill method was performed to rectify the detected publication bias and then the pooled effect size for each subgroup (with $P < 0.1$) was filled.

DISCUSSION

Gastrointestinal infections due to pathogenic *E. coli* are significant causes of outbreaks and sporadic cases worldwide, particularly in children from countries in South Asia and Sub-Saharan Africa.^[3,28] The present systematic review and meta-analysis was designed to estimate the prevalence of DEC pathotypes in the Iranian population according to available data from articles collected from various regions of the country by Iranian researchers. The findings of this study highlight the low frequency of DEC pathotypes in various geographical areas of Iran. The ETEC was identified as one of the most common pathotypes (16%; 95% CI: 11%–23%) among the studied data. ETEC strains are the significant cause of diarrhea in travelers, and there is major morbidity and mortality in children residing in developing countries.^[29,30] Annually, this pathogen causes 280–400 million diarrheal episodes in children aged <5 years and causes substantial disease in adults in developing countries, with an estimated 400 million cases per year in people aged over 15 years.^[31] Several studies conducted in Iran have also revealed the high prevalence rate of *E. coli* isolates to ETEC in different parts.^[15-17,32,33] According to the report of Gupta *et al.*, ETEC was the etiological agent isolated in a median of 13% of diarrheal cases in children of developing countries.^[34] Previous studies showed that ETEC is usually a frequent cause of diarrhea in infants younger than 2 years of age.^[35,36] In Iran, it was found to be the most common cause of diarrhea in children younger than 5 years of age.^[17,28,33,37] This variation may be because children under 3 months became susceptible to a primary infection; ETEC strains to produce STh and LT were most common, whereas at 6–7 months, ETEC strains to produce STp, STpLT, and SThLT were dominant.^[35] The susceptibility of young children has also been reported in other settings which have poor hygiene conditions.

VTEC, also known as STEC infections, causes a wide spectrum of clinical manifestations ranging from symptom-free carriage forms of intestinal illnesses to bloody diarrhea. EHEC is a subset of STEC capable of causing hemorrhagic colitis and hemolytic uremic syndrome in humans.^[38,39] In earlier studies in Iran, the prevalence of STEC isolates ranged from 0.0% among *E. coli* isolated from children <5 years of age^[28,40-42] to 30%–48% among *E. coli* isolated from patients of unknown age.^[12-15,43] In developing countries, where studies typically focus solely on children, STEC has also been detected as a pathogen of concern in this age group.^[44,45] However, in developed countries, studies investigating all ages typically identified STEC more frequently and with greater severity in young children.^[46,47]

Unfortunately, despite the existence of many data of aEPEC in Iran (39 publications), there is not sufficient data about the incidence of tEPEC (12 publications). The results of our study indicated that the incidence of aEPEC in the investigated studies varies in different provinces, such that the highest rate of incidence was reported from Sanandaj with 59.6% (west of Iran),^[19] central, western, and northern Iran with 38.8%,^[13] Khuzestan with 31% (south west of Iran),^[43] and Kashan with 28.6% (central of Iran).^[48] Previous studies in Northeast India,^[49] Ghana,^[50] and Kenya^[51] showed that EPEC was the most frequently identified bacterial pathogen.

In Iran, moderately high reports are available on the occurrence of EIEC (17 publications). In the present study, 4.5% (95% CI: 2%–6%) of *E. coli* isolates were confirmed as EIEC, of which the most prevalent were from Sanandaj (west)^[19] and Tehran (central).^[26] Other studies in the world also reported less percentage of EIEC (0%–1.5%).^[52,53]

EAEC is well known as a diarrhea-causing agent in people of all ages in developing and industrialized countries, most prominently in association with persistent diarrhea.^[54] According to our results, the total prevalence of EAEC strains was 11.1% (95% CI: 8%–15%). It is consistent with some studies conducted in Switzerland (10.2%) and Kenya (8.9%).^[51,55] Another study in urban and rural South Korea showed that the prevalence of EAEC was 0.3%–3.7% of acute diarrhea samples.^[56]

There are very few reports on the epidemiology of DAEC infections in Iran (two publications). However, the frequency of this pathotype was 8.7%. Both studies were conducted in Brazil, and DAEC was significantly associated with diarrhea in children.^[57,58] In a study in Iran, DAEC strains were isolated in 6% of patients with UTI.^[16] DAEC strains may represent the reservoir for uropathogenic *E. coli*, since several virulence factors of DAEC, such as adhesins of the Afa/Dr family, are found in uropathogenic *E. coli* strains.^[59] Four *E. coli* isolates presenting mixed characteristics (mixed EAEC/DAEC genes) were identified.^[15] Several studies showed the presence of diarrheagenic isolates presenting mixed characteristics of two different pathotypes.^[60,61]

CONCLUSION

By combining the results from 73 studies, this systematic review and meta-analysis identified the lower frequency of DEC infections in Iran. Our data suggest that the ETEC pathotype is one of the most important etiological agents of disease in this country. However, the prevalence of DEC pathotypes is diverse in different regions of Iran. The limitation of the study was associated with high heterogeneity, especially in sample size subgroup. We used

subgroup analysis to find the source of heterogeneity, but in all moderator variables, there is a high heterogeneity. Maybe there is a possibility that a moderator variable is missing that does, in fact, explain the heterogeneity (i.e., age and sex). Furthermore, nonuniform study design and various types of publication bias may be the other causes of heterogeneity in these studies. Our study included other limitations such as it cannot fully represent the prevalence of DEC infections in Iran because the extent of DEC has not yet been examined in some regions of the country.

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Conflicts of interest

There are no conflicts of interest.

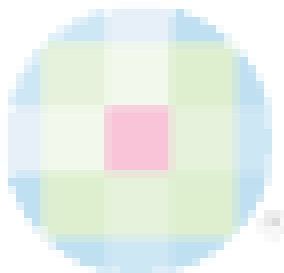
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Appendix 1: Characteristics of studies included in the meta-analysis

| Study | Study period | Published time | Age | Location | Source of sample | Number of isolates/samples | Prevalence of DEC pathotype | Study quality |
|---|--------------|----------------|-------------------|----------------------------|--------------------|----------------------------|--|---------------|
| Abbasi <i>et al.</i> ^[62] | 2012 | 2014a | 3-61 years | Shiraz | Diarrhea | 52 | ETEC=52 | 20 |
| Abbasi <i>et al.</i> ^[63] | 2012 | 2014b | 1-26 months | Shiraz | Diarrhea | 49 | aEPEC=13 EHEC=15 | 20 |
| Abbasi <i>et al.</i> ^[64] | 2012 | 2014c | 2 months-63 years | Shiraz | Diarrhea | 101 | EAEC=5 | 20 |
| Abbasi <i>et al.</i> ^[25] | 2012 | 2015 | 1-24 months | Shiraz | Diarrhea | 49 | EIEC=7 | 20 |
| Abbasi <i>et al.</i> ^[27] | 2012-2013 | 2017 | 2 months-63 years | Shiraz | Diarrhea | 101 | DAEC=8 | 20 |
| Abri <i>et al.</i> ^[65] | - | 2015 | - | Tabriz | Diarrhea | 60 | ETEC=10 aEPEC=2 tEPEC=1 | 20 |
| Aein <i>et al.</i> ^[98] | 2011-2012 | 2014 | <5 years | Yasuj | Diarrhea | 200 | EIEC=16 | 16 |
| Adeli <i>et al.</i> ^[104] | 2011-2012 | 2013 | - | Lorestan | UTI | 100 | EHEC=3 | 16 |
| Ahangarzadeh-Rezaee <i>et al.</i> ^[22] | 2013 | 2015 | <10 years | Tabriz | Diarrhea | 194 | EAEC=55 | 21 |
| Akbari <i>et al.</i> ^[97] | 2009 | 2010 | <5 years | Tehran | Diarrhea | 39 | EIEC=7 | 18 |
| Akhi <i>et al.</i> ^[66] | 2014 | 2015 | - | Tabriz | Diarrhea, stool | 200 | EHEC=11 aEPEC=5 | 21 |
| Alikhani <i>et al.</i> ^[21] | - | 2006 | 0-10 years | Tehran, Ilam, Mazandaran | Diarrhea | 247 | aEPEC=23 tEPEC=35 | 22 |
| Alikhani <i>et al.</i> ^[21] | - | 2006 | 0-10 years | Tehran, Ilam, Mazandaran | Stool | 1108 | aEPEC=13 tEPEC=8 | 20 |
| Alikhani <i>et al.</i> ^[67] | 2007 | 2012 | Children | Hamadan | Diarrhea | 251 | ETEC=13 aEPEC=41 EHEC=7 EIEC=0 EAEC=16 | 20 |
| Alikhani <i>et al.</i> ^[68] | 2009 | 2013 | 12-65 years | Hamadan | Acute diarrhea | 40 | ETEC=7 aEPEC=19 EHEC=6 EAEC=8 | 20 |
| Alizade <i>et al.</i> ^[28] | 2010-2012 | 2014a | <5 years | Kerman | Diarrhea | 142 | ETEC=52 aEPEC=9 EHEC=0 EIEC=2 EAEC=23 | 20 |
| Alizade <i>et al.</i> ^[38] | 2010-2011 | 2014b | - | Kerman | Diarrhea | 96 | aEPEC=5 EHEC=0 | 20 |
| Alizade <i>et al.</i> ^[15] | 2014 | 2017 | - | Kerman | Stool, HIV | 49 | ETEC=29 aEPEC=8 EHEC=13 | 20 |
| Alizade <i>et al.</i> ^[15] | 2014 | 2017 | - | Kerman | Stool, thalassemia | 68 | ETEC=46 aEPEC=13 EHEC=23 | 20 |
| Alizade <i>et al.</i> ^[32] | 2010 | 2015 | - | Bam | Diarrhea | 155 | ETEC=52 | 19 |
| Alizadeh <i>et al.</i> ^[69] | 2003 | 2007 | 5 months-90 years | Hamadan | Acute diarrhea | 144 | ETEC=22 aEPEC=2 EHEC=15 EAEC=10 | 20 |
| Asadi Karam <i>et al.</i> ^[40] | - | 2010 | <5 years | Tehran | Diarrhea | 321 | aEPEC=17 EHEC=0 | 19 |
| Askari Badouei <i>et al.</i> ^[8] | - | 2014 | 2-10 years | Garmsar | Diarrhea | 75 | aEPEC=1 EHEC=4 | 21 |
| Aslani <i>et al.</i> ^[13] | - | 2008a | - | Central, western, northern | Diarrhea | 193 | ETEC=14 aEPEC=74 EHEC=86 EAEC=19 | 19 |
| Aslani <i>et al.</i> ^[70] | 2007-2008 | 2011 | <12 years | Hamadan | Stool | 140 | EAEC=15 | 21 |

Contd...

Appendix 1: Contd...

| Study | Study period | Published time | Age | Location | Source of sample | Number of isolates/samples | Prevalence of DEC pathotype | Study quality |
|--|--------------|----------------|------------------|------------|---------------------|----------------------------|---|---------------|
| Aslani <i>et al.</i> ^[96] | 2005 | 2008b | Children | Tehran | Diarrhea | 70 | EHEC=12 | 20 |
| Aslani <i>et al.</i> ^[96] | 2005 | 2008b | Children | Tehran | Hemorrhagic colitis | 70 | EHEC=2 | |
| Bafandeh <i>et al.</i> ^[23] | - | 2015 | <30->45 years | Zanjan | Diarrhea | 350 | EAEC=97 | 21 |
| Bafandeh <i>et al.</i> ^[23] | - | 2015 | <30->45 years | Zanjan | Stool | 200 | EAEC=44 | |
| Bagheri <i>et al.</i> ^[99] | 2006-2007 | 2009 | 1 month-66 years | Gorgan | Diarrhea | 455 | EAEC=20 | 19 |
| Bakhshi <i>et al.</i> ^[41] | 2009-2010 | 2012 | <5 years | Tehran | Acute diarrhea | 309 | aEPEC=17 tEPEC=11 EHEC=0 | 21 |
| Bakhshi <i>et al.</i> ^[71] | - | 2014 | - | Tehran | Diarrhea | 120 | aEPEC=28 | 20 |
| Bazzar <i>et al.</i> ^[100] | - | 2011 | <5 years | Ardabil | Diarrhea | 194 | aEPEC=28 tEPEC=2 | 19 |
| Bayat <i>et al.</i> ^[101] | 2012-2013 | 2014 | <5 years | Zanjan | Diarrhea | 140 | aEPEC=19 | 18 |
| Bonyadian <i>et al.</i> ^[12] | 2007-2008 | 2010 | - | Shahrekord | Diarrhea | 58 | EHEC=28 | 20 |
| Bouzari <i>et al.</i> ^[24] | 2000 | 2007 | Children | Tehran | Diarrhea | 200 | ETEC=22 EHEC=38 EAEC=40 | 20 |
| Bouzari <i>et al.</i> ^[72] | - | 2011 | - | Tehran | Diarrhea | 500 | aEPEC=14 tEPEC=27 | 19 |
| Darbandi <i>et al.</i> ^[43] | 2012-2013 | 2016 | - | Khuzestan | Diarrhea | 158 | ETEC=21 aEPEC=49 tEPEC=1 EHEC=50 EIEC=1 EAEC=5 | 20 |
| Haghi <i>et al.</i> ^[33] | 2011-2012 | 2014 | <5 years | Tabriz | Diarrhea | 140 | ETEC=65 aEPEC=13 tEPEC=6 EHEC=17 EAEC=36 | 21 |
| Haghi <i>et al.</i> ^[33] | 2011-2012 | 2014 | <5 years | Tabriz | Stool | 90 | ETEC=8 aEPEC=3 tEPEC=0 EHEC=0 EAEC=7 | |
| Hoseinzadeh <i>et al.</i> ^[73] | 2014 | 2016 | - | Sirjan | Diarrhea | 110 | ETEC=32 EIEC=6 | 19 |
| Hosseini Nave <i>et al.</i> ^[74] | 2013-2014 | 2016 | - | Kerman | Diarrhea | 620 | EIEC=11 | 20 |
| Jafari <i>et al.</i> ^[75] | - | 2001 | Children | Tehran | Diarrhea | 1200 | EHEC=60 | 21 |
| Jafari <i>et al.</i> ^[76] | 2004-2005 | 2008 | 5-60 years | Tehran | Acute diarrhea | 808 | ETEC=41 aEPEC=11 EHEC=52 EAEC=13 | 21 |
| Jafari <i>et al.</i> ^[77] | 2003-2005 | 2009 | <5 years | Tehran | Acute diarrhea | 305 | ETEC=38 aEPEC=70 EHEC=105 EAEC=92 | 21 |
| Kalantar <i>et al.</i> ^[19] | 2008 | 2009 | <12 years | Sanandaj | Acute diarrhea | 99 | ETEC=7 aEPEC=59 EHEC=11 EIEC=22 | 21 |
| Kargar <i>et al.</i> ^[78] | 2011-2012 | 2014 | <5 years | Yasuj | Diarrhea | 300 | EHEC=104 | 20 |
| Kargar <i>et al.</i> ^[79] | 2010 | 2013 | <2 years | Shiraz | Diarrhea | 285 | ETEC=7 | 19 |
| Kargar and Homayoon <i>et al.</i> ^[105] | 2006-2007 | 2009 | <5 years | Marvdasht | Diarrhea | 89 | EHEC=1 | 20 |

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| Study | Study period | Published time | Age | Location | Source of sample | Number of isolates/samples | Prevalence of DEC pathotype | Study quality |
|--|--------------|----------------|----------------------|--|------------------|----------------------------|---|---------------|
| Kermani <i>et al.</i> ^[26] | - | 2010 | <5 years | Tehran | Acute diarrhea | 341 | ETEC=21 aEPEC=18 EHEC=25 EIEC=31 EAEC=60 | 20 |
| Kermani <i>et al.</i> ^[26] | - | 2010 | <5 years | Tehran | Persist diarrhea | 83 | ETEC=5 aEPEC=5 EHEC=6 EIEC=5 EAEC=15 | |
| Khorshidi <i>et al.</i> ^[80] | 2009-2010 | 2011 | <5 years | Kashan | Diarrhea | 178 | EPEC=51 | 19 |
| Khoshvaght <i>et al.</i> ^[81] | 2011-2012 | 2014 | 0-60 months | Zanjan | Diarrhea | 140 | EAEC=36 | 21 |
| Khoshvaght <i>et al.</i> ^[81] | 2011-2012 | 2014 | 0-60 months | Zanjan | Stool | 90 | EAEC=7 | |
| Mahmoudi-Aznavah <i>et al.</i> ^[42] | 2012-2013 | 2016 | <5 years | Tehran | Diarrhea | 349 | aEPEC=30 tEPEC=1 EHEC=0 | 21 |
| Memariani <i>et al.</i> ^[82] | 2011-2013 | 2015 | <10 years | Tehran | Diarrhea | 398 | aEPEC=26 tEPEC=16 | 21 |
| Miri <i>et al.</i> ^[83] | 2012-2013 | 2017 | - | East-Azerbaijan, Gilan, Zanjan, Kurdistan, Tehran, Hamedan | Stool | 145 | ETEC=10 aEPEC=17 tEPEC=1 EHEC=18 EIEC=0 EAEC=0 | 19 |
| Mirzarazi <i>et al.</i> ^[84] | - | 2015 | - | Isfahan | UTI | 138 | EIEC=2 EAEC=13 | 19 |
| Mirzarazi <i>et al.</i> ^[84] | - | 2015 | - | Isfahan | Stool | 30 | EIEC=0 EAEC=5 | |
| Mirsalehian <i>et al.</i> ^[107] | 2003 | 2004 | - | Tehran | Bloody diarrhea | 103 | EHEC=3 | 17 |
| Mohammadzadeh <i>et al.</i> ^[20] | - | 2013 | - | Tehran | Diarrhea | 130 | aEPEC=22 tEPEC=28 EHEC=0 | 20 |
| Mohammadzadeh <i>et al.</i> ^[85] | 2013 | 2015a | - | Tehran | Diarrhea | 140 | EIEC=5 | 20 |
| Mohammadzadeh <i>et al.</i> ^[86] | 2013 | 2015b | Mean age 38 years | Tehran | Diarrhea | 140 | ETEC=9 | 20 |
| Mohammadzadeh <i>et al.</i> ^[86] | 2013 | 2015b | Mean age 34 years | Tehran | Stool | 110 | ETEC=1 | |
| Mohammadzadeh <i>et al.</i> ^[106] | - | 2016 | - | Tehran | Diarrhea | 140 | EAEC=6 | 19 |
| Mohammadzadeh <i>et al.</i> ^[106] | - | 2016 | - | Tehran | Stool | 136 | EAEC=0 | |
| Motallebi <i>et al.</i> ^[48] | 2009-2010 | 2011 | <5 years | Kashan | Diarrhea | 178 | aEPEC=51 | 20 |
| Nakhjavani <i>et al.</i> ^[88] | 2009-2010 | 2013 | <10 years | Tehran | Diarrhea | 412 | aEPEC=16 tEPEC=7 | 21 |
| Navidinia <i>et al.</i> ^[89] | 2008-2009 | 2012 | 1-12 years | Tehran | UTI | 378 | EHEC=9 | 19 |
| Nazarian <i>et al.</i> ^[90] | 2010-2011 | 2014 | <5 years | Tehran, Kerman, Golestan | Diarrhea | 261 | ETEC=21 | 21 |
| Nazemi <i>et al.</i> ^[91] | 2010-2011 | 2012 | - | Tehran | UTI | 100 | ETEC=2 EHEC=17 | 18 |
| Nezarieh <i>et al.</i> ^[92] | 2013-2014 | 2015 | 1-10 years | Kerman | Diarrhea | 322 | EAEC=23 | 18 |
| Pourakbari <i>et al.</i> ^[18] | 2010-2011 | 2013 | 1 month-12 years | Tehran | Acute diarrhea | 50 | ETEC=21 aEPEC=0 EHEC=14 EIEC=0 EAEC=10 | 18 |

Contd...

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| Study | Study period | Published time | Age | Location | Source of sample | Number of isolates/samples | Prevalence of DEC pathotype | Study quality |
|--|--------------|----------------|------------------|------------------|------------------|----------------------------|---|---------------|
| Pourakbari <i>et al.</i> ^[18] | 2010-2011 | 2013 | 1 month-12 years | Tehran | Stool | 50 | ETEC=5 aEPEC=0 EHEC=3 EIEC=0 EAEC=2 | |
| Rajaee <i>et al.</i> ^[14] | 2014-2015 | 2017 | - | Shiraz | Diarrhea | 306 | EHEC=108 | 20 |
| Salmani <i>et al.</i> ^[16] | - | 2016 | - | Tehran, Sanandaj | Diarrhea | 200 | ETEC=153 aEPEC=10 EIEC=13 EAEC=39 DAEC=21 | 20 |
| Salmani <i>et al.</i> ^[16] | - | 2016 | - | Tehran, Sanandaj | UTI | 100 | ETEC=22 aEPEC=0 EIEC=6 EAEC=23 DAEC=6 | |
| Salmanzadeh-Ahrabi <i>et al.</i> ^[93] | 2003 | 2005 | <5 years | Tehran | Acute diarrhea | 200 | ETEC=31 aEPEC=12 EHEC=30 EAEC=48 | 16 |
| Salmanzadeh-Ahrabi <i>et al.</i> ^[93] | 2003 | 2005 | <5 years | Tehran | Stool | 200 | ETEC=0 aEPEC=10 EHEC=4 EAEC=16 | |
| Shams <i>et al.</i> ^[94] | 2008-2009 | 2013 | <14 years | Tehran | Diarrhea | 947 | EHEC=27 | 19 |
| Sharifi Yazdi <i>et al.</i> ^[95] | 2008 | 2011 | <5 years | Tehran | Diarrhea | 39 | aEPEC=20 EHEC=9 EIEC=7 | 15 |
| Soleimanifard <i>et al.</i> ^[103] | - | 2015 | - | Saveh | UTI | 50 | EAEC=1 | 20 |
| Soltan Dallal <i>et al.</i> ^[102] | 2013 | 2015 | <5 years | Tehran | Diarrhea | 300 | aEPEC=36 | 20 |
| Zeighami <i>et al.</i> ^[17] | 2011-2012 | 2014 | <5 years | Tabriz | Diarrhea | 140 | ETEC=65 EHEC=17 | 20 |

EHEC=Enterohemorrhagic *E. coli*; *E. coli*=*Escherichia coli*; EPEC=Enteropathogenic *E. coli*; aEPEC=Atypical EPEC; tEPEC=Typical EPEC; ETEC=Enterotoxigenic *E. coli*; STEC=Shiga toxin-producing *E. coli*; EAEC=Enteraggregative *E. coli*; EIEC=Enteroinvasive *E. coli*; DAEC=Diffuse adherent *E. coli*; UTI=Urinary tract infection; DEC=Diarrheagenic *E. coli*