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Review

Risk factors for *Clostridioides difficile* infection in children: a systematic review and meta-analysis

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SUMMARY

Background: *Clostridioides difficile* is considered an urgent threat to human health by the US Centers for Disease Control and Prevention. In recent years, *C. difficile* has been reported increasingly as a cause of gastrointestinal disease in children, and the prevalence of hospital-acquired *C. difficile* infection and community-acquired CDI in children is increasing.

Aim: To perform a systematic review and meta-analysis of risk factors for CDI in children.

Methods: MEDLINE/PubMed, EMBASE, Web of Science, Scopus, OVID, China National Knowledge Infrastructure, Wanfang (Chinese), SinoMed (Chinese) and Weipu (Chinese) were searched from inception to 12th January 2022. Observational studies (cohort, case–control and cross-sectional) on CDI in children were included in the analysis. Data were pooled using a fixed or random-effects model, and odds ratios (OR) were calculated.

Findings: In total, 25 observational studies were included in the analysis. Prior antibiotic exposure [OR 1.93, 95% confidence interval (CI) 1.25–2.97], prolonged hospitalization (OR 14.68, 95% CI 13.24–16.28), history of hospitalization (OR 3.67, 95% CI 1.91–7.06), gastric acid suppressants (OR 1.96, 95% CI 1.41–2.73), male gender (OR 1.18, 95% CI 1.05–1.32), neoplastic disease (OR 3.40, 95% CI, 2.85–4.07), immunodeficiency (OR 4.18, 95% CI 3.25–5.37), solid organ transplantation (OR 4.56, 95% CI 3.95–5.27) and enteral feeding (OR 2.21, 95% CI 1.05–4.62) were associated with increased risk of CDI.

Conclusion: This systematic review and meta-analysis provides further evidence for the susceptibility factors of CDI to improve clinicians' awareness of CDI, and prevent *C. difficile*-associated diarrhoea in children.

Introduction

Clostridioides difficile, a Gram-positive spore-forming anaerobic bacterium, is considered an 'urgent threat' to human health by the US Centers for Disease Control and Prevention [1]. Over the past two decades, *C. difficile* has caused

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outbreaks of hospital-acquired infection in many parts of the world, with clinical symptoms ranging from self-limiting diarrhoea to pseudomembranous colitis, toxic megacolon, septic shock, colon perforation, multi-organ failure and death [2]. It is estimated that *C. difficile* infection (CDI) is responsible for over 500,000 enteric infections, 29,000 deaths and over $4.8 billion in healthcare costs each year in the USA [3]. Furthermore, based on the 2016–2017 point prevalence survey of the European Centre for Disease Prevention and Control, it is estimated that 189,526 cases of CDI are reported annually in acute care hospitals, resulting in considerable morbidity and mortality [4,5]. Although the incidence of hospital-acquired CDI (HA-CDI) in the USA has decreased moderately in recent years, the rates of community-acquired CDI (CA-CDI) have remained largely unchanged or even increased slightly [6,7].

CDI has been studied extensively in adults, and traditional risk factors include history of antibiotic use, old age, comorbidities, disease severity and hospitalization [8,9]. However, despite being isolated initially from infants, little is known about CDI in children. In recent years, *C. difficile* has caused gastrointestinal diseases in children, and is more prevalent in children with diarrhoea than in children with rotavirus or *Cryptosporidium* infection [10]. In addition, the prevalence rates of HA-CDI and CA-CDI in children are increasing [11–13]. Although several systematic reviews and meta-analyses have shown that antibiotic therapy and the use of proton pump inhibitors (PPIs) increase the risk of CDI in paediatric inpatients, few studies have evaluated other risk factors for CDI in children [14,15]. To this end, this study systematically retrieved and summarized relevant studies in order to assess the risk factors for CDI in children comprehensively.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Table S1, see online supplementary material) [16]. The protocol of this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022339371).

Eligibility criteria

The inclusion criteria were: (i) observational studies (cohort, case–control and cross-sectional) on primary CDI in children (age ≤18 years); (ii) studies with sufficient data to estimate the odds ratio (OR), relative risk (RR) or hazard ratio (HR) and 95% confidence interval (CI); (iii) studies that evaluated more than one risk factor for CDI, including, but not limited to, pharmacological agents [e.g. antibiotics, PPIs, H2 receptor antagonists (H2RAs)], age, gender, comorbidities, history of hospitalization, history of CDI, and other clinical risk factors; and (iv) no restrictions on study setting (inpatient or outpatient). Studies with recurrent CDI or asymptomatic colonization in children were excluded, as were reviews, case reports, non-human trials, letters, conference abstracts and comments.

Data sources and search strategy

A comprehensive search of MEDLINE/PubMed, EMBASE, Web of Science, Scopus, OVID, China National Knowledge Infrastructure, Wanfang (Chinese), SinoMed (Chinese), and Weipu (Chinese) from inception to 12th January 2022 was conducted, using the following medical subject headings: 'child', 'children', '*Clostridioides difficile* infection', '*C. difficile* infection', 'CDI', '*Clostridium difficile* infection', '*Clostridium difficile* associated infection', 'CDAD' combined with 'risk factors', 'risk', 'predictor' and 'relative risk.' The search strategy is shown in the online supplementary material.

Study selection and data extraction

Titles, abstracts and full texts were screened independently by two investigators to assess suitability for inclusion in the final review according to the criteria defined above. Data were extracted for each study, including study setting and design, patient demographics, year of publication, country where the study was undertaken, methods used to diagnose CDI, and identified risk factors for CDI. For all studies, adjusted data were extracted where possible to calculate the OR. Disagreements in data extraction were resolved by consensus.

Outcomes assessment

This systematic review and meta-analysis focused on assessing risk factors associated with CDI in children. In the included studies, CDI was defined by symptoms (usually diarrhoea), a stool test positive for *C. difficile* toxins, the detection of toxigenic *C. difficile*, colonoscopy, or histopathological findings revealing pseudomembranous colitis. HA-CDI was defined as symptom onset within ≥48 h after hospital admission and <4 weeks after hospital discharge. CA-CDI was defined as disease in the community, symptom onset within <48 h of hospitalization in children without previous hospitalization, or symptom onset >12 weeks after hospital discharge. In addition, some studies defined CDI cases as patients with an International Classification of Diseases, Ninth Revision (ICD-9) diagnostic code of 008.45, which is considered the only code devoted to CDI, and it has been validated previously as an accurate determinant of actual disease.

Quality assessment

The quality of the observational studies (including cross-sectional, cohort and case–control) was assessed independently by two investigators using the Newcastle–Ottawa Scale (NOS). The NOS comprises three domains: selection (four questions), comparability (two questions), and outcome (cohort studies) or exposure (case–control studies) (three questions). The NOS assigns a maximum of four points for selection, two points for comparability (the study controlled for age or other confounding factors) and three points for exposure or outcome. Studies with a cumulative score >7 were considered to be high quality; scores of 5–7 and <5 were considered to indicate moderate quality and low quality, respectively. Any disagreements or discrepancies were resolved by consensus.

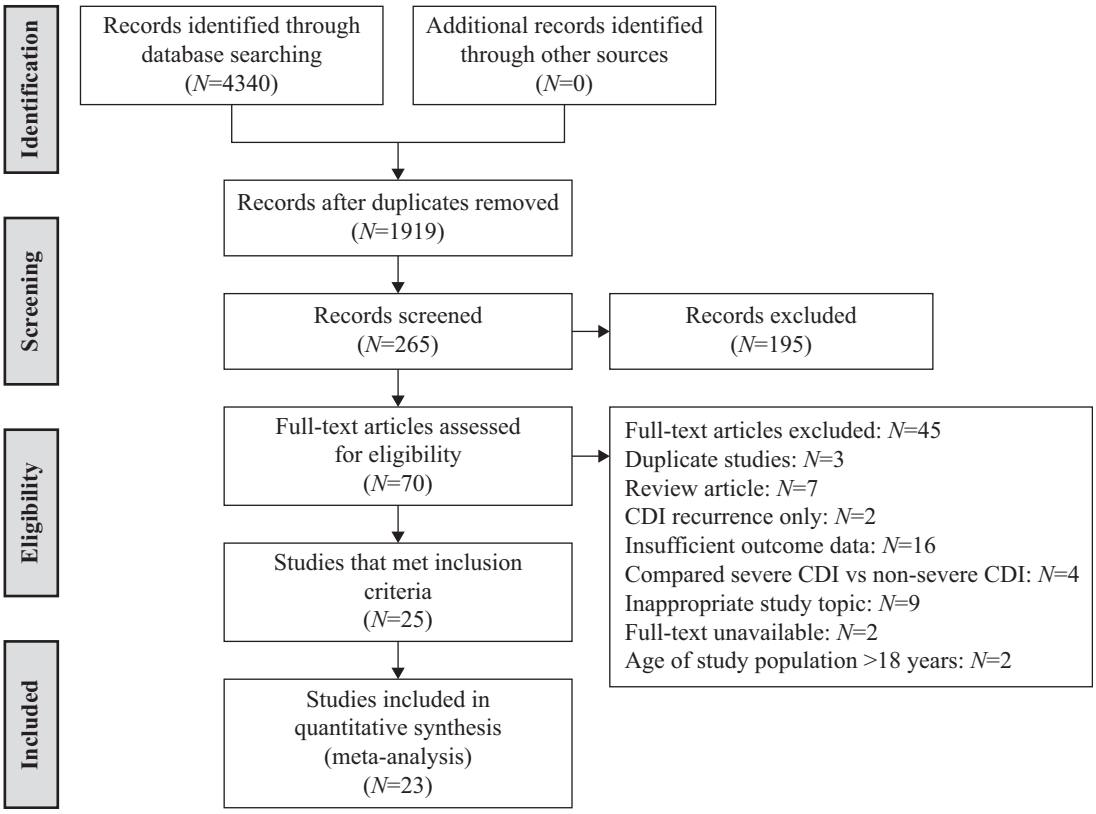

Figure 1. Flowchart of study selection according to PRISMA guidelines. CDI, *Clostridioides difficile* infection.

Statistical analysis

Statistical analysis was performed using STATA Version 14.0 (using the packages 'metan,' 'metafunnel,' 'metaninf' and 'metabias') to calculate the pooled effect size of studies that reported OR and 95% CI in multi-variate analyses. Considering the low disease frequency and prevalence of CDI in this population, any RR and HR with similar values were combined into the OR. The pooled OR and 95% CI was used to describe the relationship between various risk factors and CDI.

Heterogeneity was assessed by Cochran *Q* test and I^2 statistics. Significant heterogeneity was defined as $P<0.10$ or $I^2>75\%$, and moderate and low heterogeneity was defined as I^2 of 51–75% and <50%, respectively [17]. A random-effects model was used when $I^2>50\%$ or $P<0.10$. Otherwise, a fixed-effects model was applied. Potential causes of heterogeneity with stratification were explored by clinical and methodological features of the studies. This stratification included duration of antibiotic exposure, type of gastric acid suppressant (PPI or H2RA), study setting, study design, and CDI diagnostic assays. Secondary analyses considered the risk associated with cephalosporin subclasses. Given that seven and six meta-analyses were performed to assess the significance of prior antibiotic exposure and gastric acid suppressants, the Bonferroni corrected significance levels were 0.007 (=0.05/7) and 0.008 (=0.05/6), which provides a stringent approach for preventing false-positive findings. In contrast, for the analysis of publication bias and heterogeneity, an uncorrected significance level of 0.05 was used to ensure that any of these potential problems with the findings could be detected. Publication bias was assessed by generating funnel plots, and tested used Egger's asymmetry test.

Results

Characteristics and quality of studies

The search retrieved 4340 studies, of which 70 were selected for full-text review after screening by title and abstract. Forty-five studies were excluded (Figure 1). Twenty-five studies were included in the analysis [13,18–41], and their characteristics are shown in Table I.

HA-CDI, hospital-acquired *Clostridioides difficile* infection; CA-CDI, community-acquired *Clostridioides difficile* infection; PCR, polymerase chain reaction; GDH, glutamate dehydrogenase; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; RT-PCR, real-time PCR; qPCR, quantitative polymerase chain reaction; ICD-9, International Classification of Diseases, Ninth Revision; THIN, Health Improvement Network.

The studies were published from 2010 to 2020, and evaluated 10,844,084 participants, of whom 31,225 had CDI. Of the 25 included studies, nine were cohort studies [13,19,22,27–29,31,34,41], 14 were case–control studies [18,20,21,24–26,30,32,35–40] and two were cross-sectional studies [23,33]. Most studies (19/25) [18–23,25–27,29,30,32–35,37–39,41] used enzyme immunoassays or nucleic acid amplification assays to detect *C. difficile* toxins, four studies [13,24,28,36] used ICD-9 or other billing codes to screen CDI patients, and the remaining studies did not mention the testing

Table I
Characteristics of studies included in the meta-analysis

Study	Year	Study location	Study period	Study design	Route of acquisition	Setting	Sample size (*N*)	Age range (years)	Diagnostic test
Miranda-Katz *et al.* [18]	2020	USA	January 2012 —December 2016	Case—control	CA-CDI	Inpatients and outpatients	898	1—17	EIA, PCR (Toxin A/B); GDH
Zhao *et al.* [19]	2020	China	January 2011—January 2014	Retrospective cohort	-	Inpatients	197	1—15.6	PCR (Toxin A/B)
Mayer *et al.* [20]	2020	USA	January 2010—June 2013	Nested case—control	-	Inpatients	2586	0—18	EIA, PCR (Toxin A/B)
Weng *et al.* [21]	2019	USA	October 2014—February 2016	Case—control	CA-CDI	Outpatients	136	1—5	EIA, PCR (Toxin A/B)
Khalil *et al.* [22]	2019	Qatar	January 2015 —December 2015	Retrospective cohort	HA-CDI	Inpatients	200	2—14	RT-PCR (Toxin A/B)
Migriauli *et al.* [23]	2018	USA	May 2016 —December 2017	Cross-sectional	-	Inpatients	220	0—18	EIA, PCR (Toxin A/B)
Adams *et al.* [24]	2017	USA	2001—2013	Case—control	CA-CDI	Inpatients	5324	1—18	ICD-9 Code (008.45)
Daida *et al.* [25]	2017	Japan	July 2003 —September 2012	Case—control	HA-CDI	Inpatients	145	0—19	EIA (Toxin A/B)
Crews *et al.* [26]	2015	USA	January 2012—June 2013	Case—control	CA-CDI	Inpatients and outpatients	207	1—18	RT-PCR (Toxin A/B)
Santiago *et al.* [27]	2015	Spain	September 2010—October 2011	Retrospective cohort	-	Inpatients	250	0—15	Culture; PCR (Toxin A/B)
De Blank *et al.* [28]	2013	USA	1999—2011	Retrospective cohort	HA-CDI	Inpatients	33,095	1—18	ICD-9 Code (008.45)
Guo *et al.* [29]	2012	China	December 2010—March 2011	Cohort	HA-CDI	Inpatients	198	0—18	PCR (Toxin A/B)
TURCO *et al.* [30]	2010	Italy	June 2005—July 2009	Case—control	-	Inpatients	136	1—18	EIA (Toxin A/B)
Tai *et al.* [31]	2010	USA	2000, 2003, 2006	Retrospective cohort	-	Inpatients	297,461	0—18	-
Samady *et al.* [32]	2014	USA	June 2008—May 2010	Case—control	CA-CDI and HA-CDI	Inpatients	408	1—18	EIA (Toxin A/B)
Sathyendran *et al.* [33]	2014	New Zealand	November 2011—June 2012	Cross-sectional	CA-CDI and HA-CDI	Inpatients	320	0—15	EIA, PCR (Toxin A/B); GDH
Banaszkiewicz *et al.* [34]	2011	Poland	2007—2010	Retrospective cohort	-	Inpatients	134	0—18	EIA (Toxin A/B)
Nylund *et al.* [13]	2011	USA	1997, 2000, 2003, and 2006	Retrospective cohort	-	Inpatients	10,495,728	1—17	ICD-9 Code (008.45)
Brown *et al.* [35]	2015	USA	June 2008 —June 2012	Case—control	-	Inpatients	458	1—17	RT-qPCR (Toxin B)
Freedberg *et al.* [36]	2015	USA	1995—2014	Nested case—control	-	Inpatients	3850	0—17	THIN Code
Predrag *et al.* [37]	2018	Serbia	January 2012 —May 2017	Prospective case—control	CA-CDI	Outpatients and community	189	1—12	ELISA, RT-PCR (Toxin A/B)

(*continued on next page*)

Table I (*continued*)

Study	Year	Study location	Study period	Study design	Route of acquisition	Setting	Sample size (*N*)	Age range (years)	Diagnostic test
Karaaslan *et al.* [38]	2016	Turkey	January 2012–December 2014	Case–control	HA-CDI	Inpatients	986	0–18	EIA (Toxin A/B)
Jimenez *et al.* [39]	2015	USA	January 2005–December 2010	Case–control	CA-CDI and HA-CDI	Inpatients and outpatients	414	1–18	EIA (Toxin A/B)
Sandora *et al.* [40]	2011	USA	January and August 2008	Nested case–control	CA-CDI and HA-CDI	Inpatients and outpatients	333	1–18	Toxin A/B tests
Li *et al.* [41]	2015	China	June 2013–November 2013	Cohort	CA-CDI and HA-CDI	Inpatients	209	0–14	RT-PCR (Toxin A/B)

HA-CDI, hospital-acquired *Clostridioides difficile* infection; CA-CDI, community-acquired *Clostridioides difficile* infection; PCR, polymerase chain reaction; GDH, glutamate dehydrogenase; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; RT-PCR, real-time PCR; qPCR, quantitative polymerase chain reaction; ICD-9, International Classification of Diseases, Ninth Revision; THIN, Health Improvement Network.

method. The studies were conducted in China, the USA, Japan, Spain, Italy, New Zealand and other European countries. Seventeen studies [13,18,19,22,24,25,27,28,30,32,33,36–41] were of high quality and eight studies [20,21,23,26,29,31,34,35] were of moderate quality. Assessment of methodological quality is presented in Tables S2 and S3 (see online supplementary material).

Analysis of risk factors for CDI

Prior antibiotic exposure

Patients with prior antibiotic exposure had a significantly higher risk of developing CDI than patients without antibiotic exposure (OR 1.93, 95% CI 1.25–2.97; $P<0.001$) (Figure S1, see online supplementary material). However, there was high heterogeneity among these studies ($I^2=92.2\%$).

Meta-analysis of different classes of antibiotics showed that the risk of CDI was greatest with clindamycin (OR 13.92, 95% CI 2.84–68.26; $P=0.001$), followed by cephalosporins (OR 2.26, 95% CI 1.45–3.50; $P<0.001$) and amoxicillin-clavulanate (OR 1.93, 95% CI 1.20–3.12; $P=0.007$), and was lower for fluoroquinolones (OR 3.10, 95% CI 0.12–82.15; $P=0.499$) and penicillin (OR 0.42, 95% CI 0.03–5.14; $P=0.498$) (Figure S2, see online supplementary material). Furthermore, stratification by cephalosporin subclass revealed that third-generation cephalosporins (OR 3.83, 95% CI 1.32–11.12; $P=0.014$) had higher risk of CDI compared with first- (OR 2.11, 95% CI 1.35–3.30; $P=0.001$) and fourth-generation cephalosporins (OR 2.33, 95% CI 1.84–2.94; $P<0.001$). However, heterogeneity persisted, especially for third-generation cephalosporins ($I^2=94.5\%$) (Figure S3, see online supplementary material).

Given the significant heterogeneity in the meta-analyses of all included studies, subgroup analyses were performed to better understand the heterogeneity. The duration of antibiotic exposure varied between the studies (4–12 weeks), with lower heterogeneity when subgroup analysis was performed on studies with antibiotic exposure in the preceding 12 weeks (OR 2.12, 95% CI 1.64–2.76; $P<0.001$; $I^2=49.2\%$); this significant effect persisted after Bonferroni's correction was applied (Figure S4, see online supplementary material). Subgroup analysis based on study design, separating case–control and cross-sectional studies, showed that neither case–control study results (OR 1.70, 95% CI 0.99–2.93; $P=0.054$; $I^2=89.5\%$) nor cross-sectional study results (OR 1.89, 95% CI 0.60–5.93; $P=0.277$; $I^2=80.0\%$) were significant (Figure S5, see online supplementary material). Meta-analysis based on CDI diagnostic assays revealed increased risk of CDI among studies that used *C. difficile* toxin assays to detect CDI, with high heterogeneity between studies (OR 1.90, 95% CI 1.12–3.22; $P=0.017$; $I^2=91.6\%$), but this significant effect disappeared after Bonferroni's correction was applied (Figure S6, see online supplementary material). In addition, the study population was the most common source of heterogeneity. Subgroup analyses of the studies with patients from the inpatient setting only revealed increased risk of CDI after antibiotic use (OR 2.43; 95% CI 1.43–4.14; $P=0.001$; $I^2=91.3\%$); this association remained significant after Bonferroni's correction was applied (Figure S7, see online supplementary material).

Prolonged hospitalization

Three cohort studies [19,22,31] evaluated prolonged hospitalization as a risk factor for CDI. A meta-analysis of these studies using a fixed-effects model showed that patients with prolonged hospitalization had a significantly increased risk of CDI (OR 14.68, 95% CI 13.24–16.28; $P<0.001$). There was low heterogeneity among studies ($I^2=27.8\%$) (Figure S8, see online supplementary material).

History of hospitalization

The meta-analysis of three case–control studies [32,36,38] using a random-effects model demonstrated that patients with a history of hospitalization had a significantly increased risk of CDI compared with patients without a history of hospitalization (OR 3.67, 95% CI 1.91–7.06; $P<0.001$). There was moderate heterogeneity across the included studies ($I^2=58.7\%$) (Figure S9, see online supplementary material).

Gastric acid suppressants

The meta-analysis using a random-effects model demonstrated that patients receiving gastric acid suppressants had increased risk of developing CDI (OR 1.96, 95% CI 1.41–2.73; $P<0.001$). There was significant heterogeneity among the

studies, with an I^2 value of 85.5% (Figure S10, see online supplementary material).

Several studies included patients who received PPIs or H2RAs alone. This review separated studies using PPIs or H2RAs alone. Meta-analysis revealed increased risk of CDI with PPI use (OR 2.01, 95% CI 1.40–2.89; $P<0.001$; $I^2=79.9\%$), but not with H2RA use (OR 2.15, 95% CI 0.72–6.42; $P=0.171$; $I^2=85.2\%$) (Figure S11, see online supplementary material).

Subgroup analyses based on study design showed increased risk of CDI among patients receiving gastric acid suppressants in case–control studies (OR 2.78, 95% CI 1.68–4.62; $P<0.001$; $I^2=82.0\%$), but not in cohort studies (OR 1.01; 95% CI 0.53–1.91; $P=0.980$) (Figure S12, see online supplementary material). Subgroup analysis on the basis of the diagnostic assay used for CDI revealed increased risk of CDI among studies that used *C. difficile* toxin assay (OR 1.80, 95% CI 1.29–2.50; $P<0.001$; $I^2=65.8\%$) and ICD-9 or other billing codes (OR 2.45, 95% CI 1.19–5.07; $P=0.016$; $I^2=92.1\%$) to detect CDI (Figure S13, see online supplementary material). These significant effects (except for studies that used ICD-9 or other codes to detect CDI) persisted after Bonferroni's correction for multiple comparisons was applied.

Gender

Four studies reported data on gender as a risk factor for CDI [13,20,28,31]. Meta-analysis of the four included studies showed a significantly increased risk of CDI associated with male gender (OR 1.18, 95% CI 1.05–1.32; $P=0.005$). There was moderate heterogeneity between these studies ($I^2=69.0\%$) (Figure S14, see online supplementary material).

Comorbidities

Meta-analysis of comorbidities revealed that neoplastic disease (OR 3.40, 95% CI 2.85–4.07; $P<0.001$), immunodeficiency (OR 4.18; 95% CI 3.25–5.37; $P<0.001$), solid organ transplantation (OR 4.56, 95% CI 3.95–5.27; $P<0.001$) and enteral feeding (OR 2.21, 95% CI 1.05–4.62; $P=0.036$) were associated with increased risk of CDI, but inflammatory bowel disease (OR 3.54, 95% CI 0.36–35.10; $P=0.280$) and cardiac disease (OR 2.00, 95% CI 0.68–5.87; $P=0.206$) were not associated with increased risk of CDI. There was significant heterogeneity in enteral feeding ($I^2=76.1\%$) (Figure S15, see online supplementary material).

Other risk factors

The meta-analysis did not include other risk factors associated with CDI in children, including age, chemotherapy, race, immunosuppressive agents, white blood cell count and history of CDI, because each factor was only evaluated in a single study (Table S4, see online supplementary material).

Publication bias

Most of the risk factors in this study were evaluated by fewer than 10 studies. Thus, the results of antibiotic exposure and gastric acid suppressants alone were interpreted. Funnel plots and Egger's test showed little evidence of publication bias in studies on antibiotic exposure (except for gastric acid suppressants). Sensitivity analysis showed that the pooled effect of all risk factors did not change significantly after excluding any particular study, indicating that the results are stable and reliable (Figures S16–19 and Table S5, see online supplementary material).

Discussion

The present study analysed the association between various risk factors and CDI comprehensively and systematically. Antibiotic exposure, prolonged hospitalization, history of hospitalization, gastric acid suppressants, male gender and underlying comorbidities were associated with increased risk of CDI in children (Table II).

Table II
Summary of meta-regression analysis

Exposure	No. of studies	OR	95% CI	Heterogeneity, I^2, %	*P*-value	Model
Antibiotics	10	1.93	1.25–2.97	92.2	<0.0001	RAM
Amoxicillin-clavulanate	2	1.93	1.20–3.12	0.0	0.459	FEM
Cephalosporins	11	2.26	1.45–3.50	87.8	<0.0001	RAM
Clindamycin	3	13.92	2.84–68.26	79.6	0.007	RAM
Fluoroquinolones	2	3.10	0.12–82.15	96.7	<0.0001	RAM
Penicillin	2	0.42	0.03–5.14	95.4	<0.0001	RAM
Prolonged hospitalization	3	14.68	13.24–16.28	27.8	0.250	FEM
History of hospitalization	3	3.67	1.91–7.06	58.7	0.064	RAM
Gastric acid suppressants	11	1.96	1.41–2.73	85.5	<0.0001	RAM
PPI	7	2.01	1.40–2.89	79.9	<0.0001	RAM
H2RA	4	2.15	0.72–6.42	85.2	<0.0001	RAM
Male gender	4	1.18	1.05–1.32	69.0	0.022	RAM
Comorbidities						
Inflammatory bowel disease	2	3.54	0.36–35.10	99.9	<0.0001	RAM
Solid organ transplant	2	4.56	3.95–5.27	0.0	0.402	FEM
Neoplastic disease	4	3.40	2.85–4.07	69.8	0.019	RAM
Cardiac disease	2	2.00	0.68–5.87	62.5	0.103	RAM
Immunodeficiency	2	4.18	3.25–5.37	0.0	0.491	FEM
Enteral feeding	5	2.21	1.05–4.62	76.1	0.002	RAM

OR, odds ratio; CI, confidence interval; RAM, random-effects model; FEM, fixed-effects model; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist.

Exposure to antibiotics during childhood is an important determinant of long-term health, and antibiotic therapy can lead to CDI by changing the composition of the commensal gut microbiota, resulting in loss of microbiota diversity and colonization resistance, facilitating the proliferation of *C. difficile* [42—44]. These disruptions can persist and predispose to CDI for weeks to months after the interruption of antibiotic therapy [45]. The present review found that antibiotic exposure increased the risk of CDI significantly (OR 1.93). When subgroup analysis was performed by study setting, antibiotic use was shown to increase the risk of CDI in inpatients (OR 2.43). Similarly, Anjewierden *et al.* [14] found that the risk of CDI increased 2- to 3-fold in paediatric inpatients exposed to antibiotics. However, high heterogeneity was still detected, which may be related to patient characteristics and the duration and dose of antibiotic therapy. In addition, this review found that the risk of CDI remained significantly increased within 12 weeks after cessation of antibiotic therapy (OR 2.12), which is consistent with the study by Hensgens *et al.* [46]. In particular, Hensgens *et al.* found that the highest risk of CDI was during the first month after the interruption of antibiotic therapy, with more than 6-fold increased risk of CDI. However, in the present meta-analysis, only one study reported that the risk of CDI increased in the first month after the cessation of antibiotic therapy (OR 3.1); as such, the association of this period with risk of CDI could not be assessed by pooled effects. Nonetheless, these results were sufficient to suggest that the disruption of the gut microbiota by antibiotics is long term, and the risk of CDI is higher within 12 weeks of the cessation of antibiotic therapy.

Appropriate antibiotic use is critical for proper treatment and effective prevention of bacterial infections. The severe disruption of gut microbiota by clindamycin, fluoroquinolones and cephalosporins, and the low susceptibility of *C. difficile* to these classes of antibiotics, have been associated with high risk of CDI [47,48]. Previous meta-analyses showed that cephalosporins and clindamycin (broad-spectrum antibiotics) were more strongly associated with HA-CDI, whereas clindamycin, cephalosporins and quinolones were more strongly linked with CA-CDI [49—51]. In the present meta-analysis, overall antibiotic use was associated with a two-fold increased risk of CDI in children, but significant differences in risk associated with different antimicrobial classes were also detected, with clindamycin and cephalosporins (especially third-generation cephalosporins) associated with the greatest increase in risk. Although the primary meta-analysis showed a non-significant result, fluoroquinolones still need attention. Recent studies in the USA have revealed significant positive associations between the use of total, third- and fourth-generation cephalosporins, and fluoroquinolones and hospital-onset *Clostridioides difficile* infection (HO-CDI) rates. HO-CDI rates decreased when cephalosporins and fluoroquinolones were targeted to reduce use [52]. For other classes of antibiotics included in the assessment, such as non-steroidal anti-inflammatory drugs, tetracycline, macrolides and aminoglycosides, which significantly increased the risk of CDI, the present authors were unable to pool the data due to insufficient numbers of studies (Table S4, see online supplementary material). These results demonstrate that while antibiotics are necessary for treating bacterial infections, clinicians should be aware that these drugs may predispose children to CDI. Therefore, measures to optimize the appropriate use of these drugs in children are warranted.

The traditional risk factors for CDI include antibiotic therapy, hospitalization and older age (>65 years) [53]. In the present meta-analysis, prolonged hospitalization (OR 14.68) was associated with higher risk of CDI compared with previous hospitalization (OR 3.67). Human gut microbiota protects against colonization by *C. difficile* [54]. Changes in the gut microbiota caused by hospitalization or antibiotic exposure can increase susceptibility to CDI [55]. On the other hand, long-term hospitalization increases the risk of hospital-associated infections, including those caused by contact with patients with CDI [56]. Thus, isolation measures, hypochlorite-based disinfectants for environmental disinfection, and routine cleaning with germicidal bleach in paediatric wards with high rates of hospital-acquired infections can reduce the incidence of CDI.

PPIs and H2RAs are the most effective and prescribed medications for acid-related upper gastrointestinal diseases in outpatient and inpatient settings. *C. difficile* spores are acid-tolerant; thus, acid suppression is unlikely to impact spore survival directly. The increased risk of CDI may be mediated by the effect of pH changes on the diversity of the gut microbiota [57]. Although gastric acid suppression increases the risk of CDI, the risk was not significant after controlling for age, hospital stay, antibiotic exposure and comorbidities [58,59]. Nonetheless, the US Food and Drug Administration has reported that PPIs increase the risk of CDI. In this meta-analysis, the odds of CDI development following PPI therapy (OR 2.01) were similar to those after antibiotic therapy. However, there was significant heterogeneity between these studies. In addition, subgroup analyses based on the use of gastric acid suppressants (PPIs and H2RAs), case selection and study design did not identify sources of heterogeneity, possibly due to potential confounders, including comorbidities or concomitant antibiotic use. A meta-analysis of paediatric inpatients found that PPIs increased the risk of CDI 1.33-fold, and the discrepancy in the results may be due to differences in the study populations [14]. Notwithstanding, both studies demonstrated a direct association between acid-suppressive therapy and CDI. However, more research is needed to identify the most effective acid-suppressive therapy for patients with CDI or at risk of CDI.

Previous studies have found that the existence of underlying comorbidities is associated with poor prognosis in patients with CDI, including gastrointestinal diseases such as inflammatory bowel disease and liver cirrhosis, as well as congestive heart disease, chronic pulmonary disease and renal failure [60—62]. Chemotherapy for neoplastic diseases (malignancies or cancers) is another risk factor for CDI, mediated in part by the antibiotic activity of chemotherapeutic agents, but may also be associated with the immunosuppressive effects of neutropenia [63]. Among the comorbidities examined in this meta-analysis, neoplastic disease, immunodeficiency, solid organ transplantation and enteral feeding were associated with increased risk of CDI. Evidence suggests that *C. difficile* is the most common recognized cause of bacterial diarrhoea in patients infected with human immunodeficiency virus who are at increased risk for CDI due to immunosuppression, antibiotics or exposure to healthcare facilities [64]. On the other hand, enteral feeding increased the risk of CDI 2.21-fold, which might be related to the contamination of healthcare workers' hands with *C. difficile* spores, bacterial contamination in enteral feeding systems, or increased colonic pH due to lack of fibre in enteral formulas [65,66]. Hence, clinicians should pay more

attention to high-risk groups with the above-mentioned comorbidities to minimize the incidence of CDI.

Notably, early life is a critical period in which the gut microbiota impacts health status [67,68]. The gut of children aged <12 months appears to be resistant to the effects of *C. difficile* toxins A and B, and rarely develops infections. Potential mechanisms for disease resistance in neonates include the absence of toxin receptors, downstream signalling pathways in the immature intestinal mucosa, and protective factors in breast milk and gut microbiota [69]. However, the protective effect was reduced significantly after 12—24 months of life, when the gut microbiota was unstable and less resilient to changes than the adult gut microbiota. The ecosystem develops in alpha diversity until around 3—5 years of age, where stable adult-like microbiomes have been established [69—71]. Studies have shown that the incidence of CDI in paediatric inpatients varies greatly with age, and the incidence of CDI was lowest for newborns (0.5/10,000), the incidence of CDI in children aged <1 year who were not newborns (32.01/10,000) was similar to that for children aged 5—9 years (35.27/10,000), and the incidence of CDI in children aged 1—4 years (44.87/10,000) was the highest [72,73]. When reviewing the studies included in this meta-analysis, children aged 1—4 years were found to account for approximately 40% of all children with CDI (ages 1—18 years) in the studies by Zhao *et al.* [19], De Blank *et al.* [28], Samady *et al.* [32] and Jimenez *et al.* [39]. Unfortunately, the study did not further investigate whether there were differences in risk factors among children in this age group compared with children in other age groups. In addition, the included studies did not establish uniform age grouping criteria, and some studies did not distinguish between newborns and children. Secondly, these studies did not compare and analyse the risk factors of children in different age groups, so the present authors were unable to obtain specific factors for younger age groups. Considering the uniqueness of children's physiology at different ages [74—76], it is hoped that future studies can conduct more detailed grouping and analysis according to children's age in order to provide a theoretical basis for accurate prevention and control of CDI.

This meta-analysis had several strengths. First, it was a comprehensive and detailed assessment of risk factors associated with CDI in children, and subgroup analysis based on study design, study setting, case selection, time interval after the interruption of antibiotic exposure, and type of gastric acid suppressants. Second, the study included a comprehensive literature review, and the cohort was larger than that of previous meta-analyses to provide an evidence base for the prevention and control of CDI in children.

Several limitations were also observed in this systematic review. First, there was high variability in study design, patient population, and confounder adjustment methods, which was a major source of heterogeneity. Second, the dosage and number of antibiotics are risk factors for CDI [77], but only a few studies evaluated a sufficient number of confounding factors, leading to high heterogeneity. Third, different enzyme immunoassays were used across studies to diagnose CDI. While most toxin enzyme immunoassays have excellent specificity, their sensitivity varies from 40% to 100%, and some toxin enzyme immunoassays have low positive and negative predictive values in diagnosing CDI [78,79], leading to misdiagnosis.

In conclusion, this systematic review and meta-analysis showed that antibiotic therapy, prolonged hospitalization, history of hospitalization, gastric acid suppressants, male gender and comorbidities increased the risk of CDI in children significantly. Thus, clinicians should be more aware of CDI, monitor susceptible and high-risk patients, and perform effective interventions. In addition, other potential risk factors need to be evaluated to improve clinicians' awareness of CDI and its risk factors to prevent CDI and associated diarrhoea in children.

Author contributions

N. Dong and Z.R. Li conceived the study and drafted the manuscript. J.H. Zhao, C.X. Qiang, J. Yang, Y.N. Niu, W.G. Wang, Y.L. Zhang, M. Zhao and J.Y.R. Li critically revised the manuscript for important intellectual content. X.R. Niu, X.X. Liu and Z.R. Ouyang collected data. N. Dong, P. Qin and B.J. Wen performed the statistical analysis. All authors read and approved the final version.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2022.09.004.

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