



IS THE ANTIMICROBIAL RESISTANCE OF ESCHERICHIA COLI PATHOGEN IN CHILDREN WITH DIARRHEAL INFECTION STILL A CONCERN IN INDONESIA? : AN UPDATED REVIEW

Omnia Amir Osman Abdelrazig^{1*}, Fadilah Fadilah^{2,3}, Badriul Hegar⁴, Yulia Rosa Saharman⁵

¹Master's Program In Biomedical Sciences, Faculty of Medicine, University of Indonesia, DKI Jakarta, Indonesia 10430

²Department of Medical Chemistry, Faculty of Medicine, University of Indonesia, DKI Jakarta, Indonesia 10430

³Bioinformatics Core Facilities, Indonesian Medical Education And Research Institute, Faculty of Medicine, University of Indonesia, DKI Jakarta, Indonesia 10430

⁴Department of Child Health, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital DKI Jakarta, Indonesia 10430

⁵Department of Microbiology, Faculty of Medicine, University of Indonesia, DKI Jakarta, Indonesia 10430

Childhood diarrhea is increasing in developing countries like Indonesia, affecting 6.7% of children under five largely due to *Escherichia coli*. **Method:** This review aims to provide an updated review on the latest information on childhood diarrhea in Indonesia and *Escherichia coli* antibiotic resistance from recent research sources till June 2023 from databases like PubMed, Scopus, and Google Scholar using specific search terms such as diarrhea, children, Morbidity, mortality, Indonesia, *Escherichia Coli*, and Antibiotic Resistance. It includes articles from nationally and internationally accredited peer-reviewed health journals in both English and Indonesian. **Results:** Based on the studies we reviewed, it has been proven that under-five diarrhea is the most common cause of death in children in Indonesia. Our literature analysis also revealed a potential link between gender and the occurrence of diarrhea in children. Furthermore, our analysis identified risk factors, including contaminated water, inadequate sanitation, poor hygiene and suboptimal food hygiene practices as the primary causes of childhood diarrhea in Indonesia. Conversely, other studies reviewed in this paper reveal that *E. coli* is the most common pathogen responsible for childhood diarrhea in Indonesia. Our study evaluation further reveals that *Escherichia coli* exhibits a high resistance rate, possibly due to the widespread misuse of antibiotics in the country. **Conclusion:** Indonesia's under-five diarrhea is a leading cause of child mortality, with multiple risk factors including sanitation and *Escherichia coli* Pathogen. Furthermore, the antimicrobial resistance situation in the country has deteriorated

Keywords: Antimicrobial Resistance; Children; Diarrhea; *Escherichia Coli*; Indonesia

INTRODUCTION

The burden of gastrointestinal disease is disproportionately high in developing countries. Significant morbidity and mortality are caused in particular by infectious diseases.¹ According to data provided by the World Health Organization (WHO), diarrhea was

responsible for 8.8% of deaths among children under the age of five in the year 2016. Through new approaches, gastroenterology practice is continuously updated and enhanced.² However, the diagnostic and therapeutic improvements that are common in the West have not yet been applied in many developing countries including Indonesia. According to the Indonesian

National Basic Health Research, the prevalence of diarrhea in Indonesia decreased significantly from 12.3% in 2013 to 6.2% in 2018. Despite this improvement, diarrhea remains the second leading cause of death among young children under the age of five, following pneumonia.³

Nevertheless, the rate of diarrheal illnesses in Indonesia among children under the age of five years old based on diagnosis and symptoms is still a concerning issue resulting in a high mortality and morbidity rate with the largest number of cases occurring in those between the ages of twelve to twenty-three months old.⁴ Diarrhea can be brought on by a number of factors including infections, malnutrition, contaminated water and food, and other factors. There are numerous pathogens including bacteria and viruses, that can cause diarrhea. However, Nearly 88% of deaths from diarrhea are consequences of unsafe drinking water, poor sanitation, and poor hygiene.⁵ These circumstances facilitate the spread of bacteria that cause diarrhea from one person to another.

Enteric pathogenic bacteria that cause diarrhea, such as *Escherichia coli*, *Salmonella*, *Shigella*, and *Vibrio* continue to be a serious public health concern in developing nations like Indonesia. Although *Salmonella* infections are usually self-limiting, meaning the patient recovers after some time without special care in some cases and certain conditions the illness can still be severe and even deadly, necessitating the use of antibiotics.⁶ High fatality rates have been observed in cases of *Escherichia coli* infections, and diarrhea has also been linked to malnutrition and growth problems in children. *E. Coli* is linked to bad hygiene, lack of resources, and crowded living.⁷

The antibiotic sensitivity patterns of *Escherichia coli* species have changed during the past few decades. These bacteria gradually demonstrate resistance to several antibiotics, mainly those used to treat diarrhea such as ampicillin, tetracycline, and trimethoprim-sulfamethoxazole. Due to the unregulated use of antibiotics increase in recent years, antimicrobial resistance has emerged as a global issue.⁸ Apart from antibiotics used for treating illnesses, there are other factors that play a role in the rise of antibacterial resistance which includes the quality of antibiotic

production, environmental changes, and the use of antibiotics in agriculture and livestock farming.⁹

The initial section of this literature review will focus on recent developments linked to childhood diarrhea in Indonesian children. The subsequent segment of this review will center on the current status of widespread antibiotic resistance observed in *Escherichia coli* in Indonesia and the strategies used for its control and management.

Methodology

MATERIALS

This literature review used published research articles and official reports that were searched from databases such as PubMed, Web of Sciences, Scopus, and Google Scholar prioritizing researches that has recently been published until the end of June 2023 to write this manuscript. The leading search terms were “diarrhea, infectious disease, children or pediatric, Morbidity, Mortality, Risk factors, Indonesia, Bacteria, *Escherichia Coli*, Enteric pathogenic bacteria, Antibiotics, Antibiotic Resistance, surveillance of Antibiotic Resistance.” We conducted a comprehensive search for scholarly documents using relevant keywords in the titles. These documents focused on childhood diarrhea in Indonesia and the antibiotic resistance of *Escherichia coli*. Our search yielded a total of 21 peer-reviewed journal articles, eight official reports, and two theses. To enhance the comprehensiveness of our review, we incorporated additional elements such as tables, charts, and graphs during the evaluation of these primary sources. Our inclusion criteria encompassed both quantitative and qualitative studies, published in English and Indonesian, and sourced from nationally and internationally recognized peer-reviewed health journals. Studies including comments and editorials that did not provide relevant outcomes of interest were excluded from our literature review. All 21 articles were documented in a matrix that encompassed details such as authors, study titles and journals, study type, study country, study design, study population, and sample sizes (See Table 1).

Table 1: Summary of the reviewed studies.

Authors	Study Title and Journal	Country	Study Type	Study Design	Study Population	Sample Size
Amanda L., Utami K. N. et. al. 2022	Characteristics of Pediatric Patients with Diarrhea in Indonesia: A Laboratory-based Report	Indonesia	Quantitative Study	Retrospective Study	Children Under Two Years Old	1031
Ghosh, Koustav. et. al. 2021	Prevalence of diarrhoea among under five children in India and its contextual determinants: A geo-spatial analysis	India	Quantitative Study	A Geo-Spatial Analysis	Children	-
Aziz, Fazly Azry Abdul. et. al. 2018	Prevalence of and factors associated with diarrhoeal diseases among children under five in Malaysia: a cross-sectional study.	Malaysia	Quantitative Study	Cross-Sectional Study	Children	15,188
N.Puspandari. et. al. 2021	Enteric pathogen among children under five years old with diarrheal diseases in Indonesia	Indonesia	Quantitative Study	Retrospective Study	Children Aged 1 Month To 5 Years Old, With Diarrhea	2626
Enny Suswati, et. al. 2023	Prevalence of multidrug-resistant Escherichia coli isolated from Jember hospital food handler in Indonesia	Indonesia	Quantitative Study	Cross-Sectional	Food Handlers	68
AD Khosravi. et. al. 2016	Prevalence of Escherichia coli O157:H7 in Children with Bloody Diarrhea Referring to Abuzar Teaching Hospital, Ahvaz, Iran	Iran	Quantitative Study	Experimental Study	Diarrheal Stool Samples Of Children	137

Table 1: Continued.

F.Syahrul-et . al. 2020	Transmission Media of Foodborne Diseases as an Index Prediction of Diarrheagenic Escherichia coli: Study at Elementary School, Surabaya Indonesia	Indonesia	Quantitative Study	Observational Analytic Approach	Elementary School-Aged Children	218
ML Chau· et. al. 2019	Survey Of Pathogens In Pediatric Diarrhea Patients Attending A Women's And Children's Hospital In Singapore	Singapore	Quantitative Study	Respective Study	Residual Fecal Samples From Women And Children	200
Siahaan, Selma. et. al. 2022	Antimicrobial Resistance Situation in Indonesia: A Challenge of Multisector and Global Coordination	Indonesia	Quantitative Study	Purposive Study	Informants From The Health And Other Sectors And Hospital Patients	56
Oliveira, Patrícia Luciana de. et. al. 2017	Antimicrobial susceptibility profile of enterotoxigenic and enteropathogenic Escherichia coli isolates obtained from fecal specimens of children with acute diarrhea	Brazil	Quantitative Study	Observational Analytical Study	Children With Acute Diarrhea	98
Sulis, Giorgia. et. al. 2020	Antibiotic prescription practices in primary care in low- and middle-income countries	Chile	Quantitative Study	Descriptive Study	Major Private And Public Hospitals And A Nationally Representative Household	41
Fahima Chowdhury. et. al. 2015	Diarrheal Illness and Healthcare Seeking Behavior among a Population at High Risk for Diarrhea in Dhaka, Bangladesh	Bangladesh	Quantitative Study	cross-sectional	A total of 316,766 individuals in 79,438 households Among these individuals, 32,692 were under five years of age	316,766

Table 1: Continued.

Anders, Katherine L. et. al. 2015	The epidemiology and aetiology of diarrhoeal disease in infancy in southern Vietnam: a birth cohort study	Vietnam	Quantitative Study	Prospective Cohort Study	Children	6706
Getu Debalkie Demissie, et. al. 2021	Diarrhea and associated factors among under five children in sub-Saharan Africa: Evidence from demographic and health surveys of 34 sub-Saharan countries	Mozambique	Quantitative Study	Cross-sectional	under-five children	330,866
Sana Eybpoosh, et. al. 2021	Frequency of five <i>Escherichia Coli</i> pathotypes in Iranian adults and children with acute diarrhea	Iran	Quantitative Study	Cross-sectional	Iranian nationals who were residents of target provinces of Iran and referred to health centers with a chief complaint of acute diarrhea	1,306

Analysis

Our analysis of the documents was conducted utilizing the qualitative data analysis software Atlas. ti 9, developed by Atlas.ti Scientific Software Development GmbH in 2020. We used a series of codes including “childhood,” “diarrhea,” “Indonesia,” “epidemiology,” “vaccination,” “Risk factors,” “Prevention and Protection,” “Pathogenic,” “Antibiotic Usage,” “Antimicrobial Resistance,” and “Antimicrobial Resistance-control” to categorize and organize the information within the documents. Subsequently, we synthesized the data into a coherent text, supplementing it with insights from other sources in the literature to ensure the text's consistency and comprehensiveness.

RESULTS AND DISCUSSION

Results

Five different research studies have consistently highlighted that diarrhea among children under the age of five is a leading cause

of mortality, particularly in Indonesia, where children in this age group experience the highest incidence of diarrhea, with a significant rate of 6.7%. Additionally, four reviewed studies delved into the relationship between gender and the prevalence of childhood diarrhea. Out of these, three studies found that young males (those under five years old) had a notably higher likelihood of experiencing diarrhea compared to their female counterparts, while one study found no significant gender difference in the occurrence of diarrhea among young children. Furthermore, we reviewed five studies that explored the various risk factors associated with childhood diarrhea, shedding light on its substantial prevalence in economically disadvantaged regions. This prevalence was attributed not only to environmental factors such as contaminated water, inadequate sanitation, and poor hygiene practices affecting both children and mothers but also to suboptimal food hygiene practices. Additionally, the research underscored the significant role of breastfeeding and a child's lower immunity inherited from their mother in increasing the susceptibility to diarrhea in

children. In terms of the causative agent, we reviewed eight studies that consistently identified *E. coli*, particularly enterotoxigenic *Escherichia coli* (ETEC) and Diarrheagenic *E. coli* (DEC), as the most frequently isolated pathogens responsible for childhood diarrhea.

Moreover, we analyzed five studies that scrutinized the use of antibiotics and the issue of antibiotic resistance in the context of childhood diarrhea. These studies revealed that Amoxicillin and ampicillin were the most commonly prescribed antibiotics for children in Indonesia. Official national reports and two additional studies that we reviewed examined the prevalence of antibiotic resistance in *E. coli*, revealing a significant resistance pattern, particularly with ampicillin. Furthermore, children were found to harbor more antibiotic-resistant *Escherichia coli* strains than adults, indicating a concerning trend in antibiotic resistance among young individuals. In sum, we reviewed a comprehensive analysis of multiple studies that underscores the gravity of childhood diarrhea in Indonesia, emphasizing its link to various factors including gender, socioeconomic conditions, hygiene practices, breastfeeding, and antibiotic resistance, with a consistent focus on the role of *E. coli* as a causative agent.

Discussion

Childhood Diarrhea in Indonesia

Diarrheal diseases represent the second most substantial factor contributing to illness and mortality among children under the age of five, ranking as the second leading cause of infant death in developing nations.¹⁰ This condition tragically claims the lives of up to 525,000 children under the age of five. Every year, up to 1.7 billion children worldwide suffer from diarrhea. As of 2020 statistics, diarrhea stands as a prominent cause of mortality in Indonesian children aged 12-59 months, accounting for 4.55% of deaths. Other contributing factors to child mortality encompass pneumonia, congenital heart defects, traffic accidents, drowning, parasitic infections, and additional factors. Referring to the 2018 Indonesian Basic Health Research (Risksedas), the highest prevalence of diarrhea occurred among children aged 1-4 years, reaching 12.8%, followed by those below the age of 1 year, with a prevalence of 10.6%.¹¹

These rates were determined through diagnoses made by healthcare professionals, such as doctors, nurses, or midwives, or based on reported symptoms.

Gastroenteritis in children in Indonesia has various potential causes such as bacterial infections, often stemming from contaminated food and water sources, which are a common culprit, with pathogens like *Escherichia coli* (*E. coli*), *Salmonella*, and *Shigella* contributing to the illness. Viral infections, such as rotavirus, norovirus, and adenovirus, can spread easily through person-to-person contact or contaminated surfaces. Parasitic infections, notably *Giardia* and *Cryptosporidium*, can result from ingestion of contaminated water or food. Inadequate hygiene, a lack of clean drinking water, improper food storage, close contact with infected individuals, and malnutrition also increase the risk of gastroenteritis.¹² Travel-related infections can also play a role, particularly when children are exposed to new environments. Preventing gastroenteritis in children involves promoting good hygiene practices, ensuring access to safe drinking water, advocating proper food handling and storage, and timely vaccination against rotavirus when available.¹³

However, rotavirus infection remains the most prevalent cause of gastroenteritis in children under the age of five in Indonesia. While the rate of rotavirus infection is reduced in Western nations with the availability of rotavirus vaccines, this is not the case in Indonesia.¹⁴ Several studies conducted in Indonesia revealed a persistent rotavirus epidemic in 2018 and a high prevalence of rotavirus recognition among children with diarrhea, reaching 74.3%.¹⁵ Despite the fact that rotavirus infection is a condition that can potentially be prevented by vaccines, immunization is not a mandated program in Indonesia, which may explain this situation of high rates of rotaviruses.¹⁶

Epidemiology of Childhood Diarrhea In Indonesia

In accordance with the United Nations Children's Fund (UNICEF), the under-five mortality rate in Indonesia was 25.4 per 1000 live births in 2017. The number of diarrhoea cases in health facilities has grown from 6,897,463 to 7,077, 299 in 2016. In 2016, the diagnosis rate of diarrhea was 2,544,084 cases,

representing 36.9% of cases, and this **Fig.** increased to 4,274,790 cases, accounting for 60.4% in 2017.¹⁷ We have also noted comparable patterns and trends that have been observed in other developing countries like Thailand. Over the past decade, Thailand has experienced a slight increase in the annual incidence of acute diarrhea among children aged 0–5 years, rising from approximately 33.79 cases per year between 2015 and 2019. Despite this increase in incidence, diarrhea-related mortality in Thailand has remained low and relatively stable, ranging from 0.71 to 1.16 deaths per 100,000 population per year.¹⁸

This outcome could potentially explain why in Thailand, there is a lower rate of fatalities from diarrheal diseases. This parallels the factors influencing a reduced incidence rate. Firstly, the introduction of national insurance, particularly the UC scheme in 2002, which provides coverage for nearly the entire Thai population, stands as the primary factor. Secondly, the availability of easily accessible oral rehydration therapies (ORS) and enhancements in Water, Sanitation, and Hygiene (WASH) initiatives also play a significant role. Lastly, the introduction of the Rotavirus (RV) vaccine as an optional measure in 2012 rounds out the trio of factors that may have positively influenced the occurrence and mortality rates among Thai children.^{18,19}

We reviewed some data submitted to the Indonesian Directorate of Health via komdat.kesga.kemkes.go.id which showed that in 2019, 20,244 (or 69%) of the 29,322 under-five fatalities occurred during the newborn period. In contrast, 2,927 fatalities (10%) and 6,151 deaths (21%) occurred between the ages of 12 and 59 months.²⁰ We encountered comparable data from the Manhiça district in southern Mozambique, a model for a sub-Saharan African nation with limited resources, confirms diarrheal diseases as the third most common reason for hospital admission for children aged ≤ 14 months and the fourth most common reason for death for children aged 12 to 59 months.²¹ These findings help shed light on the seriousness of childhood diarrhea rates, which can be attributed to various risk factors, including limited access to clean drinking water, inadequate sanitation facilities, and suboptimal hygiene practices.

As one of the most relevant illnesses in Yogyakarta, diarrhea affected 66,698 people, or 82.8% of children, of whom 28.3% were under the age of five.²² Our review analysis also revealed that in an investigation at Cipto Mangunkusumo Hospital boys, in particular, had a greater frequency of diarrhea than girls did. It resembles another research that we analyzed which was carried out in a hospital in Yogyakarta, Indonesia where 60% of diarrhea patients at Munimbili National Hospital were boys between the ages of 7 and 12 months.²³ These findings align with another study we examined, conducted by Fahima Chowdhury et. Al in Bangladesh, where the occurrence of diarrhea was 16 cases per 1000 individuals across all age groups, with young children representing 44 cases per 1000. Notably, there was a significant difference ($p=.003$) in diarrhea prevalence between younger males (<5 years) and younger females, favoring males.²⁴ These findings could conclude and provide backing for the idea that cultural beliefs, which prioritize boys, result in differential treatment favoring boys, potentially leading to quicker diagnosis and treatment. Additionally, they lend support to the biological hypothesis, which suggests the presence of physiological sex-related distinctions that might increase boys' vulnerability to acute diarrhea. Nonetheless, these results are comparable with another study we reviewed, conducted by Fazly Azry Abdul et. Al in 2018. This research found that there was no gender disparity in the prevalence of diarrhea among children under five in Malaysia, with a rate of 4.4% (95% CI = 3.8–5.2).²⁵

In the low socioeconomic urban areas of East Jakarta, where hygiene and sanitation facilities are limited, mothers and children often develop poor hygiene habits, such as feeding their children with dirty utensils.²⁶ As much as 70% of diarrhea cases can be attributed to the consumption of water and food contaminated with harmful bacteria. Beyond the impact of inadequate hygiene practices, it has been suggested by previous research that the prevalence of diarrhea and malnutrition among children is notably high in economically disadvantaged areas like East Jakarta.²⁷ This elevated prevalence is not solely a result of exposure to environmental factors that

contribute to diarrhea, such as contaminated water, inadequate sanitation, and poor hygiene. It is also exacerbated by suboptimal food hygiene practices and food preparation methods (see Fig. 1).²⁸ This corresponds to another study we examined, which was conducted in rural southern Vietnam. This research revealed that there were over 115 instances of diarrhea per 1000 child-years among children under the age of five.²⁹ These results can be attributed to the prevalence of weaning foods for young children that are prepared in unsanitary conditions, often leading to contamination by pathogens. Such contamination serves as a significant factor contributing to the transmission of diarrhea.

However, we analyzed another research conducted in India which yielded parallel findings, indicating that children under the age of five face a higher likelihood of experiencing diarrhea in rural settings, particularly when residing in a non-permanent or less sturdy housing, when utilizing substandard sanitation facilities, when coming from disadvantaged socio-economic backgrounds, when their

mothers are younger (under 25 years old), and when living in households classified as “poor” based on the wealth index.³⁰ These findings help clarify why the lack of fundamental sanitation facilities within low socio-economic families can result in subpar food hygiene and sanitation practices within households. This connection arises from the known association between aspects like water supply, the source of drinking water, and overall household and environmental hygiene with the risk of food- or water-borne disease transmission. Moreover, the educational attainment of household members may also play a role in their decision to opt for treatment, as households with higher levels of education might possess greater health knowledge and a better understanding of the significance of sanitation in preventing diarrhea. Additionally, the presence of village infrastructure, such as health and sanitation committees, can offer valuable health-related support and serve as a motivating factor for households to construct toilets within their homes.

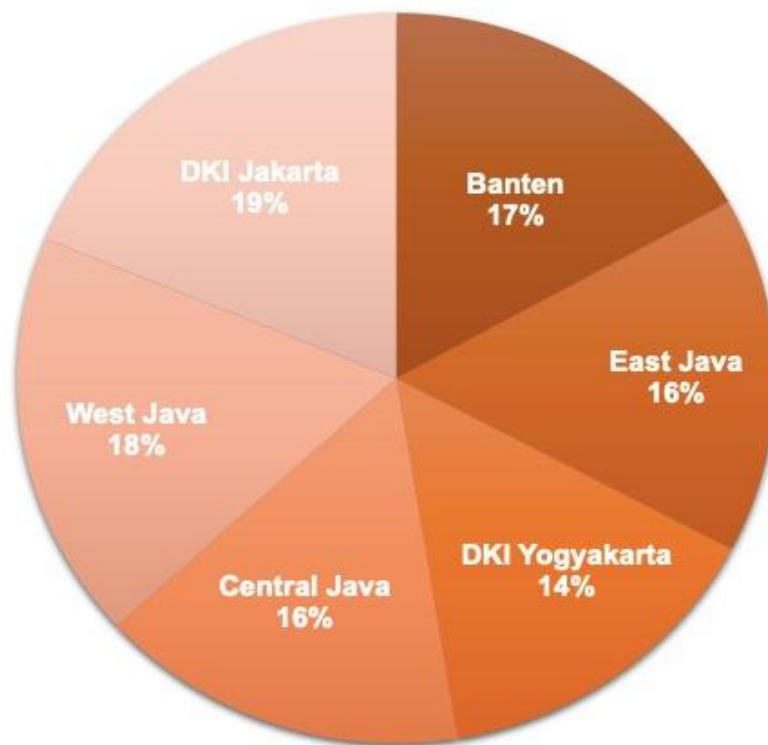


Fig. 1: Diarrheal cases among children in Java Province as per the Riskesdas (Indonesian basic health research) Raw Data ³⁵

It was also documented that diarrhea affects 16.8% of children under the age of five in Central Indonesia, with the highest rate occurring in West Nusa Tenggara (17.75%). Based on the results of the multivariate test, several factors were found to be associated with diarrhea. Specifically, home waste management (p-value: 0.017), gender (p-value: 0.003), and age (p-value: 0.001) demonstrated statistically significant relationships with diarrhea incidence.³¹ Upon further analysis, we found that the occurrence of diarrhea in children in Central Indonesia is primarily influenced by age, with an odds ratio of 2.421 (95% CI = 1.739-3.370).³² This indicates that children between the ages of 6 and 23 months have a 2.4 times higher likelihood of developing diarrhea compared to other age groups.³³ This is a result of the child's lower immunity from the mother, greater growth and development, and the beginning of weaning at that age. This information can be compared to another study we scrutinized which was carried out in Brazil by Strina A, et al, according to the study, there is evidence that currently breastfeeding is substantially linked to a 49% increased risk of getting diarrhea in children. Lack of breastfeeding has a significant Population-attributable fraction (PAF) (17%) for every individual.³⁴ These findings could substantiate the well-established notion that breast milk offers optimal nutrition for infant growth and development, along with protective benefits against various infections and potentially preventing infant mortality. Consequently, breastfeeding is known to provide significant advantages both in the short term and over the long term during childhood. It diminishes the likelihood of morbidity, mortality, and the need for hospitalization due to conditions such as diarrhea.

Prevention and Protection Strategy of Childhood Diarrhea In Indonesia

Reducing the morbidity of diarrheal disease is a long-term process that necessitates significant financial support for initiatives including increased socio-economic harmony, better environmental sanitation, especially adequate water supply, personal hygiene improvement through health education, promotion of prolonged breastfeeding, better nutrition, etc (see Fig. 2). We reviewed a

national study conducted by Djohan Kurnia et. Al, which unveiled that in an observed region in Ujung Pandang, South Sulawesi improvements of the environmental sanitation resulted in a drop in the prevalence of diarrhea by 53.4% after twelve months and by 57% after 24 months whereas in the control area, the drop was only 12.9% after twelve months and 23.4% after 24 months.³⁶ This data is comparable with the research findings we reviewed from Santosh Kumar et. Al report in India where it was found that households with a source of adequate sanitation had lower incidences of childhood diarrhea.³⁷ Having access to better sanitation prevents around 0.8 cases of diarrhea per home per year. It can hardly seem like much of an improvement to observe 0.8 cases per household year. From a public health standpoint, this is a non-negligible improvement considering that diarrhea is the second most common cause of mortality and that there are typically 3.1 cases per child-year (or 3.9 cases per household year) of the condition.³⁷ These findings may be attributed to the presence of disparities in sanitation access within villages, implying that certain household characteristics could be associated with the household's choice to have access to sanitation facilities. However, the initial stage in controlling diarrheal disease in Indonesia has been focused on decreasing the length of the illness and the case fatality rate through treatments. According to the Indonesian health ministry plan the rotavirus vaccine will be incorporated into Indonesia's regular immunization regimen in 2023.³⁸

In the context of a phase III clinical trial, Bio Farma in Indonesia and Murdoch Children's Research Institute in Australia are currently evaluating a promising rotavirus vaccine known as RV3-BB. Nevertheless, for the successful implementation of this vaccine within the nation, critical financial assessments, such as a cost-effectiveness analysis, are imperative.^{38 39} One vital element required for conducting these studies is accurate costing data related to the treatment of diarrhea. Regrettably, at present, Indonesia lacks sufficient data on the cost estimates associated with managing diarrheal cases.³⁸

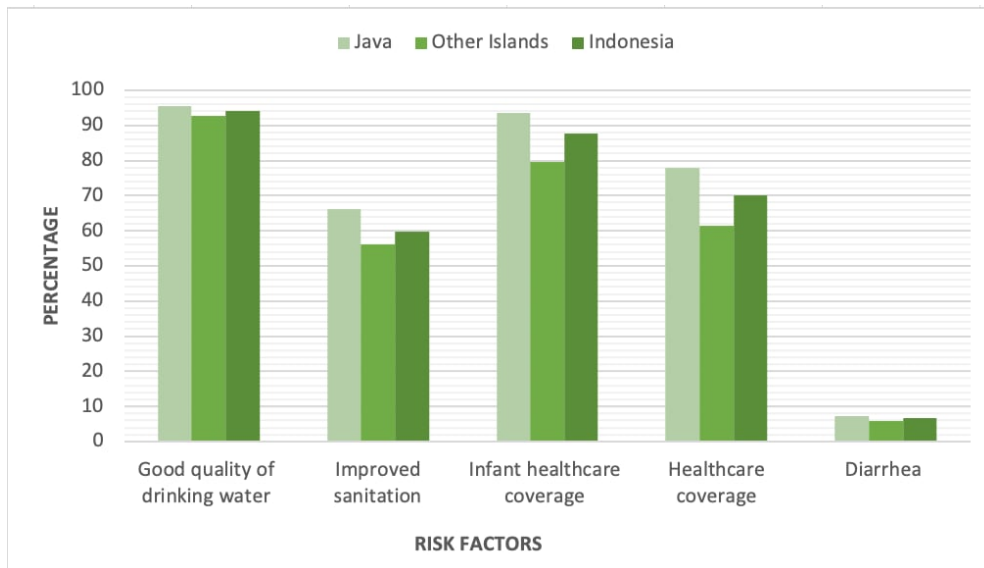


Fig. 2: Childhood diarrhea Incidence Rate post-improvement of its risk factors according to Riskesdas (Indonesian basic health research).³⁵

Pathogenic Microorganisms of childhood diarrhea in Indonesia

Vibrio cholerae, *Escherichia coli*, *Salmonella* sp., *Clostridium difficile* and *Shigella* sp. Are among the bacteria that can cause diarrhea in children in Indonesia. Rotavirus, Norovirus (Calicivirus), and Adenovirus are among the viruses that cause diarrhea. Protozoa (*Giardia lamblia*, *Cryptosporidium*) and helminths (*Strongyloides* sp.) are among the parasites. According to a report from a Jakarta referral hospital, *Aeromonas* sp. (14.29%), *V. Cholera* Ogawa (18.29%), and *E. Coli* pathogenic (38.29%) were the most common causes of acute diarrhea in children.⁴⁰

Even yet, the most common isolate of an enteropathogen is enterotoxigenic *Escherichia coli* (ETEC), which is responsible for around 210 million cases of diarrhea and nearly 380,000 fatalities each year. We reviewed a community-based study in Indonesia which revealed that ETEC diarrhea incidence peaked in the first year of life and then declined with age after that. Food or water contaminated with human or animal excrement can spread ETEC. In developing nations like Indonesia, enterotoxigenic *Escherichia coli* is a leading cause of illness and death in children under the age of five.⁴¹

Diarrheagenic *E. coli* (DEC) bacteria are a prominent culprit behind the widespread issue

of diarrhea, a leading cause of illness and mortality among children in developing countries. We reviewed a cross-sectional research study aimed at identifying the precise bacterial infections causing diarrhea in children under the age of five in the Bima District of West Nusa Tenggara Province, Indonesia. The results of this study, with a prevalence rate of 29.953%, revealed that *E. coli* bacteria stand as the primary and most frequent cause of diarrhea among children in this age group.⁴² These findings align with another study we evaluated which was conducted by Sana Eybpoosh et. Al in 2021, which identified non-O157:H7 *E. coli* as the predominant source of pediatric infections in Iran. This research suggests that diarrheagenic *E. coli* strains could be a notable contributor to acute diarrhea cases in both adults and children in Iran.⁴³ We compared the Sana Eybpoosh et. Al, study to another study conducted at Abuzar Hospital in Ahvaz, Iran which reported that out of 137 *E. coli* isolates examined, 53 of them, accounting for 38.7%, were found to contain enteropathogens. This research further underscores the significance of non-O157:H7 *E. coli* strains as the leading agents responsible for pediatric infections in the specified region of Iran.⁴⁴ This particular type of *E. coli* is highly prevalent and dominant because *E. coli* non-O157:H7 and other Shiga toxin-producing *E. coli* (STEC) strains have a bovine (cattle)

reservoir. This means Infection can occur through the consumption of contaminated food or water, often linked to cow manure contamination.⁴⁵ This is particularly relevant in outbreaks and isolated cases, which typically result from the ingestion of undercooked beef (especially ground beef, such as hamburgers) or unpasteurized milk.

We reviewed another study conducted in Surabaya, Indonesia where researchers investigated the presence of DEC (Diarrheagenic *E. coli*) in stool samples collected from 125 children experiencing diarrhea (aged 1 to 10 years) and 92 children without diarrhea. The study revealed that DEC was detected in samples from children with diarrhea in 23 out of 125 cases, representing 18.4% of the group. Surprisingly, DEC was also found in samples from children without diarrhea in 47 out of 92 cases, accounting for 51.1% of the group. These findings suggest that DEC may not exclusively be associated with diarrhea and could also be present in asymptomatic individuals.⁴⁶

We evaluated another cross-sectional study that was carried out in Makassar City, Indonesia, where 50 children with diarrhea were sampled from multiple health clinics were screened to discover the variety of bacteria that cause childhood diarrhea. The findings revealed that there were 15 *Escherichia coli* bacteria (30%), 14 *Klebsiella sp* bacteria (28%), 12 *Enterobacter sp* bacteria (24%), 4 *Proteus mirabilis* bacteria (8%), and 4 *Proteus vulgaris* bacteria (8%), but only 1 *Alcaligenes faecalis* bacteria (2%). *Escherichia coli* was identified as the most prevalent form of bacterium, according to the study's findings.⁴⁷ This is comparable to a resembling study that we reviewed which was done in Singapore where 2.7% of 2983 toddlers under the age of three who had diarrhea had Enteropathogenic *Escherichia coli* (EPEC) isolated from them. The two most prevalent serotypes out of the nine detected ones were 0126:K71(B16) and 086:K61(B7).⁴⁸

Antibiotic Usage in Indonesia

Although bacteria is the second most common cause of childhood diarrhea after rotavirus the use of antibiotics is still very relevant and common in Indonesia.⁴⁹ The significant use of antibiotics in high-income

nations, spanning community settings, hospitals, and agriculture, has played a substantial role in creating selective pressure that sustains antibiotic-resistant strains. As a consequence, healthcare providers are increasingly resorting to costlier and broader-spectrum antibiotics. Simultaneously, in low and middle-income countries (LMICs) like Indonesia, antibiotic usage is on the rise due to improving incomes, elevated rates of hospitalization, and the prevalence of hospital-acquired infections. It is worth noting that individuals with lower socioeconomic status and lower levels of education may be more prone to misconceptions about antibiotic consumption.⁵⁰

According to recent studies, we found that amoxicillin and ampicillin are the antibiotics most commonly used by children in Indonesia.⁵¹ The consumption, measured in terms of Defined Daily Doses (DDD), was notably higher within hospital settings in contrast to primary care, and there was an increased intake in recent years (from 2016 to 2021) compared to earlier years (from 2000 to 2015) (see Fig. 3). Nevertheless, we also observed that there were no appreciable variations between geographic settings. In 2015, the IMCI's first-line therapy recommendation for pneumonia was amoxicillin. Even though amoxicillin is not advised for treating children with acute diarrhea, it is still widely used in Indonesia to treat children with diarrhea.⁵² Penicillin and sulfonamides, however, are additional antibiotics that have been discovered to be taken by children rather regularly. When taking penicillin, respiratory system illnesses account for the majority of cases (68.46%), whereas sulfonamides are typically used for gastrointestinal problems (50.85%).⁵³ Based on our analysis, we determined that in 2015 Indonesia had a per capita antibiotic consumption rate of 3022 DDDs per 1000 people per year, which was lower than Vietnam (11 480), Thailand (6682), and Malaysia (4388), but was comparable to China (3060) and the Philippines (2600).⁵⁴

Antimicrobial Resistance (AMR) is a significant public health threat. As stated by the World Health Organization, resistant bacteria to antibiotics are a global danger to human health. This arises as a consequence of six

concerns that have not been sufficiently addressed, such as inadequate levels of research, shortages of infection control, absurd application of antimicrobials, inadequate antibiotics, a lack of dedication, a lack of oversight, and the introduction of evaluates that hinder the rise of antimicrobial-resistant bacteria, all of which have been noticed globally, involving in Indonesia.⁵⁵

We also inferred from studies conducted in primary healthcare settings in various countries that there are alarming rates of inappropriate antibiotic usage. These rates include 15% in Canada, 55% in South Africa, 61% in China, 88% in Pakistan, and 90% in Vietnam, among others.⁵⁶ A comprehensive examination of nine studies conducted in low and middle-income countries (LMICs) produced a wide spectrum of results, ranging from 8% to 100%.⁵⁷ Furthermore, we reviewed a global point prevalence study which indicated that less than 70% of hospitals in Latin America, Africa, and Asia reported adhering to guidelines for the proper use of antimicrobial medications. These findings underscore the need for improved antibiotic stewardship practices worldwide to address this issue effectively.⁵⁸

Indonesia *Escherichia coli* and *Staphylococcus aureus* resistance data from a research populations were made available by the AMRIN project in 2017. However, our review on the AMRIN study concluded that the AMRIN investigation revealed patients had significant rates of (multi)resistant *Escherichia coli* carriage on the day of hospital release. Resistance rates for ampicillin were 73%, cotrimoxazole was 55%, chloramphenicol was 43%, ciprofloxacin was 22%, gentamicin was 18%, and cefotaxime was 13% (see Fig. 4).⁵⁹ *Escherichia coli* resistance has increased noticeably when compared to the amount present on the day of admission. This is a result of hospitals using antibiotics selectively. However, there was not always a direct link between hospital antibiotic use and resistance rates. Children are shown to have more resistance to *Escherichia coli* than adults, according to this research. This can be seen in hospitals where pediatric wards have a higher rate of carrying resistant *Escherichia coli* than internal medicine units. There are several causes for children to carry resistant *E. coli*.

such as antibiotics are typically given to young children more regularly than to adults. In addition to the usage of antibiotics, children may be more susceptible to developing resistant bacteria than adults due to their increased exposure to unsanitary behavior (see Fig. 5).⁶⁰ This finding bears resemblance to a study we reviewed which was conducted in Brazil by Oliveira et al., which also aimed to investigate the prevalence of antibiotic resistance in the treatment of *E. coli* infections. A 49.1% of ETEC infections were resistant to ampicillin, 28.1% to amoxicillin with clavulanic acid, 26.3% to trimethoprim with sulfamethoxazole, 14% to nalidixic acid, and 12.3% to ciprofloxacin. Ampicillin (14.6%) and trimethoprim with sulfamethoxazole (19.4%) were found to have the highest rates of resistance when used to treat EPEC-caused illnesses. Ampicillin had a 34.7% resistance rate, trimethoprim and sulfamethoxazole had a 25.5% resistance rate, amoxicillin and clavulanic acid had a 17.3% resistance rate, and nalidixic acid with a 10.2% resistance rate for all samples combined.⁶¹ We conducted a comparative analysis with another research study conducted by Flor Y. Ramírez Castillo et al. in Mexico. In their study, they assessed the antimicrobial susceptibility of 150 *E. coli* isolates using the disc diffusion method. Their findings revealed that a total of 59 isolates (39.3%) exhibited resistance to ampicillin. Furthermore, the second most prevalent antibiotic resistance was observed with trimethoprim-sulfamethoxazole, affecting 28.6% (43/150) of the isolates. Carbenicillin resistance was also notable, affecting 26% (39/150) of the isolates, followed by chloramphenicol resistance in 22% (33/150) of the isolates, and cephalothin resistance in 17.3% (26/150) of the isolates. It is worth noting that only a small number of isolates, approximately 1.33% (2/150), exhibited resistance to cefotaxime, netilmicin, and amikacin. Additionally, the study reported that 7.3% (11/150) of the isolates were resistant to pefloxacin, while 4% (6/150 isolates) displayed resistance to levofloxacin.⁶² These three studies we reviewed demonstrated that *E. coli* is highly resistant to ampicillin, possibly due to its beta-lactam antibiotic resistance mechanisms or due to the excessive consumption of ampicillin.

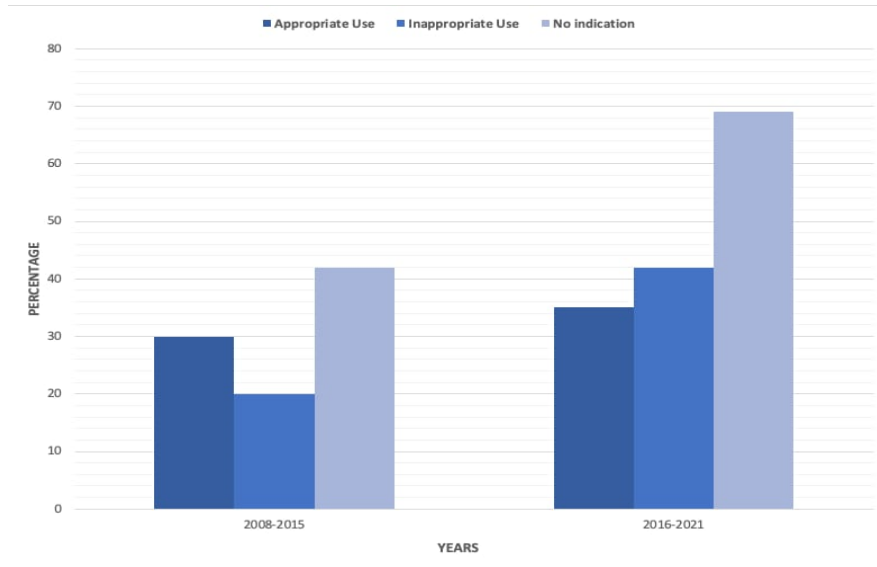


Fig. 3: Evaluating the standard of antibiotic use in recent years in contrast to previous years.

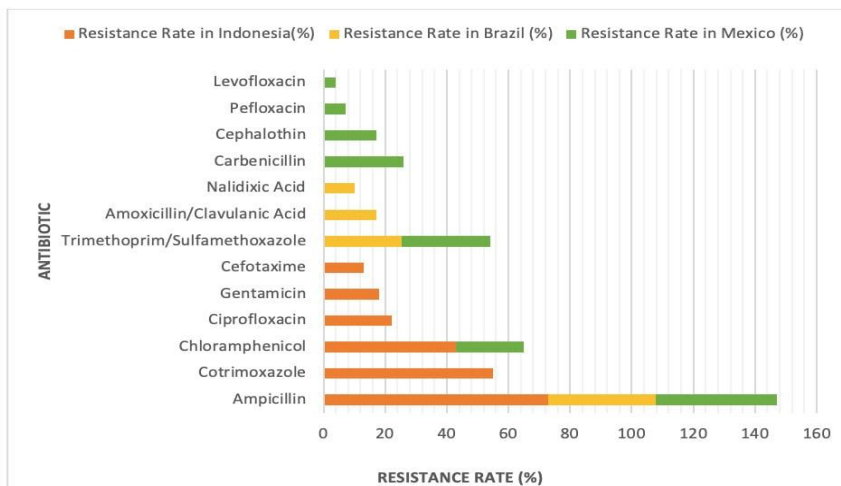


Fig. 4: The rates of antibiotic resistance observed in *Escherichia coli* bacteria in the studies from different countries that were reviewed.

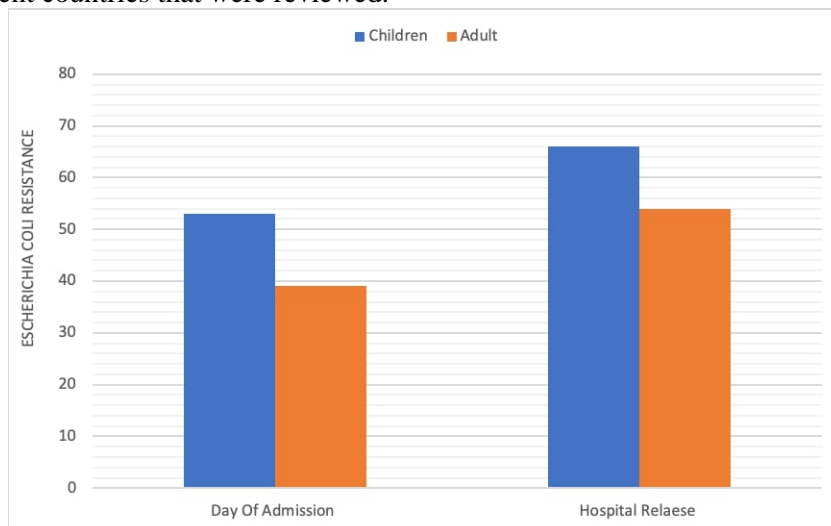


Fig. 5: Comparing *Escherichia coli* resistance rates on the day of patient admission to the day of hospital release in children and adults.

Antibiotic-Resistant Situation in Indonesia

AMR has become a serious global issue, particularly in Southeast Asian countries such as Indonesia. National data regarding AMR in Indonesia pertains to the Global Antimicrobial Resistance and Use Surveillance System (GLASS). Indonesia initiated its participation in GLASS in 2019. The data collection for GLASS was initially limited to 20 specific hospitals across Indonesia, serving as key sites for monitoring AMR. The results from GLASS in 2019 indicated an increase in the prevalence of antimicrobial resistance for certain bacteria like *E. coli* and *K. pneumoniae*.⁶³ This resistance included various antibiotics such as Carbapenems, Fluoroquinolones, and third-generation Cephalosporins. A surveillance study conducted in 2017 on *Escherichia coli* and *Klebsiella pneumoniae*, responsible for urinary tract infections, revealed that resistance to commonly used treatments was notably high in Indonesia.⁶⁴ However primary national health research in Indonesia revealed that approximately 10% of households stored antibiotics, and a substantial 86.1% acquired these medications without a prescription from a physician.⁶⁵ Another study indicates a statistically significant rise in the occurrence of infections caused by bacteria producing extended-spectrum beta-lactamases (ESBL) in hospitals. For instance, *Escherichia coli* and *Klebsiella pneumoniae* displayed resistance rates ranging from 26% to 56%. Notably, the improper use of antibiotics has further exacerbated this situation.⁶⁶

All these findings suggest that Indonesia faces a significant challenge with AMR, much like other Southeast Asian countries like India and Bangladesh. This issue primarily arises from the inappropriate use of antimicrobials in healthcare services and the livestock and fisheries sector.⁶⁷ In urban areas, the ease of obtaining antibiotics has led to the misconception that antibiotics can cure various common illnesses like influenza and diarrhea. Additionally, antibiotics can be purchased without prescriptions from drug stores and pharmacies, despite being against government regulations.⁶⁸ All these mentioned factors have contributed to deteriorating the AMR situation in the country. Noncompliance, a common occurrence in both short- and long-term antibiotic therapy for patients with chronic

diseases like tuberculosis and HIV, further exacerbates the problem as well. This misuse of antibiotics creates a conducive environment for microorganisms to develop resistance, leading to the emergence of antibiotic-resistant strains.

Antimicrobial Resistance (AMR) Government Control Program in Indonesia

The Ministry of Health just introduced the 2015-2019 plan of action for executing current rules and directives and implementing AMR-related initiatives across the country. Pilot programs for community and hospital-based measures to encourage the prudent use of antibiotics are among these initiatives. Non-governmental groups and medical associations were additionally involved in local public awareness campaigns.⁶⁹ Nevertheless, there is an urgent necessity to establish a comprehensive, multisectoral national action plan, along with the implementation of existing proven strategies for preventing and containing AMR. The initial crucial step involves setting up a governance mechanism dedicated to AMR, tasked with overseeing the issue effectively and implementing long-lasting tactics and measures for decision-makers. Furthermore, the AMR control program should prioritize three fundamental areas without delay: conducting surveillance of AMR and antimicrobial usage in human health and livestock, launching an extensive awareness-raising campaign, and facilitating the transition of national-level regulations into community-level implementation across the entire nation. To accomplish these objectives, operational strategies are being developed as integral components of the national action plan.⁵⁶

The AMR control policy is still inactive as the Ministry of Health's National Committee of Antimicrobial Resistance Control is still unable to combat AMR. The sectors represented on this committee handle AMR independently.⁷⁰ Although it can seem simple on paper, coordination with other industries is challenging in practice. The AMR strategy could involve the implementation of multi-sectoral national policies that are executed at the regional level. Additionally, collaboration with other countries is essential as a vital aspect of implementing the "One Health" approach.⁷¹

Conclusion

In recent years, there has been substantial progress in our comprehension of pediatric diarrhea, a primary cause of mortality among young children in developing nations like Indonesia. In developing nations like Indonesia, *E. coli* is a leading cause of childhood diarrhea. However, *E. coli* has a great capacity to accumulate resistance genes. Antimicrobial resistance (AMR) is a widespread worldwide health challenge. The government of Indonesia comes across an important mission in addressing Indonesia's AMR crisis. Nevertheless, the AMR crisis in Indonesia has not been improving matter of fact, it has deteriorated.

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نشرة العلوم الصيدلانية جامعة أسيوط



هل ما زالت مقاومة الإشريكية القولونية الممرضة للمضادات الحيوية في الأطفال المصابين بالعدوى الإسهالية مصدر قلق في إندونيسيا؟ : مراجعة محدثة

أمنية أمير عثمان عبد الرازق^{١*} - فضيلة فضيلة^٢ - بادريول هيجار^٤ - يوليا روزا سحرمان^٥

^١ برنامج الماجستير في العلوم الطبية الحيوية، كلية الطب، جامعة إندونيسيا، جاكرتا، إندونيسيا ١٠٤٣٠

^٢ قسم الكيمياء الطبية، كلية الطب، جامعة إندونيسيا، جاكرتا، إندونيسيا ١٠٤٣٠

^٣ مرافق البيوانفورماتيك الأساسية، معهد التعليم والبحث الطبي الإندونيسي، كلية الطب، جامعة إندونيسيا، جاكرتا، إندونيسيا ١٠٤٣٠

^٤ قسم صحة الطفل، كلية الطب، جامعة إندونيسيا، مستشفى الدكتور سيبتو مانغونكوسومو، جاكرتا ، إندونيسيا ١٠٤٣٠

^٥ قسم علم الأحياء الدقيقة، كلية الطب، جامعة إندونيسيا، جاكرتا، إندونيسيا ١٠٤٣٠

مقدمة: يتزايد الإسهال في الطفولة في البلدان النامية مثل إندونيسيا، حيث يؤثر على ٦.٧% من الأطفال دون سن الخامسة بشكل كبير بسبب الإشريكية القولونية.

الطريقة: تهدف هذه المراجعة إلى تقديم مراجعة محدثة عن أحدث المعلومات حول الإسهال في الطفولة في إندونيسيا ومقاومة الإشريكية القولونية للمضادات الحيوية من مصادر البحث الحديثة حتى يونيو ٢٠٢٣ من قواعد البيانات مثل باستخدام مصطلحات بحث محددة مثل الإسهال والأطفال والمرض والوفاة PubMed و Scopus و Google Scholar

وإندونيسيا والإشريكية القولونية ومقاومة المضادات الحيوية. وتتضمن المقالات من المجالات الصحية المحكمة المعتمدة وطنياً ودولياً باللغتين الإنجليزية والإندونيسية .

النتائج: استناداً إلى الدراسات التي راجعناها، ثبت أن الإسهال في الأطفال دون الخامسة هو السبب الأكثر شيوعاً للوفاة في الأطفال في إندونيسيا. كما كشف تحليلنا للأدبيات عن رابط محتمل بين الجنس وحدوث الإسهال في الأطفال. علاوة على ذلك، حدد تحليلنا عوامل الخطر، بما في ذلك المياه الملوثة والصرف الصحي غير الكافي وسوء النظافة وممارسات النظافة الغذائية غير المثلى كأسباب رئيسية للإسهال في الطفولة في إندونيسيا. بالمقابل، تكشف الدراسات الأخرى التي تمت مراجعتها في هذه الورقة أن الإشريكية القولونية هي العامل المسبب الأكثر شيوعاً للإسهال في الطفولة في إندونيسيا. كما يكشف تقييمنا للدراسة أن الإشريكية القولونية تظهر معدل مقاومة عال، ربما بسبب سوء استخدام المضادات الحيوية على نطاق واسع في البلاد.

الخاتمة: الإسهال في الأطفال دون الخامسة في إندونيسيا هو السبب الرئيسي لوفاة الأطفال، مع وجود عوامل خطر متعددة بما في ذلك الصرف الصحي والعامل المسبب للإشريكية القولونية. علاوة على ذلك، تدهور حالة المقاومة للمضادات الحيوية في البلاد.