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Determinants of Diarrhea Among Under-Five Children in Indonesia: A Cross-Sectional Analysis of the 2022 Indonesian Nutritional Status Survey (SSGI)

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ABSTRACT

Diarrhea remains a major public health problem among children under five in Indonesia and contributes substantially to morbidity, malnutrition, and impaired child development. Multiple healthcare, environmental, nutritional, and behavioral factors may influence diarrhea incidence among children. This study aimed to identify the determinants of diarrhea among under-five children in Indonesia using data from the 2022 Indonesian Nutritional Status Survey (SSGI). This study used a cross-sectional design based on secondary data from the 2022 SSGI. A total of 39,125 children under five were included in the analysis. Independent variables included healthcare access, nutritional status, complementary feeding practices (MP-ASI), source of drinking water, exclusive breastfeeding, and immunization status. Data were analyzed using Chi-square tests and multivariate logistic regression with a significance level of $p < 0.05$. Results the prevalence of diarrhea among under-five children was 4.1%. Bivariate analysis showed significant associations between diarrhea incidence and healthcare access, nutritional status, drinking water source, and immunization status ($p < 0.05$). In the multivariate analysis, healthcare access (OR = 0.484; 95% CI: 0.437–0.536), nutritional status (OR = 1.110; 95% CI: 1.036–1.189), complementary feeding practices (OR = 0.924; 95% CI: 0.860–0.994), drinking water source (OR = 1.197; 95% CI: 1.022–1.403), and immunization status (OR = 1.310; 95% CI: 1.220–1.407) remained significantly associated with diarrhea incidence. Incomplete immunization was identified as the most dominant determinant of diarrhea among under-five children. Diarrhea among under-five children in Indonesia is influenced by multiple healthcare, nutritional, and environmental determinants. Strengthening immunization coverage, improving access to healthcare services and safe drinking water, and enhancing nutrition and hygiene education are essential to reduce diarrhea incidence among Indonesian children.

Key Messages:

- Incomplete immunization is the most dominant determinant of diarrhea among children under five in Indonesia, emphasizing that comprehensive prevention strategies must integrate robust vaccine coverage with improved healthcare access, nutritional support, and safe water sanitation.

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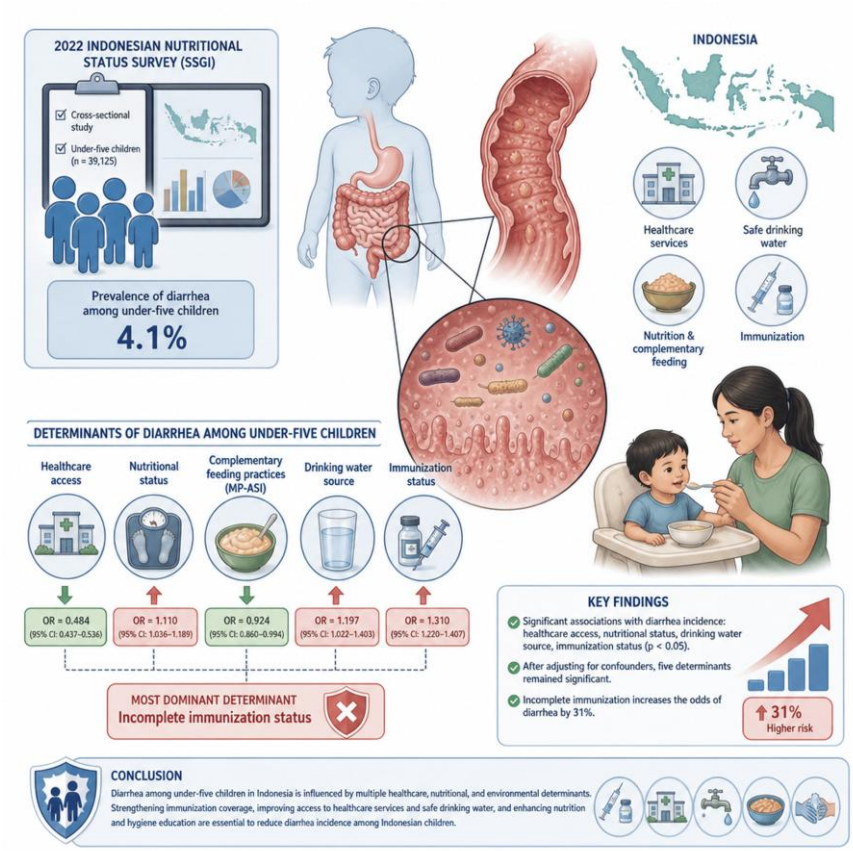
GRAPHICAL ABSTRACT



INTRODUCTION

Diarrhea remains a leading cause of morbidity and mortality among children under five years worldwide, causing approximately 525,000 deaths annually, mostly in developing countries (1). In Indonesia, the 2022 Indonesian Nutritional Status Survey (SSGI) reported a diarrhea prevalence of 4.1% among under-five children, a figure that, while lower than previous surveys, still translates into a substantial disease burden given the large toddler population (2). Recurrent diarrhea episodes increase the risk of malnutrition and stunting 2–3 times higher compared to healthy children, perpetuating a vicious cycle of poverty and impaired child development (3). Previous evidence has also demonstrated that repeated diarrheal infections contribute to impaired cognitive development, reduced nutrient absorption, and increased vulnerability to other infectious diseases among children under five, particularly in low- and middle-income countries (3,4).

Limited access to healthcare facilities is a major contributor to higher diarrhea incidence. Children in areas with inadequate health services face delayed diagnosis and treatment as well as reduced preventive education (5). Rural-urban disparities persist, with only 60% of rural households having easy access to puskesmas or hospitals (6), a situation worsened by the COVID-19 pandemic that caused a 10–15% drop in immunization coverage in several provinces (7). Malnutrition also significantly heightens susceptibility; malnourished children are twice as likely to develop diarrhea due to weakened immunity and damaged intestinal mucosa (8). Inadequate healthcare access may also reduce opportunities for early nutritional interventions, health promotion, and timely management of dehydration, thereby increasing the severity and recurrence of diarrheal episodes among children (5,7).

Environmental factors, particularly unsafe drinking water and poor sanitation, are well-established risk factors. Households using unsafe water sources show 1.2–1.5 times higher diarrhea prevalence (9,10), while integrated WASH interventions can reduce diarrhea by up to 69% (11,12). Inappropriate complementary feeding (MP-ASI) and low exclusive breastfeeding rates further exacerbate the problem; non-exclusively breastfed infants have 1.97–5.125 times higher risk of diarrhea (13,14), yet national

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exclusive breastfeeding coverage remains only 47.8% (2,15). Unsafe food preparation, inadequate hand hygiene, and contaminated household environments further increase children's exposure to enteric pathogens, particularly during the complementary feeding period (11,12,15).

Complete immunization, especially rotavirus and polio vaccines, provides substantial protection against severe diarrheal diseases, with global evidence showing up to 30% reduction in diarrhea mortality post-rotavirus vaccine introduction (16,17). Although national complete immunization coverage reached 90.4% in 2022, gaps persist, particularly in remote areas (2). Immunization not only reduces infection severity but also decreases hospitalization and mortality associated with vaccine-preventable diarrheal diseases, emphasizing the importance of maintaining high coverage across all regions (16).

Although previous studies have identified various determinants of diarrhea, most have been conducted at regional or community levels and often focus on a limited number of variables, such as sanitation, nutrition, or feeding practices (9–15). These studies provide important insights but do not fully capture the combined and relative contribution of multiple determinants at the national level using the most recent data. Furthermore, there is still limited evidence that simultaneously examines healthcare access, environmental factors, nutritional status, and immunization coverage within a single analytical framework based on nationally representative data in Indonesia. The 2022 Indonesian Nutritional Status Survey (SSGI) is particularly important because it represents one of the most recent nationally representative datasets collected after the major disruptions caused by the COVID-19 pandemic, thereby providing updated evidence regarding child health, nutrition, and healthcare disparities across Indonesia (2,7).

Therefore, this study aims to identify the key determinants of diarrhea among under-five children in Indonesia using secondary data from the 2022 Indonesian Nutritional Status Survey (SSGI). By utilizing large-scale, nationally representative data, this study seeks to provide more comprehensive and updated evidence on the relative contribution of multiple risk factors, thereby supporting the development of targeted, integrated, and evidence-based public health interventions aligned with Sustainable Development Goal (SDG) 3 (Good Health and Well-being) and SDG 6 (Clean Water and Sanitation). The findings of this study are expected to support policymakers in strengthening integrated child health interventions, particularly those related to immunization coverage, nutrition improvement, access to healthcare services, and environmental sanitation programs in Indonesia.

METHODS

This study employed a cross-sectional analytical design using secondary data from the 2022 Indonesian Nutritional Status Survey (SSGI). This design was selected to examine the association between multiple determinants and the incidence of diarrhea among children under five at a specific point in time using nationally representative data. The study population consisted of children aged 0–59 months included in the 2022 SSGI dataset. Inclusion criteria were children with complete information on diarrhea status and key determinants, including nutritional status, immunization status, access to health services, drinking water source, and feeding practices. Records with incomplete or missing data on primary outcome or independent variables were excluded. The SSGI applied a two-stage stratified cluster sampling method to ensure national representativeness across all provinces in Indonesia. After data cleaning, a total of 39,125 children under five were included in the final analysis, indicating an adequate sample size to ensure statistical power and generalizability.

Data were collected by trained enumerators from the Ministry of Health and the Central Statistics Agency (BPS) between January and December 2022. Information was obtained through structured interviews with mothers or primary caregivers using standardized questionnaires. Whenever available, responses were verified using family health cards to improve data accuracy and reduce recall bias.

The dependent variable in this study was the incidence of diarrhea (yes/no), defined as caregiver-reported diarrhea symptoms occurring within two weeks prior to the survey. Independent variables included access to health services (limited/easy), nutritional status (severely underweight/underweight/normal/overweight), complementary feeding practices (MP-ASI) (inappropriate/appropriate), source of drinking water (unsafe/safe), exclusive breastfeeding (non-

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exclusive/exclusive), and immunization status (incomplete/complete). Nutritional status was assessed using weight-for-age z-scores based on the World Health Organization (WHO) 2006 growth standards. Drinking water sources were categorized according to national guidelines into safe and unsafe sources.

Access to healthcare services was categorized as "easy access" if households reported easy geographical and transportation access to health facilities such as puskesmas or hospitals, whereas "limited access" referred to households experiencing difficulties related to distance, transportation, or availability of healthcare services. Complementary feeding practices were categorized as appropriate when feeding introduction and frequency followed age-specific national and WHO recommendations, while practices inconsistent with these recommendations were classified as inappropriate. Safe drinking water sources included piped water, protected wells, bottled water, and other improved water sources based on national sanitation guidelines, whereas unsafe sources included unprotected wells, surface water, and other unimproved sources. The SSGI dataset did not specifically provide rotavirus vaccination status; therefore, the immunization variable in this study referred to routine childhood immunization completeness recorded in the survey.

Data were analyzed using IBM SPSS Statistics version 26.0. Sampling weights and complex survey design adjustments were applied during analysis to account for stratified cluster sampling and ensure nationally representative estimates. The analysis consisted of three stages: univariate analysis to describe the distribution of variables, bivariate analysis using the Chi-square test to examine associations between independent variables and diarrhea incidence, and multivariate analysis using binary logistic regression to identify the most dominant determinants. Before multivariate logistic regression analysis, multicollinearity testing was conducted using tolerance and Variance Inflation Factor (VIF) values, and no significant multicollinearity was identified among independent variables. Variables with p-values <0.25 in the bivariate analysis were included in the multivariate model to avoid excluding potentially important predictors, consistent with epidemiological modeling recommendations. Statistical significance was set at $p < 0.05$ with a 95% confidence interval (CI).

CODE OF HEALTH ETHICS

This study received ethical approval from the Ethics Committee of the Faculty of Public Health, Malahayati University (No. 4935/EC/KEP-UNMAL/VII/2025). After obtaining ethical approval, the researcher requested permission to access the 2022 Indonesian Nutritional Status Survey (SSGI) dataset from the Ministry of Health of the Republic of Indonesia. As this study used secondary data, there was no direct interaction with participants. Informed consent had been obtained from respondents by the original survey team during data collection. All data were anonymized prior to analysis to ensure confidentiality and privacy of the participants.

RESULTS

The study involved a cross-sectional study design conducted across all provinces in Indonesia using secondary data from the 2022 Indonesian Nutritional Status Survey (SSGI). A total of 39,125 children under five were included in the analysis after data cleaning. Participants were selected based on availability of complete variables related to diarrhea incidence, with exclusion applied to subjects with missing key outcome or exposure data. The demographics of the study population included children aged 0–59 months from various regions, representing urban and rural settings in Indonesia. Key characteristics such as age, gender, nutritional status, and household environmental factors were extracted from the dataset.

Participants were categorized into diarrhea and non-diarrhea groups based on caregiver interviews regarding symptoms in the previous two weeks. Independent variables were grouped according to theoretical predictors of diarrhea, including access to health services, nutritional status, complementary feeding practices (MP-ASI), exclusive breastfeeding status, source of drinking water, and immunization status.

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Table 1. Analysis of Characteristics of Children Under Five in Indonesia, 2022

Characteristics	n	%
Diarrhea Status		
Had Diarrhea	1593	4.1
No Diarrhea	37532	95.9
Child's Sex		
Male	19864	50.8
Female	19261	49.2
Access to Health Services		
Limited Access	23376	59.7
Easy Access	15749	40.3
Nutritional Status of the Child		
Severely Underweight	506	1.3
Underweight	2382	6.1
Normal	35102	89.7
Overweight	1135	2.9
Complementary Feeding (MP-ASI)		
Inappropriate	23361	59.7
Appropriate	15764	40.3
Exclusive Breastfeeding		
Non-Exclusive	20433	52.2
Exclusive	18692	47.8
Immunization Status		
Incomplete	3752	9.6
Complete	35373	90.4
Source of Drinking Water		
Unsafe	3866	9.9
Safe	35259	90.1

The univariate analysis described the characteristics of 39,125 under-five children in Indonesia based on the 2022 Indonesian Nutritional Status Survey (SSGI). Most children were male (50.8%), while female children accounted for 49.2%. The prevalence of diarrhea among children under five was 4.1%, indicating that diarrhea remains a notable public health concern. Regarding access to health services, 59.7% of children had limited access, reflecting unequal healthcare distribution, especially in remote areas. The nutritional status of most children was normal (89.7%), although 6.1% were underweight, 1.3% severely underweight, and 2.9% overweight, showing that nutritional problems still persist. Analysis of complementary feeding (MP-ASI) showed that 59.7% received inappropriate feeding, while only 40.3% received appropriate feeding. Most households used safe drinking water (90.1%), but 9.9% still relied on unsafe sources. Meanwhile, only 47.8% of children were exclusively breastfed, and 52.2% were not, indicating low exclusive breastfeeding coverage.

For immunization status, 90.4% of children were fully immunized, while 9.6% had incomplete immunization. Overall, these findings indicate that while most children have good nutrition and immunization coverage, diarrhea incidence is still influenced by limited healthcare access, poor feeding practices, low breastfeeding rates, and unsafe water sources.

Table 2. Bivariate Analysis of Determinants of Diarrhea Among Under-Five Children in Indonesia

Characteristics	Diarrhea (%)	No Diarrhea (%)	P-value
Access to Health Services			
Limited	5.8	94.2	<0.001
Easy Access	2.9	97.1	
Nutritional Status			
Severely Underweight	5.3	94.7	0.037
Underweight	4.8	95.2	0.029
Normal	4.0	96.0	0.018
Overweight	3.1	96.9	0.109
Complementary Feeding (MP-ASI)			
Inappropriate	4.2	95.8	0.167
Appropriate	3.9	96.1	
Exclusive Breastfeeding			
Non-exclusive	4.2	95.8	0.219
Exclusive	3.9	96.1	

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Characteristics	Diarrhea (%)	No Diarrhea (%)	P-value
Immunization Status			
Incomplete	5.7	94.3	<0.001
Complete	3.9	96.1	
Source of Drinking Water			
Unsafe	4.7	95.3	0.031
Safe	4.0	96.0	

The bivariate analysis examined the relationship between independent variables and the incidence of diarrhea among children under five using the Chi-square test. The results revealed several significant associations. There was a significant relationship between access to health services and diarrhea incidence ($p < 0.001$), indicating that children with limited access to health facilities were more likely to experience diarrhea. Nutritional status was also significantly associated with diarrhea incidence ($p < 0.05$), where children with poor nutritional status had a higher risk of diarrhea compared to children with normal nutritional status. A significant relationship was also identified between drinking water sources and diarrhea incidence ($p < 0.05$), suggesting that children from households using unsafe drinking water sources were more likely to experience diarrhea. Immunization status was significantly associated with diarrhea incidence ($p < 0.001$), indicating that children with incomplete immunization had higher diarrhea prevalence.

In contrast, complementary feeding practices (MP-ASI) and exclusive breastfeeding were not significantly associated with diarrhea incidence ($p > 0.05$). Although these factors are important components of child health and nutrition, their statistical associations with diarrhea were not observed in the present dataset. Overall, the bivariate analysis suggests that diarrhea among Indonesian children under five is strongly influenced by healthcare access, nutritional status, drinking water quality, and immunization coverage.

Table 3. Multivariate Analysis

Variable	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)
Access to Health Services	<0.001	0.484	0.437–0.536
Nutritional Status	0.003	1.110	1.036–1.189
Complementary Feeding	0.035	0.924	0.860–0.994
Source of Drinking Water	0.026	1.197	1.022–1.403
Immunization Status	<0.001	1.310	1.220–1.407

The multivariate logistic regression analysis identified several significant determinants of diarrhea among children under five in Indonesia. Access to healthcare services, nutritional status, complementary feeding practices (MP-ASI), drinking water sources, and immunization status remained significantly associated with diarrhea incidence after adjustment for other variables (Table 3).

Children with easy access to healthcare services had lower odds of experiencing diarrhea compared with those with limited access (OR = 0.484; 95% CI: 0.437–0.536). Poor nutritional status was associated with increased odds of diarrhea (OR = 1.110; 95% CI: 1.036–1.189). Although complementary feeding practices showed a relatively modest association, inappropriate complementary feeding remained significantly associated with diarrhea incidence (OR = 0.924; 95% CI: 0.860–0.994). Children from households using unsafe drinking water sources had higher odds of diarrhea (OR = 1.197; 95% CI: 1.022–1.403). Among all variables, immunization status was identified as the most dominant determinant. Children with incomplete immunization had approximately 1.3 times higher odds of developing diarrhea compared with fully immunized children (OR = 1.310; 95% CI: 1.220–1.407). These findings indicate that diarrhea among Indonesian under-five children is influenced by multiple interrelated healthcare, nutritional, environmental, and immunization-related factors.

DISCUSSION

Based on the results of the univariate analysis, 4.1% of children under five in Indonesia experienced diarrhea. Although this prevalence appears relatively lower compared with several previous national reports, the absolute number of affected children remains substantial considering Indonesia's large under-five population. These findings indicate that diarrhea continues to be an important public

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health problem requiring continuous prevention and control efforts. The univariate analysis also showed that a considerable proportion of children lived in households with limited healthcare access, unsafe drinking water sources, inappropriate complementary feeding practices, and incomplete immunization coverage. In addition, exclusive breastfeeding coverage remained relatively low. These findings suggest that diarrhea among Indonesian children is influenced by complex interactions between environmental, nutritional, healthcare-related, and behavioral determinants.

The findings of this study are generally consistent with previous studies conducted both nationally and internationally. Previous studies in Indonesia identified sanitation, hygiene practices, environmental conditions, and feeding behaviors as important determinants of diarrhea among under-five children (18,19). Similarly, Komarulzaman et al. (10) reported that improved household sanitation and access to clean water significantly reduced diarrhea prevalence among Indonesian children. International evidence also supports these findings. Studies conducted in low- and middle-income countries demonstrated that integrated WASH (Water, Sanitation, and Hygiene) interventions combined with maternal and child health programs were effective in reducing diarrhea prevalence and improving child health outcomes (11,12). These findings strengthen the assumption that diarrhea prevention requires integrated interventions involving healthcare systems, environmental sanitation, and community behavioral change simultaneously.

The bivariate and multivariate analyses demonstrated that healthcare access was significantly associated with diarrhea incidence. Children with limited access to healthcare services were more likely to experience diarrhea compared with children with easier access to health facilities. This finding is supported by previous studies showing that healthcare accessibility contributes to early diagnosis, treatment-seeking behavior, preventive counseling, and immunization uptake among caregivers (20,30,31). Families living in remote or underserved areas often experience delays in obtaining medical treatment, oral rehydration therapy, and preventive health education, thereby increasing children's vulnerability to diarrheal diseases. Furthermore, limited healthcare access may reflect broader inequalities related to transportation, healthcare infrastructure, and availability of healthcare workers, particularly in rural and geographically isolated regions of Indonesia. However, because this study employed a cross-sectional design, the observed associations should be interpreted cautiously and cannot establish direct causal relationships.

Nutritional status was also significantly associated with diarrhea incidence. Children with poor nutritional status were more vulnerable to diarrhea, likely due to weakened immune responses, impaired intestinal mucosal integrity, and reduced resistance to infectious agents. These findings are consistent with previous evidence demonstrating the bidirectional relationship between malnutrition and diarrhea (3,8,22). Children experiencing recurrent diarrhea may lose essential nutrients and fluids, which subsequently worsen nutritional deficiencies and impair growth and development. Conversely, malnourished children are more susceptible to enteric infections because of compromised immunity. This cyclical relationship highlights the importance of integrating nutrition improvement programs into diarrhea prevention strategies, particularly among vulnerable populations experiencing food insecurity and limited healthcare access.

In this study, complementary feeding practices (MP-ASI) and exclusive breastfeeding were not significantly associated with diarrhea incidence in the final multivariate analysis. Although these findings differ from several previous studies reporting that exclusive breastfeeding protects children against diarrheal diseases (13,14,24,25), several explanations may account for these differences. First, environmental and sanitation-related factors such as unsafe water, poor hand hygiene, food contamination, and household sanitation conditions may have stronger influences on diarrhea incidence than feeding practices alone (22,23,26). Second, the use of secondary data may limit the precision of measurement regarding breastfeeding duration, feeding frequency, food preparation practices, and timing of complementary feeding introduction. Third, caregiver-reported information may introduce reporting inaccuracies and recall bias, particularly among mothers recalling feeding behaviors over extended periods. In addition, residual confounding factors such as maternal education, household income, parental knowledge, cultural feeding practices, and regional disparities may not have been fully captured in the

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present analysis. Therefore, the non-significant findings should not be interpreted as evidence that breastfeeding and complementary feeding are unimportant, but rather that their effects may be influenced by broader environmental and socioeconomic conditions.

The analysis also demonstrated that drinking water source remained an important determinant of diarrhea incidence. Children from households using unsafe drinking water sources had significantly higher odds of diarrhea compared with those using safe water sources. These findings are supported by previous studies indicating that unsafe water contributes substantially to fecal–oral transmission of enteric pathogens (9,10,12,27). Poor sanitation infrastructure, inadequate waste disposal systems, and overcrowded living conditions may further increase exposure to bacterial, viral, and parasitic infections. In many low-resource settings, contamination may occur not only at the source of water collection but also during household storage and handling practices. Therefore, interventions aimed at improving water quality should also incorporate household hygiene education and sanitation improvements to maximize effectiveness.

Immunization status emerged as the most dominant determinant in the multivariate analysis. Children with incomplete immunization had significantly higher odds of experiencing diarrhea compared with fully immunized children. Immunization provides protection against several infectious diseases associated with diarrhea, including rotavirus and measles (16,28,29). Previous studies have demonstrated that increasing immunization coverage contributes to substantial reductions in diarrhea morbidity, hospitalization, and mortality among children under five (16,17). The COVID-19 pandemic may also have contributed to temporary disruptions in routine immunization services in several regions of Indonesia, potentially increasing vulnerability to preventable infectious diseases (7). These findings emphasize the importance of strengthening immunization programs, improving outreach services in remote areas, and restoring routine vaccination coverage following healthcare disruptions.

Several potential confounding factors should also be considered when interpreting the findings of this study. Variables such as maternal education, socioeconomic status, household crowding, sanitation infrastructure, parental health literacy, and regional disparities may influence both exposure variables and diarrhea incidence simultaneously (18,21,23,27). Families with lower socioeconomic status may face multiple overlapping risk factors, including poor sanitation, limited healthcare access, inadequate nutrition, and lower immunization coverage. Because these variables were not comprehensively available in the secondary dataset, residual confounding may still exist and should be considered when interpreting the results.

This study has several limitations. First, the use of secondary cross-sectional data limits the ability to determine temporal or causal relationships between determinants and diarrhea incidence. Second, diarrhea status was based on caregiver-reported symptoms occurring within the previous two weeks, which may introduce recall bias and reporting bias. Some caregivers may underreport or overreport symptoms depending on their health knowledge and perception of illness. Third, several important behavioral variables such as handwashing practices, food hygiene, sanitation behavior, and environmental cleanliness were not comprehensively available in the dataset. Despite these limitations, this study also has important strengths. The use of nationally representative SSGI 2022 data provides broad generalizability across provinces and population groups in Indonesia, allowing more comprehensive understanding of diarrhea determinants at the national level.

The findings of this study have important public health and policy implications. Reducing diarrhea among Indonesian children under five requires integrated and multisectoral interventions involving healthcare services, immunization programs, nutrition improvement, water and sanitation infrastructure, and community health education. Expanding healthcare accessibility in rural and underserved regions remains essential to improve preventive care and early treatment. Strengthening routine immunization coverage, particularly among vulnerable populations, is also necessary to reduce preventable infectious diseases associated with diarrhea. In addition, improving access to safe drinking water and sanitation infrastructure should remain a national priority, particularly in areas with persistent environmental health disparities. Effective implementation of these interventions requires collaboration between healthcare providers, local governments, sanitation sectors, educational institutions, and community stakeholders to

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achieve sustainable improvements in child health outcomes and support the achievement of Sustainable Development Goals (SDGs), particularly SDG 3 and SDG 6.

CONCLUSION

This study demonstrates that diarrhea among under-five children in Indonesia remains an important public health problem influenced by multiple interrelated determinants, particularly healthcare access, nutritional status, drinking water sources, and immunization status. Among these factors, incomplete immunization emerged as the most dominant determinant associated with diarrhea incidence. The findings highlight that environmental, healthcare-related, and nutritional factors collectively contribute to the burden of diarrheal diseases among Indonesian children. These results emphasize the importance of integrated and multisectoral public health interventions to reduce diarrhea prevalence sustainably. Strengthening routine immunization programs, improving access to safe drinking water and healthcare services, and enhancing nutrition and hygiene education for caregivers are essential strategies to improve child health outcomes in Indonesia.

Future studies should consider longitudinal research designs and include additional behavioral, environmental, and socioeconomic variables, such as sanitation practices, maternal education, household income, and parental health literacy, to better understand the complex pathways influencing diarrhea among under-five children.

DECLARATION OF THE USE OF AI

The authors declare that no artificial intelligence (AI), AI-assisted technologies, or large language models (LLMs) were used in the conception of the study, data analysis, or the drafting, writing, and editing of this manuscript. The only exception is the graphical abstract, which was created using the design platform Illustrae (https://illustrae.co/). The authors take full responsibility for the content and accuracy of the graphical abstract and the entire manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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