

Socio-demographic determinants of health-care seeking options and alternative management practices of childhood diarrhoeal illness: A household survey among mothers in Iraq

Ihab Habib (✉ i.habib@murdoch.edu.au)

Murdoch University <https://orcid.org/0000-0002-0938-0607>

Ali Harb

Murdoch University

Sam Abraham

Murdoch University

Mark O'Dea

Murdoch University

Haidar Ali Hantosh

Murdoch University

David Jordan

Murdoch University

Research article

Keywords: Iraq, Child health, Social determinants, Diarrhoea, Home-based management

Posted Date: July 15th, 2019

DOI: <https://doi.org/10.21203/rs.2.11331/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Diarrhoea remains a significant cause of child morbidity and mortality in Iraq. The objective of this study was to examine the current practices of home-based management of diarrhoeal illnesses among Iraqi children. We surveyed mothers of children below five years of age in order to identify the socio-demographic factors associated with maternal health-care seeking practices. Methods A total of 500 mother-child pairs were interviewed in a cross-sectional household survey in Thi-Qar Governorate, south-eastern Iraq between March 2016 and February 2017. Logistic and multinomial regression models were utilized to infer socio-demographic predictors of the health-care seeking and alternative management practices adopted by the mothers. Results The interviewees reported that 35.2% of their children had diarrhoea in the two weeks prior to the survey. The least likelihood of reported occurrence of diarrhoea was among mother-child pairs where the mothers had received university education, as compared to mothers who were illiterate or received only primary or secondary education. Lower odds (OR=0.4, P-value <0.001) of reported childhood diarrhoea was revealed among mothers aged >25 years old compared to those younger. Self-ordered medicine from a pharmacy was the most preferred alternative management option in almost half (52.4% (262/500)) of the interviewed mothers in Thi-Qar. Interestingly, 69.6% (348/500) of the mothers reported supplying their children suffering from diarrhoea with antibiotics. Relative to mothers with university education, those with high school education had more likelihood of selecting medical center (relative risk ratio (rrr) = 2.4) and pharmacy (rrr = 3.7) as against no treatment. Conclusions Lower maternal educational level, mothers' age <25 and the district of residence were important factors associated with diarrhoea occurrence among under-five children. In light of the findings from this study, intervention aimed at improving health-care seeking for managing diarrhoea in Iraqi children should jointly consider the influence of mothers age, education, as well as the level of economic status of the communities in which mothers of these children resides. The results of this study indicate the need for enhancing public health education in order to improve the maternal management of diarrhoeal disease and the avoidance of unnecessary use of antimicrobials.

Background

Diarrhoea is one of the major causes of child morbidity and mortality in low income and developing countries. Children under the age of five years are particularly vulnerable with diarrhoea accounting for more than one-quarter of all deaths in this age group. Children under five years of age are estimated to account for 8% of total diarrhoeal deaths worldwide in 2016 [1]. The problem has been widely attributed to lack of access to quality healthcare and effective treatments [2,3,4,5].

In Iraq, the impacts of wars, sanctions and sectarian violence have left a shattered health system and an ongoing public health emergency impacting vulnerable sections of the population, particularly children [6,7-8]. The United Nations International Children's Emergency Fund (UNICEF) has indicated that diarrhoea is the second most common cause of death among Iraqi children under five years of age [9]. A study in Baghdad hospitals between 1990 and 1997 reported a mortality rate of 28.6% among children aged less

than five years experiencing diarrhoeal diseases [10]. In addition, a national study analyzing data from the Iraqi Multiple Indicator Cluster Survey showed that 21.3% of the children under-five had diarrhoea [11].

Most of the deaths attributed to diarrhoea result from dehydration following excessive losses of fluid and electrolytes. Thus, if home-based therapies are not effective at curbing symptoms then providing children with prompt access to health-care is critical for avoiding fatality [12,13]. Once health care is accessed, affordable and effective interventions exist in the form of oral rehydration therapy (ORT) combined with oral zinc supplements. When these treatments are given in a timely manner they represent the optimal approach for curtailing mortality [14,15,16]. A critical factor in the survival of these cases is therefore the level of maternal understanding of the effective options for home-based management and the symptoms that signal the need to access health-care [13-17,18,19]. Practices that conflict with the World Health Organization (WHO) treatment guidelines for the management of childhood diarrhoea [20] are sometimes relied upon in the home and include restriction of fluids, breast milk and/or food intake during diarrhoea episodes, and incorrect use of medicines [21,22]. At the very least these delay access to potentially life-saving therapy or may even act to hasten mortality.

The literature clearly establishes a socio-demographic gradient influencing the occurrence of diarrhoea in many countries [13-23,24,25]. Much less is known about the extent to which socio-demographic factors influence the maternal management of diarrhoea once it develops [23]. In Iraq, despite the dire impact of diarrhoea on the survival of children, there are no studies examining the influence of socio-demographic factors on how mothers seek access to health care when their children develop diarrhoea. The present study was therefore undertaken to examine home-based management of diarrhoeal disease in children in Thi-Qar governorate of Iraq and specifically to identify the socio-demographic factors associated with health care-seeking practices of mothers of under-five children. The results of this study provide important baseline information to inform national public health policies that address community needs on the management of childhood diarrhoea.

Methods

Study setting

A cross-sectional study was conducted in Thi-Qar Governorate, south-eastern Iraq between March 2016 and February 2017. Thi-Qar has an area of 12,900 km², and is divided into 5 districts (Nassriya, Al-Shatra, Al-Rifa'i, Suq Al-Shoyokh and Al-Chibaysih) with a total population of 1,742,852 as projected for the year 2013 [26]. Thi-Qar Governorate was targeted in this study because it is considered as the least developed governorate in Iraq; with 37.8% of the population living below the poverty line of US\$ 2.5 per day [26]. The economy of Thi-Qar is largely rural and dependent on livestock and crop production. Unpublished data from the Surveillance Unit in Thi-Qar Public Health Division has documented frequent occurrences of acute diarrhoea outbreaks among children under five years old for the past several years.

Study population and sampling procedures

In the present study we targeted mothers who had a child or children under-five years old. Information on the number of households and the population demographic map in Thi-Qar districts was supplied by the Primary Health Care Center (PHCC) in each district. A household was considered eligible for the survey if the following criteria were met: a) at least one child aged under 60 months living in the home; and, b) the caregivers (mothers) were aged above 18 years and were willing to participate in the interview. In the case where the family had more than one eligible child then only one child was randomly selected for inclusion in the study. Mothers were approached for interview in their household by field workers who were all female public health nurses affiliated with Thi-Qar Public Health Division. The principal investigator/author of this study provided five days of training for ten field workers and two quality control supervisors on the administration of the interview questions.

The sample size of the interviewed mothers was estimated using the single population proportion formula $Z^2 p (1-p) / d^2$, where p is prevalence of diarrhoea (assumed 0.5), d is the required margin of error (assumed 0.05), and Z is the normal distribution critical value corresponding to 95% confidence, resulting in a sample size of 384. Additional 116 samples (30% of the calculated sample size) were added to compensate for the anticipated non-response rate, resulting in a targeted sample size of 500 mother-child pairs. Two stages of sampling were conducted to select study participants from Thi-Qar community. In the first stage, five villages in each of the five districts of Thi-Qar were selected using a simple random sampling method; thus, a final sampling frame of 25 villages was eligible for the study. In the second stage of sampling, a listing of households with at least one child aged under-five years in each of the selected villages was obtained (based on data from PHCC for each district), and a cluster of 20 households was selected from this using a systematic random sampling technique. Hence, a total of 500 households with eligible mothers of children under-five years of age were recruited into the survey.

Questionnaire administration and ethics approvals

Household survey data were collected using a structured questionnaire. The questionnaire was prepared in English and translated to Arabic, and then back translated into English to assure the consistency and accuracy of the questions. The survey questionnaire was pilot tested with a group of mothers ($n= 10$) in one of the study districts in order to evaluate face validity and overall understanding of the questions. The questionnaire was divided into; a) general and demographic information of the mother and child; b) self-reported information on incidence of child diarrhoea; c) mother's knowledge about diarrhoeal disease; d) mother's intended actions in response to diarrhoea in their children aged under 5 years.

Informed verbal consent was obtained from the mothers before commencing the questionnaire interviews. Aim and objectives of the study were explained to all of the interviewed mothers and confidentiality of their information was confirmed. The study protocols have been reviewed and approved by the Murdoch University Human Research Ethics Committee (Permit No. 2015/224). Permission to

conduct the study was also obtained from the Ministry of Health, Iraq (Permit No.11/5/393) and Public Health Division in Thi-Qar Governorate (Permit No.1/4/29364).

Measures and statistical analysis

The collected questionnaire data were stored in Epi-Info version 3.5.1 software and then exported for descriptive analysis in Stata version 11.0 (Stata Corp, College Station, TX, USA). The interviewers gathered data on the occurrence of diarrhoea by asking mothers “*Did any of your children aged five and below pass a loose watery stool with or without blood continuously for more than three times in any particular day in the last two weeks?*”. For this response, univariable logistic regression was used to explore the relationship between predictor variables and the binary answers (yes/no) reported by the mothers (Table 1). Following from the initial univariable model, the analysis consisted of building a multivariable logistic regression model based on potential predictor factors indicated from the univariable analysis with P -value ≤ 0.25 . The most appropriate final model was selected using the backward stepwise selection approach [24]. The associations were assessed by odds ratio (OR) and 95% confidence intervals (CIs), and were considered significant at P -value ≤ 0.05 . All pairwise interactions between the variables in the final model were examined for significance. Goodness of fit of the final model was assessed using the Hosmer–Lemeshow test.

Mothers were further asked about home-based management options and types of health-care facilities that they seek in response to diarrhoea in their children under-five years old. The key outcome measures (dependent) variable were; a) mother’s choice of treatment seeking options; and b) alternative and/or home-based diarrhoea management options considered by the mother for management of childhood diarrhoea. The individual exploratory socio-demographic (independent) variables those were assessed as predictors for mother’s choices are; education level; employment status; age; district poverty index (categorized based on the proportion of population lived below the poverty line of US\$ 2.5 per day [26]). Because the outcomes consisted of categorical responses the discrete choice model based on multinomial logistic regression was used for analysis [24] by deploying the procedure “mlogit” in STATA software. In this analysis, the reference category and a set of logistic regressions were computed as follows; for health care seeking – the options were medical center, pharmacy vendor, and the reference category was the option of mothers not seeking treatment (no action). While for alternative and/or home-based – the options were purchase of medicine from pharmacy, provide homemade fluids, provide herbal remedies, and the reference category was to consult a traditional healer for assistance. These options are then, contrasted one after the other against reference categories. The relative risk ratios (rrr) were applied to examine the multivariate influence of the selected socio-demographic variables on mothers’ choices of health-care seeking and alternative management options of childhood diarrhoea. The goodness-of-fit of the model was determined by the likelihood ratio Chi-square. The importance of this statistic was to show whether the model fits significantly than an empty model, which is a model not including any of the explanatory variables of the study. Statistical significance was set at 5% (P -value ≤ 0.05).

Results

Baseline characteristics

Interviews were completed between March 2016 and February 2017 with 500 mothers in Thi-Qar, south-eastern Iraq. Of these, 35.2% (176/500) reported that a child, less than 5 years old, in their household suffered from diarrhoea in the two weeks prior to the interview. Data characteristics among the interviewed 500 mother-child pairs are presented in Table 1. The number of total inhabitants in the participating households ranged between 4 and 15 (median= 9 inhabitants), while the number of children less than 5 years old ranged between 1 and 4 (median= 2 children). Of the 500 children, 284 (56.8%) were males and 216 (43.2%) were females. Age of children ranged between 3 and 55 months (median= 20 months), while age of mothers ranged between 18 and 45 years (median= 25 years). Around one-third (34.8% (174/500)) of the mothers reported receiving a health education message on management of child diarrhoea from the local health department, and 39.2% (196/500) of them indicated they knew the signs of child diarrhoea.

Predictors associated with the occurrence of diarrhoea

Univariable logistic regression analysis was used to screen predictor factors associated with the self-reported occurrence of diarrhoea as indicated by mothers (Table 1). District of residence, age of child, number of inhabitants in the household, breastfeeding pattern in the first six months, age of mothers, employment status, education level, and the delivery of health education message to mothers (from the local health department on management of child diarrhoea) showed a P -value <0.25 and hence considered as potential predictor factors based on the univariable logistic regression model (Table 1). Out of these eight potential predictor factors, three were identified by the final multivariable logistic regression model as independently associated with the occurrence of diarrhoea reported by the mothers (Table 2). The estimated ORs and their 95% CIs of the multivariable logistic regression model are presented in Table 2. These results (Table 2) suggest that the reported occurrence of diarrhoea in their children was more likely to occur among mother-child pairs residing in Al-Rifa'i [58.9% (69/117)] and Nassriya (48.2% (42/87)) districts, and less likely to occur among mother-child pairs from Suq Al-Shoyokh district [9.3% (8/86)]. Among the study subjects, the least likelihood of reported occurrence of diarrhoea was among mother-child pairs of whom the mother received university education, as compared to mothers who were illiterate or received either primary or secondary education. Compared to mothers aged ≤ 25 years, those aged >25 years were found to have lower odds (OR=0.4, P -value <0.001) of reporting diarrhoea in their children. None of the two-way interactions between the variables were statistically significant ($P > 0.05$). The Hosmer–Lemeshow goodness-of-fit test suggested no evidence of lack of fit of the final model (Hosmer–Lemeshow $\chi^2 = 1.26$, $P = 0.8710$).

Mothers' practices and determinants of health-seeking options

Interviews also gathered information about mothers' practices and health-seeking options in response to diarrhoea occurring among their children (Table 3). Almost half of the mothers [55.2% (276/500)] indicated that they breastfeed their children less than the usual during diarrhoeal illness, and around quarter of them [27.2% (136/500)] reported providing more foods to their children while suffering from diarrhoea (Table 3). Of the 500 interviewed mothers, 36.4% preferred taking their diarrhoeic children to a medical center treatment. Self-ordered medicines from a pharmacy was the most preferred alternative management options in almost half [52.4% (262/500)] of the interviewed mothers in Thi-Qar (Table 3). Results in Table 3 revealed that 69.6% (348/500) of the mothers reported self-purchasing of antibiotics and administration to children suffering from diarrhoea. On the other hand, only 24% (120/500) indicated providing ORT to their diarrheic children. Results in Table 4 elaborate on some potential predictor factors associated with the practice of providing antibiotics and ORT among the interviewed mothers. Univariable logistic regression analysis indicated that the practice of providing antibiotics to diarrhoeic children was significantly higher among mothers aged >25 years (OR= 1.5, *P*-value= 0.038) and mothers that received high school education (OR=2.5, *P*-value= 0.051). On the other hand, the practice of providing ORT therapy was particularly associated with employed mothers (OR= 2.6, *P*-value= 0.008), as well as with mothers interviewed in districts with more favorable poverty status (OR= 2.5, *P*-value= 0.007) (Table 4).

Table 5 depicts the relative risk ratio (*rrr*) for the multinomial models. The result shows that, relative to mothers with university education, those with high school education had more likelihood of seeking help through visiting medical centers (*rrr*= 2.4) and pharmacies (*rrr*= 3.7) as against mothers seeking no treatment. Among mothers from districts with 5%-9.9% below the poverty line and relative to those from districts with 10%-24.9% below the poverty line; the likelihood of opting for pharmacy versus no treatment was two times lower (*rrr*= 0.2). As shown in Table 5, relative to mothers who received university education level, illiterate mothers were more likely to use herbal remedies and homemade fluids as alternative options for the management of diarrhoea among their children, as compared with seeking help from a traditional healer. The results also show that the likelihood of using herbal remedies was higher (*rrr*=2.3) among mothers aged >25 years compared to their younger counterparty (≤ 25 years) (Table5).

Discussion

To the best of our knowledge, this is the first study to investigate the socio-demographic factors associated with childhood diarrhoeal illness and caregiver treatment in Iraq. This study highlights the significant role of mothers in health-care seeking practices and alternative management options in relation to diarrhoeal illness among their children. In the present study, 35.2% of under-five children in Thi-Qar were report to have experienced diarrhoea in the two weeks prior to survey. This occurrence of diarrhoea is higher than the rate reported for a similar age group (21.3%) in a national household survey among Iraqi mothers in the year 2000 [11] and is also higher than levels in similar household studies conducted in the Eastern Mediterranean region including Jordan (19.1%) [27] and Egypt (23.6%) (Dakahlia) [28]. Nevertheless, a number of other community studies reported higher rates of diarrhoea in

children under five-years, for example: North and South Ethiopia (30.5- 31.3%) [22-29], Afghanistan (32.5%) [30], Burundi rural areas (32.6) [3] and Southern Nepal (36.6%) [21].

Promotion of hygiene and health education messages in the community and family is regarded as a key pillar in the fight against childhood diarrhoea [3]. However, in the present study, only 34.8% of the mothers reported receiving health education messages relating to the management of child diarrhoea from the local health department. The level of public health communication is lower than what was noted in studies in Ghana, where 73.65 % and 79.6 % of caregivers of children under-five years received health education messages on diarrhoea in the Volta and the Northern Region. In the Ghanaian studies, the majority of messages were acquired through nurses in health facilities [31] suggesting this as potentially low cost community health strategy which could receive greater emphasis in Iraq. Our results also showed that 39.2% of the mothers knew about signs of child diarrhoea. This result is comparable to surveys conducted previously in the North of Iraq (Sulaimania) [32], Iran (Zahedan) [33], Odisha [34], Tanzania (Mkuranga) [35], which reported the low level of mothers' knowledge about signs of diarrhoea. The WHO/UNICEF indicated that the mothers/caregivers perception of the signs of child diarrhoeal disease is a major determinant of the choice of care sought to reduce the risk of illness [36]. Mothers/caregivers in Iraq need to be empowered with accurate information to improve their knowledge and practices concerning diarrhoea prevention and treatment. The training and dissemination of community nursing and public health staff would be a relatively low cost, rapidly implementable intervention which could significantly improve the treatment-seeking practices of mothers in Thi Qar.

Among socio-demographic variables, place of residence, education, and age were important predictors associated with occurrence of diarrhoeal illness in the household in the two weeks before the study. In the multivariate analyses (Table 2), higher diarrhoea occurrence rates were reported in children under five years old whose mothers living in Al-Rifa'i and Nassriya districts. Such considerable spatial heterogeneity of the reported diarrhoea occurrence in Thi-Qar might be a reflection of variations in the exposure to risk factors from one district to another; such as living conditions, socioeconomic status, and drinking water quality [26]. This is specifically relevant to the situation in Al-Rifa'i district where 54.1% of the population lived below the poverty line of US\$ 2.5 per day compared to only 12.3% of the population living in Al-Chibayish district [26]. Added to that, 48.5% of the population in Al-Rifa'i relied on public water (municipality supplied) as the main source of drinking water [26]. This is supported by our previous findings demonstrating a higher likelihood of detection of enteric pathogens in children diarrhoeal cases from households supplied by public (pipe) water, versus households utilizing reverse osmosis water, in Thi-Qar [37]. A community cross-sectional study in Mbour, Senegal by Thiam et al. [38] observed children living in better-off families were less likely to have diarrhoea compared to their lower income counterparts. Our results are in line with several household studies on diarrheic children that have demonstrated that the wealth status of the family is correlated with better access to household amenities, including those related to better hygiene and environmental health, which likely reduce the risk of diarrhoea [39,40].

In the current study, the reported occurrence of diarrhoea was significantly lower in children whose mothers had received a university education, compared to children whose mothers were illiterate or received either primary or secondary education. These results are in agreement with what was reported from studies conducted in neighboring countries such as Turkey [40], Iran [33] and Jordan [27], where children belonging to mothers with a higher education level (university or diploma) were less likely to have diarrhoea compared to those whose mothers had a lower level education (primary or secondary) or were illiterate. This finding might indicate that those mothers who have a higher education level are attaining more awareness on good child feeding practices, hygiene behaviors and safe handling of water which in turn are important factors for reducing the risks associated with childhood diarrhoea [21,22-39]. In addition to mothers' education level, the present study observed that the reported occurrence of diarrhoea is likely to be less in children belonging to mothers aged >25 years compared to mothers aged ≤ 25 years. The former finding was also revealed in studies from Iraq [32], and Jordan [27], also indicating a lower likelihood of diarrhoea rates among children from mothers aged >25 years than children belonging to mothers aged ≤ 25 years. These observations are typically argued to be linked with the experience attained on matters related to childcare with the advancement in age [3].

As shown in Table 3, the findings of this study revealed that 55.2% of the mothers reportedly breastfed their diarrheic children less than usual, and 27.2% of the mothers offering more foods to their infected children during the diarrhoeal illness. Similar to our finding, a recent study on management of diarrhoeal disease among under-five children at home in Eastern Ethiopia [41] observed that 60.3% of the mothers reported breastfed their child suffering from diarrhoea less than usual and 33.6% of mothers offered food more than usual to eat during the diarrhoeal infection of the child. According to the 2004 UNICEF and WHO joint statement, encouraging mothers to continue breastfeeding and provide increased amounts of fluids and foods to children is recommended, particularly for infants with diarrhoea in order to avoid severe dehydration and death [36]. While the responses from this study were qualitative only, and thus levels or frequency of breastfeeding during diarrhoeic episodes cannot be ascribed, this is another initiative which could be promoted through an increase in public health awareness.

Our study noted that 36.4% of the mothers preferred taking their children to health centers for treatment at the time of diarrhoeal disease. It was reported in previous work that among the reasons for such low rates of approaching health facilities by mothers are; the expectations of mothers that diarrhoea will recover without treatment, or that the illness was not serious enough or due to the common perception that diarrhoea was a secondary sign to new teething [14-42]. This is also thought to be related to the common practice of self-medication through pharmacies which may also be due to the mistrust of the communities in public health facilities due to various reasons such as absenteeism of medical staff, lack of medicines and the prevailing perception that private sector medicines are more effective for the treatment of diarrhoea than those from the government sector. In the current investigation, 69.6% of the mothers reported giving their children antibiotics for the management of diarrhoea. This finding is not surprising as antibiotics, especially in developing countries like Iraq, are both widely prescribing and obtained directly without a prescription [43]. This high utilization of medicines without prescriptions from a pharmacy is alarming from a public health perspective [43,44] for multiple reasons including failure to

administer the correct antibiotic, the probability that diarrhoeal disease is not due to a bacterial agent [37], likelihood that the majority of cases require ORT rather than antibiotics and of course the promotion of antimicrobial resistance.

ORT is a primary intervention for the management of childhood diarrhoea and the most effective way to treat dehydration and decrease mortality [14]. Despite the strong advocacy by the World Health Organization (WHO) to promote awareness and the use of ORT, the use remains gravely low in developing countries [45]. We found a low proportion (24%) of mothers reported to have administered ORT to their children with diarrhoea. This result is in accordance with data from former studies performed in North Africa (Egypt) [46] and West Africa (Burkina Faso) [47], where mothers reported the lower ORT use rate in both of studies as 24% for the management of diarrhoea in children under five years. Therefore, implementation of public health outreach programmes are required to promote usage of ORT at the Iraqi community level.

As shown in the results of our data (Table 5), level of education, mother's age, and household income index are important determinants of where treatments are sought. Our study found that seeking care at a medical centre and pharmacy was positively associated with education level of mothers, which is corroborated by other studies [13-47]. These results, as well as those from other studies, suggest that educated mothers may have better knowledge about the potentially serious nature of diarrhoea, and thus were more likely to seek health care for their ill child at health facilities and pharmacy as against not seeking care [12,18-47]. While another study indicated that the choice of utilization of health facilities depend on treatment cost, service quality and severity of illness [16]. Modelling results indicate that alternative options for management of diarrhoea such as using herbal remedies was found to be associated with the mothers who were illiterate and aged >25 years, and is most likely a result of cultural beliefs in this demographic.

There are some limitations to this study. First, the assessment of diarrhoea prevalence was based on what the mother reported and there was no way to verify whether what they referred to as diarrhoea was certainly diarrhoea. Second, the survey did not ask about the type of diarrhoea when looking at the healthcare-seeking practice, that is, whether it was acute or chronic diarrhoea. However, given the nature of the study, it would not have been possible to clearly ascertain the type of diarrhoea since we rely on self-reported information, and it is possible that differential health-seeking behavior was the result of differences in sickness rather than the determinants identified in our study, thus increasing bias. Thirdly, our study relies on reported action taken by the mothers on the diarrhoea management practice and eventually, the study did not take into account other factors that could affect healthcare-seeking such as treatment cost, services quality and access to health facilities. More questions about the evaluation of health care services for the diarrhoea management at health facilities and verification of costs should be added to future studies.

Conclusions

Our study revealed that the reported occurrence of diarrhoea among children under the age of five is high in Thi-Qar (35.2%). Lower maternal educational level, mothers' age <25 and place of residence were important factors associated with diarrhoea occurrence among under-five children. The results of this study indicate that relatively cheap, cost-effective measures centered around health education, dissemination of information and higher numbers of public health outreach staff will likely to improve the maternal management of diarrhoeal disease and avoidance of unnecessary and potentially harmful use of antimicrobials.

Abbreviations

CI: Confidence interval; OR: odds ratio; *rrr*: relative risk ratio; S.E: standards error; *vs.*: Versus; ORT: Oral rehydration therapy; >: Greater than; <: Less than; %: Percent; PHCCs: Primary Health Care Centers; US\$: United States Dollars; WHO: World Health Organization; UNICEF: United Nations International Children's Emergency Fund.

Declarations

- Ethics approval and consent to participate

Informed verbal consent was obtained from the mothers before commencing the questionnaire interviews. The study protocol and verbal consent arrangements were approved by the Murdoch University Human Research Ethics Committee (Permit No. 2015/224) in order to mind the educational and cultural contexts in the study setting. Aim and objectives of the study were explained to all of the interviewed mothers and confidentiality of their information was confirmed. The study was submitted to and approved by the Ministry of Health, Iraq (Permit No.11/5/393) and ethical approval was also granted by the Scientific and Ethical Research Committee of the Training and Developing Centre for Thi-Qar Health Director (Permit No.1/4/29364).

- Consent to publish

Similarly to consent to participate, an advanced informed consent for publication was obtained in written form from the interviewed mothers.

- Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests.

- Funding

This study was supported by a PhD scholarship from the Iraqi government and Murdoch University (Perth, Western Australia).

- Authors' contributions

IH and SA designed and supervised the overall study. AH and HH conducted the investigation and collected the data. IH performed the statistical analysis. Writing -original draft: AH. Writing - review & editing: AH, IH, MO, DJ and SA. All authors read and approved the final manuscript.

- Acknowledgments

The authors would like to express profound gratitude to Thi-Qar Public Health Division, all the data collectors, field supervisors, study participants, for their contributions to the success of this study. We would also like to extend our gratitude to Thi-Qar district administrators for their facilitation of the movement of the team and data collection.

- Authors' information

¹ Antimicrobial Resistance and Infectious Diseases Laboratory (AMRID), College of Science, Health, Engineering and Education, Murdoch University, Perth6150, Australia.

² Thi-Qar Public Health Division, Ministry of Health, Thi-Qar 64007, Iraq.

³New South Wales Department of Primary Industries, 1243 Bruxner Highway, Wollongbar, NSW, 2477, Australia

⁴ High Institute of Public Health (HIPH), Alexandria University, Alexandria 21516, Egypt.

⁵ Veterinary Medicine Department, College of Food and Agriculture, United Arab of Emirates University (UAEU), Al Ain, P.O.Box 15551, United Arab of Emirates

References

[1] United Nations International Children's Emergency Fund. Diarrhoeal diseases. UNICEF Data: monitoring the situation of children and women, 2018. Available from: <https://data.unicef.org/topic/child-health/diarrhoeal-disease/>. Accessed 5 June 2018.

[2] Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhoea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health*. 2012; 12: 220.

[3] Diouf K, Tabatabai P, Rudolph J, Marx M. Diarrhoea prevalence in children under five years of age in rural Burundi: an assessment of social and behavioural factors at the household level. *Glob Health Action*. 2014; 7: 24895.

- [4] Pop M, Walker AW, Paulson J, Lindsay B, Antonio M, Hossain MA, et al. Diarrhoea in young children from low-income countries leads to large-scale alterations in intestinal microbiota composition. *Genome Biol.* 2014; 15(6): R76.
- [5] GBD 2015 Eastern Mediterranean Region Diarrhoea Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017; 17(9): 909-948.
- [6] Ascherio A, Chase R, Cote T, Dehaes G, Hoskins E, Laaouej J, et al. Effect of the Gulf War on infant and child mortality in Iraq. *N Engl J Med.* 1992; 327(13): 931-6.
- [7] Ali MM, Shah IH. Sanctions and childhood mortality in Iraq. *Lancet.* 2000; 355(9218): 1851-7.
- [8] Daponte BO, Garfield R. The effect of economic sanctions on the mortality of Iraqi children prior to the 1991 Persian Gulf War. *Am J Public Health.* 2000; 90(4): 546-52.
- [9] United Nations International Children's Emergency Fund. Evaluation of UNICEF Emergency Preparedness and Early Response in Iraq (September 2001-June 2003), 2004. Available from: https://www.unicef.org/evaldatabase/files/Iraq_evaluation_FINAL_2006.pdf
- [10] Tawfeek HI, Najim NH, Al-Mashikhi S. Studies on diarrhoeal illness among hospitalized children under 5 years of age in Baghdad during 1990-97. *East Mediterr Health J.* 2002; 8(1): 181-8.
- [11] Siziya S, Muula AS, Rudatsikira E. Diarrhoea and acute respiratory infections prevalence and risk factors among under-five children in Iraq in 2000. *Ital J Pediatr.* 2009; 35(1): 8.
- [12] Das SK, Nasrin D, Ahmed S, Wu Y, Ferdous F, Farzana FD, et al. Health care-seeking behavior for childhood diarrhoea in Mirzapur, rural Bangladesh. *Am J Trop Med Hyg.* 2013; 89(1 Suppl):62-8.
- [13] Adane M, Mengistie B, Mulat W, Kloos H, Medhin G. Utilization of health facilities and predictors of health-seeking behavior for under-five children with acute diarrhoea in slums of Addis Ababa, Ethiopia: a community-based cross-sectional study. *J Health Popul Nutr.* 2017; 36(1): 9.
- [14] Mengistie B, Berhane Y, Worku A. Predictors of Oral Rehydration Therapy use among under-five children with diarrhoea in Eastern Ethiopia: a community based case control study. *BMC Public Health.* 2012; 12: 1029.
- [15] Habib MA, Soofi S, Sadiq K, Samejo T, Hussain M, Mirani M, et al. A study to evaluate the acceptability, feasibility and impact of packaged interventions ("Diarrhoea Pack") for prevention and treatment of childhood diarrhoea in rural Pakistan. *BMC Public Health.* 2013; 13: 922.
- [16] Mahapatra T, Mahapatra S, Banerjee B, Mahapatra U, Samanta S, Pal D, et al. Predictors of rational management of diarrhoea in an endemic setting: observation from India. *PLoS One.* 2015; 10(4): e0123479.

- [17] Manna B, Nasrin D, Kanungo S, Roy S, Ramamurthy T, Kotloff KL, et al. Determinants of health care seeking for diarrhoeal illness in young children in urban slums of Kolkata, India. *Am J Trop Med Hyg.* 2013; 89(1 Suppl): 56-61.
- [18] Omoro R, O'Reilly CE, Williamson J, Moke F, Were V, Farag TH, et al. Health care-seeking behavior during childhood diarrhoeal illness: results of health care utilization and attitudes surveys of caretakers in western Kenya, 2007-2010. *Am J Trop Med Hyg.* 2013; 89(1 Suppl): 29-40.
- [19] Othero DM, Orago AS, Groenewegen T, Kaseje DO, Otengah PA. Home management of diarrhea among underfives in a rural community in Kenya: household perceptions and practices. *East Afr J Public Health.* 2008;5(3):142-6.
- [20] WHO. The treatment of diarrhoea: A manual for physicians and other senior health workers, 4th rev. 2005. Available from: <https://apps.who.int/iris/bitstream/handle/10665/43209/9241593180.pdf?sequence=1>
- [21] Acharya D, Singh JK, Adhikari M, Gautam S, Pandey P, Dayal V. Association of water handling and child feeding practice with childhood diarrhoea in rural community of Southern Nepal. *J Infect Public Health.* 2018.; 11(1): 69-74.
- [22] Gizaw Z, Woldu W, Bitew BD. Child feeding practices and diarrhoeal disease among children less than two years of age of the nomadic people in Hadaleala District, Afar Region, Northeast Ethiopia. *Int Breastfeed J.* 2017. 12: 24.
- [23] Gebru T, Taha M, Kassahun W. Risk factors of diarrhoeal disease in under-five children among health extension model and non-model families in Sheko district rural community, Southwest Ethiopia: comparative cross-sectional study. *BMC Public Health.* 2014: 14: 395.
- [24] Sinmegn Mihrete T, Asres Alemie G, Shimeka Teferra A. Determinants of childhood diarrhoea among underfive children in Benishangul Gumuz Regional State, North West Ethiopia. *BMC Pediatr.* 2014; 14:102.
- [25] Woldu W, Bitew BD, Gizaw Z. Socioeconomic factors associated with diarrhoeal diseases among under-five children of the nomadic population in northeast Ethiopia. *Trop Med Health.* 2016; 44: 40.
- [26] Joint Analysis Unit. Thi-Qar Governorate Profile. Iraq: United Nations, 2013. Available from: <http://www.cybermanual.com/thi-qar-ir-joint-analysis-unit-jau.html?page=5>. Accessed 5 October 2013.
- [27] Okour A, Al-Ghazawi Z, Gharaibeh M. Diarrhoea Among Children and the Household Conditions in a Low-Income Rural Community in the Jordan Valley. *J Med J.* 2012; 46 :108- 117.
- [28] El-Gilany AH, Hammad S. Epidemiology of diarrhoeal diseases among children under age 5 years in Dakahlia, Egypt. *East Mediterr Health J.* 2005; 11(4): 762-75.

- [29] Mohammed S, Tamiru D. The Burden of Diarrhoeal Diseases among Children under Five Years of Age in Arba Minch District, Southern Ethiopia, and Associated Risk Factors: A Cross-Sectional Study. *Int Sch Res Notices*. 2014, 2014: 654901.
- [30] Mashal T, Takano T, Nakamura K, Kizuki M, Hemat S, Watanabe M, Seino K. Factors associated with the health and nutritional status of children under 5 years of age in Afghanistan: family behaviour related to women and past experience of war-related hardships. *BMC Public Health*. 2008, 8: 301.
- [31] Escribano-Ferrer B, Gyapong M, Bruce J, Narh Bana SA, Narh CT, Allotey NK, et al. Effectiveness of two community-based strategies on disease knowledge and health behaviour regarding malaria, diarrhoea and pneumonia in Ghana. *BMC Public Health*. 2017; 17(1): 948.
- [32] Moawed SA, Saeed AA. Knowledge and practices of mothers about infants' diarrhoeal episodes. *Saudi Med J* 2000, 21(12):1147-51.
- [33] Manijeh K, Mirshahi M, Zarghami A, Rajabnia Chenari M, Farahmand F. Maternal Knowledge and Practice Regarding Childhood Diarrhoea and Diet in Zahedan, Iran. *Health Scope*. 2013; 2(1). DOI:10.5812/jhs.9885.
- [34] Padhy S, Sethi RK, Behera N. Mother's knowledge, attitude and practice regarding prevention and management of diarrhoea in children in Southern Odisha. *Int J Contemp Pediatr*. 2017; 4(3): 966-971. DOI: <http://dx.doi.org/10.18203/2349-3291.ijcp20171708>
- [35] Mashoto KO, Malebo HM, Msisiri E, Peter E. Prevalence, one week incidence and knowledge on causes of diarrhoea: household survey of under-fives and adults in Mkuranga district, Tanzania. *BMC Public Health*. 2014;14: 985.
- [36] WHO/UNICEF. Clinical management of acute diarrhoea: WHO/UNICEF joint statement. 2004. Available from: https://www.unicef.org/publications/files/ENAcute_Diarrhoea_reprint.pdf.
- [37] Harb A, Abraham S, Rusdi B, Laird T, O'Dea M, Habib I. Molecular Detection and Epidemiological Features of Selected Bacterial, Viral, and Parasitic Enteropathogens in Stool Specimens from Children with Acute Diarrhoea in Thi-Qar Governorate, Iraq. *Int. J. Environ. Res. Public Health*. 2019; 16:1573.
- [38] Thiam S, Diène AN, Fuhrmann S, Winkler MS, Sy I, Ndione JA, Schindler C, Vounatsou P, Utzinger J, Faye O, Cissé G. Prevalence of diarrhoea and risk factors among children under five years old in Mbour, Senegal: a cross-sectional study. *Infect Dis Poverty*. 2017; 6(1): 6:109.
- [39] Kumi-Kyereme A; Amo-Adjei J. Household wealth, residential status and the incidence of diarrhoea among children under-five years in Ghana. *J Epidemiol Glob Health*. 2016; 6:131- 140.
- [40] Bozkurt AI, Ozgur S, Ozcirpici B. Association between household conditions and diarrhoeal diseases among children in Turkey: a cohort study. *Pediatr Int*. 2003; 45: 443-51.

- [41] Workie HM, Sharifabdilahi AS, Addis EM. Mothers' knowledge, attitude and practice towards the prevention and home-based management of diarrhoeal disease among under-five children in Diredawa, Eastern Ethiopia, 2016: a cross-sectional study. *BMC Pediatr*, 2018; 19: 18:358.
- [42] Page AL, Hustache S, Luquero FJ, Djibo A, Manzo ML, Grais RF. Health care seeking behavior for diarrhoea in children under 5 in rural Niger: results of a cross-sectional survey. *BMC Public Health*. 2011; 11:389.
- [43] Jassim AM. In-home Drug Storage and Self-medication with Antimicrobial Drugs in Basrah, Iraq. *Oman Med J*. 2010; 25(2): 79-87.
- [44] Burnham G, Taylor CH, Hung YW, Ferati A, Dyer A, Hifi TA, et al. Perceptions and utilization of primary healthcare services in Iraq: findings from a national household survey. *World Health Popul*. 2012; 13(3): 68-79.
- [45] WHO. The World Medicines Situation 2011 - Rational Use of Medicines. 3rd Edition. 2011. Available from: <http://apps.who.int/medicinedocs/en/m/abstract/Js18064en/>
- [46] Jousilahti P, Madkour SM, Lambrechts T, Sherwin E. Diarrhoeal disease morbidity and home treatment practices in Egypt. *Public Health*. 1997;111(1):5-10.
- [47] Wilson SE, Ouedraogo CT, Prince L, Ouedraogo A, Hess SY, Rouamba N, et al. Caregiver recognition of childhood diarrhoea, care seeking behaviors and home treatment practices in rural Burkina Faso: a cross-sectional survey. *PLoS One* 2012; 7(3): e33273.

Tables

Table 1 Univariate analysis of factors associated with mothers (n= 500) reporting of the occurrences of diarrhoea among their children <5 years old in Thi-Qar governorate, Iraq

Variables	Category	Total	Reported diarrhoea (%) ^b	OR ^c (95% CI) ^d	P-value
District of residence ^a	Al-Chibaysih	115	32 (27.8)	1.0 (—)	—
	Nassriya	87	42 (48.2)	1.7 (0.8-3.8)	0.084
	Al-Rifa'i	117	69 (58.9)	3.7 (2.1-6.4)	<0.001
	Al-Shatra	95	25 (26.3)	0.9 (0.5-1.7)	0.807
	Suq Al-Shoyokh	86	8 (9.3)	0.2 (0.1-0.6)	0.002
Gender of child	Female	216	81 (37.5)	1.0 (—)	—
	Male	284	95 (33.4)	0.8 (0.5-1.2)	0.348
Age of child ^a	< 2 years	74	21 (28.3)	1.0 (—)	—
	≥ 2 years	426	155 (36.3)	1.4 (0.8-2.4)	0.185
Number of inhabitants in the household ^a	< 8	222	66 (29.7)	1.0 (—)	—
	> 8	278	110 (39.5)	1.5 (1.1-2.2)	0.022
Number of children <5 years in the household	< 2	310	105 (33.8)	1.0 (—)	—
	> 2	190	71 (37.3)	1.1 (0.7-1.6)	0.427
Mother breast feeding pattern in the first 6 months of age ^a	Exclusive bottle fed	157	65 (41.4)	1.0 (—)	—
	Exclusive breast fed	242	74 (30.58)	0.6 (0.4-0.9)	0.027
	Mix - breast and bottle	101	37 (36.6)	0.8 (0.4-	0.445

	fed			1.3)	
her age ^a	≤ 25 years	254	116 (45.6)	1.0 (—)	—
	> 25 years	246	60 (24.3)	0.3 (0.2- 0.5)	<0.001
her employment status ^a	Not working	399	153 (38.3)	1.0 (—)	—
	Working	101	23 (22.7)	0.4 (0.2- 0.7)	0.004
her education level ^a	University	44	9 (20.4)	1.0 (—)	—
	High school	55	16 (29.1)	1.5 (0.6- 4.0)	0.328
	Primary	204	77 (37.7)	2.3 (1.1- 5.1)	0.032
	Secondary	101	36 (35.6)	2.1 (0.9- 4.9)	0.073
	Illiterate	96	38 (39.6)	2.5 (1.1- 5.8)	0.029
her knew about the signs of child diarrhoea	No	304	107 (35.2)	1.0 (—)	—
	Yes	196	69 (35.2)	1.0 (0.6- 1.4)	0.999
her received a health education message from local health department on management of child diarrhoea this summer ^a	No	326	122 (37.4)	1.0 (—)	—
	Yes	174	54 (31.0)	0.7 (0.5- 1.1)	0.155

^a Variables with $P < 0.25$; predictor factor offered to the final multivariable logistic model

^b by mother regarding diarrhoea incidence in the last two weeks

^c OR: odd ratio; ^d CI: confidence interval

Table 2 Multivariable logistic regression model of factors significantly associated with mothers (n= 500) reporting of the occurrence of diarrhoea among their children <5 years old in Thi-Qar governorate, Iraq

Predictor factor	OR ^a	95% CI ^b	S.E. ^c	P-value
<i>District - versus Al-Chibaysih</i>				
Nassriya	2.4	(1.1, 5.3)	0.967	0.026
Al-Rifa'i	3.6	(2.1, 5.9)	0.924	<0.001
Suq Al-Shoyokh	0.2	(1.1, 3.9)	0.107	0.001
<i>Level of education - versus University</i>				
Primary	2.1	(1.2, 3.9)	0.664	0.011
Secondary	2.1	(1.1, 4.2)	0.742	0.031
Illiterate	2.3	(1.2, 4.8)	0.869	0.016
<i>Mother age- versus ≤ 25 years</i>				
> 25 years	0.4	(0.2, 0.6)	0.0872	<0.001

^a OR: odd ratio; ^b CI: confidence interval; ^c S.E: standards error

Table 3 Overview of some practices reported by Iraqi mothers interviewed in Thi-Qar governorate (n= 500) in relation to the management of diarrhoeal illness among their children <5 years old

Variable	Category	Frequency (<i>n</i>)	Percentage
Breastfeeding child during diarrhoea	No change in pattern (usual)	154	30.8
	Breastfeed less than usual	276	55.2
	Breastfeed more than usual	—	—
	Stop breastfeeding	70	14.0
Provide child with more frequent foods	No	364	72.8
	Yes	136	27.2
Preferred treatment seeking options	Medical centers	182	36.4
	Pharmacy	108	21.6
	No treatment	210	42.0
Preferred alternative management options	Traditional healer	170	34.0
	Herbal remedies	26	5.2
	Homemade fluids	42	8.4
	Self-ordered medicine from a pharmacy	262	52.4
Antibiotic is provided to child	No	152	30.4
	Yes	348	69.6
Oral Rehydration Therapy (ORT) is provided to child	No	380	76.0
	Yes	120	24.0

Table 4 Univariate analysis of factors associated with providing antibiotics and oral rehydration therapy (ORT) among Iraqi mothers' (n=500) in the course of management of diarrhoea among their children <5 years old

Variable	Category	Antibiotic is provided to child		ORT is provided to child	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Mother education level	University	1.0 (—)	1.0 (—)	1.0 (—)	1.0 (—)
	High school	2.5 (0.9, 6.2)	0.051	0.6 (0.2, 1.6)	0.358
	Primary	1.1 (0.4, 2.7)	0.820	1.4 (0.5, 3.6)	0.472
	Secondary	1.2 (0.5, 3.0)	0.604	0.7 (0.3, 1.9)	0.604
	Illiterate	0.8 (0.3, 2.1)	0.654	0.4 (0.1, 1.4)	0.191
Mother employment status	Not working	1.0 (—)	1.0 (—)	1.0 (—)	1.0 (—)
	Working	0.7 (0.3, 2.1)	0.492	2.6 (1.3, 5.5)	0.008
Mother age	≤ 25 years	1.0 (—)	1.0 (—)	1.0 (—)	1.0 (—)
	> 25 years	1.5 (1.0, 2.2)	0.038	1.0 (0.6, 1.5)	0.863
District poverty index	10%-24.9% below the poverty line	1.0 (—)	1.0 (—)	1.0 (—)	1.0 (—)
	5%-9.9% below the poverty line	1.5 (0.8, 2.7)	0.121	2.5 (1.2, 4.8)	0.007
	≥40% below the poverty line	1.3 (0.7, 2.3)	0.308	1.8 (0.9, 3.5)	0.087
Age of child	< 2 years	1.0 (—)	1.0 (—)	1.0 (—)	1.0 (—)
	≥ 2 years	1.1 (0.7, 1.6)	0.591	0.8 (0.5, 1.3)	0.560

Table 5 Multinomial model estimates of preferred treatment seeking options and alternative options as determined by mothers (n= 500, Thi-Qar - Iraq) socio-demographic characteristics

Model—preferred treatment seeking options (with no treatment as reference)		Medical centers	Pharmacy	
		<i>IRR</i> (95% CI)	<i>IRR</i> (95% CI)	
Mother education level	University	1.0 (—)	1.0 (—)	
	High school	2.4 (0.9, 6.1)*	3.7 (1.1, 12.2)*	
	Primary	1.4 (0.5, 3.7)	1.8 (0.5, 6.3)	
	Secondary	1.6 (0.6, 4.2)	5.7 (1.7, 18.9)*	
	Illiterate	0.9 (0.3, 2.7)	3.3 (0.9, 12.1)	
Mother employment status	Not working	1.0 (—)	1.0 (—)	
	Working	1.2 (0.6, 2.6)	1.5 (0.6, 3.5)	
Mother age	≤ 25 years	1.0 (—)	1.0 (—)	
	> 25 years	1.1 (0.7, 1.6)	0.8 (0.5, 1.4)	
District poverty index	10%-24.9% below the poverty line	1.0 (—)	1.0 (—)	
	5%-9.9% below the poverty line	0.9 (0.5, 1.7)	0.2 (0.1, 0.5)***	
	≥40% below the poverty line	0.8 (0.4, 1.6)	0.6 (0.3, 1.3)	
Model—preferred alternative management options (with traditional healer as reference)		Herbal remedies	Homemade fluids	Self-ordered medicine from a pharmacy
		<i>IRR</i> (95% CI)	<i>IRR</i> (95% CI)	<i>IRR</i> (95% CI)
Mother education level	University	1.0 (—)	1.0 (—)	1.0 (—)
	High school	1.9 (0.1, 2.3)	1.2 (0.2, 8.5)	0.8 (0.3, 2.0)
	Primary	4.6 (0.3, 6.4)	6.6 (0.8, 26.5)	1.2 (0.5, 3.1)
	Secondary	2.4 (0.18, 3.2)	1.4 (0.2, 4.4)	1.0 (0.4, 2.5)
	Illiterate	19.8 (1.3, 28.3)*	9.4 (1.1, 26.6)*	1.6 (0.6, 4.4)
Mother employment status	Not working	1.0 (—)	1.0 (—)	1.0 (—)
	Working	1.9 (0.3, 10.1)	2.4 (0.6, 9.9)	
Mother age	≤ 25 years	1.0 (—)	1.0 (—)	1.0 (—)
	> 25 years	2.3 (0.9, 5.6)*	1.1 (0.5, 2.1)	0.8 (0.4, 1.6)
District poverty index	10%-24.9% below the poverty	1.0 (—)	1.0 (—)	1.0 (—)

line			
5%-9.9% below the poverty	0.6 (0.1, 3.0)	1.2 (0.4, 3.5)	0.8 (0.4, 1.5)
line			
≥40% below the poverty line	1.1 (0.2, 4.2)	0.7 (0.2, 2.2)	0.6 (0.3, 1.1)

* *P*-value < 0.05, ** *P*-value < 0.01, ****P*-value < 0.001