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Socio-Demographic Factors Affecting the Prevalence of Typhoid Fever Among Febrile Patients in Kebbi State, Nigeria.

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Abstract

Typhoid fever is a life-threatening public health disease caused by the bacterium Salmonella Typhi. The disease is a significant health concern in underdeveloped and most developing countries, especially in Asia and Africa (including Nigeria). The study was aimed at determining the prevalence and

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sociodemographic factors associated with typhoid fever among febrile patients attending three selected hospitals in Kebbi State, Nigeria. A hospital based cross sectional study was carried out among 406 febrile patients suspected of typhoid fever aged 1-70 years (mean age 34 years) in three selected health facilities of Kebbi State, Nigeria from February2021 to October, 2021. Approximately 20 ml and 10 ml of venous blood was collected from adults and children respectively. Blood culture and biochemical tests were carried out. Patients were administered structured questionnaires to evaluate the level of knowledge and practice toward the disease. Data obtained from respondents was analysed by descriptive statistics. In this study, the culture identified Salmonella Typhi prevalence of typhoid fever among febrile study subjects in Kebbi State was 6.4%. A higher prevalence was recorded among males (7.5%) than in females (5.0%) participants. Patients within the age range of 11- 20 years had the highest prevalence (14.8%), those with informal education recorded 11.2%. It was observed that rural area dwellers had higher prevalence (9.4%). Out of 26 isolates, 25 were susceptible to cefotaxime, 11 isolates were resistant to cotrimoxazole and amoxicillin-clavulanate antibiotics. Salmonella enterica serovar Typhi is an important and common cause of febrile illness in our population. Lack of good quality drinking water in rural areas has a greater impact on the burden of typhoid fever among study participants. Cefotaxime and ciprofloxacin therapy are suitable treatments for typhoid fever. The identification of sociodemographic characteristics associated with the disease are of great importance in providing holistic preventive approach and control strategies of the disease.

INTRODUCTION

Typhoid fever is a systemic bacterial infection caused by *Salmonella enterica* serovar Typhi and other *Salmonella* serotypes viz: *S. paratyphi* A, B and C (Bhandari *et al.,* 2022). This disease is a noteworthy cause of morbidity and mortality in under-developed and developing countries, especially when antibiotic resistance exists (Akinyemi *et al.,* 2005). Children and young adults are the most vulnerable groups. Worldwide, an estimated 212 million cases and 129,000 deaths occur yearly (Steele *et al.,* 2016). Studies by Mike (2008) shows that the disease is associated with decreased socio-economic status and inadequate hygiene. Humans are the only natural reservoir host of the infection, and the bacteria grows best at 37 °C which corresponds to the human body temperature. Transmission of the disease is through ingestion of contaminated food or water via the faecal oral route (WHO, 2018). The symptoms of the disease include; malaise, fever, vomiting, abdominal pain, constipation, splenomegaly and hepatomegaly (Nsutebu *et al.,* 2003). Its major complications include internal haemorrhage and perforation (Evanson and Mike 2008). In the absence of adequate/effective treatment and preventive measures, fatality rate could be about 10 to 30% (Buckle *et al.,* 2012).

Data from the Nigerian Public Health Department of the Ministry of Health shows that typhoid is a public health concern due to frequent diagnosis within health facilities (Sarkinfada e*t al.,* 2003). Thus, the disease is considered an endemic disease in Nigeria. One major challenge in the prevention of the disease in Nigeria is the high turnaround time of blood culture diagnosis and the cost of treatment. Control strategies are a possible way to reduce the disease spread. However, lack of reliable rapid diagnostic tests with high specificity and sensitivity, coupled with scarcity of data associated with risk factors especially in children has made it impossible to bring about effective control strategies to manage the disease in Nigeria. The knowledge of risk factors associated with typhoid fever will help in bringing about rational control measures of the disease, thus mitigating its spread.

MATERIALS AND METHODS

Ethical Clearance

The study was conducted based on the principles expressed in the Declaration of Helsinki/Belmont Report. The ethical clearance was obtained from the Research and Ethics

Committee of the Department of Research and Statistics of Kebbi State Ministry of Health, Birnin Kebbi with reference number MOH/KSREC/VOL.1/56 and KSHREC Reg. No. 105: 6/2020.

Study Area/Site

Kebbi is a state in the north-western Nigeria, with its capital city at Birnin Kebbi. The state was created out of a part of Sokoto State in 1991. Kebbi State is bordered by Sokoto State, Niger State, Zamfara State, the Dosso region of the Republic of Niger and the Benin Republic. The state has a total population of 4,440,000 people and an area of 36,800 km². Sir Yahaya Memorial Hospital is located in Birnin Kebbi, Kebbi State, established in 1952. It serves an estimated population of 366,200 people with a bed capacity of 250 beds. General Hospital Argungu is located in Argungu of Argungu Emirate Council. Argungu has a total population of 273,000 people. The hospital was established in 1975 with a bed capacity of 150 beds. Aisha Muhammadu Buhari General Hospital is located in Jega along Birnin Kebbi-Jega road. Jega has a total population of 269,600 people. The hospital was established in the year 2016 with a bed capacity of 100 beds.

Study design

A hospital based cross sectional study involving febrile subjects with suspected typhoid fever illness was conducted from February to October 2021, in three selected hospitals in Kebbi State, Nigeria i.e. Sir Yahaya Memorial Hospital Birnin Kebbi, Aisha Muhammadu Buhari General Hospital Jega, and General Hospital Argungu. Subjects aged 1 - 70 years were enrolled. Structured questionnaires were administered to the patients. Questions were based on the demographic area of the patients and typhoid fever associated social factors. A total of four hundred and six (406) blood samples were obtained from consented patients with symptoms of typhoid fever. Isolation and detection were done using BacT/ALERT 3D detection machine and the identification was done by subculture and biochemical tests. Antimicrobial sensitivity testing was done using disc diffusion method.

Study Population

Adults and children admitted at the medical and paediatric wards of the three selected hospitals with an axillary temperature of 38^{o}C within 48 hours of admission and a history of fever for <2 weeks were recruited in the study.

Consent of the Subject

Written and verbal consent was obtained from the subjects prior to data and blood specimen collection respectively.

Exclusion Criteria

Patients clinically suspected as having typhoid fever but unconscious during the study period, on antibiotic treatment and those that did not consent to participate in the study were excluded.

Data collection

A structured questionnaire was used for the collection of data. The information obtained include sex, age, occupation, level of education, residence, history of typhoid fever, usage of toilet, hand washing with or without soap and antibiotics therapy. While medical history was obtained from the patient's hospital records.

Specimen Collection, Preparation and Storage

A total of 406 blood specimens were collected from the febrile participants who accepted/consented having explained to them the procedures involved. Every participant was assigned a unique and confidential identifier code for questionnaire and samples. The required volume of blood specimens was collected aseptically before the commencement of antibiotic treatment. BacT/ALERT 3D select was used for the rapid detection of bacteria from the blood specimens. The specimens were collected in BacT/ALERT 3D standard culture vials for aerobic and facultative anaerobic bacteria. For adults, two bottles were used (for anaerobic and aerobic), while for children only anaerobic bottles were used. The venous blood from the appropriate peripheral vein was collected with the aid of tourniquet after the site of collection was thoroughly cleaned with 70% alcohol solution using a 20mls and 10 mls syringe for adults and children respectively. From the 20 mls of blood collected from adults, 18 ml was dispensed aseptically into each of the bottles. The 10 mls of blood collected from children was dispensed to the anaerobic bottles. The bottles were loaded into the BacT/ALERT 3D machine within 4hrs of samples collection.

Transfer of Samples

The collected samples were transferred to the Medical Microbiology Laboratory (Molecular Unit of Federal Medical Centre, Birnin Kebbi) where culture detection was done using a BacT/ALERT 3D machine and identification was done using biochemical reactions.

Chemical/Reagents

Bacteriological media from Oxoid (Hampshire, England) were used. The other chemicals and reagents used in this study were purchased from Sigma Company (USA) and Fittrust Nigeria Limited.

Laboratory analysis

Blood Culture Technique

BacT/ALERT 3D select was used for the rapid detection of bacteria from the blood specimens. The specimens were collected for adults in both aerobic and anaerobic BacT/ALERT 3D standard culture vials, while for children only anaerobic standard culture vials were used. The bottles were loaded into the BacT/ALERT 3D machine within 4hrs of specimen collection. Whenever the machine gave an alert signal, the specific bottle was removed. Gram staining and subcultures were done on microbiological culture media that include *Salmonella - Shigella* agar, brilliant agar, blood agar, chocolate agar, and MacConkey's agar. The isolates were identified as *Salmonella* Typhi based on colony morphology, Gram staining reaction, and biochemical test results (such as oxidase test, the catalase test, motility, and triple-sugar iron (TSI) fermentation). The pure culture was stored in the slant bottles for further studies (Naheed *et al*., 2010).

Identification of Bacteria

Visual examination based on colony morphological properties (colony form, colour, size, Margene, and texture) was done. A single colony of each primary positive blood culture was identified and analysed under microscope after being stained with Gram's stain. Biochemical tests on each isolate were performed to complete the identification.

Data Analysis

Microsoft Excel was used to enter data from questionnaires and results of laboratory analyses. GraphPad Prism version 6.0 was used to analyse the collated data. Quantitative variables were

presented as mean (±SD) or median (IQR). Level of significance of 95% was adopted while p ≤ 0.05 was considered significant. Percentage prevalence was calculated and tabulated.

RESULTS

Using standard culture detection (BacT/ALERT 3D series) and biochemical technique, 26 specimens (representing 6.4%) of the 406 febrile patient samples were isolated and identified as *Salmonella* Typhi, while the remaining 380 samples representing 93.6% were found not to be *Salmonella* Typhi infected (i.e. negative). When the samples were subjected to culture in the BacT/ALERT 3D machine, 129 samples were BacT/Alert 3D culture positive. Out of these, only 26 were morphologically and biochemically confirmed to contain *Salmonella* Typhi isolates. The results for culture confirmed cases are presented in Table 1.

Table 1: Culture detection frequency among febrile patients.

Parameters	Positive	Negative	Total	Frequency
BACT/Alert	129	277	406	31.8%
Culture	26	380	406	6.4%

Association between socio-demographic characteristics and biochemically identified *salmonella* typhi infection among study subjects.

Out of the 406 study subjects recruited, the culture and biochemical identified-*salmonella* typhi was 26 (6.4%). Based on the age group, the study subject age range 11-20 years recorded more occurrence 4 (14.8%), while age group 31-40 years had least occurrence 3 (2.9%). Males had a prevalence of 17 (7.5%). There was no statistically significant association between *Salmonella* Typhi infection and sex group (p=0.1730). There was a strong statistical significant association of *Salmonella* Typhi infection across the age groups (p= 0.0010). Participants with an informal level of education had the highest frequency of 12 (11.2%), while 3 (3.0%) had a secondary level of education. There was no statistically significant association between *Salmonella* Typhi infection and level of education (p= 0.084). Daily labourer participants had the highest culture confirmed positivity corresponding to 5 (9.3%), while only 1 (2.6%) positive case was recorded among students. There was no statistically significant association between *Salmonella* Typhi infection and occupation (p= 0.853). Rural residents had positivity of 17 (9.4%) prevalence. There was strong statistically significant association between *Salmonella* Typhi infection and patients' residence (p= 0.027) as depicted in Table 2 below.

Attitude and practice associated with risk factors of typhoid fever infection among study subjects

Based on the associated risk factors and typhoid fever infection among the study participants, 134 (33.0%) participants had responded to have previously had typhoid fever infection, out of which 16 (11.9%) were typhoid fever positive. Two hundred and seventy two (67.0%) had responded not had previously infected with typhoid fever, out of which 10 (3.7%) were positive for typhoid fever (p = 0.0014). On the usage of toilet, 292 (72%) participants responded yes out of which 8 (2.7%) were typhoid fever positive, 72 says sometimes on the toilet usage out of which 9 (12.5%) were positive, and 42 (10.3%) participants responded to had not been using toilet out of which 8 (21.4%) were biochemically identified to be infected by *Salmonella* Typhi isolates (p = 0.0004). Of the 256 (63.1%) participants who had the habit of hand wash after the used of toilet, 10 (3.9%) were biochemically identified to be *Salmonella* Typhi positive. Among the 150 (36.9%) participants who responded not wash their hand after toilet, 16 (10.7%) were biochemically identified *Salmonella* Typhi positive (p = 0.0072). Among the participants, 233 (57.4%) responded yes on the usage of soap after toilet use out of which 7 (3.0%) were positive. Among the 173 (42.6%) responded who responded not to use soap, 19 (11.0%) were

biochemically identified to be *Salmonella* Typhi positive (p = 0.0012). Out of the 239 (58.9%) participants that used pipe and borehole water for drinking, 3 (1.3%) were positive. However, out of the 119 (29.3%) participants that use well water, 17 (14.3%) were culture positive. Of the 48 (11.8%) participants that used river water as a source of drinking water, 6 (12.5%) were biochemically identified to be *Salmonella* Typhi positive. There is statistically strong association between typhoid fever and source of drinking water among the study subjects (p=0.0001) as shown in Table 3.

Table 2. Socio-demographic characteristics base on biochemically identified *Salmonella* Typhi infection.

Variable	Number Tested (n=406)	Number Positive (%)	Statistics χ^2	df	p-value	Odd ratio
Sex						
Male	227	17 (7.5)	1.86	1	0.173	1.33(0.88-2.0)
Female	179	9 (5.0)				
Age Group (years)						
1 – 10	21	3 (14.3)				
11 – 20	27	4 (14.8)				
21 – 30	86	5 (5.8)	20.50	5	0.001	
31 – 40	102	3 (2.9)				
41- 50	100	4 (4.0)				
>50	70	7 (10.0)				
Level of Education						
Primary	107	5 (5.3)				
Secondary	95	3 (3.0)	6.65	3	0.084	
Tertiary	99	6 (5.7)				
Informal	105	12 (11.2)				
Occupation						
Civil Servant	77	5 (6.5)				
Merchant	72	4 (5.6)				
Farmer	112	8 (7.1)	1.97	5	0.853	
Daily labourer	54	5 (9.3)				
House wife	53	3 (5.7)				
Student	38	1 (2.6)				
Residence						
Urban	225	9 (4.0)	4.26	1	0.039	0.43 (0.18-0.99)
Rural	181	17 (9.4)				

Key: n; Number subjects

Table 3. Relationship between risk factors and biochemically identified *Salmonella* Typhi among febrile study subjects.

Variable	Number Tested (%)	Number Positive (%)	Statistics χ^2	df	p-value	Odds ratio
History of TF						
Yes	134 (33.0)	16 (11.9)	10.23	1	0.0014	0.2815 (0.1278-.6563)
No	272 (67.0)	10 (3.7)				
Toilet Usage						
Yes	292 (72)	8 (2.7)				
Sometimes	72 (17.7)	9 (12.5)	12.36	1	0.0004	5.0712 (000-13.56)
No	42 (10.3)	9 (21.4)				
Hand wash after toilet	256 (63.1)	10 (3.9)	7.212	1	0.0072	2.9371 (1.265-6.455)
Yes	150 (36.9)	16 (10.7)				

No						
Usage of soap						
Yes	233 (57.4)	7 (3.0)	10.54	1	0.0012	3.983 (1.623-10.33)
No	173 (42.6)	19 (11.0)				
Source of water						
Pipe/borehole water	239 (58.9)	3 (1.3)				
Well water	119 (29.3)	17 (14.3)	25.88	2	<0.0001	
River water	48 (11.8)	6 (12.5)				

Key: TF= Typhoid fever

Antimicrobial susceptibility profile of *Salmonella* Typhi isolates from febrile study Subjects.

Of the 8 antibiotics tested against 26 culture-confirmed *Salmonella* Typhi isolates, cefotaxime had the highest susceptibility rate of 96.2%, followed by ciprofloxacin and ceftazidime with 92.3% each. Tetracycline exhibited the highest resistance rate of 69.2%, followed by amoxicillin and cotrimoxazole with 42.3% each as shown in Table 4.

Table 4 Antimicrobial susceptibility pattern of *Salmonella* Typhi isolates from febrile study subjects (n=26).

Drugs tested	Resistant (%)	Susceptible (%)
Amoxicillin- clavulanate	11 (42.3)	15 (57.7)
Ceftazidime	2 (7.7)	24 (92.3)
Ceftriazone	4 (15.4)	22 (84.6)
Ciprofloxacin	2 (7.7)	24 (92.3)
Cotrimoxazole	11 (42.3)	15 (57.7)
Cefotaxime	1 (3.8)	25 (96.2)
Gentamicin	5 (19.2)	21 (80.8)
Tetracycline	18 (69.2)	8 (30.8)

DISCUSSION

Typhoid fever is caused by *Salmonella enterica* serovar Typhi (*Salmonella* Typhi). The disease is a global public health problem and a life-threatening systemic bacterial infection in low- and middle-income countries. It is endemic in communities with limited safe drinking water and epileptic health care system. Currently, the gold standard method in diagnosis of typhoid fever is through blood, stool, urine and bone marrow culture, followed by morphological and biochemical identification tests. These techniques are tedious, time consuming and require sophisticated equipment and highly experienced medical/technical personnel (Baker *et al*., 2010). Isolation of the causative agent by culture method has lingered the gold standard for the diagnosis of typhoid fever. Blood culture has turned out to be a limited utility due to its low sensitivity.

In this present study, 406 specimens from febrile study subjects with symptoms such fever, headache, nausea and abdominal pains and clinically diagnosed of typhoid fever by clinicians were selected and screened for isolation and identification of *Salmonella* Typhi by blood culture. Out of the 406 specimens, 129 were BacT/ALERT 3D positive, among which 26 (6.4%) were culture positive and biochemically identified *Salmonella* Typhi isolates (this constituted the bacteriologically proven enteric fever based on biochemical test reactions). The remaining 380 negative blood cultures are clinically presumptive of typhoid fever. Comparatively similar studies in Nigeria by Omotola *et al.* (2020), Ethiopia by Habte *et al.* (2018) and Egypt by Srikantiah *et al.* (2006) have been reported. A study by Sharanya *et al*. (2016) in India reported a higher culture-confirmed *Salmonella* Typhi (16%). Similarly, a lower proportion of

culture-confirmed typhoid fever cases was reported in some Asian countries (2%) by Gupta *et al.* (2013), and Laos (1.5%) by Robert *et al.* (2020). Variations in *Salmonella* Typhi prevalence can occur due to difference in place, time and even in consecutive years at the same geographical location as suggested by Dewan *et al.* (2013), and/or seasonal variability as demonstrated by Marchello *et al.* (2019). Furthermore, differences in laboratory detection methods used might also contribute to the difference observed. In contrast to our findings, previous studies in Nigeria by Ohanu *et al.* (2019), Jigjiga in Ethiopia by Admassu *et al.* (2019), India by John *et al.* (2016), and Sudan by Ali *et al.,* (2019) showed a higher culture confirmed typhoid fever cases among febrile patients ranging from 11 to 14.1%. This might be due to the varied incidence of typhoid fever in different study areas and periods (Mogasale *et al.,* 2016). Moreover, the geographical heterogeneous nature of typhoid fever burden might also contribute to the difference observed (Marchello *et al.,* 2019). Contrarily, a lower incidence of culture-confirmed typhoid fever case was reported in Nigeria (5%) by Gambo *et al.* (2017), in Kenya (4.8%) by Jyotshna *et al.* (2022), in Asian countries (2%) by Gupta *et al.* (2013), and Laos (1.5%) by Robert *et al.* (2020).

The present study reported the frequency based on biochemical reactions of culture-identified *Salmonella* Typhi among participants, based on the associated sociodemographic characteristics to *Salmonella* Typhi infection. The highest proportion of culture-confirmed typhoid fever among the participants was in the 11-20 age group. This age category is part of the active labour force nowadays. The high incidence is connected to the high-risk behaviours associated with the age category; such as frequent contact outside home with unhygienic foods, drinking contaminated water and eating of undercooked meat. Similar, the same age range of 11-20 years was reported to have a high prevalence of 31.3% among culture-confirmed typhoid fever participants in Nigeria (Omotola *et al.,* 2021). Based on gender, males had higher blood culture-confirmed positive cases than females. This outcome is similar to the research conducted by Chalya (2012), Charles *et al*. (2012) and Ramyil *et al*. (2013) in which males had more positive cases than their female counterparts. With regards to educational background, those with no formal education tend to have higher frequency of blood culture-confirmed cases of typhoid fever. Participants with secondary education had the least proportion of culture confirmed cases. Rural residents were seen to have the highest proportion of culture-confirmed typhoid fever than urban residents. These outcomes agree with a similar study conducted by Genet *et al.* (2021).

The present study indicates that there was significant positive correlation between risk factors for typhoid fever infection. The major risk factors include source of drinking water and previous history of typhoid fever among febrile patients. According to UNICEF, unimproved drinking water sources such as rivers, streams, unguided wells and boreholes can be a source of exposure to the disease following contamination (UNICEF, 2012). The outcomes of the present study are in agreement with previous reports from Nigeria (Omotola *et al.,* 2021; Mujahid *et al.,* 2022), Ethiopia (Genet *et al.,* 2021), and Cameroon (Habte *et al.,* 2018; Mogasale, 2018; Admassu *et al.,* 2019; Akwa and Simone, 2020),). The significant association of previous history of typhoid fever with current typhoid fever infection might be due to the reactivation from previous infections. With regards to risk factors associated with environmental hygiene, usage of toilet, hand washing and the use of soap were significantly associated with incidence of the disease. This is not unconnected with the fact that typhoid fever is more of an intra-household affair, introduced by an active/recent typhoid case in the households, and facilitated by poor hand-washing/personal hygiene. The present outcomes are consistent with an earlier report of Omotola *et al.* (2012) and Black *et al.* (1985). The relationship between poor handwashing hygiene and typhoid fever has been previously demonstrated in Nigeria,

Indonesia and India (Valema *et al*., 1997; Gasem *et al*., 2001; Bhan *et al*., 2002). The use of soap for hand washing has been shown to be essential for the reduction of the incidence of diarrheal diseases among others (Curtis and Cairncross, 2003).

In the present study, *Salmonella* Typhi showed variable levels of resistance to different categories of antibiotics tested. Resistance to tetracycline was very high (69.2%) in the current study. The resistance level against tetracycline by *Salmonella* Typhi isolates was almost comparable with studies from Ethiopia (Admassu *et al*., 2019; Genet *et al*., 2021), and Nigeria (Ohanu *et al*., 2019). Equally, Acharya (2011) reported a much lower resistance level of *Salmonella* Typhi to tetracycline in Nepal (13.56%). Moreover, 42.3% of *S*. Typhi isolates in the current study were resistant for amoxicillin-clavulanate and cotrimoxazole which was comparable with studies of Ohanu *et al*. (2019), Roberts *et al*. (2020) and Genet *et al*. (2021) from Nigeria, Laos and Ethiopia respectively, but higher than that reported by Misra *et al*. (2015) and Gupta *et al*. (2013) in India. This variation might be due to study period and setting difference. Besides this, increased resistance level from year to- year for different antibiotics like cotrimoxazole might be a contributing factor (Hassan *et al*., 2008).

About 15.4% of study subjects in the present study were found to be resistant to ceftriaxone. Studies from different parts of the world also show that ceftriaxone resistance is increasing (Bayramoglu *et al*., 2014). However, some studies have shown less than one percent resistance to ceftriaxone (Qamar *et al*., 2018). This contrast may be due to differences in the catchment area. Furthermore, 92.3% of *Salmonella* Typhi isolates were susceptible to ciprofloxacin and ceftazidime, and 84.6% susceptible to ceftriazone. Comparable susceptible results were reported for *Salmonella* Typhi isolates in previous studies for ceftriaxone and ceftazidime (Misra *et al*., 2015; Ohanu *et al*., 2019; Ganet *et al*., 2021). In the present study, the resistance level of *Salmonella* Typhi against ciprofloxacin was almost comparable with a previous report (Mannan *et al*., 2014). The increased resistance of *S*. Typhi in the present study against different classes of antibiotics might be due to antibiotic misuse, and inappropriate prescription practice by health professionals coupled with resistance gene transfer among different *Salmonella* species.

CONCLUSION

The present cross-sectional and hospital-based study of typhoid fever from three selected hospitals in Kebbi State, Nigeria has indicated that lack of good quality drinking water and inadequate sanitation among rural communities were of greater impact on the burden of typhoid fever among study participants. Cefotaxime and ciprofloxacin therapy were suitable treatments for typhoid fever. The identification of sociodemographic characteristics associated with the disease are of great importance in providing holistic preventive approach and control strategies of the disease.

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