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EPIDEMIOLOGICAL PATTERNS, RISK FACTORS, AND PREVENTIVE STRATEGIES ASSOCIATED WITH MEASLES INFECTION IN CHILDREN OF TEHSIL MATTA, DISTRICT SWAT PAKISTAN

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Abstract

Background: Measles is a highly contagious viral disease that continues to pose significant health risks for children globally, despite the availability of reliable vaccines. Measles is caused by a single-stranded RNA virus belonging to the genus Morbillivirus within the family Paramyxoviridae. Measles stands as a prominent cause of mortality among children in developing nations. Measles is the fifth leading cause of death worldwide for children under the age of five.

Objective: The current study was conducted to evaluate the main risk factors associated with measles infection in children of Tehsil Matta, District Swat, from March 2019 to August 2019.

Methodology: In the present study, a total number of n= 190 children were observed who suffered from measles. Data was collected from different government and private hospitals and other local

areas using a closed type of questionnaire which consisted of different factors like age, socioeconomic status, birth rank, vaccination status, favorite diet of the child, mother literacy, and contact with measles affected children, and other medical conditions etc.

Results: Children of the age group up to 2 years n=84 (44.21%) were found to have a significantly higher rate of measles infection. Individuals having poor socioeconomic status n=96 (50.52) were found significantly infected by measles. Similarly, children having birth rank 1st n=65 (34.21%) were found to be more susceptible to the infection. Unvaccinated children n=116 (61.05%) were found to have more risk of infection. Children who preferred spicy snacks as their favorite food n=73 (38.42%) were found more infected. Children of illiterate mothers n=78 (41.05%) were found prone to measles to a large extent. The infection spread in healthy children n=108 (56.84%) through contact with infected individuals. Most symptoms of infection occurred in facial areas n=88 (46.32%). The higher rate of infection occurred in children living in low altitudes n=101 (53.57%) non cemented houses n=98 (51.57%) and those having other medical conditions n=98 (51.57%).

Conclusion: The current study concludes that various factors contribute to measles infection in children. The current study concludes that the measles disease is most common in children aged less than 5 years. During the current study, poor socioeconomic status, low altitudes, junk food especially spicy snacks, and illiterate mothers were found as the promoting factors in measles disease. The current study shows no relationship between measles with children's sleep cycle and a weak relationship between measles with children's parental smoking. On time vaccination, intake of food containing vitamin A, and immediate treatment will reduce the infection.

Keywords: Measles, Risk Factors, Epidemiological Pattern, Socioeconomic Status, Sleep Cycle, Immunization Status.

INTRODUCTION

Measles is a highly contagious viral disease that continues to pose significant health risks for children globally, despite the availability of reliable vaccines[1]. Measles is caused by a single-stranded RNA virus belonging to the genus Morbillivirus within the family Paramyxoviridae[2]. The measles virus spreads easily through respiratory droplets or aerosols. Measles virus after entering the body via the respiratory system infects local immune cells and the respiratory epithelium cells by binding to receptors on them[3]. The virus can remain viable in the air for about two hours after an infected child coughs or sneezes[4]. Measles stands as a prominent cause of mortality among children in developing nations. The typical incubation period ranges between 8 to 12 days[5]. Early symptoms encompass fever, often exceeding 38˚C, along with cough, runny nose, or conjunctivitis, progressing subsequently to a widespread rash marked by Koplik's spots within the oral cavity[6]. The infectious period spans approximately four to five days post rash onset. Factors predisposing individuals to measles include vitamin A deficiency, pregnancy, and immunodeficiency[7]. Notable complications associated with measles comprise bronchitis, encephalitis, otitis media, and pneumonia[8, 9]. Management in pediatric cases often involves analgesics, bed rest, humidified air, and vitamin A supplementation to mitigate symptom severity. Infections can also be acquired through direct contact with an already infected individual[10]. The disease remains prevalent in developing nations, particularly in regions of Asia and Africa, and stands as a prominent cause of mortality among children under the age of five worldwide. Despite the implementation of a single-dose vaccination strategy, measles outbreaks have persisted in Sri Lanka, Romania, Latin America, and South Korea[11]. Measles is still a fatal disease that kills over a million people every year worldwide, even though it is preventable[12]. As per the World Health Organization (WHO), measles is a primary cause of mortality among children, accounting for 139,000 deaths worldwide in 2010. It is noteworthy that 95% of measles-related deaths occur in low-income nations with inadequate health infrastructure[13]. Global estimates for 2013 indicate that measles-related mortality accounted for approximately 0.14 million deaths, or about 16 deaths every hour. Research indicates that over 50% of measles-related deaths globally have been reported

in India alone[14, 15]. The World Health Organization (WHO) projected that 424,000 fatalities in children under five were attributed to measles in 2004, with 142,000 of those deaths occurring in India. Over 82,000 patients and 900 deaths were reported in Nepal for all of the outbreaks in 2004. The outbreaks of measles in various regions of Pakistan have led to the loss of hundreds of lives. In 2012, Pakistan recorded 15,000 cases of measles, resulting in 305 fatalities associated with the disease. Over 500 kids were affected by the outbreaks that began in December 2012 in the Sindh province of Pakistan. The outbreaks later expanded to different regions of the country, taking more lives. However, there were 94 deaths in Punjab in the first half of 2013 compared to just 16 in 2012. The tragic scenario is indicated by the fact that the majority of these deaths were reported from Lahore city[5].

Large-scale measles outbreaks happened in Sub-Saharan Africa between 2009 and 2011, despite efforts to achieve the worldwide target of 95% reduction in measles mortality by 2015 compared with 2000. Advancements in hospitalization and healthcare systems have led to a significant reduction in the fatality rate among infected patients in developed countries, plummeting from around 30% in the 1920s to less than 0.5% at present. Mortality rates can still reach 10% in populations with high rates of malnutrition and inadequate access to healthcare. Mortality rates can still reach 20–30% in populations with severe complications. Measles deaths have decreased by 60–75% as a result of increased immunization, accounting for 25% of the decrease in mortality in children under five[16]. According to estimates, the measles case mortality rate in Indonesia ranges from 3% to 4%, with outbreaks potentially reaching 10%[17].Between 2000 and 2016, the measles vaccine played a pivotal role in preventing an estimated 20.4 million deaths globally. During this period, global measles-related fatalities witnessed a substantial decline of 84%, plummeting from an estimated 550,100 in 2000 to 89,780 in 2016. By 2016, approximately 85% of children worldwide had received at least one dose of the measles vaccine by their first birthday through routine health services, a notable increase from 72% in 2004[18].Measles outbreak is associated with morbidity and mortality of the affected children. Regions characterized by low vaccination rates and inadequate vaccination handling systems are at a heightened risk of experiencing measles outbreaks[19]. Some parents refrain from vaccinating their children against measles, mumps, and rubella (MMR) due to religious, personal, or philosophical beliefs, as well as safety concerns. A considerable number of parents choose to use single antigen immunizations instead of the measles, mumps, and rubella (MMR) vaccine[20]. The majority of nations have incorporated vaccination into their regular childhood immunization programs, administering two doses of the vaccine. When the mother's protective antibodies are no longer present, which is often around the age of 9 to 12 months, the first dosage (MCV1) should be given. It is generally advised that the second vaccination (MCV2) be given at least 4 weeks after the first one, ideally between the ages of 15 and 18 months. In nations with high MCV1 coverage but low measles transmission, this recommendation may even be extended. Infants as early as 6–9 months are recommended to start receiving the MMR vaccination during an epidemic when exposure risk is elevated. In 2004, the World Health Organization (WHO) suggested that infants with HIV who are not severely immunocompromised should have a dose of the measles vaccine at six months of age and another at nine months[21]. Antiretroviral drugs play an important role in the control of disease burden.MCV1 and MCV2 coverage improved significantly in Pakistan between 2000 and 2017, reaching 76% and 45%, respectively, but they still fell well short of the WHO's recommended standard of ≥95%[22]. In Pakistan, the proportion of children incompletely immunized against measles fluctuates between 37% and 58%[23].There were significant measles outbreaks in Pakistan in 2012–2014 and 2016–2018, which exposed vaccination deficiencies.

Gender-based inequalities are especially concerning because pro-son prejudice has been extensively documented and has a negative impact on child health outcomes. There is ample evidence in the literature of discrimination against girls in India, which leads to high rates of female child death and unfavorable sex ratios for women[1]. Usually, females are not as much alert about prevention and treatment as are males[24]. Urban slums are recognized as high-risk locations with a high rate of

measles transmission, and they present a significant challenge to the control of the disease. Reports indicate that within the slums of Surat city in India, there is a notable incidence rate of 7.67% among children under the age of 5, making the distribution of measles cases a significant health concern for children. In 1999, Vadodara, Ahmadabad, Rajkot, and Jamnagar exhibited respective incidence rates of 4.2%, 11.4%, 10.4%, and 12.0%[25].All six World Health Organization (WHO) regions have established some goals for the elimination of measles. Nowadays measles is rare in the Netherlands but it has not yet been eliminated throughout the world. The measles vaccine has been integrated into Dutch immunization programs since 1976, contributing to a notable reduction in disease incidence[26, 27]. Recent investigations in developing countries have revealed that administering vitamin A treatment to children affected by measles yields significant reductions in both morbidity and mortality. Vitamin A deficiency detrimentally affects the body's immune system and the integrity of cells that protect the linings of the lungs and gut. When these protective mechanisms are compromised, they fail to adequately control and prevent infections. Consequently, vitamin A deficiency contributes to elevated rates of measles incidence and mortality[28]. The primary risk factors contributing to the prevalence of measles include inadequate child immunization, maternal educational deficiency, insufficient awareness, overcrowding, substandard sanitation, malnutrition, and unfavorable community habits and beliefs[17]. The current study has several strengths, such as well-characterized factors including transmission by contact, socioeconomic status, vaccination status of the child, birth rank, types of housing, types of areas, educational levels of children's mothers, and other medical conditions.

MATERIALS AND METHODS

Study Area:

The current study was conducted in Tehsil Matta district Swat, Khyber Pakhtunkhwa Pakistan. Matta is situated about 20 km away from the central city of Mingora. Tehsil Matta is the largest subdivision of Swat and the largest Tehsil of Swat Valley which consists of three Sub-valleys Sakhra, Biha, and Shower Valley. Its total population consists of more than 1400000. The total area of Tehsil Matta is about 683 square kilometers. It is situated at 35º5´35´´N 72º18´35´ E and has an average elevation of 1,120 m (3,670 feet). June is the warmest month in which the highest temperature is about 33ºC and the lowest temperature is 16ºC. The coldest month is January, in which the mean temperature varies between 11ºC and -2ºC, correspondingly. Winter time is long from the month of November to March. The highest degree of rainfall was recorded in the month of March which was about 242 mm (District census report, 1998).

Study Design and Duration:

The highlighted methods followed by Gupta et al [11]and Younas et al [5] were adopted during the current study for data collection. The current research was conducted in different areas of Matta Swat. The research duration was 06 months and the data collection was performed from March 2019 to August 2019. The research data was collected from Zakir Khan Shaheed Hospital Matta, BHU Durushkhela Swat, and from outside local regions. The data was collected from children affected by measles. The measles disease was confirmed by a registered child specialist based on measles symptoms. A total of 190 patients were studied during the study duration through a well-designed multi-factorial questionnaire approach.

RESULTS

The current study highlighted the measles risks among children in Tehsil Matta, District Swat, Khyber Pakhtunkhwa. During the current study, a total of n=190 measles children cases were examined and investigated by a multifactorial questionnaire. The current study included low percentage of male cases n=82(43.15%) and high percentages of female cases n=108(56.84%). According to current study, a higher number of measles children were found non vaccinated n=116(61.05%) while less number of measles children n=74(38.94%) were found vaccinated. The

maximum percentage of measles-affected children n=101(53.57%) belonged to areas having low altitudes while the minimum number of measles children belonged to areas having high altitudes n=89(46.84%). During the current study, a higher number of children having measles belonged to non-cemented houses n=98(51.57%) while less number of children having measles belonged to cemented houses n=92(48.42%). The information regarding gender, vaccination status, area and type of house is given in (Figure 1).

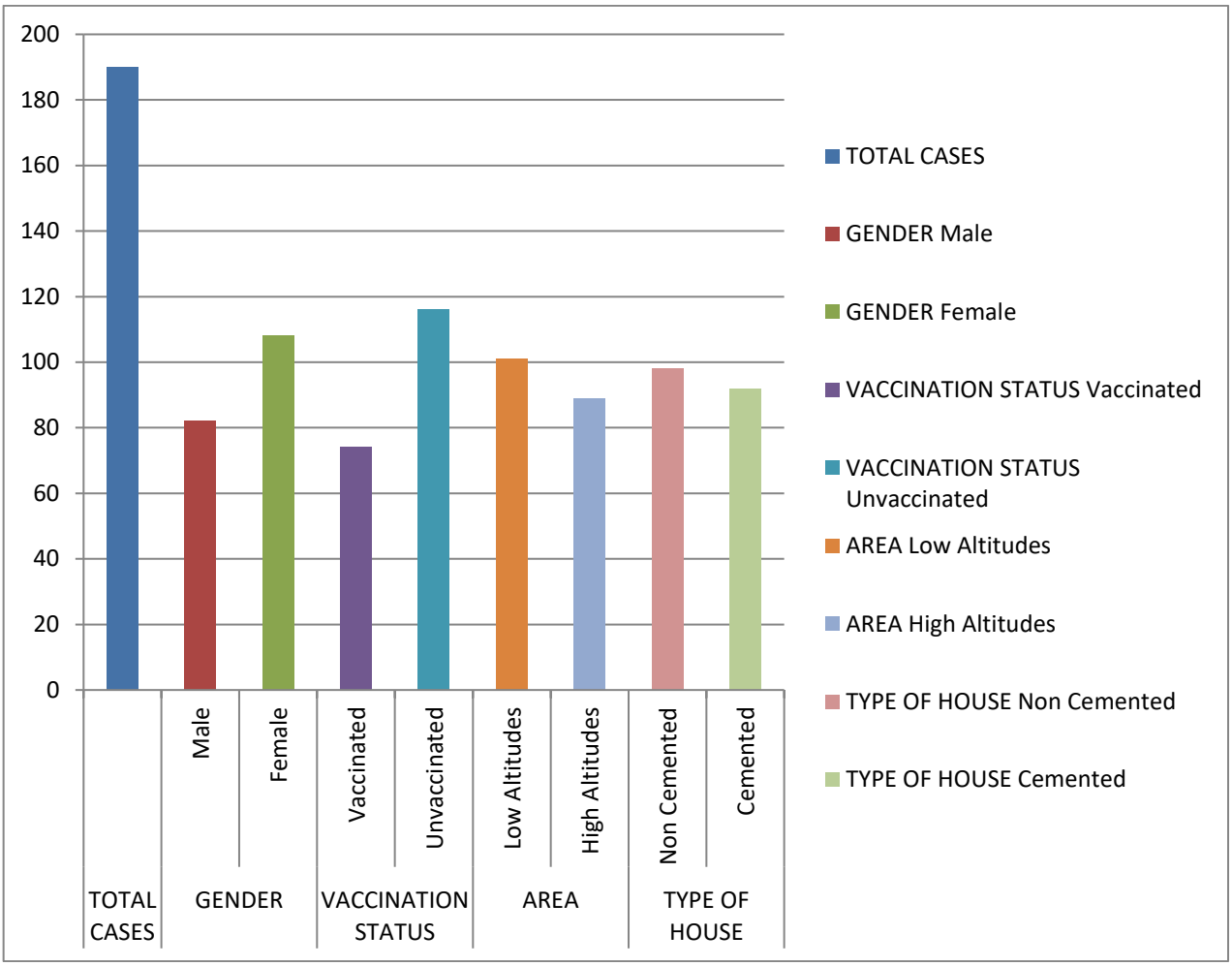

Figure 1: Gender, vaccination status, type of house, and area wise distribution of measles cases.

A higher number of children having measles n=108 (56.84%) were infected by other measles affected children while a lesser number of children having measles n=82(43.15%) did not come in contact with other measles affected children. All children in the study, n=190 (100%), had family members who had previously experienced measles. The study included a higher number of measles children whose parents were smokers n=96(50.53%) while a lesser number of child's parents were non smoker n=94 (49.47%). A higher percentage of suspected measles children n=98(51.57%) were affected by other medical conditions while the lower percentage of suspected measles children n=92(48.42%) were not affected by other medical conditions. The information regarding contact with measles affected person, family member's suffered from measles in past, parents smoking status, and children's suffered from other medical conditions is given in (Figure 2).

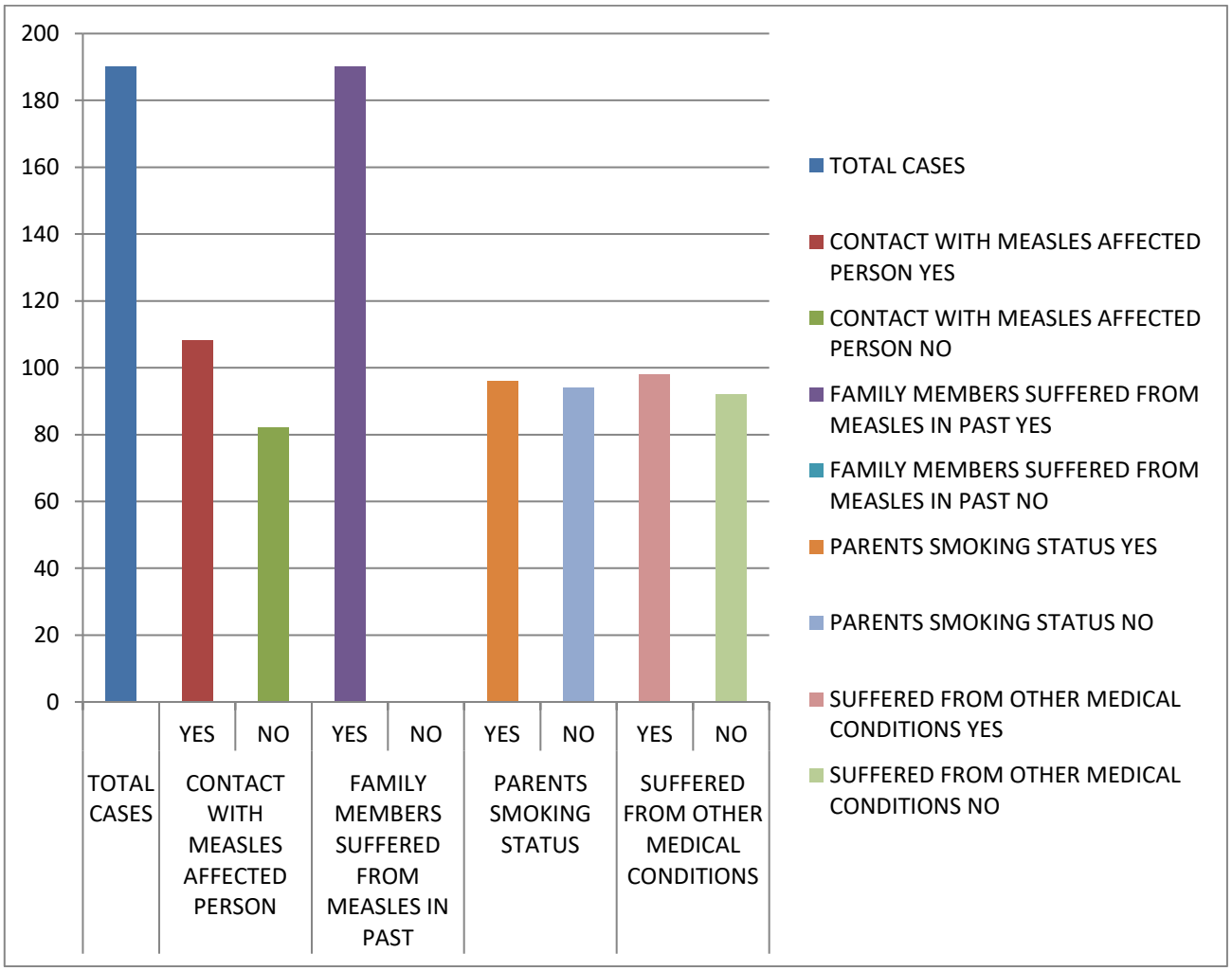

Figure 2: Distribution of measles cases according to contact with measles affected person, family members suffered from measles in past, parents smoking status, and children suffered from other medical conditions.

In the current study the measles cases were distributed in different age groups such as n=84(44.21%) cases were observed in the less than 2 year age group, in the 2-4 year age group n=50(26.31%) cases were observed, in 5-9 year age group n=44(23.15%) cases were observed, and in above 9 year age group n=12(6.31%) cases were observed. A maximum number of measles-affected individuals n=84(44.21%) belonged to the age category less than 2 years while a minimum number n=12(6.31%) of measles-affected individuals belonging to the age category above 9 years. During the current study the measles cases were distributed in different weight groups such as n=18(9.47%) cases were observed in the less than 10 Kg weight group, in the 10-15 Kg weight group n=98(51.57%) cases were observed, in 16-20 Kg weight group n=62(32.63%) cases were observed, and in above 20 Kg weight group n=12(6.31%) cases were observed. The information regarding age and weight of children's is given in (Figure 3).

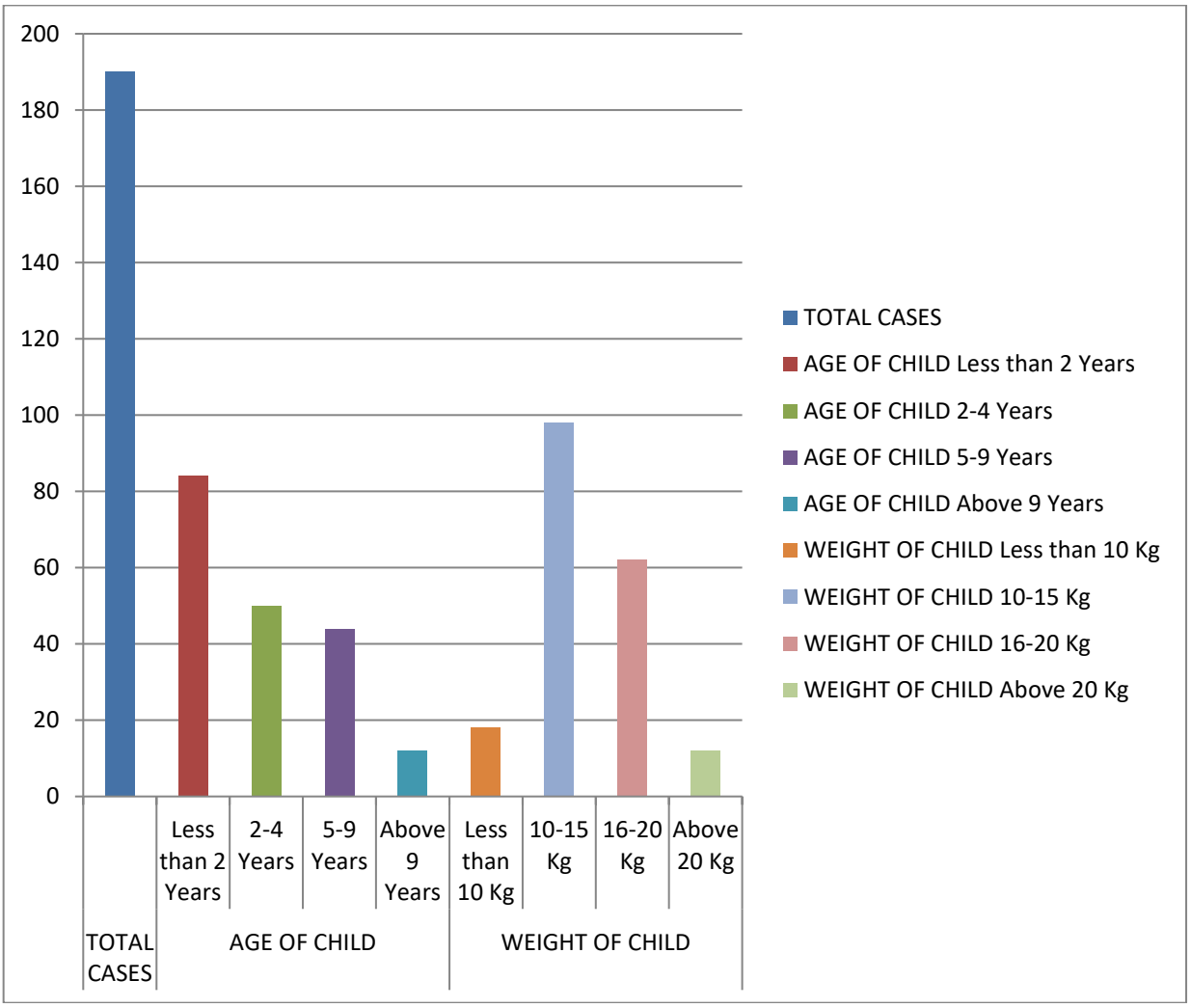

Figure 3: Distribution of measles cases according to age of child and weight of child.

In the current study, the measles cases were distributed in different categories based on socioeconomic status. In the current study n=96(50.52%) measles cases were found in the poor class, n=63(33.15%) cases in the lower middle class, n=23(12.10%) in the upper middle class, and n=8(4.21%) in higher class. According to the current study, maximum measles cases were reported in poor class and minimum cases were reported in higher class. In the current study, the measles cases were distributed in different categories based on the favorite diet of children. In the current study n=50(26.31%) measles affected children liked fatty food, n=52(27.36%) liked milk, n=73(38.42%) liked spicy snacks, and n=15(7.89%) liked vegetables. According to the current study, the maximum measles cases were reported in spicy snack consumers and a minimum number of cases in vegetable consumers. The information regarding socioeconomic status and favorite diet of children is given in (Figure 4).

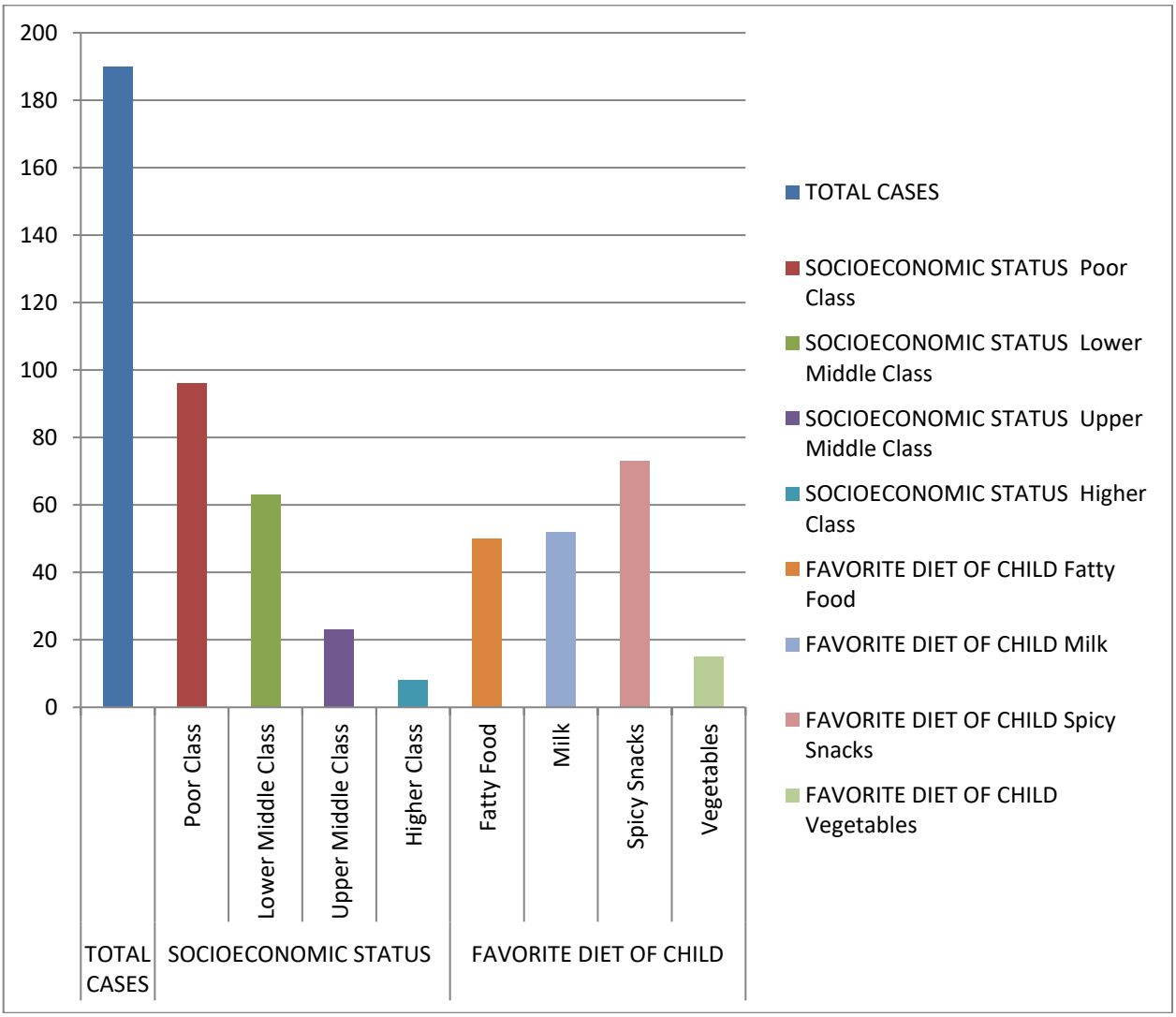

Figure 4: Distribution of measles cases according to socioeconomic status and favorite diet of child.

In the current study the measles cases were distributed in different groups based on birth rank, n=65(34.21%) cases were related to 1st birth rank, n=51(26.84%) cases were related to 2nd birth rank, n=39(20.52%) cases were related to 3rd birth rank and n=35(18.42%) cases were related to 4th or higher birth rank. According to the current study a greater number of children having measles belonging to the 1st birth rank n=65(34.21%) and a lower number of children having measles n=35 (18.42%) belonging to the 4th or higher birth rank. In the current study n=78(41.05%) measles cases were reported in children whose mothers were non-educated, n=57(30%) cases were reported in children whose mothers possessed primary education, n=45(23.90%) cases were reported in children whose mothers possessed secondary education and n=10(5.26%) cases were reported in children whose mothers possessed college or university education. The information regarding birth rank and mother literacy is given in (Figure 5).

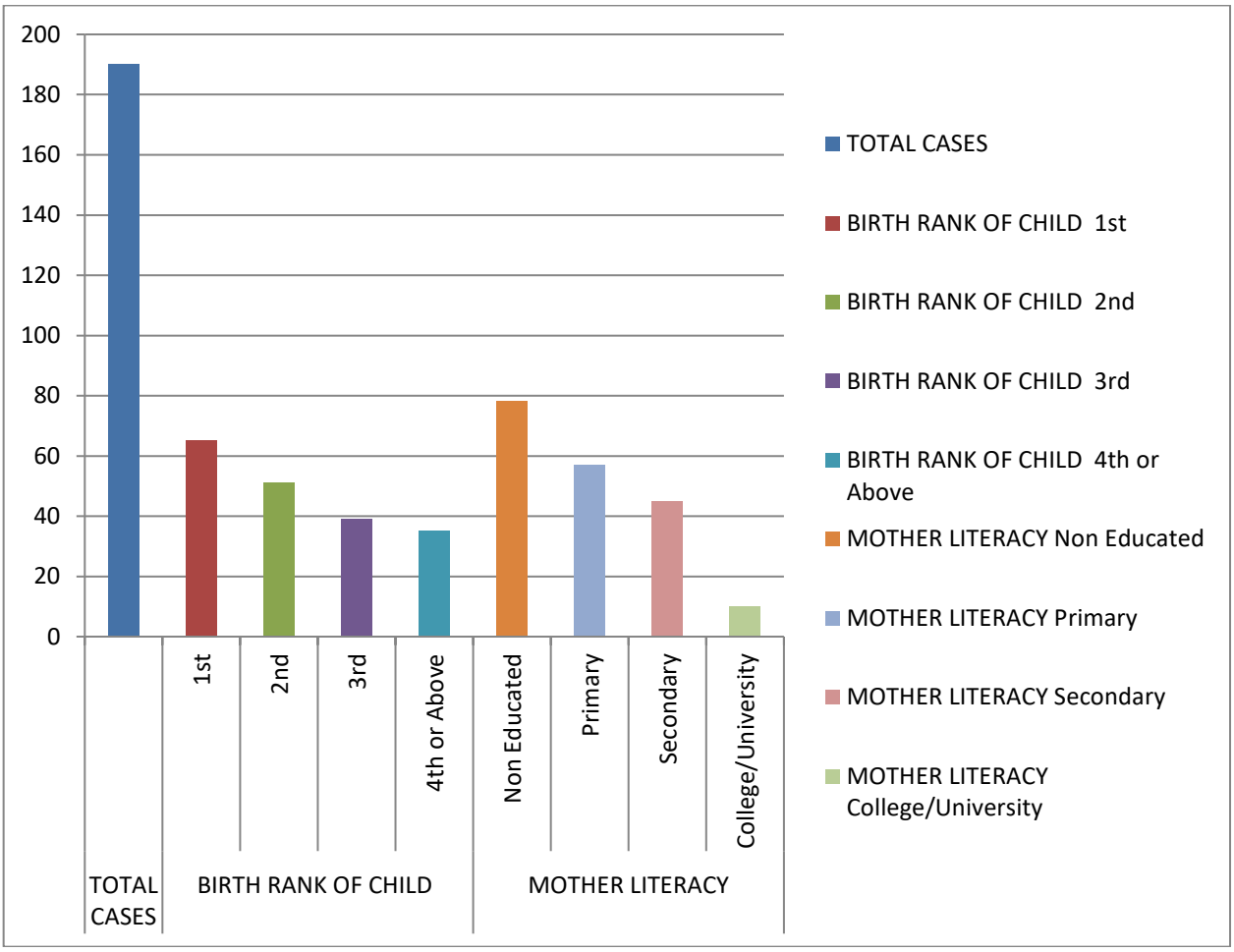

Figure 5: Distribution of measles cases according to birth rank of child and mother literacy rate.

In the current study the measles cases were distributed in different groups based on sleep duration, n=56(29.47%) cases were in the 1-7 hours sleep duration group, n=65(34.21%) cases were in the 8-12 hours group, n=49(25.78%) cases were in 13-16 hours group and n=20(10.52%) cases were in 17 and above 17 hours sleep group. According to the current study, maximum measles cases n=65(34.21%) were in the 8-12 hours group and minimum cases n=20(10.52%) were in the 17 and above 17 hours sleep group. In the current study the measles cases were distributed in different groups based on the appearance of rashes on body parts, n=88(46.31%) measles cases were identified by the current study having rashes on the face, n=18(9.47%) cases having rashes on back, n=68(35.78%) having rashes on abdomen and n=16(8.42%) cases having rashes on extremities. According to the current study, maximum measles cases n=88(46.31%) had rashes on the face and minimum cases n=16(8.42%) cases having rashes on the extremities. The information regarding sleep duration of child and distribution of rashes on body parts is given in (Figure 6).

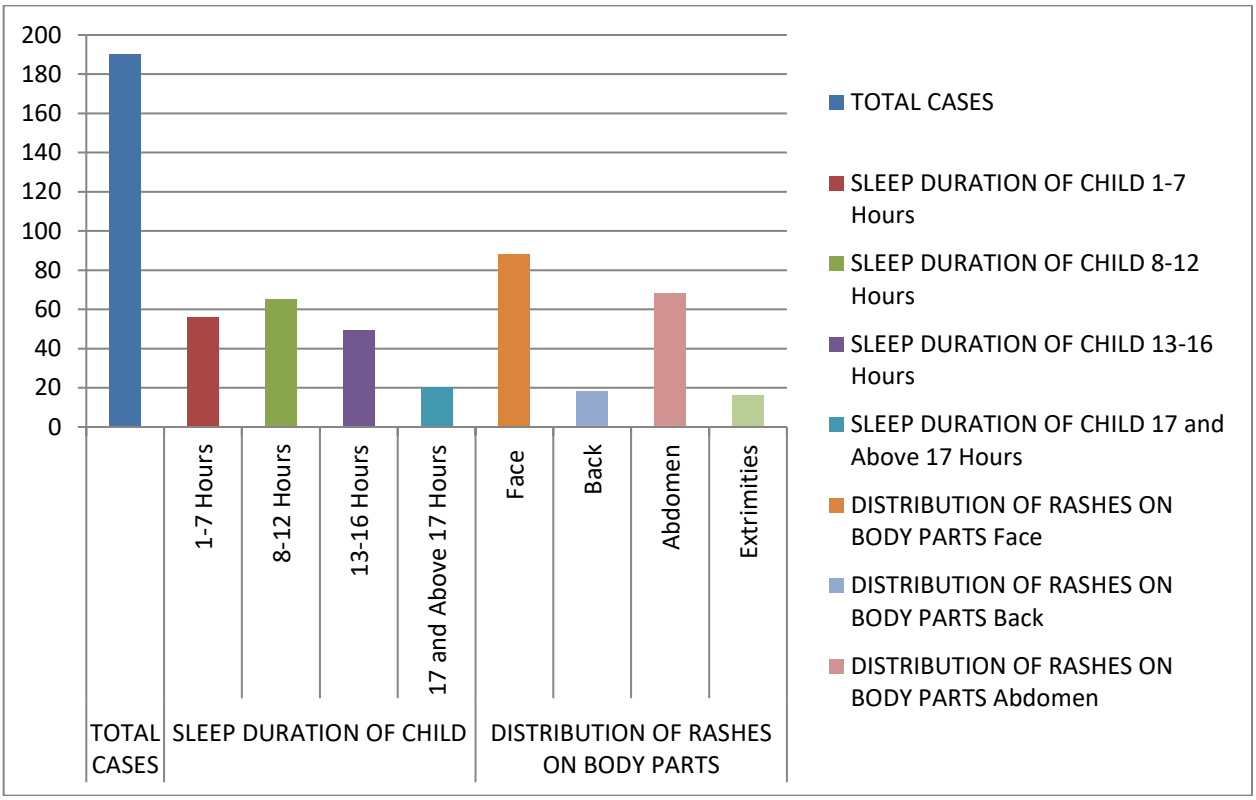

Figure 6: Distribution of measles cases according to sleep duration of child and distribution of rashes on body parts.

DISCUSSION

Measles is a highly contagious viral disease that can infect the respiratory tract and then spread throughout the body. The measles virus can survive for up to 2 hours in the airspace where an infected child coughs or sneezes. Symptoms of measles include fever, cough, runny nose, itchy, watery eyes, and characteristic rashes on the body. In many developing countries, especially in parts of Asia and Africa, measles remains common and is a significant cause of death worldwide. Measles is endemic to Pakistan, with periodic epidemics occurring every two to three years, particularly in densely populated areas where vaccination coverage is low. More than 95% of deaths occur in poor countries with low health infrastructures. Measles in children is caused by the Morbillivirus, which resides in an infected person's nose and throat. In some cases, it can lead to lifelong problems such as brain damage, deafness, and blindness. Mortality from measles has decreased with the discovery of vaccines. The World Health Organization (WHO) recommends immunization for all susceptible children and adults. The main risk factors for measles include lack of child immunization, maternal education, awareness, overcrowding, low income, and inadequate nutrition. The current study has several strengths, such as well-characterized factors including transmission by contact, socioeconomic status, vaccination status of the child, birth rank, types of housing, types of areas, educational levels of children's mothers, and other medical conditions. In the current study, there were n=82(43.15%) male cases and n=108(56.84%) female cases. According to the current study female children are at more risk as compared to male children. Females are more immune to measles as measles antibody is marginally higher in females than in males [29] but in the current study female children are at higher risk may be due to gender-based inequalities. The results of the current study are similar to a few studies conducted by Sheikh et al [30]] in Karachi, a study conducted by Ilyas et al [9]] in Peshawar, a study conducted by Khan et al [31] in Bannu as in these studies female children are more susceptible to measles as compared to males. The results of the current study are not similar to studies conducted by Zaidi et al [32] in Punjab, a study conducted by Ahmed et al [33] in Baluchistan, a study conducted by Fayyaz et al [34] in Karachi, a study conducted by Younas et al [5] in Karak KPK as in these studies, male children are more

prone to measles as compared to female children. The results of the current study are similar to a study conducted by Bassy et al [29], and a study conducted by Maseut et al [35].In the current study majority of cases, n=84(44.21%) were observed in the less than 2-year age group category. The results of the current study regarding the maximum number of cases in less than 2-year age groups are supported by a large number of studies. These results are supported by similar studies conducted by Lee et al [36], and a study conducted by Olaitan et al [37]. The majority of instances in the current study were found in children under the age of two. This is because the population under study had a poor vaccination rate, which weakened the children's immunity. These results are supported by a study conducted by Olaitan et al [37]. In the current study majority of measles cases, n=96(50.25%) were reported to socioeconomically poor children. The current study shows that socioeconomically poor children have a high possibility of acquiring measles because mothers of children belonging to poor families and low educational levels were less likely to receive measles vaccines on time and get less awareness about life issues. The results of the current study are supported by a study conducted by Koenig et al [38]. According to the current study, the weight of a maximum number of measles-affected children n=98(51.57%) was recorded in a range of 10-15 kg while the weight of less number of measles-affected children n=12(6.31%) was found above 20 kg. The current study showed that some children lost their weight during measles. Weight loss during measles is associated with decreasing levels of serum proteins. Serum protein has a most important role in the circulatory system that serves the transport of lipids, hormones, vitamins, and the regulation of cellular activity and functioning of the immune system. Vitamin A is involved in the development of the immune system but in the case of measles immune system gets compromised due to low levels of serum vitamin A and Retinol Binding Protein (RBP). These results are supported by a study conducted by Reddy et al [39]. According to the current study, spicy snacks were found as the favorite diet of measles-affected children. Spicy snacks contain monosodium glutamate (MSG) which has a negative effect on the spleen and thymus gland. MSG is involved in the reduction of lymphocyte production. This result was supported by the studies conducted by Banerjee et al[40] and a study conducted by Dar et al [41]. The current study found that the risks of measles are high in the non-vaccinated child population as compared to the vaccinated child population because vaccination prevents measles disease in children by improving immunity. The results of the current study are similar to a study conducted by Bekele et al [20] and a study conducted by Mushtaq et al [42].

The current study showed that the high risk of measles in the child population mostly lived in low-altitude areas as compared to high-altitude areas. Low-altitude areas were mainly overcrowded and polluted. Due to this, the risks of measles were high in areas of low altitude. The current study revealed a strong relationship between birth rank and measles. The infections of the measles virus occur due to weak immunity development in the first child. The results of the current study are supported by a study conducted by Datta et al [43]. According to the current study, children whose mothers were uneducated had a higher risk of having measles. On the other hand, fewer kids had mothers with education. Compared to women with more education, mothers with less education were less likely to immunize their children. Due to education, the females get awareness about the basic issues of children's lives. The results of the current study are supported by a study conducted by Chowdhury et al [44]. The study showed that the risks of measles were high among children living in non-cemented houses as compared to children living in cemented houses. This is because germs thrive more easily in non-cemented structures. The measles virus is found at a high rate in non-cemented houses where the hygienic condition is poor as compared to cemented houses. The results of the current study are supported by a study conducted by Sasmi et al [17]. According to the current study children populations suffering from measles have other medical conditions such as Pneumonia, Diarrhea, Encephalitis, Corneal ulcers, Fever, Rash, Coryza, Cough, and Conjunctivitis etc. The rate of viral infection is very high because in such conditions the immune system is unable to fight against germs and morbillivirus harbor the respiratory tract and show their effects. The results of the current study are supported by a study conducted by Younas et al [5]. The current

study showed that no relationship exists between measles disease in children and sleep duration. According to the results of the current study similar percentage of measles-affected children belonging to each category of sleep duration were found which shows that no relationship exists between sleep and measles disease. Similarly, in comparison no data exists regarding the relationship between sleep cycle and measles in children and perhaps this may be the first study. The current study found a weak relationship between parental smoking with measles measles-affected children. The chemical composition of tobacco smoke is complex therefore it has negative effects on smoker health but smoking is not considered as the causative agent of measles. Smoking is indirectly related to smoking as smoking causes household income to be diverted from food to tobacco, increasing the risk of chronic malnutrition in infants and children. The results of the current study are supported by a study conducted by Semba et al [45]. The current study showed that a large number of children were infected from contact with measles affected child. Measles is a highly contagious disease and it spreads from person to person through the air by infectious droplets. The parents should keep their affected child away from other children and those who have been not immunized during the infectivity period. The results of the current study are supported by a study conducted by Afzal et al [10]. The current study showed that in a large number of measles-affected children rash development was observed on the face. Initially rash develops on the face and then spreads downwards because viruses circulate in the blood which can infect capillaries in the skin. The virus can cause swelling and damage to host cells due to which the skin becomes itchy and a rash appears on the skin at 104°F temperature. The results of the current study are supported by studies conducted by Yoshida et al [46], and a study conducted by Premaratna et al[47]. Based on the findings of the current study, it is recommended to prioritize measles vaccination, especially for children under 5 years old, and to focus on improving maternal education and nutritional status. Promoting healthy dietary habits and avoiding contact between infected and healthy children can help prevent transmission. Additionally, efforts to reduce parental smoking may contribute to mitigating the risk.

CONCLUSION

The current study concludes that various factors contribute to measles infection in children. The current study concludes that the measles disease is most common in children aged less than 5 years. During the current study, poor socioeconomic status, low altitudes, junk food especially spicy snacks, and illiterate mothers were found as the promoting factors in measles disease. A large number of measles affected children was found as unvaccinated. Measles affected children could transfer infection to healthy children; therefore measles affected children should be prevented from coming in contact with healthy children. To a large extent the disease symptoms invades the facial areas of the measles affected children. The current study shows no relationship between measles with children's sleep cycle and a weak relationship between measles with children's parental smoking. On time vaccination, intake of food containing vitamin A, and immediate treatment will reduce the infection.

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AUTHORS' CONTRIBUTIONS

The current research work was carried out in collaboration among all authors. Authors MS, TZ, GN, SR, MHK, AK, and MN performed analysis, literature review and wrote the first draft of the manuscript. Authors AK, SA, and AGK designed the study and wrote the protocol. Authors AK, MHK, and NS performed the data collection.All authors read and approved the final version.

CONFLICTS OF INTREST

Authors have declared that no competing interests exist.

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