

The Resurgence of Measles Infection and its Associated Complications in Early Childhood at a Tertiary Care Hospital in Peshawar, Pakistan

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Abstract

Measles infection is of substantial interest to immunologists due to its paradoxical interaction with the immune system. After the acquisition of the measles infection, secondary infection plays a pivotal role in measles-related deaths. A cross-sectional study conducted between December 2018 and July 2019 is presented here. A total of one hundred children of both genders presented with measles complications were included following WHO criteria. Measles confirmation was done by quantitative determination of anti-measles antibodies (IgM) in patients' sera while patient-related demographic data, vaccination status, and other clinical information were obtained on a separate form. The number of female patients (52%) slightly exceeded the number of males (48%). 43% of patients' parents were illiterate, and half of the patients (50%) were from a poor background. The majority of children (76%) who presented with the complications did not receive a measles vaccine. 56% of children were breastfed while 58% received vitamin A supplements but developed complications. The elevated levels of anti-measles IgM were observed in 77% of cases. In both genders, the major complications were pneumonia, lower respiratory tract infection (LRTI), acute diarrhea, diarrhea and LRTI, pneumonia and diarrhea, otitis media and pneumonia, myocarditis and LRTI, and pneumothorax. The majority of the infected children ($n = 48$) under 12 months of age had associated complications. It has been observed that the measles virus strikes early age children in the northwestern region of Pakistan, which is an alarming situation and is associated with the aforementioned complications, especially in unvaccinated children. Anti-measles IgM is an important serological parameter for early diagnosis of measles infection.

Key words: measles, pneumonia, subacute-sclerosing panencephalitis, IgM, myocarditis, pneumothorax

Introduction

Measles is a highly contagious systemic viral infection caused by the Measles virus (MeV). This virus belongs to the Paramyxoviridae family, has ssRNA genome and a lipid envelope. It spreads through respiratory droplets and also through conjunctiva contact (Khan et al. 2013). Its diagnostic criteria include high-grade fever (38°C lasting for >3 days), generalized maculopapular rashes, cough, coryza, and conjunctivitis (WHO 2018a). Measles viral infection is the leading cause of morbidity and mortality worldwide among children, even though there is a safe and effective live attenuated viral vaccine (Wolfson et al. 2009). In 2010,

there were about 20 million measles infections reported with 0.14 million deaths (Simons et al. 2012). The death toll surged to approximately 0.16 million in 2011, with 95% of deaths reported from developing countries (WHO 2013). Presently, 45 million new measles cases were recorded, with one million deaths per year (Li et al. 2015). In 2011, measles hit 4386 people in Pakistan, with 64 deaths reported. In 2012, 2,676 laboratory-confirmed cases, and 310 deaths were reported in this country (Khan and Qazi 2014; CDC 2018). Measles viral infection is of substantial interest to immunologists due to its paradoxical interaction with the immune system. Many manifestations of the disease like rashes, conjunctivitis, and stomatitis are tagged with the immune response to

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infection. This immune response clears the virus from the body, providing lifelong immunity. After the acute phase of measles infection, the presence of the viral genome and its proteins in the lymphatic tissues leads to a suppressed immune system. Furthermore, as the immune suppression spans to several weeks, there is an opportunity for secondary microbial infections, which increase the mortality rate among children (Beckford et al. 1985; De Vries et al. 2012).

After measles infection, secondary infections play a crucial role in measles-related deaths. Lower respiratory tract infections (LRTI) like bronchial pneumonia, are the leading cause of death in measles cases, particularly among children under 5 years of age (Li et al. 2015). Other serious complications, particularly among immunocompromised and malnourished children, include blindness, acute diarrhea, otitis media, encephalitis, and myocarditis (WHO 2016). One of the fatal complications related to measles is sub-acute sclerosing panencephalitis (SSPE), which is a progressive, disabling, and deadly brain disorder of the central nervous system, usually developed between 7 and 10 years after a person is infected by the measles virus (Bellini et al. 2005). In a recent study conducted in Pakistan, complications like pneumonia, oral lesions, and acute diarrhea were reported due to measles infection among unvaccinated children (Hussain et al. 2016). Associated factors that are instrumental in the generation of complications include vitamin A deficiency, weakened immunity, living in congested environments, and poor access to health care facilities (Sultana et al. 2015).

Developed countries were successful in the reduction of measles infections through effective immunization. Under the auspices of the WHO, a campaign of immunization against communicable diseases started in Pakistan in 1978 (Bugvi et al. 2006). However, like other developing countries, the coverage of measles vaccination is below 60% in Pakistan (Mere et al. 2019). In preventing and reduction of measles infection and associated complications, the only hope is effective measles vaccination, which can significantly reduce the incidence of measles infection and related deaths among children (Gafaar et al. 2003). Unfortunately, recent outbreaks of measles infection (in 2018) in Pakistan occurred in different regions of the country (WHO 2019). The primary reasons for these measles episodes are lack of awareness regarding vaccination among the general population due to reduced literacy rate, lack of motivation among health care staff, and poor health care infrastructure.

Keeping in view the current scenario, this study was designed to investigate the measles incidence and its associated complications among the children of Khyber Pakhtunkhwa (KP) located in the northwestern region of Pakistan.

Experimental

Materials and Methods

The present study is a cross-sectional study conducted in the pediatric unit of the Lady Reading Hospital (LRH), a tertiary care hospital in District Peshawar, KP. Measles cases were defined in accordance with WHO criteria (2018), i.e., fever (38°C lasting for more than three days) and maculopapular rash, cough, coryza, or conjunctivitis. Measles cases were confirmed by detecting measles-specific IgM antibodies (anti-MeV IgM) in a patient serum through enzyme-linked immunosorbent assays (ELISA). A total of one hundred measles cases were studied for anti-MeV IgM confirmation. Venereal blood samples were collected aseptically between December 2018 and July 2019 from measles-infected children of both genders, above four months of age but under ten years, with measles complications and having been admitted to the pediatric unit of LRH Peshawar. Children aged less than 4 months or over ten years old or having congenital heart disease, thalassemia, or other congenital diseases were excluded from the study. Measles complications were diagnosed by physicians based on clinical findings with the support of laboratory and radiological findings, like X-ray chest, electrocardiogram, serum electrolytes, and complete blood count.

Patient demographic data and clinical information like age, sex, socio-economic status, educational level of parents, feeding history, vitamin A intake, and complications were recorded on a separate predesigned form. The measles vaccination status of a patient was established either through a vaccination card or through verbal confirmation with parents (if vaccination card not available). A written consent form was given to the parents, explaining the use of their data for research and publication.

Detection of measles-specific IgM antibodies. For the detection of measles-specific IgM antibodies, a fresh blood sample of about 2 ml from measles-infected children was collected by the vein puncture method in a gel tube. All the samples were centrifuged at 8,000 rpm in order to obtain a clear serum and to send for estimation of measles-specific IgM antibodies (ORGENTEC Diagnostka Alegria Anti Measles IgM Assay). The measuring range of Alegria assay was 0–200 U/ml. The cut-off value for the assay was 25 U/ml. Interpretation of the result was as follows: patient value less than 20 U/ml was considered negative, while a value between 20–25 U/ml was considered borderline, and a value > 25 U/ml was considered positive (Alegria Orgentec).

Principle of the assay. Detection of measles-specific IgM antibodies was done using Alegria[®], a fully automated random access analyzer. The Alegria[®] Test Strip is designed for a single determination of one patient

sample, which holds a complete set of reagents, including enzyme conjugate (Anti-human IgM HRP labeled), enzyme substrate (Tetramethyle benzidin), sample buffer, and a test specific control (Test specific antibodies). Antibodies quantification is based on an indirect enzyme-linked immune reaction in which purified particles of inactivated measles virus coated on a well surface interact with the corresponding anti-measles antibodies present in patient serum. After subsequent washing, an enzyme conjugate that binds to the immobilized antibody-antigen complex is added. After incubation, the addition of the enzyme substrate results in the development of a blue color, which is proportional to the concentration of the antibody-antigen complex measured at $\lambda = 650 \text{ nm}$.

Results

Patients' demographic data (Table I) shows that out of 100 patients, 52 (52%) were females with a mean age of 15.06 (± 9.42), while 48 (48%) were males aged 15.94 (± 9.70). As far as the educational status of the parents was concerned, a high percentage (43%) were uneducated, while 28% had Grade 10 (Secondary education level), and 22% had Grade 5 level (Primary education) educational competence. Only 7% of parents were found to have beyond Grade 10 level education (Higher education).

As far as the socio-economic position is concerned, half (50%) of the patients belonged to low-income families ($\leq \$1,700$ per annum), while 38% were from middle-class families ($\geq \$1,701$ and $\leq \$4,300$ per annum). Only 7% of patients were from the upper class ($\geq \$4,301$ per annum). Criteria of income per annum of the parents were sited, according to Hussain et al. (2016) with little modification.

Breast-feeding of babies in this region of Pakistan is a common practice in early childhood, although trends

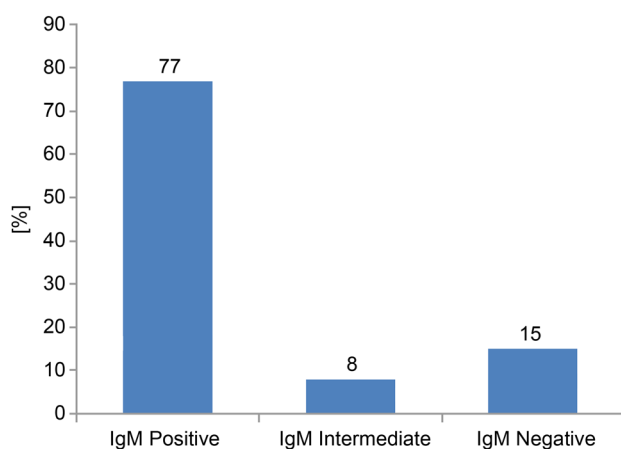


Fig. 1. The overall distribution of anti-measles antibody (IgM) in patients' sera (n = 100).

Table I
Demographic and related data of the patients.

Parameters	Patient
Patient-related	
Total Number	100
Male	48 (48%)
Female	52 (52%)
<i>Age-wise (in months)</i>	
Male	15.06 (± 9.42)
Female	15.94 (± 9.42)
<i>Feeding history (%)</i>	
Breastfeed	56%
Formula feed	32%
Breast + Formula	12%
<i>Measles vaccination status (%)</i>	
Vaccinated (Total)	24%
< 12 months	(n = 2)
12–24 months	(n = 17)
> 24 months	(n = 5)
Unvaccinated (Total)	76%
< 12 months	(n = 42)
12–24 months	(n = 23)
> 24 months	(n = 11)
Vitamin A intake (both genders)	58%
Parents-related	
<i>Socio-economic status (%)</i>	
High ($\geq \$4,301$ per annum)	12%
Middle ($\geq \$1,701$ and $\leq \$4,300$ per annum)	38%
Lower ($\leq \$1,700$ per annum)	50%
<i>Educational status (%)</i>	
Higher	7%
Secondary	28%
Primary	22%
Uneducated	43%

are changing. It was observed that 56% of children were breastfed while 32% were given formula milk. A comparatively small group of babies (12%) was found to be on formula as well as being breast-fed. It was also observed that 58% of measles-infected children had received vitamin A drops during the routine vaccination schedule.

The antibody (IgM) levels (Fig. 1) were found to be elevated in a majority (77%) of cases, while 8% of cases indicated intermediate levels, and 15% were found negative for the IgM presence. The measles infection was found in 76% of children who did not receive the vaccination, but 24% of cases were resurgence, where children had received one dose of measles vaccination (Table I).

The gender distributions of measles-associated complications are given in Fig. 2. In male patients major complications were pneumonia (n = 20; 41.7%) followed

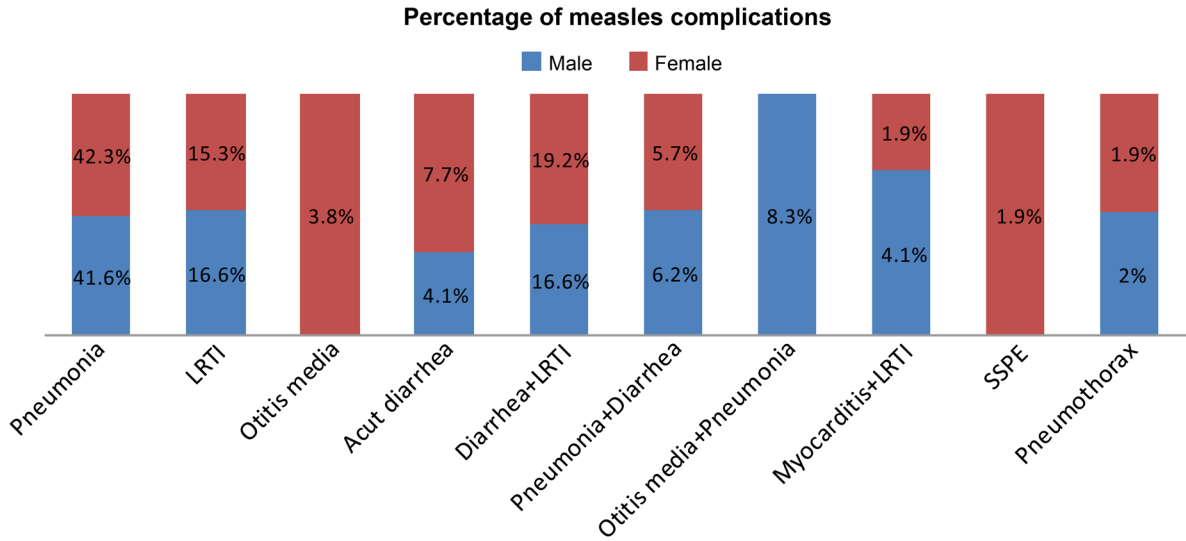


Fig. 2. Gender distribution of measles complications (Percentage).

by LRTI (n = 8; 16.7%), acute diarrhea (n = 2; 4.2%), diarrhea and LRTI (n = 8; 16.6%), pneumonia and diarrhea (n = 3; 6.2%), otitis media and pneumonia (n = 4; 8.3%), myocarditis and LRTI (n = 2; 4.1%), and pneumothorax (n = 1; 2.0%), respectively. In female patients, pneumonia (n = 21; 42.4%) was the major complication followed by LRTI (n = 10; 19.2%), otitis media (n = 2; 3.8%), acute diarrhea (n = 4; 7.7%), diarrhea and LRTI (n = 10; 19.2%), pneumonia and diarrhea (n = 3; 5.7%), myocarditis and LRTI (n = 1; 1.9%), SSPE (n = 1; 1.9%), and pneumothorax (n = 1; 1.9%).

The age distribution (Table II) of clinical complications showed a high frequency of pneumonia (n = 23; 47.9%), followed by LRTI (n = 8; 16.7%), acute diarrhea (n = 4; 8.3%), diarrhea and LRTI (n = 6; 12.5%), pneumonia and diarrhea (n = 3; 6.25%), otitis media and

pneumonia (n = 2; 4.1%), myocarditis and LRTI (n = 1; 2%), and pneumothorax (n = 1; 2%) in patients less than 12 months old. While for the age group 12–24 months, pneumonia (n = 15; 37.5%) was the major complication, followed by LRTI (n = 8; 20%), otitis media (n = 1; 2.5%), acute diarrhea (n = 1; 2.5%), diarrhea and LRTI (n = 8; 20.0%), pneumonia and diarrhea (n = 2; 5%), otitis media and pneumonia (n = 1; 2.5%), myocarditis and LRTI (n = 2; 5%), SSPE (n = 1; 2.5%) and pneumothorax 1 (2.5%). Complications presentation for the age group > 24 months were predominated by pneumonia (n = 3; 25%) and diarrhea + LRTI (n = 3; 25%), followed by LRTI (n = 2; 16.7%), otitis media (n = 1; 8.3%), acute diarrhea (n = 1; 8.3%), pneumonia and diarrhea (n = 1; 8.3%) and otitis media and pneumonia (n = 1; 8.3%). In the current study, the majority of the children (n = 76)

Table II
Frequency and distribution of measles complications in different age groups of patients

Clinical complications	Age-wise distribution			
	< 12 months	12–24 months	> 24 months	Total
Pneumonia	23 (47.9%)	15 (37.5%)	3 (25%)	41
LRTI	8 (16.7)	8 (20%)	2 (16.7%)	18
Otitis media	–	1 (2.5%)	1 (8.3%)	2
Acute diarrhea	4 (8.3%)	1 (2.5%)	1 (8.3%)	6
Diarrhea + LRTI*	6 (12.5%)	8 (20%)	3 (25%)	17
Pneumonia + Diarrhea	3 (6.25%)	2 (5%)	1 (8.3%)	6
Otitis media + Pneumonia	2 (4.1%)	1 (2.5%)	1 (8.3%)	4
Myocarditis + LRTI	1 (2.0%)	2 (5%)	–	3
SSPE†	–	1 (2.5%)	–	1
Pneumothorax	1 (2.0%)	1 (2.5%)	–	2
Total	48	40	12	100

* LRTI – Lower respiratory tract infection
 † SSPE – Subacute sclerosing panencephalitis

suffering from measles complications were unvaccinated, while only 24 children who had received one dose of measles vaccination were shown in Fig. 4.

Discussion

Measles is a highly contagious viral disease that leads to increased morbidity and mortality among children, especially in developing countries. Measles infection has the potential to lead to life-threatening complications (Filia et al. 2013).

Eradication of measles is an crucial section of Millennium Development Goal 4 of the WHO. Pakistan, as a member of the Eastern Mediterranean Region, agreed in 1997 to eliminate measles infection by 2010 (Gafaar et al. 2003). Unfortunately, the resurgence of measles is continuously reported from different regions of Pakistan over the last decade. According to a WHO 2019 report, during 2011, 2012, and 2013, the number of confirmed measles cases in Pakistan was 2,676, 8,048, and 8,030, respectively. More recently, in 2017 and 2018, significant measles episodes were reported throughout the country (Fig. 3). According to the Pakistan demographic health survey and social living standard measurement, the Expanded Program on Immunization (EPI) coverage is currently 65% and each year about 2 million Pakistani children do not receive their first dose of measles vaccination, while the coverage of the second dose of measles is lower (<60%) (CDC 2018).

The upsurge of measles in Pakistan could be attributed to several factors. Graft in the healthcare system,

which encompasses illicit allocation of funds, poor attitude of healthcare workers, quackery, fake vaccination campaigns, and marketing of expired drugs, plays a central role. Another hurdle is dissatisfactory health infrastructure in the country contributes to the resurgence of measles outbreaks (Islam et al. 2019).

Detection of measles-specific immunoglobulin (IgM), produced as a result of the primary immune response, serves as the gold standard in accurate diagnosis of measles infection. These antibodies are easily detected in patient serum within a few days after the onset of the rashes through an enzyme-linked immunosorbent-based assay (Xavier et al. 2019). In the current study, the WHO-recommended ELISA technique was used for the detection of serum antibodies with 77% positive results (Patient value > 25 IU). Grey zone or borderline titers, i.e., values between 20–25 IU, were observed in 8% cases, while 15% of cases were negative (Patient value < 20 IU). The borderline titers or seronegative results may be attributed to inadequate immune responses of the host or maybe due to early blood sample collection before elevated IgM level in the serum of the respective patients. IgM may also be negative in a true measles case if the specimen is collected too early or too late in the course of the illness. In the first 72 hours after rash onset, a negative result for measles IgM may be obtained from up to 30% of measles cases. The sensitivity of the test is lower \leq three days after rash onset (WHO 2018b). The vitamin A deficiency often leads to increase in the risk of blindness among the measles-infected children. In the present study, vitamin A had been administered in 58% of measles-infected

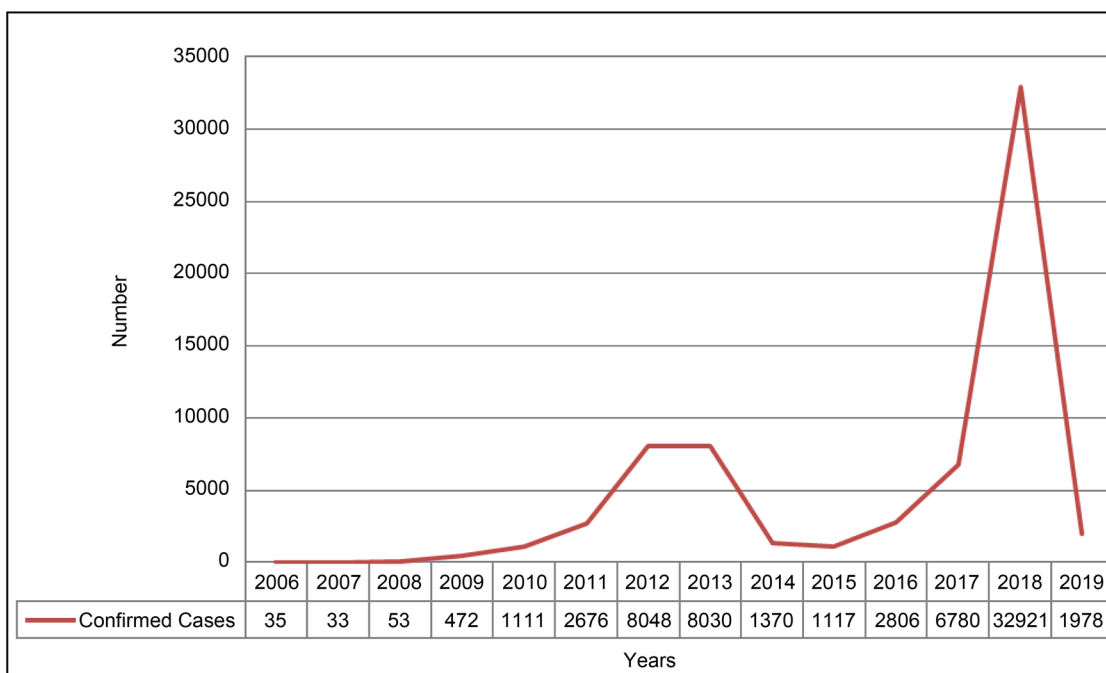


Fig. 3. Number of confirmed measles cases from 2006 to 2019 in Pakistan (WHO 2019; updates).

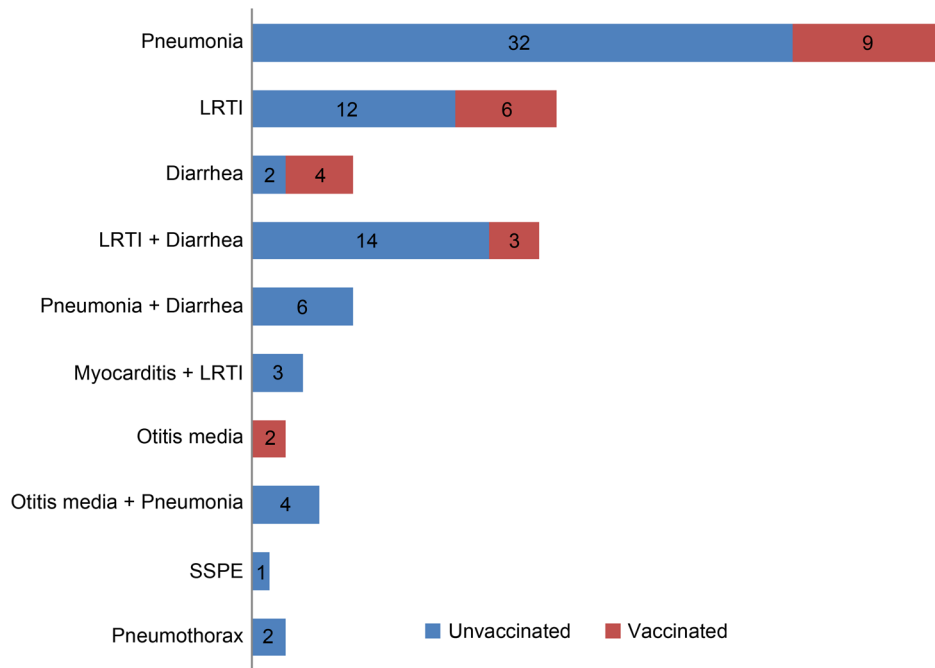


Fig. 4. Distribution of measles complications among measles-vaccinated and unvaccinated children.

children, although vitamin A administration is not a regular part of the vaccine schedule followed in Pakistan. Poor immune response, improper maintenance of cold chain during transportation, and neglectful attitude of health care staff may be factors leading to the development of complications. In the present study, vitamin A intake information was made through verbal communication with the parents of the children.

The age-wise distribution, status of vaccination, and incidence of measles infection for the period September 2018 to August 2019 in Pakistan was given in 2019 WHO report. The findings suggest an emergency and the need for quick intervention. Furthermore, prompt education on the awareness and benefits of immunization among the population of this region is needed.

In the present study, pneumonia (41%) and diarrhea were the major complications associated with measles infection, and these observations are similar to a report by Khan et al. (2013), while in a separate study conducted by Rashid et al. (2016), a slightly high frequency for the complications mentioned above was reported. In the present study, co-infections like diarrhea with LRTI, pneumonia and diarrhea, otitis media and pneumonia, and myocarditis and LRTI were observed. In the present study, the vaccination status of the measles-infected children was established through vaccination cards issued by EPI Health department KP, Pakistan. The vaccination status of the patients was confirmed through a vaccination card in more than 80 children. Only for a few children was vaccination status confirmed by parents through verbal communication. Negligence, low education status, and less awareness

about vaccination schedules among the parents determine their mindset regarding the prevention of measles in this region. It is evident from the present study that significant factors that may contribute to the resurgence of measles infections include low vaccination (24 vaccinated babies versus 76 unvaccinated) that may be due to lack of vaccination awareness, poor health infrastructure, malnutrition, and missing of a booster dose. Malnutrition is a significant risk factor in measles-infected children around acquiring complications that lead to increased mortality among unvaccinated children. Furthermore, the majority of the infected children (76%) were not vaccinated, which highlights the higher risk of acquiring infection and resultant complications. In a report by Husain et al. (2016), 75% of children with pneumonia were malnourished, while 83.3% of such children also had diarrhea. In the present study, children under one year of age, particularly between 7–8 months, developed measles complications. The principal reason behind this may be the underdeveloped immune system that makes children more prone to this disease and its subsequent complications.

In Pakistan, the vaccination schedule for measles vaccination is nine months, while the booster dose is at 14 or 15 months (Table III). For this disease, it has been recommended that the administration of booster dose be made at 14 to 15 months of age, increasing the vaccine efficacy up to 99% and providing more protection compared to a single dose (De Serres et al. 2012). However, in the present research, we did not observe any booster dose administration for the children infected by measles. It is an alarming finding that necessitates

Table III
Vaccination schedule for children in Pakistan.

Age of vaccine administration	Name of vaccine
Immediate after birth	1. BCG
	2. OPV
	3. Hepatitis-B
After 6 weeks	1. OPV-1
	2. Penta-1
	3. Pneumo-1
After 10 weeks	1. OPV-2
	2. Penta-2
	3. Pneumo-2
After 14 weeks	1. OPV-3
	2. Penta-3
	3. Pneumo-3
	4. IPV
After 9 months	Measles-1
After 15 months	Measles-2

<http://www.epi.gov.pk/immunisation-schedule/>

a mandatory administration of the primary as well as the booster dose among children.

Measles remains a leading cause of death among young children worldwide despite the availability of a live attenuated effective vaccine. In the present study, severe complications like pneumonia, acute diarrhea, myocarditis, and pneumothorax were observed in children under one year of age. Only one case of SSPE was observed that was confirmed through the detection of anti-measles antibodies in cerebrospinal fluid (CSF) of the patient. The number of children with SSPE may be underestimated; generally, it is developed 7–10 years after a person has measles, even though the person seems to have fully recovered from the illness.

Multiple outbreaks of measles have been reported from different parts of the world (Wolfson et al. 2009) and particularly from this region of Pakistan. It is not only worrisome but needs an effective strategy in the health care system to devise a national strategy for measles vaccinations. Combined efforts of the health care staff, awareness through social media, and related health professionals are required to augment awareness among the general public regarding the vaccination program and clinical consequences of measles infection in order to prevent the disease from resurging as endemic.

Conclusions

The measles virus has potentially fatal consequences at an early age of childhood, not only in Pakistan but worldwide, which is alarming. Major complications

observed in the present case included pneumonia, LRTI, diarrhea, otitis media, myocarditis, and SSPE, with some patients presenting more than one complication. Primarily, the complications were observed among unvaccinated and among children vaccinated only with one dose of vaccine, which illustrates the importance of the measles vaccination. Moreover, the booster dose administration can be made mandatory in order to achieve better immunization. Furthermore, the workhorse method proved to be significant and can be effectively utilized in the early diagnosis of measles infection.

Authors' contributions

MI carried out samples collection, participated in the experimental work, and wrote the manuscript. SA designed the overall study and critically reviewed the manuscript. JA, SAG, and MK helped in manuscript writing, drafting of tables of figures, and funds arrangement. All the authors edited and approved the final manuscript.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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