

Original Article

The measles epidemic in northern Kosovo and Metohija, Serbia, October 2017–August 2019

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Abstract

Introduction: Measles is among the most contagious and vaccine-preventable respiratory diseases. The aim of this research was to describe the socio-demographic profile, clinical manifestations and laboratory parameters of measles patients hospitalized at Kosovska Mitrovica Clinical Centre during the 2017–2019 outbreak.

Methodology: The prospective study included all patients that had contracted measles (107) who were hospitalized at Kosovska Mitrovica Clinical Centre during the outbreak. All complications that led to hospitalization were analyzed and the frequencies of complications with respect to patient age and vaccination status were recorded.

Results: More than half (51%) of the patients were unvaccinated. Patients' age varied statistically significantly with respect to vaccination status. Pneumonia was noted in 65% of the patients from the younger age group, compared to 32% of adults, and this difference was statistically significant. Hepatitis was a significantly more frequent complication in adults, affecting 36% of measles patients in this age group, compared to only 7% of those aged below 18 years. In the unvaccinated group, 71% pneumonia frequency was noted, compared to 11% and 35% in the vaccinated and unknown vaccination status groups, respectively. The differences in frequencies based on vaccination status were statistically significant.

Conclusions: Most hospitalized patients were unvaccinated. Complications showed a significant difference with respect to the age and vaccination status of patients. Therefore, it is necessary to carry out continuous health promotion activities to raise awareness among the entire population of the importance and need for vaccination of children against measles, but also adults who have not been previously vaccinated.

Key words: Measles; outbreaks; immunization; complications.

J Infect Dev Ctries 2022; 16(5):850-856. doi:10.3855/jidc.13055

(Received 14 May 2020 – Accepted 30 November 2020)

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Introduction

Measles is among the world's most contagious diseases. It is a vaccine-preventable respiratory disease. Prior to the introduction of the vaccine, 90% children contracted measles in the first 15 years of life [1]. Despite having a safe vaccine, measles remains one of the leading causes of death among young children worldwide. According to the World Health Organization (WHO), 158,000 deaths were caused by measles in 2011, and more than 95% of these cases occurred in countries with low economic status and poor healthcare infrastructure [2]. Although vaccination protects more than 90% of those inoculated, measles outbreaks still occur in areas with high vaccination

coverage as a result of imported transmission [3]. In 2008, measles cases were reported from some countries of the European Union, where this infectious disease was thought to have been eradicated [4]. From January to June 2018, WHO European Region countries reported more than 41,000 patients with measles. Ukraine reported a majority of these cases, however, France, Georgia, Greece, Italy, the Russian Federation, and Serbia also reported high case counts [5].

In Serbia, the first measles vaccine was introduced in 1971 as a mono-vaccine, and was replaced in 1981 by a combined MM (measles and mumps) vaccine. Since 1991 a combined MMR (measles, mumps, and rubella) vaccine has been administered in two doses [6].

Prior to the latest outbreak, a major measles epidemic in the Republic of Serbia was reported in 1997. Two decades later, in the beginning of October 2017, a new major epidemic was registered in the country. The first case of measles in the territory of Kosovo and Metohija was reported on 1st October 2017, whereas the measles epidemic in parts of Kosovo and Metohija with majority Serb and non-Albanian population was reported on 23rd October 2017, where 410 cases were registered until 18th October 2018 [7].

The aim of this research was to describe the socio-demographic profile, clinical features, and laboratory parameters of measles patients hospitalized at Kosovska Mitrovica Clinical Centre during the 2017–2019 outbreak. A further goal was to identify the complications most commonly associated with the hospitalization of measles patients during this epidemic.

Methodology

A prospective study was carried at the Kosovska Mitrovica Clinical Centre during the epidemic period between 1st October 2017 and 27th August 2019. The study included all patients that had contracted measles (107) who were hospitalized. This health facility is the main hospital in northern Kosovo and Metohija and all patients from those areas requiring hospitalization were admitted to either the Infectious Diseases Ward (74) or the Pediatric Ward (33), depending on their age.

At the beginning of the epidemic, the diagnosis of first 10 patients, infected with measles, was confirmed based on positive specific IgM antibodies (Anti-Measles Virus ELISA (enzyme-linked immunosorbent assay), IgM) and PCR (Polymerase Chain Reaction) which was used to detect nucleic acid from nasopharyngeal swabs. Sample analysis was conducted in the National Reference Laboratory of the Institute of Virology, Vaccines and Sera “Torlak” in Belgrade. Different commercial ELISA kits were used for IgM antibody testing and only the National Reference Laboratory performed viral RNA detection by PCR. In the further course of the epidemic, diagnosis was established on the basis of clinical features and epidemiological data, with the exception of patients that presented with atypical clinical features (absence of rash or fever) who were still tested for measles during the epidemic.

Demographic characteristics and vaccination status was obtained for all patients, and their clinical manifestations and laboratory parameters (total leukocytes, lymphocytes, neutrophil, C-reactive protein (CRP), alanine aminotransferase (ALT), erythrocyte

sedimentation rate (ESR), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH)) were monitored. We collected initial laboratory parameters to compare. Also, we collected the highest body temperature of each patient. Patient demographic data, clinical information 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 was not available). Measles complications were diagnosed by physicians based on clinical findings with the support of laboratory and radiological findings, like X-ray chest, abdominal ultrasound, blood biochemistry, and complete blood count. The sample was segregated into two groups based on age, with those aged ≤ 18 years assigned to pediatric (Group 1) and those aged > 18 years into adult group (Group 2). Based on vaccination status, patients were classified into three groups, denoted as “vaccinated”, “unvaccinated”, and “unknown vaccination status”. All complications (pneumonia, otitis media, hepatitis, encephalitis, sinusitis, laryngitis, diarrhea) that led to hospitalization were analyzed and the frequencies of complications with respect to patient age and vaccination status were recorded.

The gathered data was subjected to descriptive statistical analyses and statistical hypothesis tests. Continuous variables were presented as arithmetic mean, median, standard deviation, minimum (min) and maximum (max) value, and categorical variables as absolute and relative numbers. For continuous variables, normality of the distribution was checked via the Shapiro-Wilk test.

Since the continuous variables did not meet the normal distribution criteria, nonparametric methods were utilized to compare the differences between two groups, whereby Mann–Whitney U test was applied to the rank sums, and Kruskal–Wallis test was utilized to compare the differences among three groups. A chi-squared test and Fisher's exact test were performed when analyzing the frequency differences among groups. All hypotheses were tested at a statistical significance level (alpha level) of 0.05. The SPSS Statistics 22 software program (SPSS Inc., Chicago, IL, USA) was used for statistical processing of the results.

Results

The study included 107 subjects, 60 (56%) of whom were male and 47 (44%) were female. The median age of the sample was 8.5 years (IQR 2.0 - 27.25 years).

More than half (51%) of the patients were unvaccinated, 17% were vaccinated, and in the remaining 32% vaccination status was unknown. The median age of unvaccinated subjects was 2.0 years (IQR 1.0 - 5.0 years), while 22.5 (IQR 22.0 - 28.75 years) and 28.0 (IQR 20.5 - 35.0 years) was obtained for the vaccinated subgroup and that with unknown vaccination status. Patients' age varied statistically significantly with respect to vaccination status ($p < 0.001$) (Figure 1).

All clinical measles manifestations occurred with high frequency. Rash was the most common complaint, affecting 98% of the patients, followed by cough (90%), fever (84%), and conjunctivitis (71%), as shown in Table 1.

Majority of patients experienced one (31.8%) or two (30.8%) complications, while no complications were noted in 13.1% cases, and 24.3% of the sample was affected by three or more complications. According to age groups, the difference in the frequency of complications did not show statistical significance, however, patients without complications were significantly more frequent in the group of vaccinated ($p = 0.042$). The most common measles complication was pneumonia (49.5%), followed by diarrhea (39%), and hepatitis and laryngitis (20%), while other complications were relatively infrequent.

Encephalitis as a measles complication was not diagnosed in any of the patients included in the study. One patient who developed severe pneumonia with suspected acute respiratory distress syndrome (ARDS) was transferred to the intensive care unit where he successfully recovered. There were no fatalities in our hospital (Table 1).

As noted previously, participants were grouped by age into Group 1 (aged ≤ 18 years) and Group 2 (aged > 18 years). The median age of patients in Group 1 was 2.0 years (IQR 1.0 - 5.25 years), while 29.5 years (IQR 23.75 - 36.0 years) was measured for Group 2. Measles incidence was slightly higher among younger patients (58%) compared to older individuals (42%). No statistically significant differences in the clinical manifestation frequencies were noted between the two age groups.

In Group 1, pneumonia affected 65% of the patients, compared to 32% in Group 2, and this difference was statistically significant ($p = 0.001$). Hepatitis was noted in 7% of patients in the younger age group, while it occurred in 36% of adults. This difference was also statistically significant ($p < 0.001$). Only 30% of patients in Group 1 experienced diarrhea, which affected 48% of Group 2, but the difference was not statistically significant ($p = 0.065$).

No statistically significant differences in the frequency of sinusitis, laryngitis and conjunctivitis as measles complications were noted between the two age groups. Only younger patients were affected by otitis (Table 2).

The total leukocyte and lymphocyte values were statistically significantly higher in Group 1 ($p = 0.002$ and $p < 0.001$, respectively), while the values of granulocytes, C-reactive protein (CRP) and alanine aminotransferase (ALT) were significantly higher in Group 2 ($p < 0.001$). The sedimentation, aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) values did not differ with respect to patients' age (Table 2).

Table 1. Distribution of clinical manifestations and complications in patients with measles.

| | N (%) |
|-----------------------------------|------------|
| Clinical manifestations | |
| Fever | 90 (84.1) |
| Rash | 105 (98.1) |
| Cough | 96 (89.7) |
| Conjunctivitis | 76 (71.0) |
| Complications | |
| Hepatitis | 21 (19.6) |
| Diarrhea | 42 (39.3) |
| Otitis Media | 4 (3.7) |
| Sinusitis | 2 (1.9) |
| Laryngitis | 22 (20.6) |
| Pneumonia | 53 (49.5) |
| Encephalitis | 0 (0) |
| Frequency of complications | |
| Without complications | 14 (13.1) |
| One complication | 34 (31.8) |
| Two complications | 33 (30.8) |
| Three and more complications | 26 (24.3) |

Figure 1. Vaccination status compared to the age of hospitalized patients.

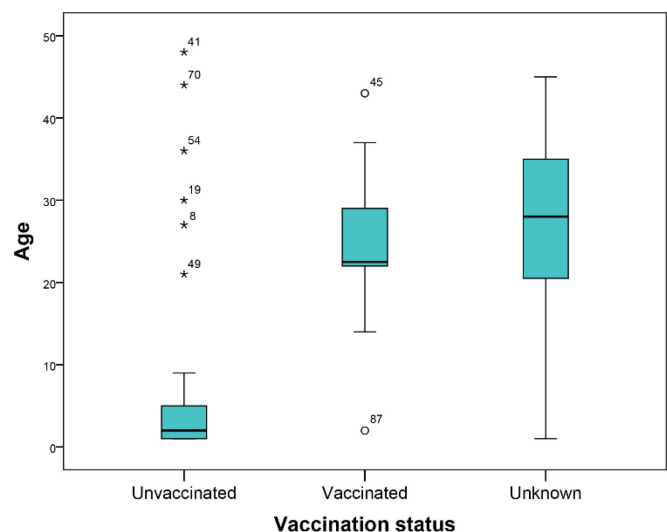


Table 2. Clinical manifestations, complications and biochemical analyzes of patients with measles by age.

| | Age | | p value |
|---------------------------------------|----------------------------|-------------------------------|----------|
| | Up to 18 years 60 (58%) | For over 18 years 44 (42%) | |
| Clinical manifestations | | | |
| Fever | 52 (86.7) | 35 (79.5) | 0.332 |
| Rash | 58 (96.7) | 44 (100.0) | 0.221 |
| Cough | 55 (91.7) | 39 (88.6) | 0.605 |
| Conjunctivitis | 42 (70.0) | 32 (72.7) | 0.762 |
| Complications | | | |
| Otitis Media | 4 (6.7) | 0 (0) | 0.081 |
| Sinusitis | 1 (1.7) | 1 (2.3) | 1.00 |
| Laryngitis | 14 (23.3) | 7 (15.9) | 0.351 |
| Pneumonia | 39 (65.0) | 14 (31.8) | 0.001* |
| Diarrhea | 18 (30.0) | 21 (47.7) | 0.065 |
| Hepatitis | 4 (6.7) | 16 (36.4) | < 0.001* |
| Encephalitis | 0 | 0 | / |
| Blood biochemistry | | | |
| Leukocytes, Median(range) | 6.8 (2.3-43.4) | 4.2 (2.7-16.6) | 0.002* |
| Lymphocytes, Median(range) | 28.2 (3.5-73.0) | 12.8 (3.8-64.8) | < 0.001* |
| Neutrophils, Median(range) | 64.5 (2.1-88.5) | 80.3 (5.1-96.0) | < 0.001* |
| CRP, Median(range) | 7.8 (0.7-57.2) | 34.9 (2.3-124.8) | < 0.001* |
| ESR (mm in first hour), Median(range) | 17.5 (7.0-76.0) | 25.0 (3.0-80.0) | 0.151 |
| AST, Median(range) | 55.5 (23.0-712.0) | 72.0 (17.0-655.0) | 0.110 |
| ALT, Median(range) | 31.0 (9.0-584.0) | 55.0 (9.0-428.0) | < 0.001* |
| LDH, Median(range) | 1000.0 (682.0-1624.0) | 634.0 (407.0-1789.0) | 0.080 |

*- Statistically significant difference; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: Lactate dehydrogenase.

Table 3. Clinical manifestations, complications and biochemical analyzes of patients with measles according to vaccination status.

| | Vaccination status | | | p value |
|---------------------------------------|--------------------------|------------------------|-----------------------|----------|
| | Unvaccinated 55 (51%) | Vaccinated 18 (17%) | Unknown 34 (32%) | |
| Clinical manifestations | | | | |
| Fever | 48 (87.3) | 12 (66.7) | 30 (88.2) | 0.084 |
| Rach | 53 (96.4) | 18 (100.0) | 34 (100.0) | / |
| Cough | 51 (92.7) | 14 (77.8) | 31 (91.2) | 0.183 |
| Conjunctivitis | 39 (70.9) | 10 (55.6) | 27 (79.4) | 0.196 |
| Complications | | | | |
| Otitis media | 3 (5.5) | 1 (5.6) | 0 (0) | / |
| Sinusitis | 0 (0) | 1 (5.6) | 1 (2.9) | / |
| Laryngitis | 12 (21.8) | 5 (27.8) | 5 (14.7) | 0.511 |
| Pneumonia | 39 (70.9) | 2 (11.1) | 12 (35.3) | < 0.001 |
| Diarrhea | 15 (27.3) | 6 (33.3) | 21 (61.8) | 0.005* |
| Hepatitis | 6 (10.9) | 5 (27.8) | 10 (29.4) | 0.065 |
| Encephalitis | 0 (0) | 0 (0) | 0 (0) | / |
| Blood biochemistry | | | | |
| Leukocytes, Median (range) | 6.2 (2.5-43.4) | 3.9 (2.7-16.6) | 5.0 (2.3-20.1) | 0.133 |
| Lymphocytes, Median(range) | 28.8 (3.9-73.0) | 19.0 (3.5-64.8) | 13.1 (3.8-59.5) | 0.001* |
| Neutrophils, Median(range) | 63.6 (2.1-90.6) | 71.1 (5.1-87.4) | 80.5 (32.4-96.0) | 0.005* |
| CRP, Median(range) | 7.8 (0.7-102.1) | 22.7 (2.3-88.0) | 22.6 (1.5-124.8) | < 0.001* |
| ESR (mm in first hour), Median(range) | 17.5 (7.0-53.0) | 30.0 (7.0-80.0) | 24.5 (3.0-45.0) | 0.269 |
| AST, Median(range) | 55.5 (23.0-712.0) | 57.5 (17.0-519.0) | 70.5 (21.0-655.0) | 0.174 |
| ALT, Median(range) | 31.0 (9.0-584.0) | 47.0 (17.0-428.0) | 53.0 (9.0-365.0) | 0.010* |
| LDH, Median(range) | 988.0 (487.0-1624.0) | 1223.0 (455.0-1461.0) | 1008.0 (407.0-1789.0) | 0.725 |

*- Statistically significant difference; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: Lactate dehydrogenase.

The median hospitalization duration in patients aged ≤ 18 and > 18 was 5 days (1–16) and 6 days (1–22), respectively, and this difference was not statistically significant ($p = 0.179$).

The mean body temperature in patients aged ≤ 18 was $38.6\text{ }^{\circ}\text{C}$ ($36.6\text{--}41.7\text{ }^{\circ}\text{C}$) compared to $38.2\text{ }^{\circ}\text{C}$ ($36.0\text{--}40.0\text{ }^{\circ}\text{C}$) in patients aged > 18 . The difference was statistically significant ($p = 0.041$).

Based on vaccination status, patients were classified into three groups (vaccinated, unvaccinated, and unknown vaccination status) and the relationship between vaccination status and frequency of measles complications was investigated.

The frequencies of most clinical manifestations did not show a statistically significant difference among the three vaccination status groups. However, elevated body temperature was least common among the vaccinated patients (67%). Body temperature values also differed significantly between unvaccinated and vaccinated groups ($p = 0.009$), as well as between the vaccinated and those of unknown vaccination status ($p = 0.041$). Mean body temperature in unvaccinated patients was $38.8\text{ }^{\circ}\text{C}$ ($36.6\text{--}41.7\text{ }^{\circ}\text{C}$), $37.8\text{ }^{\circ}\text{C}$ ($36.0\text{--}39.6\text{ }^{\circ}\text{C}$) was measured in the vaccinated group, and in patients with unknown vaccination status the mean body temperature was $38.5\text{ }^{\circ}\text{C}$ ($36.3\text{--}40.0\text{ }^{\circ}\text{C}$).

In the unvaccinated group, 71% pneumonia frequency was noted, compared to 11% and 35% in the vaccinated and unknown vaccination status groups, respectively. The differences in frequencies based on vaccination status were statistically significant ($p < 0.001$). Diarrhea affected 27%, 33%, and 62% of vaccinated, unvaccinated, and patients with unknown vaccination status, respectively, and these differences were statistically significant ($p = 0.005$).

When patients were grouped by vaccination status, frequencies of other measles complications were low, as shown in Table 3. CRP values (median) were 7.8, 22.7, and 22.6 for unvaccinated, vaccinated, and patients with unknown vaccination status, respectively. CRP values differed statistically significantly in relation to vaccination status ($p < 0.001$), with statistically significant differences between unvaccinated and vaccinated participants ($p = 0.003$), as well as between unvaccinated individuals and those with unknown vaccination status ($p = 0.001$) (Table 3).

Discussion

On 1st October 2017, 20 years after the previous measles outbreak in the Republic of Serbia, the first suspected cases corresponding to the clinical features of measles were reported on the territory of Kosovo and

Metohija with majority Serb and non-Albanian population. Virological and serological laboratory analyses performed at the Reference Laboratory of the Institute of Virology, Vaccines and Sera “Torlak” confirmed the circulation of this virus in our population on 6th October 2017, and the measles epidemic was declared on 23rd October 2017. Although, at the time, only seven laboratory-confirmed cases were registered, low levels of collective immunity to the smallpox virus and high contagiousness of this causative agent led to the rapid spread of the virus throughout the country. Namely, the incidence of MMR vaccination in the second year of life was 81% at the outset of the nationwide epidemic [7]. The highest proportion of measles seronegativity was observed among children aged one to two years (56.1%) and adults aged 20 to 39 years (18.5%) in Vojvodina, Serbia before the occurrence of outbreak in 2017/18 [8]. On the other hand, only 17% of measles patients admitted to our hospital had been vaccinated, and the percentage was even lower among the youngest patients.

All clinical measles manifestations occurred with high frequency, which was the highest (98%) for rash, followed by fever (84%), which was least common among the vaccinated patients (67%). Moreover, body temperature values were significantly lower in vaccinated patients. Our results show that not all patients have classic symptom triad [9], as vaccinated individuals, in particular, may not develop rash or fever. Hence, based on epidemiological information on the contact and the symptoms they had, these patients were tested and the presence of measles virus was confirmed. The findings of this research are in line with those reported by Grammens *et al.*, who also indicated the possibility of the absence of some of the classic measles symptoms, such as rash or fever, especially in vaccinated individuals [10]. Kohlmaier *et al.* also suggest that doctors should test patients with atypical measles symptoms, especially during outbreaks [11].

Measles can be accompanied by complications, such as pneumonia, otitis, encephalitis, hepatitis, and diarrhea, as well as a rare long-term sequela, subacute sclerosing panencephalitis.

In 13% of our hospitalized patients, the disease was uncomplicated. Most had one (32%) or two (31%) complications, while a quarter of hospitalized patients had three or more complications. Patients without complications were significantly more frequent in the vaccinated group.

Pneumonia has been shown to be the most common and most lethal complication of measles [12,13]. It was also the most frequently occurring complication in

measles among the patients admitted to our hospital, affecting about 50% of these individuals. These findings are consistent with the data reported by Han *et al.*, who also found that pneumonia was the most common measles complication and was present in 52.4% of the patients [14]. In the present study, the highest pneumonia prevalence was noted for younger and unvaccinated patients. A similar pattern was observed by Sultana *et al.*, whose analyses revealed that pneumonia was the most common complication, followed by diarrhea, both of which were significantly more frequent in unvaccinated patients, whereas in 77.8% of vaccinated patients measles progression was uncomplicated [15].

Unlike pneumonia, hepatitis was a significantly more frequent complication in adults, affecting 36% of measles patients in this age group, compared to only 7% of those aged below 18 years. These data are supported by the findings yielded by a French study, in which hepatitis was the most frequent complication in young adults, affecting 37.5% of these patients [16]. Similar trends were described previously by other authors [17], while some even suggest that hepatitis should be considered a common finding in adults, rather than a measles complication [18].

Available evidence indicates that measles-related diarrhea increases mortality risk; however, this risk is limited to the period spanning from one week before to four weeks after the emergence of rash, without posing long-term risk [19]. In our patients, after pneumonia, diarrhea was the second most frequent complication and affected 39% of individuals. Although there was no significant difference in the frequency of this complication with respect to age, diarrhea was significantly more common among unvaccinated subjects.

Similar results were obtained in a Bulgarian study, where diarrhea was frequently (40%) observed in measles patients, with only pneumonia being more prevalent [20]. However, some authors have shown that diarrhea was the most common complication in their studied populations [21]. These discrepancies in the results likely arise due to the inclusion of all persons with measles in the latter analyses, rather than only those that were hospitalized.

In our sample, otitis was only present in younger patients, whereas encephalitis was not diagnosed in any of the subjects.

In addition to the complications, values of most laboratory tests also showed a significant difference in the age and vaccination status of hospitalized patients. When we consider the age of our respondents, the

younger ones had higher values of total leukocytes and lymphocytes, while our elderly patients had higher values of neutrophils, CRP and ALT. Regarding vaccination status, unvaccinated patients from our survey had the highest levels of lymphocytes, while patients with unknown vaccination status had the highest values of neutrophils. When it comes to CRP, vaccinated respondents and those with the unknown vaccination status had the higher values compared to unvaccinated patients.

Limitations

Our study involved some limitations. Firstly, we did not have access into vaccine cards of all patients. Furthermore, due to lack of equipment, the diagnosis in all patients was not confirmed by PCR. However, this study provided insight into the most common reason for hospitalization of measles patients.

Conclusions

Most patients included in the analyses presented here were unvaccinated, indicating a low level of public health education pertaining to this specific primary prevention measure. Therefore, it is necessary to carry out activities to raise awareness among the population regarding the importance and need for vaccination against measles for not only children, but also adults who have not been previously vaccinated. Complications are still the leading cause for hospitalization of measles patients, most of whom are children at risk. This research also points to the poor resistance to measles in adults.

Acknowledgements

Our deepest thanks to the Kosovska Mitrovica Clinical Centre, Infectious Diseases Ward and Pediatric Ward.

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Conflict of interests: No conflict of interests is declared.