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FROM TIMISOARA
FACULTY OF MEDICINE
DEPARTMENT XIII - INFECTIOUS DISEASES**

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DOCTORAL THESIS

**MEASLES IN ADULTS AND CHILDREN:
EPIDEMIOLOGICAL CHARACTERISTICS,
CLINICAL-EVOLUTION FEATURES**

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**Timisoara
2023**

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CHAPTER 1. BIOLOGICAL PROFILE AND CLINICAL CHARACTERISTICS AS DETERMINANTS OF PROLONGED HOSPITALIZATION IN ADULT PATIENTS WITH MEASLES: A SINGLE-CENTER STUDY IN WESTERN ROMANIA

CONTEXT

Measles is a highly infectious and potentially fatal disease that can be prevented by vaccination. It is caused by measles morbillivirus, commonly known as measles virus. It is classified in the genus Morbillivirus, family Paramyxoviridae and subfamily Orthoparamyxovirinae. Measles virus is a closed virus, approximately 100-300 nm in diameter, with a single-stranded, negative-sense, unsegmented RNA. The expected annual global measles mortality worldwide fell to less than 100,000 in 2016 but rose to more than 200,000 in 2019. However, between 2000 and 2019, measles vaccine prevented an estimated 25 million+ deaths globally, while the current SARS-CoV-2 pandemic may have altered the usual pattern of disease spread and vaccination practices. By July 2022, Romania has recorded a total of 20,204 cases and 64 deaths since the start of the ongoing outbreak in 2016. The present study intends to analyze the most recent measles epidemic in Romania, in a population with a decreasing willingness to receive vaccines, by describing the clinical picture and biological profile of hospitalized patients. A secondary objective of the current study is to determine the risk factors for longer hospitalization and development of measles-related pneumonia.

RESULTS

After data collection and exclusion of patients based on study protocol and differential diagnosis, a total of 114 adult patients with measles were included for data analysis. Further processing was implemented by stratifying the data into two comparison groups based on length of hospital stay. There were 68 (59.6%) patients whose hospital stay was shorter than or equal to the median of 6 days in the existing cohort. The remaining 46 (40.4%) patients had a hospital stay longer than 6 days. The median age in the short hospitalization group was 28.1 years compared to 31.9 years in the long hospitalization group, with a statistically significant difference between means (p -value = 0.009). The background characteristics of adult patients hospitalized with measles resulted in a statistically significant difference in the proportion of Roma in the study groups, where 17.4% had a long hospitalization compared to 5.9% in the short hospitalization group. Patients who were hospitalized for more than 6 days had an average of 14.8 years since their last dose of MMR, compared to 6.6 years in patients in the short hospitalization group ($p < 0.001$).

There were significantly more unvaccinated patients or patients with incomplete measles vaccination status in the long-term hospitalization group (5.9% incomplete vaccinations versus 21.7% incomplete vaccinations in the long-term hospitalization group). It was also noted that the proportions of comorbidities were significantly different between the two study groups. Thus, diabetes mellitus and chronic lung disease were more prevalent in the long hospitalisation group (6.5% vs. 0.0%). Also, 94.1% of adult measles patients had no comorbid conditions compared to 73.9% in the long hospitalisation group. The most common signs and symptoms were fever (92.6% in the short-term hospitalization group and 100% in the long-term hospitalization group), maculopapular rash (96.8% in the short-term hospitalization group and 84.8% in the long-term hospitalization group), followed by cough, which affected more than 80% of all patients. Significant differences were observed in the prevalence of diarrhea (p -value = 0.007), fatigue (p -value = 0.003) and altered mental status (p -value = 0.045), with the highest proportion among the long-term hospitalization patients. The same group of patients suffered complications such as liver damage and pneumonia in greater numbers than patients with shorter hospitalisation (28.3% vs. 13.2%) and (52.2% vs. 32.4%), respectively. Chest radiography showed statistically more patterns of bilateral consolidation and interstitial inflammation in patients with longer hospitalisation.

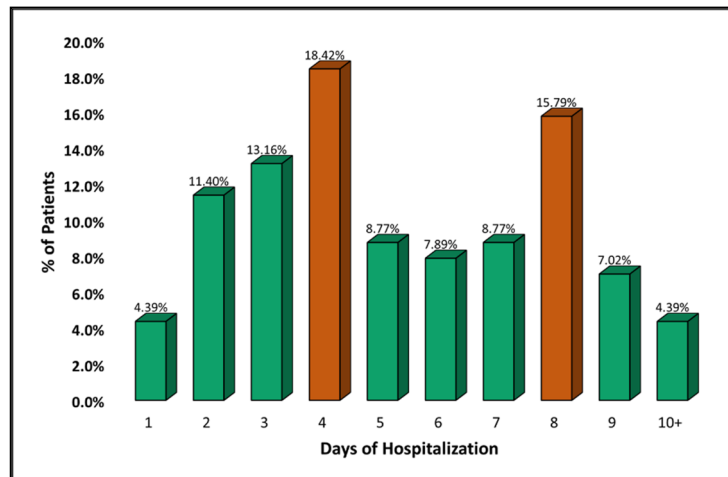


Image 2 - Distribution of patients by length of hospitalisation.

A total of 39 (89.1%) of these patients received antibiotics, compared to 40 (58.8%) among those who stayed less than 7 days in hospital. The most commonly used antibiotics were cephalosporins in about 50% of all patients treated. Finally, ICU admissions were significantly more frequent in patients with prolonged hospital stay compared to the other group (10.9% vs. 1.5%, p -value = 0.027), although no deaths were reported in the studied cohort. It was observed that a significantly higher proportion of patients who stayed in hospital for more than 6 days had serum parameters outside the normal range compared to those with a short hospital stay. Thus, white blood cell count, lymphocyte count, alanine aminotransferase, lactate dehydrogenase, procalcitonin, C-reactive protein and fibrinogen were statistically significantly higher. In contrast, hemoglobin was lower in long-term hospitalized patients (41.2% vs. 22.1%). Risk factor analysis identified, in ascending order of likelihood ratio, chronic lung disease, liver impairment, Roma ethnicity, duration since last MMR dose, CRP, bilateral lung condensation on X-ray and elevated procalcitonin as statistically significant independent risk factors for long-term hospitalization and development of pneumonia in adult patients with measles. The analysis was adjusted for confounders such as positive measles vaccination status.

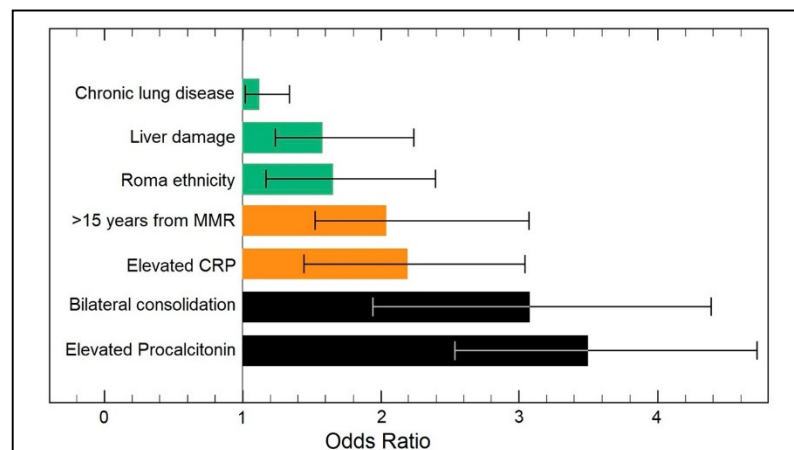


Image 3 - Multivariate analysis of risk factors for long-term hospitalization in adult patients with measles.

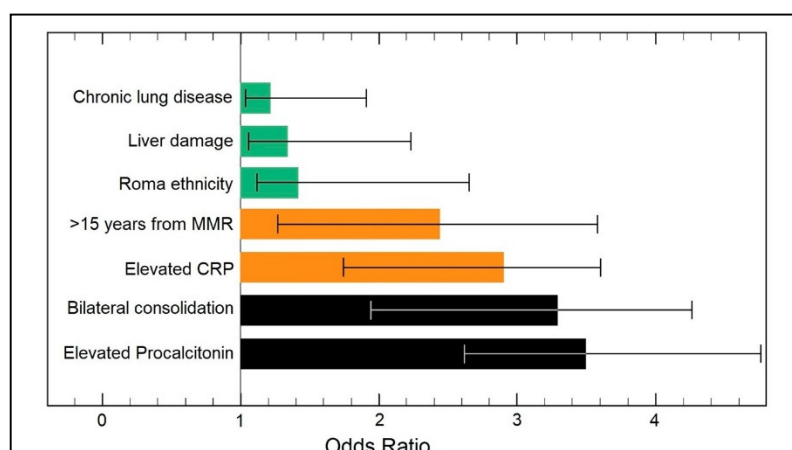


Image 4 - Multivariate analysis of risk factors for pneumonia in adult patients with measles.

CONCLUSIONS

In the current investigation, the biological profile and clinical aspects of adult patients with measles were presented in detail, which have been shown to be predictive factors for prolonged hospitalization. It was found that many patients had a prolonged hospitalization that was associated with chronic lung disease, liver damage, Roma ethnicity; a long duration elapsed since the last MMR dose, elevated C-reactive protein levels, presence of bilateral lung condensations on radiographs and elevated procalcitonin levels. Given the findings of this study, which indicate a downward trend in measles vaccination in Romania, significant efforts are still needed to ensure improved protection against measles outbreaks in a given region and especially in patients with significant risk factors for complications as described in this study. These patients need to be vaccinated. Chronic lung disease, liver disease, Roma ethnicity, time since last MMR dose, CRP, bilateral lung condensation on X-ray and elevated procalcitonin were found to be independent risk factors for prolonged hospitalization and development of pneumonia in the group that was investigated.

We also need to consider the financial benefits of preventing measles on a national scale. Prolonged hospitalizations are not only costly, but also require isolation of patients and the use of hospital beds that could be used for patients suffering from other conditions, such as COVID-19. Catch-up vaccinations with up to two doses of MMR vaccine are still recommended for all people who do not know their measles vaccination status, especially for older people who have not benefited from vaccination campaigns, with the aim of achieving more than 95% vaccination coverage nationwide. This measles study could potentially be applied to the treatment of other diseases, such as COVID-19, leading to fewer deaths and reduced healthcare costs. Last but not least, eradicating measles in Romania would require large-scale coordinated efforts, as in more prosperous countries such as the United States.

CHAPTER 2. DISEASE COURSE, CLINICAL FEATURES AND RISK FACTORS FOR PNEUMONIA IN UNVACCINATED CHILDREN AND ADOLESCENTS WITH MEASLES: A RE-EMERGING DISEASE IN ROMANIA

CONTEXT

Measles is a highly contagious viral disease caused by Morbillivirus of the Paramyxoviridae family. When someone coughs or sneezes, the virus spreads through droplets. The most contagious period is considered the prodrome which lasts 3-5 days after the onset of the rash, although it can extend even longer as measles RNA can be present in blood, urine and nasopharyngeal mucosa for long periods of time, even months after the onset of the rash. The infectious period is greatest during the phase when the virus replicates mainly in the upper respiratory tract rather than the lower respiratory tract. Measles is defined by cyclical outbreaks, occurring mainly in winter, in correlation with social risk factors such as crowded confined spaces, school assemblies, etc. Measles outbreaks also appear to be characterised by longer, multi-year cycles, due to a trend towards an increase in the number of susceptible individuals not immunised during previous outbreaks. According to several studies, another significant element affecting the cyclicity and duration of epidemics is the birth rate. Measles has an incubation period of about 10-14 days, starting four days before the onset of the rash and ending four days after its onset. High levels of viremia linked to the period of more violent coughing, which produces more drops and increases the intensity of viral transmission. However, the virus can only be maintained in human populations through unbroken chains of transmission, as it does not induce known infections in animals nor is it detectable in animal reservoirs. Uncomplicated sick patients can recover fairly quickly and without complications or adverse effects. However, some of the following complications of the disease may occur: encephalitis (1 in 1000 cases), middle ear infections and measles-related pneumonia or secondary bacterial pneumonia affecting up to 60 in 1000 patients and.

Measles is no longer considered just a childhood disease, as it can occur at any age. However, people over the age of 20 are at higher risk of developing complications, moreover, if the patient has not been vaccinated or has been fully vaccinated, or when vaccine coverage is less than the required minimum of 95% to prevent viral spread. Recent vaccination strategies have pushed the age structure of measles infection towards adolescence and adulthood in populations that received two doses of measles vaccine. With this shift in the epidemic slope by age, the number of measles outbreaks has multiplied in areas with low vaccine coverage and in health care settings with vulnerable unvaccinated communities, such as the very young and patients with multiple comorbidities. Between 1980 and 2015, Romania documented a small number of measles cases after the introduction of measles immunization in the National Immunization Program. Since 2005, Romania's immunisation campaign has included two doses of MMR trivaccine at 12 months and 6-7 years. Since 2015, Romania has seen a large spike in measles infections, due to a considerable drop in the number of people willing to be vaccinated. As a result, a measles epidemic was proclaimed in 2016 and an additional dose of MMR trivaccine became mandatory at 9 months of age. According to the official measles vaccination coverage percentages reported in Romania in 2019, 76% of the target population for vaccination had received the second dose of measles vaccine, while 65.4% of the target population for vaccination had received two doses of measles vaccine, resulting in 90.9% of the target population protected against measles. After four years of administration following this schedule, from August 2020, the additional MMR dose given in childhood will be stopped. Thus, we set out to study the paediatric population in Romania four years after the governmental change in the vaccination schedule in the western region that encountered the most measles cases during the 2016 outbreak. Our aim was to provide a comprehensive overview of paediatric clinical characteristics, course and risk factors for pneumonia development, stratified by patient age group in children and adolescents.

RESULTS

The authors conducted a retrospective cohort analysis to follow the characteristics and effects of measles virus infection in the pediatric population under 18 years of age. Clinical and analytical data of patients admitted to the "Victor Babeș" Hospital of Infectious Diseases and Pneumology in Timișoara were analyzed. During the one-year study period allocated for data collection, a total of 136 measles patients under 18 years of age were eligible for inclusion in the present analysis. From the cohort of paediatric patients, there were 104 children younger than ten years and 32 patients aged 10 to 18 years who formed the two comparison groups. The mean age in the children's group was 2.4 years, with a statistically significant difference from the adolescent group with a mean of 12.5 years (p -value < 0.001). An important feature of both study groups was the high prevalence of Roma patients, which, although a minority in Romania, was more than 40% prevalent in the current study.

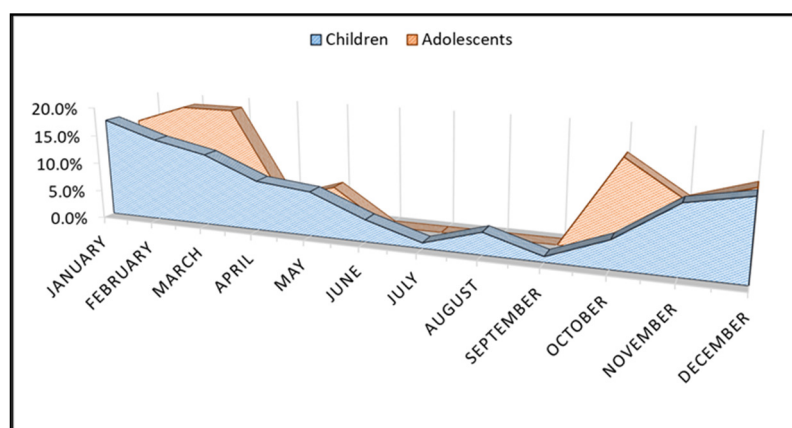


Image 5 - Comparison of measles case proportions by month of infection with stratification by groups of children and adolescents.

The source of infection was considered to be a familial, cluster or isolated infection when epidemiological analysis could not trace the source to a positive contact. The collective source of infection was considered to be a community measles infection that occurred outside the family. A total of 40.4% of children had a family source of infection, while only 21.9% of adolescents were infected from a family source (p -value = 0.047). However, 71.9% of adolescent measles infections were isolated. The proportion of paediatric patients with poor nutritional status was significantly higher in the child group compared to the adolescent group (30.8% vs. 12.5%). Although the majority of patients were not vaccinated against measles (91.9%), there were six patients with an incomplete vaccination status and four others with a complete vaccination profile who still had a symptomatic infection. It was observed that the mean duration from the last MMR dose to measles infection was significantly longer in the adolescent group compared to children (70.2 months vs. 9.6 months, p -value < 0.001). Comparison of the proportions of measles infections per month between children and adolescents showed that the highest incidence ($> 20\%$) was between October-November and February-March among adolescents, and between November and January among children. Koplik's spots were more frequently observed among adolescents (37.5%) compared to children (20.2%), with a statistically significant difference between groups (p -value = 0.045).

Apart from Koplik's spots, other hallmarks of measles infection in children, such as conjunctivitis and coryza, were seen in about 50% and 25% of all patients studied, respectively, probably due to late presentations when the characteristics of the infection change. Of the complications, children had significantly more cases of otitis media (11.5% vs. 0.0%, $p = 0.044$), although there were more adolescents with pneumonia and acute respiratory failure (81.3% vs. 60.6%), respectively (12.5% vs. 2.9%, $p = 0.031$), respectively (12.5% vs. 2.9%). Accordingly, imaging studies by X-ray or CT showed more cases with bilateral

consolidation appearance among adolescents (p-value = 0.045). There were also 25.0% adolescents who did not require antibiotic treatment during hospitalisation, compared with 10.6% children (p-value = 0.039). There were only five patients (3.6%) out of the entire cohort of paediatric patients who required admission to the ICU and there were no cases of mortality. It was observed that the mean white blood cell count in children was statistically significantly higher than in adolescents (8.8 thousand vs. 5.2 thousand, p-value <0.001). The same observation was made for lymphocytes and platelets. However, mean red blood cell and haemoglobin values were significantly lower in children (3.9 million vs. 4.4 million, p = 0.040), respectively (10.8 vs. 12.3). Although alanine aminotransferase levels were on average higher than the normal range, the difference between study groups was not statistically significant. Finally, procalcitonin levels among inflammatory markers were significantly higher in the adolescent group (0.9mg/L vs. 0.5mg/L, p-value <0.001). Multivariate analysis of risk factors shown in Figure 12 included a total of 126 unvaccinated children and identified patient age (OR=1.62), poor nutritional status (OR=1.25), Roma ethnicity (OR=2.44), anemia (OR=1.58) and elevated procalcitonin (OR=3.09) as independent and statistically significant risk factors for the development of pneumonia in pediatric patients with measles.

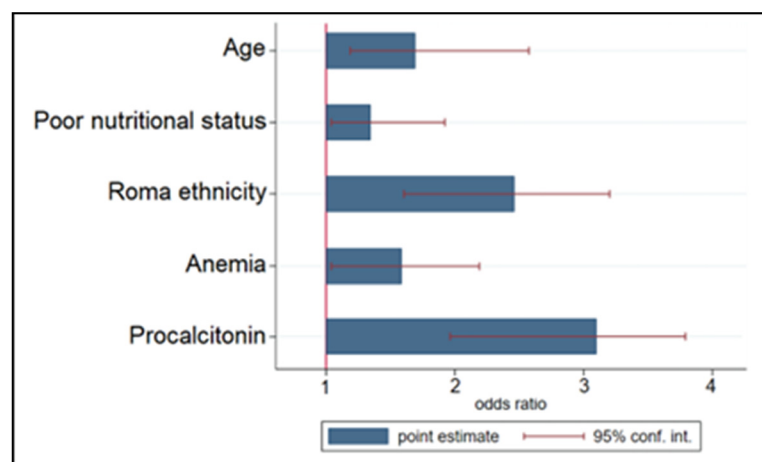


Image 7 - Multivariate analysis of risk factors for pneumonia in children and adolescents with measles.

CONCLUSIONS

Patients infected with measles are at risk of developing measles pneumonia, which is a potentially fatal complication. It was found that the vast majority of paediatric patients hospitalised with measles had not been vaccinated, which is a significant concern for Roma patients, who accounted for over forty percent of these hospitalised patients. Pneumonia was a serious outcome for these patients and it is important to carefully consider risk variables such as patient age, inadequate nutritional status, Roma ethnicity, anaemia and procalcitonin levels before serious problems develop. Even though there are a few different treatment options available for pneumonia, the most important aspect of healthcare is prevention. If parents continue to show resistance to vaccination, doctors should listen to them and address any questions or concerns they may have. This is particularly important in the case of the Roma population, which has the lowest vaccination rate in the world; therefore, this is an excellent opportunity for doctors to educate parents and work towards the complete eradication of the disease through vaccination.