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Research Article

Hospital exposure as a risk factor for the transmission of measles: A case-control study in Turkey.

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Abstract

Objective: During a nationwide measles epidemic in 2013, we conducted an investigation in Sanliurfa province to assess risk factors for measles infections. **Methods:** In a case-control design, we compared the history of hospital exposures for 189 randomly selected laboratory-confirmed patients (aged <15 years) residing in the central district and control-individuals matched for neighbourhood and age. We estimated the effectiveness of the vaccine (VE). **Results:** For infants from 0-11 months, 53.8% of the case and 23.8% of the controls had visited a hospital during one the month prior to the onset of the case's rash (ORadj=3.7, 95% CI=1.6–8.6). For children from 1–6 years, 48.2% of the cases and 14.3% of the controls visited a hospital during one month prior to the onset case's rash (ORadj=5.5,95% CI=2.5–12.8) and 59.7% of cases had not completed one dose of measles vaccine by 12 months, compared with

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14.7% of controls (ORadj=7.4,95% CI=2.1–26.9; VE=86%,95% CI=52-96%). For children from 7– 14 years, 53.8% of the cases had not completed one dose of measles vaccination by age 12 months, compared with 15.4% of controls (ORadj=6.7,95% CI=1.7–26.6; VE=85%, 95% CI=41-96%). **Conclusion:** We conclude that the hospitals facilitated measles transmission during this epidemic. We recommend triage febrile patients and patients with a rash in healthcare settings, and strengthening measles vaccination programme..

Keywords: Measles; Measles Vaccine; Nosocomial Infections; Risk Factors; Case Control Study.

Kızamık bulaşında bir risk faktörü olarak hastane maruziyeti: Vaka-kontrol çalışması, Türkiye.

Özet

Amaç: Türkiye'de 2013 yılında kızamık vakalarında artış görülmüştür. Bu çalışma, vakaların en sık görüldüğü Şanlıurfa ilinde kızamık hastalığını etkileyen risk faktörlerini değerlendirmek için yapılmıştır. **Yöntem:** Bu vaka-kontrol çalışmasında, merkez ilçede yaşayan ve rasgele seçilen, 15 yaş altı, laboratuvarda doğrulanmış 189 vaka ile komşu ve yaş eşleştirmesi yapılan kontrolleri karşılaştırılmıştır. Aşı etkililiği (AE) hesaplanmıştır. **Bulgular:** Döküntü başlamadan bir ay öncesinde herhangi bir sağlık kuruluşuna başvuranlar; 0–11 aylık yaş grubunda vakaların %53.8'i, kontrollerin %23.8'i (TRR_{adj}=3.7, %95 GA=1.6–8.6) 1–6 yaş grubunda vakaların % 48.2'i, kontrollerin %14.3 (TRR_{adj}=5.5, %95 GA=2.5–12.8), 7–14 yaş grubunda ise vakaların %22.5'i, kontrollerin %12.8'idir (TRR_{adj}=1.9, %95 GA=0.5–8.3). 12. aydaki kızamık aşı dozunu yaptırmayanlar; 1–6 yaş grubunda vakaların %59.7'si, kontrollerin %14.7'si (TRR_{adj}=7.4, 95% GA=2.1–26.9; AE=%86, %95 GA=%52-96), 7– 14 yaş grubunda ise vakaların %53.8'i, kontrollerin %15.4'üdür (TRR_{adj}=6.7,%95 GA=1.7–26.6; AE=%85, %95 GA=%41-96). **Sonuç:** Bu salgında hastanelerin kızamık bulaşını kolaylaştırdığı saptanmıştır. Çalışma sonuçlarına göre; ateş ve döküntülü vakalara triaj uygulanması ve kızamık aşı programının güçlendirilmesi önerilmiştir.

Anahtar kelimeler: Kızamık, kızamık aşısı, hastane kaynaklı enfeksiyonlar, risk faktörleri, vaka kontrol çalışması.

Introduction

Measles is a highly contagious viral disease. It remains an important cause of death among young children globally.[1] Measles-containing vaccine (MCV) is safe and effective, and vaccination is the most important strategy to control and prevent measles. In 2000, 548 000 children died from measles globally; by 2011, this number was reduced to 122 000, 78% reduction, which is largely due to improved vaccination coverage.[1] The World Health Organization (WHO) listed measles immunization coverage as one of the indicators for tracking progress towards the fourth Millennium Development Goal to reduce child mortality.[1] WHO's goal for 2015 is to reduce global measles deaths by ≥95% compared with 2000 levels and to achieve regional measles and rubella/congenital rubella syndrome elimination goals. [1,2] In the European Region, measles elimination goals for 2007 and 2010 were not met, therefore a new commitment is made to meet the goal by 2015.[3] Turkey's Measles Elimination Programme was initiated in 2002 in line with the WHO initiative. One of the main immunization strategies of the elimination programme is to reach and maintain at least 95% vaccination coverage for two doses of MCV for each and every province and district.[4] Turkey started using monovalent

vaccine in 1970s. In 1998, a second dose of MCV was added to the vaccination schedule for first graders of elementary school. Since 2006, Turkey has maintained a two-dose MMR vaccination schedule for children at 12 months and 6 years of age (elementary school entry), respectively. Over time, the vaccination coverage has been gradually increased to 98% in 2006. [5] As a result, the numbers of reported measles cases have been decreased from 30,509 in 2001 to single digits during 2007-2010.[6]

In 2010, outbreaks of measles occurred in many European countries.[7,8] Towards the end of 2010, Istanbul reported a localized outbreak of 111 measles cases, which were virologically similar to the European strains. On 13 January 2012, measles cases started to occur in other parts of Turkey; during 13 January 2012 to 10 April 2013, a total of 3405 cases had been reported throughout the country.[9]

We conducted an investigation in Sanliurfa province southeast Turkey (2012 population: 1 762 075), which had the highest case count in all provinces in Turkey as of April 2013; according to the National Measles Surveillance Database.[9]

The objectives of this investigation were to identify risk factors for measles transmission and to evaluate the effectiveness of measles vaccination, so as to provide evidence-based recommendations for control and prevention of measles.

Methods

In this investigation, we identified the cases from the National Measles Surveillance Database. All the cases in the database were laboratory confirmed which was defined as onset of maculopapular rash, plus measles-specific IgM positivity or detection of measles virus RNA with polymerase chain reaction (PCR) in throat swab, nasal or nasopharyngeal swab or urine specimen.

At the time of this investigation in April 2013, Sanliurfa province had the highest case-count. Measles cases in the province started to increase on 18 December 2012, and peaked in March 2013 (Figure 1).

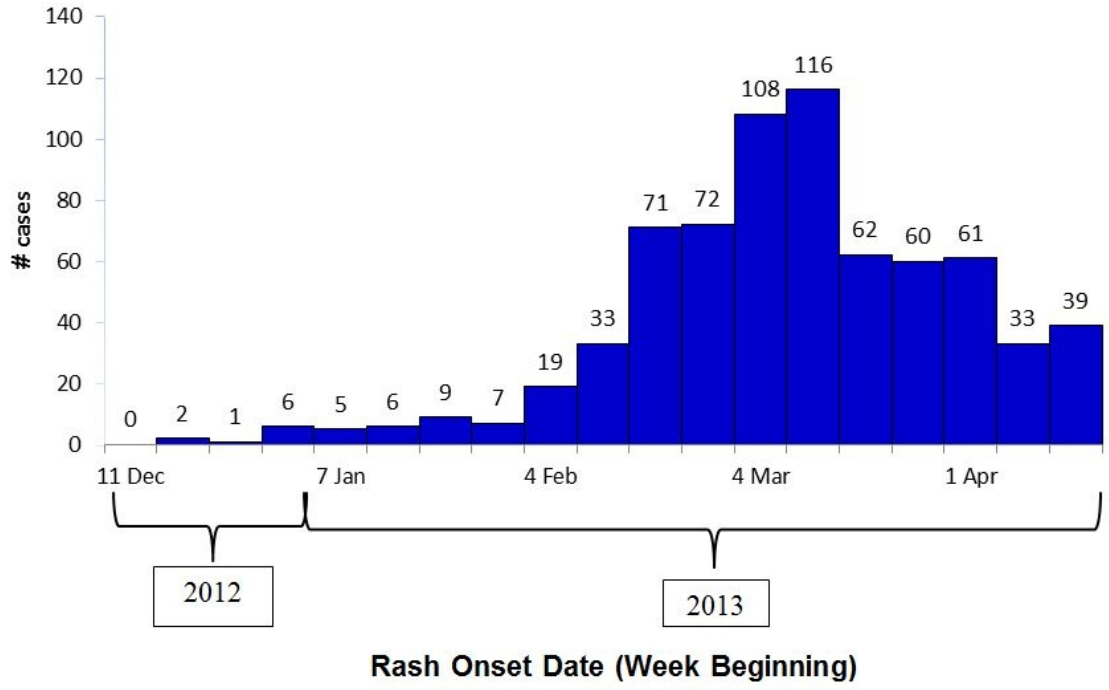

Figure 1. Weekly distribution of measles cases according to the rash onset (Sanliurfa, 18th Dec 2012-10th April 2013, n: 594)

By 10 April 2013, the province had reported 594 cases (incidence rate: 33.7/100 000), representing 17.5% of all measles cases reported in Turkey. For the year 2012 the 1st and 2nd dose of vaccine coverage were 94% and 91% respectively in Sanliurfa province.[8] Of the 11 districts in the province, three had the highest attack rates: Harran (0.8‰), Central (0.6‰) and Akcakale (0.3‰). We conducted the case-control investigation in the Central District because it had the largest number of cases. We randomly selected laboratory confirmed case-persons who were Turkish citizens, <15 years of age (born after 1998) and who lived in the Central District during 1 December 2012 to 10 April 2013. We selected the control-persons the neighbourhoods of the case persons and matched by age group (0 –11 months, 1– 6 years, and 7–14 years). The criteria for control selection were: Same age group with the case; no maculopapuler rash during the past month; and residing on the right next door or right-side next house to the case-patient's residence. Interviewers showed pictures of measles rash to the control-person's family members to make sure that they did not have the disease.

Interviewers from Provincial Public Health Directorate and Communicable Diseases Unit in Provincial Health Directorate were trained. We interviewed parents of case and control-persons using a structured-face to face questionnaire to collect information on some socio-demographic characteristics, disease information, epidemiologic history, travel history, vaccination status, registration with a family physician, and exposure to a healthcare facility (hospital, family health centre, private clinic) in April 2013. For the information on vaccination status, we asked them to show the vaccination card; if the vaccination card was unavailable, we asked the parents to recall whether the children had been vaccinated by 12 months of age by a family physician, and whether they had been vaccinated after enrolling in elementary school, as is the current vaccination practice in Turkey.

We calculated matched odds ratios (mOR) and their 95% confidence intervals (95% CI) based on the matched case-control design, %5 significance level was used. Using conditional and unconditional logistic regression, we controlled for sex and whether the child is registered with a family physician for infants aged 0 –11 months; for children aged 1– 6 years, and 7–14 years, we controlled for sex and whether the child had a vaccination card. We calculated the vaccine effectiveness (VE) for children aged 1– 6 years and 7-14 years using the following formula, assuming the mOR is a good approximation of the relative risk under the rare-disease assumption.[10,11]

$VE = 1 - 1 / OR.$

Because this investigation was part of an emergency public health response to a nation-wide measles epidemic, human subject review was exempted.

This investigation was a part of a response to a public health emergency event; therefore, human subject review was not required according to the rules of the Institutional Review Board at the Public Health Institute of Turkey.

We interviewed parents of case and control-persons and all participants gave verbal consent before administering the questionnaire.

Results

In the Central District of Sanliurfa province where this investigation was conducted, the attack rate (per 1000) was 6.38 for infants aged 0–11months (6.32 for infant boys and 6.44 for infant girls) 0.65 for children aged 1–6 years (0.75 for boys and 0.54 for girls) and 0.12 for children aged 7–14 years (0.12 for boys and 0.12 for girls).

A total of 193 case-patients and 193 neighbourhood-matched control-persons participated in our case-control investigation. During the analysis we excluded four case-control pairs because of age-mismatch. The final analysis dataset contained 189 case-control pairs, including 65 pairs in the 0–11 month age group, 84 pairs in the 1–6 year age group and 40 pairs

in the 7–14 year age group. In both infants (0 –11m) and children (1– 6y) and (7–14y), case and control- persons did not differ significantly by sex, total number of persons in the household, number of children (<15 years) in the household, and travel history (Table 1). However, for 7–14 years children, 80% of cases had more than 3 children (<15 years) in the household, compared with 55% of controls (ORcrude=3.2, 95% CI: 1.2-9.1) (Table 1).

0–11 months case-infants visited respectively 38.5% of a hospital, 12.3% family health center, 4.6 % private hospital, 9.2% private clinic at least once during the month prior to rash onset. 1-14 years case-children visited respectively 30.9% of a hospital, 7.3% family health center, 0.8 % private hospital, 6.5% private clinic at least once during the month prior to rash onset.

For infants aged 0–11 months, 53.8% of case-infants visited a hospital at least once during the month prior to rash onset, compared with 23.8% of control-infants during the same period (OR_{crude}=3.7, 95% CI: 1.6-8.6; OR_{adj}=3.7, 95% CI: 1.6-8.5). Similarly, for children aged 1–6 years 48.2% of case-children and 14.3% of control-children visited a hospital at least once during the month before the case-children's rash onset (OR_{crude}=5.5, 95% CI: 2.5-12.9; OR_{adj}=3.5, 95% CI: 1.1-11.8), for children 7–14 years, 22.5% of case-children and 12.8% of control-children visited a hospital at least once during the month before the case-children's rash onset (OR_{crude}=1.9, 95% CI: 0.5-8.3; OR_{adj}=5.9, 95% CI: 1.1-34.9) (Table 2, Table 3). Because in Turkey the first dose of MCV is administered at the age of 12 months and the second dose of MCV is administered after entry into elementary school (typically at the age of seven years), we calculated VE for the one-dose MCV for children in the 1– 6 year age group. In this age group, 59.7% (40/67) of case-children compared with 14.7% (11/75) of control-children did not receive one dose of MCV by 12 months of age (OR_{crude}=8.5, 95% CI:3.6-21.2; OR_{adj}=7.4, 95% CI: 2.1-26.9).

Table 1. Characteristics of case- and control-persons during an investigation of risk factors for measles: Sanliurfa province, April 2013

	0-11 months			1-6 years			7-14 years		
Risk Factors	Cases (n=65)	Controls (n=65)	p	Cases (n=84)	Controls (n=84)	p	Cases (n=40)	Controls (n=40)	p
Sex Male (%)	53.8	53.8	1.0	53.6	46.4	0.4	55.0	65.0	0.4
Female (%)	46.2	46.2		46.4	53.6		45.0	35.0	
Persons in household									
7-35 persons (%)	46.2	44.6	0.9	56.0	48.8	0.4	72.5	62.5	0.3
1-6 persons (%)	53.8	55.4		44.0	51.2		27.5	37.5	
Children <15 years in household									
4-18 children (%)	56.9	55.4	0.9	56.0	57.1	0.9	80.0	55.0	0.01
1-3 children (%)	43.1	44.6		44.0	42.9		20.0	45.0	
Travel history (yes)	7.7	3.3	0.3	3.6	4.8	0.7	5.1	2.7	0.6

Table 2. Risk factors for measles in cases and controls: Sanliurfa province, April 2013

Risk Factors	**Age Groups**		
	Aged 0-11 months		
	% Cases (n=65)	% Controls (n=65)	OR_{crude}(95% CI)
Visiting hospital ≥1 time during the month before rash onset	53.8	23.8	3.7 (1.6-8.6)
Contact history[a]	40.0	18.5	2.9 (1.2-7.2)
Lack of vaccination card	9.2	7.8	1.2 (0.3-5.2)
Lack of ≥1 dose of MMR	95.4	80.0	5.1 (1.3-29.4)
Not registered with a family physician	1.5	1.5	1.0 (0.06-15.9)
	Aged 1-6 years		
	% Cases (n=84)	% Controls (n=84)	OR_{crude}(95% CI)
Visiting hospital ≥1 time during the month before rash onset	48.2	14.3	5.5 (2.5-12.9)
Contact history[a]	46.4	39.3	1.3 (0.7-2.6)
Lack of vaccination card	51.9	28.8	2.6 (1.3-5.4)
Lack of MMR at 12 m	59.7	14.7	8.5 (3.6-21.2)
Lack of ≥1 dose of MMR	66.7	22.6	6.7 (3.2-14.4)
Not registered with a family physician	2.4	6.0	0.5 (0.1-2.0)
	Aged 7-14 years		
	% Cases (n=40)	% Controls (n=40)	OR_{crude}(95% CI)
Visiting hospital ≥1 time during the month before rash onset	22.5	12.8	1.9 (0.5-8.3)
Contact history[a]	35.0	22.5	1.8 (0.6-5.6)
Lack of vaccination card	71.4	57.1	1.8 (0.6-5.7)
Lack of MMR at 12 m	53.8	15.4	6.2 (1.5-31.7)
Lack of ≥1 dose of MMR	60.0	35.0	2.7 (1.1-7.6)
Not registered with a family physician	5.0	5.0	1 (0.06-14.4)

[a]Any contact with a rash patient at home, school, or neighbourhood.

Table 3. Risk factors for measles transmission during a measles outbreak, by age group, using conditional logistic regression: Sanliurfa province, April 2013

Risk Factors	n (%) of cases	n (%) of controls	OR_{adj} (95% CI)
0-11 months			
Visiting hospital ≥1 time during the month before rash onset	35 (53.8)	15 (23.8)	3.7 (1.6-8.5)[a]
1-6 years			
Visiting hospital ≥1 time during the month before rash onset	40 (48.2)	12 (14.3)	3.5 (1.1-11.8)[b]
Lack of MMR at 12 months	56 (66.7)	19 (22.6)	7.4 (2.1-26.9) [b]
7-14 years			
Visiting hospital ≥1 time during the month before rash onset	9 (22.5)	5 (12.8)	5.9 (1.1-34.9) [c]
Lack of MMR at 12 months	24 (60.0)	14 (35.0)	6.7 (1.7-26.6) [c]

[a] *Controlled for sex and whether the child is registered with a family physician, using conditional logistic regression.*

[b] *Controlled for sex and whether the child has a vaccination card, using conditional logistic regression.*

[c] *Controlled for sex and whether the child has a vaccination card, using unconditional logistic regression.*

The estimated VE based on the adjusted OR was 86% (95% CI: 52%-96%) for one dose of MCV. VE for two-dose MCV could not be calculated because most parents do not have their children's vaccine card for the second-dose MCV and they could not remember whether or not their children received a second-dose MCV. VE for the one-dose MCV for children in the 7– 14 year age group, 53.8% (14/26) of case-children compared with 15.4% (4/26) of control-children did not receive one dose of MCV by 12 months of age (OR_{crude}=6.2, 95% CI:1.5 -31.7; OR_{adj}=6.7, 95% CI: 1.7-26.6). The estimated vaccine effectiveness based on the adjusted OR was 85% (95% CI: 41%-96%) for one (first) dose of MCV.

Discussion

Since 1980, measles morbidity and mortality have significantly declined in Turkey as in the world due to the successful implementation of measles vaccination. Since 2006, the reported measles vaccination coverage for two doses has been above 90% in Turkey.[5] However, since 2010, an unexpected increase in the number of measles cases has occurred throughout Turkey.[12] Therefore, it is important to evaluate the effectiveness of the measles vaccination, and to identify other risk factors so more effective measles control and prevention strategies can be developed.[13]

Measles is one of the most contagious diseases. Infected people are contagious from four days before and four days after rash onset. [14] When there is active measles transmission in the community, health facilities serve as an important venue for measles patients to transmit the disease to other patients. [15]

This case-control study showed that for both infants (0 –11months) and children (children 1–6, 7–14 years); visit to hospitals during the measles outbreak between 2012 and 2013 increased the risk of measles transmission. Despite high routine vaccine coverage, measles outbreaks still occur due to the accumulation of susceptible persons who are unvaccinated or unimmunized. Susceptible persons (including those too young for vaccination and patients who are ill and debilitated) tend to congregate at medical facilities, thereby providing a milieu for the circulation of measles virus, even in populations with good routine vaccine coverage. Previously published studies also showed that nosocomial transmission of measles is the biggest challenge for elimination of measles.[16] A measles outbreak investigation in Granada during 2010-11 revealed that in some regions where the vaccine coverage rates are low, nosocomial transmission was one of the main risk factors.[17] Similar results have been observed in China [18,19], Republic of Korea [20]and Singapore [21]. Biellik et al. pointed out that as a result of the highly contagious nature of measles before the onset of rash, nosocomial transmission will remain a threat until the disease is eradicated. It is therefore vital to maximize awareness among healthcare staff that an individual with measles can enter a health facility at any time and a continual risk of the nosocomial transmission of measles exists.[15] However, a number of strategies can minimize the nosocomial spread. These strategies include admission and discharge vaccination checks, vaccination of staff and isolation of patients with fever and rash, particularly in epidemic situation.[15]

The first dose of MCV is administered at 12 months of age in Turkey. Therefore, infants under 12 months of age are unvaccinated due to age, and are expected to be at higher risk for measles virus infection. Meanwhile, these infants are the most frequent visitors to health facilities for vaccination, screening and clinical diagnosis purposes.[22]

Our findings highlight the importance of preventing nosocomial transmission of measles for those infants.

For children (aged 1–6, 7 –14 years), even though they are age-appropriate for vaccination, some are unvaccinated or vaccinated with only one dose of MCV. Since these children are also frequent visitors to healthcare facilities, they are also easily exposed to other measles patients where there is measles transmission in the community, as demonstrated by our case-control study. Previous studies have shown similar results. For example, a study in China showed that for unvaccinated children aged 8 months–2 years, the odds of being ill was 65 times higher than those who were vaccinated.[18] In a study conducted in Burkino Faso in 2009, unvaccination was the main risk factor for measles for children aged 1–14 years in all geographic areas under study.[23]

The vaccine effectiveness for one-dose MCV observed in our study varied when compared to those reported by CDC's Advisory Committee on Immunization Practices (for one-dose MCV: VE=93%, 95% CI: 39%-100%).[24] Field investigations in other countries where reliable cold-chain is available also showed high effectiveness of MCV. [19,23,25,26] The fact that measles outbreaks can still occur even though the vaccine is effective and vaccination coverage is high again underscores the importance of addressing other risk factors (such as nosocomial transmission) for measles elimination.

Our study had two main limitations. First, the vaccination history data for a high percentage of the children aged 1–6 and 7–14 years was based on parental recall. This could have led a decrease in vaccine effectiveness. A previous study showed that the estimated VE was 94% (95% CI: 83-98%) in the group with a vaccination record, and 81% (95% CI: 46-93%) in the group that relied on parental recall.[27] Second, vaccine effectiveness could only be calculated for one-dose MCV vaccination for children aged 1– 6 years and 7– 14 years because few parents remembered whether or not their children had received a second-

dose MCV after school entry. We couldn't calculate for second-dose MCV vaccination for children aged 7– 14 years.

In conclusion, our study found that nosocomial transmission increased the risk for measles transmission for both infants (0–11 months) and children (1–6, 7–14 years). Lack of vaccination exposed children to high risk of measles infection.

We recommended that hospitals and other healthcare facilities should triage and isolate febrile and rash patients. The Ministry of Health should strengthen vaccination activities for unvaccinated and under-vaccinated children in Turkey.

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Potential conflicts of interest

All authors report no conflicts of interest relevant to this article.

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