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Recommended Citation

Zahidie, A., Wasim, S., Fatmi, Z. (2014). Vaccine effectiveness and risk factors associated with measles among children presenting to the hospitals of Karachi, Pakistan.. *Journal of the College of Physicians and Surgeons Pakistan*, 24(12), 882-888.

Available at: http://ecommons.aku.edu/pakistan_fhs_mc_chs_chs/238

Vaccine Effectiveness and Risk Factors Associated with Measles Among Children Presenting to the Hospitals of Karachi, Pakistan

Aysha Zahidie, Saba Wasim and Zafar Fatmi

ABSTRACT

Objective: To determine the risk factors regarding guardian's practices associated with development of Measles and also find out effectiveness of Measles vaccine among children less than 12 years of age presenting to the hospitals of Karachi.

Study Design: Matched case control study.

Place and Duration of Study: Multicenter surveillance was conducted in 11 public and private sector hospitals of Karachi from January 2011 to September 2012 in consultation with World Health Organization Measles Surveillance Cell.

Methodology: Cases were children aged less than 12 years with Measles presenting to the hospitals. Controls for cases were enrolled from the same hospitals without Measles, matched for age and gender. Studied variables were analyzed by multivariate conditional logistic regression analysis adjusted for age and gender.

Results: Measles cases were more likely to have mothers with 'lower education' [adjusted matched Odds Ratio or mOR: 3.2 (95% CI: 1.2 - 7.6), for < 5 years of schooling adjusted mOR: 2.2 (95% CI: 1.0 - 5.7) for 6 - 10 years of schooling]. Children with Measles were also more likely to be not given breast milk in initial 2 years of life [adjusted mOR: 2.6, 95% CI 1.0 - 7.0]. Cases were also more likely to have never received vaccination [adjusted mOR: 10.1, 95% CI 4.5 - 22.5] and having no other children vaccinated at home [adjusted mOR: 3, 95% CI 1.5 - 5.3]. Vaccine effectiveness for single dose was found to be 87.4 (95% CI: 76.1 - 93.4), while for two doses it was approximately 93% (95% CI: 86.2 - 96.6).

Conclusion: For Measles elimination, mother's education on breast feeding and appropriate weaning practices is required.

Key Words: Measles. Children. Risk factors. Karachi.

INTRODUCTION

Although a safe and cost effective vaccine is available that costs less than 1 US\$, Measles is still a leading cause of death among children belonging to low income countries.¹ Around 164,000 Measles related deaths were reported in 2008, mostly in African and South Asian countries with poor health infrastructures.²

Pakistan is included among World Health Organization's (WHO) 47 high priority regions for Measles control. Annually 2.1 million Pakistani children develop Measles and 19000 - 20000 suffer with Measles complications or disease fatality. Everyday 58 children die from Measles in Pakistan.³ United Nations Millennium Development Goals include two-third reductions in overall child mortality by 2015. Since many unvaccinated children die of Measles, routine coverage of Measles vaccine has become an indicator for progress towards this goal.⁴

In Pakistan, Measles vaccine is administered under the Expanded Program of Immunization (EPI). Though

initiatives such as supplementary immunization campaigns have markedly increased frequency of Measles immunization among target populations, associated factors as low immunization coverage and floating populations are thought to be important causes of high Measles incidence in the country.^{5,6} Malnutrition and low vaccine efficacy due to cold chain related issues with poor coverage is known to make Measles endemic in Pakistan.⁶ In most industrialized countries high vaccine coverage (> 80 - 90%), good surveillance and a two-dose vaccine strategy have reduced Measles burden.⁷

Information about local risk factors for Measles among children is important to allow effective planning of services and designing appropriate interventions. Existing literature helps to form a broad model of intervention, however, local data is of utmost importance to tailor a region-specific intervention model.⁸

Data of patients presenting with Measles in healthcare facilities of Karachi can provide important information about vaccination rates among Measles cases and controls along with associated variables describing local factors associated with the disease. Therefore, the primary purpose of this study was to determine the risk factors associated with development of Measles among children less than 12 years of age presenting to 11 hospitals of Karachi, while effectiveness of Measles

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Received: December 04, 2013; Accepted: September 16, 2014.

vaccine among the study population was also determined as a secondary objective testing Measles specific IgM levels on a subgroup of study subjects.

METHODOLOGY

It was a matched case control study (matching was done on age and gender). For this study, data was collected from 11 public and private sector hospitals of Karachi. These hospitals were selected in consultation with World Health Organization (WHO) Measles Surveillance Cell, including all cases reported by the Surveillance system. However, a few large hospitals in the city did not report cases to the Surveillance Cell and were approached by developing liaison with the administration of Pediatric Departments of those hospitals. Data was collected from January 2011 to September 2012. Cases and controls were matched on age and gender.

Among cases, children were included in the study who were up to 12 years of age suffering with a generalized rash lasting greater than or equal to 3 days, temperature greater than or equal to 101°F / 38.4°C and cough or coryza, or conjunctivitis in hospital settings (outpatients, emergency department or wards) of Karachi and whose parents were residents of Karachi at least for last one year. While matched controls were children up to 12 years of age presenting in pediatrics outpatient departments or admitted in ward with diseases other than Measles at the same health care setting. Matching was done on the basis of age and gender.

Children with gross congenital anomalies and the surgical cases were not eligible to be enrolled because evidence suggests that their mothers' perceptions of severity and usefulness of medical care is different from general population. Similarly cases with pertussis, poliomyelitis and tuberculosis were excluded to avoid probability of nosocomial transmission of Measles.⁸

Data collection tools included questionnaire, anthropometric assessment and measurement of IgM levels. There were eight main sections in the questionnaire to inquire about socio-demographic characteristics of the child and his parents, birth and nutritional history of the child along with breast feeding details, vaccination status and vaccine administration details in terms of person, place and cold chain maintenance methodology, current nutritional status of the child, details of the current illness including signs and symptoms of Measles and its possible complications, and finally the exposure details specific to Measles.

Body weight and height of the child were recorded according to the recommended standard procedure. After taking weight and height of the child; he/she was labeled as well-nourished or malnourished as per Modified Gomez classification.

Measles specific IgM levels were checked in a subgroup of cases to validate case definition. Enzygnost, Behring

Diagnostics, Frankfurt, Germany (Novagnost Products) kit was used to perform case validation test.

Data was double entered in Epi Data version 3.1 and analyzed using Statistical Package for Social Sciences (SPSS) version 19.0. Univariate conditional logistic regression analysis was carried out to estimate the crude matched Odds Ratios (mOR) and their 95% Confidence Intervals (CI). A p-value of 0.25 was considered significant at univariate level.

Table 1: Descriptive analysis for Measles cases only, presenting to the hospitals in Karachi (n=292).

Variables	n (%)
Age (year)	
Median (IQR) in months	24 (12 - 48)
Age category	
Less than 9 months	32 (11.0)
9 - less than 15 months	61 (21.0)
15 - less than 59 months	134 (45.9)
60 months and above	65 (22.3)
Gender	
Male	138 (47.3)
Female	154 (52.7)
Case diagnosis as per complications	
Measles	122 (41.8)
Measles and pneumonia	71 (24.3)
Measles and diarrhea	31 (10.6)
Measles and conjunctivitis	13 (4.5)
Measles and otitis	50 (17.1)
Measles and encephalitis	4 (1.4)
Others ¹	1 (0.3)
Measles category as per IMCI classification	
Severe Measles	26 (8.9)
Measles with complications	151 (51.7)
Mild Measles	115 (39.4)
First symptom	
Fever	281 (96.2)
Rash	4 (1.4)
Coryza	5 (1.7)
Cough	2 (0.7)
Symptom followed	
Fever	17 (6.0)
Rash	250 (86.2)
Coryza	146 (50.3)
Cough	101 (34.8)
Conjunctivitis	26 (9.0)
Time lapse to report in the health facility (days)	
Immediately (within 1-2 hours)	70 (24.0)
After 24 hours	89 (30.5)
After 2 days	37 (12.7)
After 3 days	67 (23.0)
More than 3 days	27 (9.2)
Received Measles vaccine at 9 months of age	
Yes	82 (58.2)
No	43 (30.5)
Not applicable to age	16 (11.3)
Received Measles vaccine at 15 months of age	
Yes	12 (8.7)
No	83 (60.1)
Not applicable to age	43 (31.2)

¹ Measles with some other disease as malaria.

Independent variables with statistically significant and having biologically plausible association with the Measles development (outcome), in univariate analysis, were assessed further in multivariate conditional logistic regression analysis. Multicollinearity among independent variables was also checked. Biologically plausible interactions were checked between various independent variables.

The study was reviewed and approved by the Ethical Review Committee of The Aga Khan University Hospital, Karachi, Pakistan.

RESULTS

A total of 292 children with Measles and 292 children with medical problems other than Measles were enrolled by matching on age and gender. Descriptive analysis for age, gender, signs, symptoms and diagnosis only for Measles cases are presented in Table I.

Univariate matched Odds Ratio (mOR) with 95% Confidence Intervals (CI) for potential risk factors were evaluated for their association with Measles (Tables II and III).

On multivariate conditional logistic regression analysis (Table IV), Measles cases were more likely to have

mothers with lower education as compared to controls [adjusted mOR: 3.2, 95% CI: 1.2 - 7.6 for < 5 years of schooling and adjusted mOR: 2.2, 95% CI: 1.0 - 5.7 for 6 - 10 years of schooling] while keeping 11 years of schooling and above as the reference group. Number of household members was significantly associated with development of Measles ($p=0.006$), for every two members increase in a family was increasing the risk of Measles 1.24 times [adjusted mOR: 1.24, 95% CI: 1.1 - 1.5].

Children with Measles were also more likely to be not given breast milk in initial 2 years of life [adjusted mOR: 2.6, 95% CI: 1.0 - 7.0] to be classified as low weight as per Modified Gomez classification [Adjusted mOR: 2.7, 95% CI: 1.4 - 5.0]. Cases were also 10 times more likely to have not received any vaccination [adjusted mOR: 10.1, 95% CI: 4.5 - 22.5], and having no other children vaccinated at home [adjusted mOR: 3, 95% CI: 1.5 - 5.3].

Biological plausible interactions were checked between vaccination in pregnancy, place of delivery, father's education, job status and weaning and mother's education. A criterion to find an interaction significant was set as $p < 0.15$, however, no significant interaction was found. In multivariate model, variables that were not

Table II: Socio-demographic characteristics of measles cases ($n=292$) and their matched controls presenting to hospital in Karachi ($n=292$) along with univariate unadjusted matched Odds Ratio (mOR) and 95% Confidence Intervals for possible association of risk factors with Measles.

Variable	Cases n (%)	Controls n (%)	Crude matched Odds ratio (95%CI)	p-value
*Mother tongue				
Punjabi	107 (36.6)	127 (43.5)	1.6 (0.9 - 2.8)	0.054
Sindhi	37 (12.7)	27 (9.2)	0.6 (0.3 - 1.2)	0.095
Pashtu	15 (5.1)	30 (10.3)	1.6 (1.1 - 2.4)	0.17
Baluchi	94 (32.2)	70 (24.0)	1.1 (0.4 - 3.7)	0.037
Other ²	6 (2.1)	6 (2.1)	1.2 (0.7 - 2.1)	0.84
Urdu	33 (11.3)	32 (11.0)	1.0	0.587
*Mother's education				
< 5 years of schooling	207 (70.9)	132 (45.2)	5.2 (2.7 - 10.0)	< 0.0001
6 - 10 years of schooling	71 (24.3)	111 (38.0)	2.2 (1.1 - 4.3)	<0.0001
11 years of schooling and above	14 (4.8)	49 (16.8)	1.0	0.027
*Father's education				
< 5 years of schooling	144 (49.3)	116 (39.7)	2.0 (1.2 - 3.3)	0.018
6 - 10 years of schooling	116 (39.7)	123 (42.1)	1.5 (1.0 - 2.4)	0.006
11 years of schooling and above	32 (11.0)	53 (18.2)	1.0	0.105
*Father's job status				
Unemployed	286 (98.0)	287 (98.3)	0.83 (0.25-2.7)	0.763
Employed	6 (2.0)	5 (1.7)	1.0	
Mother's job status				
House wife	276 (94.8)	264 (92.0)	1.53 (0.80-3.0)	0.198
Working women	15 (5.1)	23 (8.0)		
*Number of children under 12 years within household				
Median (IQR)	2.0 (1.0 - 4.0)	2.0 (1.0 - 3.0)	1.2 (1.1 - 1.3)	0.115
*Number of household members				
Median (IQR) (for every 2 person increase in household members)	7.0 (5.0 - 9.0)	6.0 (5.0 - 8.0)	1.1 (1.0-1.2)	0.006
Monthly household income equivalent ³ in PKR				
Median (IQR)	3535.5 (2629.8 - 5000.0)	4041.5 (2886.75 - 6030.23)	-	-

²Other languages included Bengali, Balochi, Makrani, Persian, Hindku and Burmi. ³Monthly household income/square root of the number of persons in the household.

*Variables used for univariate analysis

Table III: Birth, weaning, nutritional and disease characteristics of Measles cases (n=292) and their matched controls presenting to hospital in Karachi (n=292) along with univariate unadjusted matched Odds Ratio (mOR) and 95% Confidence Intervals for possible association of risk factors with measles.

Variable	Cases n (%)	Controls n (%)	Crude matched Odds ratio (95%CI)	p-value
*Birth order				
Median (IQR) (for every unit increase in birth order)	2.0 (1.0 - 4.0)	2.0 (1.0 -3.0)	1.1 (1.1 - 1.2)	0.019
*Mother's vaccination during pregnancy				
No	149 (51.0)	87 (29.8)	2.5 (1.8 - 3.6)	< 0.0001
Yes	143 (49.0)	205 (70.2)	1.0	
*Place of delivery				
Home	111 (38.0)	81 (27.7)	1.6 (1.1 - 2.2)	0.062
Health facility	181 (62.0)	211 (72.3)	1.0	
*Mode of delivery				
SVD/Forceps delivery	264 (90.4)	242 (83.0)	2.0 (1.2 - 3.2)	0.032
C-section	28 (9.6)	50 (17.0)	1.0	
*Birth weight				
Less than normal birth weight	32 (11.0)	26 (9.0)	1.4 (0.7 - 2.6)	0.332
Normal birth weight	260 (89.0)	266 (91.0)	1.0	
*Problems after birth				
Any illness	120 (41.0)	95 (32.5)	1.12 (0.94 - 1.5)	0.13
None	172 (59.0)	197 (67.5)	1.0	
*Breast feeding				
No	29 (10.0)	24 (8.2)	1.2 (0.7 - 2.2)	0.61
Yes	263 (90.0)	268 (91.8)	1.0	
*Weaning				
4 months	92 (31.5)	126 (43.2)	0.7 (0.5 - 1.0)	0.015
7 months and above	77 (26.3)	40 (13.7)	2.1 (1.3 - 3.4)	
6 months	123 (42.0)	40 (13.7)	1.0	
*Child's current classification as per Modified Gomez classification				
Low weight	136 (48.6)	79 (27.3)	3.0 (2.0 - 4.5)	< 0.0001
Normal	144 (51.4)	210 (72.7)	1.0	
*Bitot's spots				
Present	6 (2.0)	4 (1.4)	2.0 (0.5 - 8.0)	0.65
Absent	282 (98.0)	282 (98.6)	1.0	
*Ever received any vaccine				
Yes	148 (50.7)	17 (5.8)	15.6 (8.0 - 30.5)	< 0.0001
No	144 (49.3)	275 (94.2)	1.0	
*Other children at home vaccinated				
No	160 (55.0)	44 (15.0)	8.0 (5.0 - 13.1)	< 0.0001
Don't know	31 (10.7)	27 (9.2)	2.6 (1.4 - 5.0)	
Yes	100 (34.4)	221 (75.5)	1.0	0.009
Similar illness in last 3 weeks				
Yes	102 (35.0)	12 (4.0)	-	-
No	190 (65.0)	280 (96.0)	-	-
Health facility visited in last 3 weeks				
Yes	66 (22.6)	28 (9.6)	-	-
No	226 (77.4)	264 (90.4)	-	-
Reason for visiting health facilities				
Some illness	46 (68.7)	24 (85.7)	-	-
Complementary visit	21 (31.3)	4 (14.3)	-	-

significant ($p < 0.05$), not a confounder or effect modifier excluded from the final model (Table IV).

Subgroup analysis was performed only for the children who were ever vaccinated as reported by parents including 144 Measles cases and 275 controls. Vaccination characteristics revealed marked differences among cases and controls as cases were 7 times more likely not to have received vaccines according to the age

[unadjusted OR: 7, 95% CI: 3.6 - 13.3]. Cases were almost 5 times more likely to be vaccinated by vaccine that was not taken from refrigerator [unadjusted OR: 4.5, 95% CI: 1.7 - 12.0] and the date of expiry was not checked at the time of vaccine administration [unadjusted OR = 5.2, 95% CI: 2.0 - 13.6].

For children who were given single dose of vaccine at 9 months of age, vaccine effectiveness was found to be

Table IV: Final multivariable conditional logistic regression model of risk factors associated with Measles among children presenting in the hospitals of Karachi, Pakistan (matched for age and gender of the subjects).

Variables	Adjusted matched Odds ratio (95% CI)	p-value
Mother's education		
< 5 years of schooling	3.0 (1.2 - 7.6)	0.053
6 - 10 years of schooling	2.2 (1.0 - 5.7)	0.021
11 years of schooling and above	1.0	0.125
Number of household members (for every 2 person increase in household members)	1.24 (1.1 - 1.5)	0.013
Breast feeding		
No	2.6 (1.0 - 7.0)	0.056
Yes	1.0	
Child classification as per Modified Gomez classification		
Low weight	2.7 (1.4 - 5.0)	0.002
Normal	1.0	
Ever received any vaccine		
No	10.1 (4.5 - 22.5)	< 0.0001
Yes	1.0	
Other children at home vaccinated		
No	3.0 (1.5 - 5.3)	0.004
Don't know	1.8 (0.7 - 4.6)	0.001
Yes	1.0	0.23

87.4 (95% CI: 76.1 - 93.4), 309 were vaccinated and 58 were unvaccinated.

For children who were given two doses at 9 months and 15 months respectively, vaccine effectiveness was found to be 93.0 (95% CI: 86.2 - 96.6), 148 were vaccinated and 101 were unvaccinated.

DISCUSSION

The focus of this study was to identify the risk factors for Measles among children up to 12 years of age presenting to the hospitals or healthcare settings in the city of Karachi.

Previous studies in Pakistan were conducted in single tertiary care settings of private hospitals. There have also been inconsistencies in the diagnosis of Measles as some used clinical as well as laboratories diagnosis of Measles while some relied only on clinical case definition.^{5,6,8} In this study, private and public healthcare settings of various levels of care were included based on information provided by World Health Organization Measles Surveillance Cell. Majority of the cases were selected from public sector hospitals, however, use of surveillance cell for case notification helped to collect data from variable locations in the city. WHO based management guidelines were used to identify Measles with precision and to avoid miss classification of severe and mild cases of Measles. These guidelines are simple for diagnosis and classification of Measles cases in hospital as well as in community settings.⁹

This study looked at the practices of guardians in terms of mother's vaccination practices during pregnancy, initiation of breast feeding and weaning practices, as well as common food used for initiation of weaning for

children with Measles compared to their matched hospital controls. These variables were identified after visiting households and discussion with senior pediatricians in hospitals included in the study. The inclusion of these variables was intended to identify the modifiable risk factors on which intervention is possible.

For the interpretation of the results of this study, we categorized Measles cases as less than 9 months, 9 - less than 15 months, 15 - less than 59 months and 60 months and above. This distribution was based on current recommended ages for Measles vaccination in developing countries that is first dose at 9 months and booster dose at 15 months of age, while less than 5 years of age still remains a susceptible group for Measles in developing countries.^{9,10} This data showed a similar incidence of Measles in infants < 9 months (11%) as reported earlier (20 - 22% in South Asian region (3.9% - 11.5%).⁹⁻¹¹ Results of this study also revealed that majority of cases were in age group less than 24 months of age.

In this study, Measles cases were also more likely to have mothers with lower education as compared to controls [AOR: 3.2 (CI: 1.2 - 7.6) for < 5 years of schooling and OR: 2.2 (CI: 1.0 - 5.7) for 6 - 10 years of schooling while 11 years of schooling and above taken as reference].

Among well conducted studies to estimate the effect of maternal education on the proximate determinants of child mortality, maternal education has been found as a significant correlate of child mortality and morbidity outcomes and even low levels of education improve child survival prospects and health-related behaviors.^{12,13}

On average each one-year increment in mother's education corresponds with a 7 - 9% decline in mortality of children under 5 years of age. Fiscal advantages associated with education (i.e. income, water and latrine facilities, housing quality, etc.) may explain the overall relationship of mothers' education with reduced child morbidity with infectious diseases.

In this study, Measles was also more common in households with larger number of members in the family as for every two members increase in a family was associated with Measles [AOR: 1.24 (1.1 - 1.5)]. Studies conducted in the background of developing countries suggest that overcrowding could reflect an increased risk of exposure to Measles cases.⁸ Data from a rural area of Guinea-Bissau suggest that overcrowding and age may be more important as determinants than nutritional status.¹⁴

Few community based studies from Africa and Asia have also found overcrowding and intensive exposure as significant determinants of Measles mortality. Thus, socio-cultural factors that bring closer many susceptible children in the home also increase the case-fatality ratio in Measles. Crowding and intensive exposure may also partly explain regional and historical variations in Measles mortality. High immunization coverage can dilute this effect of overcrowding as Measles vaccination increases herd immunity and diminishes the clustering of several cases in a family. Vaccination may, therefore, reduce mortality even among unvaccinated children as well who contract Measles.^{15,16}

Children with Measles were also more likely to be not given breast milk in initial 2 years of life [AOR: 2.6 (1.0 - 7.0)]. This could also explain low weight prevalence among cases as compared to controls. The few well documented studies on infant feeding practices and the incidence of Measles have already demonstrated a protective effect of breast feeding.¹⁴ Literature has shown that breastfeeding for more than 3 months was negatively associated with a diagnosis of clinical Measles infection after adjustment for crowding, social class, Measles vaccination, parity and gender with an odds ratio of 0.69 (0.60 - 0.81) compared with those who never breastfed.¹⁷⁻¹⁹

Measles cases were more likely to be classified as low weight as per Modified Gomez classification [AOR: 2.7 (1.4 - 5.0)]. Under weight is already a cause of high likelihood for early childhood infections as shown in previous studies as well. Odds ratio for mortality because of low weight-for-age was elevated for death due to diarrhea, pneumonia, malaria, and Measles and for all-cause mortality. Previous large scale studies has already evidenced that overall 52.5% of all deaths in young children were attributable to undernutrition, that lead to low immunity and high susceptibility to childhood infections. It was also evidenced that 44.8% of deaths

among malnourished children were due to Measles and for deaths because of Measles 60.7% of deaths were because of diarrhea.¹⁶

The cases were also more likely to have never received any vaccination [AOR: 10.1 (4.5 - 22.5)] and having no other children vaccinated at home [AOR: 3 (1.5 - 5.3)]. Literature has already revealed that Measles vaccination was highly associated with low risk for Measles [OR: 0.14 (0.13 - 0.16)].¹⁷

Expanded Program on Immunization (EPI) emphasizes routine vaccination coverage and long-term sustainability for vaccine preventable childhood diseases by emphasizing national and sub-national Immunization Days. Ministry of Health aims to achieve the target of 90% routine immunization coverage of all EPI vaccines with at least 80% coverage in every district by 2012. However, Measles vaccination coverage has increased only slightly or remained stagnated in some provinces in the last few years. Variable vaccination coverage may be related to increasing inequities.²⁰⁻²²

Regarding vaccine effectiveness Measles vaccine has been developed over decades to prevent and control Measles. Vaccination efficacy is high when appropriately utilized and stored; however, developing countries like Pakistan have shown variable effectiveness due to cold chain and vaccine maintenance related issues.²³⁻²⁵

Although the researchers tried to avoid or control for factors that might limit the findings of this study, there are still important limitations and the results of this study need to be interpreted in the light of these limitations with caution.

An important limitation was the selection of controls from hospital settings only. Ill children presenting in the hospital may have relatively high prevalence of risk factors than healthy children and this could have resulted in dilution of results in final analysis. However, previous studies using neighborhood control show that most of the findings for hospital controls were broadly similar to those of neighborhood controls.⁸

An additional limitation was reliance on the verbal report of parents or guardians regarding weight at birth and vaccination status of our study children. However, as both the cases and controls were selected from the hospital settings and information was elicited from the parents of ill children in both groups, there was little likelihood that parents of cases would recall vaccination details differently as compared to controls.

CONCLUSION

The data from the present study support the hypothesis that to improve Measles control in Karachi missed immunization opportunities must be reduced in all healthcare facilities by following WHO guidelines. Moreover, mother's education on breast feeding and

appropriate weaning practices is required to increase child's immunity against vaccine preventable diseases. There is a need for organized efforts to increase the coverage of vaccines locally and globally to avert the burden of Measles in children.

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