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Factors affecting on compliance of childhood immunization in Ilam District of Nepal; A case-control study



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ARTICLE INFO

Keywords: Routine immunization Compliance Case-control study Nepal

ABSTRACT

Childhood immunization is one of the most important public health interventions to reduce child morbidity and mortality. Reaching all children with full immunization services is critical to meet Nepal's commitment to Sustainable Development Goals (SDGs). This study aimed to identify factors affecting compliance with childhood immunization in children aged 16 to 36 months in Nepal. A community-based unmatched case-control study was conducted with 250 (83 cases and 167 controls) respondents in the Ilam district of Nepal. Respondents were randomly selected using a multi-stage cluster sampling technique. Data were collected using a structured questionnaire and analysed using SPSS version 16 statistical software. Bivariate and multivariate logistic regression analyses were done to identify the factors influencing compliance with childhood immunization of the sampled respondents. More than two-thirds (66.8%) of the sampled children were fully immunized, and 19.3% of the children defaulted to the Measles-Rubella vaccines. Only 19.2% of the respondents had good knowledge about the type of vaccine, and more than half (59.2%) of the respondents had a positive attitude towards immunization. Multivariate logistic regression analysis revealed that lack of knowledge about vaccines (AOR = 49.4, 95% CI = 12.94 to 188.59), father's level of education (AOR = 2.1, 95% CI = 1.05 to 4.30), not getting immunization on the day of the appointment (AOR = 4.8, 95% CI = 2.30 to 9.89), lack of knowledge about immunization schedule (AOR = 2.4, 95% CI = 1.14 to 4.84), and negative attitude towards immunization (AOR = 2.1, 95% CI = 1.03 to 4.19) were independently impeded on compliance on the childhood immunization. Targeted intervention in health promotion activities at the household level should be promoted and integrated immunization services into the existing primary health care services.

1. Introduction

Routine childhood immunization is one of the most successful and cost-effective public health interventions for reducing mortality, morbidity, disability and the burden of disease [1,2]. In 1974, the World Health Organization (WHO) launched the Expanded Program on Immunization (EPI) to ensure that all children have access to the routinely recommended vaccines [3]. After the initiation of the EPI, global infant mortality has been reduced, smallpox has been eradicated, and some infant and child health-related diseases are in the elimination phase [1]. There was a global commitment and ensure that no one misses out on routine immunization by 2020. However, the global vaccination coverage was only 86% in 2019 but due to the COVID-19 pandemic, the global coverage dropped 5% in 2021 [1,4]. The coverage gaps persist between countries, as well as within countries and are reported 76% in the African region to 89% in Southeast Asia [5,6].

Before the COVID-19 pandemic, inequity in childhood immunization was reported among the poorest households and rural areas due to inadequate health infrastructure and supply chain problems [7]. Although, the national immunization programme is one of the top priorities in Nepal and all children aged 0 to 15 months in Nepal need to complete at least 18 different types of immunizations [8] which are summarised in Table 1.

The national target for immunization is to achieve and maintain at least 90% by the end of 2020 and 95% coverage by 2030 [8], but the national prevalence of immunization is reported only at 78% as per the Nepal Demographic Health Survey 2016 [9]. This proportion is much lower (68%) in our study district [10]. This proportion was even lower due to the COVID-19 pandemic and it has also heightened existing inequity [11].

Although the expanded program on immunization has contributed to increasing coverage and access, the proportion of children who have completed the recommended vaccination schedule has not increased as

http://dx.doi.org/10.1016/j.dialog.2023.100140

Received 30 December 2022; Received in revised form 25 May 2023; Accepted 25 May 2023 Available online 29 May 2023

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Table 1

Routine immunization schedule in Nepal.

Name of vaccines	Schedule	
BCG	at birth	
DPT-HEP-B-HIB	at 6, 10 and 14 weeks	
Oral Polio vaccine	at 6, 10 and 14 weeks	
Rotavirus vaccine	at 6 and 10 weeks	
FIPV	at 6 and 14 weeks	
PCV	at 6 weeks, 10 weeks and 9 months	
Measles-Rubella	at 9 and 15 months	
Japanese Encephalitis	at 12-23 months	
Typhoid	At 15 months	

BCG- Bacille Calmette-Guerin, DPT- Diptheria Pertussis Tetanus, HEP-B- Hepatitis B, HIB- Haemophilus Influenza type b, FIPV- Fractional Inactivated Poliovirus Vaccine, PCV- Pneumococcal Conjugate Vaccine

anticipated. The factors and barriers that influence the childhood immunization programme include child demographic factors and family factors [12]. Other factors influencing refusal to comply with routine vaccination include inconvenient clinic locations, financial difficulties to reach the clinic, a lack of information, psychological distress, religious reasons, a long distance to reach immunization clinics, and poor knowledge about the importance of immunization among parents [13-16]. Similarly, a study in Nepal also highlighted that children born in health facilities and children who have vaccination cards have high vaccination coverage [17]. Vaccine-preventable diseases are still prevalent in Nepal, and there is very little known about these factors and assessed the factors that influenced compliance with childhood immunization in Nepal. It is important to identify the factors that influence compliance with childhood immunization and the need to understand the strategies to increase immunization compliance and rates. Therefore, the aim of the study was to identify the factors that influence compliance with childhood immunization services in Ilam district of Nepal.

2. Methodology

2.1. Study design, setting and population

A community-based unmatched case-control study was designed and conducted in two municipalities of the Ilam district in Nepal. Data were collected from July to August 2018. The study population consisted of mothers/ caregivers who had children aged 16 to 36 months and lived in two municipalities of the study district. The reason behind selecting 16 months and above was because childhood immunization has been completed in 15 months for a child [8]. Cases were (incompletely immunized group) children aged 16 to 36 months who did not complete the scheduled national immunization, whereas controls were (completely immunized) children who completed the recommended routine immunization.

2.2. Sample size and sampling techniques

The sample size was determined based on knowledge of the benefits of the vaccine as the key indicator, taken from a study previously conducted in Nepal [18]. The sample size was calculated by using Epi Info 7 statistical software, considering a 95% confidence interval, 80% power calculation with design effects 2 and the case-control ratio of 1:2, the percentage of knowledge of the benefit of the vaccine in respondents having case 88.1% and in control 97.7% [18]. However, a 10% non-response rate was also added as per the Fleiss formula [19], and it determined a total of 250 (83 incompletely immunized children as case and 167 completely immunized children as control) samples.

A multistage cluster sampling technique was used to obtain a representative study sample. There are a total of 10 municipalities (six rural and four urban) in the Ilam district of Nepal. In the first stage, two municipalities were randomly selected; secondly, six out of twelve vaccination centres in Mai municipality and five out of ten vaccination centres in Chulachuli rural municipality were also randomly selected. From each selected vaccination centre, a list of incompletely immunized and completely immunized children and their full addresses were prepared from the immunization records of the selected health facilities. Two separate lists of fully immunized and partially immunized children were prepared from the immunization records. The respondent was either the mother or the caretaker, depending on whoever was available during the interview period, and the study respondents were randomly selected for the final interviews.

2.3. Data collection

A structured questionnaire was used to collect data, which was first written in English and then translated into Nepali by a bilingual expert. The majority of the variables in the socio-demographic section were adopted from the previous study of Nepal [18] Likewise, other sections were adopted from the previously validated tools of the World Health Organization [20] and a similar study of Ethiopia [21]. The questionnaire was pretested on other similar study populations, taking a total of 15 mothers out of the study sites. Necessary modifications to the questionnaire were also made. The test-retest reliability of the instrument was 0.91, and the value of Cronbach's alpha was 0.66 for the whole instrument. An expert review of the instrument was conducted, and all items scored 3 or 4, so each item had an item-level content validity index of 1. The data were collected by trained field researchers with a nursing degree and a public health background who had extensive experience collecting data in similar settings. One-day orientation was provided to the field researchers and the data were collected through face-to-face interviews in the Nepali language. Individual participants' households were identified with the help of the selected community female community health volunteer.

2.3.1. Outcome variables

The outcome variable of this study was compliance with immunization. Children who received all basic immunizations as per the schedule of the national immunization programme were categorized as having complete immunization and children who missed any vaccines as per the schedule were categorized as having incomplete immunization [18]. The status of the immunization of the children was identified through the immunization register.

2.3.2. Independent variables

Socio-demographic factors, knowledge, attitude and behaviour towards immunization and factors related to immunization service delivery were included in this study as independent variables to identify the independent predictors of the status of immunization. These variables were extracted from previous studies [18,21,22]. Demographic characteristics include maternal age, educational level, family income, sex of a child, religion, residence area, race, number of children, number of antenatal visits, and place of delivery. There were seven questions to assess the knowledge, another seven items to assess the attitude and five questions were included to assess the behaviour of the respondents towards immunization. Some variables were measured as;

- Knowledge about type of vaccine: Knowing four or more types of vaccines was considered to have good knowledge of the type of vaccine [18].
- Knowledge about the schedule of vaccines: Knowing the four or more vaccine schedules were considered to have good knowledge about the schedule of vaccines [18].
- Knowledge about the benefit of immunization: Knowing two or more benefits of immunization was considered as having good knowledge of the benefits of immunization [18].
- Attitude towards immunization: A score above the mean stand for a positive attitude towards immunization.

Factors related to immunization service delivery were measured by twelve questions including distance from home to the vaccination centre, the convenience of the immunization clinic, visited to the health institution for other services, informed about vaccination during health institution visits, advice got from the providers about vaccination after delivery, be informed about next vaccination shoot, information received about side effects of vaccination, explained about the significance of immunization by the health worker, waiting time during vaccination, either waiting time was reasonable, postponed of vaccination, and causes of vaccination postponed.

2.4. Data analysis

The data were coded, entered, and analysed using the Statistical Package for the Social Science (SPSS) version 16. Descriptive statistics were used to describe the responses given by the respondents on the independent and dependent variables. Bivariate analysis (Chi-square and Fisher exact test) was carried out to determine the factors affecting compliance with childhood immunization. All variables having a *p*-value less than 0.05 in bivariate analysis were entered into a backward stepwise binary logistic regression to identify the independent factors influencing compliance with childhood immunization. The strength of the association was calculated using an odds ratio with a 95% confidence interval and a *p*-value of less than 0.05 was used to define statistical significance.

2.5. Ethical consideration

Ethical approval was obtained from the Human Research Ethics Committee of Xiang-Ya School of Nursing, Central South University, China (Registration number 12018011) and the Nepal Health Research Council, Nepal (Registration number 19). Individual verbal consent was obtained before interviewing the participants, and each participant was also given the right to withdraw from the study at any time.

3. Results

3.1. Socio-demographic characteristics

A total of 250 respondents were interviewed. Among them, almost all (99.6%) respondents were mothers, and more than two-thirds (71.2%) of the respondents were 29 years and younger age. The mother's and father's educational attainment were almost similar, with 15.2% of mothers and 10.8% of fathers being illiterate. About two-thirds (65.2%) of the respondents depended on agriculture. More than two-thirds (70%) of the respondents were Janajati by ethnicity, and around half (48.8%) of the respondents belonged to the Hindu religion. More than half (54.4%) of the children were male, and a greater number (85.2%) of the respondents had one to two children. Likewise, more than half (52%) of the respondents had completed four antenatal care visits, and 64% delivered their child to the health institution (Table 2).

3.2. Status of incompletely immunized children

Among the 83 children who had not received complete immunization, all of them had received the BCG vaccine. Almost all (96.4%) of the children had received the third dose of the DPT-HepB-Hib vaccine. Similarly, 92.8% of the children had received their third dose of the oral polio vaccine, whereas only 69.9% of them had received three doses of PCV (Pneumococcal Conjugated Vaccine), 44.6% received JE (Japanese Encephalitis) vaccine, 36.1% had received IPV (Injectable Polio Vaccine), and only 19.3% received both doses of Measles and Rubella vaccine in 9 and 15 months (Fig. 1).

3.3. Factors affecting compliance with childhood immunization

The strongest predictor of non-compliance with immunization was lack of information as a reason for missing immunization (AOR = 49.41, 95%CI: 12.94 to 188.59) compared to information recipients. The children whose parents' education was of higher secondary level and above were

Table 2

Socio-demographic characteristics of respondents.

Variables	Frequency	Percent
Caregiver		
Mother	249	99.6
Grandmother	1	0.4
Age		
<29 year	178	71.2
≥30 year	72	28.8
Mother education		
Illiterate	38	15.2
Primary level	76	30.4
Secondary level	111	44.4
Higher secondary and above	25	10.0
Father education		
Illiterate	27	10.8
Primary level	84	33.6
Secondary level	115	46.0
Higher secondary and above	24	9.6
Main occupation of respondents		
Agriculture	163	65.2
Service	4	1.6
Business	19	7.6
Housewife	64	25.6
Caste/ethnicity		
Brahmin/Chhetri	52	20.8
Janajati	175	70.0
Dalit	21	8.4
Others	2	0.8
Religion		
Hindu	121	48.4
Buddhist	12	4.8
Christian	20	8.0
Kirat	97	38.8
Monthly income		
<nrs 10,000<="" td=""><td>112</td><td>44.8</td></nrs>	112	44.8
>NRs 10,000	138	55.2
Sex of child		
Male	136	54.4
Female	114	45.6
Number of living children		
1 to 2	213	85.2
3 and more	37	14.8
Mean number of children	$1.66 (SD \pm 0.82)$	
Number of ANC visits		
ANC visit less than 4 times	120	48.0
ANC visit 4 times and more	130	52.0
Place of delivery		
Home	90	36.0
Health institution	160	64.0

two times more likely to complete their immunization schedule than illiterate parents (AOR = 2.12, 95% CI: 1.05 to 4.30). Respondents who returned from health institutions without getting immunization at the time of appointment were five times more likely to be non-compliant with having the immunization schedule (AOR = 4.77, 95% CI: 2.30 to 9.89). Similarly, the respondents who didn't know the immunization schedule were significantly more likely to have incomplete immunization than those who knew the schedule (AOR = 2.08, 95% CI: 1.14 to 4.84). Respondents with negative attitudes towards immunization were twice as likely to have non-compliant children as those with positive attitudes (AOR = 2.08, 95% CI: 1.03 to 4.19) (Table 3).

4. Discussion

The childhood immunization program is a proven most cost-effective public health intervention, but still, a large proportion of children had not been immunized in complete doses. Our findings revealed that only 19.3% of children had received both doses (9 and 15 months) of the measles and rubella vaccine. It was higher than Ethiopia (10%) [21] and much lower than the national annual status (66.2%) in Nepal [8]. However, the measles rubella's first vaccine coverage was found at 90% in the Nepal



Fig. 1. Status of incompletely immunized children (n = 83).

Demographic and Health Survey in 2016 [9]. Although, the Measles and rubella second vaccine program was started in 2015 in Nepal [8]. In this regard, most community members who are from ethnic minority backgrounds and geographically marginalized communities living in slum and rural areas may not know about the second dose of the measles and rubella vaccine. An earlier study also shows that incomplete immunization was even higher in slum area [18]. Therefore, there should have continuous awareness-raising programs for routine vaccination programs at the grass root level and that should go with the existing Female Community Health Volunteer (FCHVs) community health programs such as antenatal and postnatal counselling services. Study shows that the vaccine introduction was found to be associated with improvement health equity and service utilization [23]. This perhaps helps to sustainably improve the awareness, knowledge of the mothers and the general community on the benefits of immunizing their children.

The finding shows that parents who were illiterate or had lower educational status are another factor that influences compliance with immunization. Similar findings were also revealed in the studies conducted in Iraq [24] and Bangladesh [25]. People's knowledge and educational attainment were found to be strong influencing factors on decision-making which completely aligned with the earlier studies elsewhere [14,25]. Likewise, being a male household head was also found negatively influenced by completing the schedule of childhood immunization. Therefore, all the community people should be well informed and educated about vaccination, its importance and the schedule for the full coverage of the services.

Similarly, the unawareness of the respondent about the vaccination schedule was also found as a predictor of compliance with immunization. This finding is consistent with the study conducted in Ethiopia [26] and Sub-Saharan Africa [27]. Similarly, other previous studies regarding the knowledge of vaccination were also an important determinant of whether to immunize or not immunize their children [28–30]. In the current study, a lack of awareness, especially about new vaccines and their schedule, was found to be a predictor of not completing the routine vaccination. Therefore, awareness-raising programmes should be implemented at the community level to complete child immunization.

Moreover, the lack of information about vaccines also impeded the completion of immunization in this study. This finding was also supported by previous studies conducted elsewhere that found due to a lack of information immunization and immunization schedules were not fully immunized [25,31]. The lack of information about vaccines may be due to not providing clear and sufficient information at the community level. Therefore, the general public needs to understand the importance of compliance because incomplete information and misconceptions about the regimens are associated with poor therapeutic outcomes [32]. The government should mobilize female community health volunteers and health mother groups, which are stable platforms for working at the community level and disseminating routine immunization-related messages to the entire community. Moreover, the health workers should also carry out the home visit and identify non-vaccinated children. In the case of the mother being absent, they can teach the caregivers about the immunization schedule, its side effects, and management at home that may help to complete the immunization schedule.

Respondents who returned from a health institution without getting immunization on the day of appointment also impeded the compliance of immunization. This finding is supported by the studies conducted in Ethiopia [21] and Lao PDR [28]. Due to a shortage of vaccines at health facilities, mothers were forced to return home without immunizing their children. Therefore, the logistics division of the Ministry of Health should manage an uninterrupted supply of the vaccine at the health facilities, and the health facility staff should also timely place orders for continuous service. An orientation program regarding new vaccines, vaccination coverage, and measures should be provided to grass-roots healthcare providers for the interrupted supply of services.

The respondents who had a negative attitude were partially immunizing their children as compared to those who had a positive attitude. This finding is consistent with a study conducted in China [29], and Sudan [33]. A negative attitude towards immunization might be due to a lack of information about immunization and its importance among the respondents. Sufficient information and positive attitudes towards compliance with childhood immunization would motivate compliance with childhood immunization.

4.1. Strengths and limitations of the study

This study was conducted in one of the eastern districts of Nepal, which has a diverse socio-cultural society, which might differ in access to and cultural practices from other districts of Nepal. Due to financial constraints and

Table 3

Factors affecting compliance with childhood immunization.

Variables	Immunization status		Crude OR	Adjusted OR
	Incomplete No (%)	Complete No (%)	(95% CI), P-value	(95% CI), P-value
<29 years	57 (68.7)	121 (72.5)	0.83 (0.47-1.48), 0.53	
\geq 30 years and above	26 (31.3)	46 (27.5)	1	
Parent education				
Illiterate/Primary level	51 (61.4)	60 (35.9)	2.84 (1.65-4.89), <0.001	2.12 (1.05-4.30), 0.04
Secondary/Higher secondary level and above	32 (38.6)	107 (64.1)	1	1
Main occupation of respondents	52 (50.0)	107 (04.1)	Ŧ	1
	F9 (60 0)	105 (62.0)	1 27 (0 77 2 40) 0 27	
Agriculture	58 (69.9) 25 (30.1)	105 (62.9)	1.37 (0.77–2.40), 0.27	
Others (Service, Business, Housewife)	25 (30.1)	62 (37.1)	1	
Caste/ethnicity				
Janajati	66 (79.5)	109 (65.3)	2.06 (1.11–3.84), 0.02	
Others (Brahmin/Chhetry, Madhesi, Dalit, Others)	17 (20.5)	58 (34.7)	1	
Religion				
Hindu	32 (38.6)	89 (53.3)	1	
Kirat	21 (25.3)	26 (15.6)	0.78 (0.68-1.19)	
Others (Buddhist, Christian, Islam)	30 (36.1)	52 (31.1)	0.59 (0.79-1.04), 0.08	
Monthly income				
<nrs 10,000<="" td=""><td>45 (54.2)</td><td>67 (40.1)</td><td>1.76 (1.03-3.01), 0.04</td><td></td></nrs>	45 (54.2)	67 (40.1)	1.76 (1.03-3.01), 0.04	
>NRs 10,000	38 (45.8)	100 (59.9)	1	
Sex of child	30 (43.0)	100 (35.5)	1	
	40 (57.0)	00 (50 7)	1 22 (0 72 2 00) 0 44	
Male	48 (57.8)	88 (52.7)	1.23 (0.72–2.09), 0.44	
Female	35 (42.2)	79 (47.3)	1	
Number of living children				
1 to 2	67 (80.7)	146 (87.4)	1	
3 and more	16 (19.3)	21 (12.6)	0.60 (0.29–1.22), 0.16	
Number of ANC visits				
ANC visit less than 4 times	40 (48.2)	80 (47.9)	1.01 (0.59-1.71), 0.96	
ANC visit 4 times and more	43 (51.8)	87 (52.1)	1	
Place of delivery				
Home	37 (44.6)	53 (31.7)	1.73 (1.01–2.97), 0.05	
Health institution	46 (55.4)	114 (68.3)	1	
	40 (00.4)	114 (00.3)	1	
Knowledge of the type of vaccine	(0 (02 1)	100 (70 6)	1 26 (0.62, 2.51), 0.62	
Poor	69 (83.1)	133 (79.6)	1.26 (0.63–2.51), 0.62	
Good	14 (16.9)	34 (20.4)	1	
Knew immunization schedule				
No	44 (75.9)	133 (79.6)	1.96 (1.15–3.34), 0.02	2.35 (1.14-4.84), 0.02
Yes	14 (24.1)	34 (20.4)	1	1
Attitude towards immunization				
Negative	54 (65.1)	48 (28.7)	4.62 (2.63-8.1), <0.001	2.08 (1.03-4.19), 0.04
Positive	29 (34.9)	119 (71.3)	1	1
Said no information about the vaccine as a reason for miss				
Yes	35 (42.2)	3 (1.8)	39.86 (11.74–135.31), <0.001	49.41 (12.94–188.59), <0.00
No	48 (57.8)	164 (98.2)	1	1
Distance from immunization centre	46 (37.6)	104 (96.2)	1	1
	44 (50)	00 (50 7)	1 01 (0 (1 70) 1	
< 30 min within walking distance	44 (53)	88 (52.7)	1.01 (0.6–1.72), 1	
>30 min within walking distance	39 (47)	79 (47.3)	1	
Informed about next immunization shot				
No	11 (13.3)	13 (7.8)	1.81 (0.77-4.24), 0.25	
Yes	72 (86.7)	154 (92.2)	1	
Convenience of immunization centre				
No	27 (32.5)	34 (20.4)	1.88 (1.04-3.41), 0.05	
Yes	56 (67.5)	133 (79.6)		
Returned without getting immunization	,			
Yes	42 (50.6)	45 (26.9)	2.78 (1.6-4.81), <0.001	4.77 (2.30–9.89), <0.001
No	41 (49.4)	122 (73.1)	1	1
		122 (/ 3.1)	ī	1
Vaccine not available reason for returning without getting		190 (77.0)	0 44 (1 00 4 01) 0 01	
No	49 (59)	130 (77.8)	2.44 (1.38–4.31), 0.01	
Yes	34 (41)	37 (22.2)	1	
Be informed about side effects following immunization				
No	59 (79.1)	96 (57.5)	1.81 (1.03–3.19), 0.05	
Yes	24 (28.9)	71 (42.5)		

time limitations, the study was only conducted in one of the purposively selected districts and two municipalities that may not be representative of the entire country. The study used self-reported data and there is a possibility of recall bias. Future studies should verify the immunization cards with health facility dates to ensure immunization status. This study did not collect qualitative data but this could have added more value to the study. Therefore, future studies could use the mixedmethods approach to study issues associated with the low coverage of immunization services with a larger sample -representing the seven provinces of Nepal that may give comprehensive pictures to develop the appropriate intervention packages to foster childhood immunization coverage in Nepal. Despite these limitations, the study findings have important implications for the individual, organization, and policy levels to improve childhood immunization coverage. This study provided strong support for further efforts to enhance immunization coverage by identifying the crucial factors in the compliance of childhood immunization coverage.

5. Conclusion

The childhood immunization program is a proven most cost-effective child survival intervention, but still, a large proportion of children are out of these vaccines. Our findings revealed that around four-fifths of children were non-compliant with the measles and rubella vaccines. Lack of information about the vaccine, parental education, not getting immunization due to stock out, lack of knowledge about immunization schedule, and a negative attitude towards immunization was significantly associated with the non-compliance of childhood immunization. The local governments should make a pragmatic plan for mothers with risk profiles and ensure the availability of vaccines all the time. Community-level awareness programs should be integrated into the FCHV's health activities such as postnatal home visits about the benefits of childhood immunization and the risks of vaccine-preventable diseases. Provide accurate information and promotion activities through various mass media, social media and community engagement with local leaders and influencers. An orientation program regarding new vaccines, vaccination coverage, and measures should be provided to grass-roots health care providers. The government should coordinate with other agencies, such as requiring a complete dose of vaccination cards at the time of school admission. Last but not least, future studies could use the qualitative approach to study issues associated with the low coverage of immunization services.

Funding

The University of China provided the fieldwork funding for this research project.

Authors' contributions

BS and JY jointly designed the study. BS, DP, LT and GPK completed the data collection and BS drafted the paper. JY, DP, GPK and SPW provided critical feedback and helped shape the research, analysis and manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Central South University, Changsha, China for providing financial and academic support for the completion of this research. We wish to thank all participants in this study for taking their time and for sharing their experiences. Without their involvement, this study would not have been possible. We additionally like to thank the Nepal Health Research Council for granting ethical approval.

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