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Varicella vaccine uptake in Shandong province, China

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Varicella vaccine has been licensed in China for decade to be used as single dose in children aged ≥ 12 mo of age in private sector. Little data were available on varicella uptake to date in China yet. A cross-sectional study was conducted in Shandong Province in May 2011 to examine varicella vaccination coverage among children aged 16–40 mo and examine factors associated with varicella vaccine uptake. The overall coverage among children eligible for varicella vaccine was 62% (range 16.7–94.7% by county), much lower than the coverage of the eight vaccines included in the national immunization program (all above 97%). Though proximity to immunization services (< 5 km) was linked with higher vaccine uptake (62.6 vs. 37.4%, p = 0.02), county-level economic development (77.8, 61.0 and 47.1% for developed, sub-developed and developing regions, respectively, p < 0.001) played an even more important role in varicella vaccination. Moreover, there was little variation in coverage of vaccines included in the national immunization program along with county-level economic development. Even though varicella vaccine uptake is relatively high for use on a private basis, the vaccination coverage is not high enough to prevent epidemiology shift to adolescents and adults who are more prone to develop severe outcomes to varicella. Further enhancement on varicella vaccination coverage is necessary and inclusion to national immunization program seems to be a promising option for achieving and maintaining high coverage.

Introduction

Varicella (chickenpox) is a highly contagious disease caused by the varicella zoster virus (VZV). In the absence of vaccination, varicella is a universal infection, usually acquired in childhood in countries with a temperate climate. In China, a seroprevalence study conducted in five cities (Beijing, Shanghai, Dalian, Chengdu and Guangzhou) before vaccine era showed that more than 90% of adults aged ≥ 20 y had been infected by VZV.[1] Though varicella is generally benign and self-limiting, severe complications, including death, can occur.[2]

Varicella vaccines have become widely available throughout the world since developed in 1974. Currently, varicella vaccine is not included in the national or provincial immunization programs in China, but is available for purchase on a private basis. Several highly effective varicella vaccines with similar VZV concentrations and storage requirements have been licensed for distribution in China since 1998 and are used for vaccination of children aged ≥ 12 mo as a single-dose regimen.[3] To date, there is little data on varicella vaccination coverage in China. Studies of varicella vaccination coverage have ranged from 42.4% among 2–3 y olds in an immunization clinic in central China in 2006 to 47.6% among 1–10 y olds in a community in southern China in 2009, to 74.4% among 0–6 y olds in an immunization clinic in Beijing in 2005.[4-6] However, the sample sizes were small in these studies (490, 697 and 990, respectively) and only the local communities or catchment of an immunization clinic was examined, so the findings were not generalizable to other regions since these communities were very homogeneous in socioeconomic status and access to immunization services.[4-6] Given that the vaccine is not provided through the national immunization program (NIP), varicella vaccination coverage would be expected to vary by economic and other access factors. In order to understand the extent of varicella vaccination uptake province-wide in 2011 and factors associated with uptake, Shandong Provincial Center for Disease Control and Prevention (CDC) analyzed data from a population-based vaccination coverage survey.

Materials and Methods

Shandong province, located 300 miles south to Beijing, is a large coastal province with a combination of urban and less developed rural areas. In 2011, it was ranked third in Gross Domestic Product per capita in China. Since China targets to eliminate measles in 2012, but measles incidence was still high in 2010, in May 2011, Shandong Provincial CDC conducted a cross-sectional study on measles vaccination coverage to collect data for decision-making on measles elimination. The coverage of other vaccines in NIP (Bacille Calmette-Guérin, Diphtheria-Pertussis-Tetanus, hepatitis A, hepatitis B, Japanese encephalitis, meningitis, and polio) among 251,300 children born during

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Table 1. Coverage of the 9 vaccines under study among children aged 16–40 mo in Shandong province, China, 2011

Vaccine	Overall vaccination coverage: % (range)	Coverage by county-level economic development: % (range)			
		Developed	Sub-Developed	Developing	p value
Varicella	62.0 (16.7–94.7)	77.8 (45.3–93.2)	61.0 (35.3–94.7)	47.1 (16.7–77.5)	< 0.001
BacilleCalmette-Guérin*	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	NA
Diphtheria-Pertussis-Tetanus*	99.9 (98.6–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	99.8 (98.5–100.0)	0.23
Japanese encephalitis*	98.1 (75.4–100.0)	99.1 (97.6–100.0)	99.1 (98.0–100.0)	96.4 (75.4–100.0)	< 0.001
Hepatitis A*	96.2 (84.5–100.0)	98.4 (95.2–100.0)	96.7 (94.6–98.4)	93.7 (84.2–100.0)	< 0.001
Hepatitis B*	99.9 (99.3–100.0)	99.9 (99.3–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	0.73
Measles*	97.9 (69.6–100.0)	99.6 (98.7–100.0)	99.8 (99.3–100.0)	95.3 (69.6–100.0)	< 0.001
Meningitis*	97.6 (66.7–100.0)	99.3 (96.0–100.0)	99.3 (98.0–100.0)	95.0 (66.7–100.0)	< 0.001
Polio*	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	NA

*Vaccines included in the National Immunization Program; NA, not available.

2008–2009 (aged 16–40 mo at the time of investigation) was also assessed. Varicella vaccine was added to this study since varicella vaccine is available for private purchase and coverage in the province was unknown. The investigation was conducted in all the 17 prefectures of Shandong province with average eight counties per prefecture. Stratified cluster sampling design recommended from World Health Organization (WHO) was used to select children.[7] In brief, one county was randomly selected in each prefecture from the counties with above average measles incidence during 2008–2010. In each county, five cities and three villages/communities per city were randomly selected with probability proportional to 2010 population size. In each village/community, a total of ten children, five born in 2008 and five in 2009, were enrolled starting with a randomly selected household. The nearest household was interviewed next and the enrollment process continued until the target number of eligible children was reached. Participants' vaccination information came from parent-held immunization cards and immunization clinic records; prior varicella disease history was collected from recall of parents or guardians during interview. Each county was categorized as developed, sub-developed or developing according to the economic development of the prefecture.[8] Distance to the designated immunization clinic (< 5 vs. ≥ 5 km)[9] and rural or urban residency were used as markers of access to immunization services since all vaccines funded publicly or privately were only available in specialized immunization clinics in Shandong province. Pearson chi-square or Mantel-Haenszel chi-square tests were used for univariate analysis to assess the factors associated with varicella vaccine uptake and trend effect if applicable. Multivariable logistic regression models were built to assess the relative contribution of factors potentially associated with varicella vaccine uptake with the full model included all the factors since the number of factors was small (n = 5) whereas the number of subjects was big (n = 2532). The population attributable risk (PAR) was calculated to provide a quantitative assessment of the potential risk factors on vaccine uptake at a population level accounting for the odds ratio (OR) and prevalence of the risk factors in the population. All the analyses were performed with SAS V9.2 (SAS Institute).

Results

After excluding six children with prior disease history, the majority of the 2,532 enrolled children were rural residents (2,044, 80.7%). Among these 2,532 children, 1,327 (52%) were female, 1,264 (50%) were born in 2008, and 895 (35%), 749(30%), and 888 (35%) were from developed, sub-developed and developing regions, respectively. Most (2,095, 82.7%) of the participating children lived within five kilometers of a designated immunization clinic. There was no significant difference between urban and rural residents in whether living within five kilometers of the designated immunization clinic (p = 0.22).

Overall varicella vaccination coverage was 62% with substantial variation by county (range: 16.7–94.7%) (**Table 1**). There was no difference in varicella vaccination coverage between males and females (60.3 vs. 64.0%, p = 0.16). Children from more developed regions were more likely to be vaccinated (77.8, 61.0 and 47.1% in developed, sub-developed and developing regions, respectively, p < 0.001). Urban children were more likely to be vaccinated than rural children (72.1 vs. 59.6%, p < 0.001), as were those living within five kilometers of their designated immunization clinic (62.6 vs. 59.3%, p = 0.02). Children born in 2008 had higher varicella vaccination coverage than those born in 2009 (64.7 vs. 59.4%, p = 0.005) (**Table 2**).

Although urban residency and living within five kilometers of designated immunization clinic were associated with receiving varicella vaccine (OR = 1.5 and 1.3, p < 0.001 and = 0.02, respectively) (**Table 2**), these two factors had low PARs of 7.5 and 4.2%, respectively. Economic development had a PAR of 55% and a dose response effect on varicella vaccine uptake (p < 0.001) with increasing vaccination coverage among children from: developed vs. developing region OR = 3.9 (p < 0.001), and sub-developed vs. developing region OR = 1.7 (p < 0.001).

Coverage with vaccines in NIP was much higher than for varicella vaccine, averaging 98.8% and ranging from 96.2% for hepatitis A vaccine to 100% for Bacille Calmette-Guérin and polio vaccines. Though economic development was found to be significantly associated with receipt of some vaccines (Japanese encephalitis, hepatitis A, measles and meningitis), the absolute differences between developed and developing regions in

Table 2. Potential factors associated with varicella vaccine uptake among children aged 16–40 mo in Shandong province, China, 2011

	Vaccination status		Multivariable logistic regression*	
	Vaccinated (n = 1,571)	Unvaccinated (n = 961)	Odds ratio (95% confidence interval)	p value
Sex				
Female	771 (64.0)	434 (36.0)	1.1 (0.9, 1.3)	0.28
Male	800 (60.3)	527 (39.7)	Reference	
County-level economic development				
Developed	696 (77.8)	199 (22.2)	3.9 (3.1, 4.8)	< 0.001
Sub-developed	457 (61.0)	292 (39.0)	1.7 (1.4, 2.1)	< 0.001
Developing	418 (47.1)	470 (52.9)	Reference	
Residency				
Urban	352 (72.1)	136 (27.9)	1.5 (1.2, 1.9)	< 0.001
Rural	1219 (59.6)	825 (40.4)	Reference	
Distance to designated immunization clinic				
< 5 km	1312 (62.6)	783 (37.4)	1.3 (1.0, 1.6)	0.02
≥ 5 km	259 (59.3)	178 (40.7)	Reference	
Year of birth				
2008	818 (64.7)	446 (35.3)	1.3 (1.1, 1.5)	0.004
2009	753 (59.4)	515 (40.6)	Reference	

*Multivariable logistic regression with variables listed in the table.

vaccination coverage for these vaccines was small, ranging from 0 to 4.7%. The coverage of all vaccines in NIP was above 95% in the developed and sub-developed regions, and only coverage of hepatitis A vaccine was lower than 95% (93.7%) in the developing region (**Table 1**).

Discussion

This study showed that relatively high varicella (62%) vaccination coverage has been achieved among children aged 16–40 mo in Shandong province, although coverage varied substantially by county. Though proximity to immunization services had an effect on varicella vaccine uptake, county-level economic development had a much larger effect on varicella vaccination coverage. Not surprisingly, coverage with vaccines in NIP that are provided without charge was much higher with less variation observed by level of economic development.

Although varicella vaccine is highly effective in reducing disease transmission and preventing varicella and its severe complications, a variety of varicella vaccination strategies have been taken by different countries. The US was the first country to adopt a universal routine two dose varicella vaccination program; while many countries implemented routine universal 1-dose programs. Several countries (e.g., China, Japan and New Zealand) have single dose recommendation for varicella vaccination, with vaccine available for private purchase.[10,11] Our finding of 62% varicella vaccination coverage in Shandong, China is higher than that of Bavaria, Germany (53% in 2008), where varicella immunization has been universally recommended and free of charge since 2004 and Japan, where coverage was 32% in 2005, 18 y after introduction in the private sector.[10,12] Our findings and those from previous studies[4-6] indicate varicella vaccine is well accepted in China, even though currently available only in the private sector at an average cost of 30 USD/dose. The higher vaccination coverage in children born in 2008 than those born in 2009 in current study is also an evidence of well acceptance of varicella vaccine, in that only one more year of eligible time for varicella vaccination could make difference between children born in 2008 and 2009. The same finding is observed in a study in Beijing with increased varicella vaccination coverage when the children were getting older from 2006 to 2010.[13] Given the dramatic increase of varicella vaccine production in China from < 6 million doses in 2007 to > 13 million doses per year thereafter,[14] the varicella vaccination coverage we report in Shandong Province is reasonable, considering annual birth cohort in China is approximately 17–18 million and Shandong is a relatively highly economically developed province in China.

The striking difference in coverage of varicella vaccine and those in the NIP may mainly be driven by financial consideration. Since all vaccines are only distributed by specialized immunization clinics in Shandong province, there should be no difference in access to immunization service for vaccines in public or private sectors for a child, and the high coverage of vaccines in NIP clarifies that immunization service is readily accessible. The little difference in varicella vaccination coverage among children with different distance to immunization clinics also verifies access to immunization service should be not an obstacle for varicella vaccine uptake. The price of varicella vaccine (> 25 USD for domestic varicella vaccine, and > 50 USD for imported varicella vaccine) might be a concern to parents, particularly those in

developing regions, and they are less likely to get their children vaccinated out of pocket there. Moreover, the less likely eligible children get vaccinated, the less likely for the immunization clinic to provide service for varicella vaccination. This vicious feedback loop will reinforce lower vaccination coverage since even parents without concern on cost cannot get their children vaccinated due to unavailable service for varicella vaccination in the designated immunization clinic.

The WHO recommends that varicella vaccine be used on an individual level to protect susceptible adolescents and adults or at a population level to cover all children considering the relative disease burden and program cost compared with other diseases that may be vaccine preventable.[15] Since incomplete vaccination coverage can lead to the accumulation of susceptible adults, who are more prone to develop severe disease if varicella occurs, the WHO recommended that routine varicella vaccination of children should be introduced only if high (85–90%) and sustained coverage can be achieved.[15] Uptake of varicella vaccine on the private market has been brisk in Shandong. If coverage among children remains at 62% and does not continue to rise, a shift in the epidemiology of varicella could occur that would result in an increase in incidence of disease among older individuals. The high cost of varicella vaccine in China may be an obstacle to achieving high enough coverage levels among children necessary to prevent the accumulation of susceptible adolescents and adults, and reliance on private sector purchase alone may not be adequate for achieving coverage levels of 85–90%. Increasing access to immunization services may help, but are unlikely to fully remove economic barriers to varicella vaccination population-wide. Incorporation of varicella vaccine into the NIP may be promising, but challenging since the price of varicella vaccine in China approaches the cost of all vaccines in NIP. Some local governments with adequate budgets may consider incorporating varicella vaccine into their local immunization programs.

Several limitations should be considered in interpreting our findings. The finding of 62% varicella vaccine coverage may be an underestimate since the counties in our study are those with higher than average measles incidence in each prefecture. The high measles incidence indicates the quality of immunization service in the counties under study might not be as good as in those with low measles incidence. Therefore, there is still some room for varicella vaccination coverage to improve if better immunization service is provided. The restriction that only counties with higher than average measles incidence in each prefecture were eligible for enrollment would mitigate the representativeness of our finding. Moreover, the clustering effect from the non-random household selection may affect vaccine uptake since adjacent neighbors may share other factors in common in addition to spatial location.[16] Even though we had accounted for the clustering effect with increased the sample size from 80 (calculated from acceptable lowest measles vaccination coverage as 70%) to 150, we still cannot rule out the potential contribution of clustering effect to vaccine uptake in this study. In addition, immunization cards or records were the only source used for determining vaccination status and may underestimate varicella vaccination coverage as healthcare providers may not record varicella vaccination as consistently as they do for those vaccines included in NIP. Very few children in this study reported a history of varicella disease. The single-child policy and age eligibility for daycare (≥ 3 y) may lead to low disease transmission in this age group. We cannot exclude the possibility of underreporting of varicella disease history, particularly among those whose information on disease was collected from available guardians rather than parents. In addition, we used the regional economic development rather than individual family income as an indicator of economic status, thus further work is needed to understand individual level factors on varicella vaccine uptake in order to develop strategy to increase vaccination coverage and reduce regional disparity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, US. Department of Health and Human Services.

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References

1. Cao H, Du J, Jia Z. Prevalence of Varicella-Zoster Virus Infection in China. Chinese journal of vaccines and immunization 1998; 4:38-40.
2. Atkinson W, Wolfe S. Hamborsky J. Epidemiology and Prevention of Vaccine-Preventable Diseases. 12 ed: Washington DC: Public Health Foundation; 2011.
3. Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. Pediatr Infect Dis J 2010; 29:690-3; PMID:20216242; http://dx.doi.org/10.1097/INF.0b013e3181d7380e.
4. Huang Y, He Y. Analysis on Varicella Vaccination among Children and its Impact Factors in Xixiang Community, Baoan District. Prev Med Trib 2010; 16:1155-7.
5. Tian Z. Investigation on 8 Types of Extra EPI Vaccines in Vaccination Clinic in Henan Oil-field Center for Disease Control and Prevention. Mod Prev Med 2008; 35:327-30.
6. Shen H. Analysis on the Vaccine Coverages in the Children from a Local Community. Mod Med J China 2007; 9:106-7.
7. Henderson RH, Davis H, Eddins DL, Foege WH. Assessment of vaccination coverage, vaccination scar rates, and smallpox scarring in five areas of West Africa. Bull World Health Organ 1973; 48:183-94; PMID:4541684.
8. Chen D, Jiang H. Current Regional Industrial and Economic Difference and Solution in Shandong Province. [Philosophy and Social Sciences]. Journal of Shandong University 1997; 32:100-5.
9. Mitchell S, Andersson N, Ansari NM, Omer K, Soberanis JL, Cockcroft A. Equity and vaccine uptake: a cross-sectional study of measles vaccination in Lasbela District, Pakistan. BMC Int Health Hum Rights 2009; 9(Suppl 1):S7; PMID:19828065; http://dx.doi.org/10.1186/1472-698X-9-S1-S7.
10. Sadzot-Delvaux C, Rentier B, Wutzler P, Asano Y, Suga S, Yoshikawa T, et al. Varicella vaccination in Japan, South Korea, and Europe. J Infect Dis 2008; 197(Suppl 2):S185-90; PMID:18419395; http://dx.doi.org/10.1086/522163.
11. Macartney KK, Burgess MA. Varicella vaccination in Australia and New Zealand. J Infect Dis 2008; 197(Suppl 2):S191-5; PMID:18419396; http://dx.doi.org/10.1086/522157.

12. Streng A, Seeger K, Grote V, Liese JG. Varicella vaccination coverage in Bavaria (Germany) after general vaccine recommendation in 2004. Vaccine 2010; 28:5738-45; PMID:20600490; http://dx.doi.org/10.1016/j.vaccine.2010.06.007.
13. Lu L, Wang C, Suo L, et al. Varicella Disease in Beijing, 2007-2010. In: International Conference on Emerging Infectious Diseases. Atlanta, Georgia; 2012.
14. National Institutes for Food and Drug Control. Accessed August 30, 2011, at http://www.nicpbp.org.cn/CL0108/.
15. Varicella vaccines. WHO position paper. Wkly Epidemiol Rec 1998; 73:241-8; PMID:9715106.
16. Lemeshow S, Robinson D. Surveys to measure programme coverage and impact: a review of the methodology used by the expanded programme on immunization. World Health Stat Q 1985; 38:65-75; PMID:4002731.