Non-specific effect of measles vaccination on overall child mortality in an area of rural India with high vaccination coverage: a population-based case—control study

Zubair Kabir, 1 Jean Long, 2 Vankadara P. Reddaiah, 3 John Kevany, 4 & Suresh K. Kapoor 5

Objective To determine whether vaccination against measles in a population with sustained high vaccination coverage and relatively low child mortality reduces overall child mortality.

Methods In April and May 2000, a population-based, case—control study was conducted at Ballabgarh (an area in rural northern India). Eligible cases were 330 children born between 1 January 1991 and 31 December 1998 who died aged 12–59 months. A programme was used to match 320 controls for age, sex, family size, and area of residence from a birth cohort of 15 578 born during the same time period.

Findings The analysis used 318 matched pairs and suggested that children aged 12–59 months who did not receive measles vaccination in infancy were three times more likely to die than those vaccinated against measles. Children from lower caste households who were not vaccinated in infancy had the highest risk of mortality (odds ratio, 8.9). A 27% increase in child mortality was attributable to failure to vaccinate against measles in the study population.

Conclusion Measles vaccine seems to have a non-specific reducing effect on overall child mortality in this population. If true, children in lower castes may reap the greatest gains in survival. The findings should be interpreted with caution because the nutritional status of the children was not recorded and may be a residual confounder. "All-cause mortality" is a potentially useful epidemiological endpoint for future vaccine trials.

Keywords Measles vaccine; Infant mortality; Treatment outcome; Sensitivity and specificity; Socioeconomic factors; Case-control studies; India (*source: MeSH, NLM*).

Mots clés Vaccin antimorbilleux; Mortalité nourrisson; Evaluation résultats traitement; Sensibilité et spécificité (Epidémiologie); Facteur socio-économique; Etude cas-témoins; Inde (*source: MeSH, INSERM*).

Palabras clave Vacuna antisarampión; Mortalidad infantil; Resultado del tratamiento; Sensibilidad y especificidad; Factores socioeconómicos; Estudios de casos y controles; India (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: لقاح الحصبة، وفيات الأطفال، نتيجة المعالجة، الحساسية والنوعية، عوامل اجتماعية واقتصادية، الهند، دراسة الحالات والشواهد (المصدر: رؤوس الموضوعات الطبية، إقليم شرق المتوسط).

Bulletin of the World Health Organization 2003;81:244-250.

Voir page 248 le résumé en français. En la página 249 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية على الصفحة ٢٤٩.

Introduction

Since 1974, the WHO Expanded Programme on Immunization has led to steady reductions in childhood mortality from vaccine-preventable diseases (1). It also may have increased the levels of life expectancy by over four years, particularly in populations with high mortality (1).

In the late 1970s, measles vaccination produced an overall improvement in child survival, especially in those aged 12–24 months old (2). Subsequent studies of child mortality and measles vaccination status across different populations reported substantial reductions in overall mortality (3–9). For example, all-cause child mortality was reduced by a minimum

of 30% among children who had seroconversion after measles vaccination in populations with high mortality (10). This interesting phenomenon, observed consistently across different populations, was recently termed the "non-specific effect of vaccines" (11, 12), and it is possibly linked to a Th1-type immune response similar to that observed with bacille Calmette–Guérin (BCG) vaccination (13). Recently, Kristensen et al. reinforced this observation in a follow-up study in Guinea-Bissau (14).

Non-specific effects of vaccines, if plausible, may be evident in populations with sustained high vaccination coverage and relatively low child mortality. This study aimed to

Ref No. 02-0250

¹ Research Fellow, Department of Respiratory Medicine, University of Dublin (Trinity College), St James's Hospital, Dublin 8, Ireland (email: kabirz@tcd.ie). Correspondence should be addressed to this author.

² Lecturer in International Health, Department of Community Health and General Practice, Trinity College Centre for Health Sciences, Adelaide and Meath Hospital, Dublin, incorporating the National Children's Hospital, Tallaght, Dublin, Ireland.

³ Professor and Head of Community Medicine, Centre for Community Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

⁴ Associate Professor of Community Health, Department of Community Health and General Practice, Trinity College Centre for Health Sciences, Adelaide and Meath Hospital, Dublin, incorporating the National Children's Hospital, Tallaght, Dublin, Ireland.

⁵ Professor of Community Medicine, Comprehensive Rural Health Services Project, Ballabgarh, AllMS, Haryana, India.

determine the possible long-term effect of measles vaccination on child mortality (from any cause) in a special project area of rural India with high childhood vaccination coverage sustained over a nine-year period (15).

Methods

Setting

Since 1965, the All India Institute of Medical Sciences, New Delhi, in collaboration with the State Government of Haryana had run the Comprehensive Rural Health Services Project at Ballabgarh. In 1999, the population of the 28 villages served by the project was 74 007, with health care provided in line with National Health Service protocols. At the time of the study, two primary health centres each catered for about 37 000 people, and ten multipurpose health workers delivered services in the community. The multipurpose health workers registered births and deaths during routine domiciliary visits. Subsequently, registered infants were visited to encourage vaccination. In addition to continuous collection of routine sociodemographic data, the workers conduct a census in May and June each year.

All the sociodemographic data, including births and deaths in the population served by the two primary health centres, were entered into an electronic database from 1987 to date. Each year, health supervisors randomly selected 20% of households and cross-checked the information collected. In addition, the medical officers in the two primary health centres cross-checked the data for completeness and accuracy in another 5% of households. The electronic database was considered to be complete and accurate from 1991 onwards (15).

Sample size

Sample size was calculated based on a significance level of 0.05, with a power of 80% and an expected odds ratio of 2. Based on these criteria, the estimated sample size, with 25% allowance for confounding, was 381 pairs (16). The sample size was based on 90% measles vaccination coverage (in children aged 12–23 months), which reflected a rare exposure rate of 10% in the study population (the worst-case scenario).

Participants

In April and May 2000, a population-based matched case—control study was conducted. The study population comprised all children aged 12–59 months old from 1991 to 1998, as recorded in the electronic database of the project area. Overall, there were 330 eligible cases and 320 eligible controls. Cases were children born between 1 January 1991 and 31 December 1998 who died aged 12–59 months. The controls were chosen from a cohort of 15 578 children born during the same period and alive at the time of the study. They were individually matched for age, sex, family's size, and area of residence by use of a computerized program specifically written for the purpose.

Age matching for each control was based on the date of birth (with 15 days' deviation) of its matched case. Cases and controls were sex-matched to control for documented inequalities in child mortality by sex (17). Family's size was matched to control because of the possible higher risk of mortality in larger families. Each control was matched to a case from the same village to reduce the possible influence of living conditions and distance from health services. Overall,

318 cases and controls formed matched pairs and were used for matched analysis.

The outcome measured was death of a child aged 12–59 months, and the exposure of interest was failure to receive measles vaccination at the end of the twelfth month of life, as recorded in the database. Children aged >12 months were chosen because the Universal Immunization Programme of India recommends measles vaccine when an infant is aged ten months (18); if administered at this age, the vaccination protects 85% of children from measles infection under normal conditions (19). It is appropriate, therefore, to examine the long-term effects of measles vaccines on child survival in those aged 12–59 months.

Analysis

Analyses were performed using EpiInfo 6.04b software, and odds ratios with 95% confidence intervals (CI) were calculated as the primary measure of effect. Matched-paired analysis was compared with unmatched analysis to confirm whether matching was effective (20). McNemar's χ^2 values were calculated to test the association between the paired proportions. Stratification was performed to control for measured factors. Schlesselman's χ^2 test was estimated to observe effect modification (21). Other measures of association — attributable risk and population attributable risk — were calculated on the basis of documented formulae (22).

The Trinity College Public Health Ethics Committee, Dublin, and the All India Institute of Medical Sciences, New Delhi, India, gave ethical approval for this study.

Results

Overall, 330 deaths (cases) aged 12–59 months were recorded from 1991 to 1998, and 320 eligible controls were identified for individual pairing. In the final analysis, 318 pairs were suitable for the matched-paired analysis. Two controls were excluded by the matched-pair analysis, because they did not fulfil the complete matching criteria for any of the remaining 12 cases.

Table 1 presents the baseline characteristics of the study population. Almost all the socioeconomic and demographic variables available in the database were distributed equally among the cases and controls, although the proportion of illiterate and unskilled fathers was higher in cases than controls (60% vs 40%).

The matched-paired analysis showed a significant association between measles vaccination status and risk of child mortality from any cause (Table 2). The findings indicated that children aged 12–59 months who failed to receive measles vaccination in infancy were three times more likely to die than children vaccinated against measles (crude matched odds ratio, 3; 95% CI, 1.7–5.4; McNemar's $\chi^2=17$; P<0.0001). The unmatched analysis showed that children who failed to receive measles vaccination in infancy were two and a half times more likely to die than children who received measles vaccination (crude unmatched odds ratio, 2.5; 95% CI, 1.4–4.1) (Table 3).

Table 4 shows the relation between child mortality and a child receiving measles vaccination in infancy, stratified by the socioeconomic and demographic characteristics of the study population. The results indicate that the stratum-specific odds ratios for each of the socioeconomic and demographic characteristics differed after stratification. In the lower caste (a proxy for low socioeconomic status in rural India), children who did not receive measles vaccination in

Table 1. Baseline characteristics of the study population aged 12–59 months in Ballabgarh, India, 1991–98. Values are numbers (percentages) unless otherwise specified

Characteristic	Cases	Controls
Mother's mean ± SD ^a age (years)	31.9 (7.5)	30.7 (6.7)
Father's mean ± SD age (years)	30.8 (7.5)	27.8 (6.0)
Mother's literacy skills Literate Illiterate	52 (41) 271 (52)	75 (59) 245 (48)
Father's level of education Started or completed high school Started or completed primary school Illiterate	103 (44) 152 (52) 75 (60)	132 (56) 138 (48) 50 (40)
Mother employed outside the home Yes No	20 (44) 310 (51)	26 (56) 294 (49)
Father's occupation Government employee Farmer or farm labourer Small scale trader (low paid) Unskilled labourer Disability and/or not employed	91 (44) 129 (54) 46 (53) 36 (60) 28 (50)	118 (56) 109 (46) 41 (47) 24 (40) 28 (50)
Caste (proxy for socioeconomic status) Upper Middle Lower	165 (50) 13 (45) 152 (52)	165 (50) 16 (55) 139 (48)

^a SD = standard deviation.

Table 2. Matched-pair analysis to estimate the association between measles vaccination status and child mortality in children aged 12–59 months in Ballabgarh, India, 1991–98

Measles vaccination for cases	Measles vaccination for controls		
	No	Yes	Total
No	12	54	66
Yes	18	234	252
Total	30	288	318
Crude matched odds ratio (95% confidence interval): 3.0 (1.7-5.4)			

infancy were nine times more likely to die than those who received measles vaccination (95% CI, 3.2–27.0). Tests for effect modification (χ^2) suggest that caste was an effect modifier (P=0.0009). After stratification, the adjusted odds ratio was 2.8 (95% CI, 1.8–4.4), which closely corresponded to the unadjusted estimate of 3.0 (95% CI, 1.7–5.4). The attributable risk and population attributable risk were 67% and 27%, respectively.

Discussion

Children aged 12–59 months who lived in an area of rural India and had not undergone measles vaccination during infancy were three times more likely to die from any cause than children who had undergone measles vaccination. Children of low socioeconomic status had the highest risk of mortality, which confirmed the additional influence of poverty on adverse health outcomes observed elsewhere (17). In common with earlier studies (2–9, 14), this study shows a possible non-

Table 3. Unmatched analysis to estimate the association between measles vaccination status and child mortality in children aged 12–59 months in Ballabgarh, India, 1991–98

	Cases	Controls	Total	
No measles vaccination	66	30	96	
Measles vaccination	252	288	540	
Total	318	318	636	
Crude unmatched odds ratio (95% confidence interval): 2.5 (1.5-4.1)				

specific effect of measles vaccination, but here in a population with sustained high vaccination coverage (90% between 1990 and 1998) and relatively low child mortality (15.5 per 1000 live births) (15, 23, 24).

During the period 1991–98, we examined the individual effects of other childhood vaccines (BCG; diphtheria, pertussis, and tetanus (DPT); and polio) on overall mortality in the same study population and did not identify significant associations between not having any one of these vaccines and being more likely to die from any cause between 1–5 years of age (Table 5) (25). In addition, when all the vaccines were taken into the analysis (exposure status defined as "incomplete" primary immunization versus "full" primary immunization), the effect on overall child mortality was similar to the effect of measles vaccine alone (26). These observations suggest that the background immunization coverage of these individual antigens is less likely to contribute to the observed effect of measles vaccination on all-cause child mortality.

The sample size was less than desired, because the electronic database contained complete information only for 1991 onwards. Moreover, the selection criteria based on a 10% exposure rate and 25% allowance for confounding was robust. This is demonstrated by an observed strength of association that was greater than expected (odds ratio of 3 versus 2) and a narrow confidence interval, indicating the power of our study to be greater than 80% (16). The observed estimate was unlikely to have occurred by chance.

The project's public health surveillance system, the study design, and sample selection ensured that selection and recall biases were minimized. These biases were study design limitations acknowledged by others who examined the overall effects of measles vaccine on child mortality. Misclassification when recording measles vaccination status may have occurred, but this was likely to be random across the cases and controls and therefore did not affect the magnitude of association. There was no possibility of misclassifying death.

In the study design, matching was used to control for potential known confounders. Age, sex, and family size were known potential confounders for the association examined. Area of residence was matched to control for the effects of some ill-defined variables, such as physical access to health care. In the analysis, stratification was done to control for confounding and to observe effect modification. The adjusted odds ratio (2.8) corresponded closely to the unadjusted estimate (3.0), indicating that the measured factors (caste, age, literacy, and parents' occupational status) probably were less likely to influence the association observed. The greatest limitation of our study was that only those variables recorded in the electronic database were available for analysis. It is possible, therefore, that the observed beneficial effect is the result of residual confounding due to HIV, vitamin A, and nutritional status.

Table 4. Stratified analyses of socioeconomic and demographic status by measles vaccination in cases and controls aged 12–59 months, Ballabgarh, India, 1991–98. Values are numbers unless otherwise specified

Variables	les No measles Measles vaccination vaccination			Stratum-specific odds ratio ^a	χ ^{2b}	Adjusted odds ratios ^{a, c}	
	Cases	Controls	Cases	Controls	•		
Mother's age (years)						3.5 (0.2)	2.8 (1.8–4.4)
≤20	1	4	3	3	0.2 (0.1–6.4)		
21 to 30	41	20	126	192	3.1 (1.7–5.8)		
>30	35	7	124	94	3.8 (1.5–9.9)		
Father's age (years)						1.7 (0.4)	
≤25	11	8	29	39	1.8 (0.6-5.9)		
26 to 35	48	20	157	189	2.9 (1.6-5.3)		
>35	18	3	67	61	5.5 (1.4–24.9)		
Mother's literacy skills						0.7 (0.4)	
Literate	21	9	38	66	4.0 (1.5–10.8)	o., (o.,,	
Illiterate	56	22	215	223	2.6 (1.5–4.7)		
Father's level of education						0.8 (0.6)	
High school	25	15	78	117	2.5 (1.2–5.4)	0.0 (0.0)	
Primary school	37	11	115	127	3.7 (1.7–8.2)		
Never attended school	15	5	60	45	2.2 (0.7–7.8)		
Mother employed outside the home						0.0 (0.9)	
Yes	4	2	16	24	3.0 (0.4-27.6)	(,	
No	73	29	237	265	2.8 (1.7–4.6)		
Father's occupation						4.3 (0.4)	
Government employee	16	11	75	107	2.1 (0.8-5.1)	,	
Farmer or farm labourer	34	10	95	99	3.5 (1.6–8.2)		
Small scale trader	8	1	38	40	8.4 (0.9–191.0)		
Unskilled labourer	11	2	25	22	4.8 (0.8–36.1)		
Disability and/or not employed	8	7	20	21	1.2 (0.3–4.6)		
Caste						9.3 (0.0009)
Upper	37	23	128	142	1.8 (0.9-3.3)	,	
Middle	2	3	11	13	0.8 (0.1–7.7)		
Lower	38	5	114	134	8.9 (3.2–27.0)		

^a Numbers in parentheses are 95% confidence intervals.

Table 5. Association between immunization coverage of bacille Calmette–Guérin; diphtheria, pertussis, and tetanus; and polio vaccines on overall child mortality (children aged 12–59 months) in Ballabgarh (1991–98)

Vaccine	Odds ratio			
	Adjusted	Unadjusted		
Bacille Calmette–Guérin	1.1 (0.7, 1.9)	1.0 (0.5, 1.8)		
Diphtheria, pertussis, and tetanus	1.7 (1.0, 2.7)	1.6 (0.9, 2.8)		
Polio	1.4 (0.8, 2.3)	1.2 (0.7, 2.2)		

^a Source: Kabir, 2001 (25).

In 2002, the estimated prevalence of HIV in the area was less than 1% (Kapoor SK, personal communication, 2002). The study area is a stable population with little migration. In India, the prevalence of HIV is concentrated in high-risk groups, such as injecting drug users, commercial sex workers, and migrant populations (27). It is unlikely, therefore, that HIV was an unidentified factor that accounted for the observed association in this study.

The effect of childhood vitamin A supplementation as a possible confounder was also considered. In India, a

supplement of vitamin A was administered along with measles vaccination after the ninth month and continued every six months until the child was aged three years (18). Studies have shown an association between vitamin A supplementation and child survival (28-30). The protective effect of vitamin A supplementation on all-cause mortality is highest within the first year of life and is not significant beyond infancy (29). Vitamin A supplementation has not been shown to have a protective effect on morbidity (31), as supplementation reduces severity but not incidence of infections (32). Recent evidence shows long-term enhancement of measles-specific antibody levels in children who have simultaneous administration of vitamin A and measles vaccine after the ninth month (33), although there is no documented evidence of a similar effect on the cell-mediated response in measles-vaccinated individuals (34). These variations suggest that vitamin A supplementation is less likely to have a non-differential effect on the outcome of the study population.

In India, the proportion of underweight children aged 0-5 years decreased by 10% between 1990 and 2000 (35,36). This indicates an improvement in the nation's nutritional status over the study period, and we assume that the proportion of underweight children had also decreased in the study area over

 $^{^{\}mathrm{b}}$ Schlesselman's test for effect modification, numbers in parentheses are P-values.

^c Adjusted to the exposed population, calculated as $\Sigma a / \Sigma b c / d$.

the same time period. The authors cannot deny that nutritional status may be a residual confounder in this study, although the likelihood of effect modification is reduced by evidence that suggests that hypoproteinaemia has little or no effect on the immune response to routine childhood vaccines (37, 38).

The uptake of vaccination among children aged 12-23 months for each antigen (BCG, DPT, polio, and measles) was consistently higher than 90% over the previous ten years (15, 23), and the child mortality among children aged 12-59 months was relatively low (15.5 per 1000 live births) (15, 24). In the study area, no data were available on beliefs and attitudes among parents who failed to have their children immunized, but no special characteristics that might be associated with non-vaccination were identified in the families or communities. Cost was not a factor, because routine vaccines were available free of charge to all eligible children, parents' literacy level was not a determinant (Table 4), and, as a result of weekly house-to-house visits by each health worker, parents in the project area did not lack adequate information on vaccination, consistent with evidence elsewhere (39). Further investigations are needed to identify attitudes or beliefs, as are quantitative studies that may influence vaccination uptake (40).

We showed that since 1985, when measles vaccine was introduced in the study area, the total number of deaths among children aged 12-59 months decreased from 221 (in 1982-84 cohort) to 85 (in 1995–96 cohort) (24, 41, 42). Between the two cohorts, the proportional contributions of three common causes of child deaths — malnutrition, diarrhoea, and acute respiratory infections — were also reduced (from 23% to 19%, 22% to 16%, and 24% to 8%, respectively). Between 1991 and 1999, accidents accounted for a small proportion (4%) of deaths among children aged 0-59 months, but two-thirds of all deaths of children were from infectious conditions (26). During the study period (1991-99), two reported deaths resulted from measles infection among children aged 0-59 months (15, 24), but no measles outbreaks were reported. These time-trend observations further support the possible beneficial nonspecific effect of the measles vaccine, especially on infectious causes for child deaths.

The calculated population-attributable risk indicates that almost 27% of the child deaths in the study population could have been prevented had the birth cohorts been vaccinated against measles before their first birthdays; this assumes a cause–effect relation. As expected, the observed population attributable risk was lower than other case–control studies completed in populations with high mortality (3, 4).

Conclusions and implications

Measles vaccine seems to have an unspecified favourable effect on overall child mortality in the area. If true, children in lower castes may reap the greatest gain in survival. This observation may also apply to other countries where the major causes of child deaths are infectious conditions. The findings should be interpreted with caution, as the nutritional status of the children was not recorded and may be a residual confounder.

The limitations of a case–control study mean that any robust observations are best shown through randomized controlled trials. However, large vaccine trials may be inappropriate ethically for routine vaccines for which effectiveness is already well established. The lack of evidence about the overall effect of vaccines can lead to serious errors, as observed previously (43, 44). Future vaccine trials can use "allcause mortality" as an epidemiological endpoint, which also has potential utility as an important marker in economic evaluations (45).

Non-specific effects, if biologically plausible, may be important for our further understanding of the causal pathway of targeted diseases (45). Non-specific effects of vaccines merit attention in resource-poor countries not only for the formulation of effective vaccination schedules in the future, but also to guide policy-makers to more evidence-based policies to control infectious diseases.

Acknowledgements

This study was completed as part of an MSc in Community Health at the University of Dublin in 2000 with the support of the Comprehensive Rural Health Services Project, All India Institute of Medical Sciences, New Delhi, India. We thank the following people from the institute for their help: Mr G. Kumar for creating the computerized matching programme and Dr K. Anand for his supportive advice. The authors thank the staff at the Department of Community Health, Trinity College, Dublin, particularly Dr S. Allwright, Dr A. Kelly, and Ms D. Handy. Finally, we thank the reviewers' for their valuable comments.

Funding: This study was made possible by financial support from the Ireland Aid Programme, Department of Foreign Affairs, Ireland.

Contributors: All authors developed the protocol for the study. ZK was an MSc student in the department at the time of the study and completed the data collection. All authors contributed to the analysis plan. ZK carried out the analysis with JL. ZK and JL drafted the paper with contributions from JK, VR, and SK. ZK is guarantor for the paper.

Conflicts of interest: ZK worked as a Medical Officer in the Ballabgarh Project Area before completing his MSc. Part of the findings were presented at the sixteenth World Congress of Epidemiology, International Epidemiological Association, Montreal, Canada, 2002.

Résumé

Effet non spécifique de la vaccination antirougeoleuse sur la mortalité globale de l'enfant dans une région rurale de l'Inde bénéficiant d'une bonne couverture vaccinale : étude cas-témoins en population

Objectif Déterminer si la vaccination antirougeoleuse pratiquée dans une population où la couverture vaccinale est régulièrement forte et où la mortalité de l'enfant de 12 à 59 mois est relativement faible réduit la mortalité globale dans cette tranche d'âge.

Méthodes En avril et mai 2000, une étude cas-témoins en population a été réalisée à Ballabgarh, une zone rurale du nord de l'Inde. On a retenu comme cas 330 enfants nés entre le 1^{er} janvier 1991 et le 31 décembre 1998 et décédés à l'âge de 12 à 59 mois.

On a sélectionné à l'aide d'un programme 320 témoins appariés sur l'âge, le sexe, la taille de la famille et la zone de résidence à partir d'une cohorte de naissance de 15 578 enfants nés pendant la même période.

Résultats L'analyse a porté sur 318 paires de cas et témoins et a indiqué que chez les enfants de 12 à 59 mois qui n'avaient pas été vaccinés contre la rougeole dans la première enfance le risque de décès était trois fois plus élevé que chez les enfants vaccinés. Les enfants des ménages appartenant à une caste inférieure et non vaccinés avant l'âge d'un an avaient le risque de mortalité le plus élevé (odds ratio : 8,9). Une augmentation de 27 % de la mortalité

des 12-59 mois a été attribuée à l'insuffisance de la vaccination antirougeoleuse dans la population d'étude.

Conclusion Le vaccin antirougeoleux semble avoir un effet réducteur non spécifique sur la mortalité globale de l'enfant dans cette population. Si cette observation se vérifie, le gain en termes de survie pourrait être maximal chez les enfants des castes inférieures. Ces résultats doivent être interprétés avec prudence car l'état nutritionnel des enfants n'était pas noté et pourrait constituer un facteur de confusion. La « mortalité toutes causes confondues » est un paramètre épidémiologique d'une grande utilité potentielle pour les futurs essais de vaccins.

Resumen

Efecto inespecífico de la vacunación antisarampionosa en la mortalidad infantil global en un área de la India rural con alta cobertura de vacunación: estudio de casos y controles basado en la población

Objetivo Determinar si la vacunación contra el sarampión en una población con una cobertura vacunal alta y sostenida y una mortalidad infantil relativamente baja reduce la mortalidad global en la infancia.

Métodos En abril y mayo de 2000 se llevó a cabo en Ballabgarh, un área rural del norte de la India, un estudio de casos y controles basado en la población. Se seleccionó como casos a 330 niños nacidos entre el 1 de enero de 1991 y el 31 de diciembre de 1998 que habían muerto a los 12–59 meses de edad. Se utilizó un programa para emparejarlos con 320 controles de edad, sexo, tamaño de familia y área de residencia parecidos, extraídos de una cohorte de nacimiento de 15 578 nacidos durante el mismo periodo. **Resultados** Según el análisis realizado con 318 pares concordes de casos y controles, los niños de 12–59 meses que no recibieron vacunación antisarampionosa durante la lactancia presentaban el

triple de probabilidades de morir que los vacunados contra el sarampión. Los niños de los hogares de castas bajas a los que no se vacunó en la lactancia son los que presentaban el riesgo más alto de defunción (razón de posibilidades: 8,9). Un aumento del 27% de la mortalidad infantil observada en la población estudiada era atribuible a la falta de vacunación contra el sarampión.

Conclusión La vacuna antisarampionosa parece tener un efecto inespecífico de disminución de la mortalidad global en la infancia en esta población. Si ello es cierto, los niños de las castas inferiores serían los que más podrían beneficiarse en términos de supervivencia. Los resultados deben interpretarse con cautela, pues no se registró el estado nutricional de los niños, que podría ser un factor de confusión residual. La «mortalidad por todas las causas» puede ser un valioso criterio de valoración epidemiológico en los futuros ensayos de la vacuna.

ملخص

التأثير غير النوعي للتطعيم ضد الحصبة على المعدلات العامة لوفيات الأطفال في أرياف الهند التي يرتفع فيها معدلات التغطية بالتطعيم؛ دراسة للحالات والشواهد مُرْتكِزة على السكان

والذين لم يتلقوا لقاح الحصبة في فترة رضاعتهم معرضون لخطر الموت ثلاثة أضعاف ما عليه أترابهم الذين تلقوا لقاح الحصبة. وكان لدى الأطفال من بين السكان من الطبقة الأدنى والذين لم يتلقوا تطعيماً في فترة رضاعتهم أعلى معدلات خطر الموت (نسبة الأرجحية ٩,٨). وقد عُزِيَت الزيادة التي بغت ٢٧٪ في معدلات الوفيات بين الأطفال إلى الفشل في التطعيم ضد الحصبة في المجموعة المدروسة.

الاستنتاج: يبدو أن للتطعيم ضد الحصبة أثراً غير نوعي منقصاً للمعدلات العامة لوفيات الأطفال في المجموعة المدروسة، وإذا كان هذا الاستنتاج صحيحاً فإن أطفال الطبقات الدنيا سيجنون القسط الأكبر من المكاسب في البقاء على قيد الحياة. وينبغي النظر إلى هذه النتيجة بحذر لأن الحالة التغذوية للأطفال لم تسجل، وقد تكون من العوامل المتداخلة المؤثرة. وقد يكون «معدل الوفيات الناجمة عن جميع الأسباب» هو النقطة المفيدة من وجهة النظر الإبيديمولوجية لمعرفتها في الدراسات المستقبلية

الغرض: هدفت الدراسة لمعرفة فيما إذا كان التطعيم ضد الحصبة للسكان بمعدلات تغطية عالية ومعدلات وفيات أطفال منخفضة سيساهم أيضاً في خفض معدلات وفيات الأطفال.

الطريقة: تم إجراء دراسة للحالات والشواهد مُؤتكِزة على السكان في بلابغراه (وهي منطقة ريفية تقع شمالي الهند) وذلك في شهري نيسان/إبريل وأيار/مايو ٢٠٠٠. وكانت الحالات المؤهلة للإدراج في الدراسة ٣٣٠ طفلاً ولدوا في الفترة بين الأول من كانون الثاني/يناير ١٩٩١ و٣١ كانون الأول/ديسمبر ١٩٩٨ وماتوا في عمر يتراوح بين ١٢ و٥٩ شهراً. وتم استخدام برنامج حاسوبي لتحديد ٣٢٠ حالة من الشواهد التي توافق الحالات للدروسة من حيث العمر والجنس وحجم العائلة ومكان الإقامة، وذلك من بين الأتراب المولودين في نفس الفترة والذين بلغ عددهم

الموجودات: تناول التحليل ٣١٨ من الأزواج المتوافقين من الأطفال، وتشير النتائج إلى أن الأطفال الذي تراوحت أعمارهم بين ١٢ – ٢٩ شهراً

References

- Matthews Z, Diamond I. The Expanded Programme on Immunization: mortality consequences and demographic impact in developing countries. *Genus* 1999:55:73-100.
- The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35 month old children in Kasongo, Zaire. Lancet 1981:1:764-7.
- Clemens JD, Stanton BF, Chakraborty J, Chowdhury S, Rao MR, Ali M, et al. Measles vaccination and childhood mortality in rural Bangladesh. *American Journal of Epidemiology* 1988;128:1330-9.
- Koeing MA, Khan MA, Wojtynink B, Clemens JD, Chakraborty J, Fauveau V, et al. The impact of measles vaccination upon childhood mortality in Matlab, Bangladesh. *Bulletin of the World Health Organization* 1990;68:441-7.
- Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;85:188-94.
- Velema JP, Alihonou EM, Gandaho T, Hounye FH. Childhood mortality among users and non-users of primary health care in a rural West African community. *International Journal of Epidemiology* 1991;20:474-9.
- Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, Fernandes M. Reduced childhood mortality after standard measles vaccination at 4-8 months compared with 9-11 months of age. *BMJ* 1993;307:1308-11.
- 8. Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, Bennett J, et al. Sex-specific mortality after high titre measles vaccines in rural Senegal. *Bulletin of the World Health Organization* 1994;72:761-70.
- Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, Simondon F, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *International Journal of Epidemiology* 1996;25:665-73.
- Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, Helm-Peterson NC, et al. Child mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatric Infectious Disease Journal* 1989;8:197-200.
- Shann F. Non-specific effects of vaccines in developing countries. BMJ 2000;321:1423-4.
- Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H. Non-specific beneficial effect of measles immunisation: an analysis of mortality studies from developing countries. *BMJ* 1995;311:481-5.
- Marchant A, Goetghebuer T, Ota M, Wolfe I, Ceesay SJ, de Groote D, et al. Newborns develop a T helper 1 type response to BCG vaccination. *Journal of Immunology* 1999;163:2249-55.
- Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. BMJ 2000;321:1435-9.
- Anand K, Kant S, Kumar GK, Kapoor SK. "Development" is not essential to reduce infant mortality rate in India: experience from the Ballabgarh project. *Journal of Epidemiology and Community Health* 2000;54:247-53.
- Cousens SN, Mertens TE, Kirkwood BR, Smith PG, Feachem RGA. Case-control studies of common childhood diseases: the example of diarrhoea. London: Macmillan Education; 1995. p.124-7.
- Stanton BF, Clemens JD. The influence of gender on determinants of urban childhood mortality in Bangladesh. *International Journal of Epidemiology* 1988:17:129-35.
- Kishore J. National health programmes of India. New Delhi: Century Publication; 2000.
- Clements CT, Strassbourg M, Cutts FT. The epidemiology of measles. World Health Statistics Quarterly 1992;45:285-91.
- Rosner B, Hennekens CH. Analytic methods in matched pair epidemiologic studies. *International Journal of Epidemiology* 1978;7:367-72.
- 21. Schlesselman JJ. *Case-control studies. Design, conduct, analysis.* New York: Oxford University Press; 1982. p.194.
- 22. Hennekens CH, Buring JE. *Epidemiology in medicine*. Boston: Little, Brown and Company; 1987. p.30-98.
- 23. Anand K, Kant S, Kumar G, Kapoor SK. Thirty year trend (1967-1996) in prevalence of poliomyelitis and vaccine coverage in Ballabgarh, Haryana, India. *Journal of Epidemiology and Community Health* 1998;52:823-5.

- Kabir Z, Long J. Child mortality rates in rural India: an experience from the Ballabgarh project. *Journal of Tropical Pediatrics* 2002;48:178-80.
- Kabir Z, Kevany J. Non-specific effects of routine vaccines on child mortality: a case-control study. *Paediatric and Perinatal Epidemiology* 2001;15:A17-8.
- Kabir Z. The relationship between primary immunisation and child mortality (1991-1999) in rural India: a case-control study [MSc dissertation]. Dublin: University of Dublin (Trinity College); 2000.
- Mukhopadhyay C, Nath G, Gulati AK, Mohapatra SC. Prevalence of HIV among low and high risk population of eastern part of northern India. *Journal of Communicable Diseases* 2001;33:136-42.
- Herrera MG, Nestel P, el Amin A, Fawzi WW, Mohamed KA, Weld L. Vitamin A supplementation and child survival. *Lancet* 1992;340:267-71.
- 29. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: a meta-analysis. *JAMA* 1993;269:898-903.
- Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D, et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *Journal of Pediatrics* 1996;128:489-96.
- Abdeljaber MH, Monto AS, Tilden RL, Schork MA, Tarwotjo I. The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. *American Journal of Public Health* 1991;81:1654-6.
- 32. Arthur P, Kirkwood B, Ross D, Morris S, Gyapong J, Tomkins A, et al. Impact of vitamin A supplementation on childhood morbidity in northern Ghana.
- Benn CS, Balde A, George E, Kidd M, Whittle H, Lisse IM, et al. Effect of vitamin A supplementation on measles-specific antibody levels in Guinea-Bissau. *Lancet* 2002;359:1313-4.
- Nauss KM. Influence of vitamin A status on the immune system. In: Bauernfeind JC, editor. Vitamin A deficiency and its control. Orlando (FL): Academic Press; 1986.
- 35. UNDP Human Development Report. New York: Oxford University Press; 1994.
- 36. UNDP Human Development Report. New York: Oxford University Press; 2001.
- Greenwood BM, Bradley-Moore AM, Bradley AK, Kirkwood BR, Gilles HM.
 The immune response to vaccination in undernourished and well-nourished Nigerian children. *Annals of Tropical Medical Parasitology* 1986;80:537-44.
- Shann F. Hypoproteinaemia and the effects of infections and vaccines. BMJ 2001. Available at: URL: http://bmj.com/cgi/eletters/321/7274/1423#12419
- Brugha RF, Kevany J. Maximizing immunization coverage through home visits: a controlled trial in an urban area of Ghana. *Bulletin of the World Health Organization* 1996;74:517-24.
- Roberts KA, Woods MD, Fitzpatrick R, Abrams KR, Jones DR. Factors affecting uptake of childhood immunisation: a Bayesian synthesis of qualitative and quantitative evidence. *Lancet* 2002;360:1596-9.
- Reddaiah VP, Lobo J, Kapoor SK, Nath LM. Comprehensive rural health services project, Ballabgarh: trends in under-five mortality. *Indian Journal of Pediatrics* 1988:55:287-94
- 42. Kapoor SK, Reddaiah VP. Effectiveness of measles immunisation on diarrhoea and malnutrition related mortality in 1-4 year olds. *Indian Journal of Pediatrics* 1991:58:821-3.
- 43. Aaby P, Knudsen K, Whittle H, Knudsen K, Thaarup J, Poulsen A, et al. Long-term survival after Edmonston-Zagreb measles vaccination: increased female mortality. *Journal of Pediatrics* 1993;122:904-8.
- 44. Shann F. Pneumococcal vaccine: time for another controlled trial. *Lancet* 1998;351:1600-1.
- Kabir Z. Is all-cause mortality a useful epidemiological endpoint in vaccine trials? An example of BCG. *International Journal of Epidemiology* (forthcoming).