RISK FACTORS AND LEPROSY INCIDENCE AMONG CONTACTS IN BANGLADESH: A MULTILEVEL ANALYSIS

Context

The Maltalep trial in Bangladesh assessed whether single-dose rifampicin (SDR) given after bacillus Calmette–Guérin (BCG) vaccination was able to prevent possible excess leprosy cases due to BCG in contacts of newly diagnosed leprosy patients. Simultaneously, a (non-randomized) non-intervention cohort of new patients was followed to establish incident cases among their contacts.

Objectives

To 1) establish new (incident) leprosy cases among contacts over a five-year period in both the Maltalep intervention trial and the non-intervention cohort, and 2) to perform an in-depth analysis of the relationship between leprosy incidence and associated risk factors, applying data from both the intervention trial and non-intervention cohort.

Study site

The Rural Health Program of The Leprosy Mission International in northwest Bangladesh.

Study design

The Maltalep trial was a single center cluster randomized controlled trial consisting of two arms. In one arm, SDR was given 8-12 weeks after BCG vaccination (SDR+), in the other arm no SDR was given after vaccination (SDR-). The non-interventional cohort is a prospective observational study.

Study participants and outcome

Eligible contacts of newly diagnosed leprosy (index) patients. The main outcome measure is the incidence rate of leprosy per 10,000 population at risk among contacts during a 5-year observation period.

Results

The Maltalep trial included 1,553 index patients. Of these, 14,986 eligible contacts were randomized into two arms of the trial. During a five-year observation period, 95 and 100 new cases appeared among the contacts in two arms SDR- and SDR+, respectively. Overall, there was no statistically significant difference in the incidence of leprosy between the

contacts of the two arms of the trial. The non-intervention cohort included 554 index patients and 4,216 eligible contacts, with a total of 82 new leprosy cases appearing over the five-year observation period. In comparing the Maltalep trial (both arms taken together) with the non-intervention cohort adjusted for observed factors, the odds ratio of the incidence was statistically significantly 1.33 times higher in the contacts of the non-intervention cohort.

After adjusting for observed covariates in multilevel analysis, the total unobserved variation in leprosy outcome was 45% for the differences between index patients, and 63% for the differences between contacts within the same index patient group. Regarding observed risk factors, contacts of multibacillary (MB) and slit skin smear (SSS) positive index patients, and contacts of 'blood-related other' to index patients in the intervention arm (SDR+) were statistically significantly less likely to develop leprosy than contacts in the SDR- arm of leprosy classification MB and SSS positive score of index patients, and 'blood-related other' contacts to index patients. There was a larger contribution of genetic and physical distance to the index patients to the development of leprosy in the contacts, as compared to the logistic regression analysis. Contacts with higher age were at increased risk of leprosy.

Conclusions and recommendations

There is no clear added benefit of providing SDR to reduce the number of excess leprosy cases after vaccination with BCG as preventive intervention among contacts of leprosy patients. We confirmed the protective effect of BCG vaccination of contacts in preventing leprosy. The SDR intervention was effective for the contacts of MB patients, smear positive index patients, and contacts of index patients that are blood related in the second degree (e.g. cousins, etc.). Genetic relationship is a more profound risk factor for leprosy in contacts than being a household contact only. Unobserved heterogeneity in leprosy outcome influences the effect of risk factors, such as the age of contacts and genetic relationship of contact to the index case. Therefore, to address the omitted variable problem, it is important to adjust for unobserved heterogeneity in the outcome analysis.

Multilevel analysis of potential risk factors and leprosy incidence in the contacts of the Maltalep trial after SDR was given, N=14,547.

Variables	Model 1		Model 2		Model 3		Model 4	p-value
Intervention	AORs	p-value	AORs	p-value	AORs	p-value	AORs	
SDR-	1				1		1	
SDR+	1.08 (0.81-1.43)	0.60	1.30 (0.38-4.44)	0.67	1.16 (0.76-1.79)	0.49	1.85 (0.49-7.09)	0.37
Age of contacts								
5-14	1				1		1	
15-29	1.65 (1.08-2.54)	0.02	1.84 (1.03-3.26)	0.04	1.89 (1.06-3.38)	0.03	2.36 (1.02-5.49)	0.05
30-44	2.19 (1.42-3.36)	0.00	1.69 (0.91-3.14)	0.10	2.90 (1.51-5.57)	0.00	2.20 (0.88-5.46)	0.09
44+	2.12 (1.38-3.25)	0.00	2.44 (1.38-4.31)	0.00	2.74 (1.4-5.25)	0.00	3.54 (1.45-8.67)	0.01
Leprosy classification of index patients								
Paucibacillary (PB1-5)	1				1		1	
Multibacillary (MB)	1.42 (1.05-1.92	0.04	1.96 (1.25-3.07)	0.00	1.62 (0.99-2.64)	0.05	2.69 (1.33- 5.43)	0.01
Genetic distance to index patients								
Not blood-related	1		1		1		1	
Blood-related (Brother/sister, child, parent)	2.36 (1.66-3.35)	0.00	2.87 (1.71-4.84)	0.00	3.30 (1.80-6.04)	0.00	4.75 (1.98-11.39)	0.00
Blood-related other	1.54 (1.06-2.24)	0.04	2.36 (1.38-4.03)	0.00	1.71 (1.01-2.88)	0.05	3.29 (1.37-7.90)	0.01
Physical distance to index patients								
Not a household member	1		1		1		1	
Household member (KR)	1.59 (1.08-1.35)	0.02	1.92 (1.14-3.24)	0.01	1.84 (1.05-3.22)	0.03	2.78 (1.29-6.02)	0.01
Interaction with SDR+								
Multibacillary	-		0.52 (0.28-0.96)	0.04	-		0.38 (0.15--0.96)	0.04
Genetic distance (blood-related other)	-		0.43 (0.20-0.93)	0.03	-		0.29 (0.09-0.95)	0.04
Sample size [a]	14,543		14,543		14,543		14,543	
Used IPW	yes		yes		yes		yes	
Loglikelihood	-1005.51		-995.86		-986.67		-978.85	
Parameter	14		23		14		25	
AIC	1983.56		1943.72		1944.82		1907.70	
ICC between index patients	-		-		0.42		0.45	
ICC between contacts within same index patient	-		-		0.59		0.63	

Note

ICC Intra-cluster correlation; IPW Inverse probability weight. AIC Akaike Information Criteria; Adjusted risk factors for age of index patients, gender of both contacts and index patients, occupation of index patients as labour and associated interaction terms.

Results of logistic regression analysis, Maltalep trial and Non-intervention cohort

Variable	Multalep trial vs non-intervention cohort (n=19,202)		
	Odds ratios	CIs	p-values
Intervention arm			
Maltalep trial	1		
Non-intervention cohort	1.33	1.01-1.73	0.04
Age of contacts (years)			
5-14	1		
15-29	1.30	0.91-1.85	0.16
30-44	1.91	1.33-2.73	0.00
44+	1.85	1.29-2.63	0.00
Genetic distance to index patients			
Not blood related (or unknown)	1		
Blood-related (brother/sister/child/parent)	2.02	1.50-2.73	0.00
Blood-related (other)	1.36	0.97-1.88	0.07
Physical distance to index patients			
Not a household member	1		
Household member (sharing roof and kitchen)	1.56	1.14-2.13	0.01
Age of index patient (years)	0.99	0.98-0.99	0.01
Leprosy classification index patient			
PB	1		
MB	1.38	1.07-1.78	0.01
Occupation index patient			
Others	1		
Daily labour	1.30	0.91-1.85	0.15

BCG scar of index patient was not available in the dataset of non-intervention cohort, thus not included in the analysis. Analysis was adjusted for gender of both contacts and index patient.