The Effects of Aerial Spraying with *Bacillus thuringiensis* *Kurstaki* on Children with Asthma

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ABSTRACT

Objective: To determine if aerially spraying a biological pesticide was associated with an increase in the symptoms or change in the Peak Expiratory Flow Rate of children with asthma.

Methods: A pre/post matched pairs cohort design was used. Children living in the spray zone were matched with children outside of the spray zone. Peak Expiratory Flow Rates, asthma symptoms and non-asthma symptoms were recorded in diaries.

Results: There were no differences in asthma symptom scores between subjects and controls, neither before nor after the spray; nor were there significant changes in Peak Expiratory Flow Rates for subjects after the spray period.

Conclusions: No evidence of adverse effects from the use of the biological pesticide was found. We believe that this is the first paper to address the issue of whether or not aerial spraying with Btk has a harmful effect on children with asthma.

The translation of the Abstract appears at the end of the article.

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The Research Review and Ethics Committee of the Capital Health Region granted approval for this research.

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As a result of an infestation of the North American Gypsy Moth in Southern Vancouver Island, British Columbia, the Provincial Government ordered an eradication program to avert a potential quarantine of the region. A bacterial pest control product called Foray 48B (manufactured by Abbott Laboratories) was applied by aerial spray. Foray 48B contains the bacteria *Bacillus thuringiensis* subspecies *Kurstaki* HD1 (Btk-HD1) as the active ingredient.¹ Three applications were made at 10-day intervals. A DC6 airplane flying at an altitude of 61 metres sprayed the product at design coverage of 4.0 litres per hectare. The product was applied during early morning hours on dry days.

Surveillance for human disease was conducted during aerial sprays in the United States (Washington and Oregon States), Canada (BC) and New Zealand.²⁻⁶ Despite extensive use (> 30 years and millions of litres applied) and the opinion of regulatory agencies that *B. thuringiensis*-based pesticides pose no significant risks to people,⁷ concerns regarding human health effects can be found in the public and in the scientific literature.^{8,9}

The objective of this study was to determine if spraying with Foray 48B was associated with an increase in the symptoms or change in the Peak Expiratory Flow Rate (PEFR) of children with asthma living within the spray zone. These subjects were selected as a potentially high-risk group because some of the responses of animals¹⁰ and some exposed people¹¹⁻¹³ to Btk has led to the suggestion that people with hypersensitivity conditions, such as asthma, may be at increased risk during aerial sprays. These reports indicate that animal responses were limited to lethality from toxicity at high dose (>10⁸ CFU per animal). Immune and hypersensitivity reaction reports are based mainly on production worker exposures with preexisting conditions.

METHODS

The Research Review and Ethics Committee of the Capital Health Region approved the study design. Informed written consent was obtained from a parent of each participant. Study participants were recruited from the Pediatric Asthma, Allergy, and Eczema (AAE) Program of the Capital Health Region, Victoria, BC.

Participants were followed from 1 week before the first spraying (on May 8 and 9, 1999) until 5 days after the third (and last) spraying (on June 7 and 8, 1999). Children from within the spray area were matched on gender and age with a control from outside the spray areas. The age matching was within 2 years, except that the age limits of 6 and 15 years were not exceeded. The controls were also recruited from the AAE Program.

The children, supervised by their parents, recorded symptoms daily in a diary developed by the Alberta Asthma Centre.¹⁴ Peak Expiratory Flow Rates were measured using a Truzone™ peak flow meter that was already familiar to most of the children, and recorded in a chart in the diary. The Truzone™ meets the technical standards of spirometry for portable peak flow meters established by the American Thoracic Society. Although there are significant differences in accuracy between meters, reproducibility and interdevice variability are relatively consistent between different devices.¹⁵

Two additional questionnaires were used. One was completed at the start of the study and covered such items as the past history of the child's asthma, medication use, and potential allergens or triggers in the home. The second questionnaire asked about other, mainly non-asthmatic symptoms that the child might have and was completed before and after each spray. A symptom score was calculated using a daily maximum score of 9 for questions A, B, C (see Table II for question descriptions). A daily maximum of 2 was scored for questions D and E. The scores were standardized using [Total score]/Number of days contributing to the score].

The primary determinant of exposure was whether or not the participant's residence was inside the spray zone. The spray zone was adjacent to the control zone separated by a 1 km no spray or buffer zone. Two other measures of exposure were also used. A Kromecote card (used to measure droplet deposition)¹⁶ was placed outdoors at the residence of each study participant on the evening before a spray took place. A nasal swab was taken from just inside the external nares of each participant on the evening before each spray, and a further swab was taken approximately 2 hours after the spray.^{16,17} All participants were

TABLE I

Characteristics of Subjects Within the Spray Zone, Controls, and Those Who Refused to Participate or Withdrew from the Study

	Subjects n = 29 (%)	Controls n = 29 (%)	Refused/Withdrew n = 38 (%)
Gender (# males)	19/29 (male 64)	19/29 (male 64)	18/38 (male 47)
Mean age (years)	9.79	9.84	10.4
Mean # hospitalizations or ER visits	9.0	11.4	6.4
Mean # hospitalizations in past year	0.97	1.17	N/A
Daily use of inhaler			
Corticosteroid	14 (48)	4 (14)	13 (45)
Bronchodilator	2 (7)	19 (50)	14 (39)*
Cigarette exposure at home	4 (14)	2 (7)	N/A
Cat in home	12 (41)	10 (35)	N/A
Dog in home	10 (36)	10 (35)	N/A

N/A = Not Available

* Significant at the p<0.05 level

asked to remain indoors, with windows and doors shut, until the second swab had been taken.

Research assistants, who were staff members of the AAE Program (certified asthma educators or public health nurses), instructed the children and their families about the use of the diary and the proper technique of performing the PEFR, and supervised the collection of data throughout the study.

Sample size was calculated based on PEFR change (> 20% change in post-spray mean morning PEFR compared with pre-spray mean morning PEFR). Calculations were based on the mean values for children at the 50th percentile for height in the middle of the age group, i.e., 10 year olds. A 20% change for this population would be 46 L/minute, according to normal values quoted by the Handbook of the Hospital for Sick Children in Toronto, Eighth Edition, page 487.¹⁸ Using an alpha of 0.05 and a beta of 0.2, it was calculated that 18 matched pairs would be required to show a statistically significant difference. All statistics were generated using SPSS software with one exception. The trend analysis on the total scores used the Chi squared test on EpiInfo 6.04 software.

RESULTS

The parents of 118 eligible children were contacted, and 86 (73%) agreed to have their children participate. Of these, 29 were inside the spray zone and could be matched with 29 from outside the spray zone. Table I summarizes the characteristics of the subjects, controls and children who refused to participate or withdrew before the data collection started. There

were no statistically significant differences between subjects and their matched controls.

During the 3 sprays, 78% of the Kromecote cards from the subjects within the spray zone were positive for droplets, versus 9% for those outside the spray zone. Those outside the spray zone that were positive were located close to the buffer area of the spray zone.

The results of the nasal swab cultures presented three surprising features. First, five swabs were positive on the pre-spray test at the time of the first spray. Second, there was a large increase in the number of positive swabs following each spray, compared with the pre-spray swabs, even though the post-spray swabs were taken only 2 hours approximately after the spray. Third, there were a large number of post-spray positive swabs in the children living outside the spray zone. This is particularly surprising given the small number of positive Kromecote cards in this area.

Table II compares the asthma diary symptoms of the subjects inside the spray zone with the controls. The burden of asthma symptoms for the participants was not great. The mean daily score for questions A, B, and C combined for all the participants during the 6 time periods was 0.97. The maximum possible daily score for these questions was 9. The score was zero on 61% of the days when responses were given to these questions. In each of the 6 time periods, there was no difference between the 2 groups in their scores on questions A-C or D and E combined.

In Table III, the scores for each pre-spray period are compared with those for the corresponding post-spray period, for

TABLE II

Asthma Diary Symptoms. Difference Between In Spray and Out of Spray Zone Respondents. Wilcoxon Signed Rank Test

Spray	Zone	Questions A, B, C*					Questions D, E*				
		Mean Score†	N‡	S.D.	Z	p	Mean Score‡	N‡	S.D.	Z	p
Pre-spray	1	In	24	1.07	-0.04	0.97	0.21	24	0.66	-0.56	0.58
		Out		0.87			0.13		0.61		
	2	In	23	0.77	-0.97	0.33	0.05	22	0.21	-0.82	0.41
		Out		1.05			0.14		0.47		
Post-spray	3	In	21	0.69	-0.80	0.43	0.05	22	0.21	-1.47	0.14
		Out		1.23			0.36		0.95		
	1	In	24	0.82	-0.83	0.41	0.04	24	0.20	-0.45	0.66
		Out		1.21			0.17		0.82		
	2	In	23	1.04	-0.32	0.75	0.27	22	0.77	-1.34	0.18
		Out		0.69			0.09		0.43		
	3	In	21	0.81	-1.71	0.09	0.05	22	0.21	0.00	1.00
		Out		1.21			0.05		0.21		

† mean score out of a daily maximum of 9.

‡ mean score out of a daily maximum of 2.

* A) Did you wheeze, cough or have trouble breathing today?

B) Did you wake up last night and wheeze, cough or have trouble breathing?

C) Did you have trouble playing today because of your asthma?

D) Did you miss school today because of your asthma?

E) Did you go to the doctor or hospital today because of your asthma?

§ For subsequent sections of the results, the number of pairs used in the analysis varies. This is because either member of a pair may have missing values, thus necessitating their removal from the analysis for that item. This applies both when subjects (those inside the spray zone) are compared with controls (outside the spray zone), and when an individual's pre-spray value is compared with the post-spray value.

TABLE III

Asthma Diary Symptoms, Questions A-C and D and E Combined. Differences Between Pre-spray and Post-spray Responses for the Subjects and for the Controls. Wilcoxon Signed Rank Test

Spray	Zone	Questions A, B, C					Questions D, E				
		Mean Score†	N	S.D.	Z	p	Mean Score‡	N	S.D.	Z	p
Inside Spray Zone	1	Pre	27	1.02	-0.59	0.56	0.05	27	0.15	-1.46	0.14
		Post		0.80			0.01		0.04		
	2	Pre	27	0.79	-1.26	0.21	0.01	27	0.05	-1.29	0.20
		Post		1.09			0.07		0.22		
Outside Spray Zone	3	Pre	27	0.52	-0.88	0.38	0.01	27	0.04	-1.07	0.29
		Post		0.78			0.02		0.09		
	1	Pre	25	0.95	-0.07	0.94	0.05	26	0.16	0.00	1.0
		Post		1.23			0.03		0.16		
	2	Pre	25	0.97	-1.29	0.20	0.07	24	0.22	-1.34	0.18
		Post		0.62			0.02		0.08		
	3	Pre	22	1.15	-0.49	0.62	0.07	23	0.19	-1.63	0.10
		Post		1.19			0.01		0.04		

† Mean score out of a daily maximum of 9. Scores are standardized using [Total score]/[Number of days contributing to score]

‡ Mean score out of a daily maximum of 2. Scores are standardized using [Total score]/[Number of days contributing to score]

TABLE IV

Comparison of Ratio [(Mean Post-spray PEFR/Mean Pre-spray PEFR) * 100], Subjects and Controls

Spray Number		Mean† (%)	N	S.D.	Test Statistic‡	P-Value
1	Inside	100.6	24	9.7	-0.714	0.48
	Outside	102.9		11.1		
2	Inside	99.6	23	10.4	-1.794	0.07
	Outside	105.5		12.4		
3	Inside	99.8	22	9.9	0.176	0.86
	Outside	99.2		11.2		

† Means calculated on 3 or more responses out of a possible 5.

‡ Sprays 1 and 2 required Wilcoxon Signed Ranks Test due to skewed data. Spray 3 used the Paired T test.

each individual. Again, there was no significant difference in either the subjects or the controls. In other words, neither

the subjects nor the controls developed more asthma symptoms after any of the sprays.

Table IV shows the ratio of the mean of the morning post-spray PEFRs divided by the mean of the morning pre-spray values, expressed as percentages. There were no significant differences between the subjects and the controls.

The individual items on the questionnaire for non-asthmatic symptoms were analyzed separately and no significant differences were seen (results not shown). The results for the aggregate scores showed no significant differences between the subjects and their controls at any of the 6 times, pre- and post-spray, when these data were collected. Very few symptoms of any kind were seen.

DISCUSSION

We used Peak Expiratory Flow (PEF) as an indicator of lung function. PEF is the largest expiratory flow achieved with a maximally forced effort from a position of maximum inspiration. PEF monitoring is well reviewed in a paper by Jain et al.¹⁹ The PEFR parameter which was used to assess lung function change was [(the mean morning PEFR in the 5 days following a spray / the mean morning PEFR in the 5 days before a spray) *100]. The 22 matched controls in the PEFR analysis allowed for a minimum of a 17% change in the PEFR to be detected. This equates to a change in PEFR of 41.4 l/m. We consider it unlikely that the failure to observe an effect was due to a type 2 error.

It is also unlikely that the failure to demonstrate adverse effects of the spraying was due to selection of a group of children with mild asthma. The children in this study were almost always referred to the AAE Program only after they had visited the Emergency Room or had been hospitalized. This suggests that these children are likely to be towards the more severe side of the asthma spectrum. The 1995 Canadian Consensus Guideline identifies these groups of children to be high risk for one year from the time of acute asthma treatment.²⁰ The possibility that the subjects had better controlled asthma as indicated by the differences in medication usage exists. The result of this could be that the subjects were less likely to experience symptoms or PEFR changes.

The average culturable airborne Btk concentration measured outside residences in the Victoria spray zone was 739 CFU per cubic metre of air.¹⁶ Inside residences during the spraying, average concentrations were initially 2 to 5 times lower than outdoors, but 5-6 hours after spraying began, indoor concentrations exceeded outdoor concentrations. The children were asked to stay indoors during the spray operations. Initially this appears to have been protective.

The classification of exposure to the spray was based on geographical location. The Kromecote card results appeared to confirm that this was a valid method of classification. The nasal swab results, however, showed a surprising number of positive Btk isolates in children from outside

the spray zone, and the number increased after the spray on each occasion. Hence, we need to consider whether the geographically based classification of subjects and controls led to a bias in favour of showing no effect from the spraying. There are two pieces of evidence to suggest that this was not the case. The first is that there was no evidence of increased burden of illness after any of the sprays. In no group was there a significant increase in asthma diary symptoms, deterioration in PEFR, or non-asthma symptoms. The second is that when the analysis was restricted to those whose swabs had converted from negative on the pre-spray test to positive on the post-spray, the results overall showed no effect. In one group – the responses to questions A, B, and C in spray 3 – there was an increase in the post-spray score, but this appeared to be due to chance selection of subjects with unusually low pre-spray scores. Balancing this finding was the decrease in scores seen in the first spray.

We conclude that there was no evidence of adverse effects on a group of children with asthma from the use of Foray 48B by aerial spraying, at least under the conditions existing at the time of the spraying. The population was advised to stay indoors with windows and doors closed during the spraying. It is possible that if this had not been done, adverse effects may have been seen. However, even in those in whom Btk was isolated from their nose within 2 hours of the spraying, no adverse effects could be demonstrated.

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RÉSUMÉ

Objectif : Nous avons cherché à déterminer si l'épandage aérien d'un pesticide biologique était associé à une hausse des symptômes ou à un changement du débit maximal expiratoire chez les enfants asthmatiques.

Méthode : Au moyen de cohortes avant-après en paires appariées, nous avons comparé des enfants vivant dans la zone d'épandage à des enfants vivant hors de la zone et consigné par écrit leurs débits maximaux expiratoires et leurs symptômes asthmatiques et non asthmatiques.

Résultats : Les cas et les témoins ont obtenu les mêmes scores en ce qui a trait aux symptômes de l'asthme avant et après l'épandage; nous n'avons pas non plus constaté de changements importants dans le débit maximal expiratoire des cas après l'épandage.

Conclusions : Nous n'avons relevé aucune preuve d'effets indésirables de l'emploi du pesticide biologique Btk. Selon nous, cette étude est la première sur d'éventuels effets néfastes, pour les enfants asthmatiques, de l'épandage aérien au Btk.

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