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A pilot study to quantify parental anxiety associated with enrollment of an infant or toddler in a phase III vaccine trial

Joanne M. Langley[a,b,c,*], Scott A. Halperin[a,b,c,d,e], Bruce Smith[a,e]

[a] *Clinical Trials Research Center, Dalhousie University and the IWK Health Centre, 5850 University Avenue, Halifax, Canada NS B3J 3G9*
[b] *Department of Pediatrics, Dalhousie University and the IWK Health Centre, Halifax, Canada NS B3J 3G9*
[c] *Department of Community Health and Epidemiology, Dalhousie University and the IWK Health Centre, Halifax, Canada NS B3J 3G9*
[d] *Department of Microbiology and Immunology, Dalhousie University and the IWK Health Centre, Halifax, Canada NS B3J 3G9*
[e] *Department of Mathematics and Statistics, Dalhousie University and the IWK Health Centre, Halifax, Canada NS B3J 3G9*

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Abstract

We sought to measure the anxiety felt by parents at the time of entry into a randomized controlled vaccine trial, and to determine if anxiety level was associated with parental demographic variables or past experience. The children were 2-month-old infants entering a randomized controlled clinical trial (RCT) of a diphtheria–tetanus toxoid–acellular pertussis vaccine adsorbed with *Haemophilus influenzae* B conjugate, or toddlers enrolling in a RCT of a Meningococcal C conjugate vaccine. Nurses interviewed parents to collect demographic data and parents self-administered the Spielberger Self-evaluation Questionnaire (State Anxiety STAI-Y-I) [Manual for the State-Trait Anxiety Inventory (Form Y) (Self-evaluation Questionnaire), Consulting Psychologists Press Inc., Palo Alto, 1983], a validated instrument measuring the temporary condition of "state anxiety." A regression tree (CART) (S-Plus) was used to identify factors associated with higher anxiety scores. Parents of 97 children enrolled. Anxiety scores ranged from 22.75 (lower anxiety) to 36.43 (higher anxiety). The regression tree identified a structured tree with six branches. The highest anxiety scores occurred in fathers with education less then grade 8, mothers with education less than high school, birth order of the child less then the third, previous serious illness in the family, or lack of experience with research. In a group of parents agreeing to enroll their infant or toddler in a vaccine study, certain attributes and experiences were associated with higher anxiety at the time of immunization in the context of a RCT. These factors should be considered by vaccine researchers in the recruitment process of clinical trials.

Keywords: Immunization; Controlled clinical trial; Parental attitudes

1. Introduction

Immunization is one of the most successful and cost-effective interventions to prevent infectious disease in childhood [2]. Prior to vaccine licensure, extensive evaluation occurs including pre-clinical and phase 1 testing in humans followed by studies in the target age group [3]. In order for childhood vaccine research and ultimately public health immunization programs to be implemented they must be acceptable to parents. A previous study of parents participating in vaccine research in our setting showed that altruism (desire to contribute to medical research, desire to help others) was the most important motivating factor [4]. Anthropological research indicates that a diverse number of factors varying across regional, national, cultural and socio-economic boundaries are associated with vaccine acceptability [5]. The psychological state of parents at the time of entering their child into a vaccine trial, has not previously been studied.

We assessed parental anxiety using a validated anxiety measurement instrument, the State-Trait Anxiety Inventory [1], at the time of enrollment of a child in a randomized vaccine trial in order to quantify anxiety levels in this setting and to determine if there is a relationship between parental concern and socio-demographic characteristics or past experiences.

2. Methods and materials

2.1. Participants

Parents who had just consented to enroll their child in one of two randomized controlled vaccine trials were eligible. The children were (a) 2-month-old infants entering a clinical

* Corresponding author. Tel.: +1-902-470-8498; fax: +1-902-470-7217.
E-mail address: joanne.langley@dal.ca (J.M. Langley).

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trial of a diphtheria–tetanus toxoid–acellular pertussis vaccine adsorbed with *Haemophilus influenzae* B conjugate and (b) toddlers enrolling in a clinical trial of a Meningococcal C conjugate vaccine [6]. After completing the consent process for the vaccine trial and before any procedures, parents were asked to give consent to enroll in a study of parental concerns about immunization.

2.2. Setting

Children were recruited from a group practice of primary care general practice physicians in the Halifax Regional Municipality, the capital city of the province of Nova Scotia (population 300,000). Routine childhood immunizations against diptheria, pertussis, tetanus, polio, *Haemophilus influenzae* B, measles, mumps, rubella and Hepatitis B are provided free of charge to all children and uptake is estimated at 97%.

2.3. Data collection

A research nurse interviewed parents to collect demographic data: hours employed outside home, child's gender and birth order, parental age and education (grade level less than or greater than 8, completion of high school, university degree or some university), use of out-of-home care, previous experience with research or previous serious illness in the family. Parents self-administered the State Anxiety Self-evaluation Questionnaire (STAI-Y-I) (Reproduced by special permission of the Publisher, Mind Garden Inc., 1690 Woodside Road #202, Redwood City, CA 94601, USA. http://www.mindgarden.com from the State-Trait Anxiety Inventory (Form-Y) by Charles D. Spielberger, Copyright 1977 by Charles D. Spielberger, All rights reserved.) in a private room without a time limit. This instrument, which has been used extensively in clinical practice and research settings, consists of 20 statements that measure the temporary condition of "state anxiety" or current immediate anxiety. It evaluates how respondents feel "right now, at this moment", not anxiety levels that are felt on an ongoing basis. The STAI-Y-1 has high reliability ($r = 0.93$), internal consistency, and validity [1].

2.4. Analysis

The self-evaluation questionnaires were weighted and summed according to standard scoring procedures for the State-Trait Anxiety Inventory [1].

A regression tree was used to develop a multivariate prediction model for the anxiety score, using all demographic information obtained. Such trees often provide a more parsimonious prediction than stepwise regression because of the regression tree's ability to automatically incorporate complex interactions which are not feasible with standard regression approaches. The estimated tree includes, among other things, an interaction between the variable "prior experience with research" and the variable "birth order of child". The interaction is important only for a subset of subjects, those with no prior research experience. Such interactions, which are relevant to only a subset of the data, are easily incorporated into regression trees, but impossible to accommodate in standard linear regression methods, hence the use of the term "complex interaction".

A widely used method for choosing a "best" tree is to begin by growing an overly large tree, and then prune back portions of the tree which have little predictive value, which is analogous to stepwise regression using backwards elimination. The tree is grown by a sequence of binary splits which are chosen to minimize the error sum of squares of the terminal nodes. The methodology is directed towards finding groups (terminal nodes) whose scores are homogenous (have low within-node variance). At each node, the data are partitioned into two groups using the best split based on all available predictors. We used the Splus (Version 6, MathSoft, Cambridge, MA) implementation of the regression tree algorithm in which nodes continue to be split unless they contain less than 10 subjects, or the node sum of squares is less than 1% of the total sum of squares. The tree growing procedure typically produces a tree which over-fits the data, and the second phase of tree fitting aims at finding a tree with good predictive power. A large collection of sub-trees are fit with the goal of minimizing a cost-complexity criterion. In the regression tree context, this criterion is the sum of the residual sum of squares and a penalty term proportional to the number of terminal nodes. A cross-validation scheme is used in which sub-trees are fit using randomly chosen construction data sets, and predictive power is assessed on the associated test sets. The tree which minimizes the cost-complexity criterion on test sets is chosen as the best tree. Full details of the cross-validation algorithm are described in Breiman et al. [7]. We used the default settings for the Splus implementation of the cross-validation algorithm, described by Chambers and Hastie [8], which include 10-fold cross-validation.

This study was approved by the Research Ethics Board of the IWK Health Center.

3. Results

Parents of 97 of the 104 children enrolled in the two vaccine trials also consented to enroll in this study of parental concerns about immunization (i.e. parents of seven children consenting to enroll in vaccine trials refused enrollment for the study of parental anxiety). Most families were Caucasian (96%) and had two parents in the home (96%). The median age of mothers was 29 years and of fathers was 32 years. University degrees were reported among 50% of fathers, while 63% had "some university"; 59% of mothers had "some university". Previous serious illness in the family was reported by 41% of parents, and 39% had previous experience with a research study. Participating children

were 49% male and 51% female. Only 23% were enrolled in out-of-home childcare more than 1 day weekly. Ninety-one percent of fathers and 60% of mothers worked outside the home. The anxiety scores ranged from 22.75 (lower anxiety) to 36.43 (high anxiety).

Parents of 78 of 97 enrolled children answered questions about all demographic variables and therefore were entered into the tree fitting procedure to identify factors associated with higher or lower anxiety scores. The tree fitting procedure identified a tree with six branches (Fig. 1). Average anxiety scores are included in the tree leaves and nodes. The following factors were indicative of higher anxiety scores:

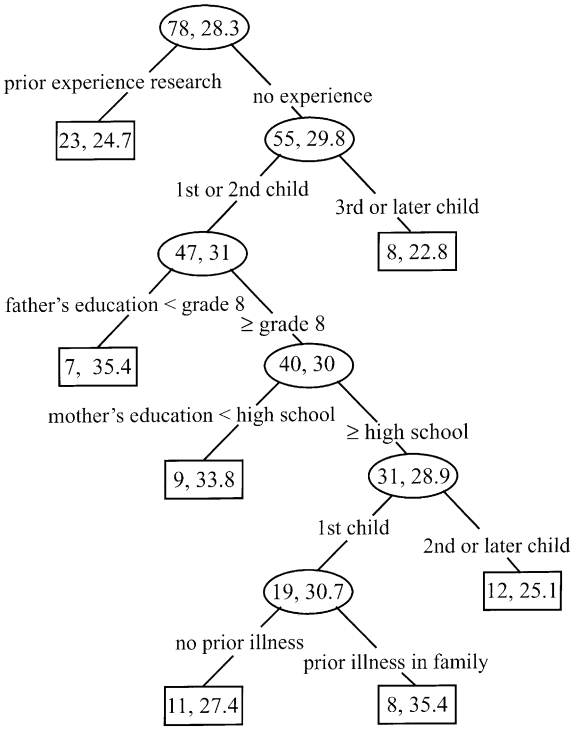

Fig. 1. Regression tree of Spielberger Self-evaluation Questionnaire (State Anxiety STAI-Y-I) anxiety scores obtained from parents who had just agreed to enroll their infant or toddler in a randomized controlled vaccine clinical trial. Internal tree nodes are marked as ovals (⬭), and terminal nodes as rectangles (▭). At each internal node, the associated cohort is split into two groups. The criteria on which the nodes were split are indicated by the branch labels: Prior experience (exp.) with research or no prior experience with research, first or second child is enrolled in this vaccine trial or third or later child is enrolled in this vaccine trial, father's education is less than grade eight or greater than grade eight, mother's education is less than high school or greater than high school, first child enrolled in this vaccine trial or second or later child enrolled, no prior serious illness (no prior illness) or prior illness in the family. The numbers within nodes are the size and average anxiety score of the associated cohort (e.g. 78, 28.3 is 78 families, average anxiety score 28.3). For example, there were 78 families with non-missing data on all variables under consideration with a total. These constitute the top node, and the average anxiety score for these families was 28.3. At this top node, the data are split into two subsets depending on whether the families had prior experience with research. The 23 families which had prior experience with research had an average anxiety score of 24.7. The remaining 55 families had an average anxiety score of 29.8.

fathers with education less than grade 8, mothers with education less than high school, the birth order of the child who was enrolled in the vaccine trial was less than the third, previous serious illness in the family, lack of experience with research.

4. Conclusions

There are few studies of factors affecting the parental decision to allow recruitment of children into clinical research. In a trial of a new asthma medication in Australia, Harth and co-workers [9,10] found that participating parents were motivated by a desire to contribute to medical research, but had lower socio-economic status and were more emotionally vulnerable than refusing parents. About 75% of French parents surveyed about a hypothetical trial said they would refuse to enroll their newborn because of concerns about possible side effects and unproven efficacy [11]. About 51% of parents of children in The Netherlands surveyed after their child had completed a trial of an antipyretic to prevent recurrent febrile seizures, indicated they participated in order to contribute to clinical science [12]. In a previous study, we asked parents of 2 month olds at the time of enrollment in a pertussis vaccine trial about their motivation for participation. Refusing parents were concerned about painful procedures and an extra immunization while participating parents were motivated by a wish to contribute to medical knowledge and to help others [4].

In this group of urban Canadian parents agreeing to enroll their infant or toddler in a vaccine study, certain attributes and experiences were associated with higher anxiety levels at the time of first enrollment visit: lower level of parental education, earlier birth order of the participating child, first experience in a medical research study and previous serious illness in the family. The range of State-Trait anxiety scores of parents (23–36), we observed are comparable to those seen in parents of children who have been assessed by a cardiologist for evaluation of an innocent heart murmur [13] but lower than the mean rating of 36.6 of parents of children going for surgery that day [14].

The external validity of our study is limited by our sample which consisted largely of educated, Caucasian, two-parent households who had agreed to participate in vaccine research. Anxiety levels may be very different in parents from other economic or educational backgrounds, family structures, or in those from other cultures, or in parents who do not consent to vaccine research on their child. We were not able to measure anxiety levels of parents who refused to participate in the vaccine trials or in the parents of the seven children who consented to the vaccine trial but not this component of the study.

Our observation that levels of anxiety correlate with the educational background of the parent and how many other children they have may have important implications for vaccine researchers. Recruitment, study information and

informed consent materials should be designed to adequately inform parents, regardless of background, so that the opportunity to benefit from participation in research studies is equally accessible to all children. Secondly, parents who agree to enter their child in a vaccine trial, or in any research study, may be very different from non-volunteering parents. If there are systematic differences in the characteristics of trial participants compared to the general population, then the generalizeability of the research findings will be affected. If the research community better understands what a parent experiences as they decide to enroll their child in a vaccine trial, then educational strategies and recruitment interventions can be designed that are relevant to parental needs and applicable to a range of different parent backgrounds.

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