RANDOMIZED CONTROLLED TRIAL OF LOW COST INTERVENTIONS TO REDUCE CHILDHOOD IMMUNIZATION DROPOUTS IN PAKISTAN

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RANDOMIZED CONTROLLED TRIAL OF LOW COST INTERVENTIONS TO
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HUSSAIN RAZA USMAN
PUBLIC HEALTH

ABSTRACT

Childhood immunization coverage in Pakistan remains sub-optimal despite universal and free of cost availability of vaccines. Structural impediments to progress may include the immunization card that is hard to read and interpret. A randomized controlled trial was conducted to assess the effect of redesigned immunization card and center-based education to mothers on immunization completion at rural immunization centers in Karachi, Pakistan. Other objectives were to identify the predictors of immunization completion and to identify factors associated with delay at first dose of diphtheria-tetanus-pertussis (DTP1).

Mother-child units were enrolled from six immunization centers at DTP1 and randomized to four study groups: 378 in redesigned card group, 376 in center-based education group, 374 in combined intervention group, and 378 in standard care group. Each child was followed-up for 90 days to record the dates of DTP2 and DTP3 visits. The study outcome was DTP3 completion by the end of follow-up.

By the end of follow-up, 39% of children in standard care group completed DTP3. Compared to this, a significantly higher proportion of children completed DTP3 in redesigned card group (crude Risk Ratio [RR] = 1.7; 95% CI = 1.5, 2.0), center-based education group (RR = 1.5; 95% CI = 1.3, 1.8), and combined intervention group (RR = 1.7; 95% CI = 1.4, 2.0).
Separate multivariable log binomial regression analysis of 366 mother-child units in standard care group revealed that DTP3 completion was higher among children who were ≤ 60 days old at enrollment, were from households with monthly household income over Rs. 3000 (USD 50), and were living < 10 minutes away from the immunization center.

In multivariable logistic regression analysis of enrollment data on 1461 mother-child units, lower education of father, father being unemployed or owned private business, Mohajir ethnicity, and travelling by bus to reach the immunization center were independently associated with delay at DTP1.

In conclusion, we found that providing an improved immunization card and center-based education are effective interventions to reduce immunization dropouts. Also, a substantial proportion of rural children in Pakistan are late for DTP1 and more than a half of them fail to return for DTP3.
DEDICATION

To my wife Faiza
ACKNOWLEDGMENTS

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I am grateful to the Expanded Programme on Immunization (EPI) Sindh, Pakistan for granting permission and extending their support for this study. I would also wish to thank the EPI center staff for their help and cooperation and the study staff for their hard work and dedication during the data collection for this study.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>v</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Immunization Coverage in Pakistan</td>
<td>2</td>
</tr>
<tr>
<td>Immunization Dropouts in Pakistan</td>
<td>4</td>
</tr>
<tr>
<td>STUDY AIMS</td>
<td>6</td>
</tr>
<tr>
<td>Aim 1: To Assess the Effect of Low Cost Interventions on Childhood Immunization Completion in Pakistan</td>
<td>6</td>
</tr>
<tr>
<td>Aim 2: To identify the determinants of childhood immunization completion in Pakistan</td>
<td>7</td>
</tr>
<tr>
<td>Aim 3: To identify factors associated with delay at first diphtheria-tetanus-pertussis (DTP1) immunization in Pakistan</td>
<td>8</td>
</tr>
<tr>
<td>METHODS</td>
<td>9</td>
</tr>
<tr>
<td>Study Setting and Enrollment</td>
<td>9</td>
</tr>
<tr>
<td>Interventions</td>
<td>11</td>
</tr>
<tr>
<td>Trial Design</td>
<td>12</td>
</tr>
<tr>
<td>Follow-up</td>
<td>13</td>
</tr>
<tr>
<td>Study outcome</td>
<td>13</td>
</tr>
</tbody>
</table>
Analysis aim 1: To Assess the Effect of Low Cost Interventions on Childhood Immunization Completion in Pakistan ......................................................... 14
Analysis aim 2: To identify the determinants of childhood immunization completion in Pakistan ................................................................................. 14
Analysis aim 3: To identify factors associated with delay at first diphtheria-tetanus-pertussis (DTP1) immunization in Pakistan ................................................................. 15
Human subjects .................................................................................................................. 16

Randomized Controlled Trial to Improve Childhood Immunization Adherence in Rural Pakistan: Redesigned Immunization Card and Maternal Education ..................... 17

Determinants of Diphtheria-Tetanus-Pertussis Third Dose (DTP3) Completion Among Children Visiting Immunization Centers for the First Dose (DTP1) in Rural Pakistan: A Cohort Study .................. 39

Factors Associated with Delay at First Diphtheria-Tetanus-Pertussis (DTP1) Immunization in Rural Pakistan ................................................................. 60

Summary Conclusions .............................................................................................................. 79

Overall Results ......................................................................................................................... 79
Strengths ................................................................................................................................. 80
Limitations ............................................................................................................................... 81
Implications ............................................................................................................................. 82

General List of References ....................................................................................................... 84

Appendix A: University of Alabama at Birmingham Institutional Review Board Approval
LIST OF TABLES

Table | Page
--- | ---

**INTRODUCTION**

1. WHO-EPI schedule for childhood immunization in Pakistan and most WHO member states ................................................................. 1

**RANDOMIZED CONTROLLED TRIAL TO IMPROVE CHILDHOOD IMMUNIZATION ADHERENCE IN RURAL PAKISTAN: REDESIGNED IMMUNIZATION CARD AND MATERNAL EDUCATION**

1. Distribution among study groups of socio-demographic characteristics of study participants at enrollment (Pakistan, 2005-2006) .......................................................... 28

2. Crude Risk Ratios (RRs) and 95% Confidence Intervals (CIs) for DTP3 completion by intervention group (Pakistan, 2005-2006) .......................................................... 31

3. Crude and adjusted Risk Ratios (RRs) with 95% Confidence Intervals (CIs) for DTP3 completion by intervention group among Mohajirs and non-Mohajirs children (Pakistan, 2005-2006) .................................................................................. 32

**DETERMINANTS OF DIPHTHERIA-TETANUS-PERTUSSIS THIRD DOSE (DTP3) COMPLETION AMONG CHILDREN VISITING IMMUNIZATION CENTERS FOR THE FIRST DOSE (DTP1) IN RURAL PAKISTAN: A COHORT STUDY**

1. Association of factors with DTP3 completion shown by crude Risk Ratios (RRs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006) ......................... 47

2. Multivariable analysis of the factors associated with DTP3 completion shown by Adjusted Risk Ratios (RRs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006) (n=366) .................................................................................. 50

**FACTORS ASSOCIATED WITH DELAY AT FIRST DIPHTHERIA-TETANUS-PERTUSSIS (DTP1) IMMUNIZATION IN RURAL PAKISTAN**

1. Association of factors with child’s age at DTP1 shown by crude Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006) (n=1461) .......... 68

2. Results of multivariable logistic regression analysis of characteristics associated with child’s age at DTP1 at six rural EPI centers in Pakistan (2005-2006) (n=1461) ....... 71
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td></td>
</tr>
<tr>
<td>1. BCG coverage – Pakistan, Global, EMR, and SEAR (2000-2005)</td>
<td>2</td>
</tr>
<tr>
<td>2. DTP1 coverage – Pakistan, Global, EMR, and SEAR (2000-2005)</td>
<td>3</td>
</tr>
<tr>
<td>3. DTP3 coverage – Pakistan, Global, EMR, and SEAR (2000-2005)</td>
<td>3</td>
</tr>
<tr>
<td>4. DTP1 and DTP3 coverage and DTP1-DTP3 dropouts in Pakistan (2000-2005)</td>
<td>4</td>
</tr>
</tbody>
</table>

METHODS

5. Flow of study participants in the randomized controlled trial and selection of study participants for follow-up and cross sectional analysis | 10 |

RANDOMIZED CONTROLLED TRIAL TO IMPROVE CHILDHOOD IMMUNIZATION ADHERENCE IN RURAL PAKISTAN:
REDESIGNED IMMUNIZATION CARD AND MATERNAL EDUCATION

1. Flow of study participants | 27 |
INTRODUCTION

Immunizations are considered to be one of the most cost-effective public health interventions for the prevention and control of childhood infections [1]. In most World Health Organization (WHO) member states, the Expanded Programme on Immunization (EPI) provides a series of childhood immunizations during the first year of life including vaccines for tuberculosis (Bacillus Calmette-Guérin; BCG), diphtheria-tetanus-pertussis (DTP), poliovirus (oral vaccine; OPV), hepatitis B virus (HBV), and measles [2]. In Pakistan and many other WHO member states, the EPI schedule includes BCG/OPV vaccines at birth, three doses of DTP/OPV/HBV vaccines at 6, 10, and 14 weeks, and measles vaccine at 9 months after birth (Table 1) [3]. The EPI in Pakistan is implemented through a countrywide network of EPI centers supplemented with outreach programs in some areas. Mostly, caregivers from the lower and middle socioeconomic tiers of the country receive immunizations at EPI centers whereas more affluent caregivers prefer the private sector.

Table 1: WHO-EPI schedule for childhood immunization in Pakistan and most WHO member states

<table>
<thead>
<tr>
<th>Age of child</th>
<th>Birth</th>
<th>6 weeks</th>
<th>10 weeks</th>
<th>14 weeks</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>BCG(^{\dagger})/OPV(^{\dagger\dagger})</td>
<td>DTP(^{\dagger})/OPV1/HBV(^{\dagger\dagger})</td>
<td>DTP2/OPV2/HBV2</td>
<td>DTP3/OPV3/HBV3</td>
<td>Measles</td>
</tr>
</tbody>
</table>

Bacille Calmette-Guérin, \(^{\dagger}\) oral polio vaccine, \(^{\dagger\dagger}\) diphtheria-tetanus-pertussis, \(^{\ddagger}\) hepatitis B virus

WHO immunization coverage estimates are mainly derived from officially reported coverage by WHO member states, EPI 30-cluster surveys, Demographic and Health Surveys (DHS), UNICEF Multiple Indicator Cluster Surveys (MICS), unpublished surveys available from Ministries of Health, and recommendations from local and external experts [3]. Officially reported estimates from member states are calculated, for
example for DTP1, by dividing the number of children who received the first dose of DTP by the estimated number of children who survived their first birthday. The principal indicator of immunization coverage levels by the WHO is the completion of three doses of DTP (DTP3) vaccine [4].

Immunization Coverage in Pakistan

The EPI in Pakistan has recorded significant progress in immunization coverage since its inception in early 1980s. BCG coverage in Pakistan has averaged around 80% in the last few years, which was almost similar to the BCG coverage in South-East Asia Region (SEAR) but a little less than in the Global and Eastern Mediterranean Region (EMR) (Figure 1).

![Figure 1: BCG coverage – Pakistan, Global, EMR, and SEAR (2000-2005)](image)

Coverage of DTP1 in Pakistan (70%-77%) between 2000-2004 was substantially lower than Global (85%-88%), EMR (82%-86%), and SEAR (83%-84%) DTP1 coverage
By 2005 however, estimates of DTP1 coverage in Pakistan (82%) showed signs of catching up with SEAR (82%) coverage. Similarly between 2000-2004, DTP3 coverage in Pakistan (61%-68%) was very close to SEAR coverage (63%-64%) (Figure 3). By 2005, it has significantly improved (72%) but still remained lower than Global (78%) and EMR (85%) coverage.

![Figure 2: DTP1 coverage – Pakistan, Global, EMR, and SEAR (2000-2005)](image2)

![Figure 3: DTP3 coverage – Pakistan, Global, EMR, and SEAR (2000-2005)](image3)
Immunization Dropouts in Pakistan

Drop in immunization coverage from DTP1 to DTP3 can be assessed by estimating percent decline in coverage from DTP1 to DTP3, commonly referred as DTP1-DTP3 dropout.

\[
\text{DTP1-DTP3 dropout} = \left( \frac{\text{DTP1 coverage} - \text{DTP3 coverage}}{\text{DTP1 coverage}} \right) \times 100
\]

![Graph showing DTP1 and DTP3 coverage and DTP1-DTP3 dropouts in Pakistan (2000-2005)](image)

In Pakistan between 2000-2005, DTP1-DTP3 dropout was recorded consistently at 11%-13% (Figure 4). The DTP1-DTP3 dropout calculation shows percent decline in DTP3 coverage with reference to the DTP1 coverage. Therefore, it should be interpreted carefully in the context of DTP1 coverage. For example, a country might have a good DTP3 coverage regardless of a substantial DTP1-DTP3 dropout, if DTP1 coverage is very high. In another situation, a country might have a very low DTP3 coverage despite minimal DTP1-DTP3 dropout, if DTP1 coverage is very low. In addition, calculating
immunization dropouts by this method does not truly reflect the magnitude of dropouts that occur in a cohort of children receiving immunizations at EPI centers.

Childhood immunization coverage in a population is a function of the proportion of newborns that an immunization system brings in for the first immunization, and the proportion of these children which completes each recommended follow-up immunization in a schedule. Therefore, interventions targeting at bringing more children in the EPI system for initial immunizations and interventions aiming at reducing the dropouts both translate in overall increase in immunization coverage at a population level.
STUDY AIMS

Aim 1: To Assess the Effect of Low Cost Interventions on Childhood Immunization Completion in Pakistan

In industrialized countries several multi-component interventions including center-based education to mothers have proved effective in reducing childhood immunization dropouts [5, 6]. Patient reminders alone [7] or in combination with other strategies [8, 9] have also been effective in reducing dropouts in these settings. Nonetheless, because these interventions are resource intensive and typically require efficient and comprehensive immunization registries; they may not be feasible in a developing country like Pakistan.

The EPI card currently used in Pakistan has two main shortcomings. First, it is small (9 cm x 8.5 cm, when folded); hence the information on child’s identity, immunization schedule, information for mothers, and next immunization visit dates is cramped and cluttered. Second, because the next immunization date is hand written by the EPI staff, often in very small and irregular letters, it is especially difficult for illiterate or less literate mothers to locate and read the date of their child’s next immunization. Moreover, in Pakistan there is currently no standardized operation procedure practiced that describes how the EPI staff should inform mothers about subsequent immunization visits. Such conditions surely contribute to childhood immunization dropouts and demand attention.

Because it is unclear, despite recent progress, whether the measures currently in place in Pakistan will be sufficient to reach desired immunization levels, and given the substantial contribution of dropouts between DTP1 and DTP3 to low overall immunization coverage in Pakistan, we designed a randomized controlled trial to assess the effects
on DTP3 completion of providing redesigned immunization card and center-based education to mothers at rural EPI centers in the peripheries of Karachi, Pakistan.

Aim 2: To identify the determinants of childhood immunization completion in Pakistan

In developing countries, low adherence to immunization schedule has been found associated with parental socio-demographic characteristics (e.g., larger family size, lower parental education) and provider based characteristics (e.g., longer distance of EPI center from home) [10-13]. Behavioral factors (e.g., mothers’ lack of information and poor motivation) have also predicted both poor adherence to immunization recommendations and high risk of dropouts [14-16].

Pakistani literature on barriers to childhood immunization is sparse and mainly reported from cross-sectional studies [17-19]. In these studies, child’s immunization status was primarily assessed by mother’s recall due to the unavailability of immunization cards at the time of interview in the survey [20, 21]. In the absence of immunization card, the assessment of child’s immunization status is liable to misclassification. Thereby, the internal validity of such studies is questionable. To address this limitation, we conducted a cohort study aimed at identifying the determinants of childhood immunization completion in Pakistan based on documented evidence of immunization status. We were particularly interested in identifying the reasons why children fail to complete the three dose DTP3 series after having received the first dose of DTP (DTP1). Therefore, we enrolled and followed-up a cohort of children visiting EPI centers for DTP1 in rural areas in the peripheries of Karachi, Pakistan.
Aim 3: To identify factors associated with delay at first diphtheria-tetanus-pertussis (DTP1) immunization in Pakistan

Receiving immunization at appropriate age is important. Children with lengthier immunization delays experience longer periods of increased susceptibility to infections than those with shorter or no immunization delays [22]. Accordingly, information on children’s age at specific immunizations is critical for assessing the risk of vaccine preventable infections in the population. It is particularly essential for those infections in which younger age is related to higher incidence and severity of illness such as measles. Also important is to identify the factors associated with delay in immunization. Knowledge of the extent of delay in immunization and its risk factors will help public health authorities in designing interventions to improve age appropriate immunizations. Therefore, to provide evidence based information for public health action, we conducted a cross-sectional study at rural EPI centers of Pakistan to document children’s age at DTP1 immunization and to identify factors associated with delay at DTP1 immunization.
METHODS

Study Setting and Enrollment

The trial was conducted at six rural EPI centers located in the peripheries of Karachi, the capital city of Province Sindh, Pakistan. Study centers were selected out of all rural centers around Karachi based on the highest number of children vaccinated for DTP1 immunizations in the previous year. Housed in government dispensaries and basic health units, these centers provide primary health care to the rural population in their catchment areas.

Any child visiting the selected EPI centers for DTP1 was eligible to participate in the study, provided that the mother had been the resident of the area for no less than six months. Traditionally in Pakistan, it is common for a pregnant woman to deliver her first child and stay for about six weeks after birth at her mother’s home. The reason for six months residency requirement for study eligibility was to exclude such mothers who were expected to leave the area in coming months. A trained interviewer read out the consent form to the mother of each eligible child to obtain the consent. If the mother agreed to participate, the form was signed by the interviewer and a witness confirming the completion of consent process and enrollment.

We used a pre-tested structured questionnaire at enrollment to record information from mothers on socio-demographic variables and potential confounders. The questionnaire included parents’ attributes (parents’ age at enrollment, mother’s age at marriage and first conception, parents’ education and occupation, monthly household income, ethnicity, and family size), child’s attributes (child’s age at enrollment, child’s sex, and num-
ber of siblings), dates of DTP immunizations (DTP1 at enrollment and DTP2 and DTP3 during follow-up), and mode of transport and travel time to reach the EPI center.

The Principal Investigator (H.R.U.) provided a computer generated randomization list to each enrollment center. At these centers, each enrolled mother-child unit received an ID and was assigned to the study group corresponding to this ID on the randomization list. Owing to the nature of interventions, neither the study participants nor the interviewers enrolling the study participants and recording the study outcome were blinded to the type of intervention received by the study participants.

Figure 5: Flow of study participants in the randomized controlled trial and selection of study participants for follow-up and cross sectional analysis
Interventions

Redesigned card: The EPI card currently used in Pakistan has two main shortcomings. First, it is small (9 cm x 8.5 cm, when folded); hence the information on child’s identity, immunization schedule, information for mothers, and next immunization visit dates is crowded together and appears disorderly. Second, because the next immunization date is hand written by the EPI staff, often in very small and irregular letters, it is difficult for generally illiterate or less literate mothers to locate and read the date of their child’s next immunization. To address these issues, we designed a new and simpler immunization card whose most important intended functions were to act as a constant reminder to mothers of the next immunization visit, and to make it easy for them to locate and read the date of the next immunization. Much larger than the existing EPI card (15.5 cm x 11.5 cm when folded), the redesigned card was bright yellow in color, placed in a plastic jacket, and provided with a hanging string. On its outer sides, the card showed nothing but the next immunization date and day of the week for DTP2 and DTP3 visits written in a large font (Times New Roman 42 Microsoft Word®) using preprinted stickers. Dedicated boxes were included on the inner sides of the folded card to record the remainder of the information (name of the EPI center, card number, card’s date of issue, child’s name and address, complete immunization schedule dates, and instructions to the mothers). The cost of each card including the plastic jacket was US$ 0.05 (Pakistani Rupees 3) even though there was a relatively small purchase volume.

Center-based education: In Pakistan there is currently no standardized procedure that describes how the EPI staff should inform mothers about subsequent immunization visits. Mother’s lack of information might contribute to childhood immunization dropouts
and demands attention. The second intervention (center-based education) was a 2-3 minutes conversation with mother that emphasized the importance of the completion of immunization schedule. This education session also explained the potential adverse impact on child’s health if the immunization schedule was not completed. The session was in simple vocabulary in the local language (Urdu) considering the low literacy level of mothers in this rural study population. The duration of the session was kept short for its potential large-scale use by EPI staff in future.

Trial Design

Mother-child units were randomly allocated to three intervention and one standard care groups. At the time of enrollment in the first intervention group (Group 1: “Redesigned card”), a trained interviewer pasted the upcoming date and day of DTP2 immunization on both outer sides of the card. The interviewer showed the information to the mother; asked her to hang the card in her home at a frequently visible place; and requested that she bring the document along on her next immunization visit to the EPI center. At the time of the DPT2 visit, the interviewer crossed out the date and day for this visit to avoid any confusion to the mothers; pasted the date and day for the upcoming DTP3 immunization visit on both sides of the card: and showed the information to the mother. Mothers in the second intervention group (Group 2: “Center-based education”) received center-based education from trained study interviewers. Mothers in the third intervention group (Group 3: “Combined intervention”) received both the redesigned card and center-based education in exactly the same way as described above. Finally, mothers
of the last group (*Group 4: “Standard care”*) underwent routine EPI center visit and received neither intervention.

**Follow-up**

We followed-up each study child at the EPI center for 90 days from the day of enrollment at DTP1. Because the first, second, and third doses of DTP vaccine were scheduled at 30-day intervals in accordance with the EPI schedule, both DTP2 and DTP3, ideally, should have been completed within 60 days after the DTP1 visit. After enrollment, study interviewers maintained with themselves a follow-up card for each study child to record upcoming dates of DTP1 and DTP2. This card was marked with the study ID, names of child’s father and mother, and date of enrollment (DTP1) and had boxes on it to record the upcoming dates of DTP2 and DTP3. Subsequently we screened every child who visited study centers during the study period and recorded dates of DTP2 and DTP3 on the follow-up card for each study child. On the completion of follow-up period, the data from follow-up cards were linked with the baseline data using the study ID as the key variable.

**Study outcome**

The study outcome was the immunization status of each child at the end of 90 days follow-up after enrollment. The immunization status was dichotomized into those who completed both DTP2 and DTP3 (termed “DTP3 completed”) or those who did not complete DTP2, DTP3, or either immunization (termed “DTP3 not completed”).
ANALYSIS

Analysis aim 1: To Assess the Effect of Low Cost Interventions on Childhood Immunization Completion in Pakistan

To determine how successful the randomization process had been, we compared frequencies and percentages of participants’ baseline characteristics across study groups. The main independent variable was the type of intervention with four categories: Group 1 (Redesigned card), Group 2 (Center-based education), Group 3 (Combined intervention), and Group 4 (Standard care). The immunization status coded ‘1’ for “DTP3 completed” and ‘0’ for “DTP3 not completed” was the dependent variable. The effect of the type of intervention on DTP3 completion was assessed by computing crude Risk Ratio (RR) and 95% Confidence Interval (CI) by univariate log-binomial regression using PROC GENMOD in SAS® (SAS Institute, Inc, Cary, NC, USA) [23-26].

Analysis aim 2: To identify the determinants of childhood immunization completion in Pakistan

For this cohort analysis, we used the data collected on the standard care group of the trial (Figure 5). The immunization status coded ‘1’ for “DTP3 completed” and ‘0’ for “DTP3 not completed” was the dependent variable. All variables with potential association with the dependent variable were considered as independent variables.

Overall distribution of participants’ characteristics in the study cohort was described by computing their computed frequencies and percentages. The distribution of DTP3 completion was assessed among the categories of independent variables by computing its percentage. Each independent variable was tested for its association with the de-
dependent variable by calculating Risk Ratio (RR) and 95% Confidence Interval (CI) estimated by univariate log-binomial regression using PROC GENMOD in SAS® [23-26].

Multivariable log-binomial regression model was constructed using proc genmod in SAS® to assess the adjusted association of independent variables with DTP3 completion. Adjusted RRs and their 95% CIs were used for the interpretation of the final model.

*Analysis aim 3: To identify factors associated with delay at first diphtheria-tetanus-pertussis (DTP1) immunization in Pakistan*

For this cross-sectional analysis, we used the baseline data collected from mothers at the enrollment (Figure 5). We calculated children’s mean and median age at DTP1 and proportion of children > 60 days old at DTP1. Child’s age at DTP1 was dichotomized into > 60 days (coded ‘1’) or ≤ 60 days (coded ‘0’) and used as the depended variable for univariate and multivariable analysis. Variables assessed for their potential association with the dependent variable were considered as independent variables.

We computed frequencies and percentages participant’s characteristics to describe the overall distribution of study variables. Child’s age at DTP1 was described by computing the percentage of children late for DTP1 (child’s age > 60 days at DTP1) among categories of all independent variables. Each independent variable was tested for its association with delay at DTP1 by computing crude Odds Ratio (OR) and its 95% Confidence Interval (CI) estimated by univariate logistic regression analysis in SAS®.

Multivariable logistic regression model was constructed in SAS® to assess the unconfounded association of independent variables with child’s age at DTP1. Adjusted ORs and their 95% CIs were used for the interpretation of the final model.
Human subjects

Approval for this study was obtained from the Ethical Review Committee (ERC) of The Aga Khan University (AKU), Karachi, Pakistan and the Institutional Review Board (IRB) of the University of Alabama at Birmingham (UAB).
RANDOMIZED CONTROLLED TRIAL TO IMPROVE CHILDHOOD IMMUNIZATION ADHERENCE IN RURAL PAKISTAN: REDESIGNED IMMUNIZATION CARD AND MATERNAL EDUCATION

by

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Format adapted for dissertation
ABSTRACT

Objective: A substantial dropout from the first dose of diphtheria-tetanus-pertussis (DTP1) to the 3rd dose of DTP (DTP3) immunization has been recorded in Pakistan. We conducted a randomized controlled trial to assess the effects on DTP3 completion of providing substantially redesigned immunization card, center-based education, or both interventions together at six rural Expanded Programme on Immunization (EPI) centers in Pakistan.

Methods: Mother-child units were enrolled at DTP1 and randomized to four study groups: redesigned card, center-based education, combined intervention, and standard care. Each child was followed-up for 90 days to record the dates of DTP2 and DTP3 visits. The study outcome was DTP3 completion by the end of follow-up period in each study group.

Findings: We enrolled 378 mother-child units in redesigned card group, 376 in center-based education group, 374 in combined intervention group, and 378 in standard care group. By the end of follow-up, 39% of children in standard care group completed DTP3. Compared to this, a significantly higher proportion of children completed DTP3 in redesigned card group (crude Risk Ratio [RR] = 1.7; 95% CI = 1.5, 2.0), center-based education group (RR = 1.5; 95% CI = 1.3, 1.8), and combined intervention group (RR = 1.7; 95% CI = 1.4, 2.0).

Conclusion: Improved immunization card alone, education to mothers alone, or both together were all effective in increasing follow-up immunization visits. The study underscores the potential of study interventions’ public health impact and necessitates their evaluation for complete EPI schedule at a large scale in the EPI system.
INTRODUCTION

In Pakistan and many other World Health Organization (WHO) member states, the Expanded Programme on Immunization (EPI) provides a series of vaccines to children during their first year of life. These include Bacillus Calmette-Guérin (BCG) and oral polio vaccine (OPV) at birth, three doses of diphtheria-tetanus-pertussis (DTP)/OPV/hepatitis B virus (HBV) vaccines at 6, 10, and 14 weeks, and measles vaccine at 9 months after birth. A principal indicator of immunization coverage levels by the WHO is the completion of three doses of DTP vaccine (DTP3) [1].

The nations in the Eastern Mediterranean Region and the South-East Asia Region of the WHO have consistently achieved higher aggregate immunization levels than has Pakistan. From 2002 to 2005, the WHO reported BCG immunization coverage in Pakistan was 80%-82% and DTP3 coverage was 65%-72%. During the same period, some 5%-26% of children who received BCG failed to complete measles immunization and 12%-13% of children who received DTP1 failed to complete DTP3 immunization [1].

The EPI in Pakistan is implemented through a countrywide network of EPI centers supplemented with outreach programs in some areas. The EPI provides all WHO recommended vaccines at no cost. Despite progress in last two decades, it is unclear whether the measures currently in place in Pakistan will be sufficient to reach desired immunization levels, given that dropouts between BCG and DPT3 are among the highest worldwide [2, 3]. These dropouts suggest that a substantial proportion of Pakistani mothers and other female caregivers (males are rarely involved; these are henceforth referred to as “mothers”) are sufficiently motivated and resourceful to visit the EPI centers once,
but are then confronted with actual or perceived barriers that preclude them to come back to the centers to complete their children’s immunization schedules.

We designed a randomized controlled trial to assess the effects on DTP3 completion of providing redesigned immunization card and center-based education to mothers at rural EPI centers in Pakistan.
METHODS

Setting

The trial was conducted at six EPI centers located in the rural peripheries of Karachi, the capital city of Sindh Province. Study centers were selected out of all rural centers around Karachi based on the highest volume of children vaccinated for DTP1 immunizations in previous year.

Eligibility and Enrollment

Any child visiting the selected EPI centers for DTP1 was eligible to participate in the study provided that the mother had been living in the area for last six months or more. This criterion was used to exclude temporary residents since Pakistani women commonly move to their mother’s house for a few weeks to deliver their first child. Given high illiteracy rates among Pakistani women, a trained interviewer read out the consent form to the mother of each eligible child. If the mother agreed to participate, the form was signed by the interviewer and a witness confirming the enrollment.

We used a structured questionnaire at enrollment to record information from mothers on socio-demographic variables and potential confounders. The questionnaire addressed parents’ attributes (age at enrollment, education, occupation, monthly household income, ethnicity, family size, and mother’s age at marriage and first conception), child’s attributes (age at enrollment, sex, and number of siblings), dates of DTP1-3 immunizations, and mode of transport and travel time to reach the EPI center.
Randomization

The lead investigator (H.R.U.) provided a computer generated randomization list to each enrollment center. At these centers, each enrolled mother-child unit received an identification number and was assigned to the study group corresponding to this number on the randomization list. Owing to the nature of interventions, neither the study participants nor the interviewers enrolling the study participants and recording the study outcome were blinded to the type of intervention received by the study participants.

Interventions

*Redesigned card:* The EPI card currently used in Pakistan has two main shortcomings. First, it is small (9 cm x 8.5 cm, when folded), hence the information on child’s identity, immunization schedule, information for mothers, and next immunization visit dates is crowded together and appears disorderly. Second, the next immunization date is hand written by the EPI staff, often in very small and irregular letters; as a result less literate mothers have difficulties reading the date of their child’s next immunization. To address these issues, we designed a new and simpler immunization card whose most important intended functions were to act as a constant reminder to mothers of the next immunization visit, and to make it easy for them to locate and read the date of the next immunization. Much larger than the existing EPI card (15.5 cm x 11.5 cm when folded), the redesigned card was bright yellow in color, placed in a plastic jacket, and provided with a hanging string. On its outer sides, the card showed nothing but the next immunization date and day of the week for DTP2 and DTP3 visits written in a large font (Times New Roman 42, Microsoft Word®) using preprinted stickers. Dedicated boxes were included
on the inner sides of the folded card to record the remainder of the information (name of the EPI center, card number, card’s date of issue, child’s name and address, complete immunization schedule dates, and instructions to the mothers). Despite a small purchase volume, the cost of each card including the plastic jacket was US$ 0.05 (Pakistani Rupees 3).

**Center-based education:** In Pakistan there is currently no standardized procedure describing how the EPI staff should inform mothers about subsequent immunization visits. Because mother’s lack of information might contribute to childhood immunization dropouts, the second intervention (center-based education) was designed as a 2-3 minutes conversation with mother to convey the importance of the completion of immunization schedule and to explain the potential adverse impact of incomplete immunization on child’s health. The session was in simple vocabulary in the local language (Urdu) and deliberately kept short in prevision of potential large-scale use by EPI staff in the future.

**Trial Design**

Mother-child units were randomly allocated to three intervention and one standard care groups. At the time of enrollment in the first intervention group ("Redesigned card"), a trained interviewer pasted the upcoming date and day of DTP2 immunization on both outer sides of the card. The interviewer showed the information to the mother; asked her to hang the card in her home at a frequently visible place; and requested that she bring the card along on her next immunization visit to the EPI center. At the time of the DPT2 visit, the interviewer crossed out the date and day for this visit to avoid any confusion to the mothers; pasted the date and day for the upcoming DTP3 immunization
visit on both sides of the card: and showed the information to the mother. Mothers in the second intervention group ("Center-based education") received center-based education from trained study interviewers. Mothers in the third intervention group ("Combined intervention") received both the redesigned card and center-based education in exactly the same way as described above. Finally, mothers of the last group ("Standard care") underwent routine EPI center visit and received neither intervention.

**Follow-up**

We followed-up each study child at the EPI center for 90 days from the day of enrollment at DTP1. Because each DTP2 and DTP3 were scheduled at 30-days intervals after DTP1 by EPI schedule, both DTP2 and DTP3 should have been completed ideally within 60 days after the DTP1 visit. During the study period, interviewers screened every child who visited a study center and recorded DPT2 and DPT3 dates of study children.

**Study outcome**

The study outcome was the immunization status of each child at the end of day 90 post enrollment. The immunization status was dichotomized into completion of both DTP2 and DTP3 (termed "DTP3 completed") versus completion of DTP2 only or neither immunization (termed "DTP3 not completed").

**Sample size**

Assuming DTP3 completion of 75% in the standard care group, we calculated that a sample size of 375 subjects in each study group would be sufficient to detect ≥ 10%
higher DTP3 completion in any one of the intervention groups than in the standard care group with 90% power and 5% unadjusted type-1 error.

Analysis

All analyses were performed using SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA) and were by intention to treat. To determine how successful the randomization process had been, we compared frequencies and percentages of participants’ baseline characteristics across study groups. The main independent variable was the type of intervention with the four group categories. The immunization status coded ‘1’ for “DTP3 completed” and ‘0’ for “DTP3 not completed” was the dependent variable. In primary analysis, we computed crude risk ratios (RRs) and their 95% confidence intervals (CIs) by univariate log-binomial regression (SAS® PROC GENMOD) to assess the effect of each intervention on DTP3 completion [4-7].

Because of important socioeconomic and cultural differences between Mohajir and non-Mohajir, we evaluated evidence of effect-measure modification by ethnicity on the efficacy of interventions. For this secondary analysis, we used log-binomial regression to compute crude and adjusted risk ratios separately among Mohajir and non-Mohajir ethnicities [4-7]. Because multivariable model constructed among Mohajirs failed to converge, the final model was reconstructed by multivariable Poisson regression with robust variance [4, 8].

Approval for this study was obtained from the Ethical Review Committee (ERC) of the Aga Khan University (AKU), Karachi, Pakistan and the Institutional Review Board (IRB) of the University of Alabama at Birmingham (UAB).
RESULTS

Of 2,371 mother-child units screened for eligibility between November 2005 and May 2006, 861 (36%) were excluded because they had arrived in the area within the past six months and four (0.2%) because they refused to participate (Figure 1). Enrollment was concluded after random allocation of 1506 study participants to the study groups. The follow-up of the last study child enrolled in the study was completed in August, 2006. Since the study participants who had not returned to the centers within 90 days of their DPT1 visit were considered DTP3 not completed, no study participant was considered lost to follow-up. In multivariable analysis, we excluded 15 children from the redesigned card group, 11 from the center-based education group, 7 from the combined intervention group, and 12 from the standard care group because of missing child’s age at enrollment.

The majority of informants in all study groups (77%-81%) were mothers; most of the other interviewees were other female caretakers, including grandmothers and aunts. The distribution of participants’ socio-demographic characteristics at enrollment was similar (p > 0.05) across study groups except for maternal age (p = 0.03; Table 1).
Figure 1: Flow of study participants
Table 1: Distribution among study groups of socio-demographic characteristics of study participants at enrollment (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Redesigned card</th>
<th>Center-based education</th>
<th>Combined intervention</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 378</td>
<td>n = 376</td>
<td>n = 378</td>
<td>n = 376</td>
</tr>
<tr>
<td></td>
<td>Column %</td>
<td>Column %</td>
<td>Column %</td>
<td>Column %</td>
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<tr>
<td>EPI center of enrollment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>20</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>D</td>
<td>28</td>
<td>28</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>E</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>17</td>
<td>16</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Mother of child as respondent</td>
<td>77</td>
<td>81</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohajir</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Pashto</td>
<td>33</td>
<td>31</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Punjabi</td>
<td>13</td>
<td>16</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Hindko</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Sindhi</td>
<td>9</td>
<td>9</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>12</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Child's age at enrollment (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>58</td>
<td>57</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>38</td>
<td>40</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Boys enrolled</td>
<td>51</td>
<td>49</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Total number of living children in the family</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>28</td>
<td>22</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Two</td>
<td>25</td>
<td>20</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Three or more</td>
<td>47</td>
<td>57</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Mother's age at enrollment (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>20 - 29</td>
<td>70</td>
<td>64</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>&gt; 29</td>
<td>20</td>
<td>30</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>
Table 1: Distribution among study groups of socio-demographic characteristics of study participants at enrollment (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Redesigned card</th>
<th>Center-based education</th>
<th>Combined intervention</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Column n = 378</td>
<td>Column n = 376</td>
<td>Column n = 378</td>
<td>Column n = 376</td>
</tr>
<tr>
<td></td>
<td>Column %</td>
<td>Column %</td>
<td>Column %</td>
<td>Column %</td>
</tr>
<tr>
<td>Mother's years of formal schooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>26</td>
<td>27</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>1 - 5</td>
<td>18</td>
<td>17</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>0</td>
<td>56</td>
<td>57</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Mother a housewife</td>
<td>96</td>
<td>99</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Father's years of formal schooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>53</td>
<td>49</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>1 - 5</td>
<td>15</td>
<td>17</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>35</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>≤ 5 household members</td>
<td>28</td>
<td>27</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Monthly household income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 5000</td>
<td>64</td>
<td>55</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>&gt; 5000</td>
<td>36</td>
<td>45</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Television in home</td>
<td>57</td>
<td>53</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Mode of transport to EPI center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public bus system</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Privately owned or rented motor</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>On foot</td>
<td>85</td>
<td>84</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>≤ 5 minutes to reach EPI center</td>
<td>20</td>
<td>22</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>from home</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
By the end of follow-up, 39% of children in the standard care group completed DTP3 (Table 2). Compared to this, a significantly higher proportion of children completed DTP3 in the redesigned card group (crude Risk Ratio [RR] = 1.7; 95% CI = 1.5, 2.0), the center-based education group (RR = 1.5; 95% CI = 1.3, 1.8), and the combined intervention group (RR = 1.7; 95% CI = 1.4, 2.0).

In secondary analysis, after adjusting for child’s age at enrollment and mother's formal years of schooling, a significantly higher proportion of Mohajir children completed DTP3 in the redesigned card group (Adjusted Risk Ratio [Adj. RR] = 3.0; 95% CI = 1.7, 5.3), the center-based education group (Adj. RR = 3.3; 95% CI = 1.9, 5.8), and the combined intervention group (Adj. RR = 3.0; 95% CI = 1.7, 5.4) compared with the standard care group (Table 3). Although a similar pattern of associations was observed among non-Mohajir children, the individual or combined effects of redesigned card and center based education on DTP3 completion were much weaker than among Mohajirs children (all pairwise comparisons: p<0.01).
Table 2: Crude Risk Ratios (RRs) and 95% Confidence Intervals (CIs) for DTP3 completion by intervention group (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Total</th>
<th>n</th>
<th>(%)</th>
<th>Crude RR*</th>
<th>95% CI**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redesigned card</td>
<td>378</td>
<td>252</td>
<td>(67)</td>
<td>1.7</td>
<td>(1.5, 2.0)</td>
</tr>
<tr>
<td>Center-based education</td>
<td>376</td>
<td>228</td>
<td>(61)</td>
<td>1.5</td>
<td>(1.3, 1.8)</td>
</tr>
<tr>
<td>Combined intervention</td>
<td>374</td>
<td>245</td>
<td>(66)</td>
<td>1.7</td>
<td>(1.4, 2.0)</td>
</tr>
<tr>
<td>Standard care</td>
<td>378</td>
<td>149</td>
<td>(39)</td>
<td>1.0†</td>
<td></td>
</tr>
</tbody>
</table>

*RR = Risk Ratio  
**CI = Confidence Interval  
†A risk ratio of 1.0 indicates the reference category
Table 3: Crude and adjusted Risk Ratios (RRs) with 95% Confidence Intervals (CIs) for DTP3 completion by intervention group among Mohajirs and non-Mohajirs children (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Total</th>
<th>n   (%)</th>
<th>Crude RR</th>
<th>95% CI**</th>
<th>Adjusted RR</th>
<th>95% CI**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mohajir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redesigned card</td>
<td>56</td>
<td>46</td>
<td>3.0</td>
<td>(2.0, 4.7)</td>
<td>3.0</td>
<td>(1.7, 5.3)</td>
</tr>
<tr>
<td>Center-based education</td>
<td>51</td>
<td>46</td>
<td>3.3</td>
<td>(2.2, 5.1)</td>
<td>3.3</td>
<td>(1.9, 5.8)</td>
</tr>
<tr>
<td>Combined intervention</td>
<td>49</td>
<td>40</td>
<td>3.0</td>
<td>(1.9, 4.7)</td>
<td>3.0</td>
<td>(1.7, 5.4)</td>
</tr>
<tr>
<td>Standard care</td>
<td>59</td>
<td>16</td>
<td>1.0†</td>
<td></td>
<td>1.0†</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Mohajir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redesigned card</td>
<td>322</td>
<td>206</td>
<td>1.5</td>
<td>(1.3, 1.8)</td>
<td>1.5</td>
<td>(1.3, 1.8)</td>
</tr>
<tr>
<td>Center-based education</td>
<td>325</td>
<td>182</td>
<td>1.3</td>
<td>(1.1, 1.6)</td>
<td>1.3</td>
<td>(1.1, 1.6)</td>
</tr>
<tr>
<td>Combined intervention</td>
<td>325</td>
<td>205</td>
<td>1.5</td>
<td>(1.3, 1.8)</td>
<td>1.5</td>
<td>(1.3, 1.7)</td>
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<tr>
<td>Standard care</td>
<td>319</td>
<td>133</td>
<td>1.0†</td>
<td></td>
<td>1.0†</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable model adjusted for child’s age at enrollment and mother’s years of formal schooling. Child’s age at enrollment was not available for one child each in Group 1, Group 2, and Group 3 among Mohajirs and 14 children in Group 1, 10 in Group 2, 6 in Group 3, and 12 in Group 4 among non-Mohajirs.

*RR = Risk Ratio
**CI = Confidence Interval
†A risk ratio of 1.0 indicates the reference category
Note: All pairwise comparisons: p<0.01
DISCUSSION

This study suggests that providing an inexpensive redesigned immunization card or a short center-based education are both effective interventions to increase subsequent immunization visits to the EPI centers. We found no evidence that providing both interventions in combination was superior to providing the redesigned immunization card or the brief education session alone. Because either intervention is inexpensive and easy to implement, there would probably be no harm in delivering them together to inspire mothers to bring their infants for subsequent vaccines.

In developing countries, interventions conducted to improve immunization coverage may be classified into those targeting the supply of immunization and those focusing on the demand for immunization. Our study assessed two demand-side interventions that targeted children who were already in the EPI system. Successful supply-side interventions have used different approaches to improve staff performance such as enhanced monitoring and supervision [9], training in a classroom [10], or training by peers in the field [11]. Other effective supply-side approaches focused on increasing access to immunization by making modifications to the vaccination schedule (e.g., delivering vaccines earlier or at shorter intervals) [12-14], reorganizing clinic procedures to shorten waiting times [15], and bringing immunization services closer to the people using outreach teams [16-18] or community health workers [19]. Interventions that have proved effective in stimulating the demand for vaccination among children with incomplete immunization include reminders sent to the home of target children [20] and door-to-door household visits to notify parents that their child is late for a vaccine [21, 22]. Redesigning the immunization card and testing its effect on immunization dropouts has not received atten-
tion in developing countries. Recent articles, reviewing published studies [23] and the grey literature [24] on strategies to improve childhood immunization coverage in low and middle-income countries, could not identify any study attempting to redesign the immunization card and evaluating its impact on immunization visits.

The redesigned immunization card tested in this study has several characteristics that make it an appealing and viable option to improve the vaccine delivery system in rural Pakistan. Because the new card was designed considering the sparse level of EPI staffing and the additional cost incurred to the EPI system, we believe that the large scale implementation of the new card in the EPI system would not require any additional work from EPI staff and only minimally add to the cost per child immunized. Based on our study estimates of DTP3 completion among the redesigned card and standard care groups (Table 2), and assuming DTP1 coverage at 72% as reported by WHO for 2004, a country wide implementation of the redesigned card in rural areas would translate into around 600,000 additional children immunized for DTP3 in an annual rural Pakistani birth cohort of 2.8 million children [25]. Another potential advantage of using the redesigned card in the EPI system is that mothers may retain the new card for a longer period due to its attractive design, plastic jacket, and larger size resulting in more accurate estimation of immunization coverage by cross-sectional surveys. At present, these surveys rely heavily on mother’s recall as the existing EPI card is usually not available with the majority of mothers at the time of surveys [26, 27].

In secondary analysis, we observed that the effects on DTP3 completion of redesigned card and center based education were stronger among Mohajirs than among non-Mohajirs. The exact reason for this finding is unclear. Although a key difference between,
the two ethnic groups is that Mohajirs are better educated on average than non-Mohajirs [25, 28], adjustment for mother’s years of formal schooling did not substantially affect the differences in intervention effects between the two ethnic groups. Future studies should explore the reasons for this discrepancy in responsiveness to interventions.

A limitation of our study is that the follow-up of study children for return visits was limited to 90 days and carried out only at the study centers. There is a chance that a small proportion of children might have returned to the study centers after 90, or days visited non-study EPI centers for DTP2 and DTP3. Supporting this hypothesis, the WHO reported coverage of 82% for DTP1 and 72% for DTP3 in Pakistan for 2005. This suggests that 88% (72/82*100) of children who received DTP1 went on to complete DTP3; in contrast, no more than 39% of the children enrolled in the standard care group of our study completed DTP3 in 90 days follow-up (Table 2). Comparison of these figures must be done with caution, however, since our estimates came from a cohort of children followed at EPI centers whereas the WHO estimates were calculated using DTP1 and DTP2 coverage. Dropouts in the rural area where our study was conducted are also likely to have been higher than the country level estimated reported by the WHO. Finally, survival curves of days to DTP3 for each study group indicated a plateau at around 80 days of follow-up making it unlikely that a large number of children returned for DTP3 after 90 days (data not shown).

Immunization coverage is a function of the proportion of newborns that an immunization system brings in for the first immunization and the proportion of these children who eventually complete all immunizations recommended in the schedule. Due to time and resource constraints, we tested the effect of study interventions on two follow-up
immunization visits (DTP2 and DTP3) scheduled after DTP1. Because complete EPI schedule in Pakistan has four follow-up visits (DTP1, DTP2, DTP3, and measles) after BCG at birth, we cannot predict the effectiveness of proposed interventions for the complete EPI schedule. Furthermore, low immunization coverage cannot be effectively addressed solely by reducing the dropouts; interventions to bring more newborns in the EPI system are equally important.

In conclusion, this study offers strong evidence that both a redesigned immunization card and maternal education were effective to enhance subsequent infant vaccine visits. Because these low-cost interventions have the potential to yield considerable benefits for children, the next step will be to evaluate them for complete EPI schedule at a large scale in the EPI system.

Acknowledgments

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Conflict of interest

None declared.
REFERENCES


DETERMINANTS OF DIPHTHERIA-TETANUS-PERTUSSIS THIRD DOSE (DTP3) COMPLETION AMONG CHILDREN VISITING IMMUNIZATION CENTERS FOR THE FIRST DOSE (DTP1) IN RURAL PAKISTAN: A COHORT STUDY

by

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ABSTRACT

Background: In Pakistan, a high proportion of children fail to complete third dose of diphtheria-tetanus-pertussis (DTP3) after having received the first dose (DTP1). A cohort study was conducted to identify the factors predicting DTP3 completion among children who have received DTP1 at Centers of Expanded Programme on Immunization (EPI) in rural Pakistan.

Methods: We analyzed a cohort of mother-child pairs enrolled at DTP1 in the standard care group of a larger randomized controlled trial. Each child was followed-up for 90 days to record dates of DTP2 and DTP3.

Results: At six EPI centers, only 39% (149/378) of enrolled children completed DTP3 during the follow-up period. After adjusting for the center of enrollment in multivariable log-binomial regression analysis, DTP3 completion was higher among children who were ≤ 60 days old at enrollment [adjusted risk ratio (Adj. RR) = 1.4, 95% confidence interval (CI): 1.1, 1.8], who were living in a household with monthly household income > Rs. 3000 (US$ 50) (Adj. RR = 1.8; 95% CI: 1.2, 2.7), and who were living ≤ 10 minutes away from EPI center (Adj. RR = 1.3; 95% CI: 1.04, 1.7).

Conclusion: This study finds that child’s younger age at DTP1, higher household income, and shorter traveling time to EPI center are significant predictors of DTP3 completion among children who received DTP1. Efforts to reduce DTP1 to DTP3 dropouts in Pakistan should focus on these factors. Geographic location of EPI centers should be reviewed with reference to population density to reduce travel time for mothers.
INTRODUCTION

In most World Health Organization (WHO) member states, the Expanded Programme on Immunization (EPI) provides a series of childhood immunizations during the first year of life including vaccines for tuberculosis (Bacillus Calmette-Guérin; BCG), diphtheria-tetanus-pertussis (DTP), poliovirus (oral vaccine; OPV), hepatitis B virus (HBV), and measles. In Pakistan and many other WHO member states, the EPI schedule includes the administration of BCG/OPV vaccines at birth, three doses of DTP/OPV/HBV vaccines at 6, 10, and 14 weeks, and measles vaccine at 9 months after birth. By the WHO, completion of three doses of DTP (DTP3) vaccine is a principal indicator of immunization coverage levels [1].

Immunization coverage levels in Pakistan have been consistently lower than the socioeconomically comparable WHO member nations of the Eastern Mediterranean Region and the South-East Asia Region. In Pakistan from 2002 to 2005, the BCG coverage was recorded at 80%-82% and DTP3 coverage at 65%-72%. During that period, about 5%-26% of the children who received BCG failed to complete measles immunization. Similarly, about 12%-13% of children who received DTP1 did not complete DTP3 [1]. These dropouts have been among the highest worldwide, only matched by some countries of the African Region [2, 3]. The current 80% BCG coverage suggests that the majority of mothers/caregivers (henceforth simply referred to as “mothers”) are both motivated and resourceful enough to visit the EPI centers for BCG vaccinations. However, the much lower DTP3 and measles coverage indicates that a substantial proportion do not manage to complete the immunization schedule.
In developing countries, low adherence to immunization schedule has been found associated with parental socio-demographic characteristics (e.g., larger family size, lower parental education) and provider based characteristics (e.g., longer distance of EPI center from home) [4-7]. Behavioral factors (e.g., mothers’ lack of information and poor motivation) have also predicted both poor adherence to immunization recommendations and high risk of dropouts [8-10].

Pakistani literature on barriers to childhood immunization is sparse and mainly reported from cross-sectional studies [11-13]. In these studies, child’s immunization status was primarily assessed by mother’s recall due to the unavailability of immunization cards at the time of interview. Such assessment of child’s immunization status is liable to misclassification [14, 15]. Thereby, the internal validity of these studies is questionable. Moreover, it is important to understand why some children do not return for subsequent immunization after visiting EPI centers for initial immunizations. To address these limitations, we used documented evidence of immunization status and conducted this cohort study to identify the determinants of DTP3 completion among children who have received their DTP1 at rural EPI centers in Pakistan.
METHODS

Study design

In a larger randomized controlled trial, mother-child pairs were enrolled at DTP1 and randomized to three intervention groups and a standard care group. For this follow-up study, only the participants enrolled in the standard care group of the trial were analyzed as a cohort of mother-child pairs.

Setting

The study was conducted at six rural EPI centers located in the peripheries of Karachi, the capital city of Sindh Province. Study centers were selected out of all rural centers around Karachi based on the highest volume of children vaccinated for DTP1 immunizations in the previous year. Housed in government dispensaries and basic health units, these centers provide primary health care to the rural population in their catchment areas. Mostly, infants from the lower and middle socio-economic tiers of the country received immunization at EPI centers. All immunizations provided by EPI are at no cost.

Participants

Any child visiting the selected EPI centers for DTP1 was eligible to participate in the study, provided that the mother had been the resident of the area for at least last six months. The six months residency requirement was used to exclude women temporarily living for few weeks in their mother’s home for the birth of the child. Given low literacy rates among Pakistani women, a trained interviewer read out the consent form to the
mother of each eligible child. The interviewer and a witness signed the consent form for each consenting mother and completed the enrollment.

After enrollment at DTP1, mother was interviewed and each study child was followed-up at the EPI center for 90 days. By the EPI schedule, each DTP2 and DTP3 was scheduled at 30-days intervals after DTP1. Therefore, both DTP2 and DTP3 should have been completed ideally within 60 days after the DTP1 visit. During the study period, interviewers screened every child who visited a study center and recorded DTP2 and DTP3 dates of study children.

Variables

A structured questionnaire, pre-tested at EPI centers not included in this study, was used at enrollment to record information from mothers on factors which could potentially influence the completion of immunization. The questionnaire included parents’ attributes (parents’ age at enrollment, mother’s age at marriage and first conception, parents’ education and occupation, monthly household income, ethnicity, and family size), child’s attributes (child’s age at enrollment, child’s sex, and number of siblings), and mode of transport and travel time to reach the EPI center. All these variable were assessed as independent variables in the analysis.

The study outcome was the immunization status of each child at the end of 90 days after enrollment. The immunization status was dichotomized into completion of both DTP2 and DTP3 (termed “DTP3 completed”) versus completion of DTP2 only or neither immunization (termed “DTP3 not completed”).

44
Statistical methods

All analyses were performed using SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA). Overall distribution of participants’ characteristics in the study cohort was described by computing their frequencies and percentages. The immunization status was the dependent variable and was coded ‘1’ for “DTP3 completed” and ‘0’ for “DTP3 not completed.” Since the study participants who had not returned to the centers for either DTP2 or DTP3 visits within 90 days of their DPT1 visit were considered DTP3 not completed, no study participant was considered lost to follow-up.

The distribution of DTP3 completion was assessed by computing its percentage among the categories of independent variables. In univariate log-binomial regression analysis (SAS® PROC GENMOD), we computed crude Risk Ratio (RR) and 95% Confidence Interval (CI) to assess the association of each independent variable with DTP3 completion [16-19]. Multivariable log-binomial regression model (SAS® PROC GENMOD) was constructed to assess the unconfounded association of independent variables with DTP3 completion. Adjusted RRs and their 95% CIs were used for the interpretation of the final model.

Approval for this study was obtained from the Institutional Review Board (IRB) of the University of Alabama at Birmingham (UAB) and the Ethical Review Committee (ERC) of The Aga Khan University (AKU), Karachi, Pakistan.
RESULTS

Between November 2005 and May 2006, a total of 378 mother-child pairs were enrolled in the study from six EPI centers. The follow-up of the last study child was completed in August, 2006. Child’s age at DTP1 was not available for 12 children; therefore data on 366 mother-child pairs were used for the multivariable analysis.

The majority (80%) of respondents in the study was mothers (Table 1). Prominent ethnic groups enrolled were Pashto (32%), Hindko (18%), and Mohajir (16%). Almost half of the study children were girls and 59% were ≤ 60 days old at enrollment. More than half of mothers never went to school and almost all were housewives. Fathers were better educated than mothers and were mostly laborers (42%), private employees (26%), or owned private business (20%). The majority (77%) of children lived in households with more than five members and 84% of households had monthly income of > 3000 Pakistani Rupees (50 USD). About half (47%) of study participants travelled ≤ 10 minutes to reach the EPI center.
Table 1: Association of factors with DTP3 completion shown by crude Risk Ratios (RRs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 378</th>
<th>Column (%)</th>
<th>Row (%)</th>
<th>Crude RR*</th>
<th>95% CIs **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relationship of respondent with child</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>304</td>
<td>(80)</td>
<td>(39)</td>
<td>0.93</td>
<td>(0.68, 1.3)</td>
</tr>
<tr>
<td>Others</td>
<td>74</td>
<td>(20)</td>
<td>(42)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindko</td>
<td>69</td>
<td>(18)</td>
<td>(52)</td>
<td>1.9</td>
<td>(1.2, 3.1)</td>
</tr>
<tr>
<td>Pashto</td>
<td>120</td>
<td>(32)</td>
<td>(46)</td>
<td>1.7</td>
<td>(1.1, 2.7)</td>
</tr>
<tr>
<td>Punjabi</td>
<td>41</td>
<td>(11)</td>
<td>(41)</td>
<td>1.5</td>
<td>(0.88, 2.7)</td>
</tr>
<tr>
<td>Sindhi</td>
<td>41</td>
<td>(11)</td>
<td>(37)</td>
<td>1.4</td>
<td>(0.75, 2.4)</td>
</tr>
<tr>
<td>Others</td>
<td>48</td>
<td>(13)</td>
<td>(21)</td>
<td>0.77</td>
<td>(0.38, 1.5)</td>
</tr>
<tr>
<td>Mohajir</td>
<td>59</td>
<td>(16)</td>
<td>(27)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Child's age at enrollment (n=366)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60 days</td>
<td>215</td>
<td>(59)</td>
<td>(47)</td>
<td>1.6</td>
<td>(1.2, 2.1)</td>
</tr>
<tr>
<td>&gt; 60 days</td>
<td>151</td>
<td>(41)</td>
<td>(30)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Child's sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>186</td>
<td>(49)</td>
<td>(40)</td>
<td>1.0</td>
<td>(0.79, 1.3)</td>
</tr>
<tr>
<td>Girl</td>
<td>192</td>
<td>(51)</td>
<td>(39)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of living children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>185</td>
<td>(49)</td>
<td>(43)</td>
<td>1.2</td>
<td>(0.94, 1.6)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>193</td>
<td>(51)</td>
<td>(36)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mother's age at enrollment (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19</td>
<td>31</td>
<td>(8)</td>
<td>(26)</td>
<td>0.73</td>
<td>(0.38, 1.4)</td>
</tr>
<tr>
<td>20-29</td>
<td>257</td>
<td>(68)</td>
<td>(42)</td>
<td>1.2</td>
<td>(0.87, 1.6)</td>
</tr>
<tr>
<td>&gt; 29</td>
<td>90</td>
<td>(24)</td>
<td>(36)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mother's age at first conception (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 18</td>
<td>252</td>
<td>(67)</td>
<td>(42)</td>
<td>1.2</td>
<td>(0.90, 1.6)</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>126</td>
<td>(33)</td>
<td>(35)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mother's years of formal schooling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 0</td>
<td>170</td>
<td>(45)</td>
<td>(42)</td>
<td>1.1</td>
<td>(0.87, 1.4)</td>
</tr>
<tr>
<td>0</td>
<td>208</td>
<td>(55)</td>
<td>(38)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mother's occupation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>House wife</td>
<td>372</td>
<td>(98)</td>
<td>(39)</td>
<td>0.78</td>
<td>(0.35, 1.8)</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>(2)</td>
<td>(50)</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
Table 1: Association of factors with DTP3 completion shown by crude Risk Ratios (RRs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 378</th>
<th>Column (%)</th>
<th>Row (%)</th>
<th>Crude RR*</th>
<th>95% CIs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP3 completed during 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father's years of formal schooling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>51</td>
<td>(13)</td>
<td>(49)</td>
<td>1.4</td>
<td>(0.98, 2.1)</td>
</tr>
<tr>
<td>1-10</td>
<td>203</td>
<td>(54)</td>
<td>(40)</td>
<td>1.2</td>
<td>(0.86, 1.6)</td>
</tr>
<tr>
<td>0</td>
<td>124</td>
<td>(33)</td>
<td>(35)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Father's occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>9</td>
<td>(2)</td>
<td>(44)</td>
<td>1.0</td>
<td>(0.48, 2.3)</td>
</tr>
<tr>
<td>Government servant</td>
<td>37</td>
<td>(10)</td>
<td>(49)</td>
<td>1.1</td>
<td>(0.75, 1.7)</td>
</tr>
<tr>
<td>Private employee</td>
<td>97</td>
<td>(26)</td>
<td>(41)</td>
<td>0.97</td>
<td>(0.68, 1.4)</td>
</tr>
<tr>
<td>Laborer (unskilled worker)</td>
<td>160</td>
<td>(42)</td>
<td>(34)</td>
<td>0.81</td>
<td>(0.57, 1.1)</td>
</tr>
<tr>
<td>Owned private business</td>
<td>75</td>
<td>(20)</td>
<td>(43)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Number of household members</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>87</td>
<td>(23)</td>
<td>(51)</td>
<td>1.4</td>
<td>(1.1, 1.8)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>291</td>
<td>(77)</td>
<td>(36)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Monthly household income (Pak Rs.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt; 3000</td>
<td>317</td>
<td>(84)</td>
<td>(42)</td>
<td>1.7</td>
<td>(1.1, 2.7)</td>
</tr>
<tr>
<td>0-3000</td>
<td>61</td>
<td>(16)</td>
<td>(25)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Mode of transport to EPI center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public bus system</td>
<td>23</td>
<td>(6)</td>
<td>(35)</td>
<td>0.70</td>
<td>(0.35, 1.4)</td>
</tr>
<tr>
<td>On foot</td>
<td>329</td>
<td>(87)</td>
<td>(39)</td>
<td>0.78</td>
<td>(0.52, 1.2)</td>
</tr>
<tr>
<td>Privately owned or rented vehicles</td>
<td>26</td>
<td>(7)</td>
<td>(50)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Travel time to reach EPI center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 minutes</td>
<td>178</td>
<td>(47)</td>
<td>(44)</td>
<td>1.3</td>
<td>(0.99, 1.6)</td>
</tr>
<tr>
<td>&gt; 10 minutes</td>
<td>200</td>
<td>(53)</td>
<td>(35)</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

*RR = Risk Ratio  
**CI = Confidence Interval
Univariate analysis

During the 90 days follow-up period, 39% (149/378) of enrolled children completed DTP3. The proportion of children completing DTP3 ranged from 14% to 65% at different study centers. In univariate analysis, children of Hindko (RR = 1.9; 95% CI = 1.2, 3.1) and Pashto (RR = 1.7; 95% CI = 1.1, 2.7) ethnicity, compared with Mohajir children, were more likely to complete DTP3 (Table 2). Also, a higher proportion of children who were ≤ 60 days old at enrollment completed DTP3 (RR = 1.6; 95% CI = 1.2, 2.1) compared to those children who were > 60 days old at enrollment. Similarly, more children from households with ≤ 5 members (RR = 1.4; 95% CI = 1.1, 1.8) and monthly income of > Rs. 3000 (US$ 50) (RR = 1.7; 95% CI = 1.1, 2.7) completed DTP3. DTP3 completion was also higher among children who traveled ≤ 10 minutes to reach the EPI center (RR = 1.3; 95% CI = 0.99, 1.6) when compared with children who traveled < 10 minutes to reach EPI center.

Multivariable analysis

After adjusting for the center of enrollment in multivariable log-binomial regression analysis, DTP3 completion was higher among children who were ≤ 60 days old at enrollment [adjusted risk ratio (Adj. RR) = 1.4, 95% confidence interval (CI): 1.1, 1.8], who were living in a household with monthly household income > Rs. 3000 (US$ 50) (Adj. RR = 1.8; 95% CI: 1.2, 2.7), and who were living ≤ 10 minutes away from the EPI center (Adj. RR = 1.3; 95% CI: 1.04, 1.7) (Table 2).
Table 2: Multivariable analysis of the factors associated with DTP3 completion shown by Adjusted Risk Ratios (RRs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006) (n=366)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted RR*</th>
<th>95% CIs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child's age at enrollment (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>1.4</td>
<td>(1.1, 1.8)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Monthly household income (Pak Rs.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>1.8</td>
<td>(1.2, 2.7)</td>
</tr>
<tr>
<td>0-3000</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Travel time to reach EPI center</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 minutes</td>
<td>1.3</td>
<td>(1.04, 1.7)</td>
</tr>
<tr>
<td>&gt; 10 minutes</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

RR = Risk Ratio, model adjusted for the center of enrollment
**CIs = Confidence Intervals

Variables: Adjusted RR* 95% CIs**
DISCUSSION

Despite having an extensive network of EPI centers and universal availability of childhood vaccines at no cost for the general population, Pakistan has never achieved desirable immunization coverage of DTP3 [1]. This study estimated that after having received DTP1 at rural EPI centers, a very low proportion (39%) of children completed DTP3 during 90 days follow-up. The study also identified that a child’s age at DTP1 immunization, monthly household income, and travel time to reach the EPI center were significant predictors of DTP3 completion.

Overall immunization coverage is determined by proportion of newborns that an immunization system brings in for the first immunization and the proportion of these children who complete subsequent immunizations. In our study, we enrolled children at DTP1 and followed them at EPI centers to estimate the proportion of these children completing DTP3. Therefore, this study only focused on those children who were already in the EPI system by having received DTP1. The factors identified in this study are primarily the predictors of DTP3 completion among children who have already received DTP1 and should be differentiated from cross sectional studies which compared fully or partially immunized children with not immunized children. That may be the reason why factors such as mother’s education [20-25], family size [23], child’s sex [23], and number of siblings [23, 25], identified frequently in low and middle income countries as predictors of immunization coverage using cross sectional design, did not show significant association with DTP3 completion in this study. This may also indicate that factors predicting immunization completion may differ both within and among developing countries, particularly when rural areas are considered. Also, possibility of differential misclassification of im-
munization status in cross sectional studies cannot be ruled out; leading to false identification of many socio-demographic factors as predictor of immunization completion.

According to the EPI schedule, a 45 day old child should be brought to the EPI centers for DTP1 immunization [1]. In this study, only 59% of the children were ≤ 60 days old at DTP1 visit. This demonstrates that delay in receiving DTP1 is common in Pakistani rural areas. Higher proportion of younger children (≤ 60 days old at DTP1) completing DTP3 in our study suggested that if children received DTP1 in a timely manner they were more likely to complete subsequent immunizations according to the schedule. Therefore, mothers should be encouraged to bring their children on time for their initial immunizations (e.g. DTP1). Not receiving DTP1 on time, on the other hand, might relate to much broader health-seeking behaviors of the population and needs further investigation.

Assessment of child’s age at initial immunizations as a predictor of subsequent immunization has been rare in developing country settings. Most of the studies conducted in these settings used a cross-sectional study design and assessed immunization status primarily by mother’s recall [11-13]. In these studies, child’s age at specific immunizations was inherently difficult to document and therefore not possible to explore it as a predictor of follow-up immunization visits. However, due to the availability of immunization records in the United States and other developed countries, studies from these settings have reported significantly higher immunization coverage of subsequent immunizations among children who were up-to-date (UTD) at 3 months of age [26-30].

Monthly household income was the strongest predictor of immunization completion in the final model. Children from households with monthly incomes > Rs. 3000
(US$ 50) were about 80% more likely to complete DTP3. Other studies have also suggested a positive association between socioeconomic status and immunization coverage [28, 31, 32].

In this study, 47% of study participants traveled ≤ 10 minutes to reach the EPI center for DTP1. These study participants were 30% more likely to complete DTP3 when compared to those who travelled > 10 minutes to reach EPI center. Close proximity to the immunization site has been found associated with a higher immunization uptake both in Pakistan [33, 34] and in other countries of the developing world [23, 35-38]. Spending more time to reach a health center is a natural disincentive especially for childhood immunizations which requires multiple visits to complete the series of doses. The reach of general population to EPI centers could be improved by setting up new EPI centers and geographic relocation of existing EPI centers based on population density.

For 2005 in Pakistan, the WHO reported DTP1 (82%) and DTP3 (72%) coverage suggests that 88% (72/82*100) of children who received DTP1 went on to complete DTP3. However, no more than 39% of the children enrolled in our study completed DTP3 in 90 days follow-up (Table 2). Our estimates came from a cohort of children followed at EPI centers whereas the WHO estimates were calculated using DTP1 and DTP3 coverage. Therefore, comparison of these very differently calculated figures may be done with caution. Secondly, this study could not account for those children who did not return to the study centers but might have gone to other centers for subsequent immunizations and those who might have returned after 90 days follow-up period. Also, dropouts in rural areas are expected to be higher than the country level estimated reported by the WHO.
Nonetheless, our stated reasoning might not fully explain the wide gap between the study and the WHO estimates.

A substantial variation in DTP3 completion across study centers was recorded in this study. This might have been due to different geographic location of EPI centers with respect to the socio-demographics characteristics of the population living in their catchment areas. The contribution of center characteristics as a predictor of immunization completion should be evaluated in future studies.

We chose RRs over odds ratios (ORs) to assess the strength of association between the predictors and DTP3 completion. Crude and adjusted RRs as well as their 95% CIs were estimated using proc genmod in SAS® by log-binomial regression [16-19]. The study outcome i.e. the proportion of children completing DTP3 was not rare and reporting OR would have been an overestimation of actual effect size.

There are limitations in our study. Due to limited time and resource constraints, the childhood immunization cohort was followed for the partial immunization schedule i.e. from DTP1 to DTP3. To fully explore the predictors of the entire immunization schedule completion, a cohort of children for the complete EPI schedule i.e. from BCG to measles will have to be followed. Another limitation was that the follow-up of study children for return visits was carried out only at the study centers. There is a chance that a small proportion of study children might have visited non-study EPI centers for DTP2 and DTP3, leading to underestimation of DTP3 completion in our study. Finally, our follow-up of each study child for not more than 90 days after enrollment (at DTP1) means that we may have lost some children who returned for DTP3 after that time. However, the survival curve of days to DTP3 (data not shown) indicated a plateau at around 80 days of
follow-up and it was not expected to have a large number of children returning for DTP3 after 90 days.

In conclusion, this study provides strong evidence that a very low proportion of children who receive DTP1 at rural EPI centers in Pakistan return to complete DTP3. Important determinants of DTP3 completion are child’s younger age at DTP1, higher monthly household income, and shorter travel time to reach an EPI center. Efforts to improve DTP3 coverage in Pakistan should target these factors. Studies exploring the factors influencing child’s age at DTP1 are needed. We also recommend studies to investigate the issue of distance to EPI center using Geographic Information Systems (GIS). Such GIS based studies should aim at evaluating the geographic locations of existing EPI centers with reference to the population density. Based on such studies, appropriate relocation of existing EPI centers and creation of new EPI centers may decrease the travel time to the EPI centers and result in fewer immunization dropouts.

Acknowledgements

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Conflict of interest

None declared.
REFERENCES


FACTORS ASSOCIATED WITH DELAY AT FIRST DIPHTHERIA-TETANUS-PERTUSSIS (DTP1) IMMUNIZATION IN RURAL PAKISTAN

by

HUSSAIN R. USMAN, SIBYLLE KRISTENSEN, M. HOSSEIN RAHBAR, STEN H. VERMUND, RUSSELL S. KIRBY, AND ERIC CHAMOT

In preparation for *Tropical Medicine & International Health*

Format adapted for dissertation
ABSTRACT

Objectives: Present reporting of childhood immunization coverage does not reveal the actual degree of under-immunization because of not fully accounting for the delay in receiving recommended immunizations. We estimated the delay at first dose of diphtheria-tetanus-pertussis (DTP1) immunization and identified the factors associated with this delay.

Methods: In this cross-sectional study, we enrolled mother-child pairs at DTP1 and recorded child’s age and socio-demographic characteristics of participants using a pre-tested structures questionnaire.

Results: A total of 1461 mother-child pairs enrolled from six immunization centers were analyzed. Child’s mean age at DTP1 was 70 days (SD 43; median 55 days) instead of recommended 45 days. About 39% of children were > 60 days old at DTP1. In the final multivariable logistic regression model, factors significantly associated with delay at DTP1 (child’s age > 60 days at DTP1) after adjusting for the center of enrollment were a child’s father educated in school for ≤ 10 years (Adjusted Odds Ratio [Adj. OR] 1.7, 95% CI: 1.2-2.4), a child’s father owning a private business (Adj. OR 2.1, 95% CI: 1.3-3.3) or being unemployed (Adj. OR 1.5, 95% CI: 1.1-2.0) compared to being a government servant, a child of Mohajir ethnicity (Adj. OR 1.9, 95% CI: 1.2-3.1) compared to Hindko, and reaching immunization centers on a public bus system (Adj. OR 1.7, 95% CI: 1.1-2.8).

Conclusions: A substantial proportion of rural children in Pakistan were late for DTP1 immunization. Specific knowledge of these factors can help target certain population sub-groups for special outreach programs.
INTRODUCTION

Immunizations are considered to be the most cost-effective public health intervention for the prevention and control of childhood infections [1]. In Pakistan and most World Health Organization (WHO) member states, the Expanded Programme on Immunization (EPI) provides a series of childhood immunizations during the first year of life for tuberculosis (Bacillus Calmette-Guérin; BCG), diphtheria-tetanus-pertussis (DTP), poliovirus (oral vaccine; OPV), hepatitis B virus (HBV), and measles [2]. The WHO Department of Immunization, Vaccines and Biologicals publish an annual global summary on immunization coverage to assess the performance of EPI in each member state [2].

Although the present WHO reporting of immunization coverage provides valuable information on immunization status at a population level [2, 3], it does not completely reveal the actual degree of under-immunization [4]. The WHO immunization coverage estimates are mainly derived from officially reported coverage by WHO member states, EPI 30-cluster surveys, Demographic and Health Surveys (DHS), UNICEF Multiple Indicator Cluster Surveys (MICS), unpublished surveys available from Ministries of Health, and recommendations from local and external experts [2]. Officially reported estimates from member states are calculated (for example for DTP1) by dividing the number of children who received the first dose of DTP with the estimated number of children who survived their first birthday. Hence, these coverage estimates do not specify the age at which children received immunization for each dose.

Other major source of coverage is population based cross sectional surveys. In these studies, the immunization status among children 13-24 months old, is primarily assessed by mother’s recall due to the unavailability of immunization cards at the time of
interview [5, 6]. Therefore, these studies inherently lack the ability to record child’s age at specific immunizations. This weakness in coverage data is not limited to developing and under developed countries [4, 7].

Receiving immunization at appropriate age is important. Children with lengthier immunization delays experience longer periods of increased susceptibility to infections than those children with shorter or no immunization delays [8]. Accordingly, information on children’s age at specific immunizations is critical for assessing the risk of vaccine preventable infections in the population. It is particularly essential for those infections in which younger age is related to higher incidence and severity of illness such as measles. Also important is to identify the factors associated with delay in immunization. Knowledge of the extent of delay in immunization and its risk factors will help public health authorities in designing interventions to improve age appropriate immunizations. Therefore, to provide evidence based information for public health action, we conducted a cross-sectional study at rural EPI centers of Pakistan to document children’s age at DTP1 immunization and to identify factors associated with delay at DTP1 immunization.
METHODS

Setting

This cross sectional study was conducted at six rural EPI centers located in the peripheries of Karachi, the capital city of Province Sindh, Pakistan. Study centers were selected out of all rural centers around Karachi based on the highest volume of children vaccinated for DTP1 immunizations in the previous year. Housed in government dispensaries and basic health units, these centers provided primary health care to the rural population in their catchment areas.

Participants

Any child visiting the selected EPI centers for DTP1 was eligible to participate in the study, provided that the mother had been the resident of the area for no less than six months. Because of low literacy among rural Pakistani women, a trained interviewer read out the consent form to the mother of each eligible child to obtain the consent. If the mother consented to participate, the consent form was signed by the interviewer and a witness to complete the enrollment. In a larger randomized controlled trial, each mother was interviewed using a structured questionnaire and randomized to either one of the three intervention groups or a standard care group. For this cross-sectional analysis, we used the baseline data collected from mothers at enrollment.

Variables

We used a pre-tested structured questionnaire at enrollment to record information from mothers on parents’ attributes (parents’ age at enrollment, mother’s age at marriage
and first conception, parents’ education and occupation, monthly household income, ethnicity, and family size), child’s attributes (child’s age at enrollment, child’s sex, and number of siblings), and mode of transport and travel time to reach the EPI center.

Study Outcome

The study outcome was child’s age at DTP1 immunization dichotomized into > 60 days or ≤ 60 days. EPI recommended age for DTP1 immunization is 45 days.

Analysis

All analyses were performed using SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA). We calculated children’s mean and median age at DTP1 and proportion of children > 60 days old at DTP1. Child’s age at DTP1 was dichotomized into > 60 days (coded ‘1’) or ≤ 60 days (coded ‘0’) and used as the depended variable for univariate and multivariable analysis. Variables assessed for their potential association with the dependent variable were considered as independent variables.

We computed frequencies and percentages participant’s characteristics to describe the overall distribution of study variables. Child’s age at DTP1 was described by computing the percentage of children late for DTP1 (child’s age > 60 days at DTP1) among categories of all independent variables. Each independent variable was tested for its association with delay at DTP1 by computing crude Odds Ratio (OR) and its 95% Confidence Interval (CI) estimated by univariate logistic regression analysis in SAS®.

Multivariable logistic regression model was constructed in SAS® to assess the unconfounded association of independent variables with delay at DTP1. The variable indi-
cating the EPI center of enrollment was always kept in the model. Other variables were entered in the model one by one, starting with the most significant variable in the univariate analysis. Significance of individual independent variable in the multivariable analysis was assessed by its confidence interval. Adjusted ORs and their 95% CIs were used for the interpretation of the final model.

Approval for this study was obtained from the Institutional Review Board (IRB) of the University of Alabama at Birmingham (UAB) and the Ethical Review Committee (ERC) of The Aga Khan University (AKU), Karachi, Pakistan.
RESULTS

Between November 2005 and May 2006, a total of 1506 mother-child pairs were enrolled in the study from the six EPI centers. Child’s age at DTP1 was not available for 45 children; therefore data on 1461 mother-child pairs were used for the analysis. Children’s mean age at DTP1 was 70 days (SD 43; median 55 days) and 39% of children were > 60 days old at DTP1 immunization. Only 9% of children were less than or equal to EPI recommended age of 45 days.

The majority (79%) of study respondents was mothers and almost half of the study children were girls (Table 1). Mother’s age at enrollment for 92% of mothers was ≥ 20 years, 57% never went to school, and 98% were housewives. Years of formal schooling for 88% of fathers was ≤ 10 years and the majority was laborers (43%) followed by private employees (26%), owned private business (19%), and government servants (10%). Prominent ethnic groups enrolled in the study were Pashto (32%), Hindko (19%), Mohajir (15%), and Punjabi (14%). Fifty one percent of the enrolled children had more than two children in their family, 75% had more than five household members, and 84% had monthly household income of > 3000 Pakistani Rupees (50 USD). About half (51%) of study participants travelled ≤ 10 minutes to reach the EPI center and the majority (92%) either travelled on foot or used privately owned or rented vehicles.
Table 1: Association of characteristics with delay at DTP1 (child's age > 60 days at DTP1) shown by crude Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total= 1461</th>
<th>Children &gt; 60 days old at DTP1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Column (%)</td>
<td>Row (%)</td>
</tr>
<tr>
<td></td>
<td>Crude OR*</td>
<td>95% CIs**</td>
</tr>
<tr>
<td>Relationship of respondent with child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>1158 (79)</td>
<td>(40)</td>
</tr>
<tr>
<td>Others</td>
<td>303 (21)</td>
<td>(35)</td>
</tr>
<tr>
<td>Child's sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>737 (50)</td>
<td>(39)</td>
</tr>
<tr>
<td>Girl</td>
<td>724 (50)</td>
<td>(39)</td>
</tr>
<tr>
<td>Mother's age at enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 29</td>
<td>367 (25)</td>
<td>(41)</td>
</tr>
<tr>
<td>20-29</td>
<td>975 (67)</td>
<td>(38)</td>
</tr>
<tr>
<td>≤ 19</td>
<td>119 (8)</td>
<td>(37)</td>
</tr>
<tr>
<td>Mother's age at first conception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 18</td>
<td>1026 (70)</td>
<td>(39)</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>435 (30)</td>
<td>(39)</td>
</tr>
<tr>
<td>Mother's years of formal schooling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>833 (57)</td>
<td>(41)</td>
</tr>
<tr>
<td>1-5</td>
<td>254 (17)</td>
<td>(38)</td>
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<tr>
<td>≥ 6</td>
<td>374 (26)</td>
<td>(34)</td>
</tr>
<tr>
<td>Mother's occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>32 (2)</td>
<td>(50)</td>
</tr>
<tr>
<td>Housewife</td>
<td>1429 (98)</td>
<td>(39)</td>
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<tr>
<td>Father's years of formal schooling</td>
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<td></td>
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<tr>
<td>≤ 10</td>
<td>1281 (88)</td>
<td>(41)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>180 (12)</td>
<td>(28)</td>
</tr>
<tr>
<td>Father's occupation</td>
<td></td>
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<tr>
<td>Owned private business</td>
<td>276 (19)</td>
<td>(45)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>34 (2)</td>
<td>(41)</td>
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<tr>
<td>Laborer (unskilled worker)</td>
<td>631 (43)</td>
<td>(40)</td>
</tr>
<tr>
<td>Private employee</td>
<td>374 (26)</td>
<td>(38)</td>
</tr>
<tr>
<td>Government servant</td>
<td>146 (10)</td>
<td>(27)</td>
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</table>
Table 1: Association of characteristics with delay at DTP1 (child's age > 60 days at DTP1) shown by crude Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) (Pakistan, 2005-2006)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total= 1461</th>
<th>Column (%)</th>
<th>Row (%)</th>
<th>Crude OR*</th>
<th>95% CIs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mohajir</td>
<td>212 (15)</td>
<td>(49)</td>
<td>2.1</td>
<td>(1.5, 3.1)</td>
<td></td>
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<tr>
<td>Sindhi</td>
<td>140 (10)</td>
<td>(41)</td>
<td>1.5</td>
<td>(1.0, 2.3)</td>
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<tr>
<td>Pashto</td>
<td>468 (32)</td>
<td>(40)</td>
<td>1.5</td>
<td>(1.1, 2.0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>166 (11)</td>
<td>(39)</td>
<td>1.4</td>
<td>(0.96, 2.1)</td>
<td></td>
</tr>
<tr>
<td>Punjabi</td>
<td>201 (14)</td>
<td>(37)</td>
<td>1.3</td>
<td>(0.90, 1.9)</td>
<td></td>
</tr>
<tr>
<td>Hindko</td>
<td>274 (19)</td>
<td>(31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of living children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2</td>
<td>745 (51)</td>
<td>(40)</td>
<td>1.1</td>
<td>(0.86, 1.3)</td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>716 (49)</td>
<td>(38)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of household members</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt; 5</td>
<td>1093 (75)</td>
<td>(40)</td>
<td>1.1</td>
<td>(0.89, 1.5)</td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>368 (25)</td>
<td>(37)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly household income (Pak Rs.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3000</td>
<td>228 (16)</td>
<td>(42)</td>
<td>1.1</td>
<td>(0.86, 1.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3000</td>
<td>1233 (84)</td>
<td>(39)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of transport to EPI center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public bus system</td>
<td>92 (6)</td>
<td>(48)</td>
<td>1.5</td>
<td>(0.96, 2.2)</td>
<td></td>
</tr>
<tr>
<td>On foot or privately owned or rented vehicle</td>
<td>1369 (94)</td>
<td>(38)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travel time to reach EPI center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 minutes</td>
<td>721 (49)</td>
<td>(39)</td>
<td>1.0</td>
<td>(0.82, 1.2)</td>
<td></td>
</tr>
<tr>
<td>≤ 10 minutes</td>
<td>740 (51)</td>
<td>(39)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR = Odds Ratio

**CI = Confidence Interval
The proportion of children late for DTP1 (child’s age > 60 days at DTP1) ranged from 27% to 54% among the study centers. In univariate logistic regression analysis, children whose mothers never attended school were more likely to be late for DTP1 (OR 1.3, 95% CI 1.0-1.7) compared to those whose mothers attended school for ≥ 6 years (Table 1). Similarly, significant delay at DTP1 was recorded among children whose fathers had ≤ 10 years of schooling (OR 1.8, 95% CI: 1.3-2.5) compared to when fathers had > 10 years of schooling. Also, more children were late for DTP1 if father owned private business (OR 2.2, 95% CI: 1.4-3.4), was a laborer (OR 1.8, 95% CI: 1.2-2.7), or was private employee (OR 1.7, 95% CI: 1.1-2.6) compared to if father was a government servant. Considering ethnicity, more Mohajir (OR 2.1, 95% CI: 1.5-3.1), Sindhi (OR 1.5, 95% CI: 1.0-2.3), and Pashto (OR 1.5, 95% CI: 1.1-2.0) children were late for DTP1 compared to Hindko children. Also, more children were late for DTP1 if they were brought to the EPI centers on public bus system (OR 1.5, 95% CI: 0.96-2.2) compared to those who came to the EPI centers on foot or privately owned or rented vehicles.

In the final multivariable logistic regression model (Table 2), factors significantly associated with delay at DTP1 (child’s age > 60 days at DTP1) after adjusting for the center of enrollment were a child’s father educated in school for ≤ 10 years (Adjusted Odds Ratio [Adj. OR] 1.7, 95% CI: 1.2-2.4) compared to > 10 years, a child’s father owning a private business (Adj. OR 2.1, 95% CI: 1.3-3.3) or being unemployed (Adj. OR 1.5, 95% CI: 1.1-2.0) compared to being a government servant, a child of Mohajir ethnicity (Adj. OR 1.9, 95% CI: 1.2-3.1) compared to Hindko, and reaching immunization centers on a public bus system (Adj. OR 1.7, 95% CI: 1.1-2.8) compared to by other means of transport.
Table 2: Results of multivariable logistic regression analysis of characteristics associated with delay at DTP1 at six rural EPI centers in Pakistan (2005-2006) (n=1461)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR*</th>
<th>95% CI**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Father's years of formal schooling</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>1.7</td>
<td>(1.2, 2.4)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Father's occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owned private business</td>
<td>2.1</td>
<td>(1.3, 3.3)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.5</td>
<td>(1.1, 2.0)</td>
</tr>
<tr>
<td>Laborer (unskilled worker)</td>
<td>1.2</td>
<td>(0.9, 1.7)</td>
</tr>
<tr>
<td>Private employee</td>
<td>1.1</td>
<td>(0.5, 2.3)</td>
</tr>
<tr>
<td>Government servant</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohajir</td>
<td>1.9</td>
<td>(1.2, 3.1)</td>
</tr>
<tr>
<td>Pashto</td>
<td>1.2</td>
<td>(0.9, 1.7)</td>
</tr>
<tr>
<td>Punjabi</td>
<td>1.1</td>
<td>(0.7, 1.7)</td>
</tr>
<tr>
<td>Others</td>
<td>1.0</td>
<td>(0.6, 1.6)</td>
</tr>
<tr>
<td>Sindhi</td>
<td>0.9</td>
<td>(0.5, 1.7)</td>
</tr>
<tr>
<td>Hindko</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of transport to EPI center</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public bus system</td>
<td>1.7</td>
<td>(1.1, 2.8)</td>
</tr>
<tr>
<td>On foot or privately owned or rented vehicle</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable model also adjusted for center of enrollment (not shown in the table)

*OR = Odds Ratio  
**CI = Confidence Interval
DISCUSSION

We found that only 9% of children received their DTP1 vaccine at less than or equal to the EPI recommended age of 45 days and 39% of children were more than 60 days old. We identified that lower education of father, father being unemployed or owning a private business, children of Mohajir ethnicity, and need to travel by bus to reach the EPI center were independently associated with DTP1 immunization delay. These data can help target highest risk subsets of the population for special vaccine advocacy and outreach.

Despite having an extensive network of EPI centers and universal availability of childhood vaccines at no cost for the general population, Pakistan has never achieved desirable immunization coverage [2]. Furthermore, the extent of under-immunization in Pakistan is even greater as the immunization status assessed solely by coverage data tends to understate the degree of under-immunization in a population [7] as indicated by the delay at DTP1 reported in our study. Therefore, present efforts directed solely at improving the immunization coverage may not translate into herd immunity at a population level for the prevention of vaccine preventable infections [9].

Nationwide surveillance of delays at each immunization visit through sentinel EPI centers in different geographic and demographic areas of Pakistan is necessary to quantify the delays and monitor its trends [4]. Currently, our EPI system records child’s age at each immunization received at the EPI centers. However, these data are not used to assess the delays at the national level. Utilization of data from at least a few representative EPI centers may successfully reflect the national picture. However, a full and efficient utilization of these data warrants computerized immunization registry that requires massive
capital and human resource investment and may not be possible for Pakistan in near future.

Our literature search revealed that immunization coverage [2] and barriers of immunization [10-14] have been the focus of studies in developing countries and the topic of age appropriate immunization has not received much attention [15, 16]. However, it has been extensively investigated in developed countries [17] especially in United States [4, 7, 18-21]. It is important to note in our study that paternal factors such as father’s years of formal schooling and occupation [10] were significantly associated with delay at DTP1 unlike other studies in which maternal factors were more likely to predict age appropriate immunization [15, 16, 21]. This may possibly have to do with decision making norms in Pakistani society. Especially in rural areas, women are not totally independent to make decisions for those tasks that require that they leave their homes, like going out to the EPI center [22-24].

Mothers travelling on public bus system were more likely to bring their children at an older age for the DTP1 visit. Public bus travel in Karachi is cumbersome both in terms of the time it takes you to reach your destination and the condition of buses. Also, our study centers were located at the rural peripheries of Karachi where the coverage of bus system is very thin [25]. An expected practice of mothers would be to procrastinate if public bus is their most likely mode of transport to the EPI center. In addition, to avoid mother’s close contact with other people on the bus, the head of the household may delay his permission to the mother to travel on bus [22-24]. Other studies have also associated transport difficulties with low immunization coverage [26, 27] and delayed or no immunization [28].
Our finding that Mohajir children are more likely to be late for DTP1 is a surprise since Mohajir are usually more educated [29], more aware of health issues, and more likely to adhere to health-related recommendations. One possible explanation is that Mohajir who mostly live in urban areas [29] might be different from the ones living in rural areas. The association of ethnicity with other health conditions in Pakistan [30-33] and ethnic difference in childhood immunization status in United States [19] is not uncommon.

There are limitations in our study. Study findings are limited to the rural areas of Pakistan and pertain to the DTP1 immunization visit only. The extent of delay in the urban areas might be different from the rural areas as there are major socio-demographic differences between urban and rural populations of Pakistan [34]. Also, other immunization visits such as at DTP3 and measles are expected to have even greater delays as these visits are scheduled to occur further down the immunization schedule. Our study did not measure the delay at those immunization visits.

In conclusion, this study documents delay at DTP1 immunization in rural Pakistan and provides baseline information for further research in the area of age appropriate immunization in Pakistan. Future studies should further explore delays at each immunization visit of the EPI schedule especially at DTP3 and measles. We also recommend modeling studies to estimate the burden of vaccine preventable diseases attributable to delay in immunization. Our study also provides important insight into the factors associated with delay at DTP1 for public health interventions targeting these factors to improve age appropriate immunization. Mode of transport to EPI center may be addressed in the short term by geographic relocation of EPI centers with reference to the population density.
This may prevent delays in immunization by enabling more mothers to walk to the EPI centers and avoiding travelling on public bus system.

Acknowledgments

This work was supported by the Sparkman Center for Global Health; and National Institute of Health grant the University of Alabama at Birmingham-Aga Khan University International Maternal and Child Health Research and Training (IMCHRT) program [D43TW005497]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank the EPI Sindh, Pakistan for granting permission and extending cooperation for this study.

Conflict of interest

None declared.
REFERENCES


SUMMARY CONCLUSIONS

Overall Results

The findings from this randomized controlled trial suggest that providing an inexpensive redesigned immunization card or a short center-based education are effective interventions to increase subsequent immunization visits to the EPI centers. We found no evidence, however, indicating that providing both interventions in combination is superior to providing the redesigned immunization card or the brief education session alone.

Only 39% of children in the standard care group completed DTP3. Compared to this, a significantly higher proportion of children completed DTP3 in the redesigned card group (crude Risk Ratio [RR] = 1.7; 95% CI = 1.5, 2.0), the center-based education group (RR = 1.5; 95% CI = 1.3, 1.8), and the combined intervention group (RR = 1.7; 95% CI = 1.4, 2.0). In secondary analysis, after adjusting for child’s age at enrollment and mother's formal years of schooling, a significantly higher proportion of Mohajir children completed DTP3 in the redesigned card group (Adjusted Risk Ratio [Adj. RR] = 3.0; 95% CI = 1.7, 5.3), the center-based education group (Adj. RR = 3.3; 95% CI = 1.9, 5.8), and the combined intervention group (Adj. RR = 3.0; 95% CI = 1.7, 5.4) compared with the standard care group. Although a similar pattern of associations was observed among non-Mohajir children, the individual or combined effects of redesigned card and center based education on DTP3 completion were much weaker than among Mohajirs children (all pairwise comparisons: p<0.01).

Separate analysis of standard care group found that after adjusting for the center of enrollment in multivariable log-binomial regression analysis, DTP3 completion was higher among children who were ≤ 60 days old at enrollment (Adj. RR = 1.4, 95% CI =
1.1, 1.80, who were living in a household with monthly household income > Rs. 3000 (US$ 50) (Adj. RR = 1.8; 95% CI = 1.2, 2.7), and who were living ≤ 10 minutes away from the EPI center (Adj. RR = 1.3; 95% CI = 1.04, 1.7).

Analysis of enrollment data estimated that children’s mean age at DTP1 was 70 days (SD 43; median 55 days) instead of recommended 45 days. In final multivariable logistic regression model, factors significantly associated with delay at DTP1 (child’s age > 60 days at DTP1) after adjusting for the center of enrollment were father educated in school for ≤ 10 years (Adjusted Odds Ratio [Adj. OR] 1.7, 95% CI = 1.2, 2.4) compared to > 10 years, father owned private business (Adj. OR 2.1, 95% CI = 1.3-3.3) or unemployed (Adj. OR 1.5, 95% CI = 1.1, 2.0) compared to a government servant, ethnically Mohajir (Adj. OR 1.9, 95% CI = 1.2, 3.1) compared to Hindko, and reaching immunization centers on public bus system (Adj. OR 1.7, 95% CI = 1.1, 2.8) compared to other means of transport.

Strengths

Because of the study design (randomized controlled trial), random allocation of participants to study arms allowed equal distribution of participants’ characteristics across study groups. Therefore, the study groups differed from each other only by the type of intervention they received, facilitating assessment of independent effect of interventions on DTP3 completion.

Findings from this study on the effect of proposed interventions on immunization completion, barriers of immunization completion, factors associated with immunization delay, and the extent of dropouts and delay in immunization add to the body of know-
ledge about the state of childhood immunization in Pakistan. We hope that these findings will help policy makers, not only in Pakistan but also in other resource poor countries, to make changes in the EPI system to improve the age appropriate immunization coverage.

Follow-up analysis, of the study arm that did not receive any intervention, to identify the predictors of immunization completion allowed us to establish a temporal relationship between the predictors and the immunization completion. Furthermore, we computed crude and adjusted RRs by Poisson regression for the trial and log-binomial regression for the follow-up study using proc genmod in SAS® to estimate the effect size. We strongly recommend these analyses techniques for follow-up studies in which the study outcome is not rare.

Limitations

There are several limitations in our study. Because of limited time and resources, we tested the effect of study interventions on two follow-up immunization visits (DTP2 and DTP3) scheduled after DTP1. However, complete EPI schedule in Pakistan has four follow-up visits (DTP1, DTP2, DTP3, and measles) after BCG at birth. Therefore, we cannot predict the effectiveness of proposed interventions for complete EPI schedule. Before recommending these interventions to policy makers for implementation in the EPI, we suggest future studies to assess their usefulness for complete EPI schedule. Another limitation was that the follow-up of study children for return visits was carried out only at the study centers. There is a chance that a small proportion of study children might have visited other EPI centers for DTP2 and DTP3. If for some reason, more mothers chose to do so in the standard care group compared to the intervention groups, then our study results might have overestimated the effect of interventions on DTP3 completion. However,
we don’t have any data to support or refute this possibility. One more limitation of the study was the follow-up of each study child for not more than 90 days after enrollment (at DTP1). It is likely that a few children might have returned for DTP3 after that. However, survival curves of days to DTP3 (data not shown) for each study group indicated a plateau at around 80 days of follow-up and we did not expect a substantial number of children returning for DTP3 after 90 days.

The findings of this study are limited to the rural areas of Pakistan. There are major socio-demographic differences between urban and rural populations of Pakistan and the effect of interventions, barriers of immunization completion, and the extent of dropouts and delay in immunization might be different in urban areas of Pakistan. Also, other scheduled immunization visits such as at DTP3 and measles are expected to have even greater delays as these visits are scheduled to occur further down in the immunization schedule. Our study did not measure the delay at those immunization visits.

Implications

This study offers strong evidence that providing an improved immunization card and center-based education designed for low literacy population are effective interventions to reduce childhood immunization dropouts. Based on our study estimates of DTP3 completion among redesigned card group (67%) and standard care group (39%) (Table 2) and assuming DTP1 coverage at 72% as reported by WHO for 2004, a country wide implementation of only redesigned card in rural areas is estimated to translate into around 600,000 additional children immunized for DTP3 in an annual rural Pakistani birth cohort of 2.8 million children.
This study documents that a significant proportion of children fail to complete DTP3 immunization after having received DTP1 and provides strong evidence that child’s age at DTP1, monthly household income, and travel time to reach EPI center are important predictors of childhood immunization completion. We recommend interventions encouraging mothers to get their children immunized on time. Our study reveals further information for policy makers by reporting that a significant proportion of rural children in Pakistan are late for DTP1 immunization and father’s education and occupation, ethnicity, and mode of transport used to reach the EPI center are important factors associated with delay at DTP1.

We recommend future research to evaluate the effect of proposed interventions on the completion of all immunizations in EPI schedule. We also recommend studies further exploring the issue of distance from EPI center by utilizing Geographic Information Systems (GIS). Such GIS based studies should aim at evaluating the geographic locations of existing EPI centers in reference to the population density and their distance from the households. Appropriate relocation of existing EPI centers and locations for new EPI centers should be recommended based on such studies. Future studies should further explore delays at each immunization visit of the EPI schedule especially at DTP3 and measles. We also recommend modeling studies to estimate the burden of vaccine preventable diseases attributable to dropouts and delay in immunization.
GENERAL LIST OF REFERENCES


Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and the approval period is for three years. The Assurance number is FWA00005960.

Principal Investigator: USMAN, HUSSAIN RAZA
Co-Investigator(s):
Protocol Number: X050713007
Protocol Title: Effect of Redesigned Immunization Card and Centre Based Education to Mothers/Caregivers on the Adherence to WHO-EPI Schedule in Rural Pakistan

The IRB reviewed and approved the above named project on 11-07-05. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.
IRB Approval Date: 11/02/05
Date IRB Approval Issued: 11-07-05

HIPAA Waiver Approved?: Yes

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
UAB IRB Approval of Waiver of Authorization/Waiver of Informed Consent

☐ Approval of Waiver of Informed Consent to Participate in Research. The IRB reviewed the proposed research and granted the request for waiver of informed consent to participate in research, based on the following findings:
1. The research involves no more than minimal risk to the subjects.
2. The research cannot practically be carried out without the waiver.
3. The waiver will not adversely affect the rights and welfare of the subjects.
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Check one: □ and Waiver of Authorization (below)
☑ or Waiver of Authorization (below)
□ Waiver of Authorization not applicable

☐ Approval of Waiver of Patient Authorization to Use PHI in Research. The IRB reviewed the proposed research and granted the request for waiver of patient authorization to use PHI in research, based on the following findings:
1. The use/disclosure of PHI involves no more than minimal risk to the privacy of individuals
   • There is an adequate plan to protect the identifiers from improper use and disclosure.
   • There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention that is otherwise required by law.
   • There is an assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The research cannot practically be conducted without the waiver or alteration.
3. The research cannot practically be conducted without access to and use of the PHI.

☐ The IRB reviewed the proposed research at a convened meeting at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The Alteration or waiver of authorization or waiver of consent (please circle) was approved by the majority of the IRB members present at the meeting.

Date of Meeting  Signature of Chair, Vice-Chair or Designee  Date

---OR---

☐ The IRB used an expedited review procedure since the research involves no more than minimal risk to the privacy of the individuals who are the subject of the protected health information for which use or disclosure is being sought. The review and approval of the alteration, waiver or authorization or waiver of consent (please circle) was carried out by the Chair of the IRB, and by one of the Vice Chairs of the IRB as designated by the Chairman of the IRB.

Date of Expedited Review  Signature of Chair, Vice-Chair or Designee  Date

11/09/05  11/09/05

Rev. 3/17/2003  470 Administration Building  205.934.3789  Fax 205.934.1301  irb@uab.edu
The University of Alabama at Birmingham  Mailing Address:
701 20th Street South  AR 470
BIRMINGHAM AL 35294-0104  1520 3RD AVE S
Title of Research: Effect of redesigned immunization card and centre based education to mothers/caregivers on the adherence to WHO-EPI schedule in rural Pakistan

Investigator: Dr. Hussain Raza Usman

Sponsors: John J. Sparkman Center for International Public Health Education
International Maternal and Child Health Research and Training
University of Alabama at Birmingham, Alabama, USA

Explanation of Procedures

You are being asked to participate in a research study to test a new immunization card and a new way to inform mothers about vaccinations for children.

If you are willing to participate in this study, we will ask you a series of questions. The interview will take about 15 to 20 minutes. Questions will be asked about you and your home. We will also ask questions to record your knowledge about childhood immunization. After the interview, you will either receive the new card or center based education or both new card and education or regular immunization card only.

Risks and Discomforts

The potential harm to you or your child from participating in this study is no greater than that encountered in day-to-day living.

Benefits

You may not personally benefit from your participation in this research; however, your participation may provide valuable information to the medical community about childhood immunization.

Alternatives

The alternative is to choose not to participate in this study.
Confidentiality

The information gathered during this study will be kept confidential. We will not share the information obtained from you with anybody other than the investigators of this project. The information obtained from you is only for scientific purposes and your identity will not be revealed to anybody at any stage of the study. The information obtained from this study will be shared with scientific community in a summarized form and no individual information will be shared with anybody. However, the University of Alabama at Birmingham, USA, Institutional Review Board for Human Use and the Sponsors, the John J. Sparkman Center for International Public Health and International Maternal and Child Health Research and Training, may review the research records for auditing purposes.

Withdrawal Without Prejudice

You are free to withdraw your consent and to discontinue participation in this project at any time without prejudice.

Cost of Participation

There will be no cost to you from participation in the research.

Payment for Participation in Research

You will not receive any payment for participating in this study.

Questions

If you have any questions about the research or a research related injury, Dr. Hussain Raza Usman will be glad to answer them. Dr. Usman’s number is 021-4864811. You may contact Ms. Farnaz Naqvi the Department of Community Health Sciences, The Aga Khan University, Karachi, regarding your rights as a research participant. She may be reached at 021-4864811.

Legal Rights

You are not waiving any of your legal rights by participating in this study.
The signatures below indicate we have read and discussed the information above with __________________ and all questions have been answered.

(Name of Participant)

__________________________  __________________
Signature of Witness        Date

__________________________  __________________
Signature of person obtaining consent  Date
Consent Form

رضامندی نام

تحقیق کا موضوع

نئی کارڈ آلر مارکر کو معلومات دینے کا بحور کے حفاظتی ثبوت کے شیڈول مکمل کرنا کے بارے میں تحقیق

معاون

John I. Sparkman Center for Global Health
University of Alabama at Birmingham, Alabama, USA

تحقیق کی مقاصد اور طریقہ کار

پر آپ سے اس تحقیق میں شمولیت کی درخواست کرتے ہیں بہت نئی کارڈ آلر مارکر کو معلومات دینے کا بحور
کی حفاظتی ثبوت کے شیڈول مکمل کرنا پر اثر دیکھنا کی سکو گا۔ پر آپ میں آپ کی بھی کہ ایک کہ
بارے میں معلومات پر بھی سال کرنا گا۔ اگر یہ پر اثر کھو گا، پر آپ کو کہ پر اثر کھو

مکمل ہے آرامی

اس سرور کے بارے میں آپ کر کونی ہے آرامی یا خطوں لاحق نہیں گا۔

تحقیق میں شمولیت کا فائدہ

پر مسکاتی ہے کہ آپ کو اس تحقیق میں شمولیت کا کونی فائدہ نظر نہ آئے سکر آپ کی شمولیت سے سماجی

مشق کو بارے میں اپ معلومات حاصل بھی گی۔

متبادل

متبادل ہے یہ کہ آپ اس تحقیق میں شمول نہیں ہوں۔

UAB-IRB
Consent Form Noted 110705
Expiration Date 110706
رائداري

اب پر حاصل کی گئی معلومات مکمل طور پر رائداري سے محفوظ رکھی جانی گئی اپ سے لی گئی معلومات
کسی کوئی فراغت نہیں جاگے گی اب سے لی گئی معلومات ریسروج کے مقصد کے لئے اپ سے اور اپ کی
شناخت کسی کو بھی نہیں باتی گئی اس ریسروج سے حاصل کی گئی والی معلومات سانداسون کے علوا
University of Alabama at Birmingham, USA, Institutional Review Board for Human Use, and the sponsors John J. Sparkman Center
for Global Health and International Maternal and Child Health Research and Training.

اس معلومات کو دیکھ سکتےہیں

بنا کوئی اثر کے تحقیق سے عملہ کی

اسن تحقیق مرنے کی شمولیت آپ کی مرنے کی سے ہوگی کسی بھی وقت آپ تحقیق میں شمولیت ختم کر
سکتے ہیں اور اپ کے کردار سے اپ بی پر کوئی اثر نہیں ہوگا.

شمولیت کا خرچ

تحقیق مرن شامل بونے کی لئی اپ کو کوئی پیسے دیں یا ضرورت نہیں.

شمولیت کا معاوضہ

تحقیق مرن شامل بونے کا اپ کو کوئی معاوضہ نہیں دیا جاتا گا.

سوالات

اگر آپ کو اس تحقیق کے بارے میں کوئی سوالات ہو تو ہم کوئی سوالات کے جوابات نہیں گی اب اس سے اپ کی سوالات کے
پر رابطہ کر سکتےہیں 021-5948-4811

قانونی ضابطہ

اس تحقیق کے رضامندی نامہ پر دستخط کرئے سے اپ کوئی قانونی حقوق نہیں چھوڑ رہی رہیہ
دستخط

بچی جہت کے دستخط سے ظاہر ہے کہ بم نیے اس فارم میں شامل ہوئے کو یہاں دیہ بہت کہ تمام سوالون کے جواب دینے کے لئے بہت تریخ

گوادر کے دستخط

فارم بہتے والے کے دستخط

تاریخ
Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB’s Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and expires on February 14, 2009. The Assurance number is FWA00005960.

Principal Investigator: USMAN, HUSSAIN RAZA
Co-Investigator(s): 
Protocol Number: X050713007
Protocol Title: Effect of Redesigned Immunization Card and Centre Based Education to Mothers/Caregivers on the Adherence to WHO-EPI Schedule in Rural Pakistan

The IRB reviewed and approved the above named project on 10/10/06. The review was conducted in accordance with UAB’s Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.
IRB Approval Date: 10-10-06
Date IRB Approval Issued: 10/10/06

HIPAA Waiver Approved?: N/A

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:
The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
Form 4: IRB Approval Form
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Principal Investigator: USMAN, HUSSAIN RAZA
Co-Investigator(s):
Protocol Number: X050713007
Protocol Title: Effect of Redesigned Immunization Card and Centre Based Education to Mothers/Caregivers on the Adherence to WHO-EPI Schedule in Rural Pakistan

The IRB reviewed and approved the above named project on 10-02-07. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 10-02-07
Date IRB Approval Issued: 10-02-07

HIPAA Waiver Approved?: N/A

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

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