The "Reducing Delays in Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination

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Amanda F. Dempsey[1]; Jason Glanz[2]; Nicole Wagner[2]; Jennifer Pyrzanowski[1]; Komal Narwaney[2]; Carter Sevick[1]; Courtney Kraus[2]; Kathy Gleason[2]; Bethany Kwan[1]; Kenneth Resnicow[3]; Jessica Cataldi[1]; Sarah Brewer[1]

Affiliations:

[1] Adult and Child Consortium for Outcomes Research and Delivery Science (ACCORDS), University of Colorado Denver, Aurora, CO

[2] Kaiser Permanente Colorado, Institute for Health Research, Denver CO

[3] School of Public Health, Division of Health Behavior and Health Education, University of Michigan, Ann Arbor, MI

Aim and Hypothesis

The primary aim of this study is to conduct a three-group randomized, intervention trial to measure the effectiveness of the values-framed individually tailored messaging Vaccines and Your Baby (VAYB) intervention. The primary hypothesis to be tested is that infants of mothers who receive the VAYB intervention will be more up to date on vaccination and mothers will have lower levels of vaccine hesitancy than those receiving an untailored version of the intervention or those receiving usual care. A secondary aim of the project is to assess the impact of the intervention on vaccination attitudes.

Methods

Study Design

This study includes longitudinal follow-up for a 3-armed, individually randomized clinical trial.

Study arms include:

1) the tailored (VAYB) intervention

2) an untailored version of the intervention (untailored)

3) usual care (UC).

Study Setting

Kaiser Permanente Colorado (KPCO) is a nonprofit, managed care organization. There are approximately 667,000 member with approximately 5,000 pregnancies annually and 140,000 children receiving care at KPCO clinics.

Study Population and Inclusion/Exclusion Criteria

Inclusion

1. Currently enrolled at KPCO
2. Plan to use KPCO medical care for their child
3. English speaking
4. >18 years of age
5. Last trimester of pregnancy, based on clinically determined expected delivery date

Exclusion Criteria

1. Any of the following conditions confirmed in the electronic medical record (EMR) or patient report
    a. fetus has a high-risk condition (e.g., fatal heart condition, trisomy 18, anencephaly),
    b. spontaneous or elective abortion
    c. social issues (such as domestic violence)
    d. serious health concerns for the mother

Participants are screened for eligibility using the (EMR). Chart reviews are conducted on patients with health indicators of exclusion criteria in the EMR. If exclusion criteria are confirmed, participants are not recruited for the study.

Study participants can enroll from the first recruitment outreach that occurs in the last trimester of pregnancy to when their infant is $\leq$ 2 months of age. Participants are removed from the study if they have a fetal demise, infant death, if the infant loses KPCO insurance coverage for greater than 90 days, if they request to be removed from the study or if they die. This data is obtained from a monthly data extraction from the EMR and patient report.

Consent and Recruitment

Eligible participants are sent a series of 2 letters, 3 emails, and one phone call 1-2 weeks apart. Participants are directed to the KPCO study registration website created specifically for this study. On this registration website the participants identity and eligibility are confirmed, and consent is electronically signed.

After consent, participants are directed to the *study* website where they set up login information and are provided with a Baseline Questionnaire.

The following topic areas are assessed in the Baseline Questionnaire:

1. intention to vaccinate
2. vaccination values
3. logistical barriers to vaccination

4. vaccine attitudes and beliefs (vaccination concerns)
5. vaccine hesitancy (used for randomization)
6. demographics.

Upon completion of this questionnaire, participants are considered to be "enrolled" in the study and are randomized.

Randomization

Participants are randomized using stratified randomization along with permuted block technique using a 1:1:1 allocation ratio between the VAYB, untailored and usual care arms. Randomization occurs using software embedded in the study website immediately following enrollment into the study. Randomization remains in place throughout the study. Participants are first stratified into either a hesitant or non-hesitant group, based on vaccine hesitancy status from the baseline questionnaire. Hesitancy status is assessed using a 5-item validated measure developed by Opel DJ (olejado). Participants are categorized based on the measure's suggested (but unpublished) cutoffs. Participants from each group are then added to their own set of blocks that each contain 6 slots. There are 2 slots available for each of the 3 study arms. These slots are randomly ordered when the block is created. When all 6 slots are filled, a new block with 6 randomly ordered slots is added.

Blinding

During the consent process, study arms are described to the participant. So, while participants are not explicitly informed about which study arm they are assigned to, they are not blinded to their study arm assignment. The project manager for the study is the only unblinded team member during analysis and data interpretation. She converts study data to unlabeled arms (i.e. arm 1, 2 or 3) allowing for the rest of the study team to be blinded to study arm assignment. Unblinding occurs after primary study outcome analysis. Clinics where participants receive care are only aware of individual's study participation if mentioned by the patient during a clinical encounter.

Interventions

Tailored Intervention

The VAYB intervention website contains content tailored to participants based on survey responses on the following topic areas:

1. intention to vaccinate
2. personal attitudes and beliefs about vaccines (vaccination concerns)
3. vaccination values
4. logistical barriers to vaccination
5. child's nickname and age (collected by the study team through birth date information from the EMR).

The most highly tailored content is in three "Just for You" tiles that are displayed prominently on the landing page. These tiles reflect the three vaccine concerns participants indicated they would like more information about. The tiles were further customized on vaccine values, vaccine intention and personal characteristics. The remaining content is lightly tailored to reflect

participant's personal characteristics and vaccine intention. Topic areas highlighted on the home page further identifies additional vaccination concerns identified by participants' survey responses.

The website tailoring on participant's vaccination concerns, values and hesitancy is refreshed 3 times during the course of the study; when the child is 4-6 months, 10-12 months, and 13-15 months of age when the child receives vaccinations.

Child is 4 to 6 months of age

Participants re-answer all questions excluding the value items, and 2 of the 5 questions assessing vaccine hesitancy. The website tailored content is refreshed accordingly.

Child is 10 to 12 months of age

All questions, including values are reassessed again in the 3rd survey. The website tailored content is refreshed accordingly.

Child is 13 to 15 months of age

Vaccine hesitancy level is reassessed at a 4th survey and the content is again refreshed. Satisfaction with the study was also assessed at the 13-15 month survey.

Untailored Intervention

The untailored intervention has the same text, content and design as the VAYB intervention, However, it does not contain any content tailoring linked to survey responses. The same questionnaires administered to participants in the VAYB arm are administered to participants in the untailored arm (baseline, and when the child is 4-6 months, 10-12 months, and 13-15 months of age), but the material is not used to tailor the website content.

Usual Care

After taking the Baseline Questionnaire, participants in the usual care arm are thanked for their time and logged off the study website. They receive an email containing the Vaccine Information Statements (VIS) for the vaccines due in the child's first year of life. They do not have access to the VAYB or untailored websites.

All arms

Routine pediatric care is available to infants of all participants in the study. At KPCO this typically consists of a series well-child care visits at 2 weeks, 2 months, 4 months, 6 months, and 12 months of age, with an optional visit at 9 months of age if desired by the healthcare provider or parent. Well child visit content is based on the Bright Futures program of American Academy of Pediatrics guidelines.[1] The visit content is focused on the needs of the child and family that typically last 20 minutes or less. Parents are provided with the VIS relevant to that visit. Providers are often asked about vaccination and can provide additional information verbally.

Vaccination intention: For all time points, vaccination intention is assessed in the survey. Vaccination intention is assessed again following exposure to the intervention, or in the case of usual care after completing the survey. Post intervention vaccination intention is obtained through an emailed survey sent within an hour of completing the survey. A reminder for this vaccination intention assessment is sent to non-responders by email after one day.

Participants receive a $20 gift card after surveys at each timepoint (baseline, and when the child is 4-6 months, 10-12 months, and 13-15 months of age) are complete.

Outcomes

Primary: Vaccination status

Vaccination data is collected routinely as part of clinical care within the KPCO health system and will be assessed from the KPCO EMR at pre-defined ages (200 days and 489 days). Colorado Immunization Information System (CIIS) will be used as a secondary vaccination data source, though internal audits demonstrate that >95% of childhood vaccines given to KPCO patients are captured within the EMR.

The primary outcome of the study is a dichotomous categorization of vaccination status (up-to-date vs. not up-to-date) that is defined based on a continuous measure of days under-vaccinated. This outcome is assessed at 200 days of age to cover vaccines in the initial infant vaccination series and to minimize the loss to follow-up. The following 6 vaccines recommended by the Advisory Committee on Immunization Practices will be assessed: hepatitis B; rotavirus; diphtheria-tetanus-acellular pertussis; Haemophilus influenzae type b; pneumococcal conjugate vaccine; and polio.

To categorize vaccination status, we will first assess the number of days under-vaccinated for the 2- and 4-month vaccines (combined), by calculating the difference between when a vaccine dose was actually administered and when a vaccine dose should have been administered according to the vaccination schedule recommended by the Advisory Committee on Immunization Practices,[2] plus an additional 30 day "leeway" to account for vaccination that did not occur at exactly the minimal interval between doses. For example, the first dose of rotavirus vaccine is due at age 2 months (61 days) but is not considered late until age 92 days. Days undervaccinated for this dose begin accruing on day 93. The number of days under-vaccinated is then summed across all doses and vaccines to calculate a total number of days under-vaccinated for each infant and can range from 0-648 days. Infants with 0 total days undervaccinated (assessed specifically for the 2 and 4 months vaccines) at 200 days will be considered up-to-date on their vaccination status; those with $\geq$1 days undervaccinated will be considered not up-to-date.

Secondary Outcomes:

1. MMR up-to-date status

A secondary vaccination metric that is assessed is up-to-date status for measles-mumps-rubella (MMR) and varicella vaccine at 489 days, when delay for the first dose of these vaccines begins. This metric is useful because it incorporates outcomes related to parents' decision-making about these two vaccines recommended at 12-15 months of age that are not offered previously.

2. Vaccination attitudes and hesitancy

Vaccine attitudes and hesitancy was in a questionnaire online. These data are used to assess changes over time in vaccination attitudes and hesitancy, and how these relate to study arm, vaccination values, and vaccination status. Vaccination attitudes are assessed using measures previously developed by our team and others.[3] vaccine values are assessed using a novel framework we have developed, and vaccine hesitancy is assessed using a 5-item validated measure (Olejado). A variety of covariates and potential moderators will be assessed as part of this analysis including parent age, gender and insurance coverage type (such as Medicaid and HMO), and mother's age, race, and ethnicity. Also included will be metrics measuring website engagement (VAYB and Untailored arms only) including time spent on the website, number of times viewing website, number and order of pages viewed, and match between stated concerns and website material viewed (VAYB arm only).

Participant retention

Even with the $20 per survey completion incentive, we expect a certain amount of drop off in survey participation. Our primary outcome is vaccination status. Thus, mothers who do not participate in all the study surveys are eligible for primary study outcome assessment, so long as their child maintains coverage and continues to seek care within the KPCO health system. Our previous studies indicate the proportion of children who discontinue KPCO coverage after the birth to be ~15%, and our study is powered with this attrition in mind.[4]

Analysis

Total days undervaccinated will be analyzed in two ways. First it will be done using a dichotomous variable (up-to-date vaccination status). Second analysis will be done as a continuous measure. The dichotomous variable will be analyzed using logistic regression to estimate odds ratios and associated 95% confidence intervals. We will use a nonparametric analysis and a rank transformation approach to assess the continuous measure as total days undervaccinated has a highly skewed distribution. We will use a modified intention to treat framework. To ensure vaccination data available for assessment of outcomes, this analytic cohort will include infants of all randomized mothers who maintained KPCO health coverage for the allotted amount of time (200 days for the primary outcome, 489 days for the secondary outcome) with no more than 90 days of no coverage. For both vaccination behavior measures, if a statistically significant association is observed in the primary analysis, we will conduct analyses stratified by baseline vaccine hesitancy as measured by the 5-item vaccine hesitancy scale described above (Olejado).

For survey measures, we will assess changes in vaccine attitudes and intention over time. All survey items are measured using Likert scales and will be analyzed as linear measures. For each survey outcome average change over time by arm will be assessed using a repeated measures ANOVA. Mixed linear models will be used to assess the "difference in difference" over time in these means, by arm, controlling for the covariates. To ensure survey outcomes for analysis, we will use a modified intention to treat analysis that includes all participants with data from at least one non-baseline questionnaire.

Missing data

Nearly all vaccines provided to KPCO patients are documented in the EMR, and doses provided outside KPCO are documented in Colorado Immunization Information System (CIIS). Therefore, we expect minimal missing data for vaccination outcomes. To ensure the most complete record, CIIS will be cross checked for all participants to identify any vaccine doses given to infants outside the KPCO system that are missing from the KPCO EMR. Participants who do not have vaccination data present in either system will be assumed to have not gotten a vaccine dose elsewhere.

For survey data, due to our recruitment strategy, we anticipate no missing data at baseline, as completion of the baseline survey was a criterion study enrollment. However, there may be missing data for subsequent surveys as completion of the subsequent surveys was not required to remain in the study. For missing data in surveys beyond baseline, multiple imputation models will be developed for analyses involving multiple survey points where greater than 10% of subjects would be lost due to missing values.

Ethics and Dissemination

Approvals

This study is approved by the Institutional Review Boards at the University of Colorado and KPCO.

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Competing Interests

Amanda Dempsey serves on Advisory Boards for Merck, Pfizer and Sanofi Pasteur, and has provided consulting services to Pfizer. She does not receive any research funding from these companies. All other authors have no competing interests to declare.

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