Behavioral Interventions to Increase Adherence to Palivizumab Prophylaxis in Children with CHD

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Abstract

Background: Palivizumab prophylaxis is crucial to protect infants with hemodynamically significant congenital heart disease against RSV infections, which affect them more commonly and severely than infections due to influenza and Covid19. The prophylaxis program requires patients to be monthly administered the palivizumab monoclonal antibody during the RSV season. However, achieving full adherence is not easy. Behavioral economics studies cognitive biases exhibited by decision makers. Its findings have been utilized to design nudge-interventions in a number of fields including medicine. By causing behavioral changes in the patients, such interventions provide significant benefits at low cost. In this paper, we designed a randomly controlled trial to analyze the implications of two nudge-interventions to increase adherence to the palivizumab prophylaxis program.

Methods: Our study included 229 infants of under 2 years who were followed by five different centers in Turkey due to congenital heart disease, and were found to be eligible for palivizumab prophylaxis in the 2020-2021 RSV season. We randomly allocated patients to one control and two treatment groups. For the 79 patients in the control group, we followed the existing practice, informing them that they needed monthly vaccination and providing them with a vaccine card that showed the appointment dates. The 75 patients in the first treatment group were additionally called two days before their appointments, to create status quo bias, and were asked to plan when and how they would come to their appointment the next day, creating implementation intention. The 75 patients in the second treatment group were included in a message list where they received biweekly messages on RSV, creating availability bias, and on adherence levels, creating social norm. All patients were asked to fill out questionnaires on medical history and socioeconomic characteristics.

Results: We found the adherence rates for Control, Treatment 1, and Treatment 2 groups as 90.9%, 97.3%, and 94.7%, respectively. Treatment 1 had a significantly higher adherence rate than the control group (p=0.014). We then focused on 0-1 year old children who are in their first RSV season. In case of these "inexperienced patients", both treatments had a significant effect on the adherence rate (p=0.031, p=0.037). We also considered confounding factors. First, families where the male primary caregiver was fully employed had a 14.2 percentage points (pp) higher adherence rate than others (p=0.001). Second, every additional child in the family was associated with a 2.2 pp decrease in the adherence rate (p=0.02). Third, patients whose birthweight was higher than 3000 grams had a 5.4 pp higher adherence rate (p=0.013). Finally, for patients in the control group, a history of ICU admission was associated with an 18.8 pp lower adherence rate (p=0.0001) whereas this association disappeared for patients in either treatment group.

Conclusion: Our study is the first randomized controlled trial which, in the context of a palivizumab prophylaxis program, analyzes the effect of nudge-interventions based on established cognitive biases. We found that status quo bias and implementation intention, used in Treatment 1, have a significant effect on adherence. The effect of availability bias and social norms, used in Treatment 2, were also positive, but only significant when the sample was restricted to inexperienced patients. We believe our results can be applied to improve adherence to other healthcare programs as well.

Key words: Respiratory syncytial virus (RSV), palivizumab prophylaxis, cognitive bias, nudge, behavioral intervention, field experiment, congenital heart disease (CHD), children, status quo bias, availability bias, social norm, implementation intention.

Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute respiratory tract infections, affecting almost every child at least once before they are 2 years old and causing up to 200,000 deaths a year worldwide as well as significant health costs (Walsh and Hall Breese 2015, Wu and Hartert 2011, Hall and Weinberg 2009, Haddadin et al 2021). In the US alone, RSV treatments of infants annually costs $709.6 million and public sources pay for more than half of this amount (Bowser et al. 2022). These costs will likely further increase in the future because since March 2021, out-of-season RSV hospitalizations (RSVH) have been mounting (CDC, 2021).

RSV infections cause significantly more severe complications in children with congenital heart disease (CHD) where, compared to otherwise healthy children, hospitalization rate due to RSV infection is three times more frequent. For CHD patients, RSV infections are one of the most important factors contributing to increased morbidity and mortality (Joshi and Tulloh 2018). When infected, these patients also incur significantly higher treatment costs (Walpert et al. 2017). For this patient group, the literature has reliably established the benefits of a palivizumab prophylaxis program (Medrano et al 2007, Stewart et al 2013, Forbes et al 2014, Chan et al 2015, Joshi and Tulloh 2018, Elhalik et al 2019). (While we focus on CHD patients in this study, there are other high-risk groups, such as children with chronic lung disease, for whom palivizumab prophylaxis programs do exist).

Palivizumab is a monoclonal antibody which, when administered monthly during the RSV season (e.g. October to March), reduces rates of hospitalization and intensive care admission. With every monthly shot, the titration of RSV monoclonal antibody increases and hence, provides protection against the virus. However, if the patient does not fully adhere to the prophylaxis program, a full titration of the RSV monoclonal antibody and hence, protection against an increased risk of lower respiratory tract infections can not be achieved. An incomplete adherence to palivizumab prophylaxis has not only health costs, as discussed above, but also significant economic costs. For example in Canada, public spending on palivizumab prophylaxis during the 2015-2016 season was 43.5 million USD (CDC News, 2017). These costs will likely increase. The American Academy of Pediatrics (AAP) recently announced that due to changes the SARSCov2 pandemic caused on RSV epidemiology, for eligible patients they now strongly support the use of palivizumab prophylaxis during the interseasonal period as well (AAP, 2021).

Achievement of higher adherence to the palivizumab prophylaxis relies critically on choices made by patient families. Hence, an improvement in family adherence behavior will significantly contribute to the success of the prophylaxis program. Choice architecture, a term coined by Thaler and Sunstein (2008), reflects the fact that the way a choice problem is presented to decision makers affects their choices without impeding freedom of choice. A fast growing literature shows that cleverly designed choice architecture, based on established cognitive biases, can “nudge” decision-makers towards making better choices (Samuelson and Zeckhauser 1988, Madrian and Shea 2001, Gollwitzer and Sheeran 2006, Schults et al 2007, Nickerson and Rogers 2010, Sunstein, 2017).

In medicine, cognitive biases faced by patients and physicians, as well as the implications of nudge-based interventions have been gaining importance in a number of fields such as cardiovascular medicine (Daugherty et al 2017, Matlock et al 2017, Ryan et al 2018, Adisumalli et al 2020), influenza immunization (Chapman 2010, Milkman et al 2011, Maltz and Sarid 2020), organ donation (Johnson and Goldstein 2003, Davidai et al 2012) as well as others (e.g. see Harrison and Patel 2020). Our paper contributes to this literature by utilizing cognitive biases of patient families to design nudge-based interventions in order to improve adherence to the palivizumab prophylaxis of 0-2 year old infants. Our findings can also be utilized in other vaccination programs such as Influenza or Covid-19.

Behavioral Interventions

The primary objective of our study is to increase patient families’ adherence to the palivizumab prophylaxis program. To do this, we utilize four well-established cognitive biases in designing two alternative nudge-interventions. Via a randomized field study carried out in five geographically distinct regions of Turkey, we measure the effectiveness of each nudge-intervention against a control group.

The first intervention that we evaluate in this study is based on the notions of status quo bias (a.k.a. default bias) and implementation intention. *Status quo bias* refers to a decision maker’s aversion to take action to change the status quo or to deviate from a predetermined action plan (Samuelson and Zeckhauser, 1988). For example, making organ donation the default alternative increases participation to organ donation programs (Johnson and Goldstein 2003, Davidai et al 2012). Also, making the generic alternative the default option in electronic health record (EHR) display screens increases doctors’ prescription of generic drugs (Patel et al 2014, 2016). *Implementation intention* refers to the phenomenon where specific planning regarding an action (by answering when, where, and how questions) increases a decision maker's likelihood of carrying out that action. For example, Nickerson et al (2010) show that calling voters on the phone and asking them to plan out how they will come to the election booth increases their likelihood of participation in an election. Milkman et al (2011) shows that e-mailing to a group of people who needs flu vaccination and asking them to plan out the day and hour they will come increases their adherence.

The second intervention that we evaluate in this study is based on the notions of availability bias and social norm. *Availability bias* (Tversky and Kahneman 1973) refers to the effect of the ease with which a piece of information is recalled on the evaluation of its importance. First, information that is easier to access is deemed to be more important by decision makers. Second, decision makers judge the frequency of events they encountered in the recent past to be higher than actual. Studies have found evidence of availability bias in the diagnoses of second year fellows in internal medicine (Mamede et al 2010), as well as in clinicians' diagnosis of bacteremia (Poses et al 1991), and infective endocarditis (Strahilevitz et al 2005). *Social norm* refers to a decision maker's tendency to conform with the decisions and actions of a society or group they belong to. Increased prevalence of a norm or behavior in the society increases the likelihood that the decision maker will conform to it. For example, a social media campaign informing individuals that seatbelt usage among drivers is very common significantly increases seatbelt usage (Linkenbach 2003).

Analyzing Factors that Affect Adherence

A secondary objective of our study is to analyze factors that affect families' adherence to the prophylaxis program. We also analyze whether and how the effects of our two interventions depend on these factors. We consider a range of parameters regarding the (i) patient, (ii) family, (iii) primary female caregiver (e.g. mother), and (iv) primary male caregiver (e.g. father). As will be detailed in the next section, we also collect data on the patients' medical history.

Method

Study Population

Our study population is 0-2 year old infants with CHD who were hemodynamically unstable, having congestive heart failure, hemodynamically significant residual defects after corrective heart surgery, cardiomyopathy or pulmonary hypertension. All patients in this group are eligible for palivizumab prophylaxis. Upon consent from families, patients were included in the study and their basic medical information, such as the name of congenital heart disease, age, sex, weight, operation time, past and current hospitalization and intensive care unit admission data was recorded.

Study design and procedures

This is a prospective study. Before the 2020-2021 RSV season, pediatric cardiologists from five children's hospitals in Turkey determined from among 0-2 year old patients those who are eligible for palivizumab prophylaxis, in accordance with AAP guidelines (AAP, 2014). The five hospitals in İstanbul, Sakarya, Kahramanmaraş, Sıvas, and Van are located in different geographical regions in Turkey, hence producing a representative sample of Turkish patients and families. Enrollment of patients to the study continued until the end of 2020. At the beginning of the study, 243 patients with CHD were included. In each hospital, the patients were randomly allocated into one of three groups (one control and two treatment), and were followed from October 2020 until April 2021. During the study, 14 of these patients were excluded either because they did not contact the hospital anymore, or became exitus. The study concluded with participation of 229 patients. This study was approved by the Ethical Committee of the Kartal Koşuyolu Cardiac Center, with approval number 2020/14/413. All vaccinations in the study were carried out in the aforementioned hospitals.

The patients in the three groups received the following treatments.

Control Group: Patients in the control group were treated as in the common current practice in Turkey. Starting with the beginning of the 2020-2021 RSV season, each patient was presented with a vaccination appointment card containing the dates of their prophylaxis appointments for that season, as well as a telephone number they can call in case they need to change an appointment date.

First Treatment Group: This group of patients were treated to induce status quo bias and implementation intention. As in the control group, they were given a vaccination appointment card and a telephone number. However, additionally these patients received a telephone call every month two days before their appointment. To induce status quo bias, they were reminded that they have a set appointment. And to induce implementation intention, they were asked to plan the day of their appointment as detailed below. The following standard script was used in every hospital during the telephone call:

> *Hello, we are calling you because you are enrolled in the palivizumab prophylaxis research program. As you know, you have a vaccination appointment on [enter date] at [enter time]. To help you plan your day of appointment, we have a few short questions.*
>
> a. *At your appointment day, will you be coming to the hospital from home, or will you need to get permission from your workplace?*
>
> b. *What kind of transportation do you plan to take to come to the hospital at your appointment day?*
>
> c. *At what time do you plan to leave home or work to come to the hospital?*

Second Treatment Group: This group of patients were subject to an intervention based on availability bias and social norm. They were given the same vaccination appointment card as in the control group. However, patients in this group were additionally included in a messaging group (on Whatsapp or SMS, depending on the family's preference) where, twice a month they received a message informing them on RSV, on the additional risks an RSV infection causes on CHD patients, and on the benefits of adherence to the prophylaxis program. The availability bias suggests that keeping such information “available” for the patients should increase for them the importance of adherence. These messages also involved statements about the high number of patient families that kept their appointments in the previous month, hence creating a social norm of adherence. As an example, below we present one of the messages sent.

> [Availability Bias]
> *Dear parent, almost every child is infected with the RSV virus at least once before they reach the age of two. For children with congenital heart disease, an RSV infection can lead to significantly more serious illness. Out of every two children with congenital heart disease, one has to be admitted to the intensive care unit due to RSV infection. However, with regular vaccination every month, we can protect our children from the life threatening risks caused by the RSV infection.*
>
> *[Social Norm]*
> *Dear parent, as of today families of 227 patients in our five centers are regularly participating in the RSV immunization program and protecting their children from RSV infection. You are one of them. We congratulate you for the effort you put in for your child’s health.*

Study Objectives and data collection

Our main variable of interest is the rate of adherence to the prophylaxis program. For each patient, the rate of adherence is defined as the total number of vaccinations received divided by the maximum number of vaccinations the patient is eligible for. Patients who are enrolled in the program at the beginning of the RSV season were eligible for five monthly doses. However, for a patient who participated in the study in the later months, exceeded two years of age during the study, had an operation, became hospitalized, or was admitted to the ICU for a time period, the maximum number could be lower than five.

Our first objective was to test whether each of the two behavioral interventions lead to an increase in the average rate of adherence in comparison to the control group. To this end, doctors from the five hospitals collected patient adherence data every month. They also collected additional relevant data on patients, such as whether the patient underwent surgery or were either hospitalized or admitted to intensive care (ICU) due to a variety of reasons, patients who completed two years of age (since at that point, the state insurance stops paying for the palivizumab prophylaxis), patients who became exitus or moved to another region.

A secondary objective of our study was to analyze factors that affect families' adherence to the prophylaxis program. To this end, we asked the participating families to fill out a demographic survey (presented in the Appendix). The questions focus on (i) the patient's medical history (10 questions), (ii) family's socio-economic descriptives (8 questions), as well as (iii) questions about the mother and the father (6 questions each).

Statistical Analysis

The statistical analysis was performed using STATA (Version 17. College Station, TX: StataCorp LLC). The descriptive statistics of the dataset are presented in Table 1. To compare the mean adherence rates of the control and treatment groups, the difference in means (t-test) was used. To comment on the role of confounding variables, as well as to test whether patients were randomly allocated to the three groups, multivariate linear regression models were employed. In addition, we also employed an interactive linear regression model to see the conditional effect of intensive care on adherence. The p values less than 0.05 were considered statistically significant.

Results

Among the 229 patients included in the study, 71 were diagnosed to be cyanotic (31%) and 158 to be acyanotic (64%). At the time they participated in our study, the mean age of our patients was

8.5 months. Female patients constituted 45.85% of our sample. In terms of birth weight, 91.22% of our sample was over 2000 grams. In terms of birth week, 30.73% of our sample was born under 37 gestational weeks. Also, 9.27% had additionally a chronic lung disease, 16.58% were previously hospitalized and 16.10% were previously admitted to intensive care due to lower respiratory tract infections. Additionally, patients in our sample came from families where the median number of children is 3, mean maternal age is 31, the median education level of the mother is middle school, and 31.71% of the fathers do not have a full time job. Table 1 presents an overview of these parameters, both overall and at the group level. Linear regressions that treat group membership as a dependent variable, and other traits of a patient as independent variables show that no traits of a patient have a significant effect on being assigned to a treatment group (please see tables A1 and A2 in the Appendix). Hence, we conclude that our patients are randomly allocated to the control and treatment groups in terms of the analyzed traits.

Table 1: Descriptive Statistics

We first analyze the effect of our interventions on the rate of adherence. For patients in the control group, the average adherence rate was 90.9%. In comparison, for patients in the first treatment group the average adherence rate was 97.4%, that is, 6.5 percentage points higher than the control group. Results of a t-test, presented in Figure 1, show this difference to be significant (p=0.014). For patients in the second treatment group, on the other hand, the average adherence rate was 94.2%. While this is 3.23 percentage points higher than that of the control group, results of a t-test show that it is not significant (p=0.26), as presented in Figure 1. Hence we conclude that, when all patients are considered, our first behavioral intervention leads to a significant increase in adherence while our second behavioral intervention does not.

Figure 1: Average Adherence Rates of Patients in Control, Treatment 1 and Treatment 2 groups.

Next, to analyze the possible effect of previous experience with the prophylaxis program, we group the patients into two. We assume that patients who were younger than 285 days at the beginning of the treatments were in their first palivizumab prophylaxis season.[1] These “inexperienced patients” constitute 148 of our 229 patients (64.62%). In the Control, Treatment 1 and Treatment 2 groups, there are 49, 51, and 48 inexperienced patients, respectively. In case of inexperienced patients, the average rate of adherence in the control group is 88.3%. On the other hand, as presented in Figure 2, the average adherence rate is 97.7% in the first treatment group and 97.1% in the second treatment group. T-tests show the average adherence rates in both treatment groups to be significantly higher than the control group (p=0.009 for Treatment 1 and p=0.018 for Treatment 2). Hence we conclude that, when only inexperienced families are considered, both our behavioral interventions lead to a significant increase in adherence.

The remaining 81 of our 229 patients are classified as experienced. In the Control, Treatment 1 and Treatment 2 groups, there are 30, 24, and 27 experienced patients, respectively. In case of experienced patients, the average rates of adherence in the Control, Treatment 1 and Treatment 2 groups are 95.4%, 96.7%, and 89.8%. T-tests show for this group that the adherence rate in the control group is not significantly different from Treatment 1 (p=0.669) and Treatment 2 (p=0.206).

Figure 2: Average Adherence Rates of Inexperienced Patients in Control, Treatment 1 and Treatment 2 groups.

In line with our secondary objective, we also analyzed which factors affect families’ adherence to the prophylaxis program. Table 2 presents our findings for the factors that have significant association with adherence. First, we found that families where the father is employed have a 14.2 percentage points higher average adherence rate than families where the father is unemployed. This difference is highly significant (p=0.0001). A second important factor affecting adherence is the number of children in the family. We observed that every additional child in the family is associated with a 2.2 percentage point decrease in the patient’s rate of adherence (p=0.02). Finally, we found the patient’s birthweight to be significantly associated with the rather of adherence. Namely, patients with birthweight greater than 3000 grams have a 5.4 percentage points higher rate of adherence than patients with birthweight lower than 3000 grams (p=0.013).

[1] These patients were born around January 15, 2020 and since the palivizumab prophylaxis does not start before they are at least a month old, would most likely not participate in the prophylaxis program in the 2019-2020 season.

Table 2: Factors that affect the patient's rate of adherence.

Finally, we found that patients with a history of admission to the intensive care unit (ICU) have, overall, a 7.1 percentage points lower adherence level than others (p=0.016). To better understand this association, we also separately analyzed the effect of ICU admission in each one of our three groups. It turns out that in the control group, ICU admission is significantly associated with a 18.8 percentage point decrease in the rate of adherence (p=0.00). On the other hand, for patients in Treatment 1 and in Treatment 2, ICU admission has no significant effect on the rate of adherence. The details are displayed in Figure 3.

Figure 3: Predicted Probabilities of Adherence by Intensive Care for Control, Treatment 1 and Treatment 2

We also inquired whether the family was informed about RSV, found the prophylaxis program important or not, where they lived, how far they needed to travel to come to the hospital, difficulties they faced in accessing the prophylaxis, family size, number of children going to school, family income, smoking, father's and mothers age, education level, work status, marital status, health condition. These variables were found not to have a significant association with the adherence rate.

Discussion

The literature unequivocally demonstrates that adherence to the palivizumab prophylaxis is effective in prevention of RSV based diseases. Lower adherence rates are associated with a higher risk of hospitalization (Golombek et al. 2004, Medrano et al. 2007, Stewart et al. 2013, Chan et al. 2015, Elhalik et al. 2019), respiratory-related ER visits (Diehl et al. 2010), and ICU admission (Forbes et al. 2014). However, full adherence to palivizumab prophylaxis is rarely achieved.

A number of studies analyze factors that affect patient families' adherence to the prophylaxis program (Langkamp and Hlavin 2001, Robbins et al. 2002, Pignotti et al. 2004, Chan et al. 2015, Sel et al 2020). Among these, perceptions and information about benefits, emotional and time costs, patient age and sex, family size and parents' education are forthcoming. Two literature reviews, by Frogel et al (2010) and Wong et al (2017), additionally mention a handful of studies that retrospectively analyze the effect of institutional strategies on adherence. These authors argue that there is a need for prospective studies which use control or contemporaneous comparison groups and use formal statistical analysis to analyze the effectiveness of systematically designed interventions to increase adherence. Indeed, the literature is lacking on this front.

We are only aware of two prospective studies that analyze the effect of institutional interventions on adherence. Bernard et al (2015) implements an education program for families of neonates and demonstrates an increase in adherence in comparison to the previous RSV season. Alternatively, Giardino et al (2009) implements an outreach program for parents and primary care physicians but does not find a significant increase in adherence. Neither study is a randomized controlled trial. Indeed, Oakes and Patel (2019) emphasizes the importance of experiments or randomized controlled studies in understanding whether an institutional intervention is effective.

Our study contributes to the literature by providing the first randomized controlled trial that measures the implications on adherence of two behavioral interventions. Furthermore, both our interventions are based on well-established cognitive biases in the literature. Initiated by a number of seminal studies of Tversky and Kahneman (e.g. 1973, 1974), the field of behavioral economics systematically studies cognitive biases decision makers exhibit and their implications in the effectiveness of behavioral interventions. As a result, behavioral studies have been flourishing in a number of fields including medicine, as discussed in the Introduction, and medical institutions have been initiating Nudge Units as in the case of the University of Pennsylvania Medical School (Adusumalli et al. 2020). Our study contributes to this literature.

Our study is the first to analyze via controlled trials the effectiveness of two nudge-interventions based on four established cognitive biases. Particularly, we are not aware of any study that brings together status quo bias and implementation intention (in case of Treatment 1) as well as availability bias and social norms (in case of Treatment 2) to design a nudge-intervention. Similarly, the literature lacks comprehensive studies that test effectiveness of interventions when statistically controlling for patient and family characteristics. Finally, our study is the first to bring together five geographically diverse medical centers in Turkey. Previous studies on Turkish data are retrospective and focus on a single medical center (e.g. Sel et al. 2020). With the exception of a retrospective study by Borecka et al (2016) on Polish data, studies in other countries also focus on a particular center or region.

When surveyed about possible ways to increase adherence (Anderson et al. 2009), physicians' top three recommendations are (in order of decreasing popularity) additional education materials, frequent reminders from the hospital, and education of the patient's family. Our treatments are in line with these recommendations, though, we do more than sending reminders or providing educational material. We also find on the overall sample that education materials (Treatment 2) are not as effective as a phone call before appointment (Treatment 1).

Next, we discuss our findings in relation to the literature. First, our study finds that families of younger (inexperienced) patients present a much stronger response to nudge-interventions. For this group, both our treatments lead to a significant increase in adherence while on the overall group of patients (including both experienced and inexperienced patients), only Treatment 1 leads to a significant increase in adherence. Furthermore, in our control group families of experienced patients exhibit higher adherence than inexperienced patients (though the difference is only significant at 90% confidence level). This is in line with studies that point to the importance of patient age (such as Borecka et al. 2016, Pignotti et al. 2004, and Chan et al. 2015) and highlights that interventions should particularly target younger patients with inexperienced families.

In a literature review, Wong et al (2017) notes our measure of adherence to be one of the few predominant ones in the literature. One popular alternative (especially in studies on health benefits of the prophylaxis program) is to measure the adherence rate as the percentage of patients who are in full compliance with the prophylaxis program. Since this measure codes patients as either a zero or a one (full compliance or not), it is obviously more crude than ours. But using it does not change our findings qualitatively.

We also analyze factors that affect families' adherence to the palivizumab prophylaxis, and how they interact with our two interventions. Among these, the first significant factor is whether the father has a full time job. Given that for almost 75% of our sample mothers are homemakers, fathers are the sole breadwinners in the family. We therefore believe that the primary mechanism through which father's job status affects adherence is via family income. Even though the Turkish state provides the prophylaxis program free of charge for all qualifying children until 2 years of age, family income makes a difference in additional costs such as transportation, especially considering that 82% of the families in our sample have a monthly total income of less than 5000 TL (roughly 678 USD at the time of the intervention). The previous literature also identifies transportation and time costs as an important determinant of adherence (e.g. see Langkamp and Hlavin, 2001; Robbins et al. 2002).

We find another important factor decreasing adherence to be the number of children in the family. For families with a higher number of children, the additional effort required to follow the prophylaxis program has a higher opportunity cost. Another important factor turns out to be the patient's birth weight where families of babies with a birthweight of over 3000 grams show higher adherence. To the best of our knowledge, ours is the first study to find an association between birthweight and adherence.

Finally, we find that, while there is negative association between a patient's intensive care history and adherence to palivizumab prophylaxis in the control group, this is not the case in our treatment groups. This highlights a second, and previously unseen contribution of our interventions. In addition to having a direct positive effect on adherence, the interventions also serve to offset the negative effect of intensive care history on the family's adherence level. This might be due to a closer follow-up of patients as well as provision of more information on the benefits of adherence.

Conclusion

Our study highlights the importance of basing the design of nudge-interventions on the established literature on cognitive biases, and evaluating their effectiveness via randomized controlled trials.

Such nudge-interventions provide an effective way of increasing health benefits of treatments at a comparatively lower cost and invasiveness. Once effective interventions are identified, future studies should focus on the trade-offs between the benefits and costs of each intervention.

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Table 1: Descriptive Statistics

	Control	Treatment 1	Treatment 2	Overall
Sex	35 (44.30%) Male 44 (55.70%) Female	43 Male (57.33%) 32 Female (42.67%)	46 Male (61.33%) 29 Female (38.67%)	124 Male (54.15%) 105 Female (45.85%)
Mean age (in days) at the first vaccination	252	224	256	244
Birth Weight (Grams)	30 (44.78%) > 3000 30 (44.78%) 2000-3000 5 (%7.46) < 2000	26 (%38.24) >3000 33 (%48.53) 2000-3000 5 (%7.35) < 2000	31 (%44.29) > 3000 30 (%42.86) 2000-3000 8 (%11.43) < 2000	87 (%42.44) > 3000 93 (%45.37) 2000-3000 18 (%8.78) < 2000
Birth Week	52 (77.61%) 37-40 12 (17.91%) 35-37 2 (2.99%) < 35	43 (63.24%) 37-40 16 (23.53%) 35-37 5 (7.35%) < 35	47 (67.14%) 37-40 12 (17.14%)35-37 11 (15.71%) < 35	142 37-40 (69.27%) 40 35-37 (19.51%) 18 (8.78%) < 35
Chronical Lung Disease	3 (4.48%) Yes 61 (91.04%) No	8 (11.76%) Yes 59 (86.76%) No	8 (11.43%) Yes 61 (87.14%) No	19 (9.27%) Yes 181 (88.29%) No
Hospitalization	53 (79.10%) Never 13 (19.41%) At least once	59 (86.76%) Never 9 (13.24%) At least once	58 (82.86%) Never 12 (17.14%) At least once	170 (82.93%) Never 34 (16.58%) At least once
Intensive Care	56 (83.58%) Never 10 (14.93%) At least once	59 (86.76%) Never 9 (13.24%) At least once	56 (80.00%) Never 14 (20.00%) At least once	171 (83.41%) Never 33 (16.10%) At least once
HOUSEHOLD				
Mother Education	33 (49.25%) ≤ Primary 24 (35.82%) Middle- High School 9 (13.43%) ≥ University	27 (39.71%) ≤ Primary 26 (38.24%) Middle- High School 15 (22.06%) ≥University	27 (38.57%) ≤ Primary 32 (45.71%) Middle- High School 11 (15.71%) ≥ University	87 (42.44) ≤ Primary 82 (40.00%) Middle- High School 35 (17.07%) ≥University
Father Education	27 (40.30%) ≤ Primary 27 (40.30 %) Middle- High School 11 (16.42%) ≥ University	14 (20.59%) ≤ Primary 32 (47.06%) Middle- High School 21 (30.88%) ≥ University	23 (32.85%) ≤ Primary 32 (45.72%) Middle- High School 14 (20.01%) ≥ University	64 (31.22%) ≤ Primary 91 (44.39%) Middle- High School 46 (22.43%) ≥ University
Number of Children in the Household	13 (21.31%) 1 36 (59.02%) 2-3 8 (13.11%) 4 4 (6.56%) > 4	24 (36.92%) 1 33 (50.77%) 2-3 (7 (10.77%) 4 1 (1.54%) > 4	12 (17.91%) 1 43 (64.18%) 2-3 5 (7.46%) 4 7 (10.45%) > 4	49 (25.39%) 1 112 (58.03%) 2-3 20 (10.36%) 4 12 (6.22%) > 4
Father Employment	8 (11.94%) No job 9 (13.43%) Part-time 44 (65.67%) Full-time	9 (13.24%) No job 7 (10.29%) Part-time 48 (70.59%) Full-time	8 (11.43%) No job 11 (15.71%) Part-time 48 (68.57%) Full-time	25 (12.20%) No job 27 (13.17%) Part-time 140 (68.29%) Full-time

Notes: The category of “No Answer” was excluded from the table.

Figure 1: Average Adherence Rates of Patients in Control, Treatment 1 and Treatment 2

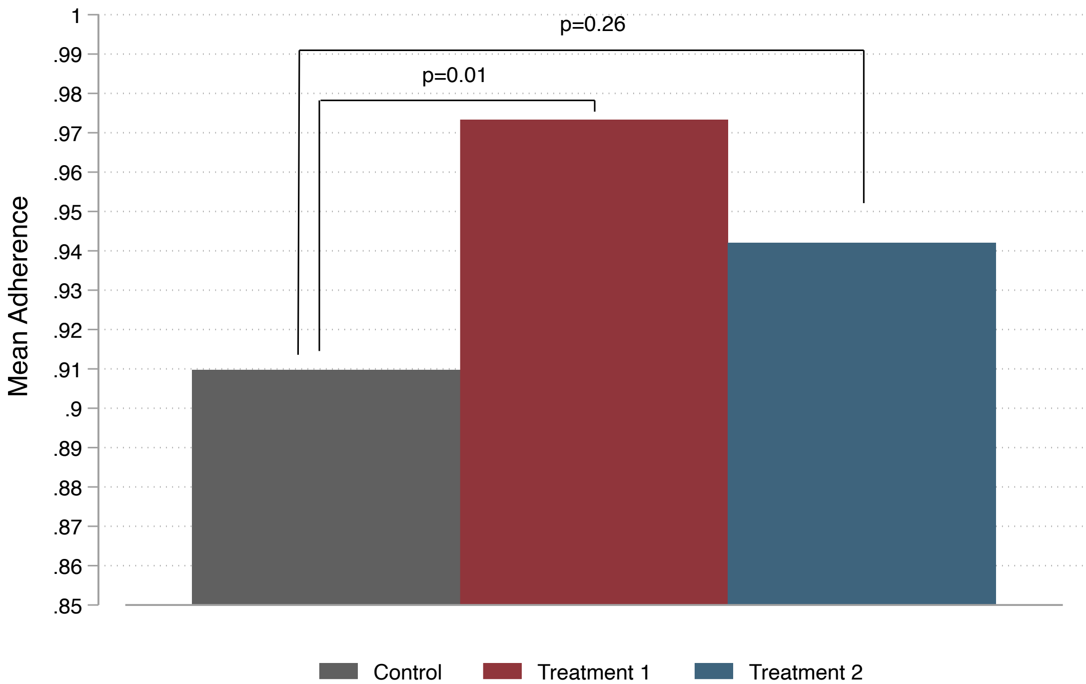

Figure 2: Average Adherence Rates of Inexperienced Patients in Control, Treatment 1 and Treatment 2.

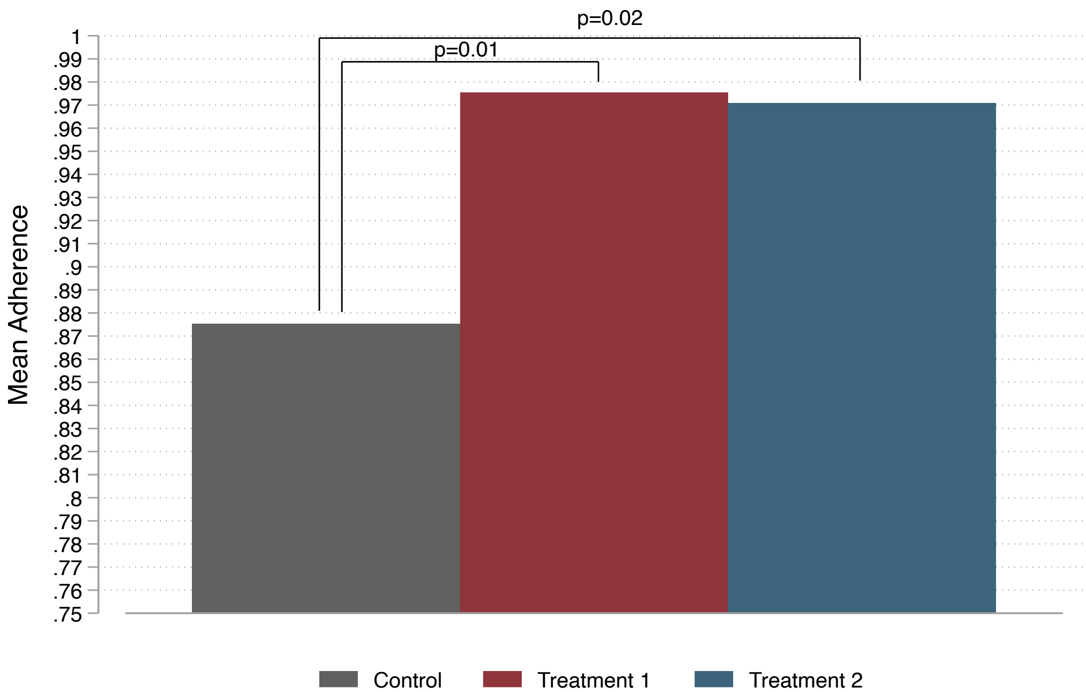

Figure 3: Predicted Probabilities of Adherence by Intensive Care for Control, Treatment 1 and Treatment 2

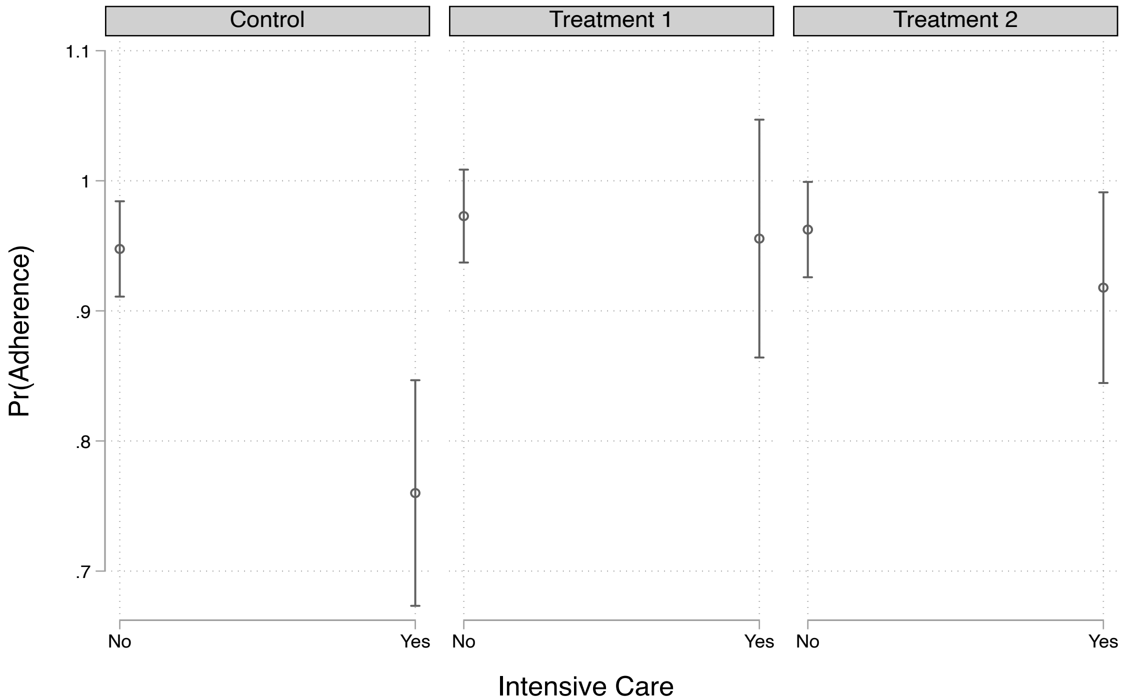

Table 2: Linear Regression Estimates of Adherence

Adherence	Coefficient	Std. Error	T-value	P-value	[95% Conf	Interval]	Sig
Father Employment	.142	.033	4.28	0	.076	.208	***
Number of Children	-.022	.01	-2.31	.022	-.041	-.003	**
Intensive Care	-.071	.029	-2.43	.016	-.128	-.013	**
Birth Weight	.054	.021	2.51	.013	.011	.096	**
Constant	.856	.04	21.36	0	.777	.935	***

Mean dependent var	0.941	SD dependent var	0.154
R-squared	0.213	Number of obs	174
F-test	11.464	Prob > F	0.000
Akaike crit. (AIC)	-189.399	Bayesian crit. (BIC)	-173.604

**** p<.01, ** p<.05, * p<.1*

APPENDIX

Table A1: Regression Estimates of Treatment 1 on Demographic Variables to Control for the Random Assignment between the Experiment Groups

Treatment	Coefficient	St. Err.	T-value	P-value	[95% Conf	Interval]	Sig.
Sex	.126	.089	1.42	.158	-.05	.302	
Mother Education	-.009	.033	-0.27	.786	-.075	.057	
Father Education	.053	.037	1.43	.156	-.02	.126	
Number of Children	-.039	.034	-1.12	.263	-.107	.029	
Constant	.347	.202	1.72	.089	-.054	.748	*
Mean dependent var		0.516	SD dependent var			0.502	
R-squared		0.070	Number of obs.			124	
F-test		2.256	Prob > F			0.067	
Akaike crit. (AIC)		180.803	Bayesian crit. (BIC)			194.905	

*** *p<.01*, ** *p<.05*, * *p<.1*

Table A2: Regression Estimates of Treatment 2 on Demographic Variables to Control for the Random Assignment between the Experiment Groups

Treatment 2	Coefficient	St. Err.	T-value	P-value	[95% Conf	Interval]	Sig
Sex	.166	.09	1.84	.069	-.013	.345	*
Mother Education	.011	.038	0.30	.764	-.064	.087	
Father Education	.031	.039	0.80	.427	-.046	.108	
Number of Children	.026	.03	0.87	.384	-.033	.085	
Constant	.186	.187	0.99	.324	-.185	.557	
Mean dependent var		0.524	SD dependent var			0.501	
R-squared		0.050	Number of obs.			126	
F-test		1.586	Prob > F			0.182	
Akaike crit. (AIC)		186.176	Bayesian crit. (BIC)			200.357	

*** *p<.01*, ** *p<.05*, * *p<.1*

Table A4: The Difference of Means in the Adherence between Control and Treatment 1 and Treatment 2

	Control	Treatment	Mean 1	Mean 2	Difference	St.Err.	T value	P value
Adherence (1)	79	75	0.909	.974	-.064	.026	-2.5	.014
Adherence (2)	79	75	0.909	.942	-.0325	.0285	-1.15	.257

Table A5: The Difference of Means in the Adherence According to Experience

	Control	Treatment	Mean 1	Mean 2	Difference	St Err.	T value	P value
Treatment 1 Inexperienced	49	51	0.883	.977	-.093	.036	-2.65	.009
Treatment 2 Inexperienced	49	48	0.883	.971	-.088	.036	-2.4	.018
Treatment 1 Experienced	30	24	0.954	.967	-.013	.031	-.45	.669
Treatment 2 Experienced	30	25	0.954	.898	.056	.043	1.3	.206