



Review

Effectiveness of digital technologies at improving vaccine uptake and series completion – A systematic review and meta-analysis of randomized controlled trials



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ARTICLE INFO

Article history:

Received 24 October 2018

Received in revised form 11 March 2019

Accepted 27 March 2019

Available online 26 April 2019

Keywords:

Immunization
Technology
Vaccination Coverage
Health Education
Mobile Applications

ABSTRACT

Background: Recent outbreaks and renewed concerns about immunization coverage call for new and effective interventions to improve vaccine uptake. Digital technologies have the potential to help address both suboptimal vaccine uptake and series completion. However, the effectiveness of pushing information and reminders to patients through digital technologies to address vaccination is not known.

Objective(s): The aim of this study is to determine if digital push interventions are effective in increasing vaccine uptake and series completion compared to non-digital interventions.

Methods: We searched for RCTs where adults or parents of children were eligible for vaccination, the intervention was digital-push and the comparison group was non-digital. We included outcomes of vaccine uptake or series completion. We estimated summary effect sizes, heterogeneity using the χ^2 test and quantified using the I^2 statistic. Where heterogeneity remained significant, we conducted subgroup analyses. We assessed risk of bias, certainty of evidence and publication bias.

Results: The search identified 159 peer-reviewed scientific publications. After review, a total of 12 manuscripts representing 13 empirical studies published between 2012 and 2016 were included. When comparing digital push interventions to non-digital ones, patients had 1.18[1.11,1.25] the odds of receiving vaccination or series completion compared to controls. In parents of children aged 18 and younger, those receiving digital push had a 1.22[1.15,1.30] increased odds compared to controls. Both analyses had high statistical heterogeneity, with I^2 values of 86% and 79% respectively. The risk of bias was low with 10 of 13 studies considered low risk in five or more domains. The certainty of evidence for series completion was very low and for vaccine uptake was assessed to be moderate.

Conclusion: This study provides evidence that digital push technologies have a modest, positive impact on vaccine uptake and series completion compared to non-digital interventions.

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1. Introduction

Immunization is considered as one of the most effective global health interventions, responsible for significantly reducing morbidity and mortality from vaccine preventable diseases (VPDs) [1]. Immunization has also been shown to lower care costs for health systems and for families, saving up to US\$6 billion globally in treatment costs [2] and US\$1 billion in reducing time needed to care for sick children. Adding long-term productivity gains resulting from immunization, averted costs are estimated to reach US \$151 billion. These economic benefits are realized by saving 6.4 million lives, avoiding 426 million cases of illness, and saving 63,000 children from being disabled due to meningitis [3]. Even a marginal increase in vaccine uptake or series completion can have massive social and economic benefits.

The literature has demonstrated the effectiveness of reminder-recall interventions such as automated telephone reminders and paper letters on improving vaccine uptake and series completion, irrespective of baseline rates, patient age, setting or vaccination [4,5]. Recall-reminder interventions inform patients or caregivers about upcoming immunizations and when they are overdue for immunizations [6]. One of the earliest reviews summarizing the evidence on the effectiveness of recall-reminders, published in 2000 in JAMA, reported that 80% of studies using patient reminder systems were effective in improving immunization rates, irrespective of baseline immunization rates, patient age, setting or vaccination type [4]. Included studies evaluated recall reminders delivered via postcards, letters and telephone calls with telephone reminders being the most effective but costliest [4]. A 2018 Cochrane review that included traditional recall reminder methods in addition to text message, autodialed telephone calls, patient portal-based interventions and in person outreach also reported improvement in immunization rates, although with more variability and a smaller reported effect size [7].

Recent outbreaks of VPDs such as measles has highlighted that gaps in immunization coverage still exist across Europe and other high income countries [8–12]. There is a renewed need to develop and evaluate modern interventions which address suboptimal vaccine uptake and series completion in both children and adults [8,9,11,13].

The widespread adoption of broadband internet and mobile telephones has created novel mechanisms by which public health

can communicate with potential vaccine recipients and vice versa. Preliminary studies suggest that individuals prefer text messages over mailings, voice mail or telephone conversations [14–16]. Text messaging can be used for large populations at low cost, particularly when integrated with IISs or EMRs [17]. Moving to digital platforms also presents opportunities to improve vaccination program delivery [18,19].

The latest statistics available from the National Centre for Health Statistics in the USA indicate that the number of homes with only wireless telephones continues to grow [20]. They also reported demographic and health differences amongst wireless-only adults compared to adults living in landline households. For example, adults living in or near poverty were more likely than higher income adults to be living in households with only wireless telephones. Wireless-only adults were also more likely to be current smokers, report higher alcohol consumption levels and be uninsured compared to adults living in households with landlines [20]. Since wireless telephone numbers have been reported to be more stable than home address or landline telephone numbers [16], interventions involving mobile phones or other digital technologies are more likely to reach the recipient compared to telephone calls.

Importantly, these technologies can facilitate the passive delivery of information directly to an intended recipient through push. A “Push” technology is when an individual opens up a connection to a server and keeps it open, such that the server will send (Push) all new events to the client in real time. In other words, “push” refers to communication whereby the transaction is initiated by the publisher and delivered to the recipient [21]. Examples of push include receipt of text messages, push notifications or email. We hypothesize that this open connection which facilitates information delivery by public health or a healthcare provider in real time offers an advantage compared to the traditional methods of recall-reminders which may require action on behalf of the recipient and be difficult to track whether they reach the intended recipient. Further, digital technologies versus landline telephones or paper mailing may be better for highly mobile individuals or those in lower socioeconomic segments. In contrast, “pull” protocols represent message transfer that are initiated by the consumer/ recipient. Examples of pull technologies include internet browsers, who make requests to web pages on behalf of the user. The user is actively involved in seeking out the message or content [22].

2. Objectives of review

The aim of this study is to synthesize the available evidence on digital technologies to improve vaccination. Specifically, we aim to ascertain whether “digital push” technologies are more effective than non-digital technologies in increasing vaccine uptake and series completion.

2.1. Primary objective

The primary objective of this study is to evaluate the effectiveness of digital push interventions compared to non-digital interventions for vaccine uptake and series completion in all patients.

2.2. Secondary objectives

The secondary objective of this review is to evaluate the effectiveness of digital push interventions compared to non-digital interventions for vaccine uptake and series completion in parents of children aged 18 years or younger

3. Methods

3.1. Eligibility criteria

Inclusion criteria: We identified randomized controlled trials (RCTs) published in peer-reviewed journals where the following criteria were met; the participants were either adults receiving vaccines themselves, including pregnant women, or parents of adolescents and children eligible for vaccination; the intervention was digital-push; the comparison group received usual care or a non-digital intervention and the outcome was either vaccine uptake or series completion. Vaccine uptake is defined as the proportion (%) of individuals in the study who received a particular dose of a vaccine. Vaccine series completion is defined as the proportion (%) of individuals in the study who received all of the vaccination doses at multiple visits within a time frame defined in the study. For vaccine series completion, this includes studies evaluating completion of the pediatric immunization series, comprised of multiple vaccine types as well as HPV vaccination which is multiple doses of the same vaccination. Both outcomes may be measured by self-report, by vaccine provider/EMR or both. We included all studies published after 2000, published in English.

Exclusion criteria: We excluded all studies where the comparison group received a digital intervention, regardless of the content. We also excluded all conference abstracts.

3.2. Information sources and search strategy

We searched the following electronic databases: PubMed; SCOPUS; EMBASE; Cochrane Central Register of Controlled Trials (CENTRAL); ISI Web of Science (Science Citation Index); Cumulative Index of Nursing and Allied Health (CINAHL), Web of Science and PDQ evidence. Electronic searches were complemented by manually searching all reference lists of published and unpublished studies and reviews for additional studies.

Level 1 screening was of titles only, Level 2 examined titles and abstracts to determine whether the article is an RCT, and if the outcome was within our inclusion criteria. Level 3 screening was full text review and examining the full scope of inclusion and exclusion criteria. All three levels of screening were conducted in parallel by two reviewers, with conflicts resolved by a third reviewer.

3.3. Study selection

We used distiller SR/Thomson ISI Research-Soft Endnote X7 to manage all references. Data was extracted using a structured data abstraction form, by two authors independently (KA and MM). Disagreements between the authors was resolved by a third reviewer (ZEK). Final data was entered by one reviewer into the Cochrane Collaboration Review Manager V.5.1 statistical software (<http://ims.cochrane.org/RevMan>) and verified by a second reviewer. A third reviewer (ZEK) was consulted to address entry errors if they arose with the primary authors.

3.4. Data abstraction

The following data elements were extracted: publication author, year, journal published, reported conflicts of interest, method of randomization, the intervention and control conditions, number of individuals included in each arm of the study, and the number of individuals with outcome of interest in each arm of the study.

3.5. Risk of bias

Risk of bias was assessed independently by two authors (KA and SE) using the following criteria: random sequence generation; allocation concealment; blinding of participants, study personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Studies were scored as having low, high or unclear risk of bias for each domain and an overall score. If the information provided was not sufficient to allow authors to make an informed judgment, we contacted study authors for clarification. Two authors resolved disagreements in the assessment of risk of bias by discussion and consensus, consulting the third author (KW or ZEK) to resolve any persistent disagreements.

3.6. Data synthesis

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in reporting the findings of this review [23]. We conducted data analysis with the Cochrane Collaboration Review Manager V.5.1 statistical software. The outcomes were dichotomous, reported as either vaccine received (yes/no) or series completed (yes/ no). We calculated risk ratios and their corresponding 95% CIs and p values. We assessed heterogeneity using the χ^2 test and quantified using the I^2 statistic. Estimated summary effect sizes were calculated using a Mantel-Haenszel fixed-effects model, with weights assigned based on the inverse of within study variance. Where heterogeneity remained significant, we explored through subgroup analyses. We performed subgroup analyses by intervention delivery mechanism, vaccine targeted and control condition. We further conducted a subgroup comparison according to participant age categories and country settings. We used the grading of recommendations assessment, development and evaluation (GRADE) approach to assess the certainty of evidence for the effectiveness of each intervention as high, moderate, low or very low at the outcome level [24].

3.7. Publication bias

Publication bias was assessed using funnel plots and quantified asymmetry between the ORs of the effect measures and the SEs quantified using the Eggers test. Funnel plots display intervention effect estimates from individual studies against a measure of each study's size or precision [25]. Visual asymmetry in funnel plots can indicate the presence of publication bias in an analyses.

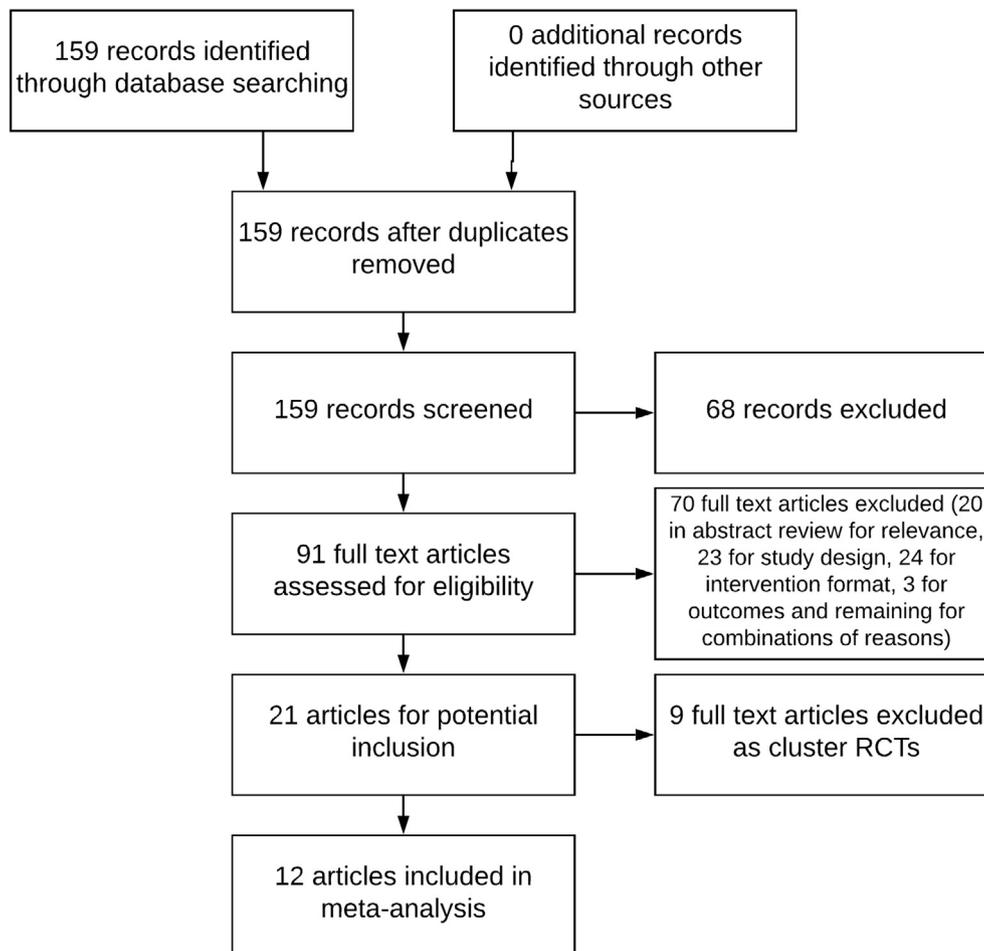


Fig. 1. PRISMA flow diagram.

4. Results

4.1. Study selection

In total, we identified 159 manuscripts through electronic database searches. We excluded 68 during abstract review, leaving 91 for full-text review. Another 70 were excluded in full text review resulting in 21 articles for potential inclusion in the review and meta-analysis. An additional nine were excluded from the meta-analysis due to study design (cluster-RCTs) resulting in leaving a total of 12 manuscripts representing 13 empirical studies in the meta-analysis (Fig. 1).

4.2. Study characteristics

The twelve manuscripts representing thirteen empirical studies were published between 2012 and 2016. In total, they summarized evidence from 24,224 participants. More than half (7/13, 53%) of studies were conducted in New York City, from a group of academically affiliated practices. All of these studies included the author Melissa Stockwell in either the first or senior author role. It appears the practices involved all served a low-income community in New York City where residents frequently travel internationally, are primarily Latino, publicly insured and where the majority are eligible to receive free vaccines from the VFC Program.

The other American studies were in a Mid-Western metropolitan area affiliated with a university hospital [26], in Colorado [27] and in North Carolina [28]. The three studies conducted outside of

the USA occurred in Beirut, Lebanon [29], Kadoma City Zimbabwe [30] and Guatemala City [31].

Five (5) of the included studies (38.5%) recruited participants traditionally, facilitated by research staff in person. The remaining eight (8) studies (61.5%) recruited passively, through the use of centralized EMRs or immunization registries containing participant contact information. Recruited occurred at various time points during the immunization process. Two (2) studies recruited parents of children in-person upon discharge from the hospital [26], or within one week postpartum during home visits [30]. Two more studies recruited in-person at the time of the first dose of an immunization series [31,32]. One study began recruiting at the time of the first HPV dose [28] but then expanded recruitment to unvaccinated students attending health education events on the University campus. The studies who used registry/EMR based recruitment either pregnant women eligible for a vaccine or parents of children who were becoming eligible for a vaccine [33,34] or those who are overdue as per the registry records [29,32,35].

Four studies focused on influenza vaccination, three on the pediatric primary series, two on adolescent vaccines, one on adult pneumococcal, pediatric Hib, MMR and HPV. The characteristics of all included studies are summarized in Table 1.

All studies included text messaging as the delivery channel, with two studies giving participants the option to choose between text message and email [28,29]. All studies included some kind of reminder, with 8 studies also including educational content. The timing or frequency of messages also differed, intervention characteristics are summarized in Table 2.

Table 1
Characteristics of included studies.

| Study name | Geographic details of study location | Population (type of intervention) | Comparison | Category and type of outcome | Total sample size |
|--------------------------|---|--|--|--|-------------------|
| Ahlers-Schmidt, 2012 (1) | Pediatric Clinic in a Mid-Western metropolitan area in the USA | English (83%) and Spanish (17%) speaking parents (83% women) of newborns being discharged from a university hospital and intending on seeking care at a University resident and faculty clinic (a). | Appointment Card | Series Completion of pediatric immunizations at 7 months | 88 |
| Bangure, 2015 (2) | Kadoma City Clinics, Mashonaland West Province of Zimbabwe | Parents of newborns, recruited at the 2nd and 7th day visits after delivery (a) | Usual Care | Series Completion of pediatric immunizations at 14 weeks | 304 |
| Domek, 2016 (3) | Two public health clinics in Guatemala which served a publicly insured, low-income population | Parents of newborns recruited at their first immunization visit (a) | Appointment Card | Series Completion of pediatric immunizations at 6 months | 321 |
| Ghadieh, 2015 (4) | Family medicine centre in Beirut, Lebanon | Unvaccinated adults 40+ who had at least one visit to the clinic in the last 12 months and were beneficiaries of the AUB Health Insurance Plan(b) | Telephone Reminder | Pneumococcal vaccine uptake at 4 weeks after final reminder sent | 1380 |
| Hofstetter, 2015a (5) | Four pediatric practices in an ambulatory care network serving low-income minority children from a community in New York City | Parents of children age 9.5mo-10.5mo at recruitment who had a clinic visit in the past 6 months (a) | Telephone Reminder | MMR vaccine uptake by 13 months of age | 2054 |
| Hofstetter, 2015b (6) | Four pediatric practices in an ambulatory care network serving low-income minority children from a community in New York City | Parents of children 6 months – 17 years old who were unvaccinated for flu as of the late fall and who had visited one of the sites within the 12 months prior to September 1, 2011(a) | Telephone Reminder and general information about influenza vaccination in clinic | Influenza vaccine uptake by March 31, 2012 | 5304 |
| O'Leary, 2015 (7) | 5 urban/suburban private pediatric practices and 2 safety-net practices in Colorado | Parents of unvaccinated 11–17 year olds who had been seen at least once in the preceding 2 years(a) | Usual Care | Vaccine Uptake of any of the eligible immunizations | 4587 |
| Richman, 2016 (8) | A rural North Carolina University with a 2011 enrollment of 26,947 students | Unvaccinated male and female university students aged 18–26 year olds (catch-up age) who were voluntarily initiating their first HPV vaccine dose from the campus student health centre or attending health education events (b) | Paper appointment card with the date of their next appointment written on it | HPV Series Completion | 264 |
| Stockwell, 2012a (9) | Six pediatric practices (2 intervention and 4 control) in an ambulatory care network serving low-income minority children from a community in New York City | Parents of unvaccinated 11–18 year olds with any visit at a study site in the previous 12 months(a) | Usual Care (no reminders) | Vaccine Uptake of either MCV4 or Tdap at 24 weeks post randomization | 361 |
| Stockwell, 2012b (9) | Four pediatric practices in an ambulatory care network serving low-income minority children from a community in New York City running 2 special immunization sessions | Parents of children 7–22 months old who were missing 1 Hib dose needed to complete their primary series and had visited a clinic for that child within the past 12 months (a) | Paper Mailing | Vaccine uptake of Hib at 2 weeks | 174 |
| Stockwell, 2012c (10) | Four pediatric practices in an ambulatory care network serving low-income minority children from a community in New York City | Parents of children who were 6mo-18 years old as of September 28, 2010 and had a clinic visit in the previous 12 months | Automated telephone message | Influenza vaccine uptake by March 31, 2011 | 7574 |
| Stockwell, 2014 (11) | Five community-based clinics affiliated with an academic medical centre in New York City | Unvaccinated pregnant women who had a first trimester obstetric visit between Feb 1 and Aug 15, 2011 and had an estimated date of delivery after August 31(a) | Telephone Reminder | Influenza vaccine uptake, calculated cumulatively at the end of each month during the intervention | 1153 |
| Stockwell, 2015 (12) | 3 community-based pediatric clinics affiliated with an academic medical centre in New York City | Parents of children 6 months – 8 years old at vaccination, had received their first dose of influenza at a study site and were in need of two doses that season ^{**} (a) | Appointment Card | Uptake of the second dose of influenza at April 30th, 2013 | 441 |

a. Digital push, text message; b. Digital Push, Text Message or Email.

^{**} During the 2012–2013 season, in the United States there were 2 acceptable options for determining who needed a second dose of influenza vaccine. The first included any child who had not received 2 doses since July 2010 and the second was any child who had not received 2 previous seasonal influenza vaccinations plus at least 1 2009 H1N1 containing vaccinations(13).

Table 2
Intervention Characteristics.

| Study Name | Enrollment Period | Content Details | Timing/Frequency of message(s) | Milestone | Reminder | Education |
|---------------------------|----------------------------------|--|---|---|----------|-----------|
| Ahlers-Schmidt, 2012 [21] | January – February 2011 | Content not specified | 7 days prior to milestone, prior to vaccines being due | 2,4 and 6 month appointments | Yes | No |
| Bangure, 2015 [18] | January – August 2013 | Routine health education and messages indicating the next appointment date | 7 days, 3 days and 1 day prior to milestone, prior to vaccines being due | 5, 10 and 14 week appointments | Yes | Yes |
| Domek, 2016 [19] | March – April 2013 | “Your child [name] is due on [date] at [clinic] for vaccines.” | 6 days, 4 days and 2 days prior to milestone, prior to vaccines being due | 2nd and 3rd visits (4 and 6 months of age) | Yes | No |
| Ghadieh, 2015a,b [17] | October 2014 – January 2015 | Reminders with additional information about the seriousness of pneumococcal disease | Three identical reminders spaced by four week intervals after enrollment | Enrollment | Yes | Yes |
| Hofstetter, 2015a [22] | June 2011 – October 2012 | Scheduling: if appointment not scheduled, message to schedule which included clinic contact information and mentioned the child’s need for important vaccines like measles following the first birthday. Reminder: Appointment reminder and letting them know the doctor would discuss needed vaccines and asking them to bring the child’s vaccination card. | Scheduling: 3 messages, one week apart Reminder: one message 2 days prior to milestone | Scheduling: one week after enrollment Reminder: One year appointment | Yes | Yes |
| Hofstetter, 2015b [23] | November 2011 | Message content used from [11]. In one arm, parents could request additional information | 5 weekly messages then two additional messages the following month | November/December then January | Yes | Yes |
| O’Leary, 2015 [24] | September 2012 – August 2013 | “We show [first name] is due for [vaccine or checkup or vaccine and checkup]. Reply 1 for us to call you to schedule , 2 if you will call us or STOP to end messages [practice name and phone number]. | Terminated after response, but no response up to 3 more messages every 2 weeks | Enrollment | Yes | No |
| Richman, 2016 [20] | August 2011- December 2013 | 4 health education messages about HPV and the HPV vaccine, 2 appointment reminder messages and 1 message for the follow up survey | Once per month for 7 months after enrollment | Enrollment | Yes | Yes |
| Stockwell, 2012a [25] | January 2009 – April 2009 | Notifying parents of their child’s need for vaccination | 1,2,3,6 and 7 weeks post milestone Or until vaccine recorded | Enrollment | Yes | No |
| Stockwell, 2012b [25] | May 2009 – June 2009 | Notified parents that their child was in need of an Hib vaccine because of a shortage and included the location, times and dates of the special immunization sessions | Up to 3 text message notifications, 2 weeks prior to milestone | Special Hib immunization recall session | Yes | No |
| Stockwell, 2012c [11] | 2010–2011 influenza season | Content developed with community input through focus groups and in depth interviews; educational information with an emphasis on vaccine safety and seriousness of infection tailored to the age of the child or adolescent and information on vaccination clinics | Up to 5 weekly text messages OR until vaccine recorded | Enrollment | Yes | Yes |
| Stockwell, 2014 [26] | September – December 2011 | Content from [28] | Up to 5 Weekly after milestone OR until vaccine recorded | Enrollment | Yes | Yes |
| Stockwell, 2015 [27] | August 29, 2012 – March 31, 2013 | Content from [11] | Day 7, day 21, day 25, day 28 and day 42 after milestone OR until vaccine recorded | First Influenza dose | Yes | Yes |

* A week before appointment date: – “Immunization protects your child against killer diseases such as polio, whooping cough, diphtheria, measles, pneumonia and tuberculosis. You are reminded that the vaccination appointment will be due in 7 days time from today.” Three days before appointment: – “You are reminded that the vaccination appointment will be due in 3 days from today.” A day before appointment: – “Your vaccination appointment is due tomorrow, visit the nearest clinic”.

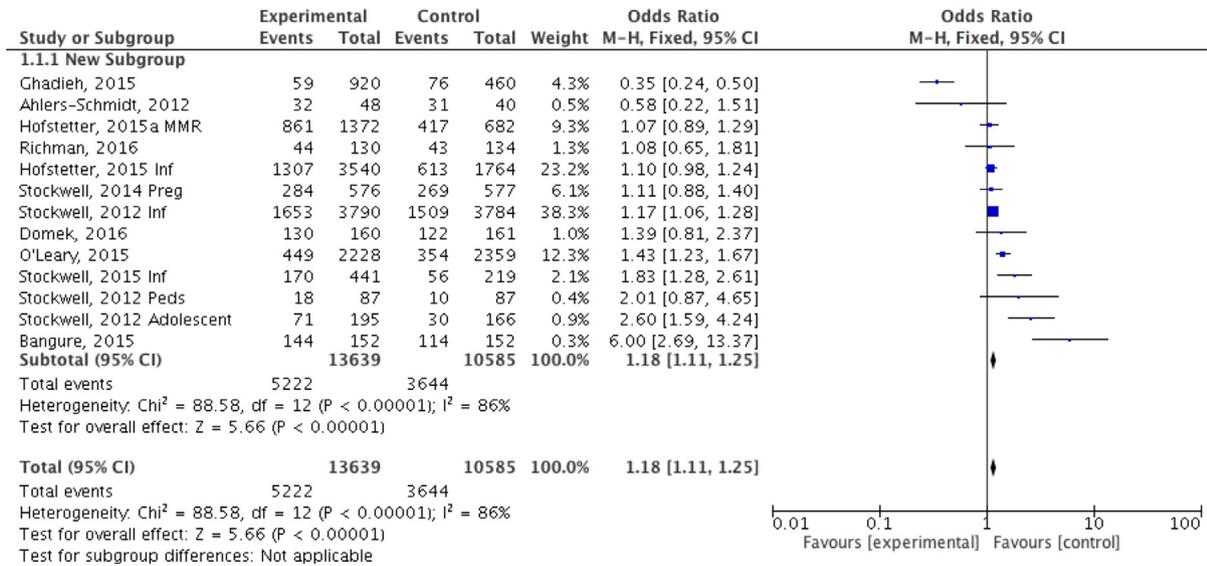


Fig. 2. Digital push interventions compared to non-digital interventions for both vaccine uptake and series completion.

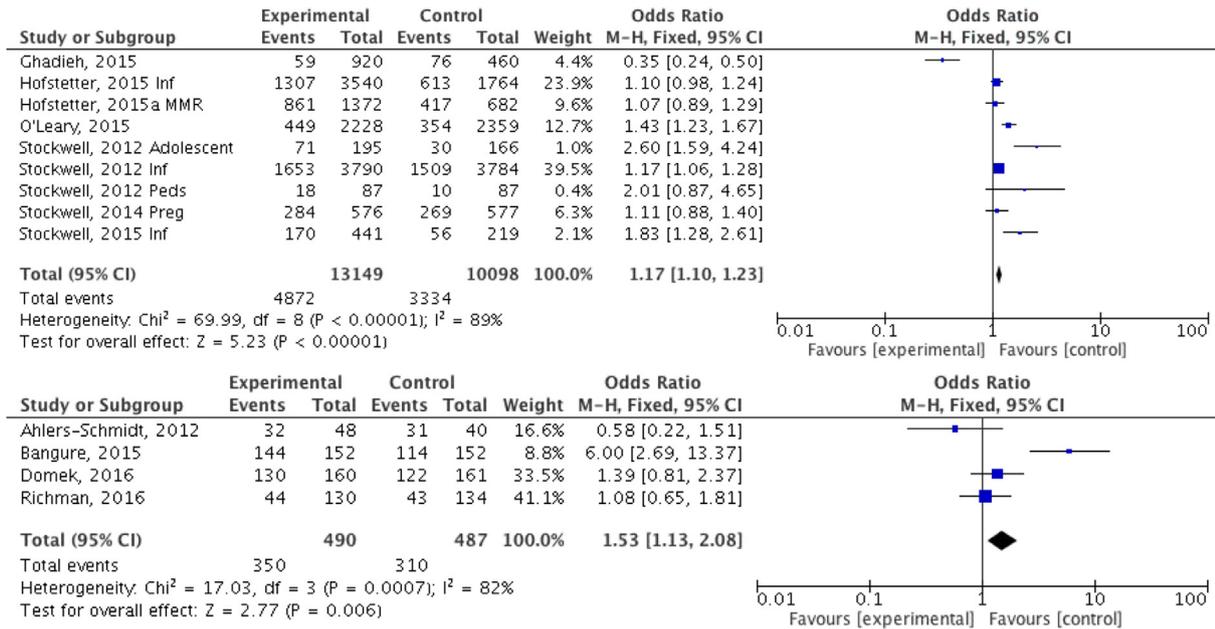


Fig. 3. Digital push interventions compared to non-digital interventions for Vaccine Uptake (a) and Series Completion (b).

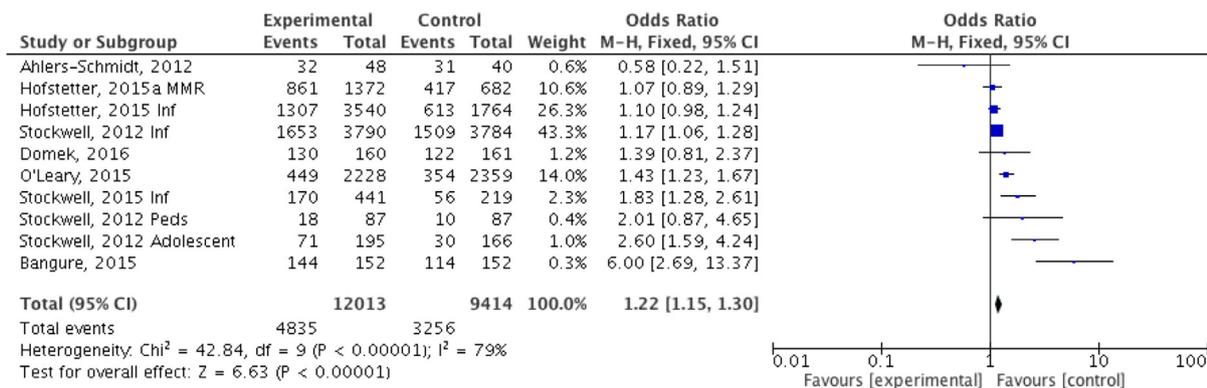


Fig. 4. Digital Push interventions compared to Non-Digital Pull interventions in parents of children aged 18 and younger.

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------------|---|---|---|---|--|--------------------------------------|------------|
| Ahlers-Schmidt, 2012 | + | + | + | ? | - | + | - |
| Bangure, 2015 | + | - | - | - | ? | + | + |
| Domek, 2016 | + | + | + | + | - | + | + |
| Ghadieh, 2015a | + | + | + | ? | + | + | + |
| Hofstetter, 2015a | + | + | + | + | ? | + | + |
| Hofstetter, 2015b | + | + | + | + | ? | + | + |
| O'Leary, 2015 | + | - | + | ? | + | + | + |
| Richman, 2016 | ? | + | + | ? | ? | ? | - |
| Stockwell, 2012a | + | + | + | ? | + | ? | + |
| Stockwell, 2012b | + | + | + | ? | + | + | + |
| Stockwell, 2012c | + | + | + | + | - | + | + |
| Stockwell, 2014 | + | + | + | + | ? | + | + |
| Stockwell, 2015 | + | + | + | + | ? | + | + |

Fig. 5. Risk of Bias Assessment. * the green + indicates low risk of bias, yellow ? indicates unclear risk of bias and red - indicates high risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5. Intervention effects

5.1. Primary objective

Examining all 13 studies, there was a 1.18 [1.11,1.25] increased odds of participants being vaccinated or completing the vaccination series with digital push interventions compared to non-digital interventions (Fig. 2). The I^2 was 86%. When evaluating by outcome, digital push interventions compared to non-digital interventions for vaccine uptake show an increased odds of 1.17 [1.10,1.23] and an increased odds of 1.53[1.13,2.08] for series completion (Fig. 3).

5.2. Secondary objective

For our secondary objective of digital push interventions compared to non-digital interventions in parents of children aged 18 years or younger, the meta-analysis included ten studies with a total of 12,013 participants. The odds of the intervention group getting vaccinated or completing the series was 1.22[1.15, 1.30] the odds in those receiving non-digital pull interventions (Fig. 4).

We conducted subgroup analyses by vaccine type where there were 3 or more studies targeting a specific vaccine or series. For

studies targeting the influenza vaccine, digital push interventions compared to non-digital show an increased odds of 1.16 [1.08,1.24] and an I^2 of 57% (Appendix A, Fig. 1). For the 3 studies targeting the pediatric series, digital push interventions compared to non-digital interventions showed an increased odds of 1.85 [1.27,2.70] and an I^2 of 87%. We also conducted subgroup analyses by recruitment type (Appendix A, Figs. 3 and 4) and by Geographic region (Appendix A, Figs. 5 and 6). When examining the studies conducted by the Stockwell group in NYC, digital push interventions compared to non-digital interventions showed an increased odds of vaccination or series completion of 1.15[1.08,1.23] and an I^2 of 46%.

5.3. Risk of bias

The Risk of Bias assessment is shown in Fig. 5. Out of the seven (7) domains assessed, 10 studies considered low risk in five (5) or more domains, six (6) studies considered high risk in at least one domain, with one study high risk for 3 domains. All studies had at least one domain which was unclear or high risk.

Random sequence generation: All but one study [28] was rated low risk for random sequence generation. The remaining study was uncertain risk[28].

Allocation Concealment: 12 out of 14 studies were low risk for allocation concealment, many utilizing immunization information system integrated notification engines such as EzVac. The other two studies [27,30] were high risk for this domain.

Blinding of Participants and Personnel: All but one study [28] was rated low risk for blinding of participants and personnel. The remaining study was rated a high risk[30].

Blinding of Outcome Assessment: Six studies were rated low risk for blinding of outcome assessment, while six were uncertain risk. Only one study [30] was assessed to be high risk for this domain [30].

Incomplete Outcome Data: Four of the 13 studies were rated low risk for this domain. Six more studies were rated as uncertain, with the remaining three being assigned high risk for Incomplete Outcome Data.

Selective Reporting: 11 of the 13 studies were rated as low risk for Selective Reporting, the remaining two were determined to be uncertain risk.

Other Bias: 11 of the 13 studies were rated as low risk for other bias, with two studies being high risk due to demographic differences between the intervention and control groups [26,28]. In one study, the participants differ significantly on gender and income [26]. In the other, participants differed by reported sexual orientation [28].

Strong evidence of heterogeneity was observed ($i^2 = 86%$, $P < 0.0000001$) which did not dissipate with subgroup analyses. To explore publication bias, a funnel plot was drawn (Fig. 6). The funnel plot did not show significant visual evidence of asymmetry although there are two studies [29,30] are visual outliers.

5.4. Certainty of evidence

The results of the GRADE assessment are summarized in Table 3. For the outcome of “Series Completion”, the certainty of evidence was assessed to be very low. For the outcome of “Vaccine Uptake”, the certainty of evidence was assessed to moderate.

6. Discussion

Our review identified 13 studies in which digital-push interventions were compared to either non-digital interventions for vaccine uptake and series completion. These studies were conducted

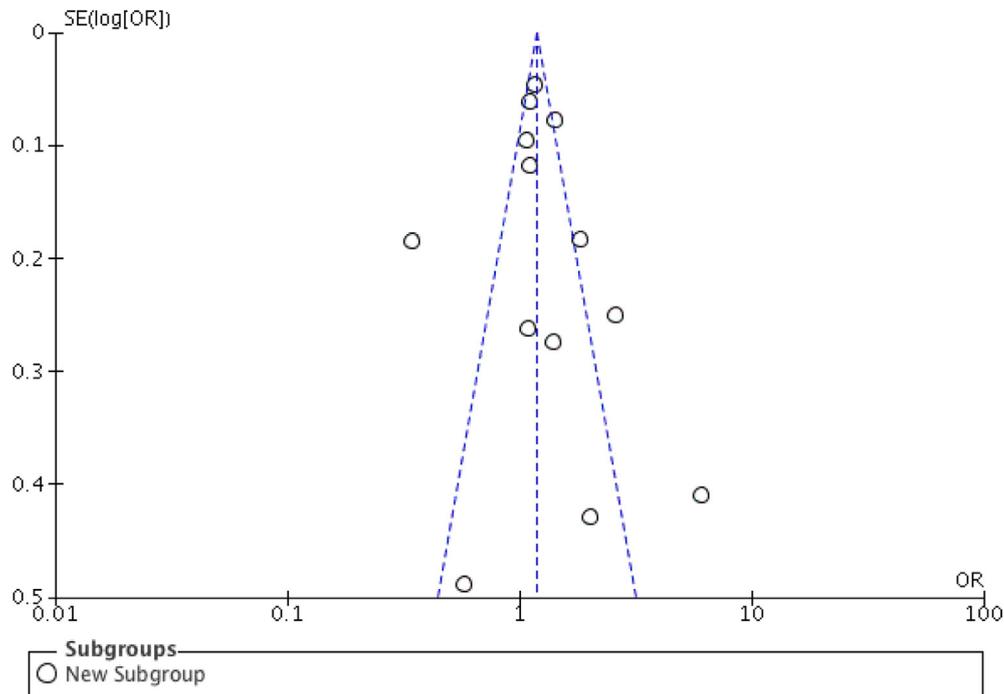


Fig. 6. Funnel Plot.

between 2012 and 2016 in the USA except for three studies which were conducted in Lebanon, Zimbabwe and Guatemala City. Overall, digital push technologies had a modest, positive impact on vaccine uptake and series completion compared to non-digital interventions. However, heterogeneity amongst the studies was very high and did not dissipate significantly in subgroup analyses (Appendix A). The lowest observed heterogeneity was in the subgroup analysis examining studies conducted in NYC by the Stockwell group, with an I^2 of 46%. The Certainty of evidence as measured by GRADE ranges from moderate (vaccine uptake) to very low (series completion).

Recruitment strategies varied across the studies included in the analysis. Less than half of the studies (38.5%) recruited in-person, with the remainder (61.5%) recruiting using centralized EMRs/immunization registries. In studies where participants were recruited at their first immunization appointment, this may have acted as a natural selector, omitting participants who were unsupportive of vaccination and favouring those who were motivated to vaccination. This pattern was observed in Richman, 2016 where participants were initially only recruited by the pharmacist at their first dose of the HPV series. When enrollment rates were lower, they expanded recruitment to special health education events. The results of this study showed those in the early-protocol group had significantly higher series completion rates for the second (67% vs 48%) and third (46% vs 29%) doses compared to the late-protocol group.

This study supports the idea that digital technologies could be a useful adjunct in improving vaccination rates, in particular, the use of these technologies to push messages to recipients. As the use of digital devices becomes nearly ubiquitous this may serve as a more efficient method than traditional approaches. Studies have shown that utilizing the capacity of mobile to personalize messages would increase the saliency and trustworthiness of content being delivered [36]. Our findings are also supported by other studies which showed modest positive improvements in vaccine uptake and series completion through cluster randomized controlled trials [37–42].

Our study had several notable strengths. To the best of our knowledge, this is the first study to assess the impact of technological interventions on vaccination rates by the characteristics of push versus pull. We included data only from randomized controlled trials which minimized the impact of bias. All assessments were conducted in duplicate to ensure reproducibility. We assessed for publication bias and identified symmetry in the funnel plot and our results are therefore not impacted by publication bias.

Our study also had several limitations. We found that there was substantial heterogeneity in our findings that could not be easily explained. We expect that this is likely due to the nature of digital technologies themselves which are heterogeneous and rapidly evolving. Further, the majority of studies were conducted in the United States, with more than half of the studies conducted in the same geographic area (NYC), in a publicly insured, majorly Latino population. Racial and ethnic disparities in vaccination coverage were well-documented in the United States in the 1980s and 1990s. During the 1989–1991 measles outbreak, racial/ethnic minority children were at a 3–16 times greater risk for measles than were non-Hispanic white children [43]. In response, the Centre for Disease Control (CDC) created the Vaccines for Children (VFC) initiative which provides vaccines at no cost to children who might otherwise not be vaccinated because of inability to pay the cost of vaccines [44]. In the 7 studies conducted in NYC, authors noted that the “vast majority of patients were eligible to receive free vaccines from the VFC program”. Because of the success of the VFC program in these populations, we do not believe that cost was a significant barrier to vaccination in these studies.

The remaining studies were conducted in Lebanon, Zimbabwe and Guatemala. In the study conducted in Lebanon, patients were beneficiaries of the American University of Beirut’s insurance plan but could access the pneumococcal vaccine for approximately \$16 USD whereas vaccinations in the other studies were provided free of charge. The differences in settings and contexts where vaccines provided may limit the generalizability of our findings. Our study also included studies which targeted a variety of vaccinations, which may not account for vaccine specific issues or barriers in

Table 3
 Certainty of Evidence Table for Vaccine Uptake and Series Completion. **Question:** Digital Push Interventions compared to Non-Digital Interventions for Vaccine Series Completion and Vaccine Uptake.

| Certainty assessment | | No. of patients | | Effect | | Certainty | Importance | | | | | |
|--------------------------|-------------------|---------------------------|---------------------------|--------------|-------------|----------------------|--------------------|--------------------|------------------------|---|---------------|----------|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | All | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| Series completion | | | | | | | | | | | | |
| 4 | Randomized trials | Very serious ^a | Very serious ^b | Not serious | Not serious | None | 340/470 (72.3%) | 306/487 (62.8%) | OR 1.73 (1.27 to 2.36) | 117 more per 1,000 (from 54 more to 171 more) | ⊕○○○ VERY LOW | CRITICAL |
| Vaccine uptake | | | | | | | | | | | | |
| 10 | Randomized trials | Not serious | Serious ^c | Not serious | Not serious | None | 4931/14068 (35.1%) | 3336/11468 (29.1%) | OR 1.20 (1.13 to 1.27) | 39 more per 1,000 (from 26 more to 52 more) | ⊕⊕⊕○ MODERATE | CRITICAL |

CI: Confidence interval; **OR:** Odds ratio. Explanations.

^a Each study had at least one domain categorized as high risk of Bias, with three of the four studies also having domains which were unclear for risk of Bias.
^b Magnitude of intervention effect varied across studies. Intervention effects were often not statistically significant. The I2 for series completion was 77%, which was not explained through subgroup analyses. The confidence interval was large, spanning from 1.27 to 2.36.
^c The I2 is 91%, which was not explained through subgroup analyses. However, the confidence interval was narrower and did not cross 1.

participants. For example, the only study that focused on the HPV vaccine did so in a University Student population where participants were eligible for HPV catch-up programs. The specific issues or barriers for HPV in a catch-up context may differ from those experienced by individuals receiving the vaccine as part of routine programs. We recommend that future studies examine both contexts separately. Another limitation of our study is that as technology changes, the impact of these technologies will also likely change.

Given the small sample of studies evaluating series completion (four), and the variation in effect sizes observed more research is needed. Specifically, the effect observed in Bangure, 2015 is significantly larger (OR of 6.00 [2.69,13.37]) than other studies. The study was conducted in Mashonaland province of Zimbabwe, in an area with suboptimal pediatric immunization rates. The study design differs from many of the other included studies in that participants were recruited in-person by healthcare workers at in-home visits following delivery of a newborn. Of the 304 participants reportedly approached, 302 were recruited with 0 loss to follow up reported. One of the excluded participants did not have a cell phone and the other died soon after delivery. This may indicate high trust in the healthcare workers or high acceptance of new interventions related to immunization, as most other studies had higher exclusion or loss to follow up rates.

Despite conducting subgroup analyses by publication date, population, comparison group and vaccination targeted, heterogeneity amongst the studies remained very high. This may indicate that there is an underlying difference in the studies which was not measured. One key component of this is baseline attitudes/ intention to vaccinate – these interventions may be particularly effective in populations where the intention to vaccinate is high and barriers are majorly logistical. Future research should consider measuring participant baseline intention to vaccinate, technology readiness, device used, familiarity with technology and any other factors that could help explain the heterogeneity observed. The Certainty of evidence as measured by GRADE ranges from moderate (vaccine uptake) to very low (series completion). Given the immaturity of this field of research, this is not surprising but future research should consider methods of improving the certainty of evidence.

The heterogeneity we observed may in part be due to technological readiness in study participants. None of the studies captured a measure of participant attitudes towards technology, or their propensity to use technology to address challenges in their life, including for health. Many studies also relied on participant opt-in which may have biased the sample towards early adopters of technology. Future research should consider capturing metrics of user technology readiness such as the technology readiness index (TRI 2.0 [45]) in order to stratify results by this demographic variable. The technology acceptance model can also be used as a guide intervention development to ensure that significant barriers to use are addressed [46].

This review offers new insight into how push and pull technologies can be leveraged to improve vaccination uptake and series completion. For decades, researchers have been evaluating “push” interventions such as telephone and paper mail recall reminders. They have been found to be effective across many settings, populations and target vaccines. With the increasing use of digital technologies and near ubiquitous smartphone usage, public health will need to understand how to adapt these proven methods for new delivery channels.

7. Conclusion

This study provided evidence that digital push technologies have a modest, positive impact on vaccine uptake and series

completion compared to non-digital pull interventions. However, more research is needed in this area.

Declaration of interest

None.

Acknowledgements

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. KA is supported through a Canadian Institute for Health Research (CIHR) Doctoral Research Award (CIHR-IRSC:0092002293). ZEK is supported by a Grand Challenges Canada-Stars in Global Health (Grant ID #R-ST-POC-1807-12490).

Conflicts of interest

None to declare

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.03.063>.

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