MOBILE PHONE TEXT MESSAGE REMINDERS TO IMPROVE VACCINATION UPTAKE: A SYSTEMATIC REVIEW

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DECLARATION

I, Gail Louw, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgments indicate otherwise) and that neither the whole work nor any part of this has been, is being, or is to be submitted for another degree in this or any other university.

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STRUCTURE OF DISSERTATION

Abstract includes a brief description of the background, methodology, results and discussion related to the evaluation of the effect of mobile phone text message reminders as an intervention on vaccination uptake.

Part A is the **research protocol** which includes a literature review that outlines the background. The research protocol also outlines the methodology used to conduct the research. The study applies systematic review methods, as outlined in the "Cochrane Handbook for Systematic Reviews of Interventions. Version 6.3" to compile and synthesize the best current evidence from published scientific literature archived in key international publication databases. Part A also includes appendices to the protocol that includes tables indicating the primary search strategy and the pre-defined inclusion and exclusion criteria for full-text eligibility, the data extraction form as well as the ethics waiver document (UCT HREC Ref No: 963/2023).

Part B presents the research project structured as a **manuscript** that are formatted according to the submission guidelines of the journal "Vaccines", which requires the publication to be written in American English. The goal for the study is presented and addressed in the background, and the study results are summarized, presented, and discussed.

Part C comprises of supplemental information related to the manuscript (Part B) that are included as **Appendices.** This includes the pre-defined inclusion and exclusion criteria, primary search strategy, Tables indicating the characteristics of included and excluded studies, figures indicating meta-analysis of data from included studies and subgroup analysis in addition to the instructions for authors for Vaccines Journal.

ABSTRACT

Background: Vaccination uptake remains of public health concern, despite reported improvements in vaccine access. Innovative strategies, such as mobile phone text message reminders (MPTMRs), have been explored and implemented globally to facilitate the increase in vaccination uptake and recall rates. This systematic review, employing best practice, evaluated the most recent scientific evidence for the use of MPTMRs as an intervention to improve vaccination uptake.

Objective: To evaluate the effectiveness of MPTMRs on vaccination uptake in children, adolescents and adults.

Methods: This systematic review included randomized controlled trials (RCT's) of caregivers of children, adolescents or adults who received MPTMRs as an intervention for improving vaccine uptake and recall visits. Studies were excluded if they did not include a comparator group or, if the comparator group was not usual care. Two authors independently searched Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, GoogleScholar and ClinicalTrials.gov to identify relevant studies published by 24 January 2024 using a pre-defined search strategy. Included studies were assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Given the heterogeneity across studies, pooled risk ratios were estimated using the random-effects model. Subgroup analyses were conducted to assess the effect of intervention type, country's economic status, study setting, and vaccination types on results of the meta-analysis.

Results: We identified 25 studies (n = 64 536) for inclusion for quantitative synthesis of evidence regarding vaccination uptake. While studies were considered as having a low risk for random sequence generation, most showed an unclear risk of bias for allocation concealment. Blinding, incomplete outcome data, selective reporting and detection bias were assessed as having a low risk of bias for most studies with high attrition bias observed in seven studies. Pooled data favoured MPTMRs (RR=1.09 [95%CI: 1.06, 1.13], I^2 = 76%) for improving vaccination uptake compared to usual care. Exclusion of studies of poor quality assessment improved heterogeneity and maintained the effect (RR=1.05 [95%CI: 1.03, 1.07]; I^2 = 33%).

Intervention characteristics, country setting, country economic status and vaccination type had no bearing on the effectiveness of the intervention.

Discussion: The overall findings from this systematic review indicate an effect in favor of MPTMRs, albeit relatively small, on vaccination uptake. These findings may assist public health practitioners, policymakers and vaccine researchers in evidence-based decision making that focus on MPTMRs and its effect on vaccination coverage.

Part A: Protocol

MOBILE PHONE TEXT MESSAGE REMINDERS TO IMPROVE VACCINATION UPTAKE: A SYSTEMATIC REVIEW PROTOCOL

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ABSTRACT

Background: Vaccination uptake remains of public health concern, despite reported improvements in vaccine access. The lowest level of global vaccination coverage in children were reported in 2021, since 2008, with approximately 25 million children unvaccinated or incompletely vaccinated. Since timely vaccination and up-to-date vaccination schedules are essential factors that limit vaccine-preventable deaths, it is important to explore interventions that could enable sustaining these factors thereby increasing vaccination uptake and decreasing vaccine preventable deaths. Recently, mobile phone text message reminders (MPTMRs) have been explored as an intervention strategy to facilitate vaccination uptake and increase recall rates. This protocol proposes to conduct a systematic review that evaluates current scientific evidence that assessed the effectiveness of MPTMRs as an intervention in improving vaccination uptake in children, adolescents and adults.

Methods/Design: This systematic review will include randomised controlled trials (RCT's) of caregivers of children, adolescents or adults who received MPTMRs as an intervention for improving vaccine uptake and recall visits. Studies will be excluded if they did not include a comparator group or, if the comparator group was not usual care. A comprehensive search will be conducted across bibliographic databases which may include PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus to identify relevant studies using a pre-defined search strategy. A standardized data extraction form will be used to extract information on the relevant studies. The risk of bias of the included studies will be assessed by applying the "Cochrane Collaboration's tool for assessing risk of bias in randomised trials". Meta-analysis of the data will be done using The Cochrane Collaboration Review Manager version 5.4.1 software. Data-analysis will be conducted based on the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity will be characterised by the I^2 statistic. Data from individual studies assessed as homogenous, will be pooled and summary effect sizes will be estimated using the fixed-effects model. The random-effects model will be applied to data deemed not poolable. This data analysis will be presented as a pooled risk ratio with 95% confidence intervals (CIs). Subgroup analysis will be done for intervention type (text messaging in addition to another component, country's economic status, study setting, and vaccination types.

Discussion: Our findings may be used by public health practitioners, policymakers and vaccine researchers in evidence-based decision-making that focus on MPTMRs and their effect on vaccination uptake. The subsequent recommendations may affect policy change and

facilitate the implementation of strategies that could increase vaccination coverage on a regional or global scale and may result in a decrease in vaccine-preventable deaths.

Keywords: vaccination uptake, mobile phone reminders, SMS, vaccine coverage

LITERATURE REVIEW

Introduction

Vaccine-preventable diseases remain a global public health concern, despite vaccine availability and vaccine access. Increasing vaccination coverage has been prioritised by the World Health Organization (WHO), in an effort to decrease the occurrence of vaccine-preventable diseases and vaccine-preventable deaths. Timely vaccination and up-to-date vaccination schedules are essential factors that promote maintaining immunity limiting vaccine-preventable deaths (Dolan et al., 2019; MacDonald et al., 2019). To facilitate the development of country-specific vaccination schedules and promote the on-time administration of vaccines, the WHO has provided guidance on defined vaccination schedules and intervals (World Health Organization, 2021a, 2022). Maintaining declines in vaccine-preventable deaths is dependent on vaccination uptake, defined as the "number of individuals that have received a specified vaccine dose(s)" (MacDonald et al., 2019). This, in turn depends on scheduling and attending the vaccination appointment, which is often not adhered to, resulting in missed or late vaccinations (Hadjipanayis et al., 2018; McLaughlin et al., 2019; Janssens et al., 2023).

Vaccination coverage generally is defined as the proportion of individuals that have received a specific vaccine within a defined population (MacDonald et al., 2019). Recent reports demonstrated a significant decrease in global vaccination coverage due to the negative impact of the coronavirus disease 2019 (COVID-19) pandemic on critical health services (Rachlin et al., 2022; Shet et al., 2022). The WHO/UNICEF Estimates of National Immunization Coverage reported that 25 million children were unvaccinated or incompletely vaccinated (indicated by the absence of a third dose of diphtheria-tetanus-pertussis-containing vaccines (DTP3)) with a reduction of vaccination coverage from 86% in 2019 to 81% in 2021 (Rachlin et al., 2022). In addition, this report highlighted a decrease in the initiation of Human Papillomavirus (HPV) vaccination in females older than 15 years of age, from 20% in 2019 to 15% in 2021 (Rachlin et al., 2022). These findings had a significant impact on achieving sustainable development goals that focus on promoting and ensuring health and well-being at all ages, through vaccination (United Nations, 2022).

Factors influencing vaccination coverage

Understanding the factors that contributes to non-adherence to vaccination schedules is a crucial element in addressing low vaccination coverage. Various studies have reported that socio-demographic factors such as age and educational level affect adherence to vaccination appointments (Nkenyi et al., 2019; Tsachouridou et al., 2019). Similarly, reports have shown

that socio-economic status affects vaccination uptake, with low-income households demonstrating lower adherence to vaccination appointments, resulting in lower vaccination coverage (Srivastava, Fledderjohann & Upadhyay, 2020; Caspi et al., 2021). Some studies also reported that lack of basic knowledge of the caregiver or adult on the importance of vaccinations, poor service delivery, religious beliefs and access to health facilities are factors that negatively affect adherence to vaccination schedules and, subsequently vaccination coverage (Monguno, 2013; Tambe et al., 2019; Jillian & Kizito, 2020; Keselman et al., 2022). Due to these factors, exploring accessible, low-cost, innovative technologies that can be implemented on a global scale is essential to improve vaccination coverage both regionally and globally.

WHO Global Vaccine Action Plan

In 2012, the WHO launched the Global Vaccine Action Plan (GVAP) 2011 – 2020, with the vision to facilitate an increase in global vaccination coverage (World Health Organization, 2013). This plan was guided by six principles which included 1) "country ownership", 2) "shared responsibility and partnership", 3) equity, 4) integration, 5) financial sustainability, and 6) innovative research and development (World Health Organization, 2013). The goal of GVAP was to achieve 90% national and 80% district level vaccination coverage of DTP3 by 2020 (World Health Organization, 2013). The national vaccination coverage goal of 90% was achieved in 125 countries, however, only 57 countries reported a 80% DTP3 coverage on a district level (World Health Organization, 2020). Although GVAP did not meet all its goals, it laid the foundation for a sold framework for the Immunization Agenda 2030, which aims to 1) reduce the number of unvaccinated children by 50%; 2) achieve ³90% coverage for childhood vaccinations and 3) achieve 500 introductions of new or under-utilized vaccines in low-and middle-income countries (World Health Organization, 2021b). This framework includes the following seven strategic priorities which include 1) "immunization programmes for primary health care and universal health coverage", 2) "commitment and demand", 3) "coverage and equity", 4) "life-course and integration", 5) "outbreaks and emergencies", 6) "supply and sustainability" and 7) "Research and Innovation" (World Health Organization, 2021b).

Impact of text message reminders on vaccination uptake

It is evident that improving vaccination coverage would require a substantial sustained global, national and regional effort and innovative strategies to implement and optimise health systems in target populations. A recent study demonstrated that modifiable factors such as lack of maternal knowledge on childhood vaccinations, schedules, side effects as well as

maternal attitude towards vaccination negatively impacted vaccination uptake in Africa (Galadima et al., 2021). For this reason, innovative strategies and interventions such as mobile Health, and digital health, in addition to mobile phone technology and social media platforms are being developed to decrease vaccine misinformation and hesitancy and increase vaccination coverage (Aranda-Jan, Mohutsiwa-Dibe & Loukanova, 2014; Odone et al., 2021; Cascini et al., 2022). Various studies have shown the efficacy of text message reminders, either alone or in combination of other interventions such as post cards, autodialer calls and letters, in improving vaccination coverage in defined target populations, for various diseases and in different clinical and country settings (Harvey, Reissland & Mason, 2015; Jacobson Vann et al., 2018; Eze, Lawani & Acharya, 2021). This indicates that text message reminders and recall have the potential to facilitate behaviour changes, leading to adherence to vaccination schedules by reminding caregivers of infants, adolescents and or adults of specific vaccination appointments and providing the required encouragement to ensure timely attendance to improve vaccination uptake.

Conclusion

Recently, a systematic review evaluating the effectiveness of various interventions on vaccine uptake demonstrated that personalised text message COVID-19 appointment reminders increased vaccination uptake (Batteux et al., 2022). However, limited published studies exist that synthesises all available scientific evidence, that assessed the impact of mobile phone text message reminders on vaccination coverage, irrespective of geographic location, population and disease. Therefore, this systematic review aims to assess the most recent and best scientific evidence that evaluates the efficacy of mobile phone text message reminders as an intervention to improve vaccination uptake.

REVIEW QUESTION

What is the effectiveness of MPTMRs in improving vaccination uptake in children, adolescents and adults?

OBJECTIVE

This systematic review will evaluate the effectiveness of mobile phone text message reminders (MPTMRs) on vaccination uptake.

METHODS

This review protocol is an update to a previously registered protocol on PROSPERO International Prospective Register of systematic reviews for publication registration number CRD42014007531 (Hohlfeld et al., 2014). The observations and findings of this systematic review will be reported as outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015; Page et al., 2021).

Criteria for considering studies for review.

Type of studies

This systematic review will include randomised controlled trials (RCT's) that evaluated the effect of mobile phone text message reminders (MPTMRs), as the intervention, on vaccination uptake compared to usual care in participants that have received an initial dose of any vaccine in the vaccination schedule.

Types of participants

Participants will be caregivers of infants or children, as well as adolescents and adults, including pregnant or breastfeeding women in any clinical setting.

Experimental interventions

We defined our intervention, MPTMRs to included short messaging service (SMS), Telegram, WhatsApp, Facebook Messenger, and any multimedia applications that use an instantaneous alert to promote vaccination uptake will be included in this study. MPTMRs should be delivered to caregivers of infants or children and adolescents or adults that require a follow-up dose/s in a routine vaccination schedule or booster vaccinations for any vaccine-preventable disease.

Comparator interventions

Comparator interventions will include but are not limited to the following: usual care at the health care facilities such as appointment cards indicating dates of next appointment, verbal reminders of next appointment, autodial telephone reminders, text messages with health education content and no appointment reminders.

Types of outcome measures

It is required that the study results include quantitative data.

Study outcome

This review will evaluate vaccination coverage as defined by the authors of the included studies, irrespective of disease.

Search methods for identification of studies

We will perform a comprehensive search of the bibliographic databases and will identify all relevant peer-reviewed journal articles that evaluated the impact of MPTMRs on vaccination coverage. Journal articles, published from 01 January 2012 to 24 January 2024, will be included for subsequent screening, irrespective of publication language and publication status.

Electronic searches

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus will be searched for RCTs evaluating the impact of mobile phone text message reminders on vaccination coverage. We will use text words as well as medical subject heading (MeSH) terms in various combinations; for example, “Immunization” [MeSH Terms], “telemedicine” [MeSH Terms], vaccin*, “text reminder” and adolescen*. Appendix A, Table 1 shows the primary search strategy that will be used for PubMed searches. This search strategy will be modified for each database.

Searching other resources

We will screen reference lists of relevant publications identified through the database search to identify additional studies for full-text eligibility assessment.

Data Collection and Analysis

Selection of studies

The database search will be independently conducted by two authors. Publications retrieved from the search will be uploaded into a semi-automated screening tool to facilitate the screening process (Johnson & Phillips, 2018). Duplicate publications retrieved from the

databases will be excluded. Inclusion criteria, as outlined in Appendix B, Table 2, will be uniformly and consistently applied by both independent authors. Titles and abstracts will be screened for relevance and will be followed by comparing the results between the two independent authors. Discrepancies will be resolved by discussion. Subsequently, we will obtain the full text publications of potentially eligible studies and two authors will independently evaluate full-text eligibility of each publication using the pre-defined inclusion and exclusion criteria as outlined in Appendix B, Table 2. The results between the two authors will be compared and discrepancies will be resolved by discussion. The reason for exclusion during full-text eligibility will be described for excluded studies.

Data extraction and management

References will be managed using SciWheel (2000-2023 SAGE Publications Limited). GL and AH will assess the data of the included studies by extracting detailed information using a standardised data extraction form (Appendix C) on the intervention and control characteristics, age category of participants, country and settings where the studies were conducted and details on the type of vaccines including vaccination schedules.

Intention-to-treat data on the overall, and visit/dose- specific vaccination coverage (i.e. timeliness of vaccinations) in the intervention and control groups will also be extracted. In addition, details on incentives provided to the participants will be extracted.

Discrepancies between the two authors will be resolved by discussion, and resolution of unresolved discrepancies will be facilitated by a third author to ensure 100% agreement. Data entry will be done by data entry into The Cochrane Collaboration Review Manager version 5.4.1 (The Cochrane Collaboration, 2020) software and a second author will perform quality control checks to ensure no data entry errors occurred.

Assessment of risk of bias in included studies

We will assess the risk of bias of the RCTs, and their respective protocols and trial registry records by independently applying the “Cochrane Collaboration’s tool for assessing risk of bias in randomised trials” (Higgins et al., 2011). The risk of bias criteria will assess bias arising due to 1) random sequence generation (selection bias); 2) allocation of concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome date (attrition bias); and 6) selective reporting (reporting bias) and other causes of biases (Higgins et al., 2011). Following this

independent assessment, any discrepant judgements for risk of bias between the two authors will be resolved by discussion, or by an impartial third author should the disagreements persist.

Measures of treatment effect

Meta-analysis will be done on the data using The Cochrane Collaboration Review Manager version 5.4.1 (The Cochrane Collaboration, 2020) software. The risk ratio (RR) with 95% Confidence Intervals (95% Cis) will be used as a measure of treatment effect for dichotomous outcomes and mean differences will be calculated for continuous outcomes.

Dealing with missing data

Authors of the specific studies will be contacted if missing data or incomplete information is identified in the included studies.

Assessment of heterogeneity

Clinical heterogeneity of the included studies will be assessed by evaluating variability in participants, intervention subtypes and study outcomes. Heterogeneity in methods of the included studies will be assessed by evaluating variability in risk of bias. Descriptive statistics will be used to characterise both clinical and methodological heterogeneity. Statistical heterogeneity will be assessed by evaluating variability in the effect of the intervention and will be characterised by the I^2 statistic.

Data synthesis

Data-analysis will be conducted based on the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022).

Data from individual RCTs, with little to no heterogeneity, will be pooled and summary effect sizes will be estimated using the fixed-effects model. If the data are not poolable, the random-effects model will be used. This data analysis will be presented as a pooled risk ratio with 95% confidence Intervals (CIs).

Subgroup Analysis

Subgroup analysis will be done to assess its effect on the results of the meta-analysis for intervention type (text messaging in addition to another component eg. appointment card reminders, routine health education), country's economic status, (LMIC vs High), study setting (urban vs other), and vaccination types (early childhood vs HPV vs other). We will also determine the effect of excluding the studies with a high risk of bias judgement on the intervention effect.

Sensitivity Analysis

The effect of excluding compared to including studies with a high risk of bias will be assessed for random sequence generation, allocation concealment, and/or incomplete outcome data.

Presenting and Reporting of Results

The search strategy and pre-defined inclusion and exclusion criteria for study eligibility will be presented in table format. The study selection process will be reported using the PRISMA flow diagram. Agreement assessment for full-text screening, data extraction and risk of bias assessment between the two authors will be assessed by the kappa statistic. Forest plots will be used to visualise study heterogeneity and publication bias will be evaluated by examining the symmetry of the funnel plots. Risk of bias assessment and characteristics of included and excluded studies will be presented in a table format.

ETHICS

This systematic review does not require formal ethical review since it does not involve human subjects (Appendix D). Authors with expertise in the methodologies of systematic reviews will review the study protocol.

DISCUSSION

Significance of the study

This study may have implications for both public health practice and vaccine research. The findings of the study will provide evidence on the feasibility of implementing mobile phone text reminders into existing health systems to facilitate behaviour change to vaccinations and subsequently influence vaccination uptake. It will guide evidence-based decision-making and

enable the evaluation of critical factors that influence achieving and sustaining immunisation coverage globally, irrespective of the target population, country setting and vaccination type.

ABBREVIATIONS

CENTRAL - *Cochrane Central Register of Controlled Trials*

DTP3 - *3rd dose of Diptheria-Tetanus-Pertussis containing vaccine*

GVAP - *Global Vaccine Action Plan*

HPV - *Human Papillomavirus*

IA2030 - *Immunization Agenda 2030*

MeSH - *Medical Subject Heading*

MPTMRs – Mobile Phone Text Message Reminders

PRISMA - *Preferred Reporting Items for Systematic Review and Meta-Analysis*

RCT - *Randomized Controlled Trial*

RoB - *Risk of Bias*

SMS - *Short Messaging Service*

WHO - *World Health Organization*

COMPETING INTERESTS

The authors declare no competing interests.

AUTHOR'S CONTRIBUTIONS

GL drafted the protocol. AH and ME critically reviewed the protocol. GL and AH will conduct the search, extract the data, and conduct the data analysis and results interpretation.

FUNDING

No funding was received for this study.

COMMUNICATION STRATEGY

The results of this study will be disseminated via a journal article. The outcome of this study will have implications for researchers and policy makers. The results are aimed at identifying the effect of MPTMRs on vaccination uptake on a global scale, irrespective of the clinical setting and the irrespective of disease type. These findings may address feasibility approaches of implementing MPTMRs in existing health systems or patient appointment notification systems that could influence vaccination uptake. The findings in this study may guide evidence-based decision-making and enable the evaluation of critical factors that facilitate global vaccination coverage.

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APPENDIX A

Table 1: Primary Search Strategy for PubMed

Search	PubMed
#1	Immunization [MeSH Terms] OR immunis* OR immuniz* OR vaccin*
#2	adolescen* OR child* OR teenager* OR adult* OR infant* OR caregiver*
#3	"SMS" OR cellphone* OR "mobile phone*" OR "text mess*" OR "short message service*" OR "text reminder*" OR "Telegram" OR "WhatsApp" OR "social media" OR "reminder system*" OR reminder OR routine* OR "telemedicine" [MeSH Terms]
#4	**(**randomized controlled trial [pt] OR controlled clinical trial [pt] OR (randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
#5	#1 AND #2 AND #3 AND #4

APPENDIX B

Table 2: Pre-Defined Inclusion and Exclusion Criteria for Full-text Eligibility

	Inclusion	Exclusion
Study design	Randomised Control Trials	Non-Randomised Control Trials
Intervention type	Mobile phone text message reminders	Voice calls reminders; Educational Videos, Autodial reminders, Postcards, Letter Correspondence; Email
Control type	Usual care, including verbal communication on the next vaccination date to caregiver or participant or informing caregiver or participant about next scheduled appointment date on the immunization card	Absence of the control arm
Vaccination status	Have had first dose of any vaccine in vaccination schedule	Vaccination Naïve

APPENDIX C

Data Extraction Form

Reviewer ID:

Study ID:

Publication Characteristics:

- Authors:
- Publication Title:
- Journal (Year):
- URL:

Study Setting Characteristics:

- Country:
- Setting:
- Economic Status, according to World Bank Classification:

Low Income	
Lower-Middle Income	
Upper-Middle Income	
High Income	

Vaccination and Disease Information:

- Disease:
- Type of Vaccination:
- Vaccination Schedule:
- Number of doses:

Participant Characteristics:

- Number of participants in trial

	Intervention group	Control Group	Total
N*			
% of Total			100%

*Number of participants

- Sex at time of study enrollment

	Intervention group		Control Group		Total	
	N*	%	N	%	N	%
Male						
Female						
Total						

*Number of participants

- Mean age at the time of study enrollment
  - Intervention group:
  - Control group:

- Age category

Adults (>18 years of age)	
Parents/Caregivers of children	
Adolescents	
Not reported	

- Pregnant Status

Pregnant	
Not Pregnant	
Not Reported	

Intervention Characteristics:

- Intervention: Mobile phone text message reminder

Number of reminders sent prior to vaccination appointment	
Number of days that message was sent before vaccination appointment	
Frequency	
Details of reminder message	
Other remarks	

Comparator Characteristics:

- Control: Usual Care

Frequency	
Details on Usual Care	
Other remarks	

Outcomes:

- Author's definition of vaccination coverage:

Primary Outcome

- Overall number vaccinated

	Intervention group		Control Group		Total	
	N*	%	N	%	N	%
N*						
Total						

- Number vaccinated per follow-up visit

	Intervention group		Control Group		Total	
	N*	%	N	%	N	%
Visit 1						
Visit 2						
Total						

- Number vaccinated on-time per follow-up visit

	Intervention group		Control Group		Total	
	N*	%	N	%	N	%
Visit 1						
Visit 2						
Total						

- Was there a secondary text message sent to remind participants to return if scheduled visit was missed to assess recall rate?

Yes	
Unclear	
No	

- Method for assessing outcomes

Objective	
Self-reported	
Unclear	

Incentives:

Monetary	
Airtime	
Gift Cards	
Other	

Overall Comment:

APPENDIX D

Ethics Waiver Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45, E-52 Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

08 December 2023

HREC REF NO: 963/2023

Dr Gail Louw
19 White Sands Circle
Hout Bay 7806
Email: lwxgai001@myuct.ac.za
Supervisor: mark.engel@uct.ac.za

Dear Dr Louw

PROJECT TITLE: MOBILE PHONE TEXT MESSAGE REMINDERS TO IMPROVE VACCINATION UPTAKE: A SYSTEMATIC REVIEW

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review and meta-analysis.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: "*Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.*"

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledges that this study is for Dr Gail Louw's as a MPH (Biostatistics and Epidemiology) Candidate. The Supervisors are Prof M Engel and Mr Ameer Hohlfeld.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

PART B: MANUSCRIPT

MOBILE PHONE TEXT MESSAGE REMINDERS TO IMPROVE VACCINATION UPTAKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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§ Joint first author

1. ABSTRACT

Background: Mobile phone text message reminders (MPTMRs) have been implemented globally to promote vaccination uptake and recall rates. This systematic review evaluated the effectiveness of MPTMRs on vaccination recall rates.

Methods: We included randomized controlled trials of caregivers of children, adolescents, or adults who received MPTMRs for improving vaccine uptake and recall visits. We searched Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, GoogleScholar and ClinicalTrials.gov to identify relevant studies published by 24 January 2024. We used Cochrane's Risk of Bias tool to assess the included studies and reported the results as risk ratios using the 95% confidence intervals and a random-effects model.

Results: We identified 25 studies for inclusion. All studies were assessed to be of low risk of bias. Evidence supports MPTMRs for improving vaccination uptake compared to usual care (RR=1.09 [95%CI: 1.06, 1.13], I^2 = 76%). Intervention characteristics, country setting, country economic status and vaccination type had no bearing on the effectiveness of the intervention.

Conclusion: MPTMRs have a positive effect, albeit relatively small, on vaccination uptake. These findings may assist public health practitioners, policymakers and vaccine researchers in evidence-based decision making that focus on MPTMRs and its effect on vaccination coverage.

PROSPERO registration number 2014: CRD42014007531

Keywords: Vaccination, text message reminders, vaccination uptake, vaccination coverage

2. Introduction

Vaccine-preventable diseases remain a global public health concern despite vaccine availability and vaccine access. Increasing vaccination coverage has been prioritized by the World Health Organization (WHO), to decrease the occurrence of morbidity and mortality from vaccine-preventable diseases. Researchers define vaccination coverage generally as the proportion of individuals that have received a specific vaccine within a defined population [1]. Recent reports demonstrated a significant decrease in global vaccination coverage due to the negative impact of the coronavirus disease 2019 (COVID-19) pandemic on critical health services [2,3]. The WHO/UNICEF Estimates of National Immunization Coverage reported that 25 million children were unvaccinated or incompletely vaccinated, with a reduction of vaccination coverage from 86% in 2019 to 81% in 2021 [2]. These findings had a significant impact on achieving sustainable development goals that focus on promoting and ensuring health and well-being at all ages through vaccination [4].

Timely vaccination and up-to-date vaccination schedules are essential factors that promote maintaining immunity and limiting vaccine-preventable deaths [1,5]. To facilitate the development of country-specific vaccination schedules and promote the on-time administration of vaccines, the WHO has provided guidance on defined vaccination schedules and intervals [6,7]. Figure 1 represents the interplay among factors that can influence vaccination uptake that would facilitate a decrease in vaccine-preventable deaths. It presents the implications of adherence/non-adherence on vaccine-preventable deaths. Maintaining the decline in vaccine-preventable deaths is dependent on vaccination uptake, defined as the "number of individuals that have received a specified vaccine dose(s)" [1]. This, in turn, depends on the scheduling and on-time attendance of the vaccination appointment [8–10]. These appointments are often missed and lead to either missed or late vaccinations, resulting in lower vaccination uptake, which could lead to an increase in vaccine-preventable deaths (Figure 1). Various studies have reported that socio-demographic factors such as age and educational level affect adherence to vaccination appointments [11,12]. Similarly, reports have shown that socio-economic status affects vaccination uptake, with low-income households demonstrating lower adherence to vaccination appointments, resulting in lower vaccination coverage [13,14]. Some studies also reported that lack of basic knowledge of the caregiver or adult on the importance of vaccinations, poor service delivery, religious beliefs and access to health facilities are factors that negatively affect adherence to vaccination schedules and, subsequently vaccination coverage [15–18]. Due to these factors, exploring accessible, innovative technologies that can be implemented on a global scale is essential to improve vaccination coverage both regionally and globally.

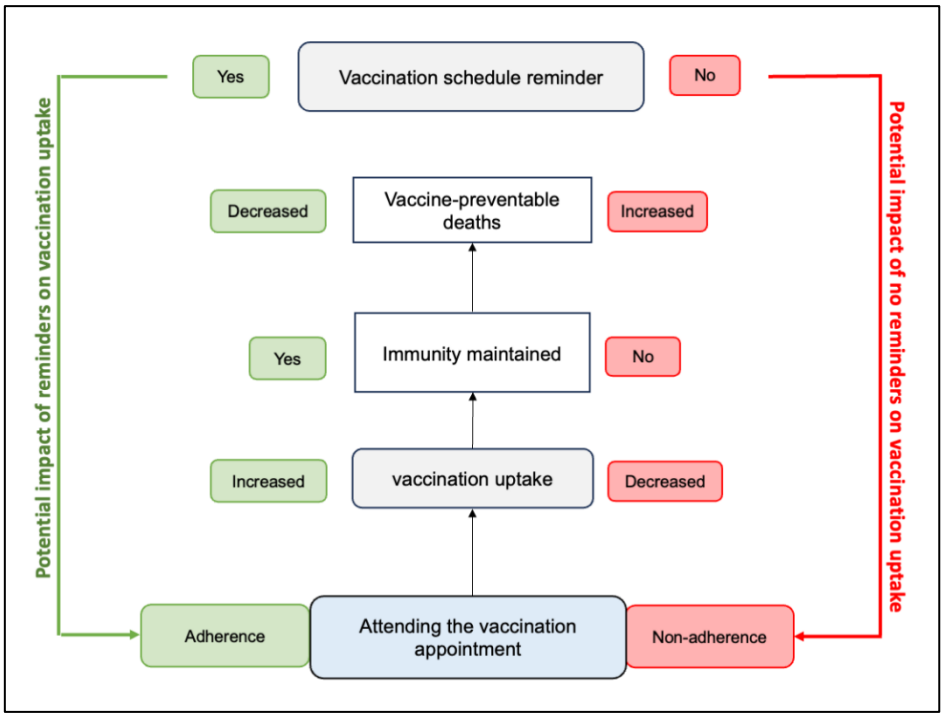

Figure 1: Interplay of factors that influence vaccination uptake.

In 2012, the WHO launched the Global Vaccine Action Plan (GVAP) 2011 – 2020, with the vision to facilitate an increase in global vaccination coverage [19]. This plan was guided by six principles which included 1) “country ownership”, 2) “shared responsibility and partnership”, 3) equity, 4) integration, 5) financial sustainability, and 6) innovative research and development [19]. The goal of GVAP was to achieve 90% national and 80% district level vaccination coverage of DTP3 by 2020 [19]. The national vaccination coverage goal of 90% was achieved in 125 countries, however, only 57 countries reported a 80% coverage in the three doses of the combined diphtheria, tetanus toxoid and pertussis (DPT3) vaccine on a district level [20]. Although GVAP did not meet all its goals, it laid the foundation for a solid framework for the Immunization Agenda 2030 , which aims to 1) reduce the number of unvaccinated children by 50%; 2) achieve 90% coverage for childhood vaccinations and 3) achieve 500 introductions of new or under-utilized vaccines in low-and middle-income countries [21]. This framework includes the following seven strategic priorities 1) “immunization programs for primary health care and universal health coverage”, 2) “commitment and demand”, 3) “coverage and equity”, 4) “life-course and integration”, 5) “outbreaks and emergencies”, 6) “supply and sustainability” and 7) “research and innovation” [21].

It is evident that improving vaccination coverage would require a substantial sustained global, national and regional effort and innovative strategies to implement and optimize health systems in target populations. A recent study demonstrated that modifiable factors such as lack of maternal knowledge on childhood vaccinations, schedules, side effects as well as

maternal attitude towards vaccination negatively impacted vaccination uptake in Africa [22]. For this reason, innovative strategies and interventions such as mobile Health, and digital health, in addition to mobile phone technology and social media platforms are being developed to decrease vaccine misinformation and hesitancy and increase vaccination coverage [23–25]. Various studies have shown the efficacy of text message reminders either alone or in combination of other interventions such as post card, auto dialer calls and letters, in improving vaccination coverage, in defined target populations, for various diseases and in different clinical and country settings [26–28]. This indicates that text message reminders and recall have the potential to facilitate behavior changes, leading to adherence to vaccination schedules by reminding caregivers of infants, adolescents and or adults of scheduled vaccination appointments and provide the required encouragement to ensure timely attendance to improve vaccination uptake.

Recently, a systematic review evaluating the effectiveness of various interventions on vaccine uptake demonstrated that personalized text message reminders for COVID-19 vaccination appointments increased vaccination uptake [29]. However, limited published studies exists that synthesizes all available scientific evidence, that assessed the effectiveness of mobile phone text message reminders (MPTMRs) on vaccination coverage, irrespective of geographic location, population and disease. Therefore, this systematic review aims to assess the most recent and best scientific evidence evaluating the efficacy of MPTMRs as an intervention to improve vaccination uptake.

3. Materials and Methods

The findings in this systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [30] and guidelines outlined in the Cochrane Handbook of Systematic Reviews for Interventions [31]. No formal institutional review board approval was required for this study since it does not involve human subjects.

3.1 Review Question

What is the effectiveness of MPTMRs in improving vaccination recall in children, adolescents and adults?

3.2 Study Outcome

This study assessed vaccination recall as the outcome including subgroup analysis based on the nature of the intervention, country's economic status, study setting and vaccination type.

3.3 Eligibility Criteria and Search Strategy

The study eligibility criteria for inclusion were pre-defined (*Table S1*). Briefly, studies were eligible if they were randomized controlled trials (RCT's) of caregivers of children, adolescents or adults who received MPTMRs as an intervention. The intervention needed to include information via short messaging service (SMS), Telegram, WhatsApp, Facebook Messenger or any multimedia applications that use an instantaneous alert delivered to caregivers of infants or children, and adolescents or adults (including women that were pregnant or breastfeeding) that required a follow-up dose(s) in a routine vaccination schedule or booster vaccinations for any vaccine-preventable disease. Our comparator interventions were usual care, which included, but were not limited to, written appointment reminders on appointment cards or immunization cards, verbal reminders of the next appointment, autodial telephone reminders, text message with health education content and no appointment reminders at the health care facilities. Studies were excluded if it did not include a comparator group or if the comparator group was not usual care.

A comprehensive strategy was developed and applied to search and subsequently identity relevant studies (*Table S2*). This search strategy included key words such as "SMS", "text reminder" in addition to medical subject heading (MeSH) terms in various combinations such as "Immunization" and was independently adapted and modified accordingly for searches in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, GoogleScholar and ClinicalTrials.gov by two investigators (GL and AH). The reference lists of relevant publications identified through the database search was assessed to identify additional studies for full-text eligibility assessment. We searched all databases until 24 January 2024.

3.4 Study Identification and Selection

The database search was independently conducted by two authors (GL and AH) and publications retrieved from the search was uploaded into Rayyan, a semi-automated review screening tool to facilitate the screening process [32]. Duplicate publications retrieved from the databases were excluded. The inclusion criteria were uniformly and consistently applied by both authors in an independent manner. Titles and abstracts were screened for relevance and the results between the two independent authors were compared; discrepancies were resolved by discussion. Subsequently, GL obtained the full text publications of potentially eligible studies, and GL and AH independently evaluated each publication for full-text eligibility using the pre-defined inclusion and exclusion criteria (*Table S1*). The results between the two authors were compared and discrepancies were resolved by discussion. The reason for exclusion is tabulated in the table of excluded studies (*Table S5*).

3.5 Data extraction and management

From studies deemed to be eligible, GL and AH extracted, using a standardized data extraction form, detailed information including intervention and control characteristics, age category of participants, country and settings where the studies were conducted and details on the type of vaccines including vaccination schedules. Visit/dose-specific vaccination coverage in the intervention and control groups in addition to details on incentives provided to the participants were extracted.

Disagreements in data extracted were resolved by discussion until 100% agreement was achieved. All relevant data was entered into The Cochrane Collaboration Review Manager version 5.4.1 [33] software and a second author conducted a quality control check to ensure no data entry errors occurred.

3.6 Assessment of Risk of Bias of Included Studies

GL and AH assessed the risk of bias of each RCT, and the respective protocols and trial registry records by independently applying the Cochrane Collaboration's tool for assessing risk of bias in randomised trial [34]. The risk of bias criteria assesses bias arising due to 1) random sequence generation (selection bias); 2) allocation of concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome date (attrition bias); and 6) selective reporting (reporting bias) [34]. Following this independent assessment, any discrepant judgements for risk of bias between the two authors were resolved by discussion between the two authors, or by an impartial third author where the disagreements persist.

We contacted authors of the specific studies where missing data or incomplete information were identified in the included studies.

3.7 Measures of effect

Risk ratio (RR) and mean differences were calculated for dichotomous outcomes and continuous outcomes, respectively.

3.8 Data synthesis

Data-analysis was conducted as outlined in the Cochrane Handbook for Systematic Review of Interventions [31]. Meta-analysis was done on the data considered homogenous, using The Cochrane Collaboration Review Manager version 5.4.1 [33] software to produce synthesis of treatment effect together with their respective 95% Confidence Intervals (95%CIs). Summary effect sizes were estimated using the random-effects model. We conducted analyses on an intention-to-treat basis for our outcomes.

Clinical heterogeneity of the included studies was assessed by evaluating variability in participants, interventions subtypes and study outcomes. Heterogeneity in methods of the included studies was assessed by evaluating variability in risk of bias. Descriptive statistics were used to characterize both clinical and methodological heterogeneity using the I^2 statistic.

3.8.1 Subgroup Analysis

Subgroup analysis was done to assess the effect of intervention type (text messaging only vs text messaging in addition to another component e.g. appointment card reminders, standard verbal counselling, educational videos and routine health education), country's economic status (low-and middle income countries (LMICs) vs high-income countries (HICs)), study setting (urban vs other), and vaccination types (early childhood vaccination vs HPV vs other) on the results of the meta-analysis.

3.8.2 Sensitivity analysis

The effect of excluding studies with a high risk of attrition bias on the intervention effect was determined.

3.9 Risk of Publication Bias Assessment

We assessed publication bias by creating a funnel plot using The Cochrane Collaboration Review Manager version 5.4.1 software, plotting the standard errors of log RRs against RRs [33,35].

4 Results

4.1 Study Identification and Selection

The search identified 5887 publications from the databases search, comprising studies from PubMed (n=3020), Scopus (n=2797), Cochrane CENTRAL (n=70), GoogleScholar (n=151) and ClinicalTrials.gov (n=93) (Figure 2). Subsequently, 723 duplicates were removed using the semi-automation tool Rayyan.ai [32] in addition to screening by GL. The titles and abstracts of the remaining 5408 publications were screened by GL and AH based on the exclusion criteria outlined in *Table S1* and most studies (n=5279) were excluded. Following this screening process, we selected 129 publications eligible for full text screening and subsequently identified 32 studies that met the inclusion criteria (*Table S1*) for data extraction and quantitative synthesis.

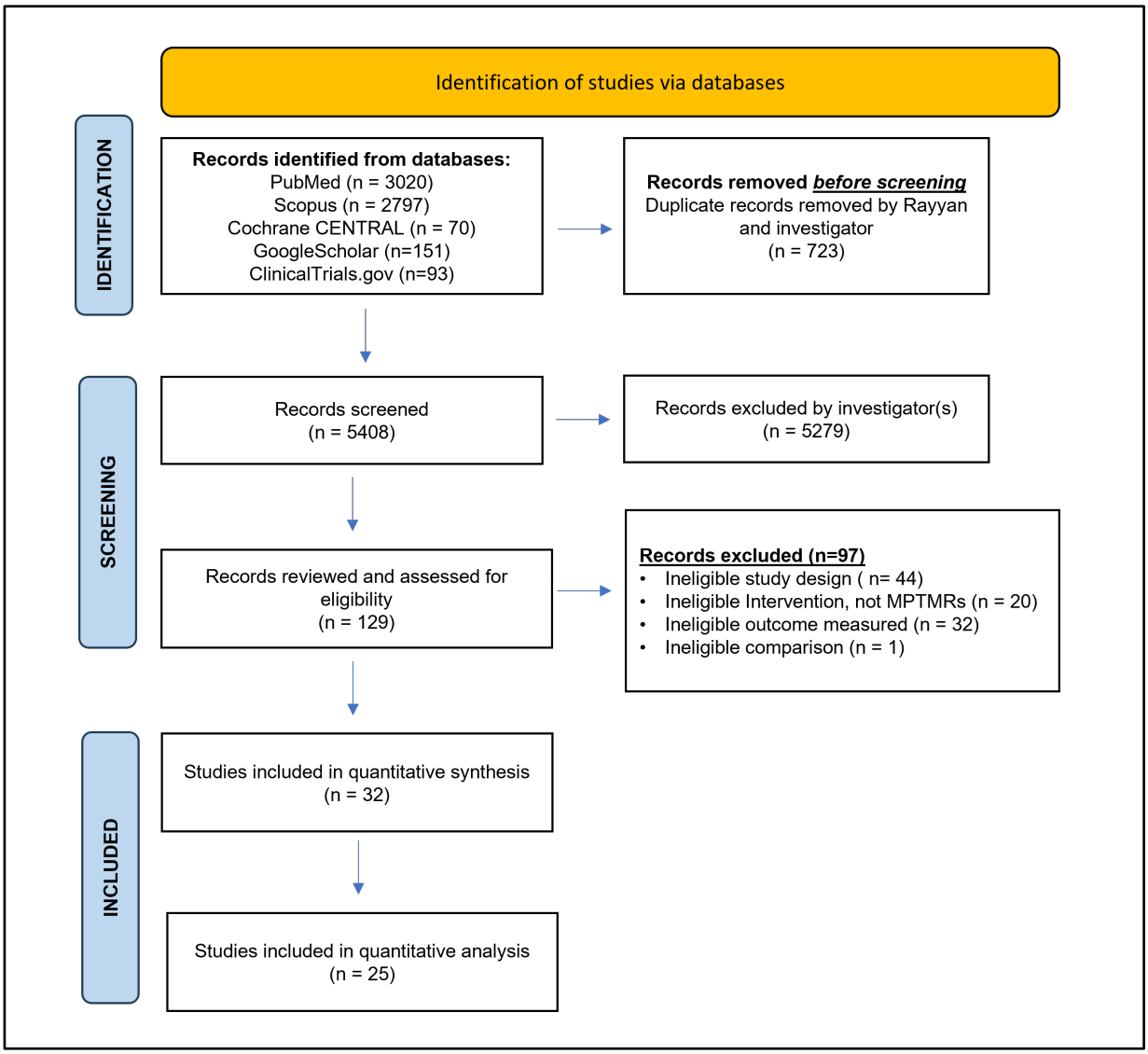

Figure 2: PRISMA diagram of the studies identified in the systematic literature search.

The included studies were characterized, with six studies conducted in a rural setting [36–41], 22 in an urban setting [42–62] and four in a combination of semi-urban and rural or urban and suburban settings [63–66] (*Table S3*). The majority of the studies were conducted in the USA (n=17) [36,40–44,46–49,52,55,58,60,62,65,67], followed by countries in Africa (n=6) [37,38,51,56,61,63], Australia (n=4) [39,42,45,50], Pakistan (n=2) [54,59], Guatemala (n=2) [57,64] and India (n=1) [66] (*Table S3*). Of the 32 studies, seven [37,40,41,48,52,53,63] were excluded from further quantitative analysis, since the outcome data were not stratified by the intervention type; thus, 25 studies were included for risk of bias assessment and meta-analysis (*Table S3*). A table summarizing the funding sources for each included study is provided in the Supplementary Material (*Table S4*).

Studies were excluded from quantitative synthesis for the following reasons: ineligible study design (n=44) [68–111], ineligible intervention, not MPTMRs (n=20) [67,112–130], ineligible outcome measured (n=32) [128,131–160] and ineligible comparison (n=1) [161] (*Table S5*). A list of unpublished and ongoing trials is provided in the Supplementary Material (Table S6)

4.2 Risk of Bias Assessment

Randomization sequence generation: All included studies were judged as having a low risk of selection bias with regards to randomization sequence generation (*Figure 3, Figure S1*).

Allocation concealment: An unclear risk of bias for allocation concealment was concluded for most studies (n=17; 68%).

Blinding: Blinding was assessed as low risk of bias for most studies (n=17; 68%).

Allocation concealment: The majority of studies (n=17; 68%) were deemed as having an unclear risk of selection bias, with the remaining studies (n=8; 32%) showing a low risk of selection bias [36,38,39,51,54,58,59]. (*Figure 3, Figure S1*).

Detection bias: The majority of studies (n=16; 64%) showed low risk of detection bias where the outcome was assessed by data retrieval and the study analysts were blinded to the group assignments [43]. The remaining studies (n=9; 36%) showed unclear risk of detection bias, since these studies did not provide information on blinding of the assessment outcome (*Figure 3*, *Figure S1*).

Incomplete outcomes: The majority of RCTs had a low risk of bias for incomplete outcome data reporting (n=18; 72%) and selective reporting (n=23; 92%) (*Figure 3, Figure S1*).

Attrition bias: High attrition bias was observed in seven studies (28%) [36,47,49,56,64,66] (*Figure 3, Figure S1*).

All but one study [56], reported a well-defined statistical analysis plan thereby indicating a high reporting bias (*Figure 3, Figure S1*). Additionally, all studies provided reasons for LTFU which included e.g., participants moved (out of state) or switched to a different clinic, study staff being unable to contact participants, telephone number disconnected, wrong telephone number or participants died. Lastly, all but one study [49] showed unclear risk of other bias (*Figure 3*, *Figure S1*), since this was challenging to assess due to the small sample size.

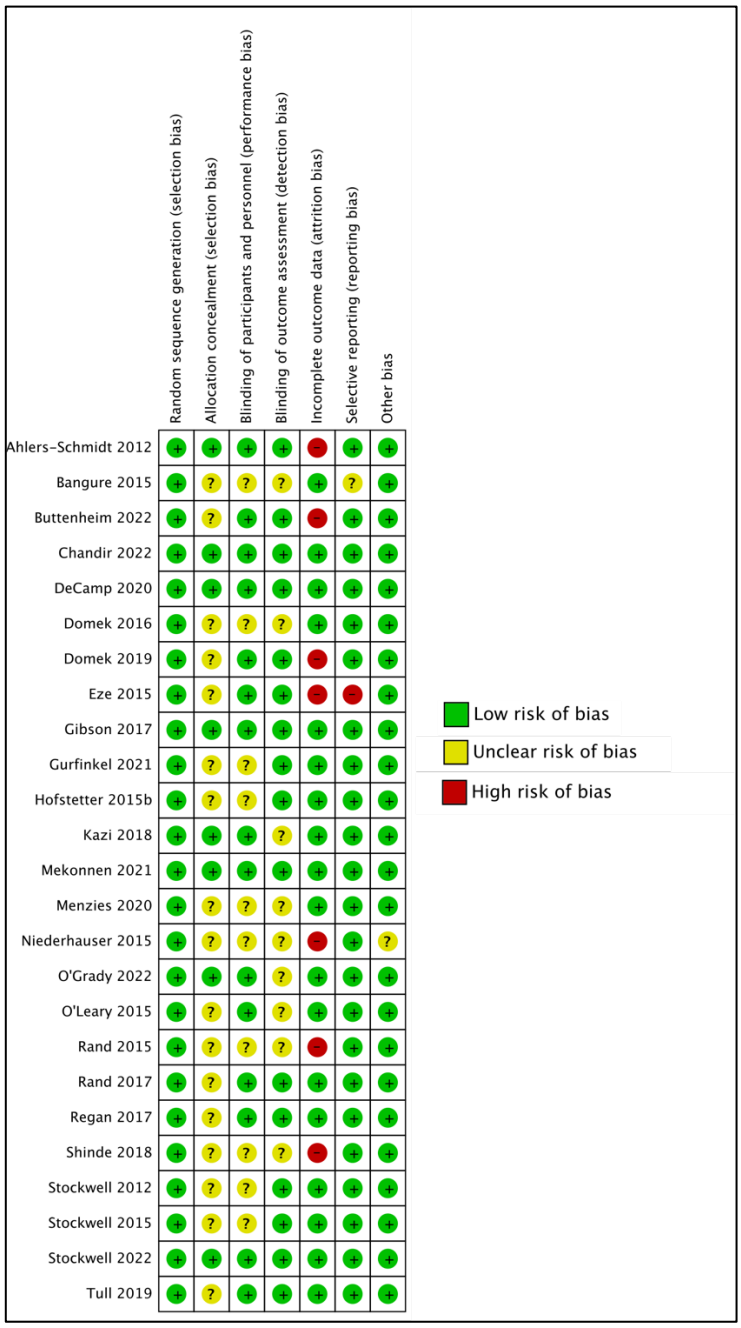

Figure 3: Risk of bias summary of included studies

4.3 Quantitative Data Synthesis

Twenty-five studies (n= 64 536 participants) were considered for quantitative synthesis of evidence regarding vaccination recall. Pooled data favored MPTMRs (RR = 1.09 [95%CI: 1.06, 1.13]; I^2=76%) for vaccination recall compared to usual care (*Figure 4, Table 1*). Given the substantial heterogeneity between the study results (*Figure 4*, *Table 1*), we conducted a sensitivity analysis of only studies deemed to be of high quality (n=6) [44–46,49,58,65]; the results remained consistent (pooled RR = 1.05 [95%CI: 1.03, 1.07]; I^2 = 33%) (*Figure S2*). Similarly, meta-analysis conducted by excluding the results of studies with a high risk of attrition bias (n=7) [36,47,49,56,60,64,66] produced similar results (pooled = 1.11 [95%CI: 1.07, 1.15]; I^2 = 79%) (*Table 1, Figure S3.*) A table summarizing the findings is provided in the Supplementary Material (*Table S7*).

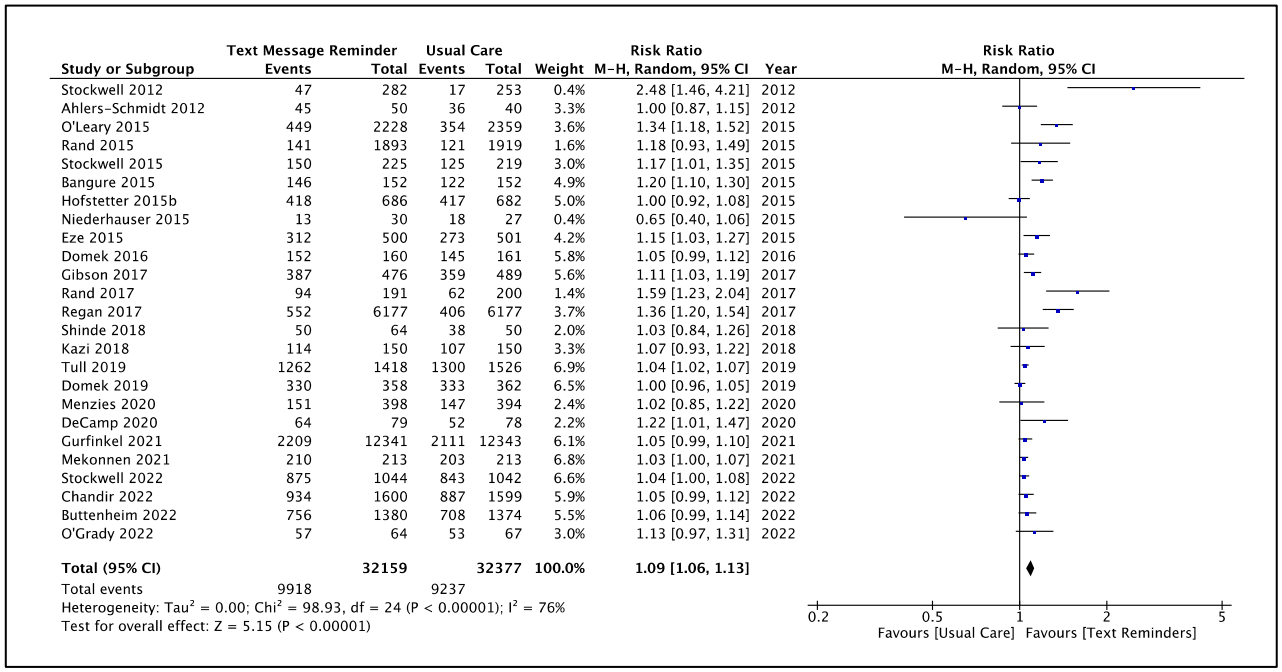

Figure 4: Meta-analysis of data from included studies for vaccination recall after the enrolment visit.

4.4 Subgroup Analysis

4.4.1 Intervention Characteristics

MPTMRs alone, as compared with text messaging with additional components, did not alter the effect on vaccination recall (RR = 1.10 [95%CI: 1.04, 1.16]; I^2 = 83%). Similarly, an effect in favor of MPTMRs was also observed in the subgroup focused on MPTMRs only (RR = 1.09 [95%CI: 1.04, 1.15]; I^2 = 71%). The test for subgroup effect based on intervention characteristics demonstrated no statistically significant effect and no heterogeneity between

the results of the two subgroups (I^2 = 0%) (*Table 1, Figure S4*). This suggests that the intervention characteristics does not modify the effect of MPTMRs compared to usual care.

4.4.2 Country Setting

Subgroup analysis based on country setting showed no effect with no heterogeneity between results in the subgroups (I^2 = 0%) (*Table 1, Figure S5*). Within the urban subgroup, the results show an effect in favor of MPTMRs (RR = 1.10 [95%CI: 1.06, 1.14]; I^2 = 73%). Rural and/or suburban and/or semi-urban, also shows an effect in favor of MPTMRs; however, this effect is not statistically significant (RR = 1.10 [95%CI: 0.97, 1.24]; I^2 = 89%) (*Table 1, Figure S5*).

4.4.3 Country Economic Status

The test for subgroup difference in country economic status shows that there is no statistically significant effect between the LMIC and HIC subgroups; moderate heterogeneity between results in the subgroups (I^2 = 42.3%) was observed (*Table 1, Figure S6*). More studies (n=16, 57 186 participants) contributed data to the high income subgroup compared to the LMIC subgroup (9 studies, 7350 participants), which may indicate that the analysis may not be able to detect subgroup differences. The results show an effect in favor of MPTMRs in the LMIC subgroup (RR = 1.07 [95%CI: 1.03, 1.11]; I^2 = 65%) and the HIC subgroup (RR = 1.12 [95%CI: 1.06, 1.18]; I^2 = 79%), with substantial heterogeneity observed in both subgroups (*Table 1, Figure S6*).

4.4.4 Vaccination Type

The test for subgroup difference in vaccination type shows that there is no statistically significant effect between the vaccination types; however, moderate heterogeneity between results in the subgroups (I^2 = 38.6%) was observed (*Table 1, Figure S7*). In all 3 subgroups, the results show an effect in favor of MPTMRs with RR = 1.07 [95%CI: 1.03, 1.11] observed in the early childhood vaccination subgroup; RR = 1.17 (95%CI: 1.05, 1.30) observed in the HPV subgroup and RR = 1.14 [95%CI: 1.01, 1.28) observed in the other vaccination subgroup that comprised of studies that investigated seasonal influenza vaccination recall. In addition, substantial heterogeneity was observed for the results in the early childhood vaccination subgroup (I^2 = 63%), HPV subgroup (I^2 = 86%) and the other vaccination type subgroup (I^2 = 88%) (*Table 1, Figure S7*).

4.5 Risk of Publication Bias Assessment

Assessment of the funnel plot indicates a symmetrical plot that suggests the absence of publication bias (Figure S8).

Table 1: Meta-analysis, by subgroup, of the effectiveness of text message reminders for vaccination recall after enrollment visit.

Outcome or Subgroup	No of studies	No of participants	Pooled RR [95% CI]	I^2 Statistic (%)	p-value[a]
All studies	25	64536	1.09 [1.06, 1.13]	76%	-
Intervention characteristics					0.84
Text message PLUS additional[b]	13	17394	1.10 [1.06, 1.16]	83%	
Text message ONLY	12	47142	1.10 [1.04, 1.15]	71%	
Country Setting					0.95
Urban	19	57929	1.09 [1.05, 1.13]	73%	
Other[c]	6	6607	1.10 [0.97, 1.24]	89%	
Country Economic Status					0.19
LMIC	9	7350	1.07 [1.03, 1.11]	65%	
HIC	16	57186	1.12 [1.06, 1.18]	79%	
Vaccination Type					0.20
Early Childhood Vaccinations	16	10480	1.07 [1.03, 1.11]	63%	
HPV	5	36418	1.17 [1.05, 1.30]	86%	
Other[d]	4	17638	1.14 [1.01, 1.28]	88%	
Studies without Attrition Bias	18	55988	1.11 [1.07, 1.15]	79%	-

RR, risk ratio; CI, confidence interval; LMIC, lower middle-income country; HIC, high-income country; HPV, human papilloma virus

[a]test for subgroup differences

[b]additional components include interactive text messages, appointment card reminders, standard verbal counseling, educational videos, routine health education

[c]includes rural, semi-urban, suburban

[d]includes seasonal Influenza vaccination

5 Discussion

5.1 Summary of main findings

This meta-analysis of 24 studies presents the best and most recent available evidence on the effectiveness of MPTMRs on vaccination uptake in adolescents, children and adults in all clinical settings, irrespective of country setting and vaccination type.

Although small in effect, our pooled data demonstrates favoring of MPTMRs for improving vaccination uptake compared to usual care. Sub analysis of the intervention effect by intervention characteristics, country setting, country economic status and vaccination type did not change the effectiveness of the intervention.

Notably, substantial heterogeneity was observed in the data of the included studies; nonetheless, similar results were obtained when excluding, from the meta-analysis, studies with high attrition bias. The exclusion of six studies of poor quality from the meta-analysis [44–46,49,58,65] resulted in improved heterogeneity. The findings in Neiderhauser *et al* demonstrated an effect in favor of usual care (RR =. 0.65; 95%CI: 0.40; 1.06) in relation to vaccination uptake. The sample size in this study was small and the effect observed was not statistically significant. In addition, this study reported a high loss to follow-up in the MPTMRs (39%) compared to 10% loss to follow-up in the control arm, that could have influenced the findings [49].

MPTMRs having a positive effect on vaccination uptake could be influenced by a number of factors: 1) participants in the MPTMR arm receiving an additional $20 as incentive to support cellular phone charges [58], 2) participants in the MPTMR arm receiving at least 3 MPTMRs that could have influenced adherence to scheduled vaccination appointments [44,46,65], and 3) a study conducted in a high-risk population in Australia that could have affected the findings [45]. We also observed relatively higher effectiveness of MPTMRs in HIC than in LMICs, which could be facilitated by easier access to health care, vaccination programs and economic advancement.

5.2 Comparison with current literature

Our findings are in agreement with findings from other published reviews that showed that MPTMRs significantly improved childhood, adolescent and adult vaccination coverage, including pregnant women in LMICs [28,162] irrespective of country setting [163]. A recent systematic review also showed that MPTMRs significantly improved the receipt of vaccinations (RR = 1.29; 95%CI: 1.15 to 1.44) compared to post card reminders [26]. In addition, findings in a systematic review conducted by Horvath *et al*, demonstrated that weekly MPTMRs lowered the risk of non-adherence to antiretroviral therapy, although quantitative synthesis was conducted on only two RCT's with adult patients only [164].

5.3 Impact of mechanism of MPTMRs

An estimated 7.41 billion people currently are mobile phone owners with an increase to 7.49 billion people expected in 2025 [165]. Since mobile phone use has also become more widespread [166] and MPTMRs were shown to be cost-effective in distributing health information in LMICs [167], it could be used as a tool to penetrate areas that are hard to reach, fuel adoption of health intervention and expand the reach of vaccination programs in LMIC.

5.4 Strengths and limitations of methods

To our knowledge, this is the first systematic review that evaluated the effectiveness of MPTMRs in children, adolescents and adults after they've received a first dose of any vaccine, irrespective of country setting. This systematic review had several strengths: we included RCTs, conducted a well-defined comprehensive search in multiple bibliographic databases, and assessed and evaluated studies irrespective of study setting, publication language or disease. These studies, therefore, represent the most recent and available published evidence that evaluated the effectiveness of MPTMRs on vaccination uptake in a wide population. In addition, we diligently applied and adhered to the international standardized guidelines for conducting and reporting systematic reviews [31]. We also observed that all the studies included in the review showed low risk of bias for random sequence generation indicating an increased likelihood that the effect observed may be attributed to MPTMRs.

Admittedly, this systematic review only included data from peer-reviewed published studies, which could bias the data in favor of MPTMRs.

5.5 Limitations of included studies

Various limitations were identified in this review that are linked to limitations of the original studies. Most studies included in this review showed unclear risk of bias since these studies did not report information on allocation concealment. In addition, seven studies showed a high risk of attrition bias, which could have influenced the study results. We did, however, conduct sensitivity analyses to better understand the impact of these limitations.

5.6 Implications for future research

The findings of this study have shown that MPTMRs are effective in the studied populations irrespective of country economic status and study setting. However, the majority of studies included in this review was conducted in HICs in an urban setting. In addition, these studies focused on assessing the effect of MPTMRs in a population with bigger sample sizes, possibly due to increased ownership of mobile phones in this study population, compared to LMICs in rural settings. Future research should focus on assessing the effectiveness of MPTMRs in LMICs, irrespective of vaccination type.

A recent report demonstrated that language could have a positive influence on vaccine hesitancy [168]. Therefore, tailoring MPTMRs to include language specific to the population could thus influence vaccine hesitancy, which may have a positive effect on appointment adherence and subsequently vaccination recall. More studies are needed to assess tailored MPTRMS on vaccination recall, irrespective of population.

MPTMRs were shown to be feasible in improving physical health in individuals with psychotic disorders [169] and cost-effective in distributing information on health and reminders in LMICs [167]. Currently, limited data are available on the feasibility and cost-effectiveness of MPTMRs in routine vaccination schedules globally. Generating this data is essential in evaluating adoptability, scalability and sustainability of this intervention in existing vaccination programs.

5.7 Implications for practice and policy

This study may have implications for both public health practice and vaccine research. The findings of this systematic review show that MPTMRs may be a useful tool to supplement existing standard practice within the health care system to facilitate behavior change that may promote vaccination uptake. These findings could enable evidence-based decision making and enable evaluation of critical factors that influence achieving and sustaining immunization coverage globally, irrespective of the target population, country setting and vaccination type.

6 Conclusion

MPTMRs have an effect, *albeit* relatively small, on vaccination uptake. Our findings indicate that MPTMRs may be an effective tool to improve vaccination uptake, irrespective of disease, country setting and economic status. These findings may assist public health practitioners, policymakers and vaccine researchers in evidence-based decision making that focus on MPTMRs and its effect on vaccination coverage.

7 Author Contributions

Conceptualization, G.L., A.H. and M.E.; Methodology, G.L, A.H., and M.E.; software, G.L.; validation, G.L. and A.H; formal analysis, G.L.; investigation, G.L. and A.H.; data curation, G.L. and A.H; writing – original draft preparation, G.L; writing – review and editing, A.H. and M.E.; visualization, G.L.; supervision, A.H. and M.E. All authors have read and agreed to the published version of the manuscript.

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9 Institutional Review Board Statement

Ethical review and approval were waived for this study since it did not involve human subjects.

10 Data Availability Statement

Detailed methods, results and additional data are available in the manuscript and the Supplementary Materials.

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All authors attest that they meet the ICMJE criteria for authorship.

12 Conflicts of Interest

The authors declare no conflict of interest.

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APPENDIX A

Supplementary Materials to:

MOBILE PHONE TEXT MESSAGE REMINDERS TO IMPROVE VACCINATION UPTAKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Table S1: Pre-Defined Inclusion and Exclusion Criteria for Full-Text Eligibility.

	Inclusion	**Exclusion**
Study design	Randomized Control Trials	Non-Randomized Control Trials
Intervention type	Mobile phone text message reminders	Voice calls reminders; E-mails, Educational Videos, Autodial reminders, Postcards, Letter Correspondence
Control type	Usual care, including verbal communication on the next vaccination date to caregiver or participant or informing caregiver or participant about next scheduled appointment date on the immunization card	Absence of the control arm, or control arm not usual care
Vaccination status	Have had first dose of any vaccine in vaccination schedule	Vaccination Naïve

Table S2: Primary Search Strategy for PubMed.

Search	**PubMed**
#1	Immunization [MeSH Terms] OR immunis* OR immuniz* OR vaccin*
#2	adolescen* OR child* OR teenager* OR adult* OR infant* OR caregiver*
#3	“SMS” OR cellphone* OR “mobile phone*” OR “text mess*” OR “short message service*” OR “text reminder*” OR “Telegram” OR “WhatsApp” OR “social media” OR “reminder system*” OR reminder OR routine* OR “telemedicine” [MeSH Terms]
#4	**(**randomized controlled trial [pt] OR controlled clinical trial [pt] OR (randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
#5	#1 AND #2 AND #3 AND #4

Table S3: Characteristics of Included Studies

Study	Country (Setting)	Nr of Participants	Vaccination Schedule	Intervention	Control	Outcomes
Ahlers-Schmidt (2012)	USA (Rural)	90	2-, 4-, and 6-month vaccinations	Appointment reminder text message (including appointment card at previous appointment)	Appointment Card at previous appointment	Receipt and timeliness of vaccines at 2,4- and 6-month visits
Bangure (2015)	Zimbabwe (Urban)	304	Penta-1, OPV-1, PCV-1 at 6 weeks Penta-2, OPV-2, PCV-2 at 10 weeks Penta-3, OPV-3, PCV-3 at 14 weeks	Appointment reminder text message (including routine health education)	Routine Health Education and informed of next appointment date	Received of vaccines at 6-, 10- and 14-week visits
Buttenheim (2022)	USA (Urban)	7479	Seasonal Influenza Vaccine (1 dose)	Appointment reminder text message and reservation of Influenza vaccine.	No text message reminder	Receipt of Influenza vaccine
Chandir (2022)	Pakistan (Urban)	3199	Penta-1, OPV-1, PCV-1 at 6 weeks Penta-2, OPV-2, PCV-2 at 10 weeks Penta-3, OPV-3 PCV-3 at 14 weeks Measles -1 and -2 at 9 and 15 months	Appointment reminder text message	No text message reminder	Full immunization coverage at 12 months

Penta-1, 2, 3: first, second or third dose of vaccine that protects against Diptheria-Pertussis-Tetanus (DPT or DTwP) and Hepatitis B (Hep B) and diseases caused by Haemophilus Influenzae type b (Hib); **OPV-1, 2, 3**: first, second or third dose of oral polio vaccine; **PCV-1, 2, 3**: first, second or third dose of the pneumococcal conjugate vaccine

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants	Vaccination Schedule	Intervention	Control	Outcomes
DeCamp (2020)	USA (Urban)	157	2- dose flu vaccine and age-specific immunisation schedule from birth to 15 months	Interactive text message reminders and educational video (with Flu vaccine reminders)	No text message reminders	Up-to-date immunization up to 15 months and receipt of 2-dose flu vaccine
Dissieka (2019)[1]	Côte d'Ivoire (Rural/ Semi-urban/Urban)	1596	Penta-1 at 6 weeks, Penta-2 at 10 weeks, Penta-3 at 14 weeks Vit A at 6 months MMR and yellow fever at 9 months	Text message or voice reminders based on participant preference	No reminders	Attendance at each visit
Domek (2016)	Guatemala (Urban)	321	Penta-1, PCV-1, OPV-1, Rota-1 at 2 months Penta-2, PCV-2, OPV-2, Rota-2 at 4 months Penta-3, OPV-3 at 6 months	Appointment text message reminders and written reminders in immunisation card for next appointment	Immunisation card for next appointment	Completion of immunisation series
Domek (2019)	Guatemala (Rural/Urban)	720	Penta-1, PCV-1, OPV-1, Rota-1 at 2 months Penta-2, PCV-2, OPV-2, Rota-2 at 4 months Penta-3, OPV-3 at 6 months	Appointment text message reminders and immunisation card for next appointment	Immunisation card for next appointment	Completion and timeliness of immunisation series

[1]Study excluded from meta-analysis and risk of bias assessment since outcome data not stratified by intervention type.

Penta-1, 2, 3: first, second or third dose of vaccine that protects against Diptheria-Pertussis-Tetanus (DPT or DTwP) and Hepatitis B (Hep B) and diseases caused by Haemophilus Influenzae type b (Hib); **VitA:** vitamin A supplementation; **MMR:** vaccine that protects against Measles, Mumps and Rubella; **OPV-1, 2, 3**: first, second or third dose of oral polio vaccine; **PCV-1, 2, 3**: first, second or third dose of the pneumococcal conjugate vaccine; **Rota 1-, 2:** first or second dose of rotavirus vaccine

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants	Vaccination Schedule	Intervention	Control	Outcomes
Ekhaguere (2019)[1]	Nigeria (Rural)	600	Penta-1, OPV-1, PCV-1, Rota-1 at 6 weeks. Penta-2, OPV-2, Rota-2, PCV-2 at 10 weeks. Penta-3, OPV-3, PCV-3, IPV at 14 weeks. Vit A at 6 months Measles and yellow fever vaccines at 9 months	Voice call, text message and email reminders	Immunisation card for next appointment	Receipt of Penta-1, 2 and 3 vaccinations
Eze (2015)	Nigeria (Urban)	1001	DPT-1 at 6 weeks DPT-2 at 10 weeks DPT-3 at 14 weeks	Appointment reminder text message	No information reported	Vaccination timeliness and coverage
Gibson (2017)	Kenya (Rural)	698	Penta-1, OPV-1 at 6 weeks, Penta-2, OPV-2 at 10 weeks Penta-3, OPV-3 at 14 weeks, Measles at 9 months	Appointment reminder text message	No information reported	Fully immunised by 12 months
Gurfinkel (2021)	USA (Urban)	24684	2-dose HPV	Appointment reminder text message	No reminders	HPV vaccination initiations and completion
Hofstetter (2015b)	USA (Urban)	1368	MMR vaccination at 13 months	Appointment reminder text message	Routine automated telephone reminders	MMR vaccination by 13 months

[1]Study excluded from meta-analysis and risk of bias assessment since outcome data not stratified by intervention type.

Penta-1-, 2, 3: first, second or third dose of vaccine that protects against Diptheria-Pertussis-Tetanus (DPT or DTwP) and Hepatitis B (Hep B) and diseases caused by Haemophilus Influenzae type b (Hib); **PCV-1, 2, 3**: first, second or third dose of the pneumococcal conjugate vaccine; **OPV-1, 2, 3**: first, second or third dose of oral polio vaccine; **Rota-1, 2:** first or second dose of rotavirus vaccine; **IPV**: Inactivated polio virus vaccine; **VitA:** vitamin A supplementation; **DPT-1, 2, 3:** first, second or third dose of vaccine against Diptheria, Pertussis and Tetanus; **HPV**: Human Papillomavirus

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants	Vaccination Schedule	Intervention	Control	Outcomes
Kazi (2018)	Pakistan (Urban)	300	Penta and OPV vaccines at 6, 10 and 14 weeks	Appointment reminder text message and standard verbal counseling	One standard verbal counseling at time of enrollment	Immunisation at 18 weeks
Kempe (2016)[1]	USA (Urban)	893	3-dose HPV	Preferred method of reminders (text, email or automated telephone message)	Usual care for immunization and well-care reminder or recall	Vaccination series completion rates
Lerner (2021)[1]	USA (Urban)	689	Seasonal Influenza vaccine (first and second dose)	Reminder by patient portals using text or email (based on patient portal preference)	No reminders	Completion of 2-dose Influenza vaccination
Mekonnen (2021)	Ethiopia (Urban)	434	Penta-1, OPV-1, PCV-1 and Rota-1 at 6 weeks. Penta-2, OPV-2, Rota-2 and PCV-2 at 10 weeks. Penta-3, OPV-3, PCV-3 and IPV at 14 weeks. Measles at 9 and 12 months	Appointment text message reminders and routine vaccination appointment reminders	Immunisation cards and verbal reminder of next appointment	Vaccination coverage and timeliness
Menzies (2020)	Australia (Urban)	792	Vaccines due at 2, 4, 6, 12 and 18 months	Appointment reminder text message	No reminders	Receipt of vaccines at 2, 4-, 6-, 12- and 18-months including timeliness of vaccinations

[1]Study excluded from meta-analysis and risk of bias assessment since outcome data not stratified by intervention type

Penta-1-, 2, 3: first, second or third dose of vaccine against Diptheria-Pertussis-Tetanus (DPT or DTwP) and Hepatitis B (Hep B) and diseases caused by Haemophilus Influenzae type b (Hib); **MMR:** vaccine that protects against Measles, Mumps and Rubella; **OPV-1, 2, 3**: first, second or third dose of oral polio vaccine; **HPV**: Human Papillomavirus

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants	Vaccination Schedule	Intervention	Control	Outcomes
Niederhauser (2015)	Hawaii (Urban)	57	DTaP, PCV, Hib, HepB and Polio at 2, 4 and 6 months	Appointment reminder text message	Age-Appropriate newborn health topics messages	Immunization compliance
O'Grady (2022)	Australia (Rural)	196	Vaccines due at 2, 4 and 6 months	Appointment reminder text message	No intervention or contact until infant turned 7 months old	Proportion of infants age-appropriately vaccinates at 7 months.
O'Leary (2015)	USA (Urban and suburban)	4587	DTaP at 11 to 12 years MCV at age 11 to 12 with a booster at age 16 3-dose HPV vaccine series, to be started at age 11 to 12 Annual Influenza vaccine	Interactive, bidirectional short messages	No reminders	Completion of all needed and any vaccinations
Patel (2014)[1]	USA (Urban)	365	3-dose HPV	Appointment reminders based on preference (text message, email, phone call, private Facebook message or standard mail)	No reminders	Completion of HPV series
Rand (2015)	USA (Urban)	3812	3-dose HPV	Interactive Text message reminders	General adolescent health text messages	Receipt of first HPV dose (primary outcome), but receipt of second and third dose assessed

[1]Study excluded from meta-analysis and risk of bias assessment since outcome data not stratified by intervention type

DTaP: Vaccine against Diptheria-Tetanus and Pertussis; **PCV**: pneumococcal conjugate vaccine; **Hib:** Haemophilus Influenzae type b vaccine; **HepB:** Hepatitis B; **MCV**: Meningococcal conjugate vaccine; **HPV**: Human Papillomavirus Vaccine

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants randomized	Vaccination Schedule	Intervention	Control	Outcomes
Rand (2017)	USA (Urban)	391	3-dose HPV	Reminder message based on preference (text or telephone)	No reminders	Receipt of third dose of HPV vaccine and HPV vaccination rates
Regan (2017)	Australia (Urban)	12354	Seasonal Influenza Vaccine	Appointment reminder text message	No SMS reminders	Receipt of influenza vaccine
Richman (2016)[1]	USA (Rural)	264	3-dose HPV	Electronic intervention (text or e-mail appointment reminders and education messages)	Standard of care which was paper card with next appointment date	HPV vaccine completion rates
Richman (2019)[1]	USA (Rural)	257	3-dose HPV	Electronic intervention (text or e-mail appointment reminders and education messages)	Standard of care which was paper card with next appointment date	HPV vaccine completion rates
Shinde (2018)	India (Rural and semi-urban)	125	6- and 10-week vaccination schedule	Appointment reminder text message	Immunization cards of next appointment	Vaccination receipt by 10 weeks
Stockwell (2012)	USA (Urban)	Text4Health (Adolescents) = 361 Text4Health (Paediatric) = 174	Text4Health (Adolescents): MCV4 and DTaP Text4Health (Paediatric): Hib	Text4Health (Adolescents): automated text message reminders Text4Health (Paediatric): Text message reminders and paper mail	Text4Health (Adolescents): No immunization reminders Text4Health (Paediatric): Paper mail	Text4Health (Adolescents): Receipt of MCV4 or Tdap Text4Health (Paediatric): Receipt of Hib vaccine as part of primary vaccination series

[1]Study excluded from meta-analysis and risk of bias assessment since outcome data not stratified by intervention type

HPV: Human Papillomavirus Vaccine; **DTaP**: Vaccine that protects against Diptheria-Tetanus and Pertussis**; MCV**: Meningococcal conjugate vaccine; **Hib:** Haemophilus Influenzae type b vaccine

Table S3: Characteristics of Included Studies (cont.)

Study	Country (Setting)	Nr of Participants randomized	Vaccination Schedule	Intervention	Control	Outcomes
Stockwell (2015)	USA (Urban)	444	2-dose Influenza vaccine	Appointment reminder text message and written reminder	Written reminder only	Receipt and timeliness of second dose of influenza vaccine
Stockwell (2022)	USA (Urban)	2086	2-dose Influenza	Appointment reminder text message	Variable reminder systems*	Receipt of second dose of influenza vaccine
Tull (2019)	Australia (Urban)	2944	3-dose HPV	Self-regulatory SMS	No reminders	Receipt of any dose HPV vaccine

***** Variable reminder systems included no second dose reminders or letter, phone, email or patient portal message, or a written card
HPV: Human Papillomavirus Vaccine

Table S4: Funding Sources for the Included Studies

Study ID	Funding Source
Ahlers-Schmidt (2012)	Wichita Center for Graduate Medical Education and Kansas Biosciences Authority Level III grant
Bangure (2015)	Centre for Disease Control and Prevention, Zimbabwe
Buttenheim (2022)	NIA/NIH, the Bill and Melinda Gates Foundation, Flu Lab, Penn Center for Precision Medicine Accelerator Fund and in part by the AKO Foundation and John Alexander, Marc J Leder, and Warren G Lichtenstein
Chandir (2022)	Global Innovation Fund, GiveWell
DeCamp (2020)	Gordon and Betty Moore Foundation
Dissieka (2019)	None
Domek (2016)	Bill and Melinda Gates Foundation, Pan American Organization
Domek (2019)	Eunice Kennedy Shriver National Institute of Child Health & Human Development at NIH, Thrasher Research Fund Early Career Award Program, REDCap supported by NIH and National Center for Research Resources Colorado CTSI
Ekhaguere (2019)	Thrasher Research Fund
Eze (2015)	No funding information available
Gibson (2017)	Bill and Melinda Gates Foundation
Gurfinkel (2021)	National Cancer Institute of the NIH
Hofstetter (2015b)	Pfizer Medical Education Group
Kazi (2018)	World Health Organization
Kempe (2016)	Centers of Disease Control and Prevention
Lerner (2021)	NIH National Institutes of Allergy and Infectious Diseases, NIH Center for Advancing Translational Sciences
Mekonnen (2021)	Doris Dukes Charitable Foundation Project
Menzies (2020)	Seqirus
Niederhauser (2015)	No funding information available
O'Grady (2022)	Children's Hospital Foundation Queensland
O'Leary (2015)	National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention
Patel (2014)	Merk Sharp & Dohme Corp
Rand (2015)	Society for Adolescent Health and Medicine
Rand (2017)	Agency for Healthcare Research and Quality
Regan (2017)	Department of Health Western Australia
Richman (2016)	Merck &Co Inc., Merck Sharp & Dohme Corp
Richman (2019)	Merck &Co Inc.
Shinde (2018)	No funding information available
Stockwell (2012)	Maternal and Health Bureau, Health Resources and Services Administration, Department of Health and Human Services
Stockwell (2015)	NIH/ National Cancer Institute
Stockwell (2022)	NIH National Institute of Child Health and Health Development
Tull (2019)	Victoria Public Sector Innovation Fund

Table S5: Characteristics of Excluded Studies [ordered by study ID]

Study ID	**Reason for Exclusion**
Adams (2012)	Ineligible outcome measured
Ahmed (2018)	Ineligible study design
Alonge (2023)	Ineligible study design
Aragones (2015)	Ineligible study design
Atchison (2013)	Ineligible study design
Atkinson (2016)	Ineligible study design
Atnafu (2017)	Ineligible outcome measured
Bar-Shain (2015)	Ineligible study design
Bay (2017)	Ineligible study design
Brigham (2012)	Ineligible intervention, not MPTMRs
Brown (2017)	Ineligible intervention, not MPTMRs
Bundy (2013)	Ineligible intervention, not MPTMRs
Bushar (2017)	Ineligible study design
Busso (2015)	Ineligible intervention, not MPTMRs
Chai (2013)	Ineligible outcome measured
Cutrona (2018)	Ineligible outcome measured
Davis (2020)	Ineligible study design
Debroy (2023)	Ineligible intervention, not MPTMRs
de Oliveira Bressane Lima (2020)	Ineligible study design
Di Mauro (2022)	Ineligible study design
Diallo (2012)	Ineligible study design
Dombkowski (2014)	Ineligible study design
Dombkowski (2017)	Ineligible study design
Erwin (2019)	Ineligible outcome measured
Fiks (2015)	Ineligible study design
Frew (2017)	Ineligible study design
Garcia-Dia (2017)	Ineligible study design
Gerend (2020)	Ineligible study design
Gerend (2021)	Ineligible outcome measured
Ghadieh (2015)	Ineligible outcome measured
Glanz (2017)	Ineligible intervention, not MPTMRs
Gold (2021)	Ineligible intervention, not MPTMRs
Haji (2016)	Ineligible study design

Table S5: Characteristics of Excluded Studies [ordered by study ID] (cont.)

Study ID	Reason for Exclusion
Haskew (2015)	Ineligible study design
Henrikson (2018)	Ineligible intervention, not MPTMRs
Herrett (2016)	Ineligible outcome measured
Hofstetter (2015)	Ineligible outcome measured
Hofstetter (2017)	Ineligible outcome measured
Hurley (2018)	Ineligible intervention, not MPTMRs
Hurley (2019)	Ineligible intervention, not MPTMRs
Ibraheem (2021)	Ineligible study design
James (2021)	Ineligible study design
Johri (2020)	Ineligible intervention, not MPTMRs
Jones Cooper (2013)	Ineligible study design
Jordan (2015)	Ineligible study design
Juon (2016)	Ineligible intervention, not MPTMRs
Kagucia (2021)	Ineligible outcome measured
Kahn (2018)	Ineligible study design
Kawakatsu (2020)	Ineligible outcome measured
Kazi (2017)	Ineligible study design
Keeshin (2017)	Ineligible study design
Kempe (2020)	Ineligible intervention, not MPTMRs
Kempe (2015)	Ineligible intervention, not MPTMRs
Kim (2017)	Ineligible study design
Kiwanuka (2018)	Ineligible outcome measured
Lee (2016)	Ineligible study design
Lee (2020)	Ineligible outcome measured
Levine (2021)	Ineligible intervention, not MPTMRs
Liao (2020)	Ineligible outcome measured
Liao (2022)	Ineligible outcome measured
Manderson (2023)	Ineligible study design
Masresha (2020)	Ineligible study design
Matheson (2014)	Ineligible study design
McGlone (2017)	Ineligible study design
Milkman (2021)	Ineligible outcome measured
Mohanty (2018)	Ineligible study design
Moniz (2013)	Ineligible outcome measured
Morris (2015)	Ineligible study design
Nehme (2019)	Ineligible outcome measured

Table S5: Characteristics of Excluded Studies [ordered by study ID] (cont.)

Study ID	Reason for Exclusion
Oladepo (2021)	Ineligible study design
O'Leary (2019)	Ineligible intervention, not MPTMRs
Patel (2023)	Ineligible outcome measured
Qamar (2020)	Ineligible study design
Regan (2023)	Ineligible study design
Schlumberger (2015)	Ineligible study design
Seth (2018)	Ineligible outcome measured
Staras (2021)	Ineligible outcome measured
Stockwell (2012)	Ineligible outcome measured
Stockwell (2014)	Ineligible outcome measured
Suh (2012)	Ineligible intervention, not MPTMRs
Suppli (2017)	Ineligible study design
Szilagyi (2013)	Ineligible intervention, not MPTMRs
Szilagyi (2019)	Ineligible outcome measured
Szilagyi (2020a)	Ineligible intervention, not MPTMRs
Szilagyi (2020b)	Ineligible outcome measured
Szilagyi (2022)	Ineligible intervention, not MPTMRs
Tuckerman (2023)	Ineligible outcome measured
Ueberroth (2022)	Ineligible outcome measured
Venci (2015)	Ineligible study design
Venkatesh (2020)	Ineligible study design
Wagner (2021)	Ineligible outcome measured
Wijesundara (2020)	Ineligible outcome measured
Wynn (2021)	Ineligible comparison
Xeuatvongsa (2016)	Ineligible study design
Yeung (2018)	Ineligible outcome measured
Yudin (2017)	Ineligible outcome measured
Yunusa (2022)	Ineligible study design

Table S6: Summary of Findings

Messaging services compared to standard of care for Vaccination recall

Patient or population: Vaccination recall
Setting: Primary setting
Intervention: MPTMRs
Comparison: standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	**Risk with messaging services**				
Vaccination recall (Pooled data)	285 per 1,000	311 per 1,000 (302 to 322)	**RR 1.09** (1.06 to 1.13)	64536 (25 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in vaccination recall.
MPTMRs with additional components	411 per 1,000	453 per 1,000 (428 to 477)	**RR 1.10** (1.04 to 1.16)	17394 (13 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in mPTMRs (+).
MPTMRs (alone)	238 per 1,000	260 per 1,000 (248 to 274)	**RR 1.09** (1.04 to 1.15)	47142 (12 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in mPTMRs (alone).
Country setting (Urban)	278 per 1,000	306 per 1,000 (295 to 317)	**RR 1.10** (1.06 to 1.14)	57929 (19 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in country setting (Urban).
Country setting (Rural and/or suburban and/or semi-urban)	348 per 1,000	383 per 1,000 (338 to 432)	**RR 1.10** (0.97 to 1.24)	6607 (6 RCTs)	⊕◯◯◯ Very low[c,d]	The evidence is very uncertain about the effect of messaging services on country setting (Rural).
LMIC	671 per 1,000	718 per 1,000 (691 to 745)	**RR 1.07** (1.03 to 1.11)	7350 (9 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in LMIC.
HIC	236 per 1,000	264 per 1,000 (250 to 278)	**RR 1.12** (1.06 to 1.18)	57186 (16 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests messaging services results in a slight increase in HIC.
Early Childhood	615 per 1,000	658 per 1,000 (633 to 682)	**RR 1.07** (1.03 to 1.11)	10480 (16 RCTs)	⊕◯◯◯ Very low[a,b,d,e]	The evidence is very uncertain about the effect of messaging services on early Childhood.
HPV	215 per 1,000	252 per 1,000 (226 to 280)	**RR 1.17** (1.05 to 1.30)	36418 (5 RCTs)	⊕◯◯◯ Very low[b,f,g]	The evidence is very uncertain about the effect of messaging services on HPV.

Messaging services compared to standard of care for Vaccination recall

Patient or population: Vaccination recall
Setting: Primary setting
Intervention: MPTMRs
Comparison: standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	**Risk with messaging services**				
Seasonal Influenza	236 per 1,000	269 per 1,000 (239 to 302)	**RR 1.14** (1.01 to 1.28)	17638 (4 RCTs)	⊕◯◯◯ Very low[c,f,h]	The evidence is very uncertain about the effect of messaging services on seasonal Influenza.
Omitting poor quality studies	274 per 1,000	305 per 1,000 (294 to 315)	**RR 1.11** (1.07 to 1.15)	55988 (19 RCTs)	⊕⊕⊕⊕ High[i]	Messaging services results in a slight increase in omitting poor quality.
Omitting High Attrition Bias Studies	274 per 1,000	305 per 1,000 (294 to 315)	**RR 1.11** (1.07 to 1.15)	55988 (18 RCTs)	⊕⊕⊕◯ Moderate[b,j]	Messaging services probably results in a slight increase in omitting High Attrition Bias Studies.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. -1 (Mixed quality across studies)
b. -1 (High heterogeneity)
c. -2 (Very high heterogeneity)
d. -1 (Large imprecision, wide confidence interval that crosses 1)
e. The CI (1.03 to 1.11) is narrow. Assuming a threshold for small effect at 1% or 10 per 1,000, this CI may cross one threshold
f. -2 (Large imprecision)
g. The CI (1.05 to 1.30) likely crosses two thresholds (small and moderate effects)
h. The CI (1.01 to 1.28) likely crosses two thresholds (small and moderate effects)
i. Large sample size (23172 vs 23283) Narrow confidence interval (1.03 to 1.07) that doesn't cross 1 Assessment: No serious concerns if we assume the threshold for a small effect is outside this range. If the threshold for a small effect is within this range, we might consider rating down by one level
j. Large sample size (27884 vs 28104) Confidence interval (1.07 to 1.15) doesn't cross 1 Assessment: No serious concerns if we assume the threshold for a small effect is outside this range.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	messaging services	standard of care	Relative (95% CI)	Absolute (95% CI)		
Vaccination recall (Pooled data)												
25	randomised trials	serious[a]	serious[b]	not serious	not serious	none	9918/32159 (30.8%)	9237/32377 (28.5%)	**RR 1.09** (1.06 to 1.13)	**26 more per 1,000** (from 17 more to 37 more)	⊕⊕◯◯ Low[a,b]	
MPTMRs with additional components												
13	randomised trials	serious[a]	serious[b]	not serious	not serious	none	3866/8588 (45.0%)	3623/8806 (41.1%)	**RR 1.10** (1.04 to 1.16)	**41 more per 1,000** (from 16 more to 66 more)	⊕⊕◯◯ Low[a,b]	
MPTMRs (alone)												
12	randomised trials	serious[a]	serious[b]	not serious	not serious	none	6052/23571 (25.7%)	5614/23571 (23.8%)	**RR 1.09** (1.04 to 1.15)	**21 more per 1,000** (from 10 more to 36 more)	⊕⊕◯◯ Low[a,b]	
Country setting (Urban)												
19	randomised trials	serious[a]	serious[b]	not serious	not serious	none	8600/28919 (29.7%)	8064/29010 (27.8%)	**RR 1.10** (1.06 to 1.14)	**28 more per 1,000** (from 17 more to 39 more)	⊕⊕◯◯ Low[a,b]	
Country setting (Rural and/or suburban and/or semi-urban)												
6	randomised trials	not serious	very serious[c]	not serious	serious[d]	none	1318/3240 (40.7%)	1173/3367 (34.8%)	**RR 1.10** (0.97 to 1.24)	**35 more per 1,000** (from 10 fewer to 84 more)	⊕◯◯◯ Very low[c,d]	
LMIC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	messaging services	standard of care	Relative (95% CI)	Absolute (95% CI)		
9	randomised trials	serious[a]	serious[b]	not serious	not serious	none	2635/3673 (71.7%)	2467/3677 (67.1%)	**RR 1.07** (1.03 to 1.11)	**47 more per 1,000** (from 20 more to 74 more)	⨁⨁◯◯ Low[a,b]	
HIC												
16	randomised trials	serious[a]	serious[b]	not serious	not serious	none	7283/28486 (25.6%)	6770/28700 (23.6%)	**RR 1.12** (1.06 to 1.18)	**28 more per 1,000** (from 14 more to 42 more)	⨁⨁◯◯ Low[a,b]	
Early Childhood												
16	randomised trials	serious[a]	serious[b]	not serious	serious[d,e]	none	3430/5262 (65.2%)	3207/5218 (61.5%)	**RR 1.07** (1.03 to 1.11)	**43 more per 1,000** (from 18 more to 68 more)	⨁◯◯◯ Very low[a,b,d,e]	
HPV												
5	randomised trials	not serious	serious[b]	not serious	very serious[f,g]	none	4155/18071 (23.0%)	3948/18347 (21.5%)	**RR 1.17** (1.05 to 1.30)	**37 more per 1,000** (from 11 more to 65 more)	⨁◯◯◯ Very low[b,f,g]	
Seasonal Influenza												
4	randomised trials	not serious	very serious[c]	not serious	very serious[f,h]	none	2333/8826 (26.4%)	2082/8812 (23.6%)	**RR 1.14** (1.01 to 1.28)	**33 more per 1,000** (from 2 more to 66 more)	⨁◯◯◯ Very low[c,f,h]	
Omitting poor quality studies												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	messaging services	standard of care	Relative (95% CI)	Absolute (95% CI)		
19	randomised trials	not serious	not serious	not serious	not serious[i]	none	8271/27884 (29.7%)	7710/28104 (27.4%)	**RR 1.11** (1.07 to 1.15)	**30 more per 1,000** (from 19 more to 41 more)	⨁⨁⨁⨁ High[i]	
Omitting High Attrition Bias Studies												
18	randomised trials	not serious	serious[b]	not serious	not serious[j]	none	8271/27884 (29.7%)	7710/28104 (27.4%)	**RR 1.11** (1.07 to 1.15)	**30 more per 1,000** (from 19 more to 41 more)	⨁⨁⨁◯ Moderate[b,j]	

Explanations
a. -1 (Mixed quality across studies)
b. -1 (High heterogeneity)
c. -2 (Very high heterogeneity)
d. -1 (Large imprecision, wide confidence interval that crosses 1)
e. The CI (1.03 to 1.11) is narrow. Assuming a threshold for small effect at 1% or 10 per 1,000, this CI may cross one threshold
f. -2 (Large imprecision)
g. The CI (1.05 to 1.30) likely crosses two thresholds (small and moderate effects)
h. The CI (1.01 to 1.28) likely crosses two thresholds (small and moderate effects)
i. Large sample size (23172 vs 23283) Narrow confidence interval (1.03 to 1.07) that doesn't cross 1 Assessment: No serious concerns if we assume the threshold for a small effect is outside this range. If the threshold for a small effect is within this range, we might consider rating down by one level
j. Large sample size (27884 vs 28104) Confidence interval (1.07 to 1.15) doesn't cross 1 Assessment: No serious concerns if we assume the threshold for a small effect is outside this range.

Table S7. Ongoing Interventional Clinical Trials related to MPTMRs and Vaccination Uptake [Current as of 10 December 2024]

NCT Number	Study Title	Study Status
NCT06603090	Text4Vax: Text Message Reminders for Pediatric COVID-19 and Influenza Vaccines 2024-25 Season	Not yet recruiting
NCT06161831	HPV Vaccine Reminders - SEARCH II Study	Recruiting
NCT06000397	Reminder Emails to Improve Pneumococcal Vaccine Completion at 12 Months of Age	Recruiting
NCT06470919	The Next Generation Vaccine Card: Innovative Technology to Improve Vaccine Equity in Rural and Urban Settings in East Africa	Recruiting
NCT03429413	Maximizing HPV Vaccination: Real-time Reminders, Guidance, and Recommendations - Part 4: Feasibility Trial	Not yet recruiting
NCT06062264	Patient Portal Flu Vaccine Reminders (RCT 6)	Active – Not Recruiting
NCT06024317	Chanjo Kwa Wakati - Improving Vaccination Coverage and Timeliness in Rural Settings	Recruiting
NCT06218368	A Tool Kit to Improve Vaccine Confidence in the Philippines	Recruiting
NCT04452526	I Vaccinate: Testing Multi-Level Interventions to Improve HPV Vaccination	Active – Not Recruiting
NCT06626321	Behavioral Economics to Improve Flu Vaccination Using EHR Nudges Replication	Enrolling by Invitation
NCT05665543	Increasing HPV Vaccination in Pediatric, Adolescent, and Young Adult (PAYA) Cancer Survivors	Recruiting
NCT03209713	Edtech-HPV: A Community Approach Using Education and Technology to Increase HPV Vaccination	Active – Not Recruiting
NCT05500339	Effectiveness of a mHealth App for Supporting the First 1000 Days of Life	Recruiting
NCT06686849	Comparing Technological and Relational Approaches to Support Families After a Missed Well Child Visit	Not yet recruiting
NCT05595486	Baby2Home (B2H) Mobile Health Application	Active – Not Recruiting

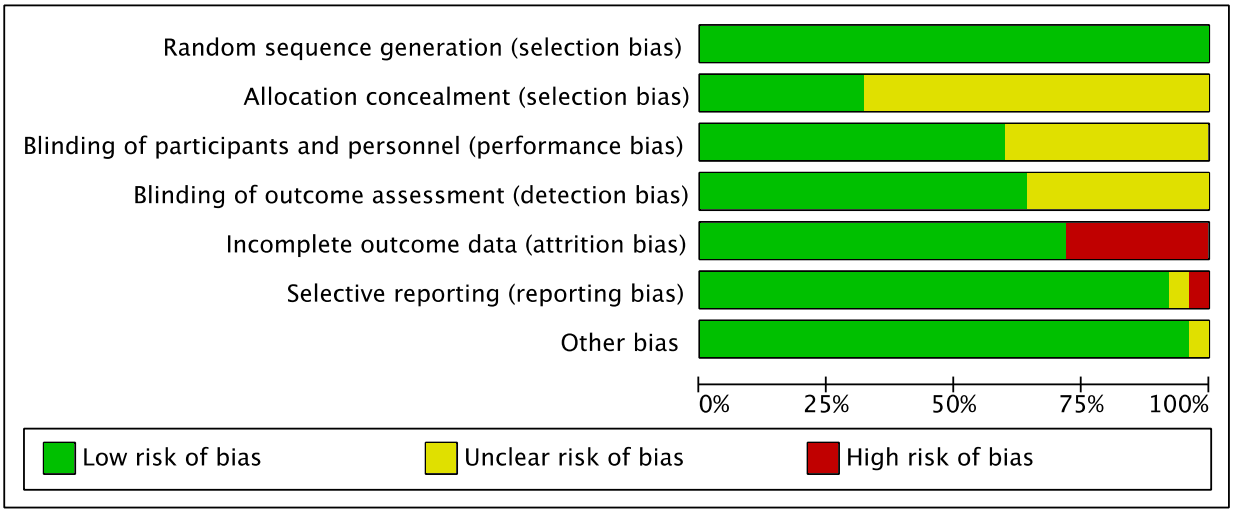

Figure S1: Summary of Risk of Bias Graph for Included Studies.

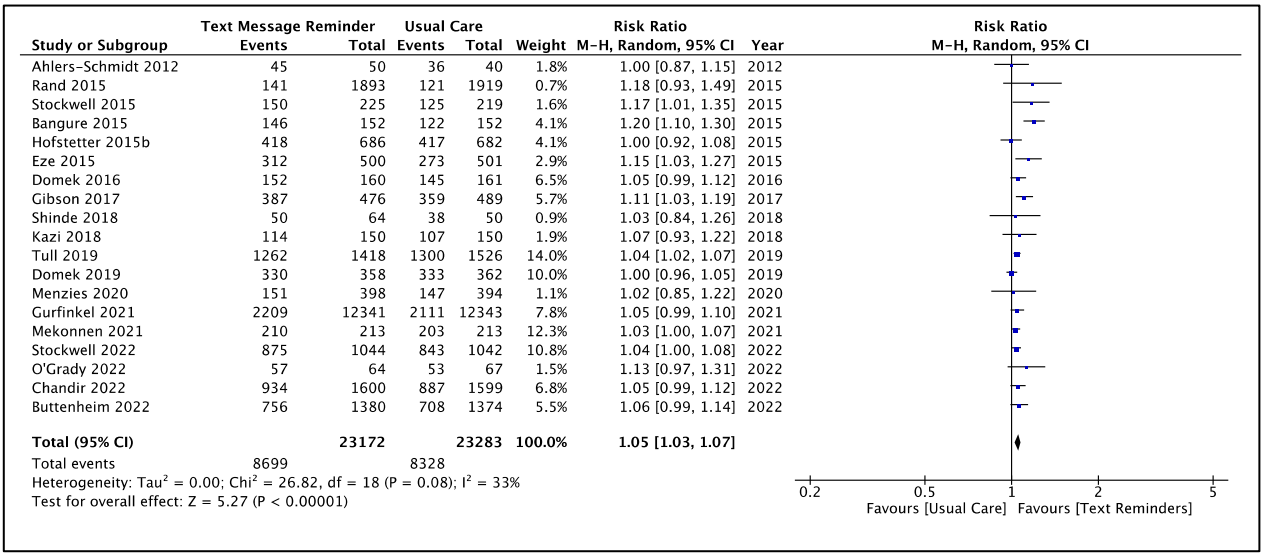

Figure S2: Meta-analysis of data from included studies omitting studies of poor quality

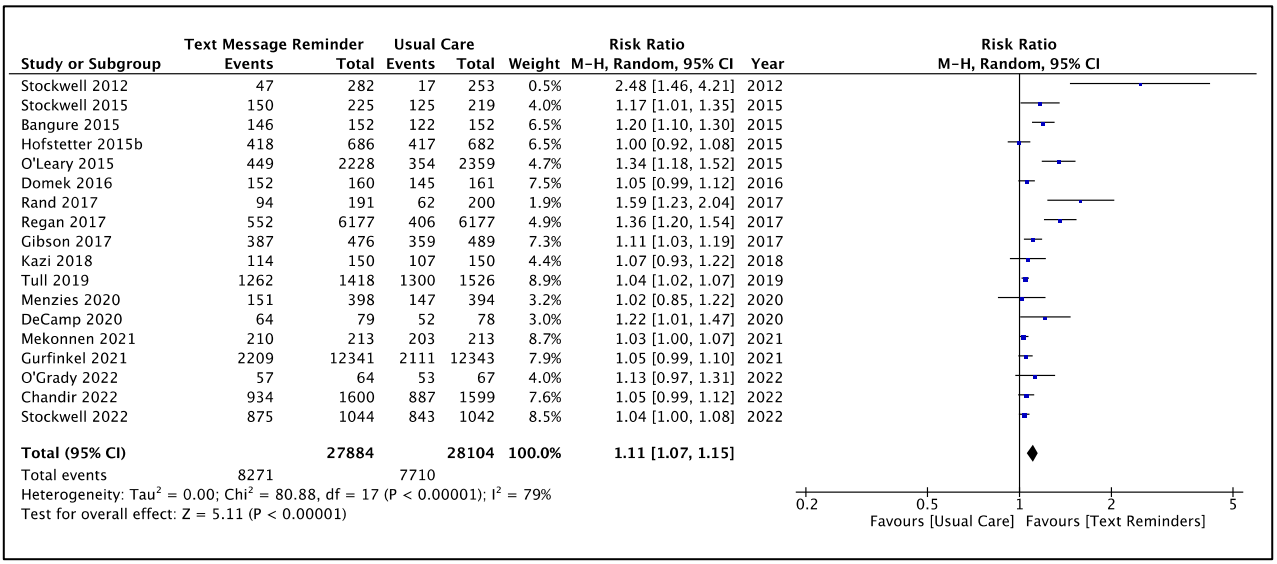

Figure S3: Meta-analysis of data from included studies that excluded studies with high attrition bias.

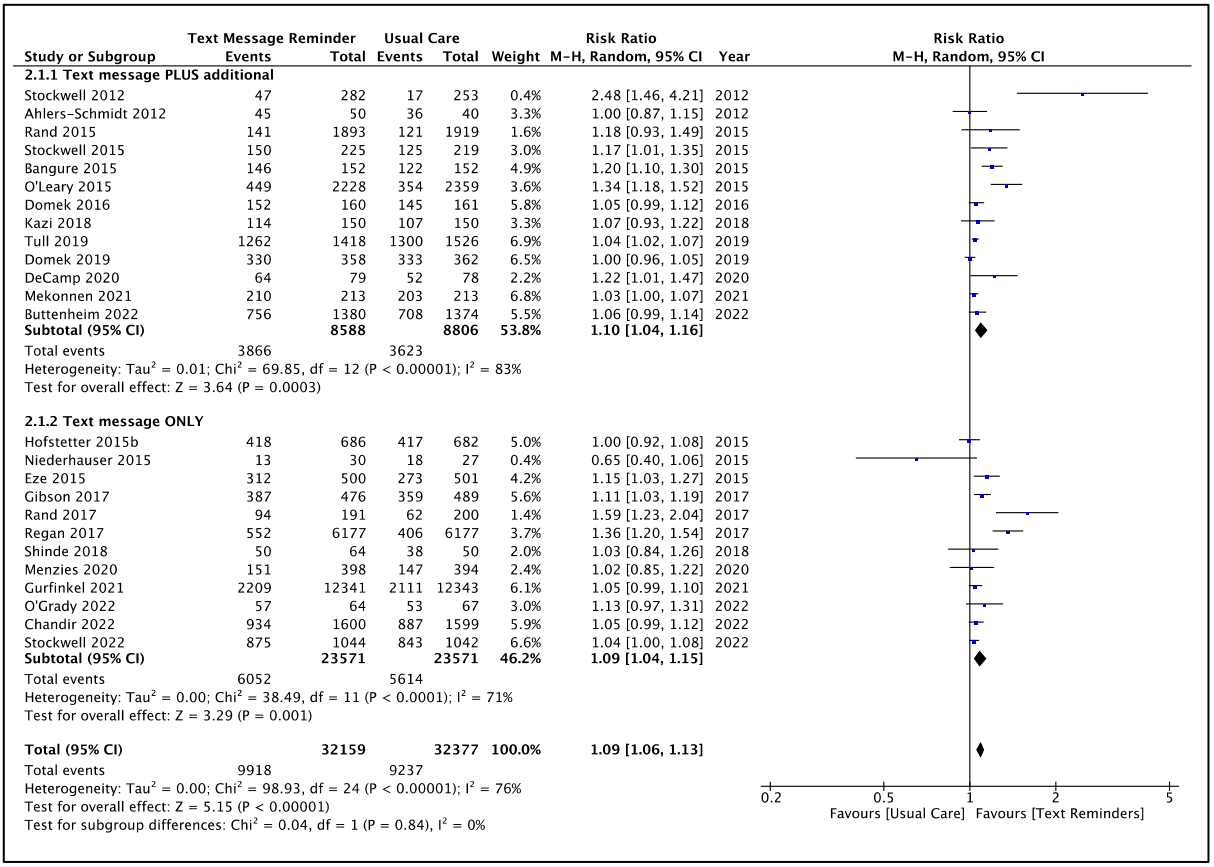

Figure S4: Subgroup analysis based on intervention characteristics.

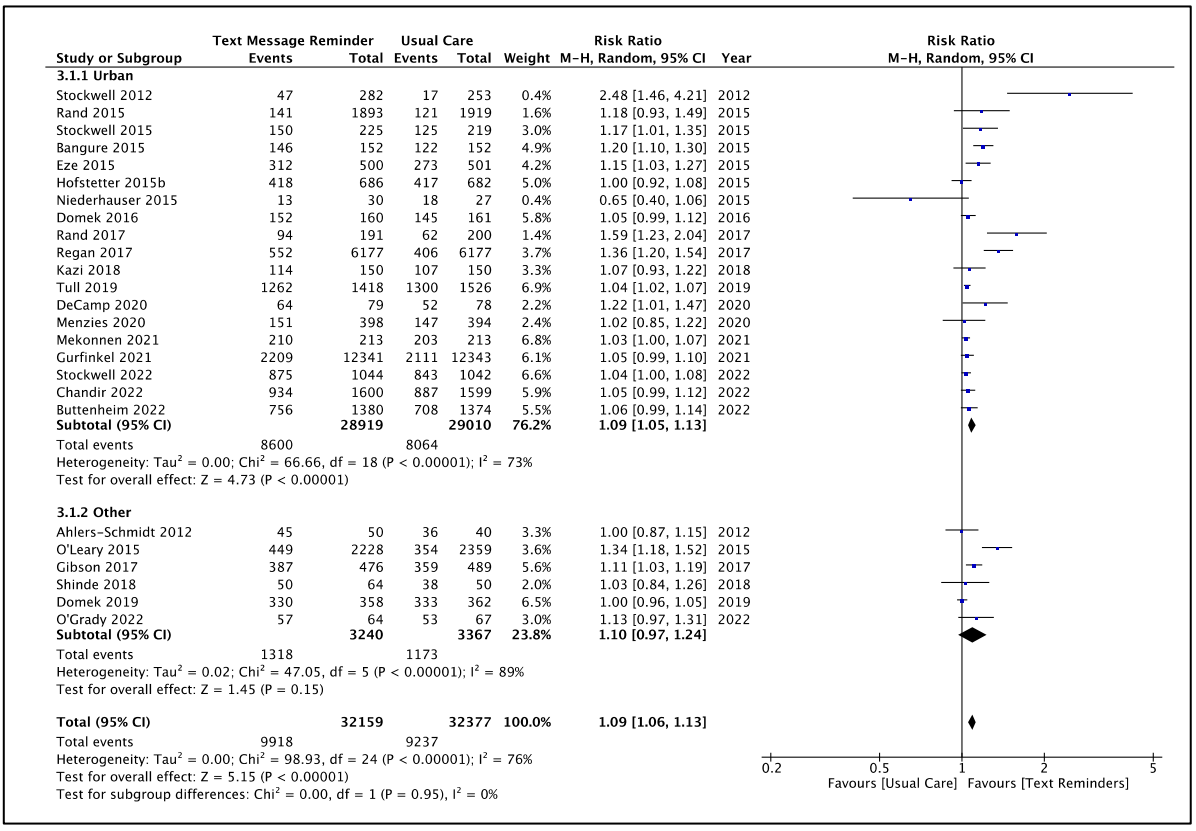

Figure S5: Subgroup analysis based on country setting

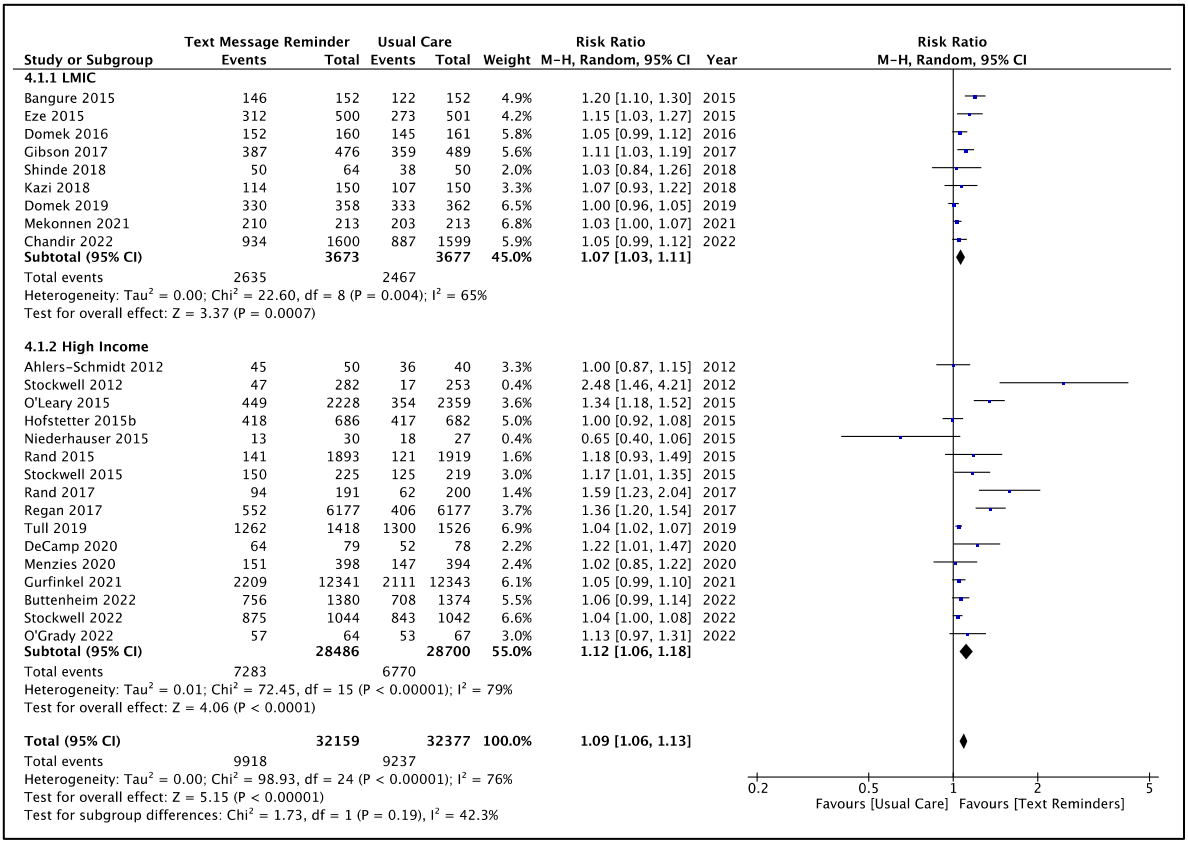

Figure S6: Subgroup analysis based on country economic status

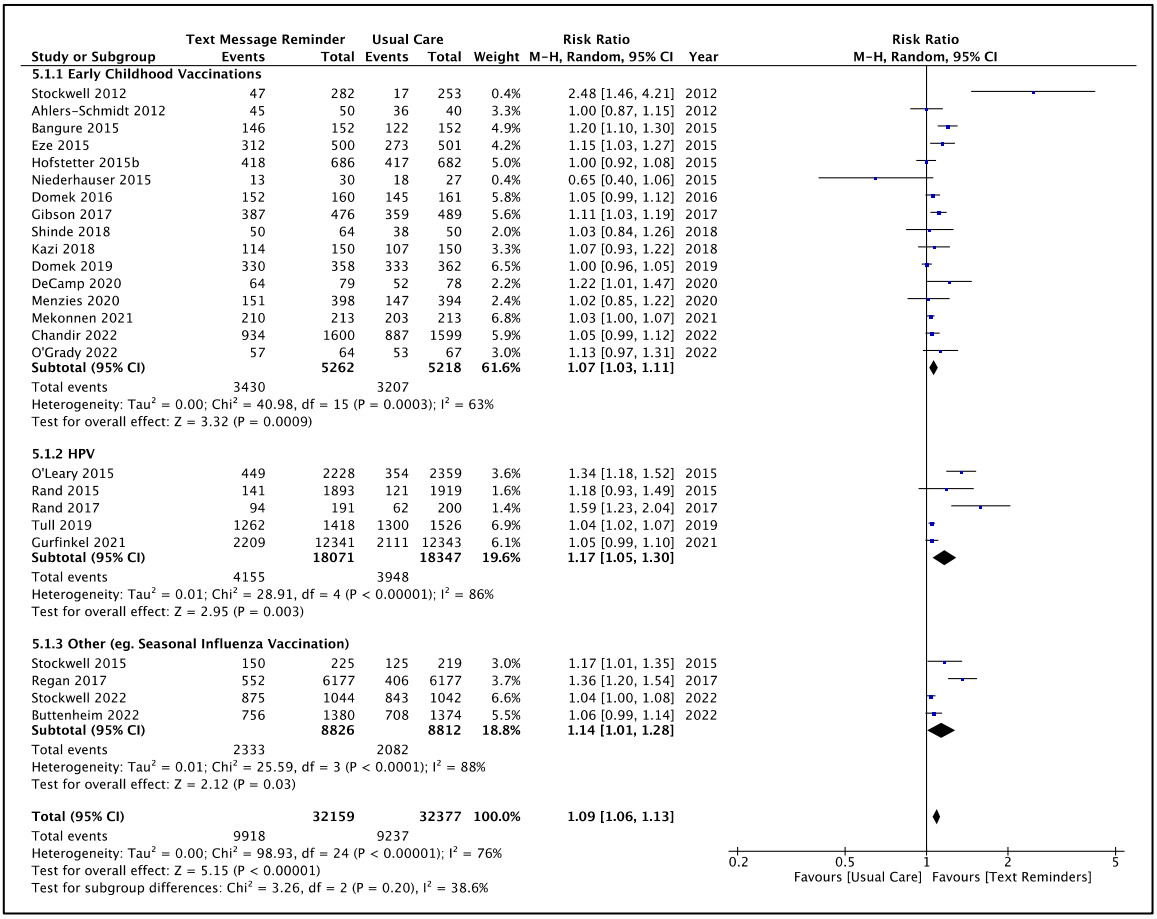

Figure S7: Subgroup analysis based on vaccination type

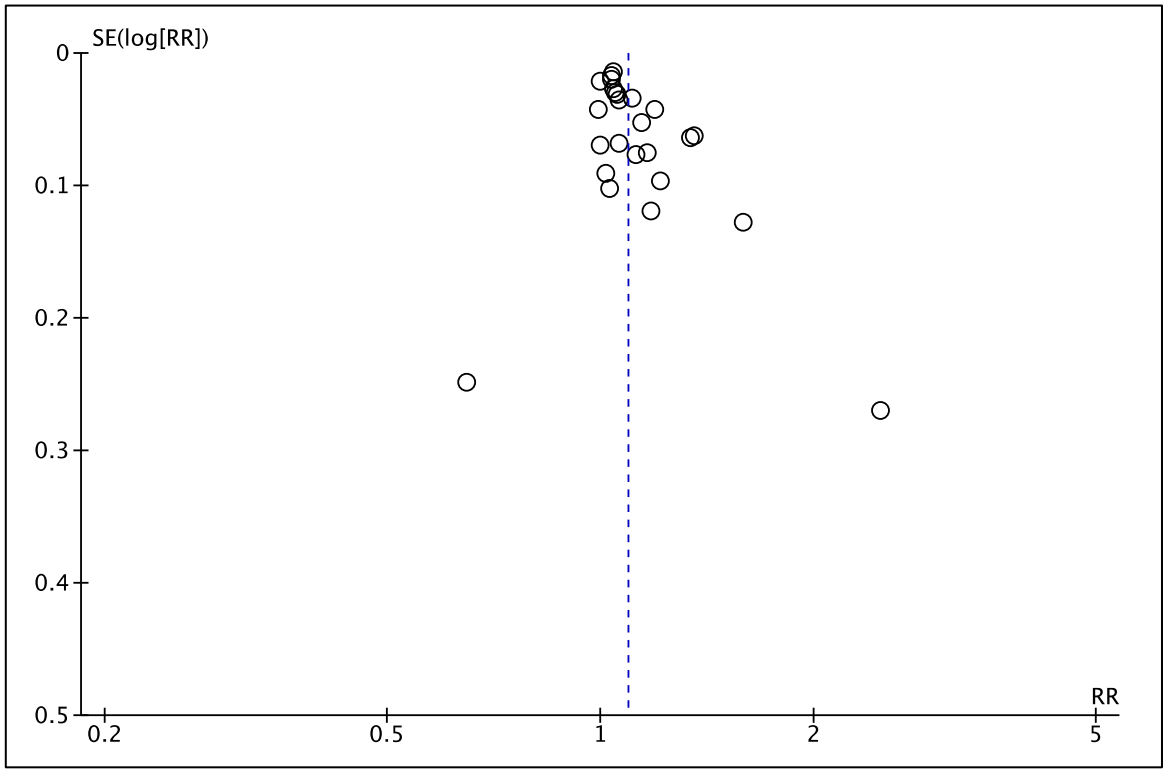

Figure S8: Funnel plot illustrating publication bias.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pg 6; Pg 2 – supplementary material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 7 -8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 7 - 8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 7 - 8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg 7 - 8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg 8

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg 10; Pg 11 – 13 – Supplementary material
Study characteristics	17	Cite each included study and present its characteristics.	Pg 10; Pg 3 - 9 – Supplementary material
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg 10 - 11; Pg 20 – Supplementary Material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg 12 - 13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg 12 - 13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pg 12 - 13; Pg 21 - 23 – Supplementary material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg 12 - 13; Pg 21 - 23 – Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg 12 - 13; Pg 21 - 23 – Supplementary material

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 10 - 11 Pg 20 – Supplementary material
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg 15 – 18 Supplementary material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 15
	23b	Discuss any limitations of the evidence included in the review.	Pg 16
	23c	Discuss any limitations of the review processes used.	Pg 16
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 16 -17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg 18
Competing interests	26	Declare any competing interests of review authors.	Pg 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg 18

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

APPENDIX B

Instructions to Authors: *Vaccines*

(Retrieved from https://www.mdpi.com/journal/vaccines/instructions on 13 Oct 2023)

Submission Checklist

Please:

1. Read the **Aims & Scope** to gain an overview and assess if your manuscript is suitable for this journal;
2. Use the **Microsoft Word template** or **LaTeX template** or **Free Format Submission** to prepare your manuscript;
3. Make sure that issues about **publication ethics**, **research ethics**, **copyright**, **authorship**, **figure formats**, **data** and **references format** have been appropriately considered;
4. Ensure that all authors have approved the content of the submitted manuscript and confirm that they read the Instructions for Authors.
5. Authors are encouraged to add a **biography** (optional) to the submission and post it to **SciProfiles**.

Manuscript Submission Overview

Types of Publications

Full experimental details must be provided so that the results can be reproduced. *Vaccines* requires that authors publish all experimental controls and make full datasets available where possible (see the guidelines on **Supplementary Materials** and references to unpublished data).

Manuscripts submitted to *Vaccines* should neither be published previously nor be under consideration for publication in another journal. The main article types are listed below and a comprehensive list of article types can be found **here.**

- *Article:* These are original research manuscripts. The work should report scientifically sound experiments and provide a substantial amount of new information. The article should include the most recent and relevant references in the field. The structure should include an Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, and Conclusions (optional) sections, with a suggested minimum word count of 4000 words.
- *Review:* Reviews offer a comprehensive analysis of the existing literature within a field of study, identifying current gaps or problems. They should be critical and constructive and provide recommendations for future research. No new, unpublished data should be presented. The structure can include an Abstract, Keywords, Introduction, Relevant Sections, Discussion, Conclusions, and Future Directions, with a suggested minimum word count of 4000 words.

Submission Process

Manuscripts for *Vaccines* should be submitted online at **susy.mdpi.com**. The submitting author, who is generally the corresponding author, is responsible for the manuscript during the

submission and peer-review process. The submitting author must ensure that all eligible co-authors have been included in the author list (read the **criteria to qualify for authorship**) and that they have all read and approved the submitted version of the manuscript. To submit your manuscript, register and log in to the **submission website**. Once you have registered, **click here to go to the submission form for *Vaccines***. All co-authors can see the manuscript details in the submission system, if they register and log in using the e-mail address provided during manuscript submission.

Accepted File Formats

Authors are encouraged to use the **Microsoft Word template** or **LaTeX template** to prepare their manuscript. Using the template file will substantially shorten the time to complete copy-editing and publication of accepted manuscripts. The total amount of data for all files must not exceed 120 MB. If this is a problem, please contact the Editorial Office **vaccines@mdpi.com**. Accepted file formats are:

- *Microsoft Word:* Manuscripts prepared in Microsoft Word must be converted into a single file before submission. When preparing manuscripts in Microsoft Word, we encourage you to use the ***Vaccines*** **Microsoft Word template file**. Please insert your graphics (schemes, figures, *etc.*) in the main text after the paragraph of its first citation.
- *LaTeX:* Manuscripts prepared in LaTeX must be collated into one ZIP folder (including all source files and images, so that the Editorial Office can recompile the submitted PDF). When preparing manuscripts in LaTeX, we encourage you to use the ***Vaccines*** **LaTeX template files**. You can now also use the online application **writeLaTeX** to submit articles directly to *Vaccines*. The MDPI LaTeX template file should be selected from the **writeLaTeX template gallery**.
- *Supplementary files:* May be any format, but it is recommended that you use common, non-proprietary formats where possible (see **below** for further details).

Disclaimer: Usage of these templates is exclusively intended for submission to the journal for peer-review, and strictly limited to this purpose and it cannot be used for posting online on preprint servers or other websites.

Free Format Submission

Vaccines now accepts free format submission:

- We do not have strict formatting requirements, but all manuscripts must contain the required sections: Author Information, Abstract, Keywords, Introduction, Materials & Methods, Results, Conclusions, Figures and Tables with Captions, Funding Information, Author Contributions, Conflict of Interest and other Ethics Statements. Check the Journal ***Instructions for Authors*** for more details.
- Your references may be in any style, provided that you use the consistent formatting throughout. It is essential to include author(s) name(s), journal or book title, article or chapter title (where required), year of publication, volume and issue (where appropriate) and pagination. DOI numbers (Digital Object Identifier) are not mandatory but highly encouraged. The bibliography software package *EndNote*, ***Zotero***, *Mendeley*, *Reference Manager* are recommended.
- When your manuscript reaches the revision stage, you will be requested to format the manuscript according to the journal guidelines.

Cover Letter

A cover letter must be included with each manuscript submission. It should be concise and explain why the content of the paper is significant, placing the findings in the context of existing work. It should explain why the manuscript fits the scope of the journal.

Any prior submissions of the manuscript to MDPI journals must be acknowledged. If this is the case, it is strongly recommended that the previous manuscript ID is provided in the submission system, which will ease your current submission process. The names of proposed and excluded reviewers should be provided in the submission system, not in the cover letter.

All cover letters are required to include the statements:

- We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.
- All authors have approved the manuscript and agree with its submission to (journal name).

Author Identification

Authors are encouraged to add a biography (300–1500 characters) to the submission and upload it to **SciProfiles**. This should be a single paragraph and should contain the following points:

1. Authors' full names followed by current positions;
2. Education background including institution information and year of graduation (type and level of degree received);
3. Work experience;
4. Current and previous research interests;
5. Memberships of professional societies and awards received.

If a manuscript is accepted for publication, we will add an icon linking to your online **ORCID** profile in the final version of the published paper.

Author Affiliation

All authors should list their current affiliation and the affiliation where most research was carried out for the preparation of their manuscript. We recommend adding as primary the affiliation where most of the research was conducted or supported, but please check with your institution for any contractual agreement requirements.

It is very important that author names and affiliations are correct. Incorrect information can mean a lack of proper attribution or incorrect citation and can even lead to problems with promotion or funding. After the publication of an article, updates or corrections to the author's address or affiliation may not be permitted.

Independent Researcher

If one or all the authors are not currently affiliated with a university, institution or company, or have not been during the development of the manuscript, they should list themselves as an "Independent Researcher".

Manuscript Preparation

General Considerations

- **Research manuscripts** should comprise:
    - **Front matter**: Title, Author list, Affiliations, Abstract, Keywords.
    - **Research manuscript sections**: Introduction, Materials and Methods, Results, Discussion, Conclusions (optional).
    - **Back matter**: Supplementary Materials, Acknowledgments, Author Contributions, Conflicts of Interest, **References**.
- **Review manuscripts** should comprise the **front matter**, literature review sections and the **back matter**. The template file can also be used to prepare the front and back matter of your review manuscript. It is not necessary to follow the remaining structure. Structured reviews and meta-analyses should use the same structure as research articles and ensure they conform to the **PRISMA** guidelines.
- **Case reports** should include a succinct introduction about the general medical condition or relevant symptoms that will be discussed in the case report; the case presentation including all of the relevant de-identified demographic and descriptive information about the patient(s), and a description of the symptoms, diagnosis, treatment, and outcome; a discussion providing context and any necessary explanation of specific treatment decisions; a conclusion briefly outlining the take-home message and the lessons learned.
- **Graphical Abstract:**

  A graphical abstract (GA) is an image that appears alongside the text abstract in the Table of Contents. In addition to summarizing the content, it should represent the topic of the article in an attention-grabbing way. Moreover, it should not be exactly the same as the Figure in the paper or just a simple superposition of several subfigures. Note that the GA must be original and unpublished artwork. Any postage stamps, currency from any country, or trademarked items should not be included in it.

  The GA should be a high-quality illustration or diagram in any of the following formats: PNG, JPEG, or TIFF. Written text in a GA should be clear and easy to read, using one of the following fonts: Times, Arial, Courier, Helvetica, Ubuntu or Calibri.

  The minimum required size for the GA is 560 × 1100 pixels (height × width). The size should be of high quality in order to reproduce well.
- **Acronyms/Abbreviations/Initialisms** should be defined the first time they appear in each of three sections: the abstract; the main text; the first figure or table. When defined for the first time, the acronym/abbreviation/initialism should be added in parentheses after the written-out form.
- **SI Units** (International System of Units) should be used. Imperial, US customary and other units should be converted to SI units whenever possible.
- **Accession numbers** of RNA, DNA and protein sequences used in the manuscript should be provided in the Materials and Methods section. Also see the section on **Deposition of Sequences and Expression Data**.
- **Equations:** If you are using Word, please use either the Microsoft Equation Editor or the MathType add-on. Equations should be editable by the editorial office and not appear in a picture format.
- **Research Data and supplementary materials:** Note that publication of your manuscript implies that you must make all materials, data, and protocols associated

with the publication available to readers. Disclose at the submission stage any restrictions on the availability of materials or information. Read the information about **Supplementary Materials** and Data Deposit for additional guidelines.

- **Preregistration:** Where authors have preregistered studies or analysis plans, links to the preregistration must be provided in the manuscript.
- **Guidelines and standards:** MDPI follows standards and guidelines for certain types of research. See **https://www.mdpi.com/editorial_process** for further information.

Front Matter

These sections should appear in all manuscript types

- **Title:** The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis or replication study. When gene or protein names are included, the abbreviated name rather than full name should be used. Please do not include abbreviated or short forms of the title, such as a running title or head. These will be removed by our Editorial Office.
- **Author List and Affiliations:** The authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations, which is as follows: complete address information including city, zip code, state/province, and country. At least one author should be designated as the corresponding author. The email addresses of all authors will be displayed on published papers, and hidden by Captcha on the website as standard. It is the responsibility of the corresponding author to ensure that consent for the display of email addresses is obtained from all authors. If an author (other than the corresponding author) does not wish to have their email addresses displayed in this way, the corresponding author must indicate as such during proofreading. After acceptance, changes to the authors' names or affiliations are not permitted. Typically one author, or at most two in limited cases, should be designated as the corresponding author. A maximum of two joint principal authors can be indicated by the addition of a superscript symbol. The symbol must be included below the affiliations, and the following statement must be added: "These authors contributed equally to this work". The equal roles of authors should also be adequately disclosed in the author contributions statement. Please read the **criteria to qualify for authorship** for further information.
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- **Keywords:** Three to ten pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.

Research Manuscript Sections

- **Introduction:** The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance, including specific hypotheses being tested. The current state of the research field should be reviewed carefully and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the main conclusions. Keep the introduction comprehensible to scientists working outside the topic of the paper.
- **Materials and Methods:** They should be described with sufficient detail to allow others to replicate and build on published results. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Give the name and version of any software used and make clear whether computer code used is available. Include any pre-registration codes.
- **Results:** Provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.
- **Discussion:** Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with Results.
- **Conclusions:** This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.
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Back Matter

- **Supplementary Materials:** Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.
- **Author Contributions:** Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND has approved the submitted version (and version substantially edited by journal staff that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.
  For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; Methodology, X.X.; Software, X.X.; Validation, X.X., Y.Y. and Z.Z.; Formal Analysis, X.X.; Investigation, X.X.; Resources, X.X.; Data Curation, X.X.; Writing – Original Draft Preparation, X.X.; Writing – Review & Editing, X.X.; Visualization, X.X.; Supervision, X.X.; Project Administration, X.X.; Funding Acquisition, Y.Y.", please turn to the **CRediT taxonomy** for the term explanation. For more background on CRediT, see **here**. "**Authorship must include and be limited to those who have contributed substantially to the work. Please read the section concerning the criteria to qualify for authorship carefully**".

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- **Informed Consent Statement:** Any research article describing a study involving humans should contain this statement. Please add "Informed consent was obtained from all subjects involved in the study." OR "Patient consent was waived due to REASON (please provide a detailed justification)." OR "Not applicable." for studies not involving humans. You might also choose to exclude this statement if the study did not involve humans.
  Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patient(s) to publish this paper" if applicable.

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In the text, reference numbers should be placed in square brackets [ ], and placed before the punctuation; for example [1], [1–3] or [1,3]. For embedded citations in the text with pagination, use both parentheses and brackets to indicate the reference number and page numbers; for example [5] (p. 10). or [6] (pp. 101–105).

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References should be described as follows, depending on the type of work:

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2. Author 1, A.; Author 2, B. *Book Title*, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154–196.
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Preparing Figures, Schemes and Tables

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- *Vaccines* can publish multimedia files in articles or as supplementary materials. Please contact the editorial office for further information.
- All Figures, Schemes and Tables should be inserted into the main text close to their first citation and must be numbered following their number of appearance (Figure 1, Scheme 1, Figure 2, Scheme 2, Table 1, etc.).
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Original Images for Blots and Gels Requirements

For the main text, please ensure that:

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Supplementary Materials, Data Deposit and Software Source Code

MDPI Research Data Policies

MDPI is committed to supporting open scientific exchange and enabling our authors to achieve best practices in sharing and archiving research data. We encourage all authors of articles published in MDPI journals to share their research data. Individual journal guidelines can be found at the journal 'Instructions for Authors' page. Data sharing policies concern the minimal

dataset that supports the central findings of a published study. Generated data should be publicly available and cited in accordance with journal guidelines.

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Where ethical, legal or privacy issues are present, data should not be shared. The authors should make any limitations clear in the Data Availability Statement upon submission. Authors should ensure that data shared are in accordance with consent provided by participants on the use of confidential data.

Data Availability Statements provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study.

Below are suggested Data Availability Statements:

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  The data presented in this study are openly available in [repository name e.g., FigShare] at [**doi**], reference number [reference number].
- Data available in a publicly accessible repository that does not issue DOIs
  Publicly available datasets were analyzed in this study. This data can be found here: [link/accession number]
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- [dataset] Authors. Year. Dataset title; Data repository or archive; Version (if any); Persistent identifier (e.g., DOI).

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For work where novel computer code was developed, authors should release the code either by depositing in a recognized, public repository such as **GitHub** or uploading as supplementary information to the publication. The name, version, corporation and location information for all software used should be clearly indicated. Please include all the parameters used to run software/programs analyses.

Supplementary Material

Additional data and files can be uploaded as "Supplementary Files" during the manuscript submission process. The supplementary files will also be available to the referees as part of the peer-review process. Any file format is acceptable; however, we recommend that common, non-proprietary formats are used where possible. For more information on supplementary materials, please refer to **https://www.mdpi.com/authors/layout#_bookmark83**.

References in Supplementary Files

Citations and References in Supplementary files are permitted provided that they also appear in the reference list of the main text.

Unpublished Data

Restrictions on data availability should be noted during submission and in the manuscript. "Data not shown" should be avoided: authors are encouraged to publish all observations related to the submitted manuscript as Supplementary Material. "Unpublished data" intended for publication in a manuscript that is either planned, "in preparation" or "submitted" but not yet accepted, should be cited in the text and a reference should be added in the References section. "Personal Communication" should also be cited in the text and reference added in the References section. (see also the MDPI reference list and citations style guide).

Remote Hosting and Large Data Sets

Data may be deposited with specialized service providers or institutional/subject repositories, preferably those that use the DataCite mechanism. Large data sets and files greater than 60 MB must be deposited in this way. For a list of other repositories specialized in scientific and experimental data, please consult **databib.org** or **re3data.org**. The data repository name, link to the data set (URL) and accession number, doi or handle number of the data set must be provided in the paper. The journal **Data** also accepts submissions of data set papers.

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New sequence information must be deposited to the appropriate database prior to submission of the manuscript. Accession numbers provided by the database should be included in the submitted manuscript. Manuscripts will not be published until the accession number is provided.

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All sequence names and the accession numbers provided by the databases must be provided in the Materials and Methods section of the article.

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Methods used to generate the proteomics data should be described in detail and we encourage authors to adhere to the "**Minimum Information About a Proteomics Experiment**". All generated mass spectrometry raw data must be deposited in the appropriate public database such as **ProteomeXchange**, **PRIDE** or **jPOST**. At the time of submission, please include all relevant information in the materials and methods section, such as repository where the data was submitted and link, data set identifier, username and password needed to access the data.

Research and Publication Ethics

Research Ethics

Research Involving Human Subjects

When reporting on research that involves human subjects, human material, human tissues, or human data, authors must declare that the investigations were carried out following the rules of the Declaration of Helsinki of 1975 (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**), revised in 2013. According to point 23 of this declaration, an approval from the local institutional review board (IRB) or other appropriate ethics committee must be obtained before undertaking the research to confirm the study meets national and international guidelines. As a minimum, a statement including the project identification code, date of approval, and name of the ethics committee or institutional review board must be stated in Section 'Institutional Review Board Statement' of the article.

Example of an ethical statement: "All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of XXX (Project identification code)."

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If the study reports research involving vulnerable groups, an additional check may be performed. The submitted manuscript will be scrutinized by the editorial office and upon request, documentary evidence (blank consent forms and any related discussion documents

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Ethical Guidelines for the Use of Animals in Research

The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers. Authors should particularly ensure that their research complies with the commonly-accepted '3Rs [1]':

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- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

Authors must include details on housing, husbandry and pain management in their manuscript.

For further guidance authors should refer to the Code of Practice for the Housing and Care of Animals Used in Scientific Procedures [2], American Association for Laboratory Animal Science [3] or European Animal Research Association [4].

If national legislation requires it, studies involving vertebrates or higher invertebrates must only be carried out after obtaining approval from the appropriate ethics committee. As a minimum, the project identification code, date of approval and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement'. Research procedures must be carried out in accordance with national and institutional regulations. Statements on animal welfare should confirm that the study complied with all relevant legislation. Clinical studies involving animals and interventions outside of routine care require ethics committee oversight as per the American Veterinary Medical Association. If the study involved client-owned animals, informed client consent must be obtained and certified in the manuscript report of the research. Owners must be fully informed if there are any risks associated with the procedures and that the research will be published. If available, a high standard of veterinary care must be provided. Authors are responsible for correctness of the statements provided in the manuscript.

If ethical approval is not required by national laws, authors must provide an exemption from the ethics committee, if one is available. Where a study has been granted exemption, the name of the ethics committee that provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation on why the ethical approval was not required.

If no animal ethics committee is available to review applications, authors should be aware that the ethics of their research will be evaluated by reviewers and editors. Authors should provide a statement justifying the work from an ethical perspective, using the same utilitarian framework that is used by ethics committees. Authors may be asked to provide this even if they have received ethical approval.

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1. NSW Department of Primary Industries and Animal Research Review Panel. Three Rs. Available online: **https://www.animalethics.org.au/three-rs**
2. Home Office. Animals (Scientific Procedures) Act 1986. Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes. Available online: **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/388535/CoPanimalsWeb.pdf**
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4. European Animal Research Association. EU regulations on animal research. Available online: **https://www.eara.eu/animal-research-law**

Research Involving Cell Lines

Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.

An example of Ethical Statements:

The HCT116 cell line was obtained from XXXX. The $MLH1^{+}$ cell line was provided by XXXXX, Ltd. The DLD-1 cell line was obtained from Dr. XXXX. The DR-GFP and SA-GFP reporter plasmids were obtained from Dr. XXX and the Rad51K133A expression vector was obtained from Dr. XXXX.

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Experimental research on plants (either cultivated or wild) including collection of plant material, must comply with institutional, national, or international guidelines. We recommend that authors comply with the **Convention on Biological Diversity** and the **Convention on the Trade in Endangered Species of Wild Fauna and Flora**.

For each submitted manuscript supporting genetic information and origin must be provided. For research manuscripts involving rare and non-model plants (other than, e.g., *Arabidopsis thaliana, Nicotiana benthamiana, Oryza sativa*, or many other typical model plants), voucher specimens must be deposited in an accessible herbarium or museum. Vouchers may be requested for review by future investigators to verify the identity of the material used in the study (especially if taxonomic rearrangements occur in the future). They should include details of the populations sampled on the site of collection (GPS coordinates), date of collection, and document the part(s) used in the study where appropriate. For rare, threatened or endangered species this can be waived but it is necessary for the author to describe this in the cover letter.

Editors reserve the rights to reject any submission that does not meet these requirements.

An example of Ethical Statements:

Torenia fournieri plants were used in this study. White-flowered Crown White (CrW) and violet-flowered Crown Violet (CrV) cultivars selected from 'Crown Mix' (XXX Company, City, Country) were kindly provided by Dr. XXX (XXX Institute, City, Country).

Arabidopis mutant lines (SALKxxxx, SAILxxxx,…) were kindly provided by Dr. XXX, institute, city, country).

Clinical Trials Registration

Registration

MDPI follows the International Committee of Medical Journal Editors (ICMJE) **guidelines** which require and recommend registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.

Purely observational studies do not require registration. A clinical trial not only refers to studies that take place in a hospital or involve pharmaceuticals, but also refer to all studies which involve participant randomization and group classification in the context of the intervention under assessment.

Authors are strongly encouraged to pre-register clinical trials with an international clinical trials register and cite a reference to the registration in the Methods section. Suitable databases include **clinicaltrials.gov**, **the EU Clinical Trials Register** and those listed by the World Health Organisation **International Clinical Trials Registry Platform**.

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MDPI requires a completed CONSORT 2010 **checklist** and **flow diagram** as a condition of submission when reporting the results of a randomized trial. Templates for these can be found here or on the CONSORT website (**http://www.consort-statement.org**) which also describes several CONSORT checklist extensions for different designs and types of data beyond two group parallel trials. At minimum, your article should report the content addressed by each item of the checklist.

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MDPI follows the practical framework defined in **Guidance for Editors: Research, Audit and Service Evaluations** and introduced by the Committee on Publication Ethics (COPE). Research that could pose a significant threat, with broad potential consequences to public health or national security, should be clearly indicated in the manuscript, and potential dual-use research of concern should be explained in the cover letter upon submission. Potential areas of concern include but are not limited to biosecurity, nuclear and chemical threats, and research with a military purpose or application, etc. For these manuscripts to be considered for peer review, the benefits to the general public or public health must outweigh the risks. The authors have a responsibility to comply with relevant national and international laws.

Sex and Gender in Research

We encourage our authors to follow the **'Sex and Gender Equity in Research – SAGER – guidelines'** and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We suggest that our authors consult the full **guidelines** before submission.

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- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.
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