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CONSUMER REPORTED DIGITAL IMMUNIZATION RECORDS. FEASIBILITY, APPLICABILITY AND PUBLIC HEALTH UTILITY IN THE CANADIAN CONTEXT

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Consumer reported digital immunization records. Feasibility, applicability, and public health utility in the Canadian context.

Thesis for Doctoral Degree (Ph.D)

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To my parents, without whom, none of this would have been possible.

Popular science summary of the thesis

Immunization is one of the most important public health interventions of all time. Unfortunately, the data and systems worldwide fall short of the functionality needed to collect, manage, and analyze data to determine how immunization programs should best operate. As a result, we see outbreaks of VPDs and insufficient protection in our communities. With the advent of mobile phones, and widespread adoption of smartphones, there is an opportunity to augment immunizations systems to collect self-reported vaccination data, send notifications directly to the public, and detect early signals of patterns or changes in immunization behaviour. However, there is little real-world evidence available on the feasibility and utility of this.

Through four studies, the feasibility, public health utility and applicability of mobile apps to complement immunization information systems was evaluated. The results of this thesis demonstrated that use of a Pan-Canadian mobile immunization app to provide self-reported immunization data is feasible and acceptable. Based on the volume of data available from users, it also showed the potential to provide insight into early trends in vaccination uptake and series completion and to explore associations between individual and family characteristics with vaccination behaviour. Evidence from a systematic review and meta-analysis suggests that there is a wider applicability of apps to improve immunization uptake and series completion through features such as push notifications. These are preliminary studies which were subject to several limitations. Moving forward, more research on the use of mobile apps to augment immunization programs is warranted.

Abstract

Background: Vaccination is one of the most effective public health interventions of all time. Public health programs collect data on Vaccination Coverage (VC) to determine levels of protection and guide resource allocation for further vaccination campaigns but VC data completeness and utility is a challenge in many settings. Self-report is a sensitive and relatively specific indicator of vaccination status but incorporation into VC analyses is limited. Mobile technologies can enhance Immunization Information Systems, not least by facilitating bi-directional communications with individuals. This permits collection of self-reported immunization records and a channel to deliver reminders and reliable information back to individuals. However, evaluations of consumer apps for immunization are still nascent, often small-scale, and conducted most in controlled research environments.

Aim: The overarching aim of this thesis is to shed light on the feasibility, public health utility and applicability of mHealth apps for recording, reporting, and encouraging immunization.

Methods: Paper I was an ecological, quality-assurance study describing use of Pan-Canadian mobile immunization app for parental reporting of children's primary immunization series in Ottawa, Ontario, Canada. Paper II was a single cohort interrupted time series analysis examining the impact of the COVID-19 pandemic in Canada on uptake of a Pan-Canadian mobile immunization app as well as parentally reported pneumococcal series completion rates at the child's 13-months of age. Paper III was a cross-sectional study describing the characteristics of family/parental characteristics and their association of reporting vaccinating their children against influenza among Pan-Canadian mobile immunization app users in the 2018/2019 influenza season. Paper IV was a systematic review and meta-analysis examining effectiveness of digital push interventions compared to non-digital interventions at increasing vaccine uptake and series completion.

Results: *Feasibility and Acceptability:* The first successful transmission of records occurred April 27, 2015 (Paper I). There were 63,833 pediatric records and 11,381 unique parent-child dyads that met inclusion criteria, respectively in Papers II and III. The onset of

COVID-19 restrictions was associated with an abrupt and continued decline in enrollment of children in the app compared to expected values (Paper II).

Public Health Utility: 530 (20%) of children were less than 12 months old when their record was first submitted via the app (Paper I). The onset of COVID-19 restrictions was associated with an initial increase in self-reported completion of pneumococcal series, followed by a modest decrease leading to a net effect of -20%, compared to expected values (Paper II). Influenza vaccination was reported for 32.3% (3,675/11,381) of children and 42.0% (4,788/11,381) of parents. Parents receiving the seasonal influenza vaccine was the most strongly associated characteristic with pediatric influenza vaccination (OR 17.05, 95% CI 15.08, 19.28) compared to parents who did not report being vaccinated against influenza that season (Paper III).

Applicability: When comparing digital push with non-digital interventions, patients had 1.18 (95% CI 1.11, 1.25) the odds of receiving vaccination or series completion. Analyses had high statistical heterogeneity, but risk of bias was low (Paper IV).

Conclusions: Through four studies, this thesis provided supportive evidence on the potential to mobile apps to enhance IIS. Successful transmission of self-reported immunization records to public health via mobile app was demonstrated to be feasible and acceptable. The onset of COVID-19 was associated with decreased app use and reported pediatric pneumococcal series completion. Parents receiving the seasonal influenza vaccine was associated with reporting their children as immunized. Receiving digital push notifications increases the odds of vaccine uptake and series completion. These studies are subject to limitations but show potential for mHealth apps to facilitate self-report of vaccination data, assess trends and associations in vaccine behavior and encourage immunization through push interventions.

Keywords: Vaccination, vaccine coverage, digital technology, mHealth, series completion, public health, influenza, pneumococcal immunization, Canada

List of scientific papers

I. **Atkinson, K.M.,** El-Khatib, Z., Barnum, G., Bell, C., Turcotte, M.C., Murphy, M.S., Teitelbaum, M., Chakraborty, P., Laflamme, L. and Wilson, K., 2017. Using Mobile Apps to Communicate Vaccination Records: A City-wide Evaluation with a National Immunization App, Maternal Child Registry and Public Health Authorities. *Healthcare Quarterly,20(3),* pp.41-46.

II. **Atkinson, K.M.,** Ntacyabukura, B., Hawken, S., Laflamme, L. and Wilson, K., 2022. Effects of the COVID-19 pandemic on self-reported 12-month pneumococcal vaccination series completion rates in Canada. *Human Vaccines & Immunotherapeutics, 18(7),* p.2158005.

III. **Atkinson, K.M.,** Ntacyabukura, B., Hawken, S., El-Khatib, Z., Laflamme, L., Wilson, K. Parent and family characteristics associated with self-reported uptake of pediatric influenza vaccine in a sample of Canadian digital vaccination platform users. A cross-sectional study. Under Review.

IV. **Atkinson, K.M.,** Wilson, K., Murphy, M.S., El-Halabi, S., Kahale, L.A., Laflamme, L.L. and El-Khatib, Z., 2019. Effectiveness of digital technologies at improving vaccine uptake and series completion–A systematic review and meta-analysis of randomized controlled trials. *Vaccine, 37(23),* pp.3050-3060.

These articles will be referred to in the text by their roman numerals I-IV.

Contents

List of abbreviations and definitions

AEFI	Adverse Event Following Immunization
Apps	Smartphone Applications
ARIMA	Autoregressive Integrated Moving Average
BIS	BORN Information System
BOH	Boards of Health
BORN	Better Outcomes Registry and Network
cNICS	childhood National Immunization Coverage Survey
COVID-19	Coronavirus Disease 2019
DHIR	Digital Health Immunization Repository
ECDC	European Centre for Disease Prevention and Control
EMR	Electronic Medical Record
EU	European Union
GPS	Global Positioning System
HIC	High income countries
HPV	Human Papillomavirus
IIS	Immunization Information System
iOS	iPhone Operating System
IPF	Immunization Partnership Fund
ISO	International Organization for Standardization
ISPA	Immunization of School Pupils Act
LMIC	Low-middle-income countries
mHealth	Mobile Health
OHRI	Ottawa Hospital Research Institute
OHSN REB	Ottawa Health Science Network Research Ethics Board
OPH	Ottawa Public Health
P/T	Provinces and Territories or Provincial and Territorial
PHAC	Public Health Agency of Canada
PHU	Public Health Unit
RCT	Randomized Controlled Trial
SES	Socioeconomic Status
SMS	Short Message Service

UI	User Interface
US	United States
VC	Vaccine Coverage
VE	Vaccine Effectiveness
VPD	Vaccine Preventable Disease
WHO	World Health Organization

Immunization	Refers to vaccine administration and does not imply immunity
Electronic Immunization Record	A digitalized written record of immunization history
Electronic Immunization Registry	A collation of electronic immunization records, housed in a database. Registries can be part of an immunization information system but not does constitute an IIS by itself

Introduction

Immunization is one of very few medical interventions that almost every person on this planet is eligible for, and for which the benefit expands beyond the individual vaccinated. Yet, vaccination programmes are seldom successful in their goals of vaccinating the eligible population resulting in outbreaks of vaccine preventable diseases. As I began to learn more about the complexities of the challenges facing programmes globally, vaccine hesitancy was often overstated and the lack of data and modern tools to inform decision making was hardly discussed at all.

I started my academic career exploring the use of the precautionary principle in transfusion medicine, learning about how risk-based decisions inform policy. I then began to be involved in work on understanding the gaps in the Canadian immunization system. Outside of work, iPhones were becoming more common, internet connectivity moved from ethernet cables to Wi-Fi. New parents, friends travelling, and those with careers in healthcare were complaining about the struggle with understanding vaccination requirements and how to maintain an official record to enter countries or start a new placement at a hospital.

Together with the team at The Ottawa Hospital Research Institute, I began to explore how smartphone apps could put the people in the centre of the immunization system, ensuring that the individual, provider, and public health *all* have access to the same data to make decisions at the same time. I helped create the mHealth Lab at OHRI to help providers in other areas develop mHealth solutions and evaluate their effectiveness in stroke rehabilitation, emergency medicine care, peritoneal dialysis, and perioperative care. That gave me an appreciation for the cost and complexity of developing and maintaining technology being used in healthcare settings.

This thesis is informed by previous research work I've done and continue to do in immunization (Appendix A). I am grateful that I've had the opportunity to be a part of developing a technological solution. With that came the excitement and pain of deployments, iterations, and bug fixes. The product itself changed so much during these doctoral studies. In 2012, ImmunizeON was released which became ImmunizeCA in 2014 and CANImmunize in 2016.

Since I began my doctoral studies, technology has evolved dramatically. There have been about eight new versions of the iPhone. Broadband networking keeps improving and becoming more pervasive, and 5G networks are readily accessible. We have lived through a global pandemic and witnessed the fastest ever production and rollout of a vaccine in modern history.

Despite everything that has changed, I still hear frustration about vaccine requirements and people not knowing where their yellow card is. We're far from the ideal, modern solutions needed to support immunization programs, but I hope my work contributes incrementally towards finding them.

1 Background

1.1 Vaccination and Herd Immunity

Vaccination is one of the most effective public health interventions of all time, responsible for a global reduction in morbidity and mortality from vaccine preventable diseases (VPD). Before the invention and widespread implementation of vaccines, VPD such as measles, pertussis, smallpox and diphtheria were the leading causes of infant and child mortality (1). Vaccination is unique among health interventions due to its wide-ranging impact, reaching beyond individual health to shape entire populations. It plays a crucial role in diminishing healthcare burdens, promoting overall well-being, fostering cognitive development, and bolstering economic productivity (2–5). Immunization is estimated to save up to US$6 billion globally in healthcare treatment costs and an additional US$1 billion in caregiver time (3). By saving 6.4 million lives, avoiding 426 million cases of illness, and avoiding disability from meningitis in 63,000 children the long-term productivity gains reach US$151 billion (3).

Disease eradication through vaccination hinges on achieving a critical threshold of vaccination coverage known as herd immunity (6). The basic principle of herd immunity represents the proportion of individuals required to be immune to a particular infectious disease, thereby preventing sustained transmission within the community (7).

$$Herd\ Immunity = (1 - \frac{1}{R_0})/Ve$$

Where: R_o is the basic reproductive number of the disease

V_e is the vaccine effectiveness in preventing individuals from being infected

For measles, a highly infectious virus, the R_o is somewhere between 13–20 (8), bringing the herd immunity threshold between 90 and 95% of individuals needing to be vaccinated (7). If that is reached the remaining 5% who are not vaccinated are conferred protection. For other diseases with lower reproductive numbers, such as polio, coverage rates of above 80% can protect the remaining 20% unvaccinated. While the concept of herd immunity is straightforward in principle it does assume random mixing of the population and stable viral properties (6, 7).

In practice, the determination of success for vaccine programs is much more dynamic (9). Several properties including type and duration of immunity, viral stability (emergence of new variants) and population clustering/mixing must be taken into account to truly estimate the level of vaccination required to provide protection to communities (10–12). A more realistic representation of herd immunity calculation is as follows, where the goal is reducing Rt to below one and stopping the spread of the virus (13, 14).

$$R_t = R_0 \, x \, (1 - P_{vax} \, x \, VE)$$

Where: R_t is the effective reproductive number of the virus, the number of subsequent individuals infected by each infected individual

$P_{vax:}$ is the proportion of the population effectively vaccinated, not necessarily conferring immunity

For each vaccine in a program (i.e. at the antigen level), performing a real-time assessment of R_t allows public health to evaluate what level of vaccination is appropriate, predict current or future susceptibility to VPDs, and strategically deploy resources to target under-immunized groups as needed. Together, these activities are key to effectively curbing disease transmission within a community (15). As new evidence emerges, they must be able to amend these calculations and adjust programming as needed. This includes new facets that affect may herd immunity, such as population density (16). This work requires standardization, routinization and complex systems support (17). The existence of recurrent outbreaks of VPDs, even in high-income countries (HICs) (18–22) highlight that this is not occurring in most settings.

It is important to note the evolving difference between sterilizing and protective immunity offered by vaccines. Sterilizing immunity conferred by a vaccine prevents infection, while protective immunity mitigates the severity of infection without preventing its occurrence (23). For such vaccines, where vaccine effectiveness (VE) is purely protective, or begins as sterilizing and becomes protective over time, true "herd immunity" for preventing disease transmission may never be achievable. However, that doesn't mean that the vaccine is not *valuable* to public health. Even in the absence of sterilizing immunity, vaccines that reduce the severity of illness can alleviate strain on healthcare systems (14, 24). An example of this is the pertussis vaccine, which does not prevent infection from pertussis, but

prevents serious illness, whooping cough (24). In such cases, the consequences of not being vaccinated are not borne by the individual alone, but everyone in the healthcare system by reducing healthcare burdens (23).

1.2 Vaccination Coverage

Ascertainment of P_{vax}, the measure which is commonly referred to as vaccination coverage (VC), represents a crucial focus for immunization programs. VC is defined as the proportion of individuals appropriately immunized against a VPD at a point in time (15).

All European Union (EU) countries engage in VC assessments but the timing, methods and reliability of results vary significantly (25). The majority of VC assessments in the EU are performed either at a child's second birthday or upon school-entry (25). In Canada, the National Standard for Immunization Assessment recommends that antigen level VC should be reported annually for 2-, 7- and 17-year olds in addition to any local requirements for local school-age programs (26).

The most common methods used to assess VC are administrative methods and surveys, with growing adoption of computerized systems, although paper administration persists (25). Vaccine coverage surveys employed in United States (US) and Canada suffer from multiple sources of bias, and consistently report high positive predictive value and low negative predictive values (27). In some cases, concordance of data between health facilities and higher levels of the health system show both over and under reporting (28). Utilizing vaccination data from multiple sources help to improve the validity of results (27, 29-32). An older review described VC calculated on registry data alone was 13% lower than coverage based on only provider data (29). Similarly, being immunized by multiple providers has been observed to compromise consolidated immunization records (33). Many sources of immunization data exist in local, national and global settings to aid in the calculation of VC but lack of timely and high quality remains a challenge (34), as does data accessibility, completeness and utility (due to lack of linkages and standardization) (35, 36).

Self-report is a sensitive and relatively specific indicator of vaccination status (37, 38). Assessment of self-reported immunization records has traditionally been done via paper or telephone survey at a single point in time (39). Analyses of self-report have been

described for Human Papillomavirus (HPV) vaccination with mixed results in men (40-43), immunizations given outside of traditional providers (44-46) and in higher risk groups such as those with inflammatory bowel disease (47). Studies evaluating data completeness for influenza VC in the US emphasize the need for self-report and documentation of immunization from other sources (44, 46, 48, 49) to capture the true coverage rate. A study in Spain examining self-report for influenza vaccination coverage showed that registry data underestimated VC compared to self-report, which was also seen in Australia with HPV among women (50). Strong concordance of self-reported data with registry data has also been identified for Coronavirus Disease 2019 (COVID-19) vaccination (51-53). A mobile-optimized self-interviewing instrument was used to accurately (85%, 95% CI 81-91 with a sensitivity of 89% and specificity of 80%, negative predictive value of 92%) ascertain HPV immunization status (54) which points to the potential to move away from telephone survey and paper methods to more modern technological approaches. Despite evidence supporting the incorporation of self-reported immunization data with other, validated data sources, with technology it is not well described.

Vaccination programs are widely recognized as cost-effective (55) but exact figures on program costs and derived benefits are largely missing in the literature. Available modelling studies focus on the analysis of specific programs such as seasonal influenza vaccination, COVID-19 or other targeted efforts, instead of holistic pediatric or adult programs (56-60). It is possible that lack of available data on the full cost and benefits of jurisdictional immunization programs is a barrier to investment into new tools and infrastructure which support automation and integration of self-reported data but more research in this area is needed.

1.3 Immunization Information Systems (IIS)

Immunization Information Systems (IIS) have been designed to serve as effective tools for public health to aggregate disparate sources of data to provide consolidated immunization information on individuals (Box 1) (61).

Box 1 – Definition of Immunization Information Systems (IIS), from ECDC on page 4 (61)

> Immunization information systems (IIS) are confidential, population-based, computerized information systems that record, store, and provide access to consolidated individual immunization information.

As comprehensive and community-wide systems, IIS have the capacity to cover individuals residing in a specific geographic area, across multiple healthcare providers (62-64), facilitating sophisticated VC analyses, such as dose-specific and cohort VC (65). The functionality of IIS goes beyond simply recording immunization and includes personalized information on vaccination (66, 67). IIS provide public health with a communication platform that allows for targeted communication towards healthcare professionals and the public, decision support systems for vaccine providers, recording for reasons for refusal of vaccination and adverse event reporting (61). Through utilizing these features, use of IIS can improve vaccination coverage rates (68).

Public health programs encounter several challenges in adopting IIS. A review of challenges in the adoption of IIS highlight interoperability, data quality, privacy and security, standardization, usability, internet connectivity, infrastructure, workflow, funding, government regulations, awareness, skeptical response, computer literary and staff availability as the most common barriers to adoption (69). Beyond adoption by public health, IIS must be utilized by external vaccine providers such as primary care physicians and pediatricians. However, incentivizing physician associations to adopt IIS in their clinics has been described as a barrier for uptake in Australia (70). Among pediatricians in the US, major barriers to use among pediatricians included the IIS not updating the electronic medical record (EMR) electronically and lack of ability to submit data (71). In Ontario, providers outside of public health submit data of lower specificity to IIS, as measured by vaccine specific billing codes with family doctors (72, 73).

Despite investment from countries and local governments on the implementation of IIS, these challenges have led to the format, capability, and completeness of systems vary substantially around the world (74-81). The US, Canada and Europe have described progress and challenges in detail (75, 82-84). In Australia, audits of the IIS showed children

incorrectly classified as overdue because doses administered outside the country weren't entered by primary care providers, the children had duplicate records, or there were data transmission and clinician errors as the data moved from EMRs to the IIS (85). Reviews of low- and middle-income countries (LMIC) observed similar challenges, including the need to plan for iterative processes (86) and that the quality of data residing in systems is still often poor (87-89), despite willingness to use electronic systems (90, 91).

Once adopted, the dynamic nature of immunization programs requires IIS to undergo updates of software, data standards and variable product data as new products, vaccination schedules and clinical guidelines are released. This continued investment required to maintain these systems has been described in limited settings (92) or as difficult to estimate (93). Costs of integration cited as a barrier, particularly to smaller, independent practices (94).

IIS can also be subject to limitations related to policy or regulations around their data collection and use (67). Furthermore, IIS have predominantly focused on children's vaccinations and increasingly vaccines are being given throughout the lifespan including to pregnant people and older adults. IIS may benefit from revisiting system design, legislation and regulations governing them to enable data collection across the lifespan, as is being done in Australia (79). For example, in Canada's most populous province, Ontario – the IIS is governed by a specific piece of legislation and thus does not capture data for childhood immunizations until school or daycare entry and does not have reliable data for adults (15). In the US, immunization records are collected by schools as part of school entry requirements but under the Family Education Rights and Privacy Act, it prevents schools from sharing this data with their jurisdictional IIS (36).

The COVID-19 pandemic increased use of public health information systems and digital technologies (95). For example, the US IIS network reported an estimated ten-fold increased in submissions and queries during the COVID-19 pandemic, highlighting its important role in administering public health programs (96). Lack of IIS maturity in many jurisdictions was also evident during the COVID-19 pandemic and subsequent vaccine rollout (97), leading to calls for further investments and preparedness (98-100). There have been calls to work on automation of interfaces between IIS and other sources of data, such as EMRs (101, 102). Without integration with external sources of vaccination

data, the limitations of IIS will only intensify as new vaccine types and innovative administration routes such as patches and sprays come to market (103).

In the US, a study of centralized recall-reminders from IIS described that 91% had been sent by mail, 33% by autodialed calls, only 10% by text message and 3% by email (104). While forecasters made it easier to automate the process of creating the reminders, outdated contact information in the IIS, glitches leading to duplicate reminders being sent, legal barriers, and automated calls coming from out of state numbers limited the use and effectiveness of reminders (105). Further integration of external systems with IIS would also provide public health with a communication channel that permits targeted communication to healthcare providers and the public, decision support systems for vaccine providers and to record reasons for refusal of vaccination and adverse event reporting.

1.4 Consumer Facing Digital Technology and Vaccination

In 2023, mobile phones achieved near ubiquity, with over 5.4 billion people having at least one mobile subscription (106). The widespread availability and use of mobile phones, particularly smartphones, have greatly enhanced access to information, facilitating communication and improving efficiency in nearly all aspects of life, including healthcare (107). In 2022, it was estimated that there were about 350,000 health and wellness apps on the market (108) which have been the focus of extensive research across many areas of health (109, 110).

Box 2 – Definition of Mobile Health, from the World Health Organization (111)

Mobile Health (mHealth): The use of mobile wireless technologies for public health

The use of smartphone applications (apps) in healthcare has potential to reduce human error, expedite tasks, automate data collection and enhance the reach and timeliness of interventions (112). In immunization, several countries described architecture (113) of IIS which use mobile apps, have begun evaluations of their use (114, 115) or deployed mHealth solutions at scale which allow healthcare officials and vaccine providers to submit and

access data from IIS, as well as perform tasks within immunization programs including clinical decision support (116) and generation of automated recall reminders (117-121).

The promise of mHealth for immunization programs extends to improving on-time immunization and overall immunization uptake (122-127) through features like short message service (SMS) and facilitation of convenient access and real-time updates to immunization records for citizens. Moreover, apps allow for bidirectional communication, enabling public health officials to directly engage with individuals (126). This could be used as a platform for public health officials to collect self-reported data or send recall reminders, educational content or lot-specific notifications in the case of vaccine failures or adverse events (104, 105, 128). This type of notification, when messages or alerts are sent from a server or centralized system to a user's device without the user explicitly requesting the information are referred to push notifications (129). Apps can also leverage global positioning system (GPS) for push messaging, notifying individuals of vaccination clinics or disease outbreaks in their region. Ultimately, using mobile apps to enhance IIS can help realize the goal of the individual, the healthcare provider, and public health officials always having access to the same immunization information at the same time (130). A proposed schematic for a mobile enhanced IIS is in Figure 1.

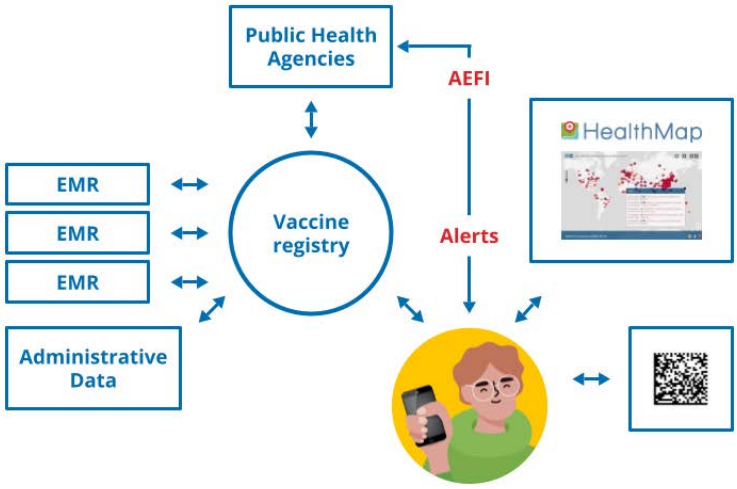

Figure 1 – Vision for a mobile enhanced immunization information system, adapted from Wilson, Atkinson et al (130).

Despite the promise of mHealth (Box 2) to augment immunization programs, governments find it challenging to assess, scale up and integrate such solutions into practice (111). Similarly, the European Centre for Disease Prevention and Control (ECDC) acknowledges that development of standalone platforms (including apps) can be developed rapidly and to serve an immediate need. However, their true value will be realized with connection to the wider health system (1).

The integration and evaluation of mHealth into immunization programs has been quite limited to date, with quality of available evidence revealed to be moderate to poor, with many aspects of the evaluation methodology remaining unclear (131-135). Reported barriers to the implementation of mHealth in immunization are lack of resources and shared standards (83). In 2021, Norway has launched a mobile app (helsenorge.no) that allows citizen to access their immunization records (97), but bidirectional data flows are not yet available. Studies are evaluating mobile phone-based programs for immunization in with migratory populations living in refugee camps or arriving to new countries (136-139), including preliminary results showing improvements in vaccination knowledge and uptake (140). Mobile apps for immunization have also been tested in with providers in rural

areas in low- and middle-income countries (141, 142) and in quaternary care settings in HIC coordinating immunization for solid organ transplant patients (143, 144). Pre-deployment studies have described technological architecture (145) and load testing (146), usability of immunization apps for understanding vaccination schedules (147) as well as interest and acceptability among caregivers to utilize a mobile app for immunization in Pakistan (148) but real-world data has not been released on the deployment or use of products.

Recognizing that there was a paucity of real-world evidence on the opportunities of a mobile-enhanced IIS, a Pan-Canadian mobile immunization app was developed that had the capacity to interact with, and enhance IIS (149, 150). Predictors of uptake were explored (151). Vaccination attitudes and mobile readiness (152) as well as barriers and facilitators to use (153) were characterized amongst subsets of users. It was also assessed if these technologies could be used to improve on-time vaccination (151), overcome jurisdictional barriers (128), support travel vaccinations (154) and place individuals in the center of care (126, 155). Finally, it was described how these tools could integrate with IIS (130), and features such as mobile 2D vaccine barcoding were piloted (156).

Despite evidence to support the utility of self-reported data in VC assessments, there were no studies evaluating the feasibility and acceptability of using a mobile app to collect and report citizen immunization data. Further, the opportunity to utilize this data beyond point-in-time VC assessments to provide insights into trends in vaccination over-time, or in response to specific events has not been studied. These systems have also not been examined for their ability to provide insights into associations between individual characteristics and vaccine uptake. Finally, it was not known if there was evidence to support the use of multimodal features within mobile apps beyond immunization recording and reporting such as push notifications (for example, from public health to app users) to improve vaccine uptake and series completion.

2 Research aim

The overarching aim of this thesis is to shed light on the feasibility, public health utility and applicability of mHealth apps for recording, reporting, and encouraging immunization.

The following research questions are addressed:

- Paper I: Is consumer recording and reporting of immunization status via a Pan-Canadian mobile immunization app feasible and acceptable? Does it have utility to public health?
- Paper II: How does COVID-19 impact enrollment on a Pan-Canadian mobile immunization app, as well as the recording and reporting of immunization status for pneumococcal disease?
- Paper III: What sociodemographic factors are associated with use of a Pan-Canadian mobile immunization app for recording and reporting influenza immunization status?
- Paper IV: What is the body of evidence on the impact of digital push interventions on vaccine uptake and series completion?

Theme	Paper	Research Question	Vaccination(s) Examined & Milestone	Data Sources	Setting
Feasibility and Acceptability	**I**	Is self- recording & reporting of immunization status via an app feasible and acceptable?	Pediatric Immunizations (0-17y) mandated under the ISPA	Pan-Canadian mobile immunization app 2017-2021	Canada
	II	How does the COVID-19 pandemic impact app enrollment?	N/A		
	III	What are the characteristics of parents and children who use an app for recording immunization status?	N/A		
Public Health Utility	**I**	Does consumer recording and reporting of immunization status have utility to public health (age of children at reporting, timeliness of reporting)	Pediatric Immunizations (0-17y) mandated under the ISPA		
	II	How does the COVID-19 pandemic impact recording & reporting of immunization status?	Pneumococcal vaccination at 13 months of age		
	III	What sociodemographic factors are associated with app use for recording & reporting of immunization status?	Seasonal influenza vaccination for children 6mo-17 y and parents		
Applicability	**IV**	What is the body of evidence on the impact of push interventions on vaccine uptake and series completion?	All	Published RCTs	Global

Table 1 – Overview of the theme, research question, vaccinations examined, data sources and setting for each Paper, I-IV.

3 Materials and methods

This thesis is based on four papers which touch on three themes, presented in Table 1. The first three papers utilized data from a free, Pan-Canadian mobile immunization app in Canada, spanning 2015-2021. The final study was a systematic review and meta-analysis of published studies globally from 2012-2016.

3.1 Setting (Papers I-III)

Canada is a country of over 40 million people living in 10 provinces and three territories covering a land area of about 10 million km^2 (157). The majority (83.9%) of people live within a census metropolitan area, with the other 16.1% living rurally. Ontario accounts for about 40% of the population with the three territories representing less than 0.4% of the population, combined. Population growth in Canada between 2016 and 2021 was 5.2%, almost twice the pace of any other G7 country (158). In 2021, more than 8.3 million people, were landed immigrants or permanent residents (159). Every year, close to 350,000 Canadians move between Provinces/Territories (160). In Canada, about 20% of the population identifies as vaccine hesitant, i.e. having some concerns about vaccination but are not firm vaccine refusers (161).

Canada has a decentralized, universal publicly funded health care system (162). The responsibility for delivering healthcare is delegated to the 13 Provinces and Territories (P/Ts), except for specific populations including eligible Indigenous peoples, members of the Canadian Armed Forces, veterans, settled refugees and inmates which are served by the Federal government (162). The federal government also remains responsible for food & drug safety, through Health Canada, and for public health & emergency preparedness, through The Public Health Agency of Canada (PHAC). In Canada, there is no national strategy for electronic health records and no national patient identifier (162). Canada lacks a specific regulatory framework for mHealth and lacks clarity in available guidance (163).

These demographic, geographic and policy realities make the governance and administration of public health in Canada complicated. Criticism and calls for accountability have been published (164), highlighting how these fragmented systems that leave individuals as the source of truth for vaccination status contribute to inaccurate

estimates of population coverage and difficulty in understanding how to improve rates (165).

Within immunization in Canada there are significant differences in how each of the 14 vaccination programs function, and how individual vaccination data is recorded and reported to the respective public health authorities (166). For example, each P/T (and federal programme) has their own publicly funded immunization schedules and is responsible for procuring, implementing, and maintaining their own databases or IIS. At the federal level, Canada lacks both a national immunization registry and IIS (75). Instead, national immunization coverage estimates are published bi-annually by PHAC. For children, this is done through the childhood National Immunization Coverage Survey (cNICS) a telephone survey for which the most recent round had just over 5,000 survey respondents (167). A study comparing the cNICS with P/T estimates of coverage show varying levels of concordance, with cNICS estimates being generally lower (168). A study also highlighted that three jurisdictions lacked mechanism to assess coverage at two years old, a national and international recognized milestone age and instead rely on assessment at school entry (168). They also highlighted that within jurisdictions the methods of data collection used for assessment of coverage vary depending on milestone (168). Nine P/Ts reported that the include home-schooled children and those attending private schools in coverage assessments, but do not report estimates for those groups separately. No P/T described routine coverage assessment for vaccination programs specific to children with high-risk medical conditions.

At the time of the last publication describing progress of IIS implementation in Canada, 5 provinces (British Columbia, Ontario, Manitoba, Saskatchewan and Quebec) had implemented, or were in the process of implementing IIS, based on the IBM product Panorama (75). Since then, both Nova Scotia and New Brunswick have implemented Open Panorama, and the Yukon leverages British Columbia's instance (169). Alberta implemented their "Immunization and Adverse Reaction to Immunization" (Imm/ARI) system in 2005. Northwest Territories, Prince Edward Island, Newfoundland and Labrador use non-IIS systems (i.e. spreadsheets or other systems) as well as paper-based records. Nunavut reported having no immunization system in place at that time (75).

In Ontario, public health administration is done by Boards of Health (BOHs), legal entities within 34 municipal and regional jurisdictions (referred to as public health units (PHUs)) (170). In Ontario, Immunization coverage for school-age children is assessed by each PHU for their catchment area using data from the Digital Health Immunization Repository (DHIR). Data entry in the DHIR is governed by the Immunization of School Pupils Act (ISPA) and thus, does not contain complete information for all immunizations administered to residents. A key limitation of the DHIR is that coverage for children before school-entry and among adults cannot be reliably assessed using the data in the DHIR (15).

3.2 Data Sources

Studies I-III utilize a Pan-Canadian mobile immunization app Developed at the Ottawa Hospital Research Institute (OHRI). The major milestones in the evolution of the app since its original inception until 2020 are described below (Figure 2). In between the large deployments described, the product was iterated numerous times through smaller updates, bug fixes and user interface (UI) updates.

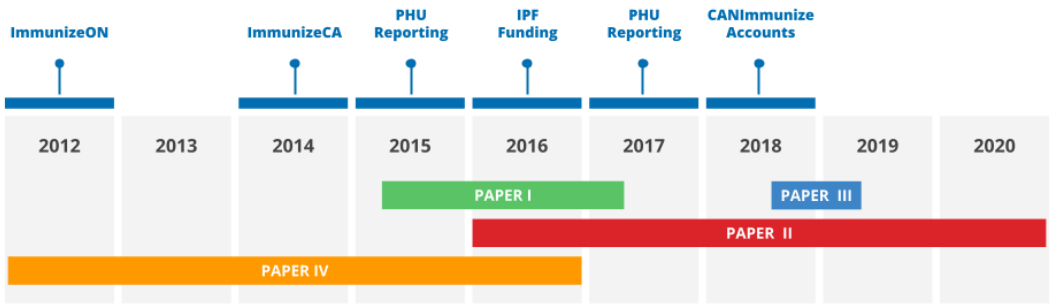

Figure 2 – Timeline of Pan-Canadian mobile immunization app development and study periods for Papers I-IV

On November 20th, 2012, ImmunizeON was launched for iPhone Operating System (iOS) devices in the iTunes App Store (150). The goal was to give people living in Ontario a simple, easy to use mobile app to hold their family's immunization records in one place. In ImmunizeON, you could create records for each member of your family. For children born after 2011, the app had the pediatric provincial immunization schedule programmed in it to create a customized schedule for the child based on its birthdate. At each visit (i.e. 2-

month, 4-month, 12-month etc.), ImmuizeON listed the recommended vaccine and allows the user to mark it as received with the date the vaccine was administered. Data for older children and adults could be manually entered. The app generated a "digital yellow card" similar to the existing paper record which could be emailed or printed directly from the phone. By linking with the calendar feature, the app could put events in to remind you of upcoming vaccinations. Finally, the app contained information for users; first, on the homepage, there were rolling banners which could be updated in real time as well as static sections with links to official sources of information on immunization such as from PHAC. It also showed the Council on Foreign Relations global outbreak map so that people could see outbreaks of VPDs in their area.

Since ImmunizeON was built to assist individuals with their own health information, there is no storage of health information by the provider of the app. To assist users with keeping this information secure, the app provided information about the potential risk of digitizing their health information and provided options to keep it safe. The app recommends users password-protect their device and provides the option to password-protect the app.

Following the release of the app ImmunizeON, there was considerable interest from public health and policymakers on expanding it for broader audiences. This led to federal funding to develop the ImmunizeON into a Pan-Canadian version in partnership with the Canadian Public Health Association. On March 20, 2014, ImmunizeCA was released for iOS, Android, and Blackberry devices. Building on the functionality of ImmunizeON, ImmunizeCA was available in both English and French, with all information written in plain language at a grade 7-8 reading level. It contained both paediatric and adult immunization schedules for each P/T, as well as travel and influenza vaccination details. It also included an "Frequently Asked Questions" section on immunization and enhanced immunization pain management information which was developed by an expert reference group. The app delivered local and push notifications for upcoming, due, and overdue vaccinations. We integrated with Healthmap so that users could see VPD outbreaks in their area. These features aimed to mitigate known barriers to vaccination (171). In general, factors known to reduce on-time vaccination include concerns about vaccine safety, challenges understanding the vaccination schedule, logistical issues related to attending vaccination appointments, and the belief that vaccination is unnecessary because VPDs are rare (171). ImmunizeCA had

features which address each of these factors and thus has the potential to impact vaccine hesitancy and on-time vaccination rates.

As with ImmunizeON, all user data entered in ImmunizeCA was stored locally on the device. This approach simplified privacy and security, feedback indicated that local data storage made it challenging to transfer to new devices and prevented the sharing of data between spouses or family members. Developing a centralized system required substantial effort and there was no funding to support such an initiative. Users also expressed a desire for a feature to easily transfer the data they entered the app to others. This included local public health authorities for the purpose of daycare, school-entry, or summer camps. The app permitted download and print of the digital yellow card but had no other export features.

In April 2015, PHU reporting functionality was built and released to users who had at least one record with "Ottawa" or another township within the Ottawa Public Health (OPH) catchment area in their City/Town Field. A banner on the home screen for eligible users gave information about the feature. Participants were prompted to agree to the consent statement and then enter parent/guardian information and contact details, as well as the child's details (first name, last name, date of birth, sex and health insurance number) (Figure 3). Participants were required confirm the inputted data on a separate screen prior to submission, upon which a 'Success' message was generated to indicate that the record had been sent to OPH.

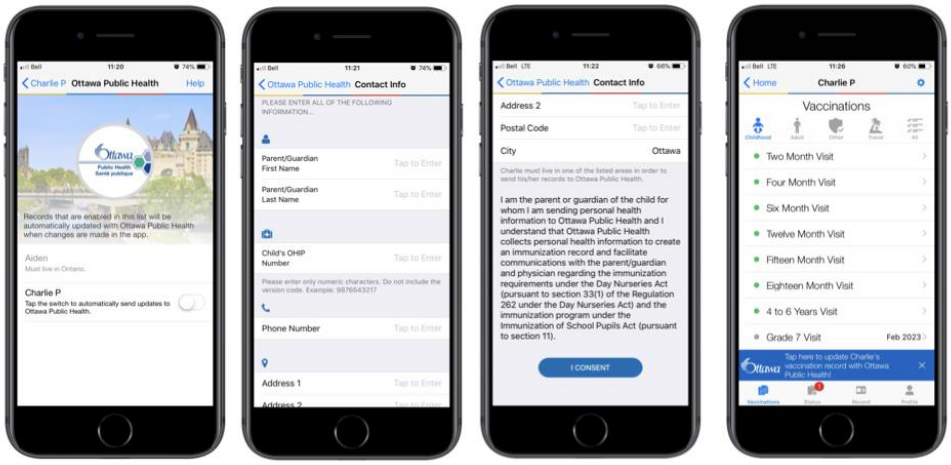

Figure 3 – Screenshots of the user flows for PHU reporting to Ottawa Public Health on iOS devices.

Users also had a choice for how subsequent updates were processed. Enabling automatic updates meant that when new doses are added, or data was edited users could set the app to automatically send the updated record to OPH without revisiting the reporting feature. Each submission contained the entire vaccination record for the child. All immunization data submitted via CANImmunize as a part of this project were disclosed to OPH under the ISPA, who in turn disclosed the records to the Better Outcomes Registry and Network (BORN) Information System (BIS) under its authority as a prescribed registry (Figure 4). Authorized OPH users then exported immunization data as a report from the BIS for review and/or manual entry into the provincial immunization repository.

The consent statement read as follows:

I am the parent or guardian of the child for whom I am sending personal health information to Ottawa Public Health and I understand that Ottawa Public Health collects personal health information to create an immunization record and facilitate communications with the parent/guardian and physician regarding the immunization requirements under the Day Nurseries Act (pursuant to section 33(1) of the Regulation 262 under the Day Nurseries Act)

and the immunization program under the Immunization of School Pupils Act (pursuant to section 11).

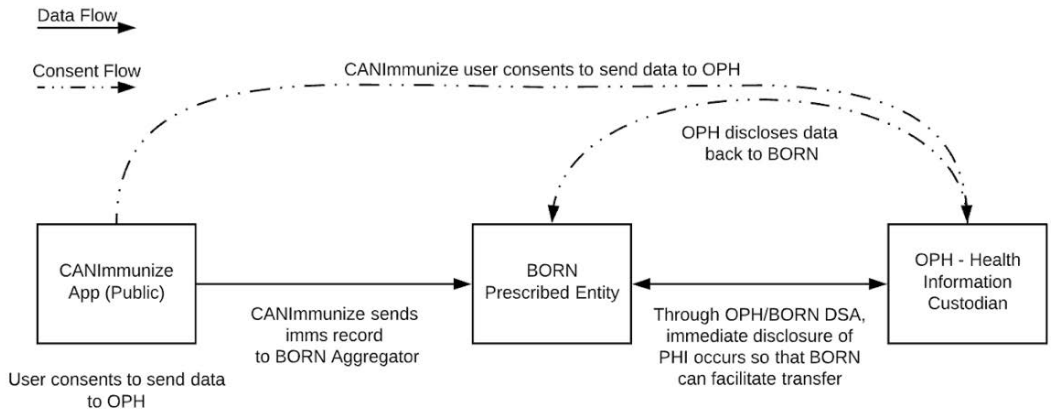

Figure 4- Data and Consent Flows for Reporting of Immunization Records from CANImmunize to Ottawa Public Health

In 2016, the Canadian Federal Government (through PHAC) launched the Immunization Partnership Fund (IPF), with the goal of funding projects that supported community-driven initiatives that helped close the gap among populations with lower vaccine uptake (172). Funding was allocated by IPF to expand ImmunizeCA and build out a full, centralized digital solution which empowers Canadians to easily manage their own immunization information (173). ImmunizeCA was rebranded to CANImmunize.

In this new solution, which became generally available in 2018, CANImmunize was now available for iOS, Android and through a web interface at CANImmunize.ca (149, 173). Beginning in Fall 2017, a soft launch to users of the original mobile app had the choice to move to the accounts system by providing informed consent to the Privacy Policy and Terms of Use (174). In 2018, the functionality was released to the public through the iTunes and Google Play app stores, again in a soft launch capacity where it was available to a small proportion of users and ramped up as platform stability data was collected. The web component, where users could sign up or sign in to their CANImmunize account via www.canimmunize.ca followed in the weeks and months after.

For those who consented, the platform was structured so that records are housed within each account and can be accessed from any device. By doing this "soft release" and reconsenting users slowly, in addition to platform stability data, feedback on the technology and the privacy framework was collected before releasing publicly. All user entered information is securely stored in the cloud which is run by Amazon Web Services out of their Canadian data centers. CANImmunize Accounts adheres to the European Union (EU) standards for privacy and the International Organization for Standardization (ISO) standards for information security (175). As part of this adherence, third-party threat-risk assessments and penetration testing is regularly performed. There is also a dedicated Privacy team which supports the platform and data governance activities of everything stored under the Account system. In 2019, PHU reporting expanded to Toronto Public Health, Kingston, Frontenac, Lennox & Addington Public Health, and Leeds Grenville Public Health Units.

3.3 Study Design and Data Analysis

Paper I was an ecological, quality-assurance study describing the use of a Pan-Canadian mobile immunization app for parental reporting of children's primary immunization series in Ottawa, Ontario, Canada (176). The primary outcome was feasibility, measured by the first successful transmission of a record from the app to public health. Secondary outcomes examined acceptability of reporting through the total number of dose transmissions and total number of unique children registered during the study period. Timeliness of data reporting following the vaccination event (i.e. same day) was also examined as a proxy for data utility for public health. The study population included all Pan-Canadian mobile immunization app users in the OPH catchment area, identified either through geolocation services or through the "City/Town" field within records. OPH listed the app an available method of reporting on their public materials but there were no direct recruitment or promotional efforts related to the project. The intervention was released publicly on iOS devices April 27, 2015, and Android devices January 10, 2017. Data was extracted April 18, 2017 from the BIS following BORN's data access process and policies. The data flows and consent flows are summarized in Figure 4.

Paper II was a single cohort interrupted time series analysis examining the impact of the COVID-19 pandemic in Canada on uptake of a Pan-Canadian mobile immunization app. Uptake was measured by the number of records created, and by parentally reported pneumococcal series completion when the child reached 13-months of age (177). Series completion was defined as 3 doses of pneumococcal containing vaccine by 13-months of age. To be included in the study, the children's record had to contain at least one dose of any pediatric vaccine and reach 13-months of age during the study period. Records created in the CANImmunize Accounts system from September 2017 to December 2021 were included in the enrollment analysis. Children born January 2016 to December 2020 were included in the series-completion analysis. Data was extracted from the CANImmunize database in February 2022 and predicted trends before and after the onset of COVID-19 restrictions were compared by means of an Autoregressive Integrated Moving Average (ARIMA). For each outcome, point estimates and confidence intervals were reported.

Paper III was a cross-sectional study describing the characteristics of family/parental characteristics and their association of reporting vaccinating their children against influenza among Pan-Canadian mobile immunization app users in the 2018/2019 influenza season (178). Inclusion criteria included CANImmunize accounts which contained at least one parental record (aged 18+) and one "child/dependent" record (between 6 months and 18 years old). The primary outcome was parentally reported pediatric influenza vaccination. Influenza season was defined as October 1, 2018 through to March 1st, 2019. Where accounts had multiple parental records, their characteristics were averaged to create unique parent-child dyads for analysis. The proportion of children reported to be immunized against influenza was calculated. Each parental and family characteristic was tested for independent association with the primary outcome using bivariate analysis. Odds ratios and 95% confidence intervals were reported Based on these results, collinearity analysis and backwards regression, a multivariate logistic regression model was fit.

Paper IV was a systematic review and meta-analysis examining effectiveness of digital push interventions compared to non-digital interventions at increasing vaccine uptake

and series completion (179). Inclusion criteria was randomized controlled trials (RCTs) published in scientific peer-reviewed journals after 2000, in English with participants that were either adults receiving vaccines themselves, including pregnant people, or parents of adolescents and children eligible for vaccination. The intervention was delivered via digital push, the comparison group was either usual care or non-digital version of the same intervention. The outcome was either vaccine uptake (reported as vaccine received yes/no) or series completion (reported as series completed yes/no). Risk ratios and corresponding 95% CIs and p values were calculated. Heterogeneity was assessed using the v2 test and quantified using the I2 statistic. Estimated summary effect sizes were calculated using a Mantel-Haenszel fixed-effects model, with weights assigned based on the inverse of within study variance. Where heterogeneity remained significant, subgroup analyses were performed by intervention delivery mechanism, vaccine targeted and control condition. Grading of recommendations assessment, development, and evaluation (GRADE) was used to assess the certainty of evidence for the effectiveness of each intervention as high, moderate, low, or very low at the outcome level. Risk of bias, certainty and evidence and publication bias was assessed.

3.4 Ethical considerations

All studies were conducted at OHRI, under the oversight of the Ottawa Health Science Network Research Ethics Board (OHSN REB), registration number IRB00002616. OHSN REB policy regarding secondary analysis, use of existing research data to find answers to a question that was different from the original work (180), is that "REB review is not required for research that relies exclusively on secondary use of anonymous information, so long as the process of data linkage or recording or dissemination of results does not generate identifiable information" (SOP Code 102.002, 2016). Studies which employ secondary analysis fall under SOP Code 102.002 and are exempt from review by OHSN REB. However, Paper II and III used data collected under the CANImmunize Accounts Privacy Policy which states that data was extracted from the CANImmunize database research using this data must be approved by REB (174). Thus, OHSN REB approvals were sought, and granted.

4 Results

4.1 Feasibility and Acceptability

In Paper I, the first successful transmission of parentally reported immunizations via a Pan-Canadian mobile immunization app on April 27, 2015 illustrating the feasibility of recording and reporting immunization records to public health. A total of 12,554 records with 36,105 immunization doses were sent between April 27, 2015, and April 18, 2017, representing 2,653 unique children. 6,362 (50.6%) of records contained updates. The most common submitter-child relationship was mother (5,297, 83.3%), followed by father (1,034, 16.3%).

In Paper II, there were 63,833 pediatric records created from 2017 to 2021 in CANImmunize met inclusion criteria. The trend for enrollment followed a seasonality pattern, with spikes toward the end of each year. The onset of COVID-19 restrictions was associated with an abrupt and continued decline in enrollment of children on CANImmunize compared to expected values.

In Paper III, a total of 6,801 CANImmunize accounts with 18,243 records (6,862 parents and 11,381 children) met inclusion criteria. After collapsing the dataset, the final sample contained 11,381 unique parent-child dyads.

4.2 Public Health Utility

In Paper I, 530 (20%) of children were less than 12 months old when their record was first submitted to OPH via the Pan-Canadian mobile immunization app. Another 259 (9.8%) were 12-24 months old at first submission. Submissions from traditional methods occur primarily at school-entry, this represented earlier access to pediatric immunization records.

Overall in Paper I, 25,732 (71.2%) of doses were reported more than a year after vaccine administration. When examining doses administered during the study period (10,066), 8,966 (89.0%) were reported within 12 months. For doses administered in the final four months of the study (January-April 2017), 35% (414/1100) were reported on the same day as the vaccine was administered.

In Paper II, 63,833 pediatric records created from 2017 to 2021 in CANImmunize met inclusion criteria. The onset of COVID-19 restrictions was associated with an initial increase in self-reported completion of pneumococcal series, followed by a modest decrease leading to a net effect of -20%, compared to expected values by the end of the study period.

In paper III, a total of 6,801 CANImmunize accounts met the inclusion criteria. After collapsing the dataset, the final sample contained 11,381 unique parent-child dyads. Most observations were from accounts with 3-4 records (68.5%), using iOS devices (61.4%) in English (97.8%) with records from the Province of Ontario (58.4%). Influenza vaccination during the 2018-2019 influenza season was reported for 32.3% of children and 42.0% of parents. In the bivariate analysis, all variables except the number of parents on the account (p 0.77) and account age (p 0.24) were independently associated with reporting children's influenza immunization. In the multivariate logistic regression analysis, parents receiving the seasonal influenza vaccine was most strongly associated with reporting pediatric influenza vaccination (OR 17.05, 95% CI 15.08, 19.28) compared to parents who did not report being vaccinated against influenza that season. Prior parental seasonal influenza vaccination (OR 1.88, 95% CI, 1.57,2.08), prior pediatric influenza vaccination (OR 1.62, 95% CI, 1.40, 1.87) and active PHU integration (OR 1.44, 95% CI 1.25,1.66) were also associated with pediatric influenza vaccination during the study period.

4.3 Applicability

In Paper IV, 159 manuscripts were identified in the systematic search. 12 manuscripts representing 13 empirical studies were included in the systematic review and meta-analysis. The RCTs were published between 2012 and 2016. When comparing digital push interventions to non-digital ones, patients had 1.18 times the odds (95% CI 1.11, 1.25) of receiving vaccination or series completion compared to controls. Analyses had high statistical heterogeneity, but the risk of bias was low. The certainty of evidence for the outcome of vaccine uptake was moderate and very low for the outcome of series completion.

5 Discussion

5.1 Main Findings

There was a paucity of real-world data examining the feasibility and acceptability of using mHealth to collect and report citizen immunization data. Further, the opportunity to utilize this data beyond point-in-time VC assessments to provide insights into trends in vaccination over-time, or insights into associations between individual characteristics and vaccine uptake has not been studied. Finally, it was not known if there was evidence to support the use of multimodal features within mobile apps beyond immunization recording and reporting such as push notifications (for example, from public health to app users) to improve vaccine uptake and series completion.

Through four studies, this thesis provided supportive evidence on the potential to mobile apps to enhance IIS. Paper I showed use of a Pan-Canadian mobile immunization app to provide self-reported immunization data to a local PHU is feasible and acceptable. Increasing timeliness of the reported doses may indicate increasing public health utility of solutions collecting immunization data over time. The volume of data available from users in Papers II and III suggests self-reported data may provide value in the detection of early trends in vaccination uptake and series completion and in exploration of associations between individual and family characteristics with vaccination behaviour. However, results of Paper II may indicate waning feasibility and acceptability during events when vaccination services and reporting may be less available or useful to individuals.

The findings in Paper IV point to the broader applicability of mHealth to improve immunization uptake and series completion through features such as push notifications. However, these are preliminary studies and much more research is needed.

5.2 Findings in context of the existing literature

Paper I described the feasibility, acceptability and public health utility of self-reported immunization data submitted to public health via a Pan-Canadian mobile immunization app. There remains a paucity of literature to compare the results of this study with. A 2020 study examining the feasibility and accuracy of a "computer-assisted self-reporting instrument" to collect history of HPV vaccination concluded it as feasible (99% of

participants were able to submit records), with an average completion time of 10 minutes and accuracy of 84% and negative predictive value of 92% (54). A Master's thesis from the University of Baltimore on the usability study of a mobile app for providing individuals access to their IIS record identified the importance of adding features which enable direct sharing of record updates but does not indicate that work has occurred (181) . It is possible that the lack of literature is in part because of the difficultly of integrating external solutions, such as mobile apps with IIS. Government agencies in Canada offer online forms to "submit or update your vaccine record" which will be reviewed by a healthcare professional (182), but analyses of use and accuracy have not been published. Grey literature was searched but lack of results does not necessarily indicate it is not occurring, but it is not being published in academic journals or elsewhere.

Paper II reported net effect of -20% in self-reported pneumococcal series completion at 13 months of age. This was observed by an immediate increase of 14.6% followed by a monthly decrease of 3.5%. Few studies have reported outcomes related to pneumococcal vaccine uptake in children 2 years of age or less. A study performed in Quebec, Canada reported that at 13 months of age, reported an approximate 10% decrease from March to April 2020, remaining low in May then recovering my August 2020 (183). A study in Italy reported -1.4% in pneumococcal uptake compared to 2019, at 24 months of age (184).

Overall, there is evidence that the COVID-19 pandemic caused a disruption to routine pediatric immunization rates (185–189) although evidence is mixed about the magnitude and duration of the effect (183, 190, 191). Some estimates have global impact on DPT3 at 7.7% lower and MCV1 at 7.9% lower than expected (192). Others show a globally 2.9% decline in DPT3 coverage, with similar results for DTP1 and MCV1 which fell more acutely in early 2020 and have rebounded (193). Other sources report a failure to recover to pre-pandemic uptake rates (191, 194) despite acceptance of vaccination increasing during this time (55). A review of low and middle income countries show a decline of 10–38% for routine childhood vaccines (195). In Europe, countries show varying levels of decline, followed by recovery in VC rates underway (196). Gambia reported no significant change in coverage for both HepB and Penta1 vaccinations, however they did report an increase in 2021 compared to pre-pandemic rates with early delays in vaccine timing (penta1 decreased by 70% in the period before the second wave, HepB dealys by 47%) (197) . A

study in China showed high COVID-19 transmissions periods, or surges were associated with lower rates of timely vaccination in China (198), returning to baseline VC rates in low transmission times.

Overall, there is an understanding that the COVID-19 pandemic has had an impact on routine immunization programs which has called for strategies to recover routine vaccination rates (100) and reports on progress and challenges in recovery (199). The results of Paper II showed the public health utility of using self-reported data as an early warning system of changing trends in vaccine uptake, however, more research is needed.

In Paper III, the multivariate logistic regression analysis showed parents receiving the seasonal influenza vaccine was most strongly associated with reporting pediatric influenza vaccination (OR 17.05, 95%CI 15.08, 19.28). Our results are consistent with other studies in this area. In a US study using the Oregon IIS in the 2010-2011 (and historical seasons) children of immunizing adults were 2.77 times more likely to be immunized for seasonal influenza across all seasons (200). They also found that when adults improved their own behavior and went from nonimmunizing to immunizing, their children were 5.44 times more likely to become immunized for influenza (200). Another study using National Health Interview survey data from 2011-2016 concluded children of adults who received influenza vaccination were 3.83-4.79 times more likely to be immunized for influenza (201).

The reported influenza immunization coverage rate for adults in Paper III was 43%. This is very similar to the PHAC published adult immunization rates for the 2018-2019 (same period) influenza season at 42% however, PHACs VC estimate is based on telephone surveys of 3,737 Canadians between January 21 and February 24, 2019. The national response rate for the survey was 20.1%. Our results are also similar to the US estimates of 37% for 2018-2019 (202) which is lower than previous years (203).

In Paper IV when comparing digital push interventions to non-digital ones, patients had a 1.18 (95% CI 1.11, 1.25) the odds of receiving vaccination or series completion compared to controls. A similar systematic review and meta-analysis, published in 2022 (204), reported that SMS reminders improved odds of improving immunization coverage by (OR = 1.671, 95% CI 1.169, 2.390, p = 0.005). Systematic reviews on digital interventions for vaccine uptake and series completion are still limited and subject to limitations regarding

modality and methodology, for example as described with HPV (205-207). The costs and effectiveness of interventions to improve vaccine coverage remain poorly characterized (208).

mHealth can be used to deliver many forms of interventions which should be considered as part of future research. For example, a study in Iran with children under the age of 1 who were 7 or more days overdue for vaccination identified parents who were randomized to a film had 1.7 the odds of get their child vaccinated compared to those exposed to the same content, but via lecture (209).

5.3 Evaluations in digital health

When considering the findings of this thesis, it is important to contextualize the work within emerging paradigms of digital product evaluations. These products present novel opportunities and challenges in assessing safety and effectiveness. Reviews summarizing evidence on mHealth effectiveness derived from RCTs find a large portion are rated as low quality (210). Common shortcomings are limited follow up periods, lack of standardized control conditions and the presence of nonspecific outcome parameters. These limitations can be attributed to two intrinsic features of mobile apps. First, they are not static and must evolve over time. The process of planning and executing RCTs can be lengthily, by the time the results are known, the technology has either evolved or is outdated. Second, mHealth apps are most often multi-faceted and simultaneously target multiple outcome parameters. This makes ascertaining control groups and specific outcomes difficult. Together, these conditions render the execution of high quality RCTs on the effectiveness and efficacy of mobile health apps almost impossible (109).

There is a need for improved methodological and evaluative approaches which recognize the value of real-world data for mHealth. Several methodologies have proposed to more appropriately evaluate mHealth interventions (211). Many of which share common components, in a non-linear cycle, summarized in the eHealth evaluation cycle (Figure 5) (211).

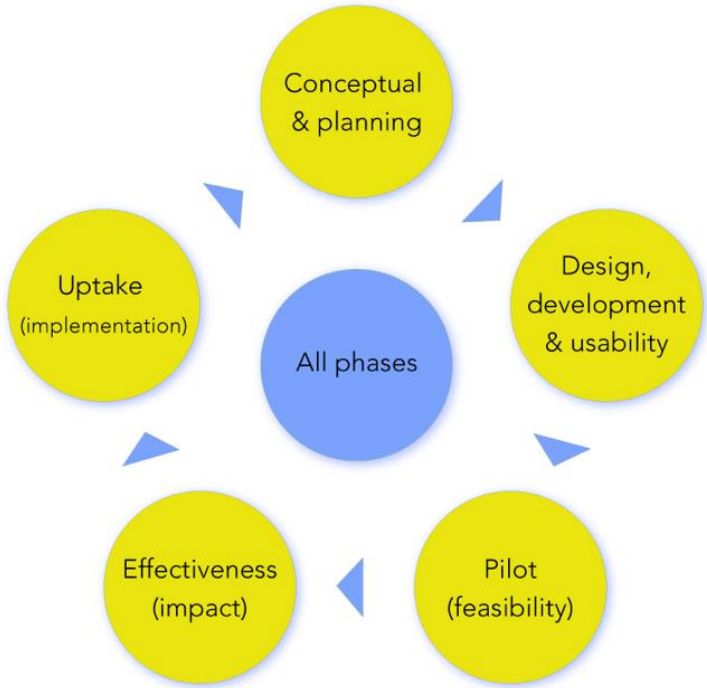

Figure 5 – Common components of proposed eHealth evaluation models, from Bonten et al, 2020 (211)

Instead of following the linear, four phases of clinical evaluation (212), with a capstone RCT followed by post-market surveillance which does not permit changes to the intervention during evaluation, these evaluation cycles are iterative. One such proposed methodology is the "mHealth Agile and User-Centered Research and Development Lifecycle" , developed by Wilson et al (213) which outlines a four stage, non-linear cycle that aims to produce "high-quality apps that solve real problems while also being safe, effective and commercializable".

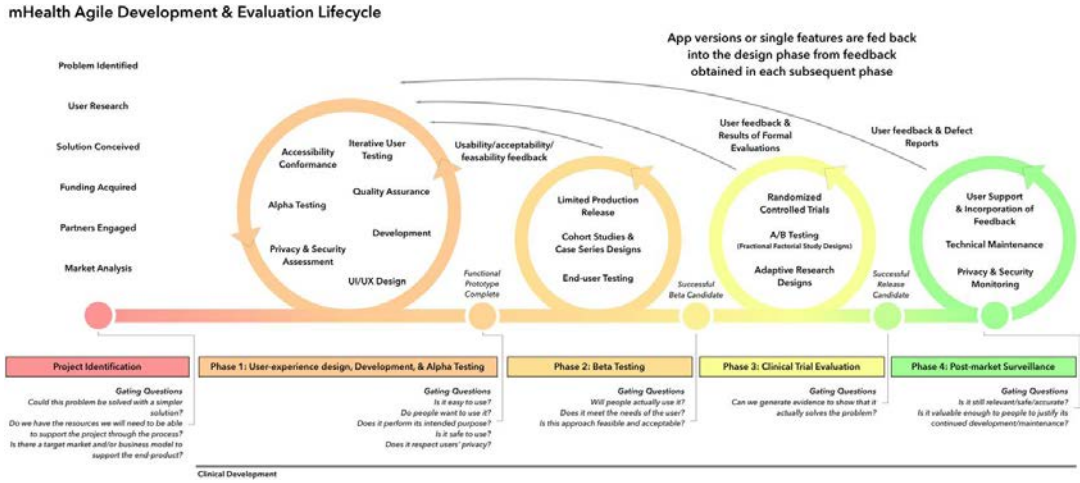

Figure 6 – mhealth Agile Development & Evaluation lifecycle, from Wilson et al, page 46 (213)

This thesis falls into the mHealth Agile Development & Evaluation lifecycle (Figure 6) as follows. Paper I was a limited production release which aligns with Phase II: Beta testing. It answers the question of "will people actually use it? Does it meet the needs of the user? Is this approach feasible and acceptable? Can it be implemented into its intended context? Is there sufficient face validity for this product to solve the challenge at hand?' Studies II-III were also under Phase II, as well as Phase IV. Phase IV answers the questions "Is it still relevant/safe/accurate? Is it valuable enough to justify its continued development/maintenance?".

Papers I-IV have important limitations which are discussed below. However, real-world data in evaluations for mHealth and digital therapeutics(214) are increasingly necessary, more representative and realistic evidence without the time and monetary costs of an RCT (215, 216). To further illustrate the need for evolving evaluations for technology in health, the emergence of adaptive artificial intelligence is a particularly extreme case of these challenges of product evolution and the need to rapidly evaluate these continually evolving products. Regulators are presently attempting to determine the best way to evaluate these solutions as they come to market (217, 218).

5.4 Strengths and Limitations

This thesis had several strengths. Papers I-III were the first evaluations of mobile app enabled, self-reporting of immunizations in a real-world setting. Utilizing empirical, observational data instead of a controlled trial setting more accurately reflects the practical applications of these technologies. Papers I-III also had large numbers of observations and thus, a low likelihood that random error introduces bias in the results presented. Further, confidence intervals were presented as part of any statistical analyses as a control for any random error.

In Papers II and III, data was derived from the CANImmunize Accounts system. In this system, the account holder specifies their relationship to the records they manage (e.g. self, child/dependent, spouse etc.). This allowed Paper III to employ parent-child dyads and explore multiple, self-reported variables including family and parental characteristics with pediatric immunization outcomes.

This thesis has several limitations. First, general limitations will be described then limitations those that are specific to each of Papers I-IV.

The data that comprises Studies I-III cannot be defined as representative of the population in general. Rather, it comes from convenience samples of Pan-Canadian mobile immunization app users which may introduce a form of membership bias. Unfortunately, this type of bias necessitates the recognition of, and then matching or adjustment to effectively mitigate which is not sufficiently characterized in this case (93). These Pan-Canadian mobile app users may not be representative of the general population of Canada (or HIC more broadly) from several perspectives. Without these measurements, we are not able to ascertain how they have impacted our results. First, socioeconomic status (SES) was not ascertained among users. The CANImmunize Privacy Policy limits the collection of data for this purpose, including full postal code which is often used to link household income data from administrative data sets in Canada. However, an early study characterizing a small sample of CANImmunize users at a tertiary care hospital seeking obstetrical care observed 93% had completed a post-secondary degree or diploma (152), indicating that users may be of higher SES compared to the general population. Thus, app users may be more technology literature or are early adopters of technology, which are often associated with higher educational levels and income brackets (219). Assessment of

technology readiness in the studies would have shed light on the magnitude of this effect in the data but this was not done. The effect of higher SES may be exacerbated in Paper I as PHU reporting was available on iOS earlier than Android and iPhone owners ret to have a higher average salary compared to Android users (220). This bias may be present in Papers II and III and be most pronounced in the earlier periods compared to later years when the platform had been publicly available for longer on all platforms.

Second, the users of a Pan-Canadian mobile immunization app may also represent those who are more accepting of vaccination compared to the general population. Studies I-III did not survey users for their baseline vaccination attitudes and beliefs, so it is not able to be confirmed. Finally, although content in the Pan-Canadian mobile immunization app was tailored to a Grade 8 reading level in both French and English, users included in these studies would exclude those who only read and speak languages other than English and French. This may include newcomers to Canada who indicated being open to utilizing a vaccine tracking app if it was translated into their primary language of communication (136).

The third limitation is use of self-reported data and the potential impact of forgery and recall bias on the accuracy of immunization data in this thesis. Paper I-III utilized exclusively self- and parentally reported vaccination data, which was not able to be verified by any clinical records or registry. Lack of controls in the studies may have reduced the impact of recall bias in Papers I-III. Paper IV compiled data from manuscripts where self-report, registry report and a mix of the two methods were utilized. As such, the vaccination data in all studies may have been forged, or subject to recall bias, for vaccinations occurring in the past. The risk of recall bias is greatest when the exposure is rare or when controls are from the community rather from hospitalized patients.

Finally, this thesis was performed by a member of the team that worked on the design, development, deployment, and enhancement the Pan-Canadian mobile immunization app. There is a possibility that this involvement may have introduced a conflict of interest or bias in the interpretation of results. However, given the pace, intricacy, and stakeholder investment in the evolving technology, it would have been extremely difficult to have a truly independent evaluation arm of the project. Each study had authors from multiple

organizations as well as the regulatory oversight from REB, there was likely a minimal risk of bias due to this conflict of interest.

5.4.1 Study Specific Strengths and Limitations

5.4.1.1 Paper I

The study period for Paper I was prior to the release of CANImmunize Accounts. Thus, all data resided directly on the user's device and was sent to the BIS then to OPH via batch reports for re-entry in the DHIR. This limited the ability to decipher the denominators of users that the feature was available to. Google analytics data showed 9,205 CANImmunize users in Ottawa during the study, but at that time, there was no reliable way to determine who had access to the feature and chose not to use it. There were also no methods of measuring privacy concerns regarding transmission of personal health information or technology readiness among users or non-users, thus we were not able to gauge what impact these concerns had on the observed level of uptake. Further, the design of the study did not have a control group comparing the timeliness of reporting immunization data compared to traditional methods of data collection. This limited the ability to ascertain true data utility to public health.

Another limitation in the study design was that over the course of the study the technology was iterated several times. Shortly following the initial feature release, OPH gave the project team feedback that submissions were consistently claiming vaccines were administered on the date they were recommended, based on the child's date and birth and vaccination schedule. After some investigation, it was surmised that users weren't actively correcting the default date when a vaccine is marked as administered, something that the technology permitted. A small patch update was released to modify the user experience such that the date of administration did not *default* to the recommended date when a vaccine was marked as received. Feedback from OPH indicated that following the patch, submissions with this anomaly stopped. While the technology was amended quickly, it is not possible to quantify the extent that this impacted the results of the study. In addition, for most of the study the feature was only available on iOS devices. The feature was only released on Android 3 months before the end of the study resulting in 8.8% of total records sent via Android devices compared to iOS (91.2%). Android was released along with a large app update that added data

validation rules and ability for users to specify trade names (in addition to generic vaccine types) within the app. Since this release was done 3 months before the end of the study, there was limited data regarding trade name use.

The limitation describe above for self-report and forged data is still present in this study but somewhat lessened as the ISPA necessitates parents reporting this data to PHUs by some means. There is no indication that forgery by submission via a Pan-Canadian mobile immunization app would be any more likely than by other methods, but future research should examine this.

5.4.1.2 *Paper II*

Paper II examined the creation of records in the CANImmunize Accounts platform and reported pneumococcal series completion at 13 months of age, beginning in September 2017 and January 2016, respectively. The study used a large dataset with observations over a long period of time which allowed for comparison and monitoring changes in trends for each outcome. As the data was derived from a register, the opportunity for observer bias is diminished (92). However, as a small group interrupted time series it lacked a parallel comparison group. A key limitation of this study was that we were unable to examine the effect of the COVID-19 pandemic on immunization rates by geography or socio-economic status amongst users.

In Paper II, the outcome of enrollment was likely affected by the deployment strategy of CANImmunize accounts. Prior to September 2017, there were more than a hundred thousand existing users of the app that were storing their records on the device. Starting in September 2017, small numbers of users were notified that they could convert to account users by agreeing to a new Privacy Policy and Terms of Use or continue to use the app as-is. If they accepted this invitation and provided informed consent, their records were moved to the Account system. When this transfer occurred, their record creation date was labelled as 2017, not reflective of the actual record creation date.

In 2018, the CANImmunize Accounts functionality was released to the public through the iTunes and Google Play app stores, again in a soft launch capacity. The web component, where users could sign up or sign in to their CANImmunize account via www.canimmunize.ca followed in the weeks and months after. Thus, the expected trend

(forecast) of enrollment behavior may have been affected by the rollout strategy of the CANImmunize Account system. The outcome of series-completion was calculated using the child's date of birth and was unaffected by the Accounts rollout strategy.

5.4.1.3 Paper III

Paper III was a cross-sectional study examining the association between parent/family characteristics and pediatric influenza immunization. Cross-sectional studies are useful for studying the association of exposures and outcomes, but they do not allow for establishment of incidence, rare outcome occurrence or causality between the exposures and outcome. This study design is susceptible to sampling bias, nonresponse bias and recall bias (94). Due to these limitations, Paper III should be interpreted as useful for generating hypotheses and informing areas for future research.

The sample for Paper III was derived by pulling CANImmunize Account data for accounts which contained at least one parent (self or spouse) and one child (child/dependent) record. After considering all inclusion criteria, 6,801 CANImmunize Accounts were included in the study with 6,862 unique parents and 11,381 unique children. To create unique parent-child dyads, the dataset was collapsed by unique child identifier. For accounts that had multiple parental records (n=61), the parental characteristics were averaged and assigned to each child. The result of this approach is well described in Table 1 of the manuscript, but it may have introduced bias into the study findings by dampening the association of certain parental characteristics.

5.4.1.4 Paper IV

Paper IV was the first systematic review and meta-analysis to assess the impact of push interventions on vaccination uptake and series completion. The results of the funnel plot results indicate absence of publication bias. However, there were several limitations in the study. The systematic review and meta-analysis only included RCTs published in peer-reviewed academic journals. As demonstrated by the work of this thesis, RCTs are not always a practical or effective method to evaluate digital interventions holistically.

Studies included in the systematic review and meta-analysis were published between 2012 and 2016. While the technological platforms available at those points in time have

evolved significantly, the mechanism which delivers push notifications remains relevant. Many of the studies were conducted in the USA, with more than half conducted in the same geographic area under a publicly funded special access program. Because the studies were conducted on a CDC Vaccine for Children eligible population, cost barriers weren't present for those included in the studies. Thus, the results may not be as generalizable to other settings where cost remains a concern when accessing vaccines.

Heterogeneity was observed in the meta-analysis, despite conducting subgroup analyses by publication date, population, comparison group and vaccination targeted. This indicates that there may be an underlying difference in the studies which was not measured. This may be a product of the multi-faceted ways that digital interventions target behaviour, as well as being rapidly evolving over the course of the studies as was observed in Studies I-III. Finally, there were only four studies examining series completion which limited the certainty of evidence.

5.5 Implications for research, policy, and practice

It is estimated that in 2022, deaths from measles rose 43% (221) and 85 million children are under-immunized as a result of the COVID-19 pandemic. In 2023 the WHO called for "urgent action" as a 30-fold increase in measles cases were reported in the WHO European Region (222). COVID-19 and the global introduction of digital vaccine certificates likely will herald the broader introduction of digital technologies to help individuals monitor vaccinations and connect with public health systems. There are an increasing number of consumer mHealth apps for immunization being developed and tested worldwide. For example, the PrimaKu application in Indonesia (124) as well as trials underway evaluating app use for COVID-19 vaccination in children (123). Regardless of methodology, future research studies should aim to collect a full set of variables related to social determinants of health, such as the domains proposed by Coss et al (223). Future research should consider measuring participant baseline intention to vaccinate, technology readiness, device used, familiarity with technology and any other factors that could help explain the heterogeneity observed in Paper IV.

In Canada, COVID-19 has highlighted the underlying issues that make it a challenge to collect, share and use health data (224). PHAC has announced the Pan-Canadian Health

Data Strategy to modernize health data collection, sharing and interoperability; streamline and update the approach to privacy and access for the digital age and clarify accountability and health data governance to bring meaningful change in the way governments share health data (224). Funding has been allocated but the work has not been delivered yet. Digital health integration should be accelerated to allow for effective delivery of vaccine, programme monitoring and surveillance (225).

6 Conclusions

Vaccination is an important intervention for reducing morbidity and mortality from VPD worldwide. Public health programs must collect data on VC to determine levels of protection within the community and guide resource allocation for further vaccination campaigns. VC data completeness and utility is a challenge in many settings. Immunization Information Systems have the capacity to be enhanced by consumer mHealth apps including to facilitate bi-directional communications with individuals. T Through four studies, this thesis provided supportive evidence on the potential to mobile apps to enhance IIS. It illustrates that recording and reporting of vaccination status via a Pan-Canadian mobile immunization app is feasible. Engaging citizens using mHealth apps may also offer opportunities to provide early warning signals when external events, such as pandemics, disrupt regular delivery of public health programs. Consumer mHealth reported data can provide insights into familial and parental characteristics affecting vaccination uptake. Lastly, synthesis of available evidence suggests that digital push interventions are effective in improving vaccine uptake and series completion compared to controls. These studies had important limitations but given these potential benefits, further research in this domain is warranted.

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8 Appendix A

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