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Exploring vaccine decision-making to identify and address barriers to vaccine uptake in Ireland

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A thesis submitted to the National University of Ireland, Cork for the degree of

Doctor of Philosophy in the School of Pharmacy

5th April 2020

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Table of Contents

Declaration 12

List of Tables 13

List of Figures 15

Peer-reviewed publications 16

Presentations 18

Oral presentations 18

Poster presentations 18

PhD Education and Training 20

Postgraduate taught modules completed 20

Other training completed 20

Thesis Abstract 21

Introduction 21

Aim 21

Methods 21

Results 22

Conclusion 22

Acknowledgements 23

Chapter 1 Introduction 26

1.1 Vaccination 27

1.2 Immunisation in Ireland 29

1.3 Vaccine decision-making 33

1.4 Vaccine hesitancy: a threat to global public health 35

1.4.1 Convenience 36

1.4.2 Complacency 42

1.4.3 Confidence 42

1.5 Addressing vaccine hesitancy to improve vaccine uptake 50

1.6 Thesis aim and objectives 58

Aim 59

Objectives 59

1.7 Methodological justification 61

1.8 Thesis outline 64

Chapter 2 Microneedle technology for immunisation: perception, acceptability and suitability for paediatric use 67

Author Contributions 68

2.1 Abstract 69

Introduction 69

Aim 69

Methods 69

Results 69

Conclusion 69

2.2 Introduction....71
2.3 Aim....73
2.4 Methods....73
2.4.1 Search strategy....73
2.5 Results....73
2.6 Discussion....75
2.6.1 Perception and acceptability of microneedle technology....76
2.6.2 Perception and acceptability for use in immunisation....77
2.6.3 Perception and acceptability for use in paediatrics....81
2.7 Conclusion....83
2.8 Chapter conclusion and context within thesis....83
Chapter 3 Acceptability of microneedle-patch vaccines: a qualitative analysis of the opinions of parents....85
Author Contributions....86
3.1 Abstract....87
Introduction....87
Aim....87
Methods....87
Results....87
Conclusion....88
3.2 Introduction....89

3.3 Aim....90
3.4 Methods....90
3.5 Results....94
3.5.1 Concern....98
3.5.2 Suitability for paediatric use....99
3.5.3 Potential for parental administration....100
3.5.4 The role of the HCP....102
3.5.5 Special populations....103
3.6 Discussion....104
3.7 Conclusion....109
3.8 Acknowledgements....110
3.9 Chapter conclusion and context within thesis....110
Chapter 4 Views of parents regarding human papillomavirus vaccination: a systematic review and meta-ethnographic synthesis of qualitative literature....111
Author Contributions....113
4.1 Abstract....114
Introduction....114
Aim....114
Methods....114
Results....114
Conclusion....115

Graphical Abstract 115
4.2 Introduction 116
4.3 Aim 117
4.4 Methods 117
4.5 Results 119
4.5.1 Is prevention better than cure? 121
4.5.2 The fear of the unknown 122
4.5.3 Limited knowledge and understanding 123
4.5.4 Complex vaccination decisions 123
4.5.6 Parental responsibility 125
4.6 Discussion 127
4.6.1 Implications and contribution: HPV vaccine crisis 131
4.8 Acknowledgements 132
4.9 Chapter conclusion and context within thesis 132
Chapter 5 A systematic approach to map the adolescent human papillomavirus vaccine decision and identify intervention strategies to address vaccine hesitancy 134
Author Contributions 136
5.1 Abstract 137
Introduction 137
Aim 137

Methods....137
Results....137
Conclusion....138
5.2 Introduction....138
5.3 Aim....140
5.4 Methods....140
5.4.1 Ethical approval....140
5.4.2 Data collection....140
5.4.3 Data analysis....141
5.5 Results....142
Theoretical Domains Framework....142
Application of the BCT Taxonomy and identification of potential intervention functions....150
5.6 Discussion....153
5.7 Conclusion....156
5.8 Acknowledgements....156
5.9 Chapter conclusion and context within thesis....156
Chapter 6 Identifying intervention strategies to improve HPV vaccine decision-making using behaviour change theory....157
Author Contributions....158
6.1 Abstract....159

Introduction 159

Aim 159

Methods 159

Results 159

Conclusion 160

6.2 Introduction 161

6.3 Aim 163

6.4 Methods 163

6.4.1 Stage 1: Understanding the behaviour [210] 163

6.4.2 Stage 2: Identifying intervention options [210] 166

6.4.3 Stage 3: Identifying intervention content and implementation options 166

6.4.4 Ethical approval 166

6.5 Results 167

6.3.1 Stage 1: Understanding the behaviour [210] 167

6.3.2 Stage 2: Identifying intervention options [210] 174

6.3.2 Stage 3: Identifying content and implementation options [215] 174

6.6 Discussion 179

6.7 Conclusion 185

6.8 Acknowledgements 185

6.9 Chapter conclusion and context within thesis 185

Chapter 7 *Is the HPV vaccine for me?* Video-based behavioural intervention associated with improved HPV knowledge and intention to vaccinate 186

Author Contributions.....187

7.1 Abstract 188

Introduction 188

Aim 188

Methods.....188

Results.....188

Conclusion.....189

7.2 Introduction.....190

7.3 Aim.....192

7.4 Methods 192

7.4.1 Ethical approval 192

7.4.2 Intervention development.....193

7.4.3 Intervention evaluation 194

7.5 Results 198

7.5.1 Outcomes.....200

7.6 Discussion 202

7.7 Conclusion 207

7.8 Acknowledgements 207

7.9 Chapter conclusion and context within thesis 207

Chapter 8 Discussion and Conclusion 209

8.1 Discussion 210

8.2 Summary of findings 210

8.3 Interpretation and implications of findings 213

8.3.1 Fear as a barrier to vaccine uptake [36] 214

8.3.2 Knowledge as a variable barrier to vaccine uptake 216

8.3.2 Implications for practice 218

8.3.3 Implications for policy 220

8.4 Strengths and limitations 223

8.5 Recommendations for future work 227

Appendices 230

Appendix 4.1 231

Inclusion and exclusion criteria 231

Appendix 4.2 232

Sample search strategy 232

Appendix 4.3 233

ENTREQ Statement 233

Appendix 4.4 235

Individual study characteristics 235

Appendix 4.5 239

Quality appraisal of included studies.....239

Appendix 4.6.....242

Occurrence of concepts and sub-themes.....242

Appendix 4.7.....247

First (italicised) and second (non-italicised)-order interpretations 247

Appendix 5.1.....254

Recruitment poster.....254

Appendix 5.2.....255

Informed Consent for Research Participants 255

Appendix 5.3.....256

Informed Consent Form.....256

Appendix 5.4.....257

Focus group topic guide.....257

Appendix 5.5.....258

Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [380]

.....258

Appendix 5.6.....260

Participant characteristics 260

Appendix 6.1.....261

TDF-based interview topic guide 261

Appendix 6.2.....262

Purposive sampling strategy and recruitment 262

Appendix 6.3.....263

Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [389].

.....263

Appendix 6.4.....265

Characteristics of interview participants (n=13) 265

References.....266

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Signed:  **Date:** 5th April 2020

Sarah Marshall

List of Tables

Table 1 Primary childhood and school immunisation programmes 30

Table 2 State of Vaccine Confidence in the EU 2018: results from Ireland [118] 43

Table 3 Definitions of intervention functions [210].....56

Table 4 Definitions of policy categories [210].....56

Table 5 Literature search inclusion and exclusion criteria.....74

Table 6 Focus group topic guide 93

Table 7 Participant demographics 95

Table 8 Focus groups: DEIS status, gender breakdown and duration 96

Table 9 Themes and sub-themes and their occurrence in each focus group.....96

Table 10 Intervention functions identified by applying the TDF and BCTT(v1) to the study findings [204].....151

Table 11 Potential Interventions Strategies to reduce HPV vaccine hesitancy [204] 152

Table 12 Intervention functions and BCTs identified using the TDF, the COM-B model and the BCW [11, 14-16].....175

Table 13 Potential intervention strategies to reduce vaccine hesitancy [11] 177

Table 14 Theoretical Domains Framework (TDF) Domains identified through qualitative research [5] 191

Table 15 Behaviour Change Techniques (BCT) identified through qualitative research [5] 192

Table 16 Intervention objectives and associated Behaviour Change Techniques (BCTs) [215] 193

Table 17 Baseline participant demographics 199

Table 18 Knowledge Assessment Scores at W0 and W2 201

List of Figures

Figure 1 Immunisation uptake at 12 months of age in Ireland (HPSC).....32

Figure 2 Immunisation uptake at 24 months of age in Ireland (HPSC).....32

Figure 3 Immunisation uptake at 4-5 years of age in Ireland (HPSC) 33

Figure 4 Immunisation uptake at 12-13 years of age in Ireland (HPSC) 33

Figure 5 The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines [50].....35

Figure 6 Theoretical Domains Framework [204] 53

Figure 7 The COM-B model [204].....54

Figure 8 The Behaviour Change Wheel [204] 55

Figure 9 Thesis outline 66

Figure 10 PRISMA flow diagram of search strategy.....74

Figure 11 Prototype, placebo microneedle-patch & magnifying glass given to participants at the outset of focus groups.....92

Figure 12 Themes, sub-themes and associated exemplar quotes.....97

Figure 13 PRISMA flow diagram of search strategy.....120

Figure 14 Developing the line of argument 126

Figure 15 Conceptual Model.....127

Figure 16 HPV and HPV vaccine knowledge questionnaire 196

Figure 17 Participant flow diagram.....198

Figure 18 Knowledge Assessment Scores at W0, comparing Control and Intervention groups.....200

Figure 19 Knowledge Assessment Scores at W2, comparing Control and Intervention groups.....201

Publications

Peer-reviewed publications

- Marshall S, Sahm LJ, Moore AC. Microneedle technology for immunisation: Perception, acceptability and suitability for paediatric use. Vaccine. 2016;34(6):723-34. doi: http://doi.org/10.1016/j.vaccine.2015.12.002 [1]

  Impact: As of September 2019, this article has been cited 21 times in peer-reviewed publications.

- Marshall S, Sahm LJ, Moore AC. The success of microneedle-mediated vaccine delivery into skin. Human vaccines & immunotherapeutics. 2016;12(11):2975-83. doi: http://doi.org/10.1080/21645515.2016.1171440 [2]

  Impact: As of September 2019, this article has been cited 51 times in peer-reviewed publications.

- Marshall S, Fleming A, Moore A, Sahm L. Acceptability of microneedle-patch vaccines: A qualitative analysis of the opinions of parents. Vaccine. 2017;35(37):4896-904. doi: http://doi.org/10.1016/j.vaccine.2017.07.083 [3]

  Impact: As of September 2019, this article has been cited 4 times in peer-reviewed publications.

- Marshall S, Fleming A, Moore A, Sahm L. Views of parents regarding human papillomavirus vaccination: a systematic review and meta-ethnographic synthesis of qualitative literature. Research in Social and Administrative Pharmacy.2018;15(4):331-337.

  doi: http://doi.org/10.1016/j.sapharm.2018.05.013 [4]

Impact: As of September 2019, this article has been cited 8 times in peer-reviewed publications.

- Marshall S, Sahm L, Moore A, Fleming A. A systematic approach to map the adolescent human papillomavirus vaccine decision and identify intervention strategies to address vaccine hesitancy. Public Health. 2019;16(177):71-79. doi: http://doi.org/10.1016/j.puhe.2019.07.009 [5]

Presentations

Oral presentations

- Views of parents regarding human papillomavirus (HPV) vaccination: a systematic review and meta-ethnographic synthesis of qualitative literature. British Society for Colposcopy and Cervical Pathology Annual Scientific Meeting, Manchester. 30th April – 2nd May 2018.

Poster presentations

- A systematic approach to map the HPV vaccine decision and identify intervention strategies to address vaccine hesitancy. International Health Conference, Oxford. 26th-28th June 2019.
- Acceptability of the human papillomavirus (HPV) vaccine among Irish adolescents. British Society for Colposcopy and Cervical Pathology Annual Scientific Meeting, Manchester. 30th April – 2nd May 2018.
- Knowledge, attitudes and beliefs of parents regarding human papillomavirus (HPV) vaccination: systematic review and meta-ethnographic synthesis. New Horizons in Medical Research, Cork. 7th December 2017.
- Systematic review and meta-ethnographic synthesis protocol: opinions on HPV vaccination. 12th Cochrane Ireland Conference, Galway. 26th May 2017.
- Acceptability of microneedle-patch vaccines: a qualitative analysis of the opinions of parents. 39th All-Ireland Schools of Pharmacy Conference, Cork. 24th – 25th April 2017.

- Acceptability of microneedle-patch vaccines: a qualitative study into the opinions of Irish parents. Health Services Research and Pharmacy Practice Conference, Nottingham. 10th – 11th April 2017.
- Microneedle-patch vaccines: a study into the opinions of Cork city parents. New Horizons in Medical Research, Cork. 8th December 2016.

PhD Education and Training

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  9th and 16th April 2019.

- Qualitative Synthesis and Systematic Reviews Workshop, Professor James Thomas, National University of Ireland, Galway.

  26th May 2017.

- Introduction to Systematic Review and Meta-Analysis, John Hopkins University.

  16th April 2017.

- "It started with a tweet" Workshop, Professor Claire Anderson, University of Nottingham.

  11th April 2017.

Thesis Abstract

Introduction

Vaccination is one of the greatest public health achievements of the last century. However, vaccine uptake rates worldwide remain sub-optimal. The vaccine decision-making process is complex and multifaceted and multiple barriers to vaccine uptake have already been identified. However, these barriers are highly variable and context specific. Therefore, there is an urgent need to identify and address the factors contributing to decreasing vaccine uptake in Ireland.

Aim

The aim of this doctoral research was to explore vaccine decision-making in order to identify, and address, barriers to vaccine uptake in Ireland.

Methods

Multiple approaches were used to address this aim. A comprehensive literature review, and subsequent qualitative research, involving parents sought to understand if and how microneedle technology could impact vaccine decision-making and vaccine uptake. In addition, a systematic review and meta-ethnographic synthesis of the qualitative literature and a series of qualitative studies, involving both adolescents and parents, sought to gain an insight into the HPV vaccine decision-making process, to identify barriers to vaccine uptake. This culminated in the development and evaluation of a theory and evidence-based intervention, involving parent-daughter dyads.

Results

The vaccine decision-making process was explored qualitatively, in a series of studies, involving multiple stakeholders. Factors such as perception of disease risk, trust in healthcare system, and to a lesser extent, knowledge, interact to impact vaccine decision-making, in the midst of variable, yet omnipresent vaccine safety concerns.

Conclusion

This thesis has provided a comprehensive overview of vaccine decision-making and has identified the barriers to vaccine uptake perceived by key stakeholders. These identified barriers may be addressed by policy-makers and vaccinators, to enhance vaccine uptake in Ireland.

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Chapter 1 Introduction

1.1 Vaccination

Vaccination is one of the greatest public health achievements of the last century and is estimated to save up to three million lives per annum worldwide [6]. According to the World Health Organisation (WHO) a vaccine is a biological preparation that improves immunity to a particular disease [7]. Vaccines act by initiating an innate immune response, which in turn activates an antigen-specific, adaptive immune response [8]. The latter is characterised by a diverse set of specialised cells known as lymphocytes which recognise and eliminate the pathogen [8]. The antigens contained in a vaccine can induce cell-mediated immunity by activating specific subsets of T lymphocytes, and humoral immunity by stimulating antibody production by B lymphocytes [8]. These antibodies persist in circulation and memory B cells are generated, that can rapidly and more efficiently reactivate upon subsequent exposure to repeat antigenic challenge [8]. This immunological memory, mediated by B and T cells, is the basis of long term protection and the goal of vaccination [9].

Vaccination is often regarded as an individual intervention with a wider public health impact [10]. By vaccinating one individual, protection can be conferred to a wider group, through the phenomenon of 'herd effect': the indirect protection of unvaccinated individuals, whereby an increase in the prevalence of vaccine immunity prevents circulation of pathogens in unvaccinated, susceptible populations [11, 12]. There are several groups within society that cannot be safely or effectively vaccinated (e.g. infants, immunocompromised, and immunosuppressed) [13]. The most effective mode in which these vulnerable

individuals can be protected against common infections is through herd protection, achieved by high vaccination rates. The threshold required for herd immunity varies by disease, but it typically ranges between 80 and 90% vaccination of the target population [14, 15].

Vaccines are generally divided into three main types: live attenuated, inactivated, and subunit [16]. Live attenuated vaccines contain pathogens that have been weakened, altered or selected to be less virulent than their wild-type counterparts [9]. Examples of live attenuated vaccines include; rabies, measles, mumps, tuberculosis, yellow fever and vaccinia virus, the latter arguably the most successful human vaccine to date, resulting in the eradication of smallpox in 1980 [16, 17]. These are highly immunogenic and can induce memory with minimal doses. Inactivated vaccines, as the name suggests, are produced by inactivating preparations of whole pathogens by heat, radiation, or chemical treatment (e.g. formaldehyde). This process destroys the pathogen's ability to replicate and cause disease, but maintains its immunogenicity [9]. Examples of inactivated vaccines include typhoid, cholera, plague, whole-cell pertussis (WCP), rabies and hepatitis A [9, 16]. Some of these vaccines, such as WCP, are highly immunogenic as they retain all of the immune stimulating proteins contained in the virulent form of the microbe. Finally, subunit vaccines contain selected fragments of the pathogens, presented as antigens. Antigenic fragments include proteins, toxoids, virus-like particles (VLP), polysaccharides, and polysaccharide conjugates [9]. Examples of subunit vaccines include tetanus toxoid, inactivated split and subunit influenza, acellular pertussis, pneumococcal polysaccharide, and VLP human papillomavirus (HPV) vaccines [9]. Subunit vaccines require immune stimulants or adjuvants, to

enhance the magnitude and duration of the immune response. As the majority of childhood vaccines are of the subunit variant, multiple doses are required to generate sufficient immunity to disease and may require periodic booster doses to counter waning immunity over time. The seasonal influenza vaccine is unique in that it requires repeated annual dosing due to changes in circulating pathogens each year (i.e. antigenic shift and drift [18]).

1.2 Immunisation in Ireland

The substantial protection offered by vaccination has led to recommendations for routine immunisation from birth to old age. In Ireland, the Health Service Executive (HSE) is responsible for the implementation of the primary childhood and school immunisation programmes, outlined in Table 1. An inspection of the immunisation schedules shows that the majority vaccines are administered in the first months of life. Between birth and 13 months; babies are recommended to get 14 vaccines, with additional doses up to the age of five years, including both single and combination vaccines (

Table 1). Combination vaccines offer protection against multiple diseases in a single product (e.g. 6-in-1, MMR) (Table 1). These products have numerous benefits: simplified immunisation schedules; fewer injections; reduced trauma; higher rates of compliance with complex vaccination schedules [19, 20]; improved vaccine coverage [21]; and timely vaccination [21]. Adolescents are recommended to receive a booster vaccine (i.e. Tdap), as well as MenC and HPV vaccines. Primary childhood and school immunisation programme vaccines are free of charge [22], and parental consent is required for children to be vaccinated. In addition, the

seasonal influenza vaccine is strongly recommended for children aged six months and over with long term health conditions (e.g. chronic respiratory disease, diabetes mellitus, and neurodevelopmental disorders) and/or those who are immunosuppressed.

Table 1 Primary childhood and school immunisation programmes

Programme	Age	Vaccine	Location
Primary childhood	2 months	6 in 1 + MenB + PCV + Rotavirus	GP surgery
	4 months	6 in 1 + MenB + Rotavirus	
	6 months	6 in 1 + PCV + MenC	
	12 months	MMR + MenB	
	13 months	Hib (booster)/MenC + PCV	
School immunisation	4-5 years	MMR + 4 in 1	School
	12-13 years	MenC* + Tdap	
	12-13 years	HPV (girls only[#])	

6 in 1: Diphtheria, Haemophilus influenza b (Hib), Hepatitis B, acellular Pertussis, inactivated Polio, Tetanus
MenB: Meningococcal B conjugate
PCV: Pneumococcal conjugate
MenC: Meningococcal C conjugate
MMR: Measles, Mumps, Rubella
4 in 1: Diphtheria, Tetanus, Pertussis, Polio
MenC*: From September 2019, the MenC vaccine administered at 12-13 years will be replaced by the MenACWY vaccine
Tdap: Tetanus, low dose diphtheria, low dose pertussis
HPV: Human papilllomavirus
[#]From September 2019, the HPV vaccine will be offered to both girls and boys in Ireland

While vaccination is recommended, it is voluntary in all cases. Vaccinators in Ireland include general practitioners (GPs), GP surgery practice nurses, community health doctors and public health nurses. More recently, pharmacists have been introduced as vaccinators and can administer influenza, pneumococcal polysaccharide (PPV23) and herpes zoster (zoster/shingles) vaccines as a private service.

The National Immunisation Advisory Committee (NIAC) is an independent committee of the Royal College of Physicians in Ireland (RCPI), that produces and routinely updates the National Immunisation Guidelines, based on best evidence regarding the safety and efficacy of vaccines, the disease burden, and

pharmacoeconomic analyses [23]. The committee then provides expert, impartial guidance to the Chief Medical Officer in the Department of Health. The Health Protection Surveillance Centre (HPSC) is Ireland's specialist agency for the surveillance of communicable diseases, collating data and reporting on the uptake of vaccines provided through the primary childhood and school immunisation programmes. Immunisation uptake statistics are presented in Figure 1-4. The European Region of the WHO recommends that, on a national basis, at least 95% of children are immunised against vaccine-preventable diseases and those targeted for elimination, or control [24] (e.g. diphtheria, tetanus, pertussis, polio, Haemophilus influenza b, measles, mumps and rubella). While a minority of the recommended vaccines have reached this 95% target (Figure 2), the uptake of the majority remains sub-optimal. In line with the Centre for Disease Control and Prevention's (CDC) Healthy People 2020 recommendations, the national target for HPV vaccination in Ireland is 80% [25]. Figure 4 illustrates the significant and rapid decline of HPV immunisation, leading to a 50% vaccine uptake in 2016-17 [26].

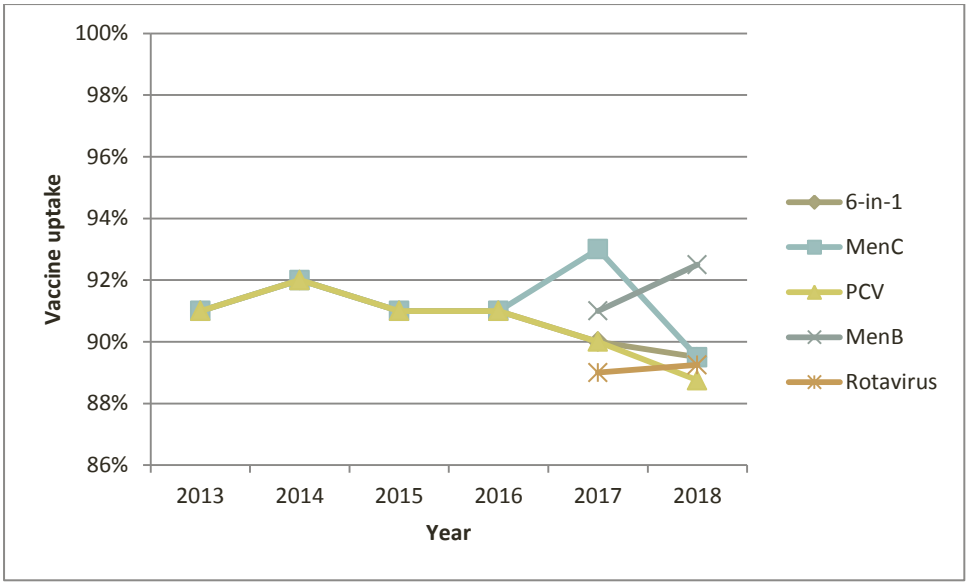


Figure 1 Immunisation uptake at 12 months of age in Ireland (HPSC)

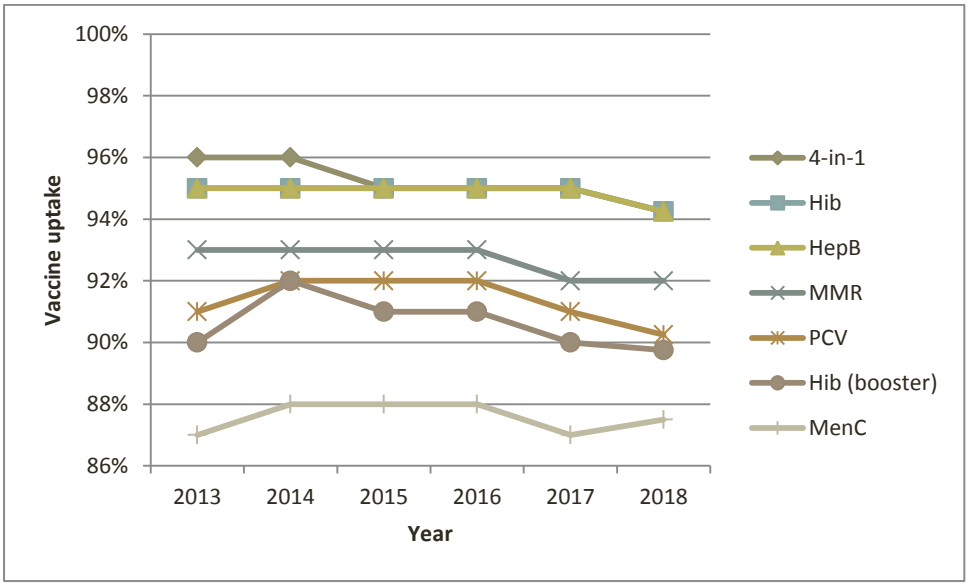


Figure 2 Immunisation uptake at 24 months of age in Ireland (HPSC)

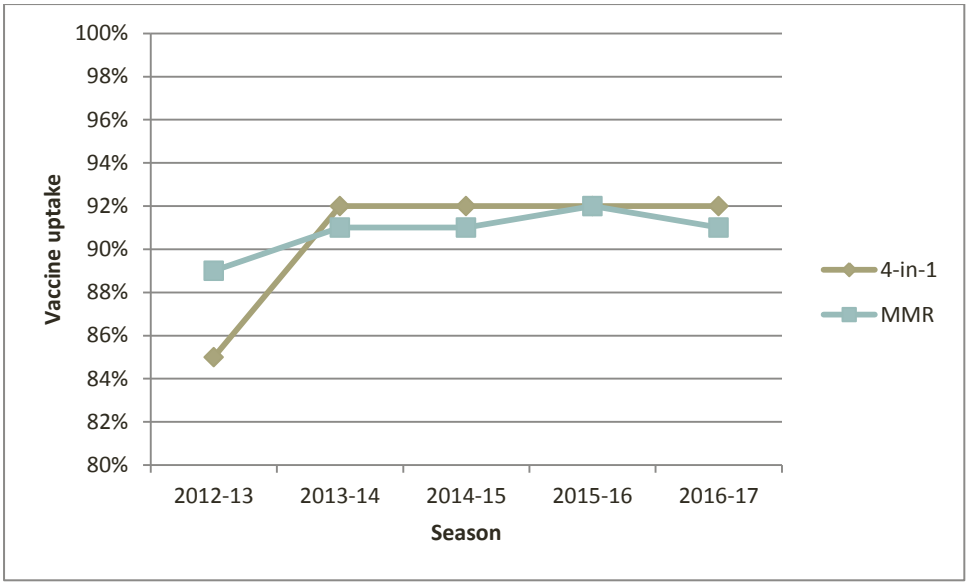


Figure 3 Immunisation uptake at 4-5 years of age in Ireland (HPSC)

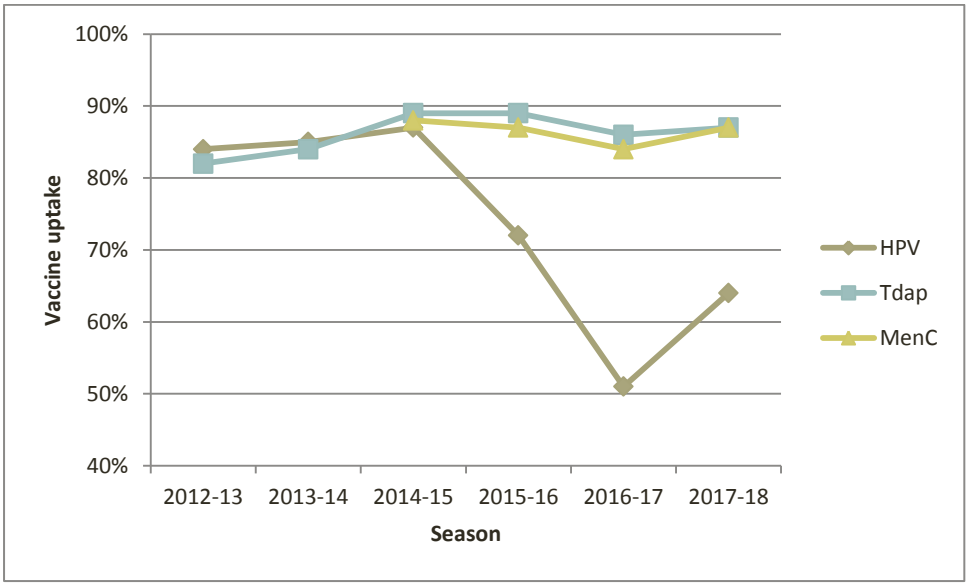


Figure 4 Immunisation uptake at 12-13 years of age in Ireland (HPSC)

1.3 Vaccine decision-making

Parental vaccine decision-making is complex and multi-dimensional. Experiences, emotions, routine ways of thinking, information sources, peers/family, risk perceptions, and trust have been shown to inform the decision-making process [27]. An individual's decision to vaccinate depends on a subjective assessment of

the benefits and costs of vaccinating [28]. Vaccination provides both personal and societal benefits. Personal benefits include protection and disease prevention [9]. The perceived personal benefit depends on the perceived risk, and the personal impact of potentially contracting the disease [28]. Societal benefits of vaccination include the attainment of herd immunity and reduction in the levels of disease, morbidity and mortality, as well as pharmaeconomic & economic benefits [10]. However, vaccination generates personal costs, broadly defined to include monetary and non-monetary individual costs. Monetary costs include the cost of the vaccine [29-31], inconvenient time or place of vaccination [29-31], or perceived time pressure [32]. Non-monetary costs include adverse effects [33, 34], safety concerns [33, 35], fear of injection [36-38], concerns that the vaccine itself could cause the disease [28], and difficulties in accessing vaccine providers due to distance or appointment delays [33, 39]. In recent years, informed decision-making has garnered much attention in the context of childhood vaccination [40]. Decisions are classified as informed when decision-makers have relevant knowledge about the subject, and the decision reflects the attitudes of the decision-maker [41]. In addition, the consequences of the decision should be deliberated [42]. Parental decision on child vaccination is a specific case of health-related decision [43, 44]. Research has identified two types of parental decision-making: non-deliberate and deliberate [45, 46]. Non-deliberate or automatic decisions are characterised by passive adherence [47]. These decisions are made rapidly, under a certain set of circumstances: when parents perceive vaccination as routine and comply with recommendations; when parents feel that they do not have a choice; and/or when parents use social norms as a heuristic (cognitive shortcut) for their decision-

making [42, 45]. In contrast, deliberate or conscious decisions are characterised by enlightened conformism [47] and are made when parents consider the advice or experience offered by others; when parents are affected by beliefs about social judgement; and/or when parents weigh up the perceived benefits and costs of vaccination [45]. Low perceived benefits and/or high costs drive the phenomenon known as vaccine hesitancy [28].

1.4 Vaccine hesitancy: a threat to global public health

Vaccine hesitancy has been defined as "the delay or refusal of vaccination despite the availability of vaccine services" [36, 48]. This definition depolarises the "pro" or "anti" vaccine stance [49]. In reality, vaccine-hesitant individuals are a heterogeneous group in a continuum, ranging from total acceptance to complete refusal [49] (Figure 5).

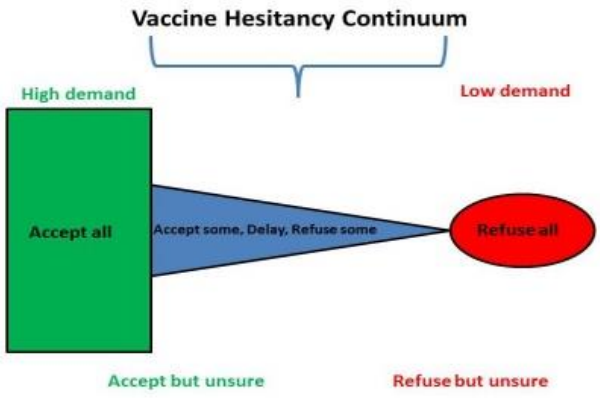


Figure 5 The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines [50]

Figure 5 demonstrates how these hesitant individuals may accept some vaccines, while refusing others, delay vaccination, or accept vaccines but remain apprehensive [49, 51]. Vaccine hesitancy is "*highly variable, and context specific, varying across time, place and vaccines involved*" [36, 48, 50]. It is a multi-layered

phenomenon, related to prior beliefs about vaccines [52, 53], perceived benefits of vaccines [54], attitudes towards vaccines [55, 56], previous experiences with vaccines [57], socioeconomic status [58], number of children [59], and marital status [58]. Peretti-Watel *et al* have proposed to define vaccine hesitancy as a decision-making process, that depends on people's level of commitment to healthism/risk culture and on their level of confidence towards health authorities and mainstream medicine [47]. Despite extensive findings, research suggests that there are still factors that need to be identified and explored, due to the highly variable and context specific nature of the phenomenon [49, 60, 61]. Three key drivers of vaccine hesitancy have been identified and include convenience, complacency and confidence [48, 50].

1.4.1 Convenience

Vaccine convenience is a significant factor when uptake is affected by physical availability, affordability and/or willingness to pay, geographical accessibility, ability to understand, and appeal of immunisation services [48]. Physical availability, affordability and willingness to pay, and geographical accessibility are factors associated with vaccination monetary costs, as previously discussed. Vaccine availability can be a key issue in low and middle-income countries (LMIC), primarily due to issues such as cold storage or administration [62]. In general, recommended vaccines are readily available in high-income countries (HIC), such as Ireland. One notable exception is the Bacillus Calmette-Guérin (BCG) vaccine. The BCG vaccine was introduced in the 1950s, for the prevention of tuberculosis. However, on a number of occasions, routine vaccination has had to be temporarily suspended, due

to vaccine shortages and inability to secure sufficient supply [63, 64]. In light of the ongoing issues with the supply of BCG vaccine, it is imperative that available vaccines are used efficiently, for maximal benefit. Due to a decline in national tuberculosis incidence, many European countries have ceased universal vaccination programmes, the majority moving towards a policy of selective vaccination of individuals deemed high risk. This approach reduces demand for the vaccine and ensures that those at highest risk of infection are prioritised for immunisation. A Health Technology Assessment (HTA) has supported the adoption of selective BCG vaccination [65]. Therefore, the HSE has been requested to undertake a review of the epidemiology of tuberculosis in Ireland, considering the public health impact of protracted BCG shortages. This review will inform an updated recommendation to the Department of Health regarding future provision of BCG vaccination.

Childhood and adolescent vaccine uptake in Ireland remains predominantly unaffected by factors such as affordability and willingness to pay. This is due to the free provision of vaccines through local health offices, GP surgeries, and schools. School-based immunisation programmes take advantage of compulsory school attendance, while minimising logistical and time constraints for vaccinators and parents alike [66]. Vaccine uptake, however, may be impacted by the ability to understand recommendations. This ability depends on both language, and health literacy. Health literacy is a multifaceted concept that deals with the capabilities of individuals to meet the complex demands of health [67]. According to the Sørensen Integrated Model, health literacy is 'linked to literacy and entails people's knowledge, motivation, and competence to access, understand, appraise, and apply health information in order to make judgements and decisions in everyday life,

concerning healthcare, disease prevention, and health promotion to maintain or improve quality of life' [68]. Research has demonstrated that limited health literacy is associated with undesirable health outcomes, including poorer overall health status [69], increased rates of hospitalisations [70], mortality [71], and healthcare costs [72]. Limited health literacy has also been associated with reduced adoption of preventive behaviours such as immunisation, possibly due to the complexity of the information and multiple steps involved [73].

1.4.1.1 Microneedle technology: addressing ease of administration and vaccine availability

Vaccines are conventionally administered using a hypodermic needle [74]. This form of administration provides a rapid and direct method of vaccine delivery. Despite familiarity, widespread use and proven efficacy, the hypodermic needle is associated with phobia, pain and significant anxiety [75-78]. The fear of needles can delay or result in avoidance of medical procedures such as vaccination [79]. According to Johnson *et al*, in a nationally representative population of US adults, 19% did not receive a pneumococcal vaccine and 20% did not receive a tetanus vaccine due to needle dislike [80]. In a survey of 100 US physicians, 71%, 71% and 69% indicated that needle fear was a contributing factor to avoiding tetanus, influenza and pneumococcal immunisation, respectively [80]. In a Canadian study, noncompliance with immunisation primarily due to needle fear occurred in 8% of children and 7% of parents, and this degree of noncompliance was positively associated with the degree of fear [37]. In an Australian study of general practice

patients, more than 64% of those with needle fear would avoid influenza immunisation, compared with nearly 20% of those without needle fear [81].

Although needle fear is acknowledged as a contributor to vaccine hesitancy, there is a paucity of research to address this concern [82], in particular the issue of the needle itself [83]. One suggested novel approach to replace typical injection procedures and mitigate needle fear, involves microneedle technology [79]. Microneedles can be 1µm in diameter and range from 50µm to 1000µm in length [84]. They can penetrate the outermost skin barrier layer, the *stratum corneum*, creating transient pathways for minimally invasive transcutaneous delivery [85]. It is reported that microneedles can facilitate delivery without stimulating the pain receptors and blood vessels that lie beneath, thus being perceived as painless and associated with a reduction in bleeding [74, 86, 87]. Other advantages of microneedle-mediated delivery include avoidance of first pass metabolism; potential for highly targeted administration to individual cells [86, 87]; improved patient compliance [88]; dose sparing [89, 90]; and potential for self-administration. There are four types of microneedles: solid, coated, hollow, and dissolving. Solid microneedles create transient micropores in the *stratum corneum*, thereby increasing permeability of this barrier layer. When the vaccine is applied onto the treated surface, it diffuses into the skin (from a loaded patch or semi-solid formulation) through the pores created by microneedle pre-treatment. In spite of immunogenicity [91, 92], the popularity of solid microneedles has reduced in recent years, potentially due to the requirement for a multi-step administration process [2]. An advanced iteration of solid microneedles was the development of coated devices. Solid microneedles are pre-coated with a vaccine in a formulation suitable

for coating and dissolution [74], thus resulting in a one-step delivery process. The vaccine coated microneedles are inserted into the skin, where dissolution of the vaccine occurs. Hollow microneedles provide a pre-defined conduit for vaccine delivery into the skin or other tissue, similar to hypodermic needles. Currently there are two hollow microneedle designs: a single microneedle or mini-needle, which mimics the conventional hypodermic needle [93] or an array of multiple microneedles [89, 94]. The latter permits the application of a vaccine formulation over a wider area of the skin. Hollow microneedle-mediated delivery of a bolus can result in higher bioavailability and, depending on the volume injected into the skin, can increase the likelihood of lymphatic uptake of presented antigens [95]. Vaccines may be delivered by passive diffusion through the microneedle. Conversely, a syringe may be attached to the microneedle, permitting active vaccine delivery. The final, most advanced and complex microneedle is the dissolvable microneedle patch. These patches are the most attractive microneedle platform for delivery of vaccines. Reasons for this choice include but are not limited to: higher dose-loading and improved efficiency of vaccine delivery into skin compared to coated microneedles, enhanced stability outside of cold-chain, and lower costs of materials. These vaccine delivery systems are based on a patch loaded with vaccine-containing microneedles. When placed on the skin, the microneedles pierce the skin and subsequently dissolve, releasing the vaccine into the body. These biodegradable microneedles are manufactured with the vaccine embedded in a formulation that permits vaccine stabilization on drying and dissolution on application and insertion [74, 96-99]. However, unlike hollow microneedles, a limitation is placed on the amount of vaccine that can be incorporated into the

system [100]. It is also important to ensure that microneedles rapidly dissociate from their adhesive backing so that the vaccine is delivered efficiently, irrespective of wear-time [99]. Microneedle technology for immunisation has been shown to have greater acceptability when compared to traditional hypodermic injection [101, 102]. Therefore it may be hypothesised that this increased acceptability could improve immunisation compliance and potentially increase vaccine uptake.

Microneedle technology may also address issues of vaccine availability, especially in LMIC, where a cold-chain infrastructure is almost prohibitively expensive, thus preventing adequate vaccine distribution [103, 104]. The thermostability of certain microneedle platforms eliminates cold-chain requirements [105-107], thus reducing logistical costs and potentially improving distribution [105-107]. This thermostability would permit stock-piling in regular drug distribution networks, combatting the frequently encountered issue of supply shortage [2]. In addition to being thermolabile, conventional vaccines often require administration by trained personnel. In LMIC countries, there are shortages of medical personnel at all levels of training [108]: Africa has 2.3 healthcare workers per 1000 population, compared to 24.8 per 1000 in the Americas [109]. Therefore, the potential for self-administration associated with microneedle technology could further improve vaccine coverage and availability in these countries [101, 110-112]. A recent narrative review collated the primary scientific literature pertaining to microneedle-mediated *in vivo* vaccination programmes [2], compiling vaccination strategies in six different models, which tested a wide range of vaccines against viral, bacterial and protozoan pathogens. Microneedle-mediated vaccines have demonstrated safety and immunogenicity in pre-clinical and clinical settings [2]. However, the adoption

of the technology as a tool to improve vaccine uptake and reduce hesitancy, will depend on end-user acceptability (e.g. HCPs, vaccinees, parents), which requires further investigation.

1.4.2 Complacency

Complacency "exists where perceived risks of vaccine-preventable diseases are low and vaccination is not deemed a necessary preventive action" [48]. Due to the effectiveness of vaccines, health risks associated with vaccine preventable diseases are perceived as low, which leads to the cognitive bias against the decision to vaccinate [113], and feelings of invulnerability [114]. Refusing a vaccine and experiencing no negative repercussions can in turn, reinforce decisions not to get vaccinated in the future [115]. If alternative life or health priorities are perceived as more important, or if impaired self-efficacy prevails, i.e. the self-perceived or actual ability to take action to vaccinate [113], complacency may increase.

1.4.3 Confidence

Confidence is defined as; the trust in the effectiveness and safety of vaccines, the system that delivers them (i.e. the reliability and competence of the health services and healthcare providers (HCPs), and the motivations of policy makers (who ascertain vaccine need) [48]. Negative vaccine safety sentiment is a global issue [116]. A recent report, conducted by the Wellcome Trust, summarised the results of a quantitative survey of public attitudes towards health, including vaccines, in more than 140 countries [117]. Globally, 79% of people agree that vaccines are safe [117]. In high-income regions this figure is lower: 72% in North America, 73% in Northern Europe, 59% in Western Europe, and 50% in Eastern Europe [117]. In

France, one in three people disagree that vaccines are safe, the highest percentage for any country worldwide [117]. In low-income regions, the proportion tends to be much higher, with highs of 95% of people in South Asia and 92% in Eastern Africa. In Ireland, 94% of the 1000 respondents had heard of vaccines and 91% agreed that vaccines are important for children to have. However, a decreased number (87%) agreed that vaccines are effective, and 74% agreed that vaccines are safe. Additionally, more than 1000 members of the Irish public were included in the State of Vaccine Confidence in the European Union (EU) 2018 report [118] (Table 2).

Table 2 State of Vaccine Confidence in the EU 2018: results from Ireland [118]

Vaccine survey statements	% of respondents in agreement with survey statements	Ireland's confidence ranking
Vaccines are important for children to have	90.4	14
Vaccines are effective	88.8	12
Vaccines are safe	84.9	10

While the majority of Irish respondents included in both reports recognised the importance of immunisation for their children, a decreased number were confident in the safety and efficacy of vaccines [117, 118]. Therefore, an effort is required to identify and address safety and efficacy concerns, to improve vaccine confidence.

Misinformation is a key factor contributing to, and amplifying issues of confidence [28, 119]. Misinformation has been categorised into several levels and occurs when information is actively shared with the intention to mislead [28]. The most harmful of these levels occurs when HCPs (i.e. perceived vaccine experts) propagate exaggerated or unfounded vaccine concerns [120]. The most notorious example of this level of misinformation was the publication by the now disgraced former doctor Andrew Wakefield, purporting to demonstrate a link between autism and

the MMR vaccine [121]. Mr Wakefield was found guilty of deliberate fraud, undisclosed and serious conflicts of interest [122] and was banned from practicing medicine in the UK due to a "callous" disregard for children in the course of his research (medical records of at least 10 of the 12 children in the Lancet paper were falsely reported) [122-124]. In spite of the publication being retracted and the revocation of his medical license, Mr Wakefield persists in his campaign against the vaccine [125]. Expert consensus has suggested that his persistence has contributed to prevailing vaccine concerns and refusals [125]. In turn, these refusals have contributed to gaps in vaccination cover and a reduction in herd immunity. Consequently, reported measles cases worldwide spiked in 2017, with multiple countries experiencing severe and protracted outbreaks, resulting in an estimated 110,000 deaths [126]. Based on 2018 data, the WHO has withdrawn the measles-free status of four European countries (i.e. UK, Greece, the Czech Republic and Albania), representing an ongoing cause for concern [127]. Vaccine misinformation is emotive and tends to be rapidly disseminated by traditional and digital media sources [128]. This spread can lead to a crisis of confidence and vaccine instability, where instability is defined as a sudden drop in vaccine coverage, often as a result of a vaccine safety scare [115].

1.4.3.1 Anti-vaccine activism

Anti-vaccine activism has been in existence for more than 200 years [129]. Online tactics used by those who are against vaccination tend to fall into four distinct areas: they skew the science; they shift hypotheses; they censor dissent; and they attack critics [130]. They tell a highly emotive story, in contrast to the messages

from official sources, which tend to be factual, cryptic, and forgettable [131]. First-person testimonies by alleged victims or their parents are commonly used, harnessing the recognised psychological finding that anecdotes about a single individual are often more influential that large population statistics [132, 133]. In addition, negative experiences are easier to perceive than the main benefits of vaccination, the absence of disease [134]. Anti-vaccine groups discredit expert authority, sometimes sourcing whistle-blower doctors or vaccine researchers, who claim an expansive cover-up of information by pharmaceutical companies conspiring with governments [135, 136]. These anti-vaccine stories elicit an emotional response, as well as an increased perception of vaccine-related risks [119], an increased mistrust of vaccine efficacy, accompanied by a suspicion of authority, including health services, HCPs, the pharmaceutical industry and policy-makers [137]. Even though anti-vaccine websites are of lower quality [138], they prominently appear in search-engine results [139]. In addition, the recognition that vaccine-hesitant individuals are more active in searching for information on the internet than their vaccine-compliant counterparts [36], further confounds the issue.

1.4.3.2 HPV vaccine instability

HPV is a group of more than 100 viruses, and is one of the most common sexually transmitted viral infections worldwide, with initial infections typically occurring soon after sexual debut [140, 141]. Although the majority of infections are transient, persistent infection is a pre-requisite for pre-cancerous lesions and malignancies [142]. HPV is responsible for approximately 4.5% of global cancer

disease burden [142, 143]. The infection is also associated with cancers of the oropharynx, anus, rectum, penis, vulva and vagina and is responsible for anogenital warts in men and women [143]. On average, 538 cases of HPV-related cancers were diagnosed in Ireland between 2010 and 2014 [143]. Of these, 75% were in women [143]. Overall rates of HPV-related invasive cancers are increasing: in the ten year period leading up to 2014, there was a 2% increase in the rate of HPV-related invasive cancers per year, for both sexes in Ireland [143]. A recent clinical audit of oropharyngeal cancer cases, diagnosed between 2014 and 2018 in Ireland, found a 37% increase in cases, when compared to data recorded by the National Cancer Registry Ireland (NCRI) between 2009 and 2013 [143]. Approximately half of these were thought to be attributed to HPV [143]. Furthermore, a significant number of pre-cancerous lesions occur in Ireland annually. The most significant pre-cancerous lesions are high grade cervical intraepithelial neoplasia (CIN2/3), with 8,885 new cases being diagnosed between September 2015 and August 2016 in Ireland [143]. In addition, anogenital warts are common, with almost 7,500 cases associated with HPV estimated to occur in Ireland each year [143]. Three vaccines are licensed and marketed for use to prevent HPV infections and their sequelae: the bivalent vaccine Cervarix®, which contains HPV 16 and 18 antigens [144]; the quadrivalent Gardasil®, containing HPV 6, 11, 16 and 18 antigens [145] and; the nonavalent Gardasil® 9, containing HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antigens [146]. The vaccines are intended to be administered to adolescents, before the onset of sexual activity. The reason for this recommendation is two-fold: (i) it ensures that the vaccinee is HPV naïve; and (ii) bridging studies demonstrated that adolescents display superior immune responses to HPV antigens compared to adults [143]. Since the first license

in 2006, more that 270 million doses of HPV vaccines have been distributed globally and at least 82 countries have included these vaccines in their national immunisation programmes [147]. In Ireland, the HSE has offered the quadrivalent vaccine to all girls in the first year of second levels schools, vaccinating more than 240,000 girls since 2010 [148]. There is high grade evidence that HPV vaccines protect against cervical pre-cancer [149], with significant decreases in vaccine-type HPV in vaccinated women [150]. A recent systematic review of efficacy demonstrated that the quadrivalent Gardasil vaccine is associated with a 90% or greater reduction in persistent HPV infection, anogenital warts, CIN, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN), in HPV-naïve women [143]. In addition, HPV vaccines have been shown to reduce abnormal screening tests, colposcopies and excisions [151]. This reduction in diagnostic and therapeutic procedures not only lowers healthcare expenditure [151, 152] but also improves health, whilst reducing negative psychological effects on the women involved [153].

More recently there has been a focus on HPV vaccine safety, linking the vaccines to 'new onset chronic diseases' and 'medically significant conditions' [141, 143, 154]. Reported chronic diseases and significant conditions include Guillain–Barré syndrome, stroke, appendicitis, seizure, syncope, migraine, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency, primary ovarian failure and venous thromboembolism, among many others [141, 143]. However, the safety of the HPV vaccines is well established [155, 156], and extensive research has consistently reported that there is no difference in the rate of serious adverse events or deaths between individuals who receive the

HPV vaccine and participants who receive a placebo or control vaccine [143, 149, 155, 157-159]. This literature supports the position of the WHO's Global Advisory Committee on Vaccine Safety (GACVS) [160], the European Medicines Agency (EMA) [161] and several country-level regulatory agencies in the US [162, 163], the UK [164] and pooled data from Denmark and Sweden [165, 166]. Despite the availability of extensive reassuring safety data, media attention has continued to focus on misinformation. In Ireland, these case reports were broadcast on television in December 2015 and propagated extensively on social media [167]. A support group was established by parents who believed their daughters had been adversely affected by the HPV vaccine (Reactions and Effects of Gardasil Resulting in Extreme Trauma; REGRET). Whilst there may have been other contributing factors, it is likely that this misinformation was a significant factor in the decrease in HPV vaccine uptake across all areas of Ireland to an estimated 51% in 2016/17, down from 87% in 2014/15 (Figure 4) [26, 168]. Similar crises have been observed in several countries worldwide, including Denmark and Japan. Immediately following the vaccine's launch in Denmark in 2009, the HPV vaccine was received positively, with over 90% vaccine uptake [169]. From 2013 onwards, the immunisation programme has been challenged by an increase in the number of reported suspected adverse events, leading to increased media interest and attention. This was further affected by the release of a similar documentary in 2015, describing a group of girls with a range of disabling symptoms, presumed to follow vaccination. After this, vaccination rates declined to 54% [169]. Similarly in Japan, the HPV vaccine was included in the national immunisation programme in April 2013 [170]. However, just two months later, the Ministry of Health, Labour

and Welfare announced a “suspension in the proactive recommendation for routine use of the vaccine” [170]. This suspension has not been revoked and HPV vaccine uptake decreased from 70% in 2013, to a current rate of less than 1% [171].

A reactive response to the HPV vaccine crisis by the National Immunisation Office (NIO) in Ireland led to the formation of cross-sectoral alliances. The NIO is government funded and is responsible for managing vaccine procurement and distribution, and developing training and communication materials for the public and HCPs. The HPV Vaccination Alliance was launched, with leadership from the NIO. This alliance consists of a group of more than 35 different organisations (e.g. Irish Pharmacy Union, Irish Cancer Society, and Irish College of General Practitioners), working in a variety of areas (e.g. medicine and health, women’s rights, child protection) that are committed to raising HPV vaccine awareness. In 2017, an information campaign was launched and featured vaccinated adolescents. This campaign was supported by the HPV vaccination Alliance, the HSE, the Department of Health and the Minister for Health [172]. This collaborative effort is likely to have contributed to the increase in the first dose uptake to an estimated 64% (from 51% in 2016/17) in 2017/18 (Figure 4) [167]. It should be noted however, that a substantial variation in uptake is seen by area; ranging from just 40% uptake in Kerry, to 74% uptake in South Dublin East [172]. This variation requires further investigation at local level, to guide intervention development to improve vaccine uptake and maintain positive momentum to decrease morbidity and mortality from HPV-related infections and sequelae [167].

1.5 Addressing vaccine hesitancy to improve vaccine uptake

There is an urgent need for the development of interventions to address sub-optimal vaccination uptake among those experiencing uncertainty about vaccines [45, 173-176]. Vaccine hesitancy is receiving unprecedented global attention, stimulated by the WHO identifying it as a priority issue [177] and declaring it one of the top ten threats to global health in 2019 [178]. It is well established that changing behaviour is complex, and a systematic approach is required to understand the factors that influence vaccine hesitancy and uptake. In general, providing information alone does not change behaviour [179, 180]. Instead, one must gain an insight into the knowledge, beliefs, attitudes and current behaviours of the target audience, and the environmental context in which they occur [28]. The European Centre for Disease Prevention and Control (ECDC) has developed a catalogue of 40 interventions, to diagnose and address vaccine hesitancy [181]. Diagnostic tools have been designed to measure or monitor vaccine hesitancy e.g. the Global Vaccine Confidence Index [182], the Vaccine Confidence Scale [183], and the Parent Attitudes About Childhood Vaccines survey [51]. Dialogue-based interventions to address vaccine hesitancy include: individual-level interventions focusing on parents; interventions focusing on improving HCPs' confidence and communication skills to respond to vaccine hesitant patients; and community-level interventions [181]. Determinants targeted include: general vaccine hesitancy, misinformation, perceived benefits, safety issues, religious and philosophical views, and trust [181].

Behaviour change has been shown to be more effective when interventions are based on principles drawn from evidence and theories of behaviour change [184].

Behaviour change theory is a broad term for a set of pre-specified ideas or predications aimed at explaining behaviour [185-187]. These theories have emerged from multiple disciplines including psychology, sociology and behaviour economics and identify multiple determinants or components of behaviour [188]. A substantive body of research, including both primary studies and syntheses, has identified the effectiveness of theory-based interventions targeting change in real world contexts [189-191]. Examples of such theories include the Health Belief Model (HBM), and the Theoretical Domains Framework (TDF). The HBM was developed initially in the 1950s by social psychologists to explain widespread under-participation in programmes to prevent and detect disease [192, 193]. The model was later extended to assess individual's responses to symptoms [194], and their behaviours in response to a diagnosed illness, such as medication adherence [195]. The HBM contains several primary constructs that predict why an individual will take action to prevent, to screen for, or to control an illness or condition: perceived susceptibility; perceived severity; perceived benefits; perceived barriers; cue to action; and self-efficacy [193]. 'Perceived susceptibility' refers to beliefs about the likelihood of getting a disease or condition. 'Perceived severity' refers to the seriousness of contracting an illness or leaving it untreated and includes an evaluation of both medical and clinical consequences (e.g. pain, death, and disability) and potential social consequences (e.g. impact on social, family and work life). 'Perceived benefits' refers to the effectiveness of the actions available to reduce disease threat. Conversely, 'perceived barriers' refers to the negative aspects of these available actions. Research has demonstrated that combined levels of susceptibility and severity provide the energy, or force, to act and the perception

of benefits (minus barriers) provide a preferred path of action [193]. Cue to action describes the stimulus needed to trigger the decision-making process to accept a recommended health action. These cues can be internal (e.g. symptom) or external (e.g. advice from others, and media coverage). Self-efficacy is defined as the conviction that one can successfully execute the behaviour required to produce the outcome(s) [196] and was added to the model in 1988 [197]. The HBM's effectiveness in predicting and explaining behaviour has been well documented in a series of meta-analyses [198-201]. In addition, the model has been used to inform the development of interventions to improve health behaviours [202]. However, there are several limitations of the HBM, which limit its utility in public health interventions: the important roles of impulsivity, habit, self-control, associative learning, emotional processing are not addressed [203, 204], contributory factors in the vaccine decision-making process.

The TDF provides a systematic and theoretical basis for understanding and changing behaviour. The framework simplifies 33 psychological theories relevant to behaviour change into 128 constructs (component parts of theories), that were sorted into 14 validated domains [205, 206]. These 14 validated domains are: (1) knowledge, (2) skills, (3) social/professional role and identity, (4) beliefs about capabilities, (5) optimism, (6) beliefs about consequences, (7) reinforcement, (8) intentions, (9) goals, (10) memory, attention and decision processes, (11) environmental context and resources, (12) social influences, (13) emotion, and (14) behavioural regulation. These domains include individual-level, social, and environment and resource factors, prompting the consideration of a wide range of influences [207]. The TDF has been applied across a wide range of healthcare

settings and clinical behaviours, with a range of objectives e.g. to process evaluations of randomised controlled trials (RCT) [208], to guide the identification of behaviour change techniques (BCT) [209] and to design broader intervention strategies [210]. Several methodological approaches have been used in its application including interview [211, 212] and questionnaire studies [213, 214]. While the TDF has been used primarily in the context of health to understand behaviour at the individual level, it can also be used in a variety of contexts to understand behaviour at the organisational and community level and to identify external factors influencing behaviours [204]. The capability, opportunity, motivation model of behaviour (COM-B) further distils the TDF domains into three sources that interact to predict behaviour. These sources are the individual's capability, motivation and opportunity for the behaviour [204] (Figure 6).



Figure 6 Theoretical Domains Framework [204]

The central tenet of the model is that for any behaviour to occur there must be: capability to do it, opportunity for the behaviour to occur; and sufficiently strong

motivation to undertake the behaviour [204]. Each of these components may be divided heuristically into two distinct types. Capability may be physical (i.e. having the physical skills, strength, or stamina) or psychological (having the knowledge, psychological skills, strength, or stamina). Opportunity may be physical (i.e. what the environment facilitates in terms of time, triggers, or resources) or social (i.e. interpersonal influences, social cues, or cultural norms). Motivation may be reflective (i.e. self-conscious deliberation) or automatic (i.e. processes involving desires, impulses, or reflex responses) [204]. These components interact, as illustrated in Figure 7.



Figure 7 The COM-B model [204]

The COM-B model forms the central component of the Behaviour Change Wheel (BCW) [210]. Within 19 frameworks for classifying behaviour change interventions, intervention functions and policy categories were discerned to construct the BCW (Figure 8).

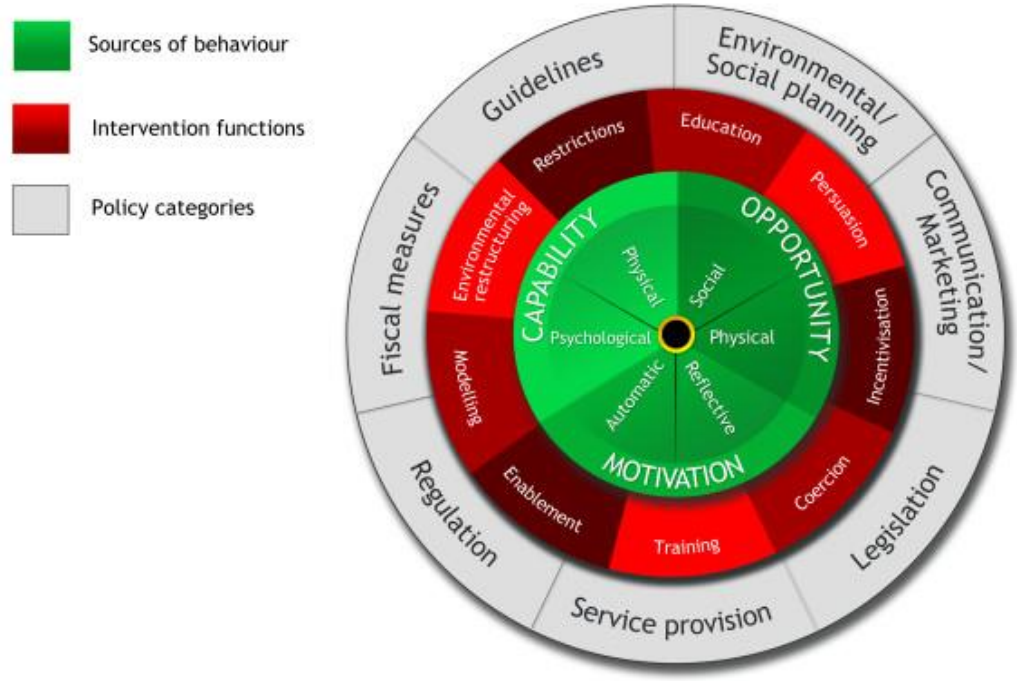


Figure 8 The Behaviour Change Wheel [204]

Nine intervention functions are specified in the BCW and mapped onto the COM-B domains: (1) education, (2) persuasion, (3) incentivisation, (4) coercion, (5) training, (6) restriction, (7) environmental restructuring, (8) modelling, and (9) enablement [210]. These intervention functions were then linked to seven policy categories: (1) communication/marketing, (2) guidelines, (3) fiscal, (4) regulation, (5) legislation,

(6) environmental/social planning, and (7) service provision. Definitions of these intervention functions and policy categories are provided in Table 3 and Table 4.

Table 3 Definitions of intervention functions [210]

Intervention functions	Definition
Education	Increasing knowledge or understanding
Persuasion	Using communication to induce positive or negative feelings or stimulate action
Incentivisation	Creating expectation of reward
Coercion	Creating expectation of punishment or cost
Training	Imparting skills
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or to increase target behaviour by reducing the opportunity to engage in competing behaviours
Environmental restructuring	Changing the physical or social context
Modelling	Providing an example for people to aspire to or imitate
Enablement	Increasing means/reducing barriers to increase capability or opportunity

Table 4 Definitions of policy categories [210]

Policy categories	Definition
Communication/marketing	Using print, electronic, telephonic or broadcast media
Guidelines	Creating documents that recommend or mandate practice
Fiscal	Using the tax system to increase or reduce the financial cost
Regulation	Establishing rules or principles of behaviour or practice
Legislation	Making or changing laws
Environmental/social planning	Designing and/or controlling the physical or social environment
Service provision	Delivering a service

A corresponding Behaviour Change Technique Taxonomy (v1) has also been developed, to standardise the content and reporting of intervention studies [204, 215]. This taxonomy includes 93 BCTs organised into 16 groups [215]. A BCT is defined as “an active component of an intervention designed to change behaviour” [204]. BCTs have been identified in relation to specific behaviours such as physical activity, healthy eating, smoking, and alcohol use [216-219]. Therefore the BCW is unique in that it not only identifies which components need to change for the target behaviour to occur but its association with the BCTTv1 also provides

guidance on the strategies and techniques that can be used to modify the behaviour [204, 215]. For this reason, the BCW (and TDF) was chosen to guide intervention design in this research.

1.6 Thesis aim and objectives

The previous discussion described how the vaccine decision-making process is complex and multifaceted, and that several barriers to vaccine uptake have already been identified. However, these barriers are highly variable and context specific. Therefore, there is an urgent need to identify and address the factors contributing to decreasing vaccine uptake in Ireland. In this doctoral research, I undertook multiple approaches to address this need.

Microneedle-mediated vaccines have demonstrated safety and immunogenicity [2]. However, the adoption of the technology as a tool to improve vaccine uptake and reduce hesitancy, will depend on end-user acceptability. Therefore, I first sought to understand if and how microneedle technology could impact vaccine decision-making and vaccine uptake. In the process of this qualitative exploration into microneedle technology, the issue of HPV vaccine instability spontaneously emerged as a discussion point within the parent focus groups. These participants would be asked to make a decision about the HPV vaccine within several years and their concern was palpable. The 2015 conduct of this research coincided with the downturn of HPV vaccine uptake and the broadcast of a documentary on a popular national television station. The participants in this documentary argued that their children not only presented with postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS), but with many other cluster symptoms, including seizures, chronic pain, syncope, sleep disorders, menstrual disorders, ovarian cysts, pancreatitis, and premature ovarian failure [220]. Similar confidence crises were observed in several countries worldwide including Japan

[221], Denmark [222], and France [223]. Therefore I reactively responded to the research findings and sought to gain an insight into the HPV vaccine decision-making process, in a series of stakeholders, to explore and identify barriers to vaccine uptake.

Aim

- To explore vaccine decision-making in order to identify, and address, barriers to vaccine uptake in Ireland.

Objectives

Three specific objectives were defined in order to achieve this aim:

1. To generate an evidence-base, describing the perception and acceptability of vaccination.
    - Review the literature on the perception, acceptability and suitability of microneedle technology for paediatric immunisation (Chapter 2).
    - Systematically review the qualitative literature on the views of parents regarding HPV vaccination (Chapter 4).
2. To ascertain the knowledge, attitudes and beliefs of key stakeholders to elucidate vaccine decision-making and to identify barriers to vaccine uptake in Ireland.
    - To investigate the knowledge, attitudes and beliefs of parents about microneedle-patch vaccines (Chapter 3).
    - To investigate the knowledge, attitudes and beliefs of female adolescents about HPV vaccination (Chapter 5).

- To investigate the knowledge, attitudes and beliefs of parents of female adolescents about HPV vaccination (Chapter 6).

3. To design, develop and evaluate a theory-based intervention to improve knowledge and intention to vaccinate.
    - To evaluate participants' baseline knowledge (Chapter 7).
    - To assess the impact of the intervention on participants' knowledge and intention to vaccinate (Chapter 7).
    - To assess participants' satisfaction with the intervention (Chapter 7).

1.7 Methodological justification

A mixed methods approach was chosen for this research based on the overall aim of the thesis and the complexity of the topic of interest [224]. Mixed methods research has been defined as an approach or methodology: focussing on research questions that call for real-life contextual understandings, multi-level perspectives, and cultural influences; employing rigorous quantitative research assessing magnitude and frequency of constructs and rigorous qualitative research exploring the meaning and understanding of constructs; utilising multiple methods (e.g. interviews and intervention trials; intentionally integrating or combining these methods to draw on the strengths of each; and framing the investigation within philosophical and theoretical positions [225]. It was determined that neither the positivist, quantitative approach nor the constructivist or post-positivist, qualitative approach alone, is adequate to develop multiple perspectives and a complete understanding of the current research question [225, 226]. Quantitative research is deductive, associated with a belief that reality can be measured and observed directly. Strengths of quantitative research include its procedures to minimise confounding and its ability to generate generalisable findings, if samples involved are sufficiently large and representative. However this quantitative approach is less suited to generating hypotheses to explain complex social or cultural phenomena [226]. Qualitative research is inductive, associated with a belief that there are multiple realities shaped by personal viewpoints, context and meaning. It provides a rich description of views and beliefs and permits hypotheses to emerge from the data [226]. High quality qualitative research can generate robust theory that is

applicable to contexts both within and without the study area, guiding practitioners and policy-makers [227]. However, for research that aims to direct impact practice and policy, qualitative research findings can be limited by small sample sizes necessary for in-depth exploratory work and the subsequent lack of generalisability [226]. Mixed methods research has the ability to harness the strengths and counterbalance the limitations of both approaches [226, 228-231]. Research has identified several advantages of this approach: it enables researchers to simultaneously address exploratory and confirmatory research questions, evaluating and generating theory at the same time; it enables researchers to provide more robust inferences than a single method or reality; and it provides an opportunity to produce a greater assortment of divergent and/or complimentary views [231]. In mixed methods research, methodological issues arise that must be anticipated [225]. Because multiple forms of data are being collected and analysed, mixed methods research requires extensive time and resources to carry out the multiple steps involved [225]. For exploratory sequential design, sampling issues arise, related to deciding what results from the initial phases to include in the follow-up phases, choosing samples and estimating reasonable sample sizes for both phases, and interpreting results from both phases [232, 233]. However, evidence in the published literature attests to the current use of mixed methods approaches in health-related research, such as cardiology [234], pharmacy [235], and public health [236].

This methodological approach is in keeping with the research paradigm of pragmatism that served as the philosophical approach to this thesis. A pragmatic perspective draws on using the most appropriate research method, using diverse

approaches, and giving primacy to the importance of the research problem and question, valuing both objective and subjective knowledge [237, 238].

The primary purpose of using mixed methods in this thesis was *development* i.e. using results from one method to inform the use of the other [226]. The overall aim of this thesis was to explore vaccine decision-making to identify and address barriers to vaccine uptake in Ireland. As with other areas of healthcare research, its undertaking is inherently complex, and to generate sufficient understanding, mixed methods are required [224]. An exploratory sequential design was adopted, beginning with a qualitative exploration followed by a quantitative follow-up [225]. The first step in this research involved a narrative (Chapter 2), and systematic (Chapter 4), review of the literature, to identify the current evidence base and to identify knowledge gaps that should be addressed in this thesis. The findings in these reviews informed the development of the individual studies that formed the thesis. Qualitative research methods (focus groups and interviews) were used to investigate the knowledge, attitudes and beliefs of stakeholders: parents and adolescents (Chapters 3, 5 and 6). The findings of this exploratory qualitative data collection were used to design a quantitative instrument, which was administered to a sample of the population, in a feasibility study (Chapter 7).

While the research design uses a mixed methods approach, a 'composite analysis' approach is applied to discussing the findings [239]. This approach recognises that the analysis is composed of independent parts, but that the whole is greater than the sum of these parts [239]. Therefore the qualitative and quantitative studies are presented and published independently, and their key findings are inter-related in

the discussion, in a manner that respects their unique characteristics, and exploits their potential to yield complementary insights [239].

1.8 Thesis outline

This thesis consists of eight chapters, which provide a thorough and detailed investigation on vaccine decision-making in an Irish setting. Figure 9 provides an overview of the thesis and demonstrates how the aim and objectives are addressed by the individual studies undertaken as part of this doctoral research.

Chapter 1 This chapter introduces the research topic and defines the overall aim and objectives of the thesis.

Chapter 2 This chapter presents the findings of a narrative literature review on the perception, acceptability and suitability of microneedle technology for paediatric immunisation (Paper 1).

Chapter 3 This is a qualitative, focus group study undertaken with parents to explore the knowledge, attitudes and beliefs about microneedle-patch vaccines for paediatric immunisation (Paper 2).

Chapter 4 This chapter presents the findings of a systematic review on the views of parents regarding HPV vaccination (Paper 3).

Chapter 5 This is a qualitative, focus group study undertaken with female adolescents to explore the knowledge, attitudes and beliefs about HPV vaccination (Paper 4).

Chapter 6 This chapter presents the findings of a qualitative, interview study undertaken with parents of female adolescents to explore their knowledge, attitudes and beliefs about HPV vaccination.

Chapter 7 This chapter describes the design of a theory and evidence-based intervention to improve vaccine knowledge and intention to vaccinate. It also presents an evaluation of the intervention.

Chapter 8 The final chapter of this thesis presents the overall discussion, taking into consideration the key findings from each study that comprises the thesis (Chapters 2 to 7).

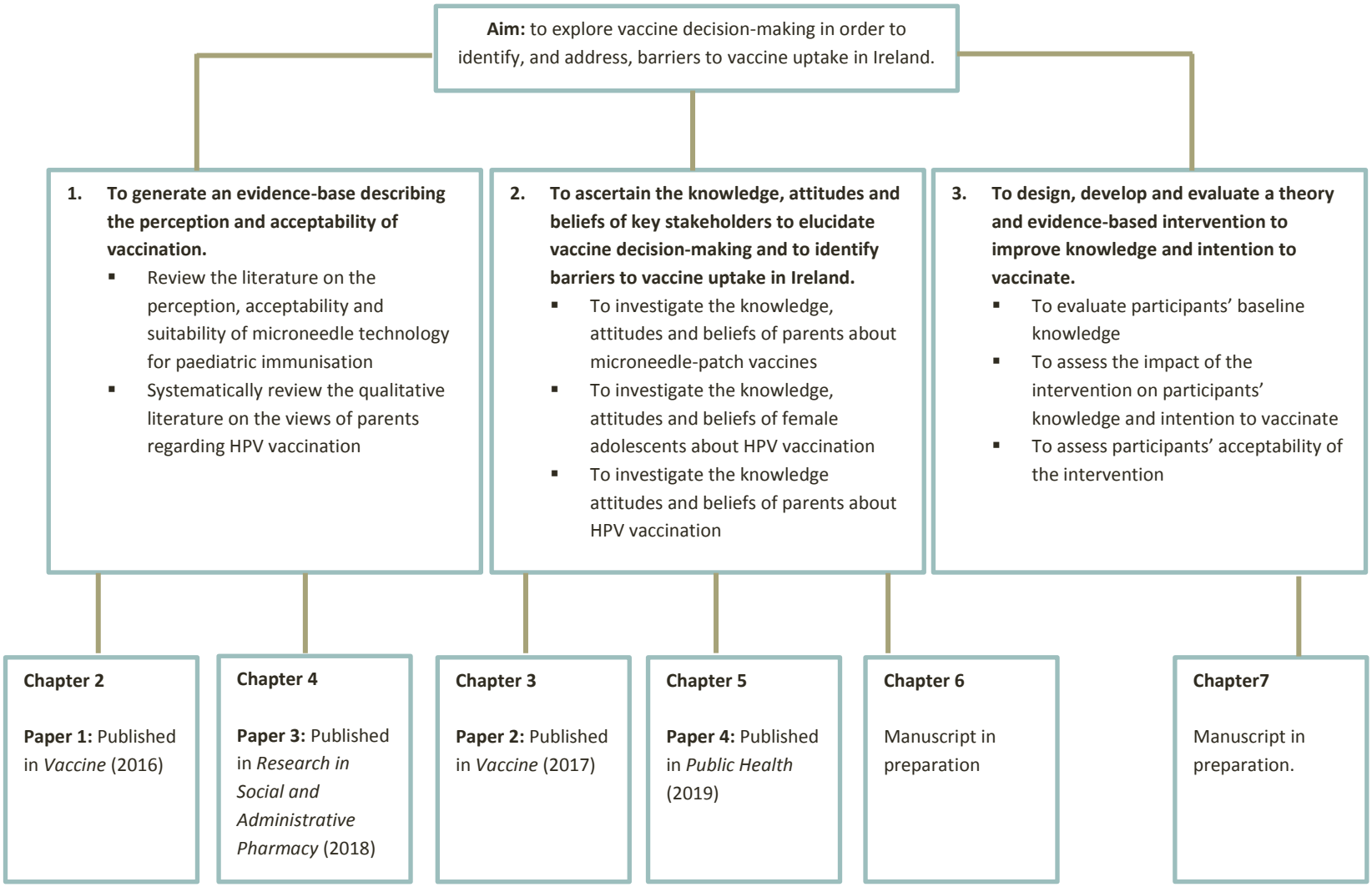


Figure 9 Thesis outline

Chapter 2 Microneedle technology for immunisation: perception, acceptability and suitability for paediatric use

Paper 1

Marshall S, Sahm LJ, Moore AC. Microneedle technology for immunisation: Perception, acceptability and suitability for paediatric use. Vaccine. 2016;34(6):723-34.

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Review

Microneedle technology for immunisation: Perception, acceptability and suitability for paediatric use

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ABSTRACT

Objective: To examine published research which explores the perception and acceptability of microneedle technology for immunisation and to investigate the suitability of this technology for paediatric use.
Methods: A series of keywords and their synonyms were combined in various combinations and permutations using Boolean operators to sequentially search four databases (PubMed, Web of Science, Embase and CINAHL). Following removal of duplications and irrelevant results, 12 research articles were included in the final literature review.
Results: The opinions of patients, parents, children and healthcare professionals (HCP) were collated. A positive perception and a high level of acceptability predominated.
Conclusion: Microneedle technology research has been focussed on demonstrating efficacy with minimal focus on determining HCP/public perception and acceptability for paediatric use, exemplified by the paucity of studies presented in this review. Commercial viability will depend on HCP/public acceptability of microneedle technology. An effort must be made to identify the barriers to acceptance and to overcome them by increasing awareness and education in stakeholder groups pertaining to the paediatric population.

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Author Contributions

Sarah Marshall (SM) was involved in the overall design of the research, designed the search strategy, performed the literature searches, interpreted the findings, wrote the draft manuscript and was involved in manuscript editing. Laura Sahm (LS) and Anne Moore (AM) directed the study and edited the manuscript.

2.1 Abstract

Introduction

Paediatric populations have been identified as desirable end-users of microneedle technology.

Aim

The aim of this literature review was to examine published research which explores the perceptions and acceptability of microneedle technology in both patients and HCPs.

Methods

A series of keywords and their synonyms were combined in various combinations and permutations using Boolean operators to sequentially search four databases (PubMed, Web of Science, EMBASE and CINAHL). Following removal of duplications and irrelevant results, 12 research articles were included in the final literature review.

Results

The opinions of patients, parents, children and HCPs were collated. A positive perception and a high level of acceptability predominated.

Conclusion

Microneedle technology research has been focussed on demonstrating efficacy with minimal focus on determining HCP/public perception and acceptability for paediatric use, exemplified by the paucity of studies presented in this review. Commercial viability will depend on HCP/public acceptability of microneedle

technology. An effort must be made to identify the barriers to acceptance and to overcome them by increasing awareness and education in stakeholder groups pertaining to the paediatric population.

2.2 Introduction

Since its invention in 1853 [240, 241], the hypodermic needle has become the most widely used medical device [242], with an estimated 16 billion injections administered worldwide [243]. This form of administration permits rapid delivery of plasma levels, careful titration of narrow therapeutic index drugs and administration of those exhibiting poor oral bioavailability by avoiding first pass metabolism and the degradative environment of the enteral system. Despite efficacy and widespread use, conventional hypodermic needles are associated with hazardous waste, accidental needle-stick, nosocomial infection as well as phobias, pain and significant anxiety in both adult and paediatric populations alike [76, 78, 242, 244]. Guided by these concerns, research has been focused on the development of alternate drug delivery methods. One such method that has emerged is delivery via microneedle technology. Microneedles are designed specifically to target the outermost, rate-limiting, skin barrier layer, the *stratum corneum*, creating transient pathways for transcutaneous delivery [85]. It is reported that microneedles can facilitate drug delivery through *stratum corneum* interruption without stimulating the pain receptors or blood vessels that lie beneath [86] thus being perceived as completely painless and devoid of bleeding. This technology has been used in a wide variety of pharmaceutical applications including the delivery of drugs [111, 245-247] and macromolecules, namely vaccines, proteins and peptides [74, 89, 93, 105-107, 248-253]. The major microneedle approaches employed in order to achieve facilitated delivery are solid, coated, hollow, dissolvable and swellable devices [254]. Solid microneedles are

primarily used for skin pre-treatment [74], whereby the needles puncture the skin, temporarily increasing permeability. This facilitates the passive diffusion of drug from a reservoir, typically in the form of a patch [254]. Coated microneedles pierce the *stratum corneum*, the drug layer dissolves and the active is deposited in the skin [74, 254]. Dissolvable microneedles are polymer based; the drug is incorporated into the formulation and is released as the system dissolves [74, 254]. Hollow microneedles facilitate drug diffusion [74], via a method of intradermal injection that is similar to that of conventional parenteral delivery. Finally swellable microneedles rapidly take up interstitial fluid upon skin insertion to form continuous, unblockable, hydrogel conduits from attached patch-like drug reservoirs to the dermal microcirculation [255]. In spite of promising results, the commercial success of microneedle technology will depend on end-user acceptability. Acceptability refers to determining how well an intervention will be received by the target population and the extent to which a new intervention or its components may meet the needs of the target population and organisational setting [256]. Interventions can often be developed without sufficient understanding of how the target population will embrace its activities [256]. A formulation with poor patient acceptability will affect compliance, prescribing practices and ultimately commercial viability [257] thus the European Medicines Agency (EMA) has recommended that acceptability studies form an integral component of pharmaceutical development.

2.3 Aim

The aim of this literature review was to examine published research which explores the perceptions and acceptability of microneedle technology in both patients and HCPs. A particular focus was placed on the amenability of this technology for use in the paediatric population, as children have been identified as desirable end-users [86].

2.4 Methods

2.4.1 Search strategy

Keywords and their synonyms or related terms were chosen which define the important concepts of the search. These included 'acceptability'; 'acceptance'; 'perception'; 'microneedle'; 'paediatric'; 'child'; 'children'; 'vaccination'; 'immunisation'; 'healthcare'; 'public'; 'parent' and 'guardian'. These keywords were combined in a variety of different permutations and combinations using the Boolean operators AND/OR. The same search was applied to four databases (PubMed; Web of Science; EMBASE and CINAHL), using Google as a search engine. No restrictions or advanced search filters were applied to the database searches. The search was repeatedly conducted from 6th October 2014 to 16th January 2015.

2.5 Results

The initial search across the chosen databases yielded 61 results. Following removal of duplications; 34 results remained.

Table 5 summarises the inclusion and exclusion criteria applied by the author.

Table 5 Literature search inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Related to the perception and acceptability of microneedle technology Published in English language Human subjects	Not related to the perception and acceptability of microneedle technology Related only to microneedle technology No abstract available Only abstract available Literature reviews Conference proceedings

Eleven of these results were excluded based on the irrelevance of their title and/or abstract. The remaining 23 results were assessed in full and their relevance to the query was determined. This process returned nine relevant results and revealed a further three results that had not been included in the initial search. Therefore, the final literature review included 12 results (Figure 10).

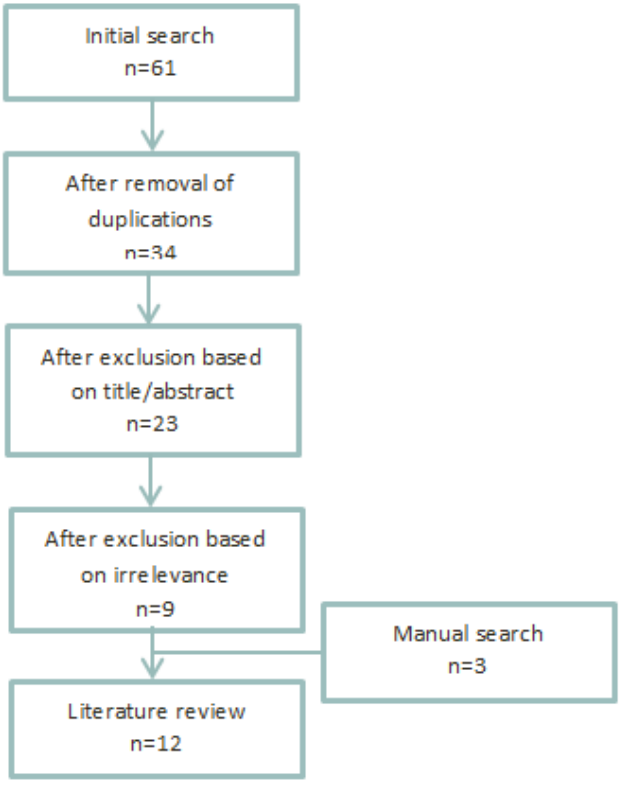


Figure 10 PRISMA flow diagram of search strategy

2.6 Discussion

The purpose of this review was to collate the literature which examined the perception and acceptability of microneedle technology for use in paediatrics. The literature search yielded 12 results directly related to the research query. Eight of the search results involved the actual administration of microneedle technology while the remaining four involved the hypothetical discussion of the technology. There are several methods to assess acceptability, both qualitative and quantitative. Popular and effective qualitative research methods include interviews and focus groups. These provide considerable opportunity for discussion between the researcher(s) and the target population. They also permit the researcher to probe topics as they emerge naturally in conversation, resulting in an in-depth understanding of forces that may impede or facilitate the intervention. During an interview, the interviewer engages an individual in a discussion about the proposed intervention. The individual may represent a member of the target population or an organisational representative with the experience to knowingly assess the acceptability of the intervention. Focus groups have been described as one of the most widely used qualitative research tools in the applied social sciences [256, 258], useful for designing healthcare interventions, pre-testing intervention materials, and establishing acceptable intervention implementation procedures. Interview techniques were used in three of the research papers presented here [84, 259, 260] and focus group methods were used in a further three [84, 86, 261]. Focus groups are advantageous as they permit and facilitate a collective brainstorming, resulting in a "synergistic group effect" [256]. In addition, focus groups are more cost effective in both time and resources. Quantitative research methods, to determine

acceptability, were also used in several of the research papers presented here. The primary method of quantitative research was the use of questionnaires [85, 86, 101, 259, 260, 262-266]. Several of the papers employed previously validated questionnaires, for example Modified Theory of Reasoned Action [101], Vaccinees' Perception of Injection [266] and McGill Pain Questionnaire-Short Form [85], while the remainder developed questionnaires for the purpose of their research.

2.6.1 Perception and acceptability of microneedle technology

Eleven of the studies reported a positive response to microneedles with only one study reporting the contrary [262]. Several recurring themes emerged which appeared to positively guide acceptability. These included; a perceived or actual reduction in pain associated with microneedle technology [84-86, 101, 259-261, 263-266]; ease and convenience of administration [86, 101, 259-261, 263-265]; potential for self-administration [86, 101, 261] and attractive visual appearance [84, 86, 261, 263, 265]. Conversely, several barriers to acceptability were identified; unfamiliarity with the technology [84, 86, 261]; allergic potential [84, 261] and the inclusion of the term 'needle' in the name of the product [261]. Research and development, particularly for paediatric markets, should focus on these barriers and strive to remove them through patient education, the development of a hypoallergenic delivery system and the adoption of novel nomenclature e.g. ImmuPatch®, to eliminate the negative connotations associated with the term 'needle'.

It is also important to consider HCP acceptability of microneedles. It has been demonstrated that the majority of patients will reserve the ultimate healthcare

decision for their HCP [84]. Five of the papers presented in this literature review included the opinions of 711 HCPs [86, 259, 260, 264, 265]. 90.65% (n=644) of those HCPs included declared a positive response to microneedle technology, with 76.37% (n=543) expressing preference for microneedle technology over conventional administration. Perceived benefits were similar to those mentioned by the general public, such as increased patient acceptability, especially in the needle-phobic [86, 264, 265] but HCPs acknowledged additional benefits such as improved immunogenicity and seroprotection [264, 265] and a reduced risk of needle-stick injury [86]. However, several barriers to acceptability were acknowledged by HCPs: risk of cross-contamination and an inability to ensure accurate delivery on microneedle application [86]. Significant efforts have been made to address these concerns with devices based on biodegradable dissolving formulations receiving increased attention. Once inserted into the skin, these polymeric systems will either rapidly dissolve or undergo such morphological changes that disable effective skin penetration if applied to another individual [267, 268], thus preventing intentional or accidental cross contamination. An effort must be made to formulate the inclusion of a delivery indicator without significantly increasing the cost of production.

2.6.2 Perception and acceptability for use in immunisation

Vaccines are a key contributor to public health [269]. Despite repeatedly demonstrating cost-effectiveness, the WHO has estimated that vaccine spending accounts for only 2–3% of the total pharmaceutical market. Total costs of providing immunisation services are divided into capital and recurrent costs [270, 271].

Capital costs are identified as items that last longer than one year and are therefore incurred every few years rather than annually. Important capital costs for immunisation services are associated with cold chain equipment vehicles. Recurrent costs are those items consumed during the year, warranting regular purchase. Recurrent costs include the vaccines themselves and training activities [270]. In recent years, the global vaccine market has undergone rapid growth. The impetus for this changing status is a combination of improved profitability with the development of 'blockbuster vaccines', defined as those with US sales of at least one billion dollars [272], such as Pfizer's Prevnar7® and Prevnar 13®, GSK's Rotarix® and MSD's Rotateq®, new funding opportunities with government grants and public–private partner-ships [269], and new manufacturing techniques, namely microneedle technology.

Vaccine delivery to the skin is a logical approach [254]. The skin is an immunogenic organ, housing a high concentration of professional antigen presenting cells [90]. This permits the induction of a strong immune response upon antigenic challenge [90]. For this reason, microneedles are especially attractive for immunisation. They have demonstrated a compatibility with live, inactivated and subunit vaccines [111, 247], the ability to induce comparable and, in some cases, improved immunogenicity when compared to conventional vaccination [89, 93, 253, 273], coupled with significant dose sparing characteristics [89, 90]. Microneedle-mediated vaccination could potentially reduce both the capital and recurrent costs associated with conventional immunisation programmes: their thermostability eliminates cold-chain transportation requirements [105-107] and their potential for self-administration could reduce the requirement for trained personnel to

administer the vaccine. There are currently 12 clinical trials at various stages involving the delivery of vaccines using microneedle technology. Ten of these have been completed; one is actively recruiting, while the other has completed recruitment. Eleven of the 12 clinical trials involve vaccine delivery using hollow microneedles (Soluvia®, MicronJet®), while the remaining trial involves delivery using a dissolvable microneedle patch. Vaccine targets under trial include varicella zoster, polio and influenza [274]. It is not possible to discuss vaccination without mentioning influenza. It is estimated that 5–10% of adults and 20–30% of children are infected with influenza globally per annum. Influenza vaccination is one of the most effective methods to prevent infection or complications from illness, providing approximately 70–90% protection against clinical disease in healthy adults aged 18–59, provided there is good correlation between the vaccine antigens and circulating viral strains [255]. The requirement for re-vaccination on an annual basis as a result of viral antigenic shift and drift explains the popularity and commercial advantage of influenza vaccine development. This review presents the results of a first-in-humans study of microneedle patch acceptability for self-vaccination against influenza [101]. In this study, etched, stain-less steel microneedles were mounted on adhesive foam backing. When this self-administered microneedle patch was offered to participants as an alternative to conventional vaccination, intention to vaccinate increased from 44% at baseline to 65%. This review also highlights the success of Intanza®, a trivalent, inactivated influenza vaccine that is delivered intradermally with the world's first proprietary microinjection system, Soluvia®. This system features a 30 gauge hollow microneedle designed for perpendicular administration into the intradermal space.

The microneedle is pre-attached to a delivery system that limits the depth of insertion to 1.5 mm from the skin's surface. The needle is attached to a glass syringe prefilled with the vaccine dose and a needle shielding system that covers the needle post injection [275]. The hollow microneedle within this system is 10–16 times shorter and 40% thinner than the conventional needles used for IM vaccinations [275]. In addition, the microinjection system allows the precise administration of 0.1ml [275]. The integrated needle-shielding system is manually activated immediately after vaccination, minimising the risk of needle-stick injury, contamination and illicit re-use [275]. Comparable acceptability studies of Intanza® have been undertaken in European countries such as the United Kingdom, France, Germany, Belgium, Spain, Czech Republic and Turkey as well as Australia and Argentina, compiling the opinions of 13,518 participants and 680 general physicians. Of the 10,740 adults that were vaccinated by Intanza®, 96.6% (95–98%) declared they were "satisfied" or "very satisfied" and 93.7% (85–99%) indicated that they would prefer to be vaccinated by this method, if given a future choice. The latter statistic is particularly significant as it provides an indication of potential uptake associated with microneedle-mediated influenza vaccination. Vaccination rates remain below the targeted coverage rate of 75% as recommended by the European Centre for Disease Prevention and Control. Many reasons have been hypothesised to explain this low vaccination uptake, including a low perception of risk, a general lack of accurate information about influenza and vaccination, a fear of possible and perceived side effects and issues of cost, availability and convenience. This literature review has highlighted how microneedle technology using either a patch system [101] or the microinjection system Soluvia®, has the

ability to ameliorate several of these concerns, exemplified by the fact that 30% of previously unvaccinated participants were willing to be vaccinated when offered this technology [101].

2.6.3 Perception and acceptability for use in paediatrics

In their exploratory study, Birchall *et al*. captured the views of the eventual end-users of microneedle technology [86]. Focus groups comprising members of the public and HCPs were convened. In all seven focus groups, microneedle technology was identified as being "good for children". Questionnaires were further used to substantiate the outputs from the qualitative focus groups. This questionnaire revealed that 92% of public respondents agreed that microneedles would be ideal for the administration of medicines to children. Three of the papers presented in this review explored the use of microneedles in the paediatric population [84, 261, 262]. One study explored children's views on microneedle use as an alternative to blood sampling and reported a positive response [261]. Similarly, a second study assessed the views of parents of premature babies on microneedle-mediated monitoring as an alternative to blood sampling and once again reported a positive response [84]. A third study explored parent's attitudes toward multiple vaccinations at a single visit, with several alternate methods, including a microneedle device. This study reported that the microneedle device, MicronJet®, was not perceived as better than the conventional syringe [262]. While this system is composed of four 0.6 mm hollow silicon microneedles, it is attached to a standard syringe barrel thus resembling a conventional vaccine system. This arrangement may explain the reduced acceptability reported in this study.

Vaccination is one of the most common causes of iatrogenic pain in the paediatric population [276]. This pain is a source of distress for children and their guardians and can lead to pre-procedural anxiety, needle phobia in later life, mistrust in HCPs and healthcare avoidance, including non-adherence with vaccination schedules [277]. While several techniques have been employed with varying success to manage pain during paediatric injections (topical anaesthetic, music distraction, oral distraction in infants, positioning techniques and pH alteration), the ability of microneedles to eliminate pain on injection is a significantly desirable attribute [84]. In Ireland, the Health Service Executive (HSE) recommends 15 vaccinations (16 for females), to be administered from birth to approximately 14 years of age. Current vaccination practices typically involve administration of two or three vaccines concomitantly at a single visit. Research has demonstrated that the most notable reason influencing a guardian's comfort level with the maximum number of injections per visit for their child was avoiding too much pain and discomfort [278, 279]. Therefore, there is a considerable commercial market for microneedle-mediated childhood immunisation. However, similar to other areas of medical research, the industry remains hesitant to invest in paediatric vaccines given the significant ethical implications associated with this special population. While the development of microneedle-mediated childhood vaccination programmes is a logical goal, microneedle technology could also be used in specific subgroups of the paediatric population to reduce treatment burden. For example, Gupta *et al*. concluded that insulin delivery using hollow microneedles in children with Type 1 diabetes was less painful and had a more rapid onset of action compared to conventional administration [248, 280]. Similarly Norman *et al.* demonstrated that

intradermal insulin delivery using a hollow microneedle device resulted in less insertion pain and faster onset and offset of action in children and adolescents, suggesting that this reduction in pain may improve compliance with insulin delivery [88]. Therefore, while the benefits of microneedle technology are multi-fold, their dose sparing characteristics, thermostability and reduced potential for needle-stick, pale in comparison to their ability to reduce pain when considering the paediatric population.

2.7 Conclusion

The purpose of this publication was to review the perception and acceptability of microneedle technology. Research in recent years has focussed on demonstrating the development and potential efficacy of the technology with little published focus on determining acceptability, as demonstrated by this review. The benefits of microneedle technology in vaccination, especially in the paediatric population are glaringly apparent. However, commercial viability will depend on acceptability of this technology by parents and HCPs who are key stakeholders who will decide the vaccination method. Therefore, research ought to focus on increasing awareness of the technology and promoting education in these stakeholder groups.

2.8 Chapter conclusion and context within thesis

This chapter presented the findings of a narrative literature review on the perception, acceptability and suitability of microneedle technology for paediatric immunisation, therefore addressing the first objective of this doctoral research i.e. to generate an evidence-base. This evidence-base identified parents as key stakeholders in the vaccine decision-making process and informed the design of the

qualitative research study, outlined in Chapter 3. This research has been published in a peer-reviewed journal.

Chapter 3 Acceptability of microneedle-patch vaccines: a qualitative analysis of the opinions of parents

Paper 2

Marshall S, Fleming A, Moore A, Sahm L. Acceptability of microneedle-patch vaccines: A qualitative analysis of the opinions of parents. Vaccine. 2017;35(37):4896-904.

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Acceptability of microneedle-patch vaccines: A qualitative analysis of the opinions of parents

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ABSTRACT

Introduction: Vaccines incorporated into microneedle-based patch platforms offer advantages over conventional hypodermic injections. However, the success and clinical utility of these platforms will depend on its acceptance among stakeholders. Minimal focus has been placed on determining parents' acceptability of microneedle-patch vaccines intended for paediatric use. This qualitative study probes the perceived acceptability of microneedle technology for paediatric vaccination in a parent population.
Research design and methodology: Focus groups (n = 6) were convened through purposive sampling of Cork city primary schools. Discussions were audio-recorded, transcribed verbatim, anonymised, independently verified and analysed by thematic analysis, with constant comparison method applied throughout.
Results: The opinions of 32 parents were included. All participants declared that their children were fully vaccinated. Five core themes were identified and defined as: (i) concern, (ii) suitability for paediatric use, (iii) potential for parental administration, (iv) the role of the healthcare professional and (v) special populations. Drivers for acceptance include; concerns with current vaccines and vaccination programmes; attributes of microneedle-patch (reduced pain, bleeding, fear and increased convenience) and endorsement by a healthcare professional. Barriers to acceptance include; lack of familiarity, concerns regarding feasibility and suitability in paediatrics, allergic potential, inability to confirm delivery and potential reduction in vaccine coverage.
Conclusion: This is the first study to explore parental acceptance of microneedle-patch vaccines. Capturing the opinions of parents, the ultimate decision makers in paediatric vaccination, is crucial in the understanding of the eventual uptake of microneedle technology and therefore adds to literature currently available. This study has revealed that even "vaccine-acceptors"; parents who agree with, or do not question vaccination, will question the safety and efficacy of this novel method. Participants in this study remained tentative. However, the study has also revealed that endorsement by healthcare professionals could reduce this tentativeness, thereby identifying the role of healthcare professionals in disseminating information and providing support to parents. An increased awareness of developments in microneedle technology is needed to permit informed decision-making by parents.
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Author Contributions

SM was involved in the overall design of the research, designed the topic guide, completed the application for ethical approval, recruited participants, facilitated the focus groups, transcribed the audio-recordings, wrote the draft manuscript and was involved in manuscript editing. SM, Aoife Fleming (AF) and LS analysed the results. AF, AM and LS directed the study and edited the manuscript.

3.1 Abstract

Introduction

Vaccines incorporated into microneedle-based patch platforms offer advantages over conventional hypodermic injections. However, the success and clinical utility of these platforms will depend on its acceptance among stakeholders. Minimal focus has been placed on determining parents' acceptability of microneedle-patch vaccines intended for paediatric use.

Aim

The aim of this qualitative study was to probe the perceived acceptability of microneedle technology for paediatric vaccination in a parent population.

Methods

Focus groups (n = 6) were convened through purposive sampling of Cork city primary schools. Discussions were audio-recorded, transcribed verbatim, anonymised, independently verified and analysed by thematic analysis, with constant comparison method applied throughout.

Results

The opinions of 32 parents were included. All participants declared that their children were fully vaccinated. Five core themes were identified and defined as: concern, suitability for paediatric use, potential for parental administration, the role of HCPs and special populations. Drivers for acceptance include; concerns with current vaccines and vaccination programmes; attributes of microneedle-patch (reduced pain, bleeding, fear and increased convenience) and endorsement by a

HCP. Barriers to acceptance include; lack of familiarity, concerns regarding feasibility and suitability in paediatrics, allergic potential, inability to confirm delivery and potential reduction in vaccine coverage.

Conclusion

This is the first study to explore parental acceptance of microneedle-patch vaccines. Capturing the opinions of parents, the ultimate decision-makers in paediatric vaccination, is crucial in the understanding of the eventual uptake of microneedle technology and therefore adds to literature currently available. This study has revealed that even “vaccine-acceptors”; parents who agree with, or do not question vaccination, will question the safety and efficacy of this novel method. Participants in this study remained tentative. However, the study has also revealed that HCP endorsement could reduce this tentativeness, thereby identifying the role of HCPs in disseminating information and providing support to parents. An increased awareness of developments in microneedle technology is needed to permit informed decision-making by parents.

3.2 Introduction

Microneedles are micron-sized needles, designed to achieve the efficacy of the conventional hypodermic injection with the simplicity of a skin patch [74, 110]. Incorporating vaccines into microneedle-based patch platforms offer the possibility of reducing costs associated with current vaccination programmes: (i) their thermostability eliminates cold-chain transportation requirements, thereby reducing distribution costs [105-107] (ii) their potential for self-administration would reduce reliance on trained personnel, reducing administration costs [101, 110-112] and (iii) their potential dose-sparing characteristics would permit a reduction in vaccine antigen per dose, reducing production costs [89, 281, 282]. In addition, microneedles may be fabricated using dissolving polymers, eliminating the biohazardous sharps waste associated with conventional vaccination methods [111, 283]. These dissolving microneedle-patches have been developed to successfully incorporate vaccines *in vivo* for multiple disease indications [2]. The ability to penetrate the skin with minimal trauma, in the absence of pain and bleeding [110] has been identified by healthcare users as an important factor in their eventual clinical use [85, 284].

Despite these desirable characteristics for HCPs and vaccinees, the success and commercial viability of this technology will depend on its acceptance among these stakeholders. It is widely accepted that obtaining and evaluating public opinion on developing scientific, technological and medical innovation and policy is important [285, 286]. The European Medicines Agency (EMA) recommends that evaluation of patient acceptability should be an integral component of pharmaceutical and

clinical development. In their exploratory research study, Birchall *et al.,* captured the perceived advantages of, and concerns with microneedles, through the convening of focus groups comprising public participants and HCPs [86]. A high percentage of participants suggested that microneedles would be 'ideal' for the administration of medicines to children [86]. In another study, children expressed a favourable viewpoint, suggesting that microneedle-based blood monitoring could offer an attractive alternative to conventional methods [261]. This research was expanded to include parental perception of microneedle-mediated blood monitoring of their infants and, once again, support for the microneedle was evident [84]. Research thus far has focussed on demonstrating safety and efficacy of microneedle-mediated delivery and assessing the acceptability of microneedle technology in general, with minimal focus on determining the acceptability of microneedle-patch vaccine delivery, in particular those intended for paediatric use.

3.3 Aim

The aim of this qualitative study was to probe the perceived acceptability of microneedle technology for paediatric vaccination in a population of parents.

3.4 Methods

The acceptability of microneedle-patch vaccines was explored through a series of focus groups. Focus groups were chosen as they can provide insights into attitudes and beliefs that underlie behaviour and give context and perspective that enable experiences to be understood more holistically [287]. These attitudes, feelings and beliefs may be partially independent of a group or its social setting but are more

likely to be revealed via the social gathering and the interactions entailed within a focus group.

A list of primary schools in Cork city, Ireland (n=50), detailing address, principal name and contact details was compiled using information freely available from the Irish Department of Education and Skills. A recruitment poster, a copy of the informed consent form and a cover letter detailing study overview, addressed to each principal, were sent via post. A follow-up email detailing the same information was sent one week later. With the permission of the principal, contact was made with the Parent Association of those schools that expressed willingness to participate and focus group participants were recruited, using purposive sampling. Inclusion criteria included self-declared satisfactory English language and parent or guardian of a child or children less than 12 years of age, with no limitation placed on age or gender of participant. Focus groups took place within the grounds of the school, often coinciding with pre-arranged Parent Association meetings, to enhance convenience for participants. Written informed consent to take part in the study and to be audio-recorded was obtained from participants prior to each focus group. Information detailing gender, age, highest level of education achieved (according to International Standard Classification of Education (ISCED)) [288], number of children less than 12 years of age in their care and the vaccination status of their children was obtained for each participant.

A brief description of microneedle-patch vaccines, explaining their ability to disrupt the outer skin barrier layer and deliver a vaccine, without impinging on the underlying pain receptors and blood vessels, was provided by the moderator. This was considered necessary given the likely unfamiliarity of participants with

microneedle technology. However, to mitigate against risk of introduction of bias, information relayed was of a factual nature only. A research prototype, placebo microneedle-patch was passed around the groups and a magnifying glass was provided, to permit visualisation of the individual microneedles, to act as a focussing exercise to stimulate discussion and to reduce bias by enabling the independent formation of opinions (Figure 11).



Figure 11 Prototype, placebo microneedle-patch & magnifying glass given to participants at the outset of focus groups

A topic guide with a semi-structured design was used during each focus group, constructed based on a comprehensive literature search [1], providing general probes in an open-questioning style (Table 6). Ethical approval was obtained from the Social Research Ethics Committee, University College Cork.

Table 6 Focus group topic guide

Opinions of vaccines
What are your opinions on current paediatric vaccination programmes?
Do you agree with current paediatric vaccination programmes?
What are the benefits of vaccination programmes?
What are your concerns about vaccination programmes?
What are the problems with current vaccination programmes?
Are you happy for your children to be vaccinated?
Do you have any issues with current vaccination methods?
Do you think cost is a major consideration with vaccination programmes?
Opinions of microneedle-patch vaccines
Before today, had you ever heard of a microneedle-patch vaccine?
What is your initial opinion of the microneedle-patch vaccine?
Do you believe that the microneedle-patch vaccine is as effective as other vaccination methods?
Would you trust this vaccination method?
Do you think there are any advantages of the microneedle-patch vaccine?
What do you like about the microneedle-patch vaccine?
Do you think there are any disadvantages of the microneedle-patch vaccine?
What do you dislike about the microneedle-patch vaccine?
Would you have any concerns in relation to the use of a microneedle-patch vaccine?
Would you allow your child or a child in your care to be vaccinated using a microneedle-patch vaccine?
Do you think the microneedle-patch vaccine could change opinions of vaccination?
What would children think of the microneedle-patch vaccine?
Do you think people would be nervous of the microneedle-patch vaccine?
If given a choice, which method of vaccination would you prefer?
Who do you think should administer the microneedle-patch vaccine?
Do you think you would be able to self-administer the microneedle-patch vaccine?
Would you be willing to administer the microneedle-patch vaccine to your child or a child in your care?
Would you be comfortable with administering the microneedle-patch vaccine to your child or a child in your care?
Is there any way you think the microneedle-patch vaccine could be improved?
What do you think of the design of the microneedle-patch vaccine?
Is there any way you think the design of the microneedle-patch vaccine could be improved?
Do you think the Health Service Executive (HSE) should endorse and invest in the microneedle-patch vaccine?

Audio-recorded sessions, using a Dictaphone (OLYMPUS Digital Voice Recorder VN-731PC), were fully transcribed verbatim within one week of each focus group. Data were entered into QSR International's NVivo V.11 software to assist analysis. Each participant was assigned an anonymised identifier. Transcripts were verified against audio-recordings with a random sample verified by an independent researcher. Focus groups transcripts were independently coded by co-investigators. Disparities were identified and resolved through discussion. Data were analysed by thematic analysis, with constant comparison method applied throughout.

3.5 Results

Six focus groups were completed from 3rd November 2015 to 12th January 2016, representing an uptake rate of 12%. The opinions of 32 participants (29 female) were compiled. The most commonly reported age range was 30-39 years (46.88%), highest education level was Higher Education (ISCED level ≥ 4) (68.75%) and the number of child(ren) under 12 years in their care was two (46.88%). All participants declared that their children were fully vaccinated, to the best of their knowledge. A summary of participant demographics, including their anonymised identifier is provided in Table 7.

Table 7 Participant demographics

Identifier	Gender	Age category (years)	*Highest education level	Children under 12
P1	Female	50-59	ISCED level 3	1
P2	Female	40-49	ISCED level 3	2
P3	Female	30-39	ISCED level ≥4	2
P4	Female	40-49	ISCED level ≥4	3
P5	Female	40-49	ISCED level ≥4	1
P6	Female	40-49	ISCED level ≥4	4
P7	Female	30-39	ISCED level ≥4	3
P8	Female	50-59	ISCED level ≥4	2
P9	Female	40-49	ISCED level ≥4	1
P10	Female	30-39	ISCED level 3	3
P11	Male	30-39	ISCED level 2	3
P12	Female	40-49	ISCED level ≥4	1
P13	Female	40-49	ISCED level ≥4	2
P14	Female	30-39	ISCED level ≥4	1
P15	Female	20-29	ISCED level 2	3
P16	Female	40-49	ISCED level 3	2
P17	Female	30-39	ISCED level ≥4	2
P18	Female	30-39	ISCED level ≥4	3
P19	Female	30-39	ISCED level ≥4	2
P20	Female	20-29	ISCED level 3	1
P21	Female	40-49	ISCED level ≥4	2
P22	Female	30-39	ISCED level 3	2
P23	Female	30-39	ISCED level ≥4	1
P24	Female	40-49	ISCED level ≥4	2
P25	Female	30-39	ISCED level ≥4	2
P26	Male	40-49	Unknown	3
P27	Female	30-39	ISCED level ≥4	1
P28	Female	30-39	ISCED level ≥4	2
P29	Male	40-49	ISCED level ≥4	2
P30	Female	30-39	ISCED level 3	2
P31	Female	30-39	ISCED level ≥4	2
P32	Female	40-49	ISCED level ≥4	1

***Highest education level**

- ISCED level 1: Primary education, equivalent to 8 years official State education
- ISCED level 2: Lower secondary education: Irish Junior/Inter Certificate, equivalent to 11 years official State education
- ISCED level 3: Upper secondary education: Irish Leaving Certificate, equivalent to 14 years official State education
- ISCED level ≥4: Higher Education including post-secondary non-tertiary education, short-cycle tertiary education, Bachelor (or equivalent), Master (or equivalent) and Doctoral (or equivalent)

Two of the six participating schools were included in the Delivering Equality of Opportunity in Schools (DEIS) programme, that is part of the Department of Education and Skills action plan which focusses on addressing and prioritising the

educational needs of children from disadvantaged communities. Focus group duration ranged from 27 to 42 minutes (Table 8).

Table 8 Focus groups: DEIS status, gender breakdown and duration

	DEIS*	Male (n)	Female (n)	Duration (mins)
FG1	No	0	4	33
FG2	Yes	0	5	42
FG3	Yes	1	5	37
FG4	No	0	5	27
FG5	No	0	5	29
FG6	No	2	5	33

***DEIS =** Delivering Equality of Opportunity in Schools

Focus groups transcripts were analysed by thematic analysis, with constant comparison method applied throughout. Five core themes were identified and defined as: concern, suitability for paediatric use, potential for parental administration, the role of the HCP and special populations (Table 9). A pictorial representation of these themes, sub-themes and associated exemplar quotes is seen in Figure 12.

Table 9 Themes and sub-themes and their occurrence in each focus group

	Focus group					
Themes and sub-themes	**FG1**	**FG2**	**FG3**	**FG4**	**FG5**	**FG6**
Concern						
Current vaccines	✓	✓	✓	✓	✓	✓
Vaccine hesitancy			✓		✓	✓
Safety & efficacy	✓	✓	✓	✓	✓	✓
Suitability for paediatric use						
Practicality	✓	✓	✓	✓	✓	✓
Child-friendly design	✓		✓	✓	✓	✓
Transfer of acceptability	✓	✓	✓	✓	✓	
Potential for parental administration						
Benefits of parental administration	✓		✓	✓		✓
Disadvantages of parental administration	✓	✓	✓	✓	✓	✓
Delivery indicator		✓		✓		✓
The role of the HCP						
Source of healthcare information	✓	✓	✓	✓	✓	✓
Special populations						
Allergic potential	✓	✓	✓	✓	✓	✓
Alternative uses		✓	✓	✓	✓	✓

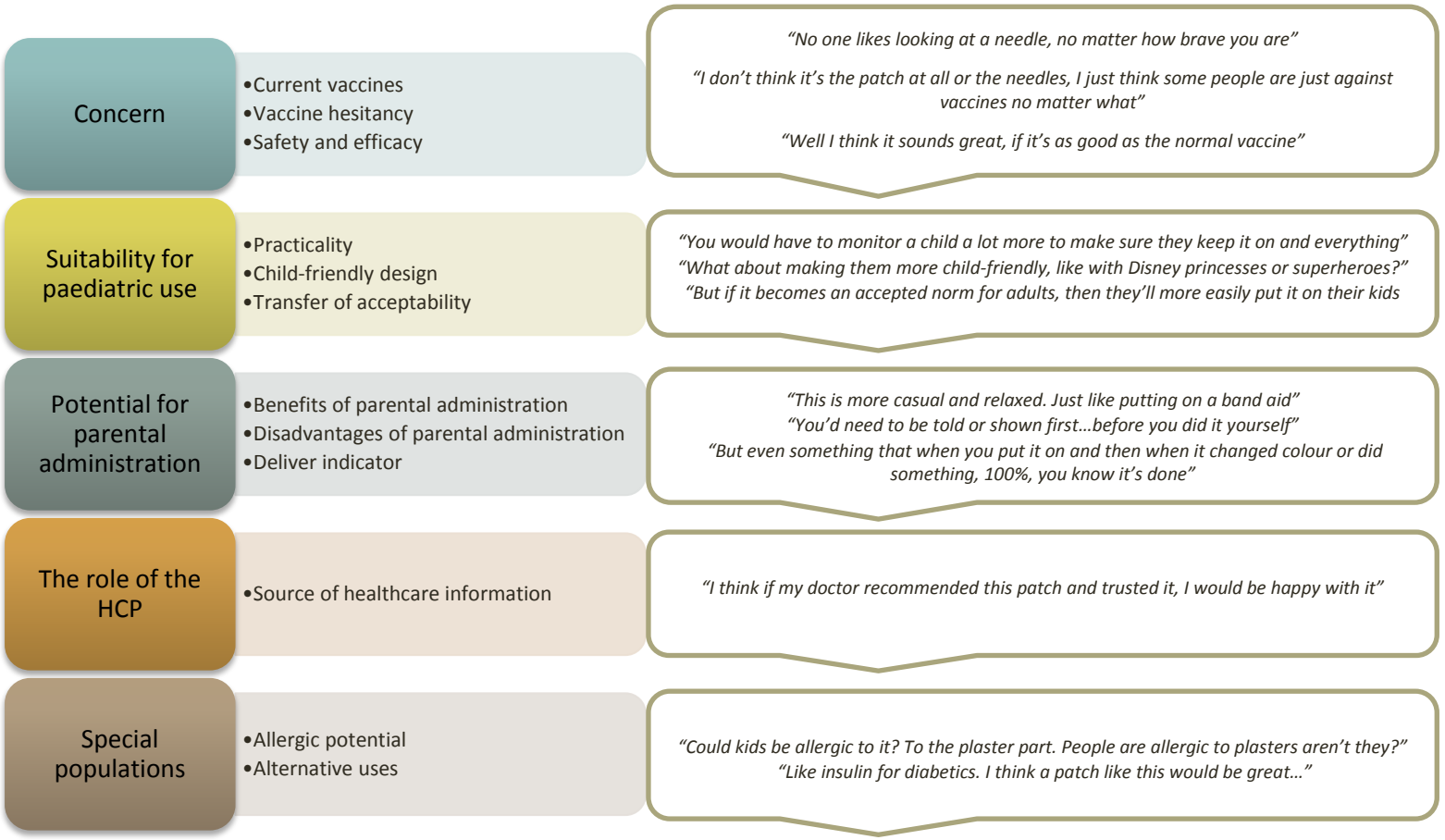


Figure 12 Themes, sub-themes and associated exemplar quotes

3.5.1 Concern

Concern emerged as a theme in all focus groups. Participants expressed concerns regarding current vaccination methods and programmes, such as unattractive visual appearance and hysteria associated with in-school programmes. In addition, participants discussed personal negative experiences with vaccines such as fear, parental and paediatric trauma, pain and side effects:

P31 *"No one likes looking at a needle, no matter how brave you are"*

P29 *"Mass fainting, hysterical crying, nightmare to deal with, this is why I'm not sure these in-school vaccine sessions are a good idea. I think it creates chaos"*

Some participants alluded to the behavioural phenomenon of vaccine hesitancy, despite declaring that all children in their care were fully vaccinated.

P11 *"Is it still as important today as it was 10 years ago to get these vaccinations?...if you listen to some media, people have gotten sicker because of these vaccinations and some people blame these vaccinations…my small one is after having the mumps even after getting the vaccine…is it really important to get them when you say it prevents these things but it's still not preventing them"*

P11 *"I don't think it's the patch at all or the needles, I just think some people are just against vaccines no matter what"*

Evidence of safety and efficacy was of paramount importance to parents, with all focus groups requiring reassurance that microneedle-patch vaccines would be as safe and efficacious as conventional vaccines.

P3 *"So they have done controls comparing with injection with needle and syringe to the patch?"*

P7 *"I actually, I love the idea of it in theory being able to give it but at the same time, before I'd give it to my child I'd want it to be tested in hundreds of thousands of people across the world for ideally at least 10 years"*

P32 *"Well I think it sounds great, if it's as good as the normal vaccine"*

P30 *"It's hard to believe the needles are big enough to give the vaccine, I mean, they're tiny"*

P31 *"By creating loads of holes in your skin are you not increasing the risk of picking up an infection?"*

3.5.2 Suitability for paediatric use

Focus groups participants acknowledged the advantages of microneedle-patch vaccines for paediatric use. These included a reduction in pain and bleeding and an attractive visual appearance. However, the practicality and feasibility of using a patch delivery system in a paediatric population was explored:

P4 *"If the child finds something on their arm, they will take it off"*

P9 *"You would have to monitor a child a lot more to make sure they keep it on and everything"*

P7 *"I'm just thinking of the practicality though you know…if you're using the thigh and what if they have an explosive nappy?"*

In addition, the current design of the patch was challenged and suggestions were offered to make the delivery system more 'child-friendly':

P4 *"If they are designing those and especially for children, they would want to make them child friendly, in other words put some type of funny face or something on the patch so that the child would keep them on…make it completely invisible so the child doesn't notice it"*

P13 *"What about making them more child-friendly, like with Disney princesses or superheroes or something?"*

Focus groups discussed that acceptability for use in a paediatric population would be increased by an initial period of use in an adult population, permitting familiarisation with the microneedle technology:

P1 *"But if it becomes an accepted norm for adults, then they'll more easily put it on their kids"*

P7 *"If it was in widespread use as a technology for adults that we were more comfortable with it, familiar with it, you know that you'd be a bit more open to extending what's normal for an adult to a child"*

3.5.3 Potential for parental administration

Participants acknowledged the potential benefits of parental administration, including convenience and a reduction in fear for the child:

P1 *"Avoids the hassle of having to go"*

P11 *"It would be a lot easier, as parents to put them on ourselves because bringing any child to a doctor is going to put fear in them anyway so doing it ourselves, it takes the fear factor completely out of it"*

P29 *"This is more casual and relaxed. Just like putting on a band aid"*

However, a large number of parents indicated a level of discomfort with administration to their own children. Many participants believed that HCPs ought to administer the vaccine, regardless of the delivery system; while others recognised the benefits of parental administration but would prefer medical supervision and reassurance should they be administering the vaccine to their own child. Participants discussed the need for reassurance that the patches would be easy to use, with minimal guidance or training.

P2 *"You'd need to be told or shown first…before you did it yourself"*

P7 *"How hard would you need to push, would you be literally ramming it against the skin?...my child I guarantee would end up with a bruised arm I'd be pushing so hard…like I presume there's no danger with us putting them on ourselves, you know, there's no special way to put them on or anything like that"*

In addition, participants raised concerns regarding the potential elimination of current vaccine surveillance and monitoring systems and reduced traceability that may be associated with wide-spread parental administration, suggesting that convenience may result in a level of complacency and/or non-compliance:

P4 *"The HSE will send you out a letter to tell you your vaccination is due. If you don't go, they will keep contacting you with letters…I know I would be quite lackadaisical, knowing it's there and I can do it any time, I won't do it"*

P14 *"People could genuinely forget, leave it in the cupboard and say I'll do it later"*

P1 *"We'd have to put something in place or else we would have no idea who was vaccinated"*

Many groups discussed how the inclusion of a delivery indicator would be necessary to provide reassurance that the appropriate dose had been administered, with participants offering suggested alterations to the current patch system.

P5 *"But even something that when you put it on and then when it changed colour or did something, 100%, you know it's done"*

P16 *"Is there any way you could tell they got the full amount? Like if it just fell off or something when it was done dissolving"*

P27 *"It would be great if it changed colour or something, like change to green when it's time to take it off and stay red when it's dissolving or whatever. That could almost turn into a game and encourage the child to leave it on"*

3.5.4 The role of the HCP

The pivotal role played by HCPs, such as doctors, nurses and pharmacists, in guiding healthcare decisions and supervising and providing medical care was revealed.

P20 *"When the doctor told me to come in for the jabs, I just did"*

P26 *"I think if my doctor recommended this patch and trusted it, I would be happy with it. I have to rely on them for information because if you gave me all the clinical study information or whatever in the world, I would not understand it"*

P3 *"Even if the pharmacist would administer it. At least there's some kind of monitoring then"*

3.5.5 Special populations

Participants identified the potential for allergy associated with microneedle-patch vaccines, suggesting that this technology may be unsuitable for hypersensitive individuals.

P8 *"Would you not expect reactions to occur, if dissolving in the skin, like allergy?"*

P18 *"Could kids be allergic to it? To the plaster part? People are allergic to plasters aren't they?"*

P23 *"Or what if a child has very sensitive skin, would the patch irritate it?"*

Focus group participants discussed alternative uses for the microneedle-patch, without prompt. It was highlighted that because a microneedle-patch would cause less pain on administration, the technology could provide an attractive alternative in the treatment of a variety of conditions, where a needle and syringe are conventionally required. This was deemed particularly useful in situations where multiple, repeated injections are required.

P13 *"You know people are on monthly injections of immune suppressants and stuff, maybe it could replace those…and diabetics as well, poor things have to inject loads of times per day"*

P17 *"My nephew is diabetic and has to give himself insulin all the time. He's 15 you know and poor fella hates being different and kind of, standing out. Wouldn't it be great if he could just stick on the patch instead? No one would even see it"*

P21 *"Wouldn't they be great for babies in neonatal? The 'preemies' or even the sick babies and children that need to get lots of daily injections?"*

P27 *"Like insulin for diabetics. I think a patch like this would be great and they'd be checking their sugars anyway so they'd be sure it was working"*

3.6 Discussion

The aim of this qualitative study was to determine the acceptability of microneedle technology for paediatric vaccination in a population of Cork city parents. According to the HSE in Ireland, the target vaccine uptake rate for childhood immunisations is ≥95%. In their most recently available data, the Health Protection and Surveillance Centre (HPSC) reports that only the 6-in-1 vaccine (D_3, T_3, P_3, Hib_3, $Polio_3$ and $HepB_3$) administered to children at 24 months of age in 2015 had reached the target uptake rate of 95% (Figure 2). Therefore, there is scope for improving vaccine uptake, potentially through the introduction of novel immunisation methods, such as microneedle technology, as explored in this study. Whilst many sub-themes emerged, the five dominant themes that were revealed by thematic analysis were: concern, suitability for paediatric use, potential for parental administration, the role of the HCP and special populations. Capturing the opinions of parents, the ultimate decision-makers in paediatric vaccination, is crucial in the understanding of the eventual uptake of microneedle technology and therefore adds to literature currently available.

Six focus groups compiled the opinions of 32 participants (29 female). Such a gender imbalance is not unusual: mothers are found to be more likely to participate in clinical research [84]. Parental concern emerged as an overarching theme in this qualitative study. Participants alluded to established issues associated with conventional hypodermic needles, including phobias, pain, side effects and paediatric and parental anxiety [75, 78, 289]. In addition, some parents expressed concern regarding school vaccination programmes and their potential to cause hysteria, particularly in association with the administration of adolescent vaccines [290, 291]. These concerns may act as drivers for the acceptance of an alternative vaccine delivery system, such as microneedle technology. However, before a novel vaccine delivery system can be considered for acceptance, an effort must be made to address current vaccine concerns. Despite declaring that their children were fully vaccinated, one participant in this study expressed opinions which questioned the safety and efficacy of vaccines. Benin *et al* would categorise this participant as "vaccine-hesitant", accepting vaccination in spite of significant concerns [265, 292]. Vaccine hesitancy presents a significant challenge, requiring a multidisciplinary approach [293]. Many studies have shown that increasing knowledge alone will not change behaviour and reduce vaccine hesitancy [294]. Efforts focussed on determining how parents make decisions regarding vaccination, how their attitudes and beliefs develop, and where they obtain information, should contribute to better understanding of vaccine hesitancy [293, 295]. This study revealed that even "vaccine-acceptors", those who agree with or do not question vaccination [292], will question the safety and efficacy of novel immunisation methods [296]. In agreement with published literature, our results suggest that lack of familiarity may

act as a barrier to acceptance [84, 86, 261]. However this barrier may be diminished by highlighting the advantages of microneedle-patch vaccines over conventional vaccination, by administering adult vaccines, such as influenza, using microneedle technology before progressing to paediatric use [89, 101, 265] and by securing HCP endorsement [296]. In addition, it is likely that parents would benefit from educational programmes that highlight the manner in which safety and efficacy assessments are conducted prior to licensure [296].

Microneedle technology has been identified as ideal for paediatric use [84, 86, 261]. However, this is the first study which asked participants to specifically consider a patch delivery system and this resulted in both the suitability and feasibility being challenged. Whilst participants recognised and acknowledged the benefits of the technology, concern was expressed regarding the wear-time required. Vaccinees must wait for the required periods of time for the microneedle to detach from the backing layer or dissolve into the skin before the patch can be removed. Participants expressed concern that paediatric tolerance of such a requirement would be low. In agreement with previous research, it was suggested that by creating a child-friendly version of the delivery system, children may be encouraged to leave the patch in place for the required amount of time [261]. Various approaches have been developed to overcome the issue of prolonged wear-time [99]. Two layered dissolving microneedle and arrowhead microneedle, consisting of a therapeutic polymer layer and a shaft, respectively, have been designed to deliver with greater efficiency [297, 298]. Alternatively, a soft lithography approach based on a water soluble patch system has been introduced to increase delivery efficiency by dissolving the patch after microneedle application [299]. Given the parental

concerns expressed, these approaches may warrant further investigation for the delivery of paediatric vaccines.

A well-documented advantage of microneedle-patch vaccines is the potential for self-administration [86, 101, 110-112, 261]. One US study which examined the usability and acceptability of microneedle patches for self-vaccination against influenza reported that when given self-administration options, intention to be immunised increased significantly, suggesting that microneedle technology could increase vaccine coverage [101]. Of those participants who expressed a preference for microneedle-mediated immunisation, 72% preferred self-administration at home, 12% preferred self-administration in the presence of a HCP and 16% preferred administration by a HCP [101]. While self-administration of paediatric vaccines is not feasible, participants were asked to consider the acceptability of parental administration. The majority of participants in our study preferred vaccine administration by a HCP, contradicting research by Birchall *et al*, who reported that 80% of participants disagreed with the statement *"I don't think I would want to administer microneedles to a child in my care"* [86]. In agreement with previous research, participants suggested that the inclusion of a delivery indicator would be a desirable augmentation of the current design [86, 261]. A colour change was also suggested, combining dual benefits of increasing paediatric appeal and confirming delivery. Participants expressed concern that widespread parental administration could result in an intentional or unintentional reduction in immunisation rates and a decrease in population vaccine coverage overall. The national childhood immunisation programme, which recommends the administration of 15 vaccines from birth to approximately five years of age, is currently co-ordinated by General

Practitioners (GPs) and a series of Local Health Offices. The introduction of parental administration of vaccines would warrant the development of a National Immunisation Database, which would facilitate self-reporting of immunisation status and ensure vaccine traceability.

The purpose of this study was to determine the acceptability of vaccine delivery by microneedle technology. However, similar to previous research, participants discussed alternative uses of this technology, particularly in the management of conditions where repeated injections are warranted, such as insulin in the management of diabetes, analgesics in the management of chronic pain, anti-rheumatic agents in the management of arthritis and chemotherapeutic agents in the treatment of cancer [86]. The clinical assessment of microneedle-mediated delivery of many drugs and macromolecules is already established [74, 245, 246, 248-250]. Parental enthusiasm for microneedle-patch technology was increased by the exploration of alternative uses other than vaccination. It may be suggested that on-going monitoring in conditions such as diabetes is routine, thus providing continuous confirmation of efficacy, unlike vaccination, where confirmation of immunity is not routinely performed. By introducing microneedle technology for the management and treatment of these identified conditions, familiarity would be increased; there would be a tangible demonstration of safety and efficacy; and parental acceptance of microneedle-patch vaccines could be increased. In agreement with previous research, parents compared the delivery system to a sticking plaster and therefore expressed concern regarding the allergenic potential of microneedle-patch vaccines [84, 86, 261]. Similar to transdermal patch products,

the use of a hypoallergenic system to ensure more widespread suitability and to reduce allergy potential would be necessary.

HCPs including doctors, nurses and pharmacists will play a crucial role in the clinical success of microneedle-patch vaccines. Parent interactions with HCPs are a key factor shaping parental attitudes to vaccination [300]. An effective interaction can alleviate concerns of vaccine supportive parents and motivate a hesitant parent towards acceptance [33, 38]. These parental concerns are likely to escalate with increased complexity of vaccination schedules, increased access to information sources of variable reliability [134] and the emergence of novel immunisation methods, such as microneedle technology. HCP endorsement of a novel technology is critical to its success. Previous research has reported a positive response to microneedle technology by HCPs [86, 101]. Continuing professional development (CPD) could facilitate training in this technology and in parent engagement, according to proposed recommendations [301-303]. Guided by parental concerns expressed in relation to parental and self-administration, it is likely HCPs will retain the responsibility of vaccination, ensuring traceability and appropriate clinical management. Limitations of this study include small sample size (n=32), participant self-selection and the necessary provision of factual information by the moderator.

3.7 Conclusion

This is the first study to explore parental acceptance of microneedle-patch vaccines. While participants in this study remained tentative regarding microneedle technology, it was revealed that this tentativeness could be reduced by HCP endorsement. Therefore, this study has identified the role of HCPs in disseminating

information and providing support to parents. An increased awareness of developments in microneedle technology is needed to permit informed decision-making by parents.

3.8 Acknowledgements

The authors wish to thank the study participants for their invaluable contribution to the research.

3.9 Chapter conclusion and context within thesis

This chapter presented the findings of a qualitative focus group study which explored the parental perception of microneedle-patch mediated paediatric immunisation, therefore addressing the second objective of this doctoral thesis i.e. to ascertain the knowledge, attitudes, and beliefs of key stakeholders to elucidate vaccine decision-making and to identify barriers to vaccine uptake in Ireland. It had been suggested in Chapter 2 that needle fear may be a barrier to vaccine uptake and that microneedle technology may offer a solution. Focus group participants recognised the positive attributes of microneedle-patch mediated vaccination i.e. reduced pain and bleeding and attractive visual experience, but expressed concern in their lack of familiarity with the technology. While needle fear was acknowledged, the participants did not feel this was a significant deterrent to vaccination. This research has been published in a peer-reviewed journal and has been presented at conferences both nationally and internationally.

Chapter 4 Views of parents regarding human papillomavirus vaccination: a systematic review and meta-ethnographic synthesis of qualitative literature

Systematic review registration

Marshall S, Fleming A, Moore A, Sahm L. Knowledge, attitudes and beliefs regarding the adolescent human papillomavirus (HPV) vaccination: a systematic review and meta-ethnographic synthesis of the qualitative literature. PROSPERO 2017:CRD42017048714.

http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42017048714

Paper 3

Marshall S, Fleming A, Moore A, Sahm L. Views of parents regarding human papillomavirus vaccination: a systematic review and meta-ethnographic synthesis of qualitative literature. Research in Social and Administrative Pharmacy. 2018;15(4):331-337.

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Views of parents regarding human papillomavirus vaccination: A systematic review and meta-ethnographic synthesis of qualitative literature

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ABSTRACT

Introduction: Human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Three prophylactic HPV vaccines are available for the prevention of HPV-related disease. Despite clinical success, immunisation rates remain sub-optimal. The purpose of this systematic review is to synthesise qualitative literature to achieve an understanding of the drivers and barriers to HPV vaccine acceptability and to determine targets for an intervention to improve vaccine uptake.

Methods: The seven-step model of meta-ethnography described by Noblit and Hare was used. The quality of the studies was assessed using the CASP (Critical Appraisal Skills Programme) for qualitative research. The ENTREQ (Enhancing transparency in reporting the synthesis of qualitative research) statement was used to guide reporting of results.

Results: Thirty-three studies were included in the final analysis, compiling the opinions of 1280 parents/guardians from 14 countries. Five key concepts that reflected the principal findings of studies were determined: is prevention better than cure; the fear of the unknown; limited knowledge and understanding; complex vaccination decisions and; parental responsibility. Third-order interpretations were developed and linked using a 'line of argument' to develop a conceptual model.

Conclusion: The majority of parents are motivated to protect their children and prevent disease. The link to sexual intercourse associated with the HPV vaccine often complicates the vaccination decision. Vaccine manufacturers, national healthcare systems and healthcare providers can reinforce the importance of HPV immunisation and reiterate the rationale behind vaccination recommendations, by providing unambiguous information in a timely manner, transparently addressing parental concerns regarding vaccine safety and efficacy, whilst taking account of cultural and religious sensitivities and varying health literacy levels. In recent years, there has been a reduction in HPV vaccine uptake worldwide. Currently, there is a paucity of published qualitative studies addressing these new vaccine concerns. Therefore, such research is required to guide intervention development, to improve HPV vaccine uptake.

Author Contributions

SM was involved in the overall design of the research, registered the project on the International Prospective Register of Systematic Reviews (PROSPERO), developed a search strategy (in consultation with a health sciences librarian), performed the literature searches, assessed titles and abstracts of all retrieved citations, retrieved full articles for all potentially relevant studies, recorded individual study characteristics, wrote the draft manuscript and was involved in manuscript editing. SM, AF and LS assessed full articles for inclusion, assessed study quality using the Critical Appraisal Skills Programme (CASP) for qualitative research, read and independently identified key concepts, and performed the meta-ethnographic synthesis. SM, AF, AM and LS defined the inclusion and exclusion criteria. AF, AM and LS directed the study and edited the manuscript.

4.1 Abstract

Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract. Three prophylactic HPV vaccines are available for the prevention of HPV-related disease. Despite clinical success, immunisation rates remain sub-optimal.

Aim

The aim of this systematic review is to synthesise qualitative literature to achieve an understanding of the drivers and barriers to HPV vaccine acceptability and to determine targets for an intervention to improve vaccine uptake.

Methods

The seven-step model of meta-ethnography described by Noblit and Hare was used. The quality of the studies was assessed using the CASP (Critical Appraisal Skills Programme) for qualitative research. The ENTREQ (Enhancing transparency in reporting the synthesis of qualitative research) statement was used to guide reporting of results.

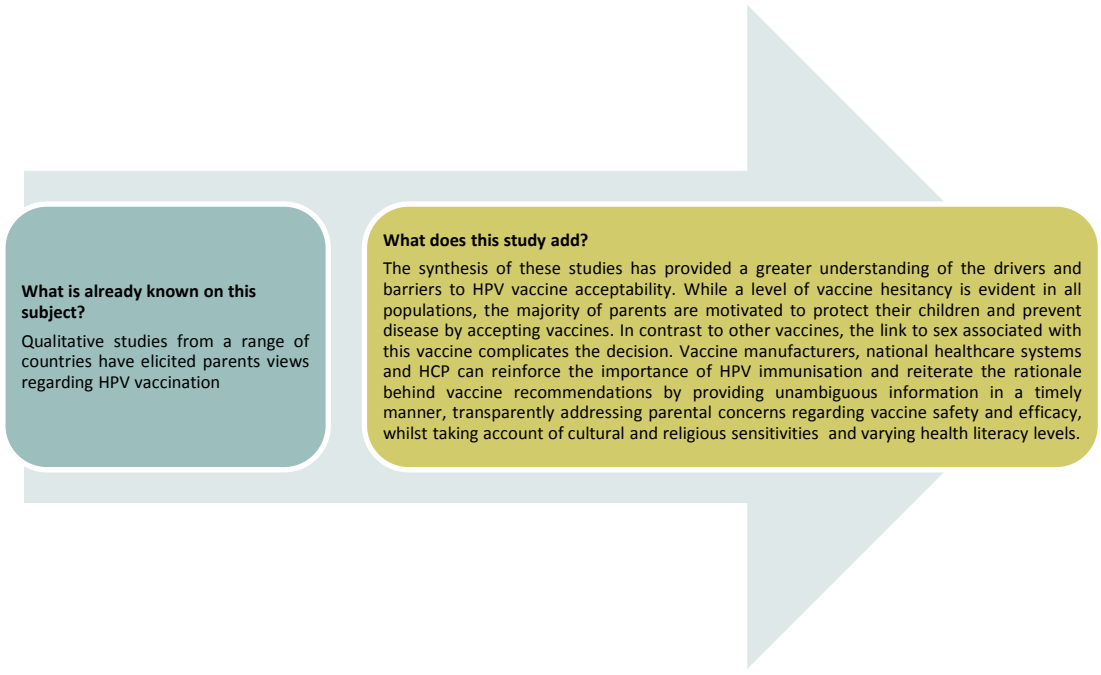
Results

Thirty-three studies were included in the final analysis, compiling the opinions of 1280 parents from 14 countries. Five key concepts that reflected the principal findings of studies were determined: is prevention better than cure; the fear of the unknown; limited knowledge and understanding; complex vaccination decisions and; parental responsibility. Third-order interpretations were developed and linked using a 'line of argument' to develop a conceptual model.

Conclusion

The majority of parents are motivated to protect their children and prevent disease. The link to sexual intercourse associated with the HPV vaccine often complicates the vaccination decision. Vaccine manufacturers, national healthcare systems and HCPs can reinforce the importance of HPV immunisation and reiterate the rationale behind vaccination recommendations, by providing unambiguous information in a timely manner, transparently addressing parental concerns regarding vaccine safety and efficacy, whilst taking account of cultural and religious sensitivities and varying health literacy levels. In recent years, there has been a reduction in HPV vaccine uptake worldwide. Currently, there is a paucity of published qualitative studies addressing these new vaccine concerns. Therefore, such research is required to guide intervention development, to improve HPV vaccine uptake.

Graphical Abstract



4.2 Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract in both men and women [304]. The virus is spread through contact with infected genital skin, mucous membranes or bodily fluids, and is transmitted through sexual intercourse [304]. Although the majority of HPV infections are asymptomatic, and resolve spontaneously within six to 18 months [305], persistent infection with HPV may result in disease, including cancers [304, 306-308]. It was estimated that 630 000 new HPV-related cancers occurred internationally in women in 2012, of which 530 000 were cervical cancer [304]. This resulted in an estimated 266 000 deaths worldwide, accounting for 8% of all female cancer deaths in that year [309]. Three prophylactic HPV vaccines are currently available and marketed in many countries worldwide for the prevention of HPV-related disease [144-146]. For the prevention of cervical cancer, the WHO recommends vaccination of girls aged 9-14 years, prior to onset of sexual activity [304]. While the maximum public health potential of HPV vaccination is not yet realised, ten years of vaccine usage has resulted in: a 90% reduction in HPV 6, 11, 16 and 18 infections and genital warts; a 45% reduction for low-grade cytological cervical abnormalities; and a 85% reduction for high-grade histologically proven cervical abnormalities [310]. Despite this clinical success, immunisation rates worldwide remain sub-optimal [147, 223], thus there is a need for interventions to increase vaccine uptake. Parents have the responsibility and authority to make healthcare decisions on behalf of their adolescent children. To develop a successful intervention, it is essential to understand the factors underlying parental apprehension. Qualitative

studies, from a range of countries have elicited parents' views regarding HPV vaccination and a synthesis of these studies has the potential to achieve a greater understanding of the drivers and barriers to HPV vaccine acceptability.

4.3 Aim

The aim of this review is to synthesise this qualitative literature and to determine targets for a theoretically informed, evidence-based intervention to improve vaccine uptake.

4.4 Methods

The seven-step model of meta-ethnography described by Noblit and Hare was used [311]. Meta-ethnography uses a process of comparison and cross-interpretation between studies while preserving the context of the primary data [311]. This synthesis method has the potential to provide a higher level of analysis, generate new research questions and reduce research duplication [312].

1. The first step involved a clear statement of the research question and the development of inclusion and exclusion criteria (Appendix 4.1). The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) and may be accessed at: http://www.crd.york.ac.uk/prospero/DisplayPDF.php?ID=CRD42017048714.
2. A search strategy was developed to retrieve articles related to the research question in consultation with a health sciences librarian at Mercy University Hospital, Cork (Appendix 4.2). The search was focused to locate primary studies that explored parent opinions on HPV vaccination. Three databases were searched using database-specific search terms: MEDLINE (Ovid), CINAHL and

EMBASE (Elsevier), from inception to December 2016. This was supplemented by searching databases of grey literature (Google Scholar) and reference lists of included citations. The search was not limited by language. Following removal of duplicates, the titles and abstracts of retrieved citations were assessed by one reviewer (SM). Full articles were retrieved for all potentially relevant articles. These articles were reviewed by three reviewers (SM, LS and AF) and were included if they fulfilled the inclusion criteria. Any disagreement regarding the eligibility of particular studies was resolved through discussion with a fourth reviewer (AM). The quality of included studies was assessed by SM, LS and AF, using the Critical Appraisal Skills Programme (CASP) for qualitative research [313]. However, studies that otherwise met the inclusion criteria, were not excluded based on the quality assessment, as lower quality studies may still provide evidence to address the research question [314].

3. Three reviewers (SM, LS and AF) carefully read the included studies and independently identified the key concepts from information detailed in the results and discussion sections of the studies. These included both first-order (views of participants) and second-order (views of authors) interpretations [315, 316]. In studies in which parents were included in focus groups with other individuals not meeting the defined inclusion criteria e.g. HCPs, the analysis was restricted to the views of the parents. In tandem with this process, SM recorded individual study characteristics, to provide the context for the interpretations and explanations of each study [316].
4. It was determined how the studies were related to each other by comparing individual findings. Key concepts were chosen which reflected the main findings

of all included studies. Data were entered into QSR International's NVivo V.11 software to assist our qualitative analysis and synthesis.

5. The studies were translated into each other, by examining the contribution of each study to a key concept. Similarities and differences in study findings were recorded.
6. Translations in each key concept were synthesised to develop third-order interpretations, linked using a 'line of argument' to develop a conceptual model which represents parental views regarding adolescent HPV vaccination.
7. Finally, the 'Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ)' statement was used to guide reporting of results [317] (Appendix 4.3).

4.5 Results

Thirty-three studies were included in the final analysis [174, 318-349] (Figure 13).

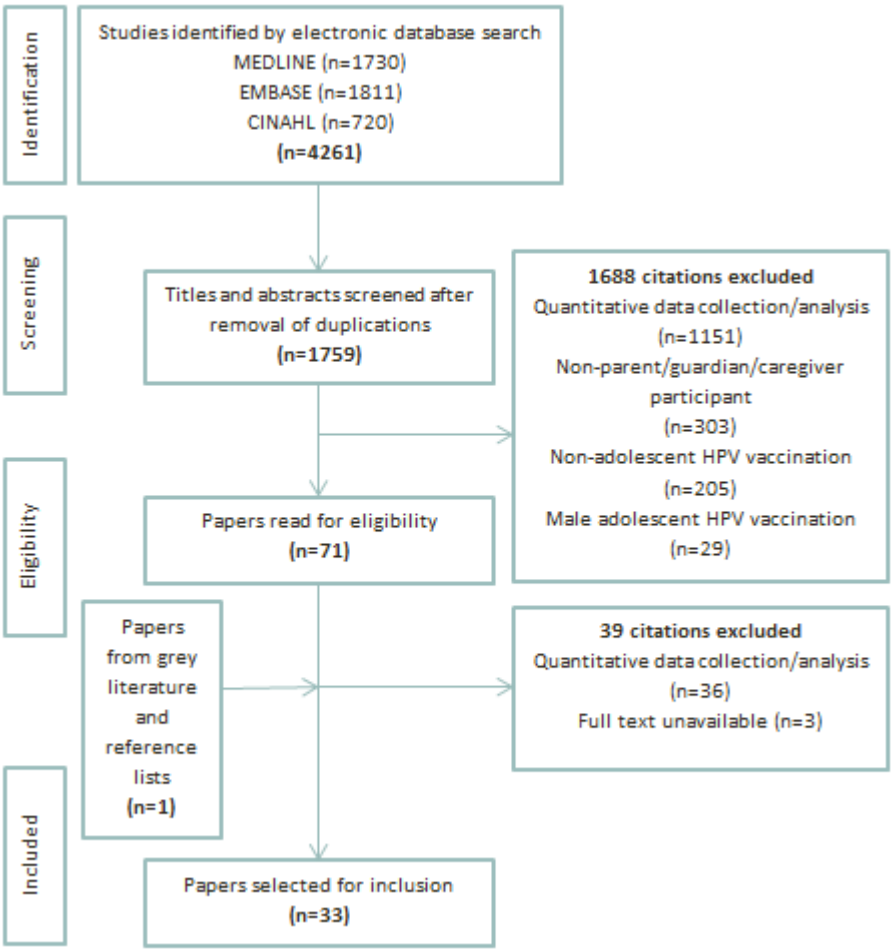


Figure 13 PRISMA flow diagram of search strategy

The included studies were conducted in 14 countries: Australia (n=1), France (n=1), Hong Kong (n=1), India (n=1), Kenya (n=1), Malaysia (n=1), Peru (n=1), Romania (n=1), South Africa (n=1), Sweden (n=1), Tanzania (n=1), United Kingdom (n=4), USA (n=17) and Vietnam (n=1). A total of 1280 parents were included. Twenty-two studies used interviews, seven studies used focus groups and four studies used a combination of interview and focus group methods. The HPV vaccine was available in the jurisdictions in which 26 of the studies were conducted, while seven studies were conducted prior to vaccine implementation [318, 326, 332, 339, 340, 343, 348] (Appendix 4.4). The overall quality of included studies was assessed to be

moderate to high (Appendix 4.5). A common weakness, found in 27 studies [318-333, 335, 338-342, 345-349] was inadequate researcher reflexivity, where the relationship between researcher and participants had not been adequately considered.

Five key concepts that reflected the principal findings of all studies were determined. Within each key concept, subthemes arose and are highlighted in bold. A summary of the occurrence of these key concepts and subthemes is provided in Appendix 4.6.

4.5.1 Is prevention better than cure?

The majority of parents expressed a desire to **prevent** HPV infection and its sequelae [174, 318, 319, 321, 324-327, 329-332, 334, 335, 337, 338, 340-343, 348, 349]. There was a high level of **vaccine acceptance in general** [174, 319-321, 326, 328, 329, 334, 339, 340, 342, 343, 348, 349], with parents recognising the **financial savings** associated with immunisations [319, 321, 325], especially in jurisdictions where there is a **lack of access to treatments** [319, 326]. Conversely, in several studies, a level of **vaccine hesitancy** was evident [174, 326, 334, 336, 337, 346, 348]: a behaviour influenced by a number of factors including issues of confidence, complacency and convenience [48]. Regarding the HPV vaccine specifically, some parents expressed **trust in the vaccine** [328, 329] and were reassured by the **use of the vaccine elsewhere** [321, 328, 334]. In addition, some parents felt it would be important to participate in immunisation programmes, if **access** was provided [174, 326, 328, 332, 349].

4.5.2 The fear of the unknown

Parents expressed their concerns and their lack of familiarity associated with this **new vaccine** [174, 321, 324, 328-330, 333, 334, 336, 343, 349]. The **safety and efficacy** of the vaccine was discussed in detail [174, 318, 320-322, 324-326, 328, 332-335, 338, 340, 341, 344-349], in particular the potential for **side effects**, ranging from mild discomfort to paralysis, infertility, impaired development, increased risk of HPV infection and cancer, allergy, autism and death [174, 319, 321, 322, 325, 326, 328, 330, 332, 334, 336, 339, 340, 342-345, 348, 349]. Some parents viewed the vaccine as **experimental** [319, 321, 322, 332, 335, 347], fearing their children could be 'guinea pigs' in a clinical trial. Others suspected a **conspiracy theory**, whereby the vaccine was a tool to impair fertility and therefore reduce the world population [322, 336, 343]. These factors encouraged **watchful waiting**; whereby parents delayed vaccination until their concerns were alleviated [174, 318, 321, 323, 324, 333, 334, 336-338, 341, 342, 349]. Some parents were concerned that vaccination would give their daughter a false sense of security and invincibility, leading her to **engage in risky behaviour** [334, 336, 341, 343, 347-349], impacting their sexual and general health. Conversely, parents discussed their **fears of HPV infection and cancer** [321, 330, 331, 335, 345]. The potential for **anticipated regret**, should they withhold vaccination was explored [328-330, 334]: the potential that their child could suffer unnecessarily from a vaccine-preventable illness. Parents also discussed how HPV vaccination could offer a level of protection and security if the **sexual history or activity of a partner is unknown** [174, 318, 324, 327, 334-336, 349].

4.5.3 Limited knowledge and understanding

The majority of parents exhibited **limited knowledge** of the HPV vaccine [174, 318, 320, 325-328, 330-332, 334-345, 347-349] and recognised that this **limited knowledge prevents them from making an informed decision** regarding vaccination [318-320, 322, 324, 330, 333, 335, 338, 341, 345, 347-349]. A **lack of understanding** was evident from the majority of studies [174, 318, 319, 321, 322, 325, 326, 329-338, 340, 341, 345-349], in particular regarding the recommendation for vaccination at such a **young age** [174, 318, 321, 322, 324, 328, 330, 333-336, 338, 341, 344, 346-349], prior to sexual debut. In some studies, the low levels of knowledge and understanding was reportedly associated with **limited health literacy** [327, 331, 340, 347], the reduced capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions [67].

4.5.4 Complex vaccination decisions

These studies highlighted the multifactorial process involved in making healthcare decisions. Parents believed that **provision of information** [174, 319, 321, 326, 328, 329, 332, 333, 337, 341, 343, 345, 347] would encourage vaccination, while **poor provision of information** [174, 318, 321, 322, 328, 331, 341, 344, 347-349] was identified as a barrier to acceptance. The desire to vaccinate was often associated with parental **perception of risk** [174, 318, 321, 323, 324, 327, 329, 331, 332, 334-339, 341, 342, 344, 348, 349]: those parents who accepted that their daughter was already or would become sexually active. Conversely, many parents declared a **low perception of risk** [174, 318, 321, 323, 324, 326, 327, 333, 334, 336-339, 341, 344,

346-349], and questioned the necessity of HPV vaccine. These believed their daughters' young age and/or their sexual education and cultural or religious upbringing would preclude sexual activity and thus protect against infection. The role of the HCP, namely the family physician, was discussed across the studies. Many parents discussed how **HCP endorsement** of the vaccine [235, 321-324, 326, 327, 329-331, 333-335, 339-341, 344, 345, 347-349], **trust in the healthcare system** [174, 322, 327-331, 340, 344, 347-349] and a **governmental immunisation programme** [321, 326, 328, 340, 343] would persuade them to vaccinate their daughters. In contrast some parents expressed a **lack of trust in the healthcare system** [174, 322, 324, 326, 349], believing that the physicians were endorsing the vaccine, in accordance with the pharmaceutical industries [328], for personal financial gain. Parents also discussed how they can be influenced by **media coverage** of the HPV vaccine and vaccines in general, both positively [321, 329] and negatively [174, 321, 328, 329, 334]. In addition, parents discussed how **vaccine support from peers** [174, 322, 327, 329, 334, 336] and **family members** [174, 329, 334, 336, 344] can encourage immunisation while indifference or a lack of vaccine support can act as a deterrent [174, 322, 327, 329, 334, 336, 344]. A minority of parents stated they would take their daughter's opinion into consideration [327, 329, 348]. Vaccine **cost** was a major consideration [325, 332, 335, 340, 344, 348, 349], with many parents discussing how pricing might prevent access. Those parents with **personal experience of HPV and HPV-related illnesses** were motivated to accept vaccination for their daughters, to prevent the suffering they had experienced [174, 319, 321, 324, 327-329, 331, 334, 335, 337, 348]. In addition, some parents felt that by **marketing as a cancer vaccine**, the sexual stigma could be

reduced [332, 337]. **Optional vaccination** appeared to reduce desire to vaccinate [333, 341, 346] while **mandatory vaccination** and inclusion in national immunisation programmes reinforced the importance of the HPV vaccine [349].

4.5.6 Parental responsibility

The majority of parents felt it was their responsibility to **protect** their daughters from HPV infection and its sequelae, by accepting vaccination [174, 235, 318, 319, 321, 324, 326-331, 334-337, 342, 344, 346-349]. In addition, some parents understood the concept of herd immunity and perceived the **societal responsibility** to vaccinate [328]. Conversely, some parents felt that it was their duty to **protect** their daughters from perceived harmful side effects associated with this novel vaccine and refuse immunisation [322]. When considering a vaccination decision, many parents chose to **defer responsibility** [318-320, 322, 324, 327, 334, 336, 339] to a family member, such as a spouse, parent or daughter, while others preferred to follow guidance provided by their HCP, as already presented. Parents were happy to exert **control over their daughters healthcare decisions** [174, 323, 328, 329, 331, 333, 344, 349]. Many parents feared that vaccinating against a sexually transmission infection might **encourage sexual activity** [318, 319, 330, 334-336, 339, 341, 342, 346-349]. Parents felt this link to sexual activity warrants a **difficult conversation** [174, 325, 326, 330, 334-336, 339, 347] with their daughters, a conversation that many would be uncomfortable with conducting. Another factor that some parents were uncomfortable with was the **requirement for parental consent** [319, 322], believing that this would equate to an acceptance of

responsibility for any harm caused by the vaccine. This last finding was only evident in jurisdictions where parental consent was not usually required for vaccination.

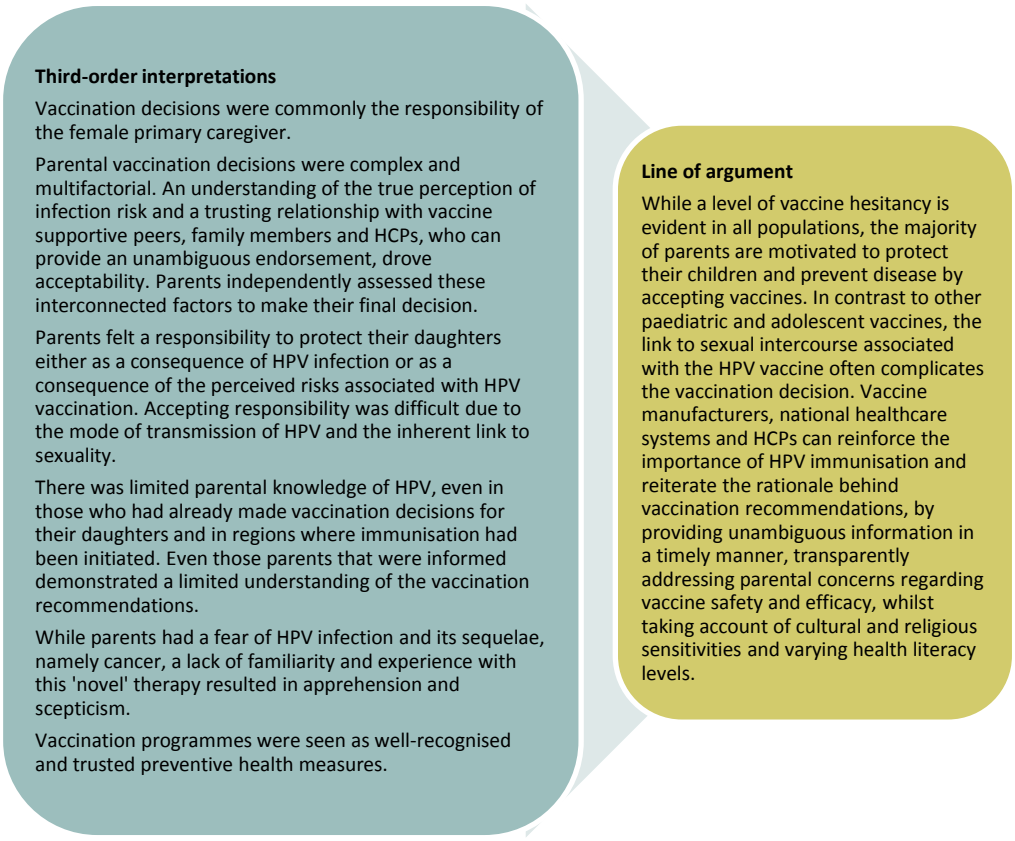


Figure 14 Developing the line of argument

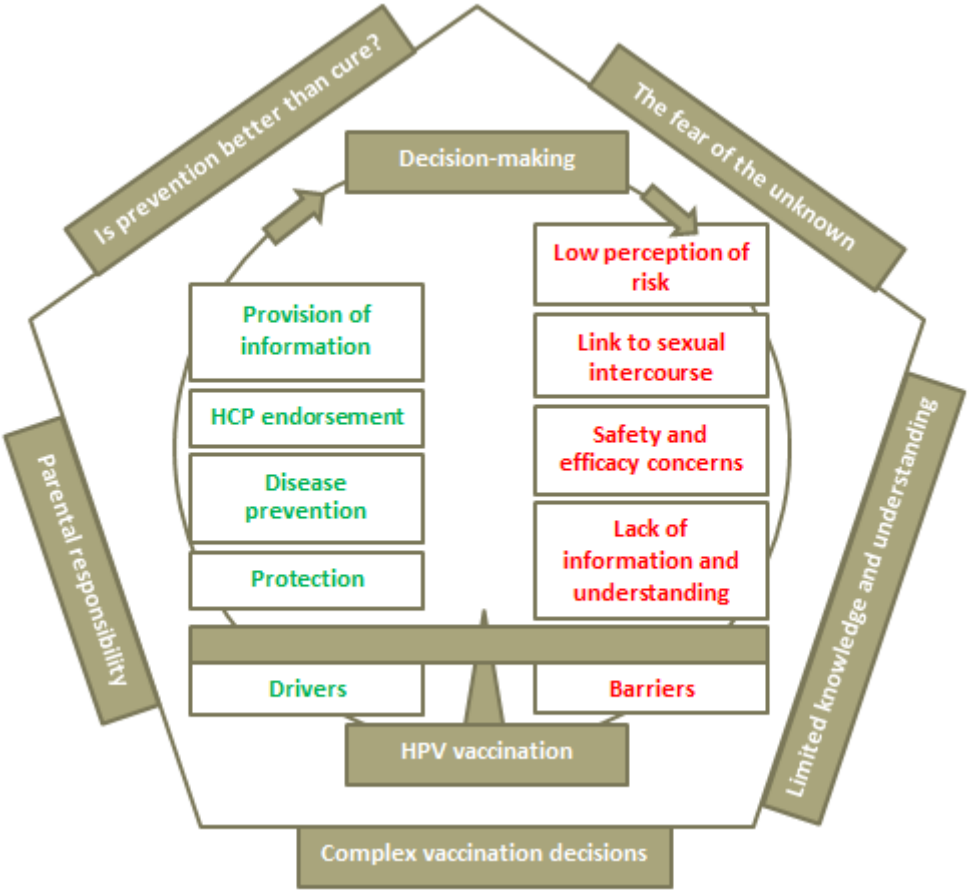


Figure 15 Conceptual Model

4.6 Discussion

This article is the first, to our knowledge, to systematically review and analyse the qualitative literature on the parental views regarding adolescent HPV vaccination. The five key concepts, combined to produce a novel conceptual model (Figure 15), highlight the separate, yet interacting factors that require intervention to improve vaccine uptake. Interestingly, there is no difference in the occurrence of concepts and sub-themes in regions where vaccination has been initiated compared to those where it has not. Nor is there a difference in their occurrence in high-income countries compared with low- to middle-income countries. However, it is important

to note that these concepts are not necessarily representative of all participants within each study, due to the qualitative nature of the research.

In agreement with published literature, this synthesis has demonstrated how healthcare decisions, such as vaccinations, are commonly the responsibility of the female primary caregiver [350-352]. However, in some studies, it was evident that the decision-making appeared to be centred on the father [319, 336]. These studies conform to certain gender culture guidelines which stipulate that males should demonstrate masculinity and strength by exerting control over their families [353], an important consideration if designing an intervention for such populations. It is clear that vaccination decisions are complex and multifactorial. The success of a vaccination programme is often dependent on parental understanding of the true perception of infection risk. Perceptions of risk are subjective and depend fundamentally on circumstances [354]. In this synthesis, a low perception of risk was primarily associated with the young vaccination age [174, 318, 321, 322, 324, 328, 330, 333-336, 338, 341, 344, 346-349]. At this age, parents do not believe their children to be sexually active, thus the urgency of vaccination is reduced. This was particularly evident in populations where religious beliefs vehemently oppose pre-marital sexual activity [174, 334, 336, 346, 347, 349]. In addition, parents were often concerned about the potential encouragement of sexual activity associated with vaccination [318, 319, 330, 334-336, 339, 341, 342, 346-349] and the difficult conversation associated with vaccination decisions due to the inherent link to sexuality [174, 325, 326, 330, 334-336, 339, 347]. The rationale for recommendation of vaccination at 9-14 years is two-fold: the immune response to the vaccine is superior in this age group and it maximises the potential for

immunisation prior to HPV virus exposure. It is important that parents understand this rationale and the importance of vaccination, regardless of their personal perception of risk.

This synthesis highlights the crucial role played by HCPs, namely physicians, in the continuing success of HPV vaccination. It was repeatedly reported that an unambiguous endorsement of vaccination will drive acceptability [183, 321-327, 329-331, 333-335, 339, 341, 344, 345, 347-349]. Effective interactions with HCPs have the potential to alleviate concerns of vaccine supportive parents and motivate a vaccine-hesitant parent towards acceptance [33, 38]. A recent study reports that HCPs endorse the HPV vaccine less enthusiastically than other vaccines [355], perceiving HPV discussions as laborious and garnering less support. These interactions are likely to discourage timely HPV vaccination and encourage watchful waiting, as evident from this synthesis [174, 318, 321, 323, 324, 333, 334, 336-338, 341, 342, 349]. This highlights the requirement for the development of communication strategies to support HCPs in recommending the HPV vaccine with confidence. This review has shown the diverse and sometimes conflicting views in parent groups within the same study, from similar social, cultural, educational and religious backgrounds. Therefore it is essential that HCPs are cognisant of these differences. Continuing professional development could facilitate training in adaptable parent engagement, according to proposed recommendations [301-303].

This review also describes the limited parental knowledge of HPV, even in those who have already made vaccination decisions for their daughter, in regions where immunisation has been initiated. Even those parents that appear knowledgeable demonstrate a limited understanding of the vaccination recommendations. An

effort should be made to evaluate the standardised information provided to parents regarding the HPV vaccine for accuracy, readability and understandability, with a special consideration for those of lower health literacy levels [356].

It is clear that parents are motivated to protect their children [174, 318, 319, 321, 322, 324-331, 334-337, 342, 344, 346-349] and are fearful of HPV infections and their sequelae, namely cancer [321, 330, 331, 335, 345]. However, a lack of familiarity with the novel HPV vaccine results in apprehension [174, 321, 324, 325, 328-330, 333, 334, 336, 343, 349] and safety and efficacy concerns [174, 318, 320-322, 324-326, 328, 332-335, 338, 340, 341, 344-349]. The most commonly suggested unknown side effect was the potential for impaired fertility following immunisation [319, 321, 322, 326, 332, 336, 343, 344, 349]. To reassure parents of the safety of HPV vaccination, information pertaining to the known side effects: pain, redness, swelling of the injection site; headache; dizziness; nausea; and/or mild pyrexia, should be transparently provided.

Research has shown how parental concerns can be escalated by increased access to information sources of variable reliability [134], namely the internet [357]. Widespread use of online information-seeking predated the rise of interactive content, targeted advertising and social networking, which prevents the regulation of information that reaches parents [357]. Much of this online information contains anti-vaccine content [130, 358-361], often presented in scientific language to lend an air of legitimacy [130]. This makes it difficult for parents to determine the accuracy and validity of retrieved information. Acknowledging this issue, the WHO initiated the Vaccine Safety Net Project, in 2003 [362]. The ongoing, ever-expanding project is a global network of websites that provide reliable, scientifically based

information on vaccines. The network is currently reviewing Facebook pages to deliver trustworthy vaccine safety messages to more diverse audiences. This expansion could permit personalisation of healthcare information: the dynamic customisation of generic vaccine information, to specifically address the needs of the individual [363].

4.6.1 Implications and contribution: HPV vaccine crisis

Due to the significant overlap and recurrent data reported by the primary studies, it would appear unlikely that further research in this area would generate new themes. However, in recent years, there has been a reduction in vaccine uptake in several countries worldwide including Denmark, France, Japan and Ireland [223, 364-366]. This observed reduction is primarily due to a series of case reports which identify a range of new onset chronic conditions, occurring post immunisation. Comprehensive reviews of both pre- and post-licensure data provide no causal link and the reported incidence of these conditions is within the expected range of the general population [367, 368]. However, countries remain unconvinced: in Denmark, the Ministry of Health announced and conducted an independent investigation into the safety of the vaccine; in Spain, the Association of People Affected by HPV vaccine (AAVP) was created and a prominent public health professor spear-headed a petition that calls for a moratorium on vaccination; in the UK, the Association of HPV Vaccine Injured Daughters (AHVID) was created; in France, a petition signed by more than 700 doctors and 300 midwives was sent to policymakers demanding further investigation; and in Japan, the Ministry of Health, Labour, and Welfare suspended proactive vaccine recommendations [171]. Since its

introduction in Ireland in 2010, maximal vaccination rates of 86.9% were reported in 2014/2015 [168]. These rates decreased to 72.3% in 2015/2016, and to 50% in 2016/2017 [26]. Interventions are urgently required to restore confidence in the HPV vaccine. It is likely that effective interventions will be multi-component, using a combination of strategies including: engagement of religious or other influential leaders to promote vaccination; mass media; improving convenience and access to vaccination; mandating vaccinations or imposing sanctions for non-vaccination; employing reminder and follow-up; communication training for HCPs and; offering non-financial incentives [189]. Currently, there is a paucity of published qualitative studies addressing these new vaccine concerns. Therefore, such research is required to guide intervention development, to improve HPV vaccine uptake.

4.8 Acknowledgements

The research team would like to thank Mr Joe Murphy, Medical Librarian, for his assistance with the search strategy for this systematic review.

4.9 Chapter conclusion and context within thesis

This chapter presented the findings of an extensive systematic review and meta-ethnographic synthesis of the qualitative literature on the views of parents regarding HPV vaccination, thereby addressing the first objective of the doctoral research i.e. to generate an evidence-base. Systematic reviews are the gold standard to search for, collate, critique and summarise the best available evidence and the meta-ethnographic synthesis method has the potential to provide a higher level of analysis, and generate new research questions. Similar to Chapter 2, the research conducted in this chapter informed the design of qualitative studies,

presented in Chapters 4 and 5. These chapters seek to address the research question: 'what are the views of key stakeholders (adolescents and parents), in light of recent HPV vaccine instability?' This research has been published in a peer-reviewed journal and has been presented at conferences both nationally and internationally.

Chapter 5 A systematic approach to map the adolescent human papillomavirus vaccine decision and identify intervention strategies to address vaccine hesitancy

Paper 4

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Original Research

A systematic approach to map the adolescent human papillomavirus vaccine decision and identify intervention strategies to address vaccine hesitancy

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ABSTRACT

Objectives: Unsubstantiated safety concerns with human papillomavirus (HPV) vaccines continue to linger. This study sought to identify factors that influence the adolescent HPV vaccine decision and systematically identify intervention functions and strategies likely to be effective in reducing vaccine hesitancy.
Study design: This is a qualitative focus group study.
Methods: Focus groups were conducted with female adolescents (aged 14–16 years) in Cork and Kerry. During focus groups, the trained facilitator used a semistructured, Theoretical Domains Framework (TDF)–based topic guide to prompt discussion. Transcripts were thematically analysed using the TDF and Behaviour Change Wheel. Behaviour Change Technique Taxonomy version 1 was used to suggest intervention functions and strategies for addressing HPV vaccine hesitancy.
Results: A total of 50 adolescents (96% vaccinated), participated in 10 focus groups. The key themes were presented by means of the relevant TDF domains. Seven domains were selected as the most relevant: knowledge, social influences, beliefs about capabilities, optimism, beliefs about consequences, emotion and environmental context and resources. Five intervention functions were identified, education, persuasion, enablement, modelling and environmental restructuring, and linked to 11 relevant Behaviour Change Technique (BCTs). Potential intervention strategies were developed.
Conclusions: This study provided a detailed insight into behavioural factors influencing the vaccine decision-making process. It was identified that awareness and knowledge about HPV and its health sequelae was low. Lack of information is a well-recognised determinant of vaccine hesitancy. Therefore, education was recommended as a key area to address in future intervention studies.
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Author Contributions

SM was involved in the overall design of the research, designed the topic guide, completed the application for ethical approval, recruited participants, facilitated the focus groups, transcribed the audio-recordings, wrote the draft manuscript and was involved in manuscript editing. SM, AF and LS analysed the results. AF, AM and LS directed the study and edited the manuscript.

5.1 Abstract

Introduction

Unsubstantiated safety concerns with Human Papillomavirus (HPV) vaccines continue to linger.

Aim

This study sought to identify factors which influence the adolescent HPV vaccine decision and systematically identify intervention functions and strategies likely to be effective in reducing vaccine hesitancy.

Methods

Focus groups were conducted with female adolescents (14-16 years) in Cork and Kerry. During focus groups, the trained facilitator used a semi-structured, Theoretical Domains Framework (TDF)-based topic guide to prompt discussion. Transcripts were thematically analysed using the TDF and Behaviour Change Wheel (BCW). The Behaviour Change Technique Taxonomy version 1 (BCTTv1) was applied to suggest intervention functions and strategies for addressing HPV vaccine hesitancy.

Results

A total of 50 adolescents (96% vaccinated), participated in 10 focus groups. The key themes were presented by means of the relevant TDF domains. Seven domains were selected as most relevant: knowledge, social influences, beliefs about capabilities, optimism, beliefs about consequences, emotion, and environmental context and resources. Five intervention functions were identified: education,

persuasion, enablement, modelling, and environmental restructuring and linked to 11 relevant BCTs. Potential intervention strategies were developed.

Conclusion

This study provided a detailed insight into behavioural factors influencing the vaccine decision-making process. It was identified that awareness and knowledge about HPV and its health sequelae was low. Lack of information is a well-recognised determinant of vaccine hesitancy. Therefore education was recommended as a key area to address in future intervention studies.

5.2 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide [140]. Although the majority of infections are transient, persistent infection is a pre-requisite for pre-cancerous lesions and malignancies, including cervical and oropharyngeal cancers [142]. Three prophylactic HPV vaccines are marketed for the prevention of HPV-related disease, intended to be administered before the onset of sexual activity. By the end of 2017, 80 countries had included the HPV vaccine in their immunisation programmes. In Ireland, the Health Service Executive (HSE) has offered the quadrivalent vaccine to all girls in the first year of second level schools, vaccinating more than 240,000 girls since 2010 [148]. There is high grade evidence that HPV vaccines protect against cervical pre-cancer in adolescent females [369], with significant decreases in vaccine-type HPV in vaccinated women [150]. In addition, HPV vaccines have been shown to reduce abnormal screening tests, colposcopies and excisions [151]. This reduction in diagnostic and therapeutic procedures not only lowers healthcare expenditure

[151, 152] but also reduces their negative psychological effects for the women involved [153]. The safety of these vaccines is well established [155, 156]. However, recently there has been a focus on a number of safety signals for the vaccines [154]. While none have been substantiated [155], they remain a public concern. In Ireland, maximal vaccination rates of 86.9% were reported in 2014/2015 [168] but these plummeted to 50% in 2016/2017 [26]. While significant research has been conducted into determining vaccine acceptability in parent populations [4], minimal research has included the views of adolescents; the intended vaccinees. Research, guidelines and policies stress the importance of including adolescents in healthcare decisions [370, 371]. Therefore stakeholder engagement, including both adolescents and parents is integral to the successful development of interventions, urgently required to restore confidence in the HPV vaccine [372].

Changing behaviour is complex and a systematic approach is required to understand the factors that influence vaccine hesitancy, so as to inform the design of future interventions. In general, providing information alone does not change behaviour [179, 180]. Instead, one must gain an insight into the knowledge, beliefs, attitudes and current behaviours of the target audience, and the environmental context in which they occur [373]. The Theoretical Domains Framework (TDF) is a framework which has synthesised 33 theories of behaviour and behaviour change, clustered into 14 domains [206]. The TDF is useful for understanding the factors influencing specific behaviours [206, 374]. The associated Behaviour Change Wheel (BCW) is a synthesis of 19 behaviour change frameworks that draw on a wide range of disciplines and approaches and connects this understanding to intervention design [210, 375]. The BCW links behaviour components with capability,

opportunity and motivation (COM-B model) [375]. The Behaviour Change Technique Taxonomy version 1 (BCTTv1) is a set of active components developed to standardise the content and reporting of intervention studies [215].

5.3 Aim

This study sought to identify factors which influence the adolescent HPV vaccine decision and systematically identify intervention functions and strategies likely to be effective in reducing vaccine hesitancy.

5.4 Methods

5.4.1 Ethical approval

Ethical approval was obtained from the Social Research and Ethics Committee, University College Cork (Log 2016-122).

5.4.2 Data collection

A list of second level schools (n=67) and education centres (n=12) was compiled and classified according to the Irish Pobal HP Deprivation Indices [376]. The (i) recruitment poster, (ii) informed consent form and (iii) cover letter detailing the project overview, (Appendix 5.1-5.3) were sent to each school principal. Focus group participants were recruited using purposive sampling: the principal invited eligible students to participate. Inclusion criteria included self-declared satisfactory English language, female gender and aged 14-16 years. A TDF-based topic guide, with a semi-structured design was developed based on a review of previous literature and discussion among the authors (Appendix 5.4). All focus groups were conducted by SM, a female pharmacist/clinical pharmacy researcher, with

experience in conducting qualitative research. Focus group methods were chosen as they are recognised as a valuable means of eliciting adolescent's views on health-related matters [377, 378]. The facilitator prompted and explored issues in more detail as appropriate [379]. Written informed consent to participate was obtained, via the school Principal, from the parent of each participant. Focus groups were conducted until no new themes emerged. Field notes were recorded after each session.

5.4.3 Data analysis

Audio-recorded sessions (OLYMPUS Digital Voice Recorder VN-731PC) were transcribed verbatim by SM and preliminary familiarisation was begun during the transcription process. Computer software (QSR International's NVivo V.11) was used to organise the data and analysis. Each participant was assigned an anonymised identifier. Transcripts were verified against audio-recordings with a random sample verified by an independent researcher and analysed using an inductive thematic analysis. Codes were compared within and between focus groups for constant comparison. Transcripts were independently coded by one other member of the research team (LS and AF) and any disagreements were resolved through discussion. The codes were then attributed to the domains of the TDF. The TDF domains were then linked to the core COM-B components of the BCW [204]. The COM-B model recognises that behaviour is part of an interacting system involving capability, opportunity and motivation [204]. Finally, the BCTTv1 was applied to suggest intervention functions and strategies for addressing HPV vaccine hesitancy [204, 210, 215]. The APEASE (Affordability, Practicability, Effectiveness

and cost-effectiveness, Acceptability, Side-effects/safety and Equity) criteria were applied to select the most appropriate intervention functions and BCTs [210]. Reporting was guided by the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [380] (Appendix 5.5).

5.5 Results

Ten focus groups were completed between the 10th November 2017 and 5th February 2018 (12.66% recruitment rate). Focus groups were completed on school grounds and had a mean duration of 36 minutes (range: 21 to 55 minutes). The opinions of 50 adolescents were compiled: two unvaccinated, 48 vaccinated (Appendix 5.6). The key themes are presented by means of the relevant domain from the TDF. Participant quotes are represented in italics.

Theoretical Domains Framework

Based on a familiarisation with the theoretical constructs under each domain [206] and a comprehensive review of the themes, seven key TDF domains were selected as the most relevant [381].

Knowledge

Knowledge of HPV, HPV-related disease and HPV vaccination was poor among all adolescents. Some were aware that the HPV vaccine was a *"cancer vaccine"*, but were unable to elaborate. Understanding of the topic was also limited, with participants being unfamiliar with the association between sexual activity, HPV and cervical cancer. In addition, some adolescents expressed doubt in their parents' understanding of the topic. The participants expressed the requirement for basic information, questioning the efficacy, safety and mechanism of action of the

vaccine, requested international data on *Gardasil®* and discussed how expected adverse drug reactions (ADRs), including potential pain should be divulged in full. However, pain was primarily discussed by those needle-phobic participants, and acknowledged as an acceptable vaccine side effect by the majority.

> *"…just a pinch and you're done I mean there are other things that definitely hurt way more…"* (P28, vaccinated, 16 years).

In spite of their poor knowledge and understanding, the participants were intrigued by the topic, constantly questioning and seeking information.

Social influences

The responsibility for vaccine decision-making was clearly assigned to the parent. Participants discussed how they were influenced by their parents and often accepted the parental recommendation, with minimal or no discussion. The requirement for parental consent further consolidated the role of the parent as decision-maker.

> *"I'd probably listen to my mam too, she's not going to let me get something that's not good for me"* (P3, vaccinated, 15 years),
>
> *"You kind of just have to do whatever your parent…or whoever is signing the form, says"* (P21, vaccinated, 15 years).

Participants acknowledged the influence of HCPs, who they believed were equipped to guide the vaccine decision, either positively or negatively. However, adolescents discussed how they felt obliged to follow recommendations without discussion and without active participation, highlighting their lack of influence in the decision.

"Because they're not going to tell you to get something if you shouldn't, they know your background and stuff so they'll know what you need, and what you don't" (P38, vaccinated, 15 years),

"…like if my doctor said not to get it, then it would be hard for me to get it then because you should probably do what your doctor says" (P42, vaccinated, 16 years).

Participants also viewed vaccinated peers as role models, as a source of information and feedback, on their experience with the vaccine. They acknowledged their own potential to become role models to unvaccinated girls, once vaccinated.

"I'd listen to people who had gotten it already 'cos they've been through it and they know the story" (P26, vaccinated, 16 years).

"If they were nervous about getting the vaccine because of the side effects, I'd say I got it and look at me, I'm grand, you should just get it" (P22, vaccinated, 15 years).

Group conformity and the power of the social norm was a major theme, with many adolescents admitting to conforming to the behaviour of their peers.

"I'd probably be more worried if a load of people weren't getting it, you'd be wondering why not…I think it might make me not want to get it" (P21, vaccinated, 15 years).

Beliefs about capabilities

Some participants felt, on reflection, that they would have been capable of making the vaccine decision and would have appreciated this empowerment and were disappointed with the lack of autonomy and choice afforded.

"If you were given, told what it was about then you might have (been able to make the decision), it's not that hard, I know parents just make the decision for you but it would be nice to know a bit about it before they just jab you in the arm…" (P31, vaccinated, 16 years),

However, many preferred to defer responsibility to the aforementioned individuals, justifying their lack of involvement in the decision with poor knowledge and young vaccination age, associated with a lack of sexual experience and an inability to comprehend the complexities of the HPV vaccine.

"…it's probably better to let the parents or whoever decide, I mean, what do you know about vaccines or even cancer, when you're 13?…" (P35, vaccinated, 15 years).

Optimism

While many participants believed that freedom of medical choice regarding immunisation should remain, they were optimistic that teenage girls and their parents would accept HPV vaccination, should they receive appropriate information.

"…if people get all the information and they understand what the vaccine is for and what will happen if they don't get it…I think people would risk a lot to stop them getting cancer" (P34, vaccinated, 16 years).

Beliefs about consequences

Vaccination was viewed as an accepted norm and participants recognised the importance and benefits of immunisation.

"Some diseases aren't even around anymore, if enough people get them… If there's a vaccine there, I'll want to get it" (P32, vaccinated, 15 years).

The participants discussed the consequences of vaccination, confident in its effect yet pragmatic in its ability to prevent cancer and acknowledged the potential for anticipated regret should vaccination be refused.

"Even if it's not guaranteed to stop you getting cancer, it's better than nothing, it means it's something less to worry about" (P31, vaccinated, 16 years).

"Imagine how they'd feel in a few years or whatever if they got cervical cancer" (P22, vaccinated, 15 years).

Emotion

Vaccination was an emotive topic. Adolescents discussed their fear of needles, fear of cancer, fear of vaccine side effects and fear of the unknown.

"…even if you're scared of needles, you should be way more scared of cancer" (P38, vaccinated, 15 years),

"…it's a way bigger deal getting cancer than it is getting another disease like a cold or whatever, cancer can kill you" (P46, vaccinated, 15 years),

"As long as they're safe...and parents are worried about the side effects…" (P7, vaccinated, 16 years),

"…it doesn't mean you will get cancer but you don't know what's going to happen in the future so it's better to just get it done" (P28, vaccinated, 16 years).

However, even those who exhibited needle-phobic tendencies revealed that these fears did not discourage vaccination.

> *"…even though I hate needles, if it stops cancer, then I'd get a million needles"* (P15, vaccinated, 16 years).

Two of the adolescents realised that they had not received the HPV vaccine. This was not an intentional avoidance of immunisation: these girls were not enrolled in formal education when the vaccine was offered and expressed fear and anxiety over this missed opportunity.

Environmental context and resources

Adolescents acknowledged the influence of the government immunisation programmes, expressing the view that the vaccine would not be offered free of charge if it was unsafe or ineffective:

> "*The government isn't going to pay for the vaccine for children unless they need it and it's good for them so if the government says to get it, I would"* (P32, vaccinated, 15 years).

Some participants acknowledged their awareness of alleged Adverse Drug Reactions (ADRs) associated with the vaccine and expressed safety concerns due to media exposure: the primary information source that was mentioned was radio. None of these girls were able to recall any details of the vaccine reactions and were non-specific in their knowledge.

> *"Wasn't there girls who said they had problems after getting the vaccine? I think it was seizures? I heard about it on the radio and there was a girl who*

had to leave school because of it, she couldn't walk after it" (P7, vaccinated, 16 years).

However, some participants discussed how this negative media attention had resulted in a variation in vaccine uptake among family members and how the participants themselves would potentially change their mind about the vaccine in light of recent information:

"Mum was like, I know you're fine but I wouldn't let you get the vaccine, if you were back in first year, I don't know if my sister got it after me either" (P7, vaccinated, 16 years).

Conversely, many participants expressed a lack of belief in the girls allegedly affected by the vaccine, believing them to be over-reactive and attention-seeking.

Participants were asked about resources accessed when making a healthcare decision. Once again HCPs were identified as excellent sources of information, highlighting the importance of the patient-HCP relationship. However, it was discussed how access to general practitioners (GPs) can be difficult and many participants felt that they would not make an appointment with their GP to speak exclusively about vaccination, perceiving this to be a waste of time.

"…I wouldn't go to the doctor just to find out about it…like I only go to the doctor when I'm properly sick" (P28, vaccinated, 16 years).

The participants were asked to discuss the internet as a source of vaccine information: while some adolescents acknowledged the internet as a useful source, being readily accessible, many participants were cynical about its use. They felt that it was often difficult to determine the reliability of content on the internet, with

websites often offering the impression of credibility while presenting excessive, inaccurate information.

> *"Because even if it's completely fake and bad, it might look really…professional or something and sound like it's been written by someone who actually knows what they're talking about, when really they don't know anything and they could be just making stuff up. You know in Wikipedia you can just write whatever you want and it goes up online"* (P32, vaccinated, 15 years).

In addition, adolescents felt that internet searches of health topics generate extreme, dramatized and sensationalised results, often terrifying the searcher.

> *"…you look up something online and it will tell you you're dying, imagine if you looked up cancer vaccine what you get back"* (P47, vaccinated, 15 years).

When questioned on the existence of reliable resources, the adolescents were mostly unaware. A minority mentioned the Health Service Executive (Ireland) and National Health Service (UK) websites. However, while these participants knew of the existence of these websites, they had not personally accessed them. When asked if they had read the information supplied prior to HPV vaccination; none had, with many believing the information was intended only for their parents:

> *"…that was for whoever was signing the forms"* (P47, vaccinated, 15 years).

Even though they had not read the information, the adolescents were quick to offer their opinion. Some participants assumed the information would have been too complex while others felt that it would have been easy to understand but boring. Participants believed information should be delivered to both vaccinees and their

parents and several methods of dissemination were suggested: a leaflet providing concise, interesting, user-friendly and accessible information, an audience with an expert, providing information and affording the opportunity to ask questions and/or an advertisement on digital or social media.

Application of the BCT Taxonomy and identification of potential intervention functions

Guided by links between COM-B and TDF domains [204], five intervention functions were identified and linked to 11 relevant BCTs, as outlined in Table 10 [210, 215]. Potential intervention strategies were developed and listed in Table 11. Some of these strategies were points raised by participants in the focus groups.

Table 10 Intervention functions identified by applying the TDF and BCTT(v1) to the study findings [204]

COM-B	TDF domain	BCT Taxonomy	BCT Label	Intervention functions
Psychological Capability	Knowledge	**5.** Natural consequences	**5.1.** Information about health consequences **5.3.** Information about social and environmental consequences **5.6.** Information about emotional consequences	Education
Social Opportunity	Social influences	**5.** Natural consequences **6.** Comparison of behaviour **9.** Comparison of outcomes **13.** Identity **15.** Self-Belief	**5.2.** Salience of consequences **5.5.** Anticipated regret **6.1.** Demonstration of the behaviour **9.2.** Pros and cons **13.1.** Identification of self as role model **15.3.** Focus on past success	Modelling Enablement
Physical Opportunity	Environmental context and resources	**5.** Natural consequences **9.** Comparison of outcomes **12.** Antecedents **13.** Identity **15.** Self-Belief	**5.2.** Salience of consequences **5.5.** Anticipated regret **9.2.** Pros and cons **12.1.** Restructuring the physical environment **13.1.** Identification of self as role model **15.3.** Focus on past success	Enablement Environmental restructuring
Reflective Motivation	Beliefs about capabilities Optimism Beliefs about consequences	**5.** Natural consequences **6.** Comparison of behaviour **9.** Comparison of outcomes **13.** Identity **15.** Self-belief	**5.1.** Information about health consequences **5.2.** Salience of consequences **5.3.** Information about social and environmental consequences **5.6.** Information about emotional consequences **6.1.** Demonstration of the behaviour **9.1.** Credible source **13.1.** Identification of self as role model **15.3.** Focus on past success	Education Persuasion Modelling Enablement
Automatic Motivation	Emotion	**5.** Natural consequences **6.** Comparison of behaviour **9.** Comparison of outcomes **13.** Identity **15.** Self-belief	**5.1.** Information about health consequences **5.2.** Salience of consequences **5.3.** Information about social and environmental consequences **5.6.** Information about emotional consequences **6.1.** Demonstration of the behaviour **9.1.** Credible source	Persuasion Modelling Enablement

			13.1. Identification of self as role model **15.3.** Focus on past success	

Table 11 Potential Interventions Strategies to reduce HPV vaccine hesitancy [204]

BCT Label	Intervention functions	Potential Intervention Strategies	Intervention target population
5.1. Information about health consequences	Education and Persuasion	Explain that not accepting the HPV vaccine can increase susceptibility to HPV-related diseases Explain the lifetime susceptibility to HPV	Adolescents & Parents
5.2. Salience of consequences	Persuasion and Enablement	Highlight the prevalence of HPV-related diseases	Adolescents & Parents
5.3. Information about social and environmental consequences	Education and Persuasion	Explain the concept of herd immunity and its importance in disease prevention	Adolescents & Parents
5.5. Anticipated regret	Enablement	Ask the person to assess the degree of regret they will feel if they do not get the vaccine and subsequently develop a HPV-related disease	Adolescents & Parents
5.6. Information about emotional consequences	Education and Persuasion	Explain that accepting the HPV vaccine will allow the person to feel protected from HPV-related diseases	Adolescents & Parents
6.1. Demonstration of the behaviour	Modelling	Present a vaccinated adolescent female discussing their experience with vaccine	Adolescents
9.1. Credible source	Persuasion	Present a speech given by an identified 'vaccine expert' to emphasise the importance of accepting the HPV vaccine e.g. Consultant in Public Health/Gynaecologist Highlight the availability of reliable sources of information	Adolescents & Parents Adolescents & Parents
9.2. Pros and cons	Enablement	Present the advantages and disadvantages (adverse effects) of HPV vaccination	Adolescents & Parents
12.1. Restructuring the physical environment	Environmental restructuring	Increase the vaccinator population by including public health nurses and pharmacists	HCPs
13.1. Identification of self as role model	Enablement	Inform the person that if they accept the vaccine, they may be a good example for unvaccinated girls	Adolescents
15.3. Focus on past success	Persuasion and Enablement	Explain the success of the HPV vaccine worldwide	Adolescents & Parents

5.6 Discussion

This is one of the first studies to investigate the views of female adolescents, living in Ireland, on the HPV vaccine and to use a behavioural change theory to analyse the findings and systematically suggest intervention functions and strategies to address vaccine hesitancy. Recommendations are based on the identified factors that influence the HPV vaccine decision and a systematic approach. All recommendations need to be considered for future public health vaccination campaigns and intervention studies, as no single recommended BCT or intervention strategy will address all identified factors.

Adolescents demonstrated poor knowledge and understanding of HPV, HPV-related diseases and/or the HPV vaccine and relied on their parent to provide information and make healthcare decisions on their behalf. Our finding is comparable with published literature [84], where parents remained the leading source of health information for 55% of the adolescents surveyed. However, a large systematic review has described the limited parental knowledge of HPV, even in those who had already made vaccination decisions for their daughter(s), in regions where immunisation had been initiated [4]. Even those parents who appeared knowledgeable demonstrated a limited understanding of recommendations [4]. Therefore, providing knowledge about HPV and HPV-related diseases ('information about health consequences' and 'salience of consequences'), explaining the societal benefits of herd immunity ('information about social and environmental consequences') and the level of protection afforded by the HPV vaccine

('information about emotional consequences' and 'focus on past success') should be key components in future interventions.

Our study highlights the importance of considering 'credible source', 'demonstration of the behaviour' and 'identification of self as role model' as possible components of an intervention. Several 'vaccine experts' were suggested by participants including HCPs, vaccine researchers and previously vaccinated girls. In addition, vaccinated participants self-identified as vaccine advocates; credible and trusted champions for immunisation to build support and trust in vaccine efficacy and safety, and raise awareness of benefits. Participants were unaware of reliable resources, had not read the HPV vaccine information leaflet provided by the HSE and were sceptical about online health information. Intervention components should highlight the availability of reliable online resources ('credible source') e.g. Health Service Executive (HSE) Immunisations, Centres for Disease Control and Prevention (CDC) Teen Website, adolescentvaccination.org., that present balanced communication about effectiveness and side effects ('pros and cons').

A major concern highlighted by this study was the exclusion of adolescents not enrolled in the State school system from the national immunisation programme. 'Restructuring the physical environment' by expanding the range of HPV vaccinators to include those in the community setting e.g. public health nurses and pharmacists, who may be able to improve vaccine accessibility to this specific adolescent cohort.

The challenge of designing interventions that combat vaccine hesitancy may be compounded by negative media representation of vaccines, in particular media

representation of vaccine 'harm' [382]. Even though adolescents in this study were offered the vaccine prior to the national decline in uptake, they were familiar with media coverage of suspected 'adverse events'. Therefore, as well as providing evidence based assurances of vaccine safety, efficacy and durability, future interventions should include an 'anticipated regret' component, where adolescents are asked to consider how they would feel should they refuse vaccination and later develop a HPV-related disease.

Limitations of this study included the fact that participants were asked to retrospectively reflect on their vaccine decision. In addition, two of the 50 participants were unvaccinated but this was not necessarily by choice. Therefore it was not possible to collect the views of true vaccine-hesitant adolescents. Finally, while the focus group facilitator was not known to the participants, the adolescents were aware that SM was a pharmacist and assumptions may have been made regarding her attitudes towards vaccination.

A key strength of this study is the systematic approach (TDF and BCW) that was applied to map the adolescent HPV vaccine decision and to recommend a range of potential intervention strategies. It has been shown that using theory to understand the mechanisms of action of intervention strategies improves the effectiveness of interventions [383]. In addition, the WHO has declared vaccine hesitancy as one of the ten global threats to health in 2019 and intervention strategies recommended by this study may be applied to other vaccines and vaccination programmes.

5.7 Conclusion

In summary, this study provided a detailed insight into behavioural factors influencing the vaccine decision-making process. It was identified that awareness and knowledge about HPV and its health sequelae was low. Lack of information is a well-recognised determinant of vaccine hesitancy [49, 384]. Therefore education was recommended as a key area to address in future intervention studies.

5.8 Acknowledgements

The authors wish to thank the study participants and their parents for their invaluable contribution to the research.

5.9 Chapter conclusion and context within thesis

This chapter described the qualitative, focus group study, undertaken with female adolescents, guided by the research questions generated in Chapter 4, to explore the knowledge, attitudes, and beliefs about HPV vaccination, thereby addressing the second objective of this doctoral thesis i.e. to elucidate vaccine decision-making and to identify barriers to vaccine uptake. It was evident that the majority of adolescents included in this study preferred to defer the responsibility of the vaccine decision to their parent(s). This finding guided the development of further qualitative research, presented in Chapter 6. This research has been published in a peer-reviewed journal and has been presented at conferences internationally.

Chapter 6 Identifying intervention strategies to improve HPV vaccine decision-making using behaviour change theory

The research presented in this chapter is being prepared for journal submission.

Author Contributions

SM was involved in the overall design of the research, designed the topic guide, completed the application for ethical approval, recruited participants, conducted the interviews, transcribed the audio-recordings, wrote the draft manuscript and was involved in manuscript editing. SM, AF and LS analysed the results. AF, AM and LS directed the study and edited the manuscript.

6.1 Abstract

Introduction

Although the HPV vaccine is highly safe and effective, its uptake is sub-optimal in many countries, including Ireland. There is therefore a need to identify appropriate interventions that will increase HPV vaccine acceptance by parents.

Aim

In this study, we took a systematic approach to understand the factors that influence HPV vaccine uptake by parents of adolescent girls in Ireland in order to define suitable behaviour change interventions that would support positive vaccine decision-making in the future.

Methods

We conducted semi-structured interviews, used a Theoretical Domains Framework (TDF)-based topic guide, to gain insight into the knowledge, beliefs, attitudes and current behaviours of parents with respect to their HPV vaccine decision. Transcripts were analysed using the TDF. The Behaviour Change Wheel (BCW) was used to identify relevant intervention functions and the Behaviour Change Technique Taxonomy version 1 (BCTTv1), to identify relevant intervention techniques.

Results

All parents discussed the essential role of healthcare providers in vaccine decision-making. Complacency and confidence were important factors in decision-making by vaccine hesitant parents. Five BCW intervention functions were identified as

appropriate, namely; education; persuasion; environmental restructuring; modelling and enablement.

Conclusion

To our knowledge, this is the first study to systematically evaluate HPV vaccine decision-making using behaviour change theory and identify suitable intervention strategies to promote positive vaccine decision-making using this approach.

6.2 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide [140]. Although the majority of infections are transient, persistent infection is a pre-requisite for pre-cancerous lesions and malignancies, including cervical and oropharyngeal cancers [142]. Three prophylactic HPV vaccines are licensed, and marketed for use for the prevention of HPV-related disease. These are intended to be administered before the onset of sexual activity. By the end of 2017, 80 countries had included the HPV vaccine in their immunisation programmes. In Ireland, the quadrivalent vaccine has been offered to all girls in the first year of second-level schools (aged 12-13 years) by the national healthcare service, the Health Service Executive (HSE), and more than 230,000 girls have been vaccinated since 2010. The vaccine is available to boys in Ireland from September 2019. However, at the time of our research, only girls were included in the vaccination programme, hence the focus of the study. There is high grade evidence that HPV vaccines protect against cervical pre-cancer, with significant decreases in vaccine-type HPV in vaccinated women [150]. The safety of these vaccines is well established [155]. However, recently there has been a focus on a number of safety signals for the vaccines [154]. While none have been substantiated [155], they remain a public concern. In Ireland, maximal vaccination rates of 87% were reported in 2014/2015 but these plummeted to 51% in 2016/2017 [26]. According to the WHO SAGE Vaccine Hesitancy Working Group, vaccine hesitancy refers to "*delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific*

varying across time, place and vaccines. It includes factors such as complacency, convenience and confidence" [48]. Currently, there is a paucity of published qualitative research addressing these new concerns [4]. Therefore, understanding the reasons why parents may accept or decline the HPV vaccine for their adolescent daughter is important, in order to inform future strategies to restore confidence and increase HPV vaccine uptake. In this study, we examined the decision-making process of parents of adolescent females in Ireland with respect to the HPV vaccine through semi-structured interviews with parents.

It is well established that changing behaviour is complex, and a systematic approach is required to understand the factors that influence vaccine uptake. In general, providing information alone does not change behaviour [179]. Instead, one must gain an insight into the knowledge, beliefs, attitudes and current behaviours of the target audience, and the environmental context in which they occur. Behavioural change has been shown to be more effective if interventions are based on principles drawn from evidence and theories of behaviour and behavioural change [184]. The Theoretical Domains Framework (TDF) provides a systematic and theoretical basis for understanding and changing behaviour [204]. It has been used in qualitative studies to guide the development of interview topic guides, and as a coding framework in the analysis of qualitative material [385]. The framework simplifies 33 theories and 128 constructs into 14 validated domains, underpinned by psychological theory [206]. The capability, opportunity, motivation model of behaviour (COM-B) distils the TDF into three domains, that interact to predict behaviour and include the individual's capability, motivation and opportunities for the behaviour [204]. Each of these components may be further subdivided:

capability may be physical or psychological; opportunity may be physical or social; and motivation may be reflective or automatic [204]. The COM-B model guides the choice of intervention functions or strategies most likely to achieve behavioural change and forms the central component of the Behaviour Change Wheel (BCW) [210]. Within 19 frameworks for classifying behaviour change interventions, over a wide range of were discerned to construct the BCW [210]. Additionally, the nine intervention functions have been linked to a taxonomy of 93 Behaviour Change Techniques (BCTs), organised into 16 groups [215]. The BCW is divided into three broad stages: understanding the behaviour; identify intervention options; and identifying content and implementation options [204]. Following this structured approach lends transparency to the intervention design process and facilitates its subsequent evaluation [204].

6.3 Aim

The aim of this study was to apply the TDF, the COM-B system of behavioural change and the associated BCW, as tools for describing the factors that influence the parental HPV vaccine decision, identified using semi-structured interviews, to inform the choice of intervention components and strategies.

6.4 Methods

6.4.1 Stage 1: Understanding the behaviour [210]

This stage was guided by methods described by Atkins *et al*. [381].

6.4.1.1 Select and specify the target behaviour

The target behaviour was parental acceptance of the HPV vaccine. This behaviour was explored in a cohort of parents of female adolescents (aged 14-16 years) who had been offered the HPV vaccine within the previous three years, when their daughters were aged 11-12 years, in accordance with national recommendations. Therefore, these parents would have been offered the vaccine prior to vaccine instability observed in 2016/2017.

6.4.1.2 Select the study design

Qualitative, semi-structured interviews were conducted.

6.4.1.3 Develop study materials

A TDF-based interview topic guide was developed by the authors, based on a review of the literature [4] and previous qualitative research [5]. The topic guide was modified following piloting and underwent iterative revision throughout the study to ensure that emerging themes were captured in subsequent interviews (Appendix 6.1).

6.4.1.4 Decide the sampling strategy

A purposive sampling strategy was used to recruit participants [386]. This strategy is outlined in Appendix 6.2. An initial analysis sample of ten and a stopping criterion of three were specified *a priori*, as outlined in the Francis method of determining data saturation [387].

6.4.1.5 Collect the data

All semi-structured interviews were conducted by SM, a research pharmacist with training in qualitative research methods and qualitative interviewing techniques. No relationship was established between the interviewer and the participants prior to study commencement. However, participants were aware that SM was a pharmacist. The interviews were conducted, in a location convenient for the participant, between 20th August 2018 and 21st January 2019. Only the interviewer and participant were present during the interview. All participants provided written informed consent. Prior to interview commencement, participants completed a demographic data collection form which recorded details including: gender; parental age; daughter age; highest education level achieved; number of children; and HPV vaccine status of daughter. The interviews were audio-recorded and transcribed verbatim by SM. Transcripts were not returned to participants and repeat interviews were not conducted. SM recorded relevant field notes after interview completion.

6.4.1.6 Analyse the data

Audio-recorded sessions (OLYMPUS Digital Voice Recorder VN-731PC) were transcribed verbatim by SM and preliminary familiarisation was begun during the transcription process. Computer software (QSR International's NVivo V.11) was used to organise the data and analysis. Each participant was assigned an anonymised identifier. Transcripts were verified against audio-recordings with a random sample verified by an independent researcher and analysed using an inductive thematic analysis [388]. Codes and themes were compared within, and

between, interviews for constant comparison. Transcripts were independently coded by one other member of the research team (LS, AF). Any disagreements were resolved through discussion. The codes were then attributed to the domains of the TDF.

6.4.1.7 Report findings

The key findings were reported in the Results section of this manuscript. Reporting was guided by the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [389].

6.4.2 Stage 2: Identifying intervention options [210]

The TDF domains were then linked to the core COM-B components of the BCW [204]. Relevant intervention functions were identified using the APEASE criteria, a set of criteria used to make context-based decisions on intervention content and delivery consisting of affordability, practicability, effectiveness and cost-effectiveness, acceptability, side-effects/safety and equity considerations [204].

6.4.3 Stage 3: Identifying intervention content and implementation options

The identified intervention functions were then linked through consensus discussion to relevant BCTs in the BCT taxonomy (v1) [215].

6.4.4 Ethical approval

Ethical approval was obtained from the Social Research Ethics Committee, University College Cork (Log 2016-122).

6.5 Results

6.3.1 Stage 1: Understanding the behaviour [210]

Characteristics of interview participants

Thirteen interviews were conducted (Appendix 6.4). Of the parents who participated in the study, 23% were male and 31% of all parents had declined the HPV vaccine for their daughter. In addition, 39% of participants were recruited from DEIS programme second level schools [390]. The interview duration ranged from 10 to 43 minutes, with an average duration of 21 minutes. No demographic appeared to associate with the decision to accept or decline the HPV vaccine in this small group of 13 parents; all parents who had declined the HPV vaccine for their daughter were female, however this is likely to be due to a higher number of females in the study.

Applying the TDF

Based on a familiarisation with the theoretical constructs under each TDF domain [206] and a comprehensive review of the interview transcripts, ten of the 14 TDF domains were selected as the most relevant [381]. It emerged that the vaccine decision was complex, and often involved interactions between several of these domains, namely knowledge, memory, attention and decision processes, social role and identity, beliefs about capabilities, optimism, beliefs about consequences, goals, emotion, environmental context and resources and social influences. Participant quotes are represented in *italics*. Vaccine-acceptors (VA) are those who accepted the HPV vaccine for their daughter, while vaccine-decliners (VD) are those who chose to decline vaccination. The identified TDF domains are in brackets.

The parental vaccine decision process began when the HPV vaccine was offered in 1st year of secondary school (adolescents are aged between 12-13 years). The parents recalled how they reflected on previous experience with vaccines, namely those included in the paediatric vaccination schedule (memory, attention and decision processes), with participants recognising the importance of immunisation (knowledge, goals): *"I mean, they're important because they stop lots of different diseases, especially in children*" (P7, VA). Vaccination appeared to be the accepted norm (memory, attention and decision processes). Even those who chose to decline the HPV vaccine, discussed how they had accepted paediatric and other adolescent vaccines: *"I mean my two have had all their baby vaccines and the ones in school like measles, mumps and all those and I never really worried that much about vaccines and didn't really give them much thought"* (P13, VD). Participants were asked to discuss what they could recall about HPV and the HPV vaccine (knowledge). Responses were variable, with some parents claiming they knew *"nothing at all"* (P3, VA), to others identifying the HPV vaccine as the *"cervical cancer vaccine"* (P12, VA). The participants readily identified and were transparent about their lack of knowledge: *"To be honest, I don't know much. I know it stops cervical cancer when she is older…and that is about it"* (P12, VA). Those participants who were able to provide vaccine-specific information revealed occupational or academic public health experience in their own occupation (environmental context and resources). The participants discussed the vaccine information leaflet, produced by the HSE (environmental context and resources). For some parents, this resource was sufficient to guide their vaccine decision: *"…I know that this vaccine can stop you getting this virus that can cause cancer. I mean that's all I really need to know to*

make my decision" (P2, VA), *"I personally don't think I needed to know any more than this vaccine will stop your daughter from getting cervical cancer…it becomes a no-brainer"* (P8, VA), while others remained ambivalent and sought out supplementary information (beliefs about capabilities). This apprehension was reported to be primarily due to circulating claims of chronic side effects, e.g. fatigue, seizures, associated with the vaccine (environmental context and resources). Participants recalled radio interviews, television documentaries, newspaper articles and online information which discussed these allegations. Parents discussed the emotive nature of these reports (emotion): *"I was listening to the radio and there was this mum and I, my heart just went out to her"* (P1, VD), *"The stories were so…powerful. It was hard to ignore them"* (P5, VD). For some participants, these reports provided more weight than the vaccine information leaflet provided by the HSE, and dictated the vaccine decision (environmental context and resources, emotion, social identity): *"I think listening to a mum affected me more than reading a leaflet"* (P1, VD). All participants had been exposed in varying degrees to these reports (environmental context and resources). Many VA acknowledged their concerns regarding these alleged side effects (emotion), but were reassured by the continued, widespread use of the vaccine (beliefs about consequences, optimism): *"My gut would tell me that obviously it's safe if it's on the market and given all over the world and yes there may be a risk of an after effect, but that's true of everything"* (P3, VA) and their trust in the scientific community (beliefs about capabilities, optimism, knowledge): *"I trust vaccines, I trust the people in charge of vaccines so no I don't really have to think about it"* (P6, VA), *"I will never understand this science and research so I have to just rely on these experts*

and trust that they know what's going on" (P2, VA). In addition, some participants appeared to discriminate between the sources of information (environmental context and resources): *"it came across as like dramatic or something…I remember there was a big difference between, we'll say, the tabloid style newspapers and the broadsheets, splashed all over the tabloids and not mentioned in the broadsheets"* (P3, VA) and were cognisant of historical vaccine controversies (memory, attention and decision processes, knowledge): *"It's MMR and autism all over again, and we know what damage that has caused"* (P6, VA).

Participants consulted with other individuals, to varying degrees, while making their vaccine decision (social influences). Those individuals included their daughters, their partners, their peers and healthcare providers (HCP). While participants acknowledged that they had discussed the HPV vaccine with their adolescent daughter, it was evident that the vaccinee had had minimal control over the vaccine decision (social identity, social influences, beliefs about capabilities): *"She doesn't really have the luxury of making that type of decision, you know what I mean? I'm her parent and I'll do what I think is best for her"* (P3, VA). Some parents discussed the importance of exerting this control over healthcare decisions that would pro-actively protect their daughters' future (social identity, belief about capabilities): *"Our daughters will be adults when they are invited for a smear, how can we control that?"* (P2, VA). The female participants revealed that while they had discussed the HPV vaccine with their partner, the responsibility of healthcare decision-making often lay with them (social influences): *"He kind of just said he was happy enough to go along with me and just support whatever decision I made"* (P13, VD), *"I would keep him…informed of course but in general, he'd be happy enough to go along with*

whatever I thought" (P11, VA). Similarly, the male participants reported how they had relied on their partner, or an alternative female, for guidance on the vaccine decision (social identity, social influences, beliefs about capabilities): *"I just let my wife deal with that kind of stuff. If she needs my opinion, she'll ask for it, the majority of time she doesn't need it"* (P9, VA), *"I suppose the topic is very…female"* (P3, VA). Some female participants acknowledged the influence of peers (social influences): *"I have a good few friends who have daughters the same age…so it's almost inevitable that it'll come up"* (P12, VA), while others believed the vaccine decision was a private matter (social influences): *"I mean, it's no one's business but my own. We made our decision and we didn't really need to hash it out"* (P5, VD). However, even VA discussed how they would have questioned their decision had vaccine uptake dropped to an *"unacceptably low level"* (environmental context and resources, social influences): *"I'd like to think I would opt in and get all the vaccines because I think that is what is for the best but if loads of people were not then maybe I'd struggle with it"* (P11, VA). However this *"unacceptably low level"* was not defined. Many participants acknowledged how HCP such as nurses or GPs are perfectly positioned to guide and support vaccine decisions (social influences): *"They're* (GPs) *probably the ideal person to talk to really"* (P2, VA) and responded positively to their GP sharing personal experiences (social influences): *"I did mention it to my doctor alright about the vaccine…he said that if he was in my shoes, he would give his daughter the vaccine and that was enough for me"* (P7, VA). However, many VA did not discuss their decision with the GP, reporting that they had not *"felt the need"*, while vaccine decliners avoided the discussion as they believed the GP would attempt to alter their decision (social influences): *"Your GP is*

going to tell you to just get the vaccine…that would be the same as reading the HSE information" (P5, VD), *"Of course they were going say 'get it done, get it done, get it done'"* (P1, VD).

The ultimate vaccine decision appeared to lie in the participants "perception of risk". VA acknowledged the risks associated with vaccination but prioritised disease and cancer prevention (beliefs about consequences, goals): *"The only side effect I care about is that it will stop my little girl from getting cancer"* (P6, VA), "*A sore arm is a small price to pay for something that could save your life"* (P3, VA). This was particularly evident in those participants who had personal experience with HPV-related conditions or cancer in general (beliefs about consequences, goals, emotion and optimism): *"I have had to get repeat smears done because of abnormalities…the worry and the fear when you get that letter, I never want her to go through that…I think she will walk into* (cervical screening) *appointments more confidently knowing that she has had the vaccine"* (P2, VA), *"Knowing what my wife went through, from the initial diagnosis to the treatment and right to the end, I wouldn't wish it on my worst enemy. Getting the vaccine for my girls and knowing they have reduced chance of going through all that, it's worth everything"* (P8, VA). In contrast, vaccine decliners prioritised the alleged risk of chronic side effects in their decision (beliefs about consequences, emotion): *"I just felt there was a higher chance of getting side effects from the vaccine than ever developing cervical cancer so it wasn't worth the risk"* (P5, vaccine decliner), *"What it really boiled down to for me was that the side effects that I was hearing about were so severe, so life changing that I just couldn't risk it"* (P13, VD). Some inaccurately believed an absence of family history of cervical cancer denoted a reduced lifetime risk of

cancer development (beliefs about consequences, knowledge): *"I suppose, if I could get an injection tomorrow against dementia, I would because my mum's father…but there's no cervical cancer in my family"* (P1, VD), *"There isn't any cervical cancer in the family so that helped it* (the decision) *too"* (P5, VD). Others failed to understand the rationale for pre-pubescent immunisation (knowledge): *"She wasn't at risk when she was that age so I didn't feel the need to put her immune system through it…where I fell short was why she really needed it now"* (P10, VD), *"If you had a daughter that you've no control over or whatever maybe you'd have to look at something then to protect her...The decision may be very different depending on the child and the circumstances"* (P1, VD). Those vaccine decliners interviewed acknowledged the potential for anticipated regret should their daughter develop HPV-related disease or malignancies (beliefs about consequences, emotion): *"I know if, God forbid, if she gets cervical cancer in the next few years, I'll blame myself"* (P1, VD), *"Like if she were to get cervical cancer, I would be completely devastated when the vaccine maybe could have stopped it"* (P13, VD). However, some believed they could protect their daughters from these consequences through sex education and promoting cervical screening (beliefs about consequences, beliefs about capabilities, optimism): *"How she can prevent HPV through her actions…practising safe sex when the time comes and making sure she goes for regular smears"* (P10, VD), *"Like sex education is just even more important for her to make sure she is safe"* (P13, VD). All participants interviewed declared they were content with their respective vaccine decisions (optimism) and it was evident that the ultimate goal of these decisions was protection of their daughters' health (goals).

6.3.2 Stage 2: Identifying intervention options [210]

The ten TDF domains described in Stage 1 were then linked to several COM-B components: psychological capability; physical and social opportunity; and reflective and automatic motivation. The BCW was then used to identify intervention functions; by consensus discussion of the data, five of the nine intervention functions were found to be relevant: education; persuasion; environmental restructuring; modelling; and enablement [210].

6.3.2 Stage 3: Identifying content and implementation options [215]

The five intervention functions from Stage 2 were linked to 13 BCTs, based on the relevance of the technique to the identified behaviours [204, 210, 215]. These are outlined in Table 12. Potential intervention strategies were developed and outlined in Table 13.

Table 12 Intervention functions and BCTs identified using the TDF, the COM-B model and the BCW [11, 14-16]

TDF domain	COM-B	Intervention functions	BCT Taxonomy	BCT Label
Knowledge Memory, attention and decision processes	Psychological Capability	Education Environmental restructuring Enablement	5. Natural consequences	5.1 Information about health consequences 5.2 Salience of consequences 5.3 Information about social and environmental consequences 5.5 Anticipated regret 5.6 Information about emotional consequences
			6. Comparison of behaviour	6.3 Information about others' approval
			7. Associations	7.1 Prompts/cues
			9. Comparison of outcomes	9.2 Pros and cons 9.3 Comparative imagining of future outcomes
			12. Antecedents	12.1 Restructuring the physical environment
			15. Self-belief	15.3 Focus on past success
Environmental context and resources	Physical Opportunity	Enablement Environmental restructuring	5. Natural consequences	5.2 Salience of consequences 5.3 Information about social and environmental consequences
			7. Associations	7.1 Prompts/cues
			9. Comparison of outcomes	9.2 Pros and cons 9.3 Comparative imagining of future outcomes
			12. Antecedents	12.1 Restructuring the physical environment
			15. Self-belief	15.3 Focus on past success
Beliefs about capabilities Optimism Beliefs about consequences	Reflective Motivation	Education Persuasion Modelling Enablement	5. Natural consequences	5.1 Information about health consequences 5.2 Salience of consequences 5.3 Information about social and environmental consequences 5.5 Anticipated regret 5.6 Information about emotional consequences
			6. Comparison of behaviour	6.1 Demonstration of the behaviour 6.2 Social comparison 6.3 Information about others' approval
			7. Associations	7.1 Prompts/cues
			9. Comparison of outcomes	9.1 Credible source 9.2 Pros and cons

			15. Self-belief	9.3 Comparative imagining of future outcomes 15.3 Focus on past success
Emotion	Automatic Motivation	Persuasion Modelling Enablement	5. Natural consequences 6. Comparison of behaviour 9. Comparison of outcomes 15. Self-belief	5.1 Information about health consequences 5.2 Salience of consequences 5.3 Information about social and environmental consequences 5.5 Anticipated regret 5.6 Information about emotional consequences 6.1 Demonstration of the behaviour 6.2 Social comparison 6.3 Information about others' approval 9.1 Credible source 9.2 Pros and cons 9.3 Comparative imagining of future outcomes 15.3 Focus on past success
Social influences	Social Opportunity	Modelling Enablement Environmental restructuring	5. Natural consequences 6. Comparison of behaviour 7. Associations 9. Comparison of outcomes 12. Antecedents 15. Self-belief	5.2 Salience of consequences 5.5 Anticipated regret 6.1 Demonstration of the behaviour 7.1 Prompts/cues 9.2 Pros and cons 9.3 Comparative imagining of future outcomes 12.1 Restructuring the physical environment 15.3 Focus on past success

Table 13 Potential intervention strategies to reduce vaccine hesitancy [11]

BCT Label	Intervention functions	Potential Intervention Strategies
5.1 Information about health consequences	Education, Persuasion	Explain that not vaccinating can increase susceptibility to future HPV infection Present the likelihood of HPV exposure and infection: HPV affects 80% of people at some point in life Provide information on the consequences of chronic HPV infection (anogenital warts, neoplasia, cervical, anogenital, head and neck cancers)
5.2 Salience of consequences	Persuasion, Enablement	Provide information on the potential interventions that could be required with chronic HPV infection (colposcopy, laser treatment, cold coagulation, surgery, radiotherapy, chemotherapy)
5.3 Information about social and environmental consequences	Education, Persuasion	Inform the parent that the majority of girls (70%) receive the HPV vaccine Educate on the importance of herd immunity
5.5 Anticipated regret	Enablement	Ask the parent to assess the degree of regret they will feel if they do not vaccinate their daughter and she were to develop HPV-related disease
5.6 Information about emotional consequences	Education, Persuasion	Explain that accepting the HPV vaccine for their daughter will offer a level of comfort, knowing that she is somewhat protected from chronic HPV infection
6.1 Demonstration of the behaviour	Modelling	Present a vaccinated adolescent or a parent who consented to vaccination, discussing their experience with the vaccine Present an unvaccinated adolescent or a parent who did not consent to vaccination, discussing how they regretted their decision
6.2 Social comparison	Persuasion	Inform that the majority of parents (70%) consent to vaccinate
6.3 Information about others' approval	Education, Persuasion	Inform that the majority of parents (70%) consent to vaccinate
7.1 Prompts/cues	Education, Environmental restructuring	Information leaflets or stickers at locations that will be seen by parents (GP surgery, pharmacy, and other healthcare environment, or school notice board, sports facilities) Targeted media campaign (television, radio, social media)
9.1 Credible source	Persuasion	Encourage HCP (GP, nurse) to engage in conversation about the HPV vaccine Encourage HCP (GP, nurse) to provide personalised guidance on the vaccine i.e. "if I were in your position, I would consent" Inform the parent that all national and international scientific and regulatory bodies recommend the HPV vaccine (e.g. World Health Organisation (WHO), Centres for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC))
9.2 Pros and cons	Enablement	Advise the parent to list and compare the advantages and disadvantages of their vaccine decision
9.3 Comparative imagining of future outcomes	Enablement	Prompt the parent to imagine and compare likely or possible outcomes following vaccinating versus not vaccinating

12.1 Restructuring the physical environment	Environmental restructuring	Offer unvaccinated girls repeated opportunity to be vaccinated
15.3 Focus on past success	Persuasion, Enablement	Advise the parent to reflect on past success with vaccines (paediatric and childhood immunisation schedules)

6.6 Discussion

To our knowledge, this is the first published study to use an understanding of the HPV vaccine decision-making process, to systematically define intervention functions and suggest strategies to promote positive decision-making for the HPV vaccine and thereby increase acceptance of this vaccine. Recommendations are based on the identified factors that influence the HPV vaccine decision in Ireland and a systematic approach of analysing these factors in the context of behaviour change theory. All recommendations should be considered for future public health vaccination campaigns and intervention studies, as no single recommended BCT or intervention strategy will address all identified factors.

Five BCW intervention functions were found to meet the APEASE criteria. Incentivisation, coercion, training and restriction were not found to be appropriate in this context. Incentivisation creates an expectation of reward [204]. Provision of financial incentives for vaccination has been used with varying effect in different countries for early childhood vaccines [391]. In a UK RCT, a combination of financial incentive and reminder text messaging increased completion of HPV immunisation [392]. However, uptake remained lower than the national target thereby questioning the cost-effectiveness and acceptability of incentivisation in regions such as Ireland where vaccination is provided free of charge.

Coercion creates an expectation of punishment or cost [204]. In the US, Virginia, Rhode Island and the District of Columbia have enacted school

entry HPV vaccine mandates [393]. In contrast, while the HPV vaccine is recommended in 31 European countries, vaccination remains voluntary [394]. There remains debate on the effectiveness of vaccine mandates and it is unclear whether mandatory vaccination may lead to opposing attitudes and reduced vaccine uptake [395, 396]. In addition, research has demonstrated that coercion, through vaccine mandates, is often viewed as unfavourable and unacceptable by parents [397]. In Ireland, similar to other European countries, vaccines are recommended by the Irish authorities, but are not compulsory: parents are entitled to withhold consent and forego vaccination. Legislating for compulsory vaccination could potentially be challenged as unconstitutional in Ireland.

Behaviour change based on restriction involves an increase in the target behaviour by reducing the opportunity to engage in competing behaviours [204]. This function would not be applicable or feasible in an intervention to increase vaccine acceptance: it is not possible to reduce the opportunity to engage in the competing behaviour i.e. vaccine refusal. Finally, training involves imparting skills [204]. While this function may be suitable in the design of an intervention involving vaccinators, it's inclusion in an intervention involving parents would be inappropriate.

Interviewees revealed that the female parent was the primary healthcare decision-maker for the family: a well-recognised phenomenon [398]. It may be suggested that future interventions to reduce HPV vaccine hesitancy should target this demographic. However, the over-identification of HPV as a female-specific disease has resulted in the feminisation of HPV and the

HPV vaccine [399]. Therefore, interventions should seek to normalise HPV vaccines as an important aspect for all (information about health consequences). Gender-neutral vaccination programmes have been introduced in Scotland and Australia, as the awareness of the burden of HPV-related cancers in men has increased [400]. Another important consideration is the additional protection provided by a gender neutral programme to vulnerable groups (e.g. men who have sex with men) [143]. In Ireland, the Health Information and Quality Authority (HIQA) has completed a health technology assessment in relation to gender neutral HPV vaccination and has recommended the adoption of gender neutral nonavalent immunisation programme, which began in September 2019 [143].

The essential role of HCP in guiding vaccine decisions was identified (credible source). However, it is clear that their potential in this role is not yet fully realised. Effective interactions with HCP have the potential to alleviate concerns of vaccine supportive parents and to motivate a vaccine hesitant parent towards acceptance [33]. A recent systematic review reported that HCP recommended vaccination less often if they were uncomfortable discussing sexual activity, if they perceived parents to be hesitant or believed patients to be low risk [401]. It was shown that parents prefer strong, unambiguous recommendations from their HCP [4] and apathetic interactions are likely to discourage timely HPV vaccination and encourage watchful waiting. Therefore there is a requirement for the development of communication strategies to support HCP in

recommending the HPV vaccine with confidence (credible source, prompts/cues). Interviewees also discussed how they had appreciated, and been reassured by, their HCP sharing their own personal vaccine decisions, a finding that has been evident elsewhere (credible source, social comparison) [402].

The parents who declined the HPV vaccine for their daughter would be considered vaccine hesitant as they had all accepted previous vaccines for their child or children [48] (focus on past success). Complacency and confidence were important factors in their decision. Parents were complacent about their daughter being at risk for HPV infection due to age, lifestyle choices and/or a lack of family history of cervical cancer. They felt, as parents, that they could protect her from future infection through sex education, encouraging safe sex practices and attendance at screening programmes. There appeared to be an over-reliance on the national cervical screening programme, which was mistaken as a diagnostic tool. This was notable considering the CervicalCheck controversy in Ireland that had saturated media in the months preceding these interviews, when significant flaws in smear test results and communications were identified. While cervical screening offers protective benefits and is associated with a reduction in the incidence of invasive cancer and mortality [403], an effort must be made to increase awareness of complementary prophylactic measures, such as HPV vaccination.

It also emerged that vaccine-hesitant parents were not confident in the safety of the vaccine, a phenomenon that has been internationally

observed [404]. Although education through the provision of accurate, balanced, scientifically-based evidence on the benefits of vaccination is essential, it is not sufficient to close the gap between current levels of public confidence and levels of trust required to ensure adequate coverage [405]. Therefore, in addition to education, both persuasion and enablement will be key components of interventions to address vaccine confidence. These components could include: providing information on HPV, lifetime risk of HPV infection and the impact of chronic infection (information about health consequences, salience of consequences, information about emotional consequences), clarifying the rationale for pre-pubescent vaccination (information about health consequences), explaining the societal benefits of herd immunity (information about social and environmental consequences, social comparison, information about others' approval), providing assurances of vaccine safety and efficacy (credible source) and asking parents to consider how they would feel should they decline vaccination and their daughter subsequently develops a HPV-related disease (comparative imaging of future outcomes, pros and cons, anticipated regret). Personal stories opposing vaccination are widespread and this anecdotal evidence is recognised as being highly persuasive, fuelling the spread of misinformation, and influencing existing health behaviours and beliefs [406]. To counter this effect, personal stories encouraging vaccination and describing the vaccine-preventable disease, should be shared, to facilitate the spread of information, and encourage vaccination. A positive example of this in Ireland was the 26 year-old HPV

vaccine, and cervical cancer, patient advocate, Ms. Laura Brennan, who campaigned tirelessly in the years preceding her untimely death in March 2019.

Limitations of this study must be acknowledged. The study participants were asked to retrospectively reflect on a decision made prior to HPV vaccine instability. It is unclear whether these parents would have altered their decision in light of circulating misinformation. As a qualitative study, the findings may not be readily generalisable to the wider population. However the participants were sampled across a relatively large geographical area, included parents of children attending both DEIS and non-DEIS programme second level schools. Furthermore, the proportion of vaccine decliners (30%) is similar to the overall population in Ireland, suggesting that the findings are transferable. However, it must also be noted that the participants comprised a self-selected sample.

The key strength of this study is the systematic approach (TDF, COM-B model and BCW) that was applied to map the parental HPV vaccine decision and to recommend a range of potential intervention strategies. It has been shown that using theory to understand the mechanisms of action of intervention strategies improves the effectiveness of interventions [383]. In addition, the World Health Organisation (WHO) has declared vaccine hesitancy as one of the ten global threats to health in 2019 and intervention strategies recommended by this study may be applied to other vaccines and vaccination programmes.

6.7 Conclusion

In summary, this study provided a detailed insight into behavioural factors influencing the vaccine decision-making process. We identified that complacency and a lack of confidence were the main factors dictating the decision to vaccinate in hesitant parents and several intervention strategies are suggested to address these factors.

6.8 Acknowledgements

The authors wish to thank the study participants for their invaluable contribution to the research.

6.9 Chapter conclusion and context within thesis

This chapter described the qualitative interview study, undertaken with parents of female adolescents and guided by the research questions generated in Chapter 4 and the research findings of Chapter 5. The chapter explored the knowledge, attitudes, and beliefs about HPV vaccination, thereby further addressing the second objective of this doctoral thesis i.e. to elucidate vaccine decision-making and to identify barriers to vaccine uptake. The evidence-base generated in Chapter 4 and the primary research conducted in Chapters 5 and 6 elucidated the HPV vaccine decision-making process in both adolescents and parents, and guided the development of an intervention to improve vaccine uptake. This theoretically-informed and evidence-based intervention is described in Chapter 7.

Chapter 7 *Is the HPV vaccine for me?*

Video-based behavioural intervention associated with improved HPV knowledge and intention to vaccinate

The research presented in this chapter is being prepared for journal submission.

Author Contributions

SM was involved in the overall design of the research, designed, created and narrated the intervention, completed the application for ethical approval, recruited participants, analysed the results, wrote the draft manuscript and was involved in manuscript editing. AF, AM and LS directed the study and edited the manuscript.

7.1 Abstract

Introduction

There is an urgent need to develop interventions, involving parents and adolescents which support positive decision-making towards the HPV vaccine.

Aim

The purpose of this study was to design, develop and evaluate a theory and evidence-based intervention to improve HPV and HPV vaccine knowledge, and intention to vaccinate, among parent-daughter dyads. The objectives of our study were to (1) evaluate participants' baseline HPV and HPV vaccine knowledge; (2) assess the impact of the intervention on (i) participants' HPV knowledge (including HPV vaccine knowledge) and (ii) intention to vaccinate; and (3) assess the feasibility of the intervention by examining the participant acceptability of the methods used.

Methods

A theory and evidence-based online behavioural intervention, "Is the HPV vaccine for me?" was developed to improve HPV and HPV vaccine knowledge, and intention to vaccinate. The impact and feasibility of the intervention was evaluated in a prospective randomised controlled feasibility trial.

Results

A total of 49 parent-daughter dyads completed baseline knowledge assessment (n=24 control, n=25 intervention), and 35 dyads completed knowledge assessment at week 2 (n=17 control, n=18 intervention). The intervention was associated with a statistically significant increase in HPV, and HPV vaccine knowledge and intention to

vaccinate. All intervention participants found the video interesting, while 96% found it useful.

Conclusion

This intervention was found to be affordable, practicable, effective (cost-effective), acceptable, safe, and equitable, in this feasibility study.

7.2 Introduction

HPV is responsible for approximately 4.5% of global cancer disease burden, with cervical cancer the most common cancer caused by HPV infection [142, 143]. The infection is also associated with cancers of the oropharynx, anus or rectum, penis, vulva and vagina and is responsible for anogenital warts in men and women [143]. Three vaccines are licensed and marketed for use to prevent HPV infections and their sequelae [144-146]. These are intended to be administered to adolescents before the onset of sexual activity [143]. The safety of the HPV vaccines is well established [155, 156]. However, unsubstantiated claims linking the administration of these vaccines to the development of a plethora of adverse effects [141, 143, 154], has led to a significant reduction in vaccine uptake worldwide [167, 169, 170]. There is therefore a need to develop interventions that support positive decision-making towards the HPV vaccine [45, 173-176]. Several interventions have been designed to address HPV vaccine hesitancy, frequently targeting parents [181], and evaluation is often based on the impact of the intervention on parents' intention to vaccinate, with several studies reporting a statistically significant impact on intentions [407-411]. However, it has been recommended that adolescents be included in healthcare decision-making [371]. Therefore, in this study, the target population of our behavioural intervention is parent-daughter dyads.

Interventions have been shown to be more effective if they are based on principles drawn from evidence and theories of behaviour change [184]. Evidence was generated in a comprehensive systematic review [4], and through a series of qualitative research studies, in both parents [5] and female adolescents. These

qualitative studies were guided by behaviour change theory, including the Theoretical Domains Framework (TDF) [206], the COM-B model [204], the Behaviour Change Wheel (BCW) [204], and the Behaviour Change Technique Taxonomy version 1 (BCTTv1) [215]. The TDF guided the development of focus group and interview topic guides, and was used as a coding framework in data analysis [204]. Ten of the 14 TDF domains were selected as the most relevant [206, 381] (Table 14).

Table 14 Theoretical Domains Framework (TDF) Domains identified through qualitative research [5]

TDF Domain	Parents	Adolescents
Knowledge	✓	✓
Memory, attention and decision processes	✓	
Social role and identity	✓	
Beliefs about capabilities	✓	✓
Optimism	✓	✓
Beliefs about consequences	✓	✓
Goals	✓	
Emotion	✓	✓
Environmental context and resources	✓	✓
Social influences	✓	✓

The ten TDF domains were linked to several components of the COM-B model: psychological capability; physical and social opportunity; and reflective and automatic motivation. The BCW was then used to identify five relevant intervention functions: education; persuasion; environmental restructuring; modelling; and enablement [210], which were linked to 15 appropriate BCTs [215] (Table 15).

Table 15 Behaviour Change Techniques (BCT) identified through qualitative research [5]

BCT	Parents	Adolescents
Information about consequences	✓	✓
Salience of consequences	✓	✓
Information about social and environmental consequences	✓	✓
Anticipated regret	✓	✓
Information about emotional consequences	✓	✓
Demonstration of the behaviour	✓	✓
Social comparison	✓	
Information about others' approval	✓	
Prompts/cues	✓	
Credible source	✓	✓
Pros and cons	✓	✓
Comparative imagining of future outcomes	✓	
Restructuring the physical environment	✓	✓
Focus on past success	✓	✓
Identification of self as role-model		✓

7.3 Aim

The purpose of the current study was to design, develop and evaluate a theory and evidence-based intervention to improve HPV and HPV vaccine knowledge, and intention to vaccinate, among parent-daughter dyads. The objectives of our study were to (1) evaluate participants' baseline HPV and HPV vaccine knowledge; (2) assess the impact of the intervention on (i) participants' HPV knowledge (including HPV vaccine knowledge) and (ii) intention to vaccinate; and (3) assess the feasibility of the intervention by examining the participant acceptability of the methods used.

7.4 Methods

7.4.1 Ethical approval

Ethical approval was obtained from the Social Research Ethics Committee, University College Cork (Log 2019-26).

7.4.2 Intervention development

We developed an online behavioural intervention, "Is the HPV vaccine for me?" to improve HPV and HPV vaccine knowledge, and intention to vaccinate. The video was created using VideoScribe 3.3.1-1 software by Sparkol®, in consultation with a Technology-Enabled Learning Co-ordinator. It is six minutes in duration. A narrative approach was applied, mapping the adolescent HPV vaccine decision journey (BCT: demonstration of the behaviour; social comparison). It is narrated by the primary researcher (SM), and definitions and numerical information are complemented by graphical illustration. The information provided is evidence-based and theoretically-informed, bridging the knowledge gaps identified through previous research [5]. It addresses the objectives outlined in Table 16, according to the identified BCTs. The video finishes with a reminder that the majority of girls in Ireland accept the HPV vaccine (BCT: information about social and environmental consequences; social comparison; information about others' approval).

Table 16 Intervention objectives and associated Behaviour Change Techniques (BCTs) [215]

Intervention objectives	BCTs
Understand how HPV is transmitted	Information about health consequences
Know how common HPV infections are	Information about health consequences Salience of consequences
Know that HPV infects both men and women	Information about health consequences
Understand the consequences of long-term HPV infection(s)	Information about health consequences Salience of consequences Anticipated regret Information about emotional consequences Comparative imaging of future outcomes Pros and cons
Understand why the vaccine is administered at the recommended age	Information about health consequences
Appreciate the safety and efficacy of the vaccine	Credible source Focus on past success
Know the vaccine side effects	Credible source Pros and cons

7.4.3 Intervention evaluation

7.4.3.1 Trial design

A prospective randomised controlled feasibility trial (RCT), containing an intervention group who had access to the video and a control group who did not have access to the video, was conducted to evaluate the intervention for parent-daughter dyads, living in Cork, Ireland. Randomisation occurred at the school level.

7.4.3.2 Participant recruitment

Eligible participants were parent-adolescent dyads including a female adolescent, pre-HPV vaccination, in her final year of primary school (ISCED level 1) [288], typically aged 11-12 years. Recruitment took place over a six-week enrolment period from April to May 2019. A list of Cork primary schools was compiled and stratified according to DEIS (Delivering Equality of Opportunity in Schools) status [390]. The DEIS programme supports children who are at greatest risk of educational disadvantage [390]. Using a purposive sampling strategy [386], school principals were contacted via email and/or telephone and provided with details of the trial. Schools interested in taking part were then randomised by simple randomisation [412]. The principals were asked to share study information, via email, with eligible participants. This email detailed trial information, expectations of participation, and instructions on accessing the trial material. Google Forms was used as the data collection platform, recording consent to participate and baseline characteristics of the parent: gender; age range; highest education level achieved; number of children (under 18 years); and vaccination status of children.

7.4.3.3 Outcome measures

1. *Evaluate participants' baseline HPV and HPV vaccine knowledge and intention to vaccinate*

A 10-item questionnaire to assess HPV and HPV vaccine knowledge was developed (Figure 16). Items assessed knowledge using a "True, False, and Don't know" format. These 10 items were identified as knowledge gaps during previous literature review and qualitative research [4, 5]. The questionnaire was developed, edited and assessed for face validity and content validity by the multi-disciplinary research team but did not undergo external validation. A knowledge score was based upon correct responses to items 1-10 of the study questionnaire (Figure 16). The knowledge score ranged from 0-10, with one point being rewarded for each correct response obtained. No points were rewarded if the participant responded as "Don't know". Participants were also asked if they intended accepting the HPV vaccine for their daughter and had the options of "Yes", "No", and "Don't know". This question was not scored.

1. **HPV is very rare**
   O True
   O False
   O Don't know
2. **8 out of 10 people will get HPV in their life**
   O True
   O False
   O Don't know
3. **HPV always has visible signs or symptoms**
   O True
   O False
   O Don't know
4. **HPV is spread through the air**
   O True
   O False
   O Don't know
5. **Only women can get HPV**
   O True
   O False
   O Don't know
6. **HPV can cause cancer in more than one part of the body**
   O True
   O False
   O Don't know
7. **You only need the HPV vaccine if someone in your family has had cervical cancer**
   O True
   O False
   O Don't know
8. **The HPV vaccine is most effective if given to 11-12-year olds**
   O True
   O False
   O Don't know
9. **The HPV vaccine has only been given in Ireland**
   O True
   O False
   O Don't know
10. **There are many unwanted, long lasting side effects from the vaccine**
    O True
    O False
    O Don't know

Figure 16 HPV and HPV vaccine knowledge questionnaire

2. *Assess the impact of the video on participants' HPV knowledge and intention to vaccinate*

Intervention Group: At the start of the study, (Week 0; W0), those in the intervention group undertook the baseline knowledge assessment and then

immediately had the opportunity to view the video. Two weeks later, they repeated the baseline knowledge assessment (Week 2; W2). They were also asked whether the video had increased the likelihood of accepting the HPV vaccine ("Yes, No, and Don't know").

Control Group: They did not have access to the video; however they completed the knowledge assessments at W0 and W2. They were provided the opportunity to view the video, upon completion at W2.

3. Assess participants' acceptability of the intervention

At W2, participants in the intervention group were asked to respond ("Yes, No, and Don't know") to the following statements to assess their acceptability: (1) Did you find this video interesting? (2) Did you find this video useful? In addition, feedback from participants regarding their impressions of the video and suggestions for improvement was obtained through the provision of a free-text box.

7.3.3.4 Statistical analyses

Data were analysed using IBM's Statistical Package for the Social Sciences (SPPS) for Windows, Version 22.0 (IBM Corp., Armonk, NY). Continuous variables were described by means and SDs for normally distributed data and by medians and IQRs for non-parametric data. Categorical variables were described by counts and percentages. Associations between categorical variables were investigated using Yates' Continuity Chi-Square tests. Mann-Whitney U tests were used to investigate differences between groups for non-parametric continuous variables. P values of <0.05 were considered statistically significant.

7.5 Results

During the six-week enrolment period, 313 schools were invited to participate (n=37 DEIS, n=276 non-DEIS). Eleven schools agreed to participate (n=4 DEIS, n=7 non-DEIS) and were randomised (n=5 control, n=6 intervention). According to information provided by the school principals, 326 parent-daughter dyads were eligible to participate. A total of 49 parent-daughter dyads completed baseline knowledge assessment at W0 (n=24 control, n=25 intervention), and 35 dyads completed knowledge assessment at W2 (n=17 control, n=18 intervention) (Figure 17). Baseline participant demographics are summarised in Table 17.

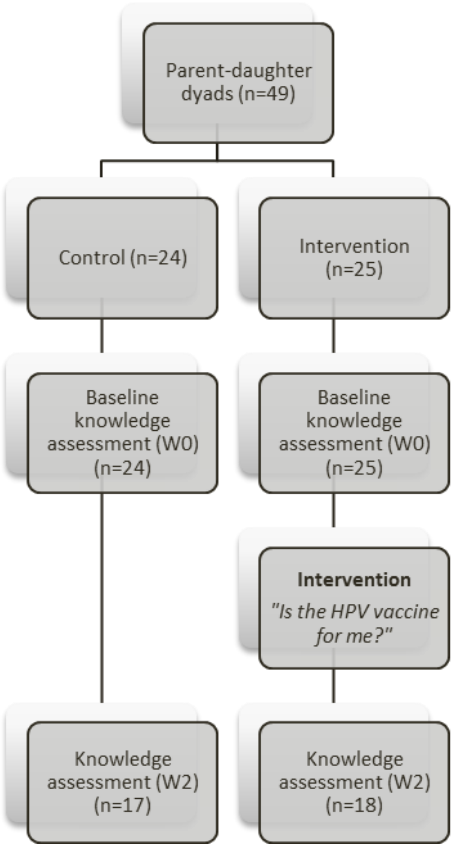


Figure 17 Participant flow diagram

Table 17 Baseline participant demographics

	Control n (%)	Intervention n (%)	p value
DEIS[a]	10 (41.7)	9 (36.0)	0.909
Females	24 (100)	25 (100)	N/A
Age range			0.063
• 20-29 years	0 (0)	0 (0)	
• 30-39 years	16 (66.7)	9 (36.0)	
• 40-49 years	8 (33.3)	13 (52.0)	
• 50-59 years	0 (0)	3 (12.0)	
Highest level of education			0.984
• ISCED[b] level 1	1 (4.17)	0 (0)	
• ISCED level 2	0 (0)	0 (0)	
• ISCED level 3	17 (70.8)	20 (80)	
• ISCED level ≥4	6 (25.0)	5 (20.0)	
Number of children (under 18 years)			0.456
• 1	2 (8.3)	6 (24)	
• 2	15 (62.5)	15 (60)	
• 3	5 (20.8)	3 (12)	
• 4	2 (8.3)	1 (4)	
• More than 4	0 (0)	0 (0)	
Children fully vaccinated			N/A
• Yes	24 (100)	25 (100)	
• No	0 (0)	0 (0)	
• Don't know	0 (0)	0 (0)	
Intend to accept HPV vaccine			0.884
• Yes	13 (54.2)	12 (48)	
• No	0 (0)	0 (0)	
• Don't know	11 (45.8)	13 (52)	

DEIS[a]: Delivering Equality of Opportunity in Schools): this programme supports children who are at greatest risk of educational disadvantage **[390]**.

ISCED[b]:
ISCED level 1: Primary education, equivalent to 8 years official State education
ISCED level 2: Lower secondary education: Irish Junior/Inter Certificate, equivalent to 11 years official State education
ISCED level 3: Upper secondary education: Irish Leaving Certificate, equivalent to 14 years official State education
ISCED level ≥4: Higher Education including post-secondary non-tertiary education, short-cycle tertiary education, Bachelor (or equivalent), Master (or equivalent) and Doctoral (or equivalent)

All participants were female and declared that, to the best of their knowledge, all children in their care were fully vaccinated. There were no statistically significant differences between the control and intervention groups based on DEIS status

(χ^2_{yates} (1)=0.013, p=0.909), age (χ^2_{yates} (1)=3.463, p= 0.063), education (χ^2_{yates} (1)=0.000, p=0.984), number of children (χ^2_{yates} (1)=0.580, p=0.456) or intention to accept the HPV vaccine (χ^2_{yates} (1)=0.021, p=0.884).

7.5.1 Outcomes

1. *Participants' baseline HPV and HPV vaccine knowledge and intention to vaccinate*

At W0, the overall median (IQR) baseline knowledge score was 5 (4, 6). There was no statistically significant difference in baseline knowledge assessment scores between control (median=5, n=24) and intervention (median=5, n=25) groups, (U=292, Z=-0.163, p=0.870) (Figure 18 and Table 18). Just over half (51%) of the participants indicated that they intended to accept the HPV vaccine, while the remaining 49% remained undecided.

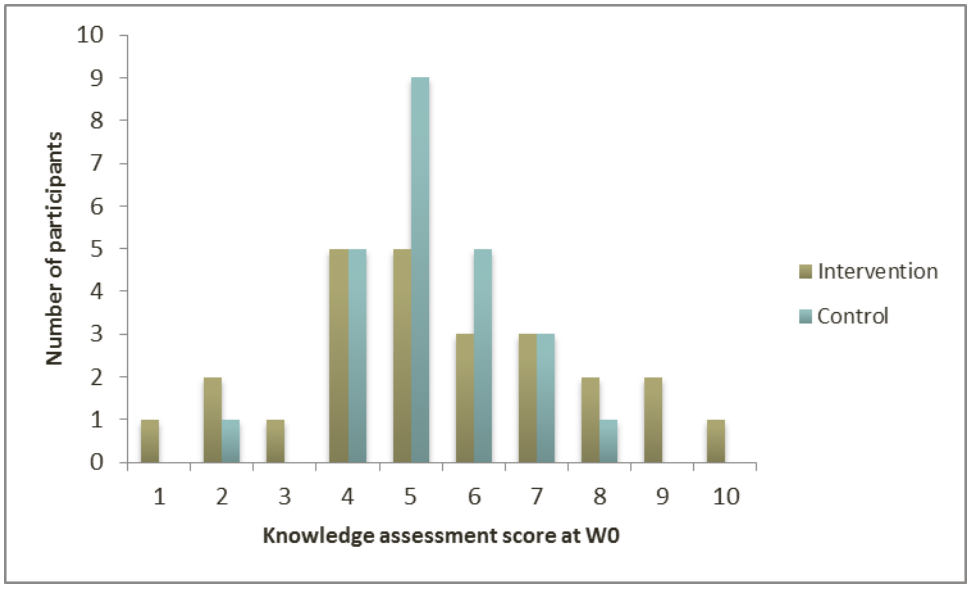


Figure 18 Knowledge Assessment Scores at W0, comparing Control and Intervention groups.
The total score for the knowledge assessment is on the X-axis, the number of participants achieving this score is on the Y-axis.

2. Impact of the video on participants' HPV knowledge and intention to vaccinate

At W2, there was a statistically significant difference in knowledge assessment scores between control (n=17) and intervention (n=18) groups, (U=1.5, Z=-5.065, p<0.01), as shown in Table 18 and **Error! Reference source not found.**. When asked whether this video had increased the likelihood of accepting the HPV vaccine, 88% indicated that it had, 4% indicated that it had not and 8% were unsure.

Table 18 Knowledge Assessment Scores at W0 and W2

	Number of participants	Control Score Median (IQR)	Intervention Score Median (IQR)	P value
W0 knowledge assessment	49	5 (4.75, 6)	5 (4, 7)	p=0.870
W2 knowledge assessment	35	5 (5, 6)	9 (9, 10)	p<0.01

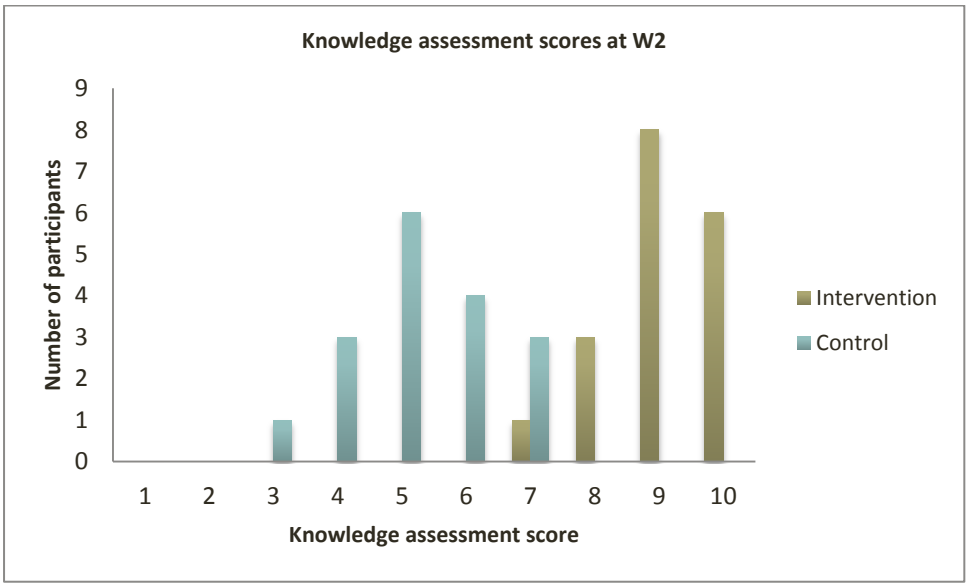


Figure 19 Knowledge Assessment Scores at W2, comparing Control and Intervention groups

3. Participants' acceptability of the intervention

All intervention participants (n=25) found the video interesting, while 96% found it useful.

7.6 Discussion

The purpose of this study was to design, develop and evaluate the feasibility of a theory, and evidence-based intervention to improve knowledge about HPV and HPV vaccines and intention to vaccinate among parent-daughter dyads. It was intended that targeting these dyads would promote open dialogue between parent-daughter pairs, leading to a scenario where the adolescent was involved and participated in the vaccine decision. The chosen mode of delivery was an online video. Digital media has several advantages: videos can be entertaining; their medium is familiar; and they may be designed as a "takeaway tool" that permits more independent application, at the viewer's own pace [413, 414]. We found that this educational intervention significantly increased knowledge of HPV and the HPV vaccine for participants who viewed the video compared to a control group. Secondly we found that this video increased the likelihood of accepting the HPV vaccine for the majority of participants in the intervention group. This study therefore provides initial "proof of concept" that an educational intervention designed from a "solid foundation" of behaviour change theory can positively influence the HPV vaccine decision-making behaviour.

While several interventions have been designed to address HPV vaccine hesitancy [407-411], there are no published examples, using the BCW to develop a *de novo* online intervention, targeted at parent-daughter dyads. The intervention was evaluated using the APEASE criteria, a set of criteria used to make context-based decisions on intervention content and delivery consisting of affordability, practicability, effectiveness and cost-effectiveness, acceptability, side-effects/safety and equity considerations [204]. While affordability is difficult to quantify in this

case, this video-based intervention was created by the lead author in consultation with a Technology-Enabled Learning Co-ordinator, with minimal financial input. This video was then hosted free of charge on a YouTube® platform (unlisted). If the intervention is adopted in its current form, no further financial investment would be required. This intervention is practicable in its mode of delivery. Because the video is hosted online, the internet is used as a platform to disseminate the content as intended to the target population. According to data collected in 2018 by Ireland's Central Statistics Office (CSO), an estimated 89% of Irish households had access to the internet at home, with 57% of individuals seeking health-related information online [415]. Research has shown that more people are accessing internet-based content by following links on social media than through direct searches [416]. Social media is defined as; *a group of internet-based applications that allow the creation and exchange of user-generated content* [417]. Social media statistics from June 2018 indicate that up to 66% of Irish individuals (over 15 years) are using social networking sites (e.g. Facebook®, Instagram®, LinkedIn®, Twitter®) [418]. It has been demonstrated that information shared via social media results in greater knowledge transfer than when shared via pamphlets [419]. In addition, it has been postulated that social media has direct public health relevance because social networks could have an important positive influence on health behaviours and outcomes [420, 421]. Therefore, social media platforms have the potential to effectively increase knowledge and facilitate behaviour change. The intervention described in this study is readily amenable to dissemination on social media platforms.

In this small feasibility study, the intervention was shown to be effective, with a statistically significant increase in knowledge assessment scores. At the outset, 49% of participants were undecided about their vaccine decision. However, on completion of the study, 88% participants indicated that the video had increased the likelihood of accepting the vaccine. While this was a positive finding, it must be acknowledged that intention alone does not necessarily predict future vaccine uptake [422]. This disparity is known as the intention-behaviour gap and is present when people hold favourable immunisation intentions yet fail to act [423, 424]. A variety of strategies have been suggested to bridge this gap: keeping these favourable immunisation intentions in mind through reminders, prompts and cues; and reducing barriers through logistics and heuristics [115]. A key strength of an anonymised data collection approach is the minimisation of social desirability bias. Social desirability bias refers to the individual's tendency to respond in a more socially desirable manner in certain situations and reflects what one believes will lead to approval from others or avoiding their disapproval [425, 426]. If intention to vaccinate was assessed through qualitative methods, such as face to face interviews by the researcher (SM), whose occupation as a pharmacist was known to the participants, the results may not have been reflective of true intentions.

There were no statistically significant differences between the control and intervention groups according to DEIS status, age range, education, number of children, child vaccination status, and intention to accept the HPV vaccine. All parent participants were female. However, such a gender imbalance is not unusual. Research has demonstrated that the female care-giver is more likely to participate in clinical research [84], and is often the primary healthcare decision-maker for the

family [352]. In agreement with previous research, baseline HPV, and HPV vaccine, knowledge was low [4].

While it would have been desirable to evaluate the impact of this intervention on actual vaccine uptake, this was not a primary objective of the study and was not included in the ethics approval. Instead, the favourable immunisation intentions generated by the intervention could be kept in mind through repeated dissemination of the video (e.g. online via social media or on television screens located at healthcare facilities such as GP surgeries and pharmacies). Due to the affordability, practicability and effectiveness of the intervention, it was determined to be cost-effective.

Acceptability has become a key consideration in the design, evaluation and implementation of healthcare interventions and is a necessary condition for effectiveness [427]. The acceptability of this intervention was evaluated: all of those asked found the video interesting, while 96% found it useful. However, only 3.5% of invited schools consented to participate. While an effort was made to understand the reasons underpinning their lack of participation, the majority of contacted schools were non-responsive. Of those eligible to complete the knowledge assessment at W0, only 15% did so and this was further reduced to 10.7% at W2. This decline in response rate between phases is frequently observed and reported [428]. However, a higher response rate was expected due to the personal relevance of the research topic [429]. This intervention was delivered in May, this is four months before the vaccine will be offered to the participants, to permit timely provision of vaccine information [430]. It is possible that the time-lag between information delivery and actual vaccination date was too long, and participants

were not yet prepared to consider their vaccine decision and thus were not personally invested in intervention content.

An intervention may be effective and practicable, but have unwanted side-effects or unintended consequences [204]. Research has shown that information provision regarding vaccine safety and efficacy can cause unpredictable effects on vaccination uptake and may even increase such concerns [431, 432]. A free-text box was provided in this study and no participants reported any such concerns. Nor did any participants contact SM, whose contact information was provided. However, the potential for such an occurrence if the intervention were to be scaled up should be considered.

The use of video as a mode of delivery facilitates equity, as it provides standardised content across learners and has been shown to be effective among viewers of lower literacy levels [433]. However, the impact of the 'digital divide' on the implementation of an online intervention must be considered. A proportion of the Irish population (11%) do not have internet access at home with 30% of these reporting that lack of skills hampered their internet access [415]. Parents (and adolescents) currently receive vaccine information in written format, (i.e. pamphlets and patient information leaflets (PIL)) and additionally, the website of the National Immunisation Office (NIO) is signposted, providing further information in a variety of formats, including both video and text. The intervention described here is not intended to replace such material, but rather to support and complement it, providing information and promoting behaviour change in a manner that is independent of the Government.

7.7 Conclusion

A video-based online behavioural intervention was associated with improved HPV (and HPV vaccine) knowledge, and intention to vaccinate, among parent-daughter dyads. The intervention was found to be affordable, practicable, effective (cost-effective), acceptable, safe, and equitable, in this feasibility study. However, it is important to acknowledge that vaccination is highly context specific [48]. Therefore the impact of this intervention will need to be evaluated in alternative contexts, for example different regions in Ireland). In addition, from September 2019, male adolescents are included in the HPV vaccination programme [143]. An assessment of the impact of our intervention in parent-son dyads is required, making alterations as required, and supplementing with further qualitative research, if indicated. Should this intervention demonstrate efficacy across multiple contexts, a national dissemination of *"Is the HPV vaccine for me?"* should be launched.

7.8 Acknowledgements

The authors wish to acknowledge the valuable contribution of Mr Patrick Kiely, Technology-Enabled-Learning Co-ordinator in the Office of the Vice-President for Teaching and Learning, University College Cork, the principals of the participating schools, and the study participants, to this research.

7.9 Chapter conclusion and context within thesis

This chapter described the design, development and quantitative evaluation of a theoretically-informed and evidence-based intervention to improve vaccine knowledge and intention to vaccinate, thereby addressing the final objective of this doctoral research. The design of the intervention was guided by principles of

behaviour change theory, the evidence-base generated in Chapter 4, and the primary qualitative research conducted in Chapters 5 and 6.

Chapter 8 Discussion and Conclusion

8.1 Discussion

This thesis investigated vaccine decision-making and identified barriers to vaccine uptake in an Irish setting. In this final chapter I will discuss the thesis as a complete body of work and interpret and contextualise the overall findings. The chapter will begin with a summary of the key findings, before integrating these findings to provide greater insights. This will involve a discussion of the implications of the research, taking into consideration previous literature, as well as healthcare practice and policy. Following this, the overall strengths and weaknesses of the thesis will be described. Finally, recommendations for future work will be provided.

8.2 Summary of findings

The first objective of this doctoral research was to review the literature on the perception and acceptability of vaccination to provide an evidence-base to inform the development of research questions for the primary research studies. Chapter 2 provided a narrative review of the literature on the perceptions, acceptability and suitability of microneedle technology for immunisation in key stakeholder groups (i.e. parents, children and HCPs). Drivers for acceptability included: a perceived or actual reduction in pain; ease and convenience of administration; potential for self-administration; and attractive visual appearance. Barriers to acceptability included: unfamiliarity; allergic potential; and the inclusion of the term 'needle' in the product name. It was identified that a paucity of studies on paediatric immunisation using microneedle patches have been published and further qualitative research was required to explore the perception, acceptability and suitability of microneedle-mediated vaccination in this population. Chapter 4 provided a

systematic review and meta-ethnographic synthesis of the qualitative literature on the views of parents regarding HPV vaccination. Five key concepts that reflected the principal findings of all 33 included studies were determined: is prevention better than cure; the fear of the unknown; limited knowledge and understanding; complex vaccination decisions; and parental responsibility. Drivers for acceptability included: provision of information; HCP endorsement; disease prevention; and child protection. Barriers to acceptability included: low perception of risk; link to sexual intercourse; safety and efficacy concerns; and lack of information. There was significant overlap and data recurrence in the review. However, 'new' vaccine concerns, in light of HPV vaccine instability, have not been addressed in the literature and further qualitative research exploring these concerns was recommended.

The second thesis objective was to address gaps identified in the literature reviews and ascertain the knowledge, attitudes and beliefs of key stakeholders to elucidate vaccine decision-making and to identify barriers to vaccine uptake in Ireland. Chapter 3 presented a qualitative focus group study that investigated the knowledge, attitudes and beliefs of parents about microneedle-patch vaccines. Five core themes were identified and defined as: concern (including general vaccine hesitancy, concerns with current vaccines and immunisation programmes and safety and efficacy concerns); suitability of microneedle technology for paediatric use (including practicality, child-friendliness and acceptability transfer); potential for parental administration (including its advantages and disadvantages and the requirement for a delivery indicator); the role of the HCP (as a source of information); and special populations (including allergic potential and alternative

uses). Chapter 5 presented a qualitative focus group study that investigated the knowledge, attitudes and beliefs of female adolescents (aged 14-16 years, including vaccine recipients and non-recipients) about HPV vaccination. Knowledge and understanding of HPV, HPV-related diseases and sequelae, and HPV vaccines was limited. General vaccine acceptance was high and vaccination was viewed as an accepted norm. The responsibility for vaccine decision-making was assigned to the parent, and adolescents accepted the parental recommendation with minimal or no discussion. Other identified social influences included HCPs, vaccinated peers, and group conformity. Adolescents were aware, albeit vaguely, of HPV vaccine instability, and discussed how negative media attention (i.e. radio) had resulted in a variation in vaccine uptake among family members. While self-efficacy in decision-making was variable, many adolescents believed that vaccine information should be delivered to both vaccinees and their parents. Chapter 6 presented a qualitative interview study that investigated the knowledge, attitudes and beliefs of parents of female adolescents (aged 14-16 years, including vaccine-acceptors and decliners) about HPV vaccination. Once again, general vaccine acceptance was high and parents recognised the importance of immunisation. Similar to the adolescents in Chapter 5, parents' knowledge and understanding of HPV, HPV-related diseases and sequelae, and HPV vaccines was limited, yet highly variable. Social influences included daughters, partners, peers, HCPs, and group conformity. It was identified that the burden of healthcare decision-making often lay with the female primary care-giver, with male care-givers relying on their partner (or an alternative female) for guidance on vaccine decision-making. Parents were aware of HPV vaccine instability and discussed the emotive nature of radio interviews, television

documentaries, newspaper articles and online information that reported on alleged chronic vaccine side effects. Vaccine-acceptors acknowledged their concerns regarding vaccine misinformation but prioritised disease and cancer prevention and were reassured by the continued, widespread use of the vaccine and their trust in the scientific community. In contrast, vaccine-decliners prioritised the alleged risk of vaccine side effects and were reassured inaccurately by a reduced perception of HPV and HPV-related disease risk. In Chapters 5 and 6, behaviour change theory (TDF, COM-B, and BCW) was applied to suggest interventions strategies to address barriers to vaccine uptake.

The final thesis objective was to design, develop and evaluate a theory and evidence-based intervention to improve knowledge and intention to vaccinate. Chapter 7 described the design of video-based online behavioural intervention (*"Is the HPV vaccine for me?"*), developed to improve HPV and HPV vaccine knowledge, and intention to vaccinate. The intervention was associated with a statistically significant improvement in HPV knowledge and intention to vaccinate among parent-daughter dyads. In addition, the intervention was found to be affordable, practicable, effective (cost-effective), acceptable, safe, and equitable.

8.3 Interpretation and implications of findings

The overall aim of this thesis was to explore vaccine decision-making to identify and address barriers to vaccine uptake in Ireland. Qualitative methods (e.g. focus groups and interviews) collated the opinions of parents of children aged less than 12 years, parents of adolescents (aged 14-16 years), and female adolescents (aged 14-16 years) (Chapters 3, 5 and 6) and included the views of both vaccine-acceptors

and vaccine-decliners. Quantitative research methods (e.g. survey) assessed knowledge and the impact of a theoretically informed intervention to improve knowledge and intention to vaccinate (Chapter 7). This combination of research methods provided an overview of the vaccine decision-making process and identified barriers to vaccine uptake.

Research in the area of vaccine decision-making is extensive and evolving. Primary and secondary studies discussing the barriers to vaccine uptake continue to be conducted and published (e.g. [434-437]). These continued research efforts are necessary due to the variability of vaccine hesitancy. It is established that vaccine hesitancy is context specific, and changes with time, place and the specific nature of the vaccine [36, 48, 50]. Therefore, the principal contribution of this thesis has been the generation of evidence in an Irish context, with a particular focus on the HPV vaccine. The findings from this thesis concur with, and add to, previous studies that have described barriers to microneedle-mediated vaccine acceptability [84, 86, 261] and HPV vaccine uptake [174, 318, 320-328, 332-341, 344-349].

8.3.1 Fear as a barrier to vaccine uptake [36]

8.3.1.1 Needle fear

It was hypothesised at the thesis outset that needle fear, as a non-monetary vaccine cost, is a barrier to vaccine uptake, a hypothesis that has been supported by the literature [37, 80, 81, 438]. A systematic review and meta-synthesis has recently evaluated the prevalence of needle fear: the majority of children included exhibited needle fear, while prevalence estimates for needle fear ranged from 20-50% in adolescents and 20-30% in young adults [79]. However, relatively few studies have

been designed to address this problem [82]. Therefore, it was suggested that alternative vaccine delivery systems, for example, microneedle patches, could remove the barrier of needle fear. However, qualitative research presented in Chapter 3, indicated that while microneedle technology offers significant advantages over conventional vaccination with a hypodermic syringe (e.g. reduced pain and bleeding, increased convenience and ease of administration), the potential trauma associated with conventional vaccination methods is not a significant deterrent to immunisation [3]. Similarly in the qualitative research presented in Chapters 5 and 6, none of the vaccine-decliners included acknowledged needle fear as a reason for refusal. This observation is reaffirmed by the fact that participating HPV vaccine-decliners had accepted all other vaccines recommended by the childhood and school immunisation programmes. Therefore, while it may be a contributory factor, needle fear alone is not a significant barrier to vaccine uptake.

8.3.1.2 Fear of adverse events following immunisation (AEFI)

An adverse event following immunisation (AEFI) is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine [439]. AEFIs are divided into five categories: vaccine product-related reaction, vaccine quality defect-related reaction, immunisation error-related reaction, immunisation anxiety-related reaction, and coincidental event [439]. A vaccine product-related reaction is an AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product e.g. extensive limb swelling following diphtheria/tetanus/pertussis vaccination. A vaccine quality defect-related reaction

is an AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device e.g. incomplete inactivation of IPV leading to paralytic polio cases. An immunisation error-related reaction is a preventable AEFI caused by inappropriate vaccine handling, prescribing or administration e.g. contamination of multi-dose vial leading to infection transmission. An immunisation anxiety-related reaction is an AEFI arising from anxiety surrounding immunisation e.g. vasovagal syncope during or after vaccination. A coincidental event is an AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety. Fear of several AEFIs was evident throughout this research. Focus group participants were concerned that parental administration of microneedle-patch vaccines could be associated with reduced efficacy due to inadequate administration training and a potential immunisation error-related reaction could occur (Chapter 3). Fear of vaccine product-related reactions was also observed in Chapter 3: participants were concerned about potential allergenic properties of microneedle-patch vaccines. Similarly in Chapters 5 and 6, participants were concerned about unsubstantiated HPV vaccine product-related reactions, as described. However, all evidence indicates that these reactions were coincidental effects i.e. a temporal association rather than a causal link between vaccine administration and the development of new onset chronic conditions was established.

8.3.2 Knowledge as a variable barrier to vaccine uptake

Lack of knowledge is a documented determinant of vaccine hesitancy [48]. However, a key finding of this thesis was that limited knowledge was not

necessarily a predictor of vaccine refusal, as limited vaccine-specific knowledge was evident across all chapters. Passive conformist vaccine-acceptors were found to have limited knowledge, making non-deliberate or automatic vaccine decisions based on general vaccine acceptance, a high perception of risk and/or a high level of trust in the healthcare system [47]. When there is a realistic perception of disease risk and trust in the healthcare system, potential AEFIs are acknowledged, but do not negatively impact the vaccine decision. Conversely, where there is a low perception of disease risk, and/or a low trust in the healthcare system, the fear of these potential AEFIs is more impactful. In Chapter 3, the acceptability of microneedle-patch mediated vaccination was explored. In spite of high trust in the healthcare system and a true perception of disease risk, unfamiliarity prevailed and fear of AEFIs, e.g. allergenic potential, negatively impacted the parental perception of the technology. In Chapters 5 and 6, a low perception of disease risk, a low trust in the healthcare system and limited knowledge were observed. Therefore potential AEFIs exerted a greater effect on the decision-making process. Low perception of disease risk is a recognised barrier to vaccine uptake [48]. Sexual activity inexperience, participation in screening programmes and a lack of familial history of cervical cancer were factors associated with an unrealistically low perception of HPV risk, as described in Chapters 4 and 6. Low trust in the healthcare system was evident, with vaccine-decliners suggesting that HCPs and governmental, and HSE representatives failed to allay vaccine safety concerns. While healthcare authorities assess safety concerns and respond to them based on available data, the public assess these concerns and respond based on emotions and heuristics,

creating a risk perception gap [113]. Further to this, individuals tend to focus more on avoiding loss (e.g. potential vaccine side effects), than obtaining gain [113].

8.3.2 Implications for practice

The crucial role of HCPs in the provision of vaccine information and guidance was evident in the findings of this thesis, and throughout the literature [440]. In the face of emerging vaccine hesitancy, HCPs still remain the most trusted advisor and influencer of vaccine decisions [440]. According to Wellcome Trust's Global Health Monitor, 93% of Irish participants reported that they trusted doctors and nurses, 85% trusted these HCPs for medical or health advice, and 95% trusted the medical or health advice they received [117]. However, research throughout this thesis indicates that their potential impact on vaccine hesitancy and vaccine uptake is not yet fully realised, with the majority of participants failing to consult their HCP to guide their vaccine decision. Research has shown that HCPs often have inadequate information or training to address specific vaccine concerns [440]. HCPs who were vaccinated themselves, or who vaccinate their own children, were more likely to recommend immunisation, providing a reassuring example to concerned patients [441, 442]. Information campaigns to increase HCP vaccine knowledge (e.g. education courses, talks/meetings, posters, or letters/emails) have been shown to increase the likelihood of recommending vaccination [443-445]. Further to knowledge provision, communication tools for HCPs have been developed, to enable HCPs to engage in difficult discussions with vaccine-hesitant individuals [446-449]. Given the context, temporal, and vaccine specificity, of vaccine hesitancy, an effort must be made to modify these interventions in light of research

conducted throughout this doctoral thesis, and to evaluate their effectiveness in the Irish context.

The capacity and confidence of HCPs are stretched as they are faced with time constraints, increased workload and limited resources. Increasing demands on the healthcare system as a direct result of the extension of free GP care to include all children under 6 years and all adults over 70 years, combined with an ageing population, has had a major impact on the GP workload. In addition there is evidence of a significant undersupply of GPs in Ireland [450]. To address this shortfall, innovative recruitment and retention strategies are required to significantly increase the annual intake into GP postgraduate specialist training [450]. To alleviate the pressures in primary care, the role of vaccinating pharmacists could be expanded to include paediatric and adolescent immunisation. In October 2011, legislation was introduced which enabled pharmacists to administer the influenza vaccine, and vaccine uptake in the community pharmacy setting has increased exponentially [451]. Pharmacist-led vaccination services lead to higher vaccination rates, and serve members of the public that have not received vaccination before [452]. Pharmacy services were expanded in 2015, to include the provision Pneumococcal Polysaccharide and Herpes Zoster vaccination. Pharmacists are the most accessible HCPs, with 1.5 million visits by the public to local pharmacies per week [452]. With the infrastructure already *in situ* within pharmacies, further expansion of the vaccination services provided by pharmacists would permit HCPs, such as GPs to focus on those patients with more complex medical needs.

8.3.3 Implications for policy

Vaccine hesitancy is a concern for the public, HCPs and policy-makers alike. Policy-makers play a crucial role in influencing whether and to what degree research findings influence health services and public health [453]. Research has identified the importance of building and strengthening trust in, and within, institutions, with a particular focus on the critical support relationship needed between policy-makers and HCPs, to ultimately build public trust [446, 454]. In tandem with the development of CPD programmes to provide HCPs with information to adequately address vaccine concerns, existing programmes and policies should be modified to train HCPs to engage more confidently with vaccine-hesitant patients. The "Making Every Contact Count" programme was established by the HSE in 2016. This online e-learning platform aims to capitalise on the opportunities that occur daily for HCPs, to support chronic disease prevention, and self-management of existing diseases. The programme provides a foundation in behaviour change theory and techniques, including the underlying principles of a patient-centred approach, and demonstrates how to carry out a brief intervention through a suite of realistic video scenarios [455]. The programme currently includes modules on smoking, alcohol and drugs, healthy eating and active living. Should a module on vaccines be included in the programme, HCPs will be prompted and encouraged to discuss upcoming vaccines with parents and adolescents, and address concerns expressed by vaccine-hesitant individuals.

The Medicinal Products (Prescription and Control of Supply) (Amendment No.2) Regulations 2015 and the Medicinal Products (Prescription and Control of Supply) (Amendment) Regulations 2011 provide for the supply and administration of

seasonal influenza, pneumococcal polysaccharide and herpes zoster vaccines by pharmacists [456, 457]. In light of sub-optimal vaccine uptake rates and the overstretched primary care sector, expansion of vaccination services offered by pharmacists could be beneficial. A proactive response by the Pharmaceutical Society of Ireland (PSI) and the HSE is required to drive legislation for further amendments to the aforementioned Regulations, and to negotiate an acceptable reimbursement contract for pharmacies.

Research has demonstrated that presenting pro-vaccination information to adults may actually encourage anti-vaccine sentiment, suggesting that, in some, these beliefs may be deeply held by adulthood, and therefore parenthood [432, 458]. Therefore, there is potentially an opportunity for policymakers to focus educational efforts on vaccination in childhood [459]. While schools facilitate the provision of immunisation programmes by the HSE, there is a need to include age-appropriate vaccine education in the primary and secondary school curricula, to instil positive views on vaccination. In 2015, the Department of Education and Skills in Ireland launched The Digital Strategy for Schools 2015-2020, providing a rationale and an action plan for integrating Information and Communications Technology (ICT) into teaching, learning and assessment practices [460]. Several digital resources for children's education on vaccination have already been developed, including comic books, videos and games [459]. These resources should complement efforts to introduce vaccination education into school curricula, offering education via multiple modalities.

This thesis describes the design, development and evaluation of a theoretically-informed behavioural intervention, to improve knowledge and increase intention to

vaccinate by parents (Chapter 7). This intervention was based on the findings of a comprehensive systematic review [4] and a series of qualitative research studies and was found to be affordable, practicable, effective (cost-effective), acceptable, safe, and equitable in a feasibility study. Although there is significant evidence that theoretically-informed behavioural interventions are effective in changing behaviour across multiple contexts, populations and behaviours, such evidence is seldom translated to population-level change [188]. This is largely due to the fact that behavioural interventions are relatively short-lived, under-funded, or fail, due to poor implementation, up-scaling, or translation [461, 462]. Therefore, an effort must be made to actively engage with stakeholders including the NIO, and the HSE, and outline the human and economic advantages of preventive strategies like behavioural interventions, instead of a treatment-focused model of healthcare provision [463]. It has been reported that for policy-makers, it is difficult to gain access to academic research findings, academic timelines often fail to align with the policy process, and preferred forms of evidence differ from academics [464, 465]. It is essential for academics to engage in knowledge exchange with policy-makers, taking a systematic approach to sharing tacit knowledge. Developing a policy brief is an effective strategy for rapidly providing scientific evidence to policy-makers [466]. A policy brief is a two page (front and back of a single sheet) document that uses graphics and text to summarise the key results of scientific research, and links those results to specific policy recommendations [467]. Constructing a policy brief compiling the evidence generated throughout the course of this doctoral thesis could facilitate effective policy-maker engagement. Finally, due to the geographical variation in vaccine uptake in Ireland, an effort must be made to engage specifically

with local government in these low uptake areas. Local authorities will have a vested interest in promoting public health in their constituencies and are more likely to engage in academic collaboration.

8.4 Strengths and limitations

The individual primary research studies (Chapters 3, 5-7) were designed based on the findings of comprehensive reviews of the literature [1, 2, 4]. Systematic reviews are the gold standard to search for, collate, critique and summarise the best available evidence [468, 469], and are seen as the pillar of evidence-based healthcare [362, 470, 471]. The research presented in Chapter 4 adhered to best practice recommendations for the conduct and reporting of systematic reviews and meta-ethnographic syntheses [317, 468, 472]. The findings of these reviews defined the current evidence on the perception and acceptability of vaccination and allowed the identification of key gaps in the literature. Subsequently, the research studies undertaken were designed to address the aims and objectives of the thesis overall, whilst ensuring that these key deficits in the literature were addressed.

A key strength of this thesis is the mixed methods approach. Chapter 1 provided a brief overview of the strengths and weaknesses of quantitative and qualitative research methods and the advantages of using a mixed methods approach. The findings of the individual quantitative and qualitative components of this thesis are complementary. The findings from one study helped in the explanations of observations from previous studies and led to the generation of research questions for subsequent qualitative and quantitative studies. The mixed methods approach

has generated deeper insights than could have been elucidated from either method in isolation.

This thesis is the first to formally explore vaccine decision-making to identify and address barriers to vaccine uptake in an Irish setting. A major contribution of this thesis was the qualitative investigation of the views of adolescents. Research on vaccine decision-making has primarily focused on exploring the views of parents and HCPs and the voice of the adolescent; the intended vaccinee has been neglected in the literature. This thesis highlights the imperative for engagement with this cohort.

A key strength of this thesis is the use of behaviour change theory (TDF, COM-B, and BCW) and the systematic approach applied. The TDF provides a theoretical basis for understanding and changing behaviour [204]. The framework simplifies 33 theories and 128 constructs into 14 validated domains, underpinned by psychological theory [206]. The capability, opportunity, motivation model of behaviour (COM-B) distils the TDF into three domains, that interact to predict behaviour and include the individual's capability, motivation and opportunities for the behaviour [204]. The COM-B model guides the choice of intervention functions or strategies most likely to achieve behavioural change and forms the central component of the Behaviour Change Wheel (BCW) [210]. Within 19 frameworks for classifying behaviour change interventions, intervention functions and policy categories were discerned to construct the BCW [210]. Additionally, the intervention functions have been linked to a taxonomy of 93 Behaviour Change Techniques (BCTs), organised into 16 groups [215]. Theory was incorporated from the outset, during qualitative exploratory studies (Chapter 5 and 6), to the design

and delivery of the intervention (Chapter 7). There is substantive evidence supporting the efficacy and effectiveness of theory-based interventions targeting behaviour change. This evidence justifies the validity of the research and increases its potential impact. While this intervention is vaccine specific, the systematic approach permits it's modification in the design of interventions to promote uptake of alternative vaccines.

The quality and rigour of the research conducted as part of this doctoral thesis is evidenced in the number of peer-reviewed academic publications and conference presentations achieved. This highlights that the research is of value, of scientific merit, of interest to academic and healthcare colleagues. Therefore, dissemination of the important findings of this research is already underway. The publication strategy targeted a series of multidisciplinary journals with a diverse audience including healthcare providers, academics, public health practitioners and policy-makers [1-4]. Open access publication encouraged broader dissemination [2]. An effort will be made to further broadcast the crucial findings of this research to parents, vaccinees, HCPs working in clinical practice, public health practitioners and policy-makers, to minimise the translation gap. Strategies for research dissemination include social media campaigns, podcast and/or blog creation, attendance at community meetings and/or seminars, and the development of policy briefs, as previously discussed [473, 474].

An additional strength of this thesis is the topical nature of the research described. The issue of vaccine hesitancy is gaining increasing traction and recognition amongst HCPs, academics, public health practitioners and policy-makers, amplified by the WHO declaring it one of the top ten threats to global public health in 2019.

This thesis provides crucial evidence which can serve as the basis for future research.

Whilst there are numerous strengths associated with this research, a number of limitations must also be acknowledged. This research was conducted in the Cork and Kerry region, in the south of Ireland and therefore limited to a small geographical and limited demographic area. This could be seen to limit the generalisability (quantitative) and transferability (qualitative) of the study findings. While the healthcare structure and immunisation programme in Cork and Kerry are akin to those in place nationally, substantial variation in vaccine uptake is observed by area. Therefore, this variation requires further investigation at local level.

Potential sources of bias associated with each research study were considered and attempts were made to minimise the impact of these biases. Bias can be introduced at any stage of the research process including selection bias, data collection bias and analysis bias. Purposive sampling strategies minimised selection bias, because the sample is constantly refined to meet the aims of the study. Furthermore, additional participants were continuously recruited into the studies during data analysis, until data saturation was reached. However research participants self-selected, potentially affecting representativeness. Using a topic guide in focus group and interview studies minimised the potential for data collection bias. Strategies to reduce analysis bias were also used and included: constant comparison across focus group and interview transcripts; acknowledging deviant cases and outliers; and independent coding and analysis of transcripts by multiple multidisciplinary researchers.

8.5 Recommendations for future work

This thesis has provided an exploration of vaccine decision-making, identifying barriers to vaccine uptake in an Irish setting and highlights the implications of this research for practice and policy. Therefore, it represents an ideal starting point for further research to address these barriers. Further research should investigate the following areas:

1. **Exploration of the views of vaccinators** (e.g. GPs, GP surgery practice nurses, community health doctors, public health nurses, and pharmacists)

   The crucial role of HCPs in the provision of vaccine information and guidance of decision-making was repeatedly identified throughout this thesis. However, this role is not yet realised. An effort must be made to explore the views of frontline vaccinators, to identify their perceived barriers to vaccine uptake, and the challenges encountered during immunisation programmes. In addition, before the vaccination services in pharmacies are expanded, the views of pharmacists on this expansion should be explored. The education needs of vaccinators should be assessed, to permit the development of suitable CPD programmes. Exploration of the views of vaccinators should take the form of qualitative investigations, supplemented by larger, quantitative research, to elucidate national views.

2. **Exploration of the views of policy-makers**

   The translation of evidence-based research will not translate into effective policy without collaboration with policy-makers. Qualitative research with policy-makers could identify: potential obstacles to the introduction of vaccine policy; data needs of policy-makers to overcome these obstacles; and

individuals or groups who play a major role in decision-making or an influential role in the introduction of vaccine policy [475]. As before, large scale quantitative approaches are likely to follow initial qualitative methods.

3. **Research on vaccine hesitancy in the Irish context**

   Further research on vaccine hesitancy in the Irish context is warranted. The framework for such research could be based on the approaches taken in this thesis. Furthermore, large scale quantitative study, using validated tools to elucidate the prevalence of vaccine hesitancy, and the individual characteristics that are associated with hesitancy could further strengthen our understanding of the facilitator and barriers of vaccine uptake. Examples of these tools include the Global Vaccine Confidence Index [182], the Vaccine Confidence Scale [183], and the Parent Attitudes About Childhood Vaccines survey [51]. This would facilitate the targeting of interventions to support those most affected.

4. **Exploration of the views of male adolescents and parents of male adolescents**

   A gender-neutral HPV vaccination programme was initiated in Ireland in September 2019. This thesis focussed on exploring the views of female adolescents and parents of female adolescents. It is unknown whether the barriers to vaccine uptake identified throughout this doctoral research are specific to female vaccination. Therefore qualitative research, in accordance with methods already described, is warranted to explore the views of male adolescents and their parents.

5. **Assess the impact of the intervention in a variety of contexts**

   The context-specificity is well established. Therefore, while our intervention to improve knowledge and intention to vaccinate was found to be effective in a

small sample of parent-daughter dyads, its impact will need to be evaluated in alternative contexts (e.g. different demographics). Given the geographic variation of HPV vaccine uptake in Ireland, it would be beneficial to evaluate the impact of the intervention in areas reported low rates e.g. Kerry [172].

6. **Assess the impact of the intervention in parent-son dyads**

   With the recent inclusion of male adolescents in the HPV vaccination programme, there is a need to assess the impact of the intervention in parent-son dyads, in accordance with procedures outlined in Chapter 7.

7. **Systematic review to guide intervention scale-up**

   Potential operational frameworks for intervention scale-up should be identified by a systematic review. This could provide evidence-based guidance to policy-makers and funding-agencies.

8. **National dissemination of intervention**

   With guidance from identified stakeholders (i.e. qualitative research participants, vaccinators, and policy-makers), the intervention could be disseminated nationally. Potential dissemination strategies include sharing the video on social media, broadcasting the video on television, or embedding the video on influential websites e.g. the NIO [476].

By conducting the aforementioned research steps, a comprehensive overview of vaccine decision-making will be provided and the barriers to vaccine uptake perceived by all key stakeholders will be elucidated i.e. policy-makers, vaccinators, and members of the public. These systematic barriers may then be addressed, to enhance vaccine uptake in Ireland.

Appendices

Appendix 4.1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Research: Primary	**Research:** Secondary e.g. review articles
Data collection and analysis: Qualitative	**Data collection and analysis:** Quantitative
Participants: Parent, guardian, caregiver	**Participants:** Non-parent, guardian, caregiver
Intervention: Female adolescent* HPV vaccination	**Intervention:** Male adolescent HPV vaccination**,** Adult HPV vaccination

*Adolescent defined as individuals aged 10-19 years (WHO definition)

Appendix 4.2

Sample search strategy

Papillomavirus vaccines (MeSH) **OR** HPV vaccin* **OR** human papillomavirus vaccin*

AND

perception* **OR** view **OR** views **OR** viewpoint **OR** accepta* **OR** knowledge **OR** belief* **OR** attitude*

(AB Abstract)

OR

perception* **OR** view **OR** views **OR** viewpoint **OR** accepta* **OR** knowledge **OR** belief* **OR** attitude*

(TI Title)

Sample MEDLINE search strategy, conducted on 14th November 2016.

Search strategy for other databases: as for MEDLINE using index terms and truncation, where appropriate.

Appendix 4.3

ENTREQ Statement

1	Aim	To determine the views of parents regarding adolescent human papillomavirus (HPV) vaccination.
2	Synthesis methodology	Meta-ethnography was chosen as the synthesis methodology as it employs a process of comparison and cross-interpretation between studies while preserving the context of the primary data, providing a higher level of analysis, generating new research questions and duplicating duplication of research.
3	Approach to searching	A comprehensive search strategy was developed to retrieve all available articles related to the research question.
4	Inclusion criteria	Inclusion and exclusion criteria are outlined in Appendix 4.1.
5	Data sources	Electronic databases: MEDLINE, CINAHL and EMBASE, from inception to December 2016. Grey literature: Google Scholar. Hand searching: Reference lists of included citations.
6	Electronic search strategy	Electronic search strategy outlined in Appendix 4.2.
7	Study screening methods	The titles and abstracts of retrieved citations were assessed by one reviewer (SM). Full articles were retrieved for all potentially relevant articles. These articles were reviewed by three reviewers (SM, LS and AF) and were included if they fulfilled the inclusion criteria. Any disagreement regarding the eligibility of particular studies was resolved through discussion with a fourth reviewer (AM).
8	Study characteristics	Study characteristics outlined in Appendix 4.4.
9	Study selection results	The study selection process in outlined in Figure 13.
10	Rationale for appraisal	The rationale for appraisal was to assess the quality of the included studies.
11	Appraisal items	The CASP tool was used to appraise the included studies.
12	Appraisal process	The appraisal was conducted independently by three reviewers and consensus reached through discussion.
13	Appraisal results	Appraisal results are summarised in Appendix 4.5.
14	Data extraction	Three reviewers (SM, LS and AF) carefully and repeatedly read the included studies and independently identified the key concepts from information detailed in the results and discussion sections of the studies. These included both first-order (views of participants) and second-order interpretations (views of authors). In tandem with this process, SM recorded individual study characteristics. These included study objective(s); sample size; participant demographics; vaccine availability; methodology; country in which research was conducted and year of publication,
15	Software	QSR International's NVivo V.11
16	Number of reviewers	Three reviewers (SM, LS and AF) were involved in reading all included studies and constructing the key concepts. Four reviewers (SM, LS, AF and AM) were involved in the translation and synthesis steps.
17	Coding	Line by line coding to search for concepts.
18	Study comparison	The data was compared and contrasted across primary studies, to identify similarities and differences. Five key concepts that reflected the principal findings of all studies were determined.
19	Derivation of themes	The process of deriving the themes and sub-themes was inductive, moving from specific observations to general concepts.

20	Quotations	Direct quotes from study participants and the interpretations of the authors are provided in Appendix 4.7.
21	Synthesis output	The translations in each key concept were synthesised to develop novel third-order interpretations. These third order interpretations were linked using a 'line of argument' to develop a conceptual model which represents parental views regarding adolescent HPV vaccination (Figure 14 and Figure 15).

Appendix 4.4

Individual study characteristics

First author	Objective(s)	Participants (n)	Vaccine availability	Data collection	Qualitative methodology/analysis	Country	Year of publication
Bair **[318]**	To describe Latina mothers' acceptance of the HPV vaccine for their daughters and explore their knowledge base regarding HPV-related issues	Mothers of daughter(s) 7-14 years (Latina descent) (n=40)	X	Interview	Thematic	USA	2008
Bartolini **[319]**	To explore the decision-making process among parents of girls eligible for HPV vaccination	Parents of daughter(s) eligible for vaccination (n=48)	✓	Interview	Thematic	Peru	2012
Cooper Robbins **[320]**	To explore knowledge about HPV and HPV vaccination post-implementation of the national school-based HPV vaccination programme	Parents of daughter(s) 12-16 years (n=38)	✓	Interview	Thematic	Australia	2010
Cover **[321]**	To explore reasons for HPV vaccine acceptance or non-acceptance and to ascertain the process by which parents make their decision	Parents of daughter(s) eligible for HPV vaccination (n=133)	✓	Focus group (n=106) Interview (n=27)	Thematic	Vietnam	2012
Craciun **[322]**	To explore the experience of Romanian mothers with the HPV vaccine, to identify their perceptions and attitudes towards the HPV vaccine and to understand their reasons for accepting or rejecting HPV vaccination for their daughters	Parents of daughter(s) in the vaccine target group (n=25)	✓	Focus group (n=16) Interview (n=9)	Thematic	Romania	2012
Dela Cruz **[323]**	To identify HPV vaccination barriers, motivators, and brochure preferences among parents of teens in Hawaii	Parents of daughter(s) 11-18 years (n=20)	✓	Interview	Inductive content analysis	USA	2016
Dempsey **[324]**	To investigate the reasons why mothers accepted or declined HPV vaccination for their daughters	Mothers of daughter(s) 11-17 years (n=52)	✓	Interview	Content analysis	USA	2010

Do **[325]**	To address HPV vaccine barriers and facilitators	Parents of daughter(s) who are age-eligible for the HPV vaccine (Cambodian descent) (n=37)	✓	Focus group	Thematic	USA	2010
Friedman **[326]**	To identify HPV vaccine communication and mobilization needs, to understand HPV vaccine-related perceptions and concerns of male and female caregivers in four rural communities in western Kenya	Caregiver of daughter(s) 9-12 years (n=56)	X	Focus group	Grounded theory	Kenya	2014
Getrich **[327]**	To examine actual HPV vaccination decision-making processes	Mothers of daughter(s) 13-27 years (n=10)	✓	Interview	Grounded theory	USA	2015
Gordon **[174]**	To explore attitudes to HPV vaccination in British Jewish mothers who had recently made a decision about vaccinating their daughter in the context of the national vaccination programme	Parents of daughter(s) 12-13 years (n=20)	✓	Interview	Framework analysis	UK	2011
Gottvall **[328]**	To explore how parents reason when they accept HPV vaccination for their young daughter and their views on HPV-related information	Parents of daughter(s) 11-12 years (n=27)	✓	Interview	Thematic content analysis	Sweden	2013
Griffioen **[329]**	To explore the factors influencing mothers' decisions to vaccinate 11-12 year old daughters against HPV, including understanding of and attitudes about HPV vaccination, interactions with others about HPV vaccination, and media/marketing exposure and mothers' and daughters' perspectives about HPV vaccine related decision-making	Mothers/primary female guardians of daughter(s) 11-12 years (n=32)	✓	Interview	Framework analysis	USA	2012
Haesebaert **[330]**	To assess mothers' acceptance of HPV vaccination for their 14-18 year old daughters and determinants of that acceptability	Parents of daughter(s) 14-18 years (n=32)	✓	Interview	Content analysis	France	2012
Hamlish **[331]**	To examine in-depth motivations and barriers to HPV vaccination among African-American mothers and their	Mothers of daughter(s) 9-18 years	✓	Interview	Thematic	USA	2012

	vaccine-eligible adolescent daughters	(n=19)					
Harries **[332]**	To explore key challenges and opinions towards HPV vaccination introduction in South Africa	Parents of daughter(s) eligible for HPV vaccination (n=43)	X	Interview	Content analysis	South Africa	2009
Hughes **[333]**	To understand decision-making at the point of care	Mothers of daughter(s) 11-18 years (n=20)	✓	Interview	Modified grounded theory	USA	2011
Marlow **[334]**	To explore attitudes to HPV vaccination among black and Asian mothers living in Britain	Parents of daughter(s) <16 years (n=20)	✓	Interview	Framework analysis	UK	2009
Morales-Campos **[335]**	To assess Hispanic mothers' and girls' perceptions about cervical cancer, HPV and the HPV vaccine	Parents of daughter(s) 11-17 years (n=24)	✓	Focus group	Grounded theory	USA	2013
Mupandawana **[336]**	To explore factors influencing UK based African parents' acceptance or decline of the HPV vaccine, whether fathers and mothers share similar views pertaining to vaccination and any interfamily tensions resulting from differing views	Parents of daughter(s) 8-14 years (n=10)	✓	Interview	Thematic analysis	UK	2016
Niccolai **[337]**	To explore parents' attitudes and beliefs about STI and cancer prevention in the context of HPV vaccination	Parents of daughter(s) 10-18 years (n=38)	✓	Interview	Thematic content analysis	USA	2014
Nodulman **[338]**	To investigate the feasibility and acceptance of a school-based HPV programme	Parents of daughter(s) (n=32)	✓	Focus group	Grounded theory	USA	2015
Olshen **[339]**	To improve understanding of parental acceptance of the HPV vaccine	Parents of daughter(s) 10-15 years (n=25)	X	Focus group Interview	Content analysis	USA	2005
Paul **[340]**	To assess STI-related knowledge and HPV specific vaccine awareness and acceptability	Parents of daughter(s) <18 years (n=36)	X	Interview	Coding matrix	India	2014
Perkins **[341]**	To identify the rationale by parents/guardians and providers for delaying or administering HPV vaccination to girls	Parents/guardians of daughter(s) 11-17 years (n=124)	✓	Interview	Thematic analysis	USA	2014

Perkins **[342]**	To explore low-income, minority parents' attitudes, intentions, and actions with regards to HPV vaccination for their daughters	Parents of daughter(s) 11-18 years (n=76)	✓	Interview	Grounded theory and content analysis	USA	2010
Remes **[343]**	To learn what people knew about cervical cancer and HPV vaccination, whether they would find HPV vaccination acceptable, and how they viewed vaccine delivery and consent procedures	Parents of daughter(s) 11-17 years (n=60)	X	Focus group (n=54) Interview (n=6)	Thematic analysis	Tanzania	2012
Sanders Thompson **[344]**	To describe attitudes and social and environmental factors that affect African American parents' intent to vaccinate their daughters against HPV	Parents of daughter(s) 9-17 years (n=30)	✓	Interview	Thematic analysis	USA	2012
Schmidt-Grimminger **[345]**	To determine the knowledge, attitudes and beliefs related to the HPV vaccine and factors that facilitate or hinder vaccination	Parents/guardians of daughter(s) (n=16)	✓	Focus group	Grounded theory	USA	2013
Siu **[346]**	To investigate the perceptions of Hong Kong mothers in regard to vaccinating their daughters against HPV	Mothers of daughter(s) 9-17 years (n=35)	✓	Interview	Thematic analysis	Hong Kong	2014
Stephens **[347]**	To identify recently immigrated Haitian mothers' beliefs about HPV vaccination and cultural factors that influence their willingness and resistance to having their daughters vaccinated	Mothers of daughter(s) 11-18 years (Haitian descent) (n=31)	✓	Interview	Thematic analysis	USA	2013
Waller **[348]**	To explore mothers' attitudes towards vaccination	Parents of daughter(s) 8-14 years (n=24)	X	Focus group	Framework analysis	UK	2006
Wong **[349]**	To assess the mother's knowledge and attitudes toward HPV vaccination	Parents of daughter(s) eligible for vaccination (n=47)	✓	Focus group	Grounded theory	Malaysia	2009

Appendix 4.5

Quality appraisal of included studies

First author	Statement of aims	Qualitative appropriate	Design appropriate	Recruitment appropriate	Data collection appropriate	Reflexivity	Ethics	Data analysis appropriate	Statement of findings	Valuable research	Quality assessment
Bair **[318]**	✓	✓	✓	✓	✓	?	✓	?	✓	✓	Moderate-to-High
Bartolini **[319]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	Moderate-to-High
Cooper Robbins **[320]**	✓	✓	?	✓	✓	?	✓	✓	✓	✓	Moderate-to-High
Cover **[321]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Craciun **[322]**	✓	✓	✓	?	✓	?	?	✓	✓	✓	Moderate
Dela Cruz **[323]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Dempsey **[324]**	✓	✓	?	✓	✓	?	✓	✓	✓	✓	Moderate-to-High
Do **[325]**	✓	✓	✓	✓	✓	?	?	✓	✓	✓	Moderate-to-High
Friedman **[326]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Getrich **[327]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Gordon **[174]**	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	High
Gottvall **[328]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High

Griffioen **[329]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Haesebaert **[330]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Hamlish **[331]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Harries **[332]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Hughes **[333]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Marlow **[334]**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Morales-Campos **[335]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Mupandawana **[336]**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Niccolai **[337]**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Nodulman **[338]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Olshen **[339]**	✓	✓	?	?	✓	?	✓	✓	✓	✓	Moderate
Paul **[340]**	✓	✓	✓	✓	✓	?	✓	?	✓	✓	Moderate-to-High
Perkins **[341]**	✓	✓	✓	✓	✓	?	✓	?	✓	✓	Moderate-to-High
Perkins **[342]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Remes **[343]**	✓	✓	✓	✓	✓	✓	?	?	✓	✓	Moderate-to-High
Sanders Thompson **[344]**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Schmidt-	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High

Grimminger **[345]**											
Siu **[346]**	✓	✓	✓	✓	✓	?	✓	?	✓	✓	Moderate-to-High
Stephens **[347]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Waller **[348]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High
Wong **[349]**	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	High

Appendix 4.6

Occurrence of concepts and sub-themes

Is prevention better than cure?

Sub-themes	Bair	Bartolini	Cooper-Robbins	Cover	Craciun	Dela Cruz	Dempsey	Do	Friedman	Getrich	Gordon	Gottvall	Griffioen	Haesebaert	Hamlish	Harries	Hughes	Marlow	Morales-Campos	Mupandawana	Niccolai	Nodulman	Olshen	Paul	Perkins	Perkins	Remes	Sanders Thompson	Schmidt-Grimminger	Siu	Stephens	Waller	Wong
Prevention		✓		✓			✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓	✓		✓	✓	✓	✓					✓	✓
General vaccine acceptance		✓	✓	✓					✓		✓	✓	✓					✓					✓	✓		✓	✓					✓	✓
Financial savings		✓	✓					✓																									
Lack of access to treatments		✓							✓																								
Vaccine hesitancy									✓		✓							✓		✓	✓									✓		✓	
Trust in HPV vaccine												✓	✓																				
HPV vaccine use elsewhere				✓								✓						✓															
Access to HPV /vaccine									✓		✓	✓				✓																	✓

The fear of the unknown

Sub-themes	Bair	Bartolini	Cooper-Robbins	Cover	Craciun	Dela Cruz	Dempsey	Do	Friedman	Getrich	Gordon	Gottvall	Griffioen	Haesebaert	Hamlish	Harries	Hughes	Marlow	Morales-Campos	Mupandawana	Niccolai	Nodulman	Olshen	Paul	Perkins	Perkins	Remes	Sanders Thompson	Schmidt-Grimminger	Siu	Stephens	Waller	Wong
New vaccine				✓			✓	✓			✓	✓	✓	✓			✓	✓		✓							✓						✓
Safety and efficacy	✓		✓	✓	✓		✓	✓	✓		✓	✓				✓	✓	✓	✓			✓		✓	✓			✓	✓	✓	✓	✓	✓
Side effects		✓		✓	✓			✓	✓		✓	✓		✓		✓		✓		✓			✓	✓		✓	✓	✓	✓			✓	✓
Experimental vaccine		✓		✓	✓											✓			✓												✓		
Conspiracy theory					✓															✓								✓					
Watchful waiting	✓			✓		✓	✓				✓						✓	✓		✓	✓	✓			✓	✓							✓
Engage in risky behaviour																		✓		✓					✓		✓				✓	✓	✓
Fears of HPV and cancer				✓										✓	✓				✓										✓				
Anticipated regret												✓	✓	✓				✓															
Unknown partner sexual history/activity	✓						✓			✓	✓							✓	✓	✓													✓

Limited knowledge and understanding

Sub-themes	Bair	Bartolini	Cooper-Robbins	Cover	Craciun	Dela Cruz	Dempsey	Do	Friedman	Getrich	Gordon	Gottvall	Griffioen	Haesebaert	Hamlish	Harries	Hughes	Marlow	Morales-Campos	Mupandawana	Niccolai	Nodulman	Olshen	Paul	Perkins	Perkins	Remes	Sanders Thompson	Schmidt-Grimminger	Siu	Stephens	Waller	Wong
Limited knowledge	✓		✓					✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Insufficient knowledge to make a decision	✓	✓	✓		✓		✓							✓			✓		✓			✓			✓				✓		✓	✓	✓
Lack of understanding	✓	✓		✓	✓			✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓				✓	✓	✓	✓	✓
Young age	✓			✓	✓		✓				✓	✓		✓			✓	✓	✓	✓		✓			✓			✓		✓	✓	✓	✓
Limit health literacy										✓					✓									✓							✓		

Complex vaccination decisions

Sub-Themes	Bair	Bartolini	Cooper-Robbins	Cover	Craciun	Dela Cruz	Dempsey	Do	Friedman	Getrich	Gordon	Gottvall	Griffioen	Haesebaert	Hamlish	Harries	Hughes	Marlow	Morales-Campos	Mupandawana	Niccolai	Nodulman	Olshen	Paul	Perkins	Perkins	Remes	Sanders Thompson	Schmidt-Grimminger	Siu	Stephens	Waller	Wong
Provision of information		✓		✓					✓		✓	✓	✓			✓	✓				✓				✓		✓		✓		✓		
Poor provision of information	✓			✓	✓						✓	✓			✓										✓			✓			✓	✓	✓
Perception of risk	✓			✓		✓	✓			✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓				✓	✓
Low perception of risk	✓			✓		✓	✓		✓	✓	✓						✓	✓		✓	✓	✓	✓		✓			✓		✓	✓	✓	✓
HCP endorsement				✓	✓	✓	✓	✓	✓	✓			✓	✓	✓		✓	✓	✓				✓	✓	✓			✓	✓		✓	✓	✓
Opinion of healthcare system					✓		✓		✓	✓	✓	✓	✓	✓	✓									✓				✓			✓	✓	✓
Opinion of governmental immunisation programme				✓					✓			✓												✓			✓					
Impact of media				✓							✓	✓	✓					✓														
Impact of peers					✓					✓	✓		✓					✓		✓												
Impact of family											✓		✓					✓		✓								✓				
Personal experience of HPV and HPV related illnesses		✓		✓			✓			✓	✓	✓	✓		✓			✓	✓		✓										✓	
Market as a cancer vaccine																✓					✓											
Optional vaccination																	✓								✓					✓			

Parental responsibility

Sub-themes	Bair	Bartolini	Cooper-Robbins	Cover	Craciun	Dela Cruz	Dempsey	Do	Friedman	Getrich	Gordon	Gottvall	Griffioen	Haesebaert	Hamilish	Harries	Hughes	Marlow	Morales-Campos	Mupandawana	Niccolai	Nodulman	Olshen	Paul	Perkins	Perkins	Remes	Sanders Thompson	Schmidt-Grimminger	Siu	Stephens	Waller	Wong
Protection	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓					✓		✓		✓	✓	✓	✓
Societal responsibility											✓																						
Defer responsibility	✓	✓	✓		✓		✓			✓								✓					✓										
Control over healthcare decisions						✓					✓	✓	✓		✓		✓											✓					✓
Encourage sexual activity	✓	✓												✓				✓	✓	✓			✓		✓	✓				✓	✓	✓	✓
Difficult conversation topic								✓	✓		✓			✓				✓	✓	✓			✓								✓		
Requirement for parental consent		✓			✓																												

Appendix 4.7

First (italicised) and second (non-italicised)-order interpretations

First author	Is prevention better than cure?	The fear of the unknown	Limited knowledge and understanding	Complex decision-making process	Parental responsibility
Bair **[318]**	The main theme provided by 25 mothers was "to prevent disease."	*"I would vaccinate her but not until it is tested on other persons and proven that the vaccine functions correctly and that there are not any types of risks."*	*"I do not know anything. I am undecided because I would like to be more informed about vaccine, to get more information."*	Most mothers viewed their children as susceptible to HPV in their teenage years.	*"We are giving them permission to have sex."*
Bartolini **[319]**	Vaccines are a well-recognised and accepted form of prevention.	*"I heard somewhere that you end up sterile after having that vaccine."*	Some parents mentioned that they did not have enough information to make the decision.	The decision-making was influenced by the context-particularly the way in which vaccination was offered, the follow-up by the health personnel, the commitment shown by the teaching staff.	*"If your husband didn't agree? They didn't give her the vaccine, because if something happened to her it was my responsibility."*
Cooper Robbins **[320]**	*"It's lumped in, it's another vaccination in the blue book-you do this at age 2, at age 5 you do this, I've never questioned the blue book."*	*"It says it only helps prevent four HPV diseases and there's a hundred or more, so it doesn't seem very effective."*	The core theme, lack of knowledge represents the confusion experienced by participants, resulted from limited understanding about a complex topic.		Some parents explained their lack of knowledge by the tendency to defer responsibility to trusted sources.
Cover **[321]**	*"Immunisation is the best way of prevention…Prevention is better than treatment."*	Vaccine safety and side effects, suspicion and misconceptions about the HPV vaccine, and concerns related to the age of the girl and her risk of cervical cancer.		*"I was advised by my doctor so I took the girl to get vaccinated. It is because I saw many people had that awful disease."*	
Craciun **[322]**		The vaccine was represented as *an experiment serving the commercial interest* of pharmaceutical companies.	Most did not understand how the vaccine works and how it is linked to cervical cancer prevention.	If the doctor is trusted in general, than his/her recommendation of the vaccine will play an important role in the vaccination decision.	As mothers they felt responsible for their children's health and take on a protective role.

Dela Cruz **[323]**		*"I'm planning on vaccination them but maybe I think like a lot of other parents that I'm seeing, 'Well, it's kinda early'"*		The physician's recommendation to vaccinate and willingness to educate parents about the vaccine are very important to a parent's decision-making process.	
Dempsey **[324]**	…wanting to protect against or prevent cervical cancer.	*"I don't want her to fall into a category where she gets this done and then ten years down the line they find that it reacts a different way"*	Concerns were related to a feeling that they personally lacked the knowledge needed to make an informed decision about HPV vaccination for their daughter, or that the medical establishment in general lacked sufficient knowledge about HPV vaccines to ensure safety.	Among mothers accepting the vaccine, the most commonly identified reasons for this decision were…perceiving that their daughter was at high risk for acquiring HPV…personal experience with HPV infection or HPV-related diseases…strong physician recommendation for HPV vaccination.	*"I figured now is the best time because it's a time that I can make the decision for her and I wanted to make sure she was protected before there was any chance of her becoming sexually active"*
Do **[325]**	*"Prevention is better than treatment. It costs less and saves time"*	*"It is new. What if you get the shot and die"*	We found that very few of our Cambodian focus group participants were aware [of HPV infection and vaccination].	*"I am concerned about those who work, have children, and do not have health insurance. Their income is little, and having to get their daughters vaccinated may cause financial hardship"*	…indicated that this was the type of topic that they did not discuss with their daughters.
Friedman **[326]**	Participants identified cultural beliefs as potential challenges to vaccination, particularly among the elderly, traditional herbalists and some men/fathers, who distrust vaccines or do not belief in preventive health services.	*"There are people in the community who are fond of spreading rumours. They may inform the parents that their children are only being used for research purposes and the vaccine would be no use to their children"*	Widespread ignorance about cervical cancer and the vaccine emerged as primary barriers to vaccination.	Community mobilisation and sensitisation were seen as critical for raising cervical cancer awareness; prompting demand for vaccination; and helping overcome stigma.	The vaccine was seen as a way to protect children from a disease associated with pain, suffering and financial cost.
Getrich **[327]**	*"Do I want my kid to have a vaccine? Are vaccines good?"*		*"I heard that it prevents…I don't know…but it does help with different cancers and stuff"*	…concern about their daughters' sexual health was raised because of behaviours of their older siblings, such as drug use and teenage pregnancy, as well as their own experience with sexually transmitted infections, childhood sexual abuse, early pregnancy, and marital infidelity.	*"Now at least I know she's protected from that. There are so many illnesses because of sex that you don't even know how to protect them"*

Gordon **[174]**	Most mothers described the importance of vaccines being safe, effective and necessary to protect against common or severe diseases, but vaccinating their children was generally seen as 'part of the routine'.	Most of the mothers who declined vaccination were also concerned about the safety of HPV vaccination given that it was relatively *"new"* and *"untested"*.	*I don't think it can be caught and therefore I don't feel that I have a communal responsibility to accept the vaccine, whereas I would do if it was something that is based on a majority having it in order for it to be successful and work"*	*"I was just about to say yes, and then there was the scare, that a girl died in the Midlands and that's what stopped me"*	…although they hoped their daughters would lead a particular lifestyle, they were not able to 'control' or 'predict' their behaviour, and it was therefore better to protect them.
Gottvall **[328]**	Many had accepted the other vaccines offered in the child vaccination programme and were positive to vaccines in general.	*"…if I say no to the vaccine and she gets sick, I would never be able to forgive myself"*	Many parents felt they had limited knowledge about the vaccine.	*"I thought it was a pretty hard decision. I thought that I got quite insufficient information in the papers that came from school"*	Most parents had their daughter vaccinated against HPV for her future health, but some also felt a responsibility to vaccinate her out of concern for others.
Griffioen **[329]**	The most commonly noted health benefit of HPV vaccination was its potential to prevent cervical cancer.	*"I think that if you don't vaccinate 'em now and then they're 30 years old and end up with cervical cancer, then you would so regret not giving her that chance to prevent it"*	Some of these beliefs about vaccine safety and efficacy…were inaccurate: one mother stated that once she *"got the knowledge that it protected them for life"*, she was in agreement.	Exposure to media and marketing about HPV vaccines played a key role in mothers' decisions to vaccinate in the following ways: by raising their awareness of HPV and HPV vaccines, reassuring them if the benefits of vaccination, triggering discussions with their daughters, and prompting them to seek out more information about HPV and HPV vaccination.	*"I know that HPV is a pretty common STD. The vaccine is available. I believe in protecting my kids whenever possible"*
Haesebaert **[330]**	…vaccination offered the opportunity of preventing a severe and potentially fatal disease, namely CC (cervical cancer), in their daughters.	Undecided and opposed mothers justified their position by the fact that we have little experience of the vaccine to look back on and by fear of side effects with what is a new vaccine.	…few mothers had a detailed recollection of the information provided.	The key role played by physicians is illustrated…*"He told me not to vaccinate my daughter"*.	14.1% preferred to rely on their physician's decision and waited to know his opinion and 7.0% preferred to let their daughters decide.
Hamlish **[331]**	Mothers demonstrated an emotional conviction to prevent the trauma and pain of CD (cervical dysplasia)/CC (cervical cancer).	Mothers' disease narratives focussed on CD/CC as the source of trauma, uncertainty, anxiety, fear and pain.	Limited health literacy and knowledge of HPV make mothers vulnerable to doubt, despite a strong conviction to immunize their daughters.	Mothers waited for a clear, unambiguous message from their doctor; a message that resembled the certainty doctors expressed for other vaccines.	Mothers regarded HPV immunisation as a window of opportunity to protect their daughters and reduce at least element of risk.

Harries **[332]**	*"Prevention is better than cure"*	*"Many a time we use vaccines that are not the same standard as first world countries…Are they going to give us a cheaper vaccine with more side effects which we only see in 30 years?"*	Overall knowledge of cervical cancer was either poor or anecdotal and the causal relationship between HPV and cervical cancer was unknown amongst all participants.	*"The children in our community are very sexual active because they are already starting at the age of 10 and 11"*	
Hughes **[333]**		*"I probably just want to know more about it and what the risks are…it's new to me…so I need more education on it"*	*"I just don't think they need to right now, at 13…it's young"*	*"I don't think she need [HPV vaccine] at this time. I guess it's for girls that's having sex…and I know my daughter and she's not into that right now"*	*"She doesn't really have a choice, it's my decision as a parent"*
Marlow **[334]**	When asked to talk about vaccine decision-making process for their children, most of the mothers described it as 'automatic' and something they just did without too much thought.	*"It's something new and people, well I for one am fearful of something new."*	Many of the mothers from both black and Asian backgrounds found it difficult to understand the reasons for giving HPV vaccination at 12/13 years of age.	…mothers said they spoke to other family members and friends about vaccinations, in particular those who already had made vaccination decisions for their own children as opposed to friends who did not have children because they would be *"just as inexperienced."*	*"…but we live in this country, you don't know what environment we live in so it's best to be protected."*
Morales-Campos **[335]**	…perceived protection and prevention as the main benefit of the vaccine.	*"Because science is just invention…but my daughter is not going to be a rabbit for invention."*	Mothers…who had heard of HPV and the vaccine had limited knowledge about HPV.	*"So I told him [the doctor] that he could not give her an injection just because they told me so. I wanted information…to know why and for what I was giving her that injection. And since they did not give it to me, I didn't vaccinate her."*	*"…a way that I, as a mother can protect my daughter is vaccinating her. I say, I am going to protect her more than just talking."*
Mupandawana **[336]**	Previous vaccination rumours and scandals such as the MMR also influenced vaccine decline.	*"Let them vaccinate their own children first, then after 20 years if nothing happens, we will also vaccinate our own."*	…even though they had received the information, it was as though there wasn't much understanding of the information, as most of the parents continued to believe that only promiscuous and sexually active girls should be vaccinated.	It was evident from most of the participants that the fathers were the ultimate decision-makers in most issues pertaining to the family and especially the children.	*"People must know that if they do this thing [consent to vaccination], they are giving their daughters a free licence to sleep around."*
Niccolai **[337]**	*"Because neither one of them are good. They're both bad. It, it kills two birds with one stone [cancer and STIs]"*	…one chose to defer vaccinations for her daughters.	*"I've heard of it; I've heard the name but I don't know what it is…I've heard people talk about it, but I don't know how it gets passed on or what it is."*	Parents…discussed personal or family experiences with cancer as motivations to vaccinate their children.	…they viewed vaccination as valuable protection in advance.

Nodulman **[338]**	*"It prevents HPV supposedly."*	Many of the parents of girls did not believe that the vaccine had been studied sufficiently and/or they wanted to know more about the vaccine before they allowed their daughters to be vaccinated.	*"I am so confused."*	Some parents did not think the vaccine was necessary because, according to them, their daughters were too young to be thinking about sex and/or are not sexually active.	
Olshen **[339]**	Parents held favourable views about vaccines their children currently receive.	Parents were concerned about major side effects.	*"What is it? If I have HPV, what will I have, an infection?"*	Physician recommendations weighed heavily on parental views of vaccines.	*"I can't imagine how I would explain to this kid what this vaccination is…"*
Paul **[340]**	Parents understood that vaccines were important *"to have good health, to keep children healthy, and prevent disease."*	…most common barriers to vaccination were…side effects…	None of the participants knew about the HPV vaccine.	Most parents were willing to vaccinate their children against HPV, especially with a health worker recommendation.	
Perkins **[341]**	*"It is important for her to get the HPV vaccine 'cause it can prevent cervical cancer. I just wanted my daughter to have every chance not to get HPV."*	*"I'd rather my child die of cervical cancer than her die of me giving her a vaccine."*	Several parents did not understand the rationale for giving HPV vaccination in advance of sexual debut.	*"When [the doctor] said it to me it wasn't like, your daughter should have this, it was like this is an option. It's like, do you want tea or coffee."*	*"Just thinking, in the long run, anything that would protect from any cancer down the road just seemed to make sense."*
Perkins **[342]**	*"If it's going to help prevent them from getting cervical cancer, why shouldn't they get it?"*	*"Probably in a few years' time I will think differently about [HPV vaccine]. By then kids who have received it, they would have monitored, and they would know if there are any long-term effects, you know, and the reactions to those vaccinations."*	…only 53% knew that HPV was a sexually transmitted infection, and only 39% knew that HPV caused genital warts.	*"She is going to be sexual at some point and I would rather have her protected than get infections or diseases."*	…parents struggled with how to protect their daughters from HPV while still asserting that they should refrain from premarital sex.
Remes **[343]**	Almost all adults said they would allow their daughters to be vaccinated since *"prevention is better than cure."*	They feared side effects; especially whether the vaccine would have a potential effect on future reproduction.	*"The disease you are talking about; we are completely in the dark about it."*	*"I know the government cannot do something malicious to children."*	

Sanders Thompson **[344]**		*"If there is a 50/50 chance that it [HPV] would leave my child handicapped or something, that would turn me off."*	Parents expressed reluctance to vaccinate girls as young as nine years old.	Men and women agreed that the final decision about HPV vaccination for their daughter's was most often made by mothers, with father consultation as the mother perceived necessary.	Most parents felt that the child could express feelings and concerns about vaccination, but ultimately the decision was made by the parent(s).
Schmidt-Grimminger **[345]**		*"If you got the shot you might get it [cancer]."*	Participants had low levels of knowledge and misconceptions about details of HPV.	Resource issues within the clinic were identified…parents noted providers not recommending the vaccine or lengthy waiting times to get an appointment.	
Siu **[346]**	*"Vaccines are made from viruses. Therefore, I believe it is not good to have too many vaccinations. After all, a vaccine is a foreign material, and this material can make your body weak."*	The HPV vaccine was a new vaccine to all participants. They expressed doubt and hesitation about its safety.	Most of the participants had little understanding or knowledge about HPV and its potential danger to women's health.	*"I have never thought about taking my daughter to be vaccinated. It is too early for her."*	Participants worried that vaccinating their daughters could convey the message that they were allowed and approved to begin their sexual lives.
Stephens **[347]**		*"People are always testing-testing on us [Haitians]."*	*"I have no heard of this."*	The mothers stated they would prefer receiving HPV vaccine information from their physician…physicians would provide them with accurate information and would understand their personal and cultural values regarding their daughters' sexual health.	Many of the women were concerned that discussing HPV with their daughters meant having to address sexual health issues.
Waller **[348]**	*"…but if there's a vaccine that's going to prevent them from getting anything that I wouldn't want them to get or they wouldn't want to have, then yeah, definitely."*	The main concern raised about vaccination was the possibility of side effects, both immediate reactions and longer-term problems.	None of the women had heard of HPV before taking part in the focus group.	Some women felt that the need for vaccination against STIs would depend on the individual characteristics of the child. One woman thought she might be more concerned if her daughters were *"messing around with the local boys."*	*"You also don't want children to become complacent and think 'Well, I've been vaccinated, I'll just go out now and I'll…'"*
Wong **[349]**	*"Prevention is better that cure."*	*"Since the vaccine is new, we want to know how well it has been tested, is it really effective? Since it is recommended to girls at such a young age, is it really safe? How many people have taken*	The link between HPV and cervical abnormalities was poorly understood even among those who had heard of HPV.	*"It depends on upbringing of the children."* They were more likely to vaccinate their children at early age if their daughters show signs of high-risk sexual behaviour; otherwise they preferred to hold immunisations.	*"You won't understand a mother's feeling…as a mother; I will give this vaccine to my daughter simply because she is my chid, so that she is protected from the*

	this vaccine in our country?" There were controversies over whether the vaccine has been researched enough to know its long term safety and efficacy.		*disease."* Most of them wanted to do the best they could to protect their daughter.

Appendix 5.1

Recruitment poster



What are your opinions of the HPV vaccine?

Would you like to share your opinions?

We are looking for **teenage girls** (14-16 years) to take part in a focus group

Your participation would involve one session lasting approximately 90 minutes

For more information about this study, or to volunteer for this study, please contact:

Sarah Marshall

Phone: 0851309228 or Email: s.marshall@umail.ucc.ie

This study has received ethical approval from the Social Research Ethics Committee, UCC

UCC
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

naji foundation

Appendix 5.2

Informed Consent for Research Participants

Purpose of the study

I am a community pharmacist currently undertaking a PhD in Clinical Pharmacy in UCC. The research is concerned with determining the opinions of female adolescents on vaccines, with a particular focus on the adolescent human papillomavirus (HPV) vaccine.

What will the study involve?

The study will involve participation in one focus group lasting 90 minutes. The focus group will be made up of approximately six participants.

Why have you been asked to take part?

Your daughter has been asked to take part as she is a teenage girl (14-16 years). We are hoping to examine knowledge, attitudes and beliefs surrounding vaccines from an adolescent point of view.

Do you have to take part?

Participation is voluntary. If you provide permission to participate, you will be asked to sign the attached consent form. You may withdraw at any stage, including mid-session and up to two weeks after data has been collected, even if you have given consent to participate. If you wish to withdraw, you may contact me directly via phone (0851309228) or email (s.marshall@umail.ucc.ie). At this stage, any identifiable data will be immediately destroyed.

Will your participation in the study be kept confidential?

Your daughter is being asked to take part in a focus group. For this reason complete confidentiality and anonymity is not possible as information is shared with other individuals in the group, with me and with my research supervisors. However, I will ensure that no clues to your daughter's identity will be published in the thesis. Any extracts that are quoted in the thesis will remain anonymous.

What will happen to the information which you give?

The focus groups will be audio-recorded. I will transcribe and anonymise the recordings. The transcript will be reviewed and verified by my supervisors, at which point the recording will be destroyed. The written data will remain confidential for the duration of the study. On completion of the thesis, the data will be retained for a further ten years before it will be destroyed.

What will happen to the results?

The results will be used to design an intervention to reduce vaccine hesitancy in adolescents. They will also be presented in the thesis, which will be available to future students. They may be published in a research journal.

What are the possible disadvantages of taking part?

I do not envisage any disadvantages to your taking part. If you agree to allow your daughter to participate, her contribution is voluntary and she will not be pressurised to speak. Should you or your daughter have any issues after completion of the focus group, I would encourage you to contact me in confidence to discuss your distress.

Who has reviewed this study?

The University College Cork Social Research Ethics Committee has reviewed and approved this study.

Any further queries?

If you need any further information, you can contact me, Sarah Marshall via phone (0851309228) or email (s.marshall@umail.ucc.ie)

If you agree to allow your child to take part in the study, please sign the consent form.

Appendix 5.3

Informed Consent Form

I.....give permission for my daughter…….to participate in Sarah Marshall's research study.
The purpose of this study has been explained to me in writing.
I am participating voluntarily.
I give permission for focus group participation to be tape-recorded.
I understand that I can withdraw from the study, without repercussions, at any time, whether before it starts or while I am participating.
I understand that I can withdraw permission to use the data within two weeks of the focus group, in which case the material will be deleted.
I understand that anonymity will be ensured in the write-up by disguising my identity.
I understand that disguised extracts from my interview may be quoted in the thesis and any subsequent publications if I give permission below:
Please tick one box

□ I agree to quotation/publication of extracts from my focus group
□ I do not agree to quotation/publication of extracts from my focus group

Signed …… Date ……

Appendix 5.4

Focus group topic guide

Topic
What do you think about vaccines?
Do you usually follow vaccine recommendations?
What do you know about HPV?
What do you know about the HPV vaccine?
What do you think happens if you get the HPV vaccine?
What do you think happens if you do not get the HPV vaccine?
How important do you think it is to get the HPV vaccine?
I want you to remember what it was like when you were offered the HPV vaccine…
How did you feel when you were asked to get the HPV vaccine?
How easy or difficult is it to understand HPV vaccine recommendations?
Do you think you were capable of making your own vaccine decision?
Did you listen to the opinions of others when you were making your HPV vaccine decision? If so, who were these people?
How important were their opinions and did they affect your vaccine decision?
What information is needed when you are making a vaccine decision?
Where do you look for this information? If internet is mentioned: what websites do you use?
Did you find it difficult to determine how reliable this HPV vaccine information was?
How difficult was it for you to find HPV vaccine information?
Imagine a friend of yours is undecided about getting the HPV vaccine, what would you say to her?
HPV vaccination rates in Ireland are quite low…
What is stopping girls from getting vaccinated?
How do you think the Health Service Executive (HSE) should deal with the low vaccination rates?

Appendix 5.5

Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [380]

Domain 1: **Research team and reflexivity**		**Location in manuscript (Section)**
Personal Characteristics		
1. Interviewer/Facilitator	SM	Methods
2. Credentials	MPharm, MPSI	Title Page
3. Occupation	Pharmacist Clinical pharmacy researcher	Methods
4. Gender	Female	Methods
5. Experience and training	Experience in conducting qualitative research	Methods
Relationship with participants		
6. Relationship established	SM was not known to the participants	Discussion
7. Participant knowledge of interviewer	Participants were aware that Author 1 was a pharmacist	Discussion
8. Interviewer characteristics	Pharmacist and clinical pharmacy researcher, with experience in conducting qualitative research	Methods
Domain 2: **Study Design**		
Theoretical framework		
9. Methodological orientation and theory	Focus groups using the TDF, BCW and BCTTv1	Methods
Participant selection		
10. Sampling	Purposive sampling	Methods
11. Method of approach	Recruited school Principals invited eligible participants to participate	Methods
12. Sample size	50 adolescents participated in 10 focus groups	Results
13. Non-participation	12.66% recruitment rate	Results
Setting		
14. Setting of data collection	School grounds	Results
15. Presence of non-participants	Only SM and participants were present	N/A
16. Description of sample	Appendix 5.6	Appendix 5.6
Data collection		
17. Interview guide	TDF-based topic guide, with a semi-structured design	Appendix 5.4
18. Repeat interviews	Repeat interviews were not conducted	N/A
19. Audio/visual recording	Focus groups were audio-recorded	Methods
20. Field notes	No field notes were taken	N/A
21. Duration	Focus groups had a mean duration of 36 minutes	Results
22. Data saturation	Focus groups were conducted until no new themes emerged	Methods
23. Transcripts returned	Transcripts were not returned	N/A
Domain 3: **Analysis and Findings**		
Data analysis		
24. Number of data coders	SM, LS, AF	Methods
25. Description of the coding tree	Transcripts were analysed by inductive thematic analysis, with constant comparison methods applied throughout.	Methods
26. Derivation of themes	The codes were attributed to the domains of the TDF	Methods
27. Software	QSR International's NVivo V.11	Methods

28.	Participant checking	Participants did not provide feedback on findings	N/A
Reporting			
29.	Quotations presented	Quotations are presented	Results
30.	Data and findings consistent	There was consistency between data presented and the findings	Results
31.	Clarity of major themes	The codes were attributed to the domains of the TDF	Methods and Results
32.	Clarity of minor themes	Minor themes are discussed	Results

Appendix 5.6

Participant characteristics

Focus Group	Participants (n)	Age (years)	Vaccination Status	Pobal HP Description (2016)	County
1	3	15	1 Vaccinated 2 Not vaccinated	Marginally below average	Cork
2	8	15-16	Vaccinated	Marginally below average	Kerry
3	7	15-16	Vaccinated	Disadvantaged	Cork
4	5	15	Vaccinated	Marginally below average	Cork
5	4	16	Vaccinated	Marginally below average	Cork
6	4	15-16	Vaccinated	Marginally above average	Cork
7	5	15-16	Vaccinated	Marginally above average	Cork
8	5	15-16	Vaccinated	Marginally above average	Cork
9	4	15-16	Vaccinated	Affluent	Cork
10	5	15-16	Vaccinated	Affluent	Cork

Appendix 6.1

TDF-based interview topic guide

What do you think about vaccines?
Do you usually follow vaccine recommendations?
What do you know about HPV?
What do you know about the HPV vaccine?
What do you think happens if someone gets the HPV vaccine?
What do you think happens if someone does not get the HPV vaccine?
How important do you think it is to get the HPV vaccine?
How did you feel when you were offered the HPV vaccine for your daughter?
How easy or difficult was it to understand HPV vaccine recommendations?
Did you listen to the opinions of others when you were making the HPV vaccine decision for your daughter? If so, who were these people?
How important were their opinions and did they affect your vaccine decision?
What information was needed when you were making the vaccine decision?
Where did you look for this information? (If internet is mentioned: what websites did you use?)
Did you find it difficult to determine how reliable HPV vaccine information was?
How difficult was it for you to find HPV vaccine information?
Imagine a friend of yours is undecided about getting the HPV vaccine, what would you say to her?
What is stopping girls from getting vaccinated?
How do you think the Health Service Executive (HSE)* should deal with the low vaccination rates?
*Health Service Executive (HSE): responsible for the implementation of the primary childhood, school immunisation and seasonal influenza vaccination programmes

Appendix 6.2

Purposive sampling strategy and recruitment

A list of second level schools (n=67) and education centres (n=12) in the Cork/Kerry region of Ireland was compiled. This included those enrolled in the Delivering Equality of Opportunity in Schools (DEIS) programme. This programme supports children who are at greatest risk of educational disadvantage. School principals were contacted by telephone or email and provided with details of the study. The principal then approached individual parents to identify potential participants. Inclusion criteria included self-declared satisfactory English language and parent or caregiver/guardian of a female adolescent aged 14-16 years. It was highlighted to parents that participation was voluntary and no incentive to participation was offered. When a parent expressed an interest in participating, the primary researcher followed up with a telephone call or email to arrange a convenient time for the interview.

Appendix 6.3

Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist [389].

Domain 1: Research team and reflexivity		**Location in manuscript (Section)**
Personal Characteristics		
33. Interviewer/Facilitator	SM	Methods
34. Credentials	MPharm, MPSI	Title Page (journal submission)
35. Occupation	Pharmacist Clinical pharmacy researcher	Methods
36. Gender	Female	Methods
37. Experience and training	Experience in conducting qualitative research	Methods
Relationship with participants		
38. Relationship established	SM was not known to the participants	Methods
39. Participant knowledge of interviewer	Participants were aware that SM was a pharmacist	Methods
40. Interviewer characteristics	Pharmacist and clinical pharmacy researcher, with experience in conducting qualitative research	Methods
Domain 2: Study Design		
Theoretical framework		
41. Methodological orientation and theory	Semi-structured interviews using the TDF	Methods
Participant selection		
42. Sampling	Purposive sampling	Methods and Appendix 6.2
43. Method of approach	Recruited school principals informed eligible participants	Methods
44. Sample size	n=13	Results
45. Non-participation	N/A	
Setting		
46. Setting of data collection	Location convenient for the participant	Methods
47. Presence of non-participants	Only SM and participant were present	Methods
48. Description of sample	Appendix 6.4	Appendix 6.4
Data collection		
49. Interview guide	TDF-based interview topic guide	Appendix 6.1
50. Repeat interviews	Repeat interviews were not conducted	Methods
51. Audio/visual recording	Interviews were audio-recorded	Methods
52. Field notes	Field notes were recorded by SM	Methods
53. Duration	Duration ranged from 10 to 43 minutes (average duration of 21 minutes)	Results
54. Data saturation	Francis method was used to determine when data saturation had been reached	Methods
55. Transcripts returned	Transcripts were not returned	Methods
Domain 3: Analysis and Findings		
Data analysis		
56. Number of data coders	3 (SM, LS, AF)	Methods

57.	Description of the coding tree	Transcripts were analysed by inductive thematic analysis, with constant comparison methods applied throughout.	Methods
58.	Derivation of themes	The codes were attributed to the domains of the TDF	Methods
59.	Software	QSR International's NVivo V.11	Methods
60.	Participant checking	Participants did not provide feedback on findings	N/A
Reporting			
61.	Quotations presented	Quotations are presented	Results
62.	Data and findings consistent	There was consistency between data presented and the findings	Results
63.	Clarity of major themes	The codes were attributed to the domains of the TDF	Results
64.	Clarity of minor themes	Minor themes are discussed	Results

Appendix 6.4

Characteristics of interview participants (n=13)

Participant	Gender	Parental Age group (years)	Daughter Age (years)	Highest education level achieved	Number of children	Accepted/Declined HPV vaccine
P1	F	40-49	14	ISCED level 3	2	Declined
P2	F	50-59	15	ISCED level 3	2	Accepted
P3	M	40-49	15	ISCED level 3	2	Accepted
P4	F	40-49	16	ISCED level ≥4	2	Accepted
P5	F	40-49	14	ISCED level 3	2	Declined
P6	F	40-49	14	ISCED level ≥4	4	Accepted
P7	F	30-39	15	ISCED level 2	2	Accepted
P8	M	50-59	15	ISCED level 3	2	Accepted
P9	M	40-49	15	ISCED level 3	2	Accepted
P10	F	50-59	14	ISCED level ≥4	> 4	Declined
P11	F	40-49	16	ISCED level ≥4	2	Accepted
P12	F	40-49	15	ISCED level 3	1	Accepted
P13	F	40-49	14	ISCED level ≥4	2	Declined

***Highest education level**

- ISCED level 1: Primary education, equivalent to 8 years official State education
- ISCED level 2: Lower secondary education: Irish Junior/Inter Certificate, equivalent to 11 years official State education
- ISCED level 3: Upper secondary education: Irish Leaving Certificate, equivalent to 14 years official State education
- ISCED level ≥4: Higher Education including post-secondary non-tertiary education, short-cycle tertiary education, Bachelor (or equivalent), Master (or equivalent) and Doctoral (or equivalent)

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