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Vaccine Safety, Vaccine Effectiveness and other Determinants for Successful Immunisation Programmes

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Vaccine Safety, Vaccine Effectiveness and other Determinants for Successful Immunisation Programmes

THESIS FOR LICENTITATE DEGREE

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Our deepest fear is not that we are inadequate. Our deepest fear is that we are powerful beyond measure. It is our light, not our darkness, that most frightens us. You playing small does not serve the world. There is nothing enlightening about shrinking so that other people won't feel insecure around you. We are all meant to shine as children do. It's not just in some of us; it is in everyone. And as we let our own lights shine, we unconsciously give other people permission to do the same. As we are liberated from our own fear, our presence automatically liberates others.

- *Marianne Williamson*

ABSTRACT

The studies in this thesis examined several key determinants for successful uptake of vaccinations in the Nordic countries, with focus on vaccine safety and vaccine effectiveness.

In *study I*, we investigated whether disease history is a risk factor for narcolepsy after vaccination with the pandemic influenza vaccine, Pandemrix, which was circulated between 2009 and 2010. The results showed that there was no association between disease history and narcolepsy. We also found evidence for confounding by indication, with a larger number of prescriptions/diagnoses for nervous system disorders and mental and behavioural disorders when we did not adjust for the timing of vaccination or vaccination status. This could suggest that early cases of narcolepsy were initially misdiagnosed prior to narcolepsy diagnosis.

In *study II*, we investigated the effect of the quadrivalent humanpapillomavirus (qHPV) vaccine on genital condyloma by the number of doses and time between doses. This cohort study followed young Swedish girls ages 10-27 for HPV vaccination and condyloma. The results showed that the greatest protection against condyloma was seen after two doses of qHPV vaccine with 4-7 months between dose one and two. We also found that girls, who initiated vaccination at a younger age, had a greater protection against condyloma.

The results from these studies show just how complex the improvement of vaccination programmes can be. On one hand, we see the difficulties in assessing what went wrong following the introduction of a vaccine into a population— it is not always possible to predict a rare outcome from a mass vaccination campaign, so vaccine safety becomes a paramount concern from a societal perspective. We also see what happens when a vaccine proves its effectiveness in a population-based setting to the point where the number of doses can be reduced without compromising its effectiveness. Improving the vaccination programmes is, therefore, a complex multifactorial problem with many key determinants that can change depending on the vaccine in question e.g. mass vaccination versus routine vaccination.

LIST OF SCIENTIFIC PAPERS

- I. **Lamb F**, Ploner A, Fink K., et al., (2016) No Evidence for Disease History as a Risk Factor for Narcolepsy after A(H1N1)pdm09 Vaccination. *PLoS ONE* 11(4): e0154296. Doi:10.1371/journal.pone.0154296
- II. **Lamb F**, Herweijer E, Ploner A., et al., Timing of two versus three doses of quadrivalent HPV vaccine and associated effectiveness against condyloma in Sweden: a nationwide cohort study. *BMJ Open* 2017;7:e015021. Doi:10.1136/bmjopen-2016-015021

RELATED PUBLICATIONS

(Not included in thesis)

- Lind A, Freyhult E, Ramelius A, Olsson T, Arnheim-Dahlström L, **Lamb F.**, et al., Antibody Affinity Against 2009 A/H1N1 Influenza and Pandemrix Vaccine Nucleoproteins Differs Between Childhood Narcolepsy Patients and Controls. *Viral Immunol*, 2017
- Bomfim IL, **Lamb F.**, et al., The Immunogenetics of narcolepsy associated to A(H1N1)PDM09 vaccination (Pandemrix) supports a potent gene-environment interaction. *Genes and Immunity* 2017 March 23;18, 75-81
- Ambati A, Poiret T, Svahn BM, Valentini D, Khademi M, Kockum I, Lima I, Arnheim-Dahlström L, **Lamb F.**, et al., Increased β -haemolytic group A streptococcal M6 serotype and streptodornase B-specific cellular immune responses in Swedish narcolepsy cases. *Journal of internal medicine*. 2015 Sep 1;278(3):264-76.
- Lind A, Ramelius A, Olsson T, Arnheim-Dahlström L, **Lamb F.**, et al., A/H1N1 antibodies and TRIB2 autoantibodies in narcolepsy patients diagnosed in conjunction with the Pandemrix vaccination campaign in Sweden 2009–2010. *Journal of autoimmunity*. 2014 May 31;50:99-106.
- Bomfim IL, Fink K, **Lamb F.**, et al., Genetic study of Pandemrix-associated narcolepsy. *Journal of Neuroimmunology*. 2014 Oct 15;275(1):50-1
- Fogelberg S, **Lamb F**, Grönlund O., et al., Differential uptake in herpes zoster vaccination associated with socioeconomic status: A population-based study in Stockholm County, Sweden. (In manuscript).
- **Lamb F**, Gottvall M, Arnheim-Dahlström L. Healthcare workers perception on communications regarding vaccines and uptake in vaccination programmes. (In manuscript).

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
qHPV	quadrivalent Human Papillomavirus
TBE	Tick-Borne Encephalitis
VAERS	Vaccine Adverse Event Reporting System
HCWs	Healthcare Workers
RCT	Randomised Control Trial
VE	Vaccine Effectiveness
A(H1N1)pdm09 or A(H1N1)	Influenza A, H1N1 (strain), pdm = Pandemrix and 2009 (year it was administered)
EU	European Union
EMA	European Medicines Agency
WHO	World Health Organization
MPA	Medical Product Agency
ECDC	European Centre for Disease Prevention and Control
VAESCO	Vaccine Adverse Event Surveillance and Communication
EDS	Excessive Daytime Sleepiness
GPs	General Practitioners
MSLT	Multiple Sleep Latency Test
REM	Rapid Eye Movement
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
VLPs	Virus-Like Particles
bHPV	Bivalent Human Papillomavirus
FDA	Food and Drug Administration
pvHPV	9-valent Human Papillomavirus
SAGE	World Health Organization Strategic Advisory Group of Experts
PIN	Personal Identity Number
TPR	Total Population Register

MGR	Multigeneration Register
NPR	National Patient Register
ICD	International Classification of Diseases
CDR	National Causes of Death Register
PDR	Prescribed Drug Register
ATC	Anatomical Therapeutic Chemical
SVEVAC	Swedish HPV Vaccination register
SKL	Swedish Association of Local Authorities and Regions
KI	Karolinska Institutet
OR	Odds Ratio
CI	Confidence Interval
IR	Crude Incidence Rate
IRR	Incident Rate Ratio
IRD	Incidence Rate Difference

1. INTRODUCTION

Although the relative time that vaccinations have been available is short, the impact they have had is hard to exaggerate [1]. The success of vaccination on reducing mortality would lead to the forming of national vaccination programmes still in use today. For some vaccines, when the coverage in the population is high enough the disease can be eradicated altogether. Smallpox, for example, was a good contender for eradication as symptoms were evident and recognisable, the lag time between exposure and disease was short (limiting transmission of disease in the population), the vaccination provided life-long immunity to disease and only humans were affected i.e. there was no animal reservoir [2]. However, for diseases that utilise animal reservoirs e.g. tick-borne encephalitis (TBE), eradication can be a far more complicated process. Even if everyone in the world was vaccinated simultaneously, the virus would still be circulating in infected animals, and should immunity falter in humans, the disease would likely re-emerge in the population. This is further complicated in vaccines with low efficacy (like TBE) as immunity wanes over time and this can result in re-emergence of disease. Further, not all vaccines offer life-long protection against disease with immunity waning over time e.g. pertussis and diphtheria or the strain in circulation continuously changing e.g. influenza [1]. These factors, therefore, make eradication of some diseases nearly impossible and the only option is to prevent and control the diseases in the population and focus on reducing the mortality and complications associated with those diseases.

1.1 HERD IMMUNITY

Disease prevention and control in a population requires enough individuals having immunity to a particular disease. This concept is known as *herd immunity*. Herd immunity can be achieved through 1) natural immunity, whereby the individual has had the disease and recovered: 2) acquired immunity, which is when the person has been vaccinated and is no longer at risk of contracting the disease. Herd immunity is best achieved through the use of immunisation programmes, which work by inducing long-term protection without the risk to the individual of acquiring the natural disease.

There is also an indirect effect of vaccinations or ‘herd protective’ effect, whereby the transmission of infection (person-to-person) within a population is hindered (as the number of individuals becomes immune from infection) and an increase in herd immunity could see a decreased risk of an uninfected person becoming infected. This can also be thought of as protection for persons who are unvaccinated in the population [3-6].

1.2 POTENTIAL STAGES IN THE EVOLUTION OF A VACCINATION PROGRAMME

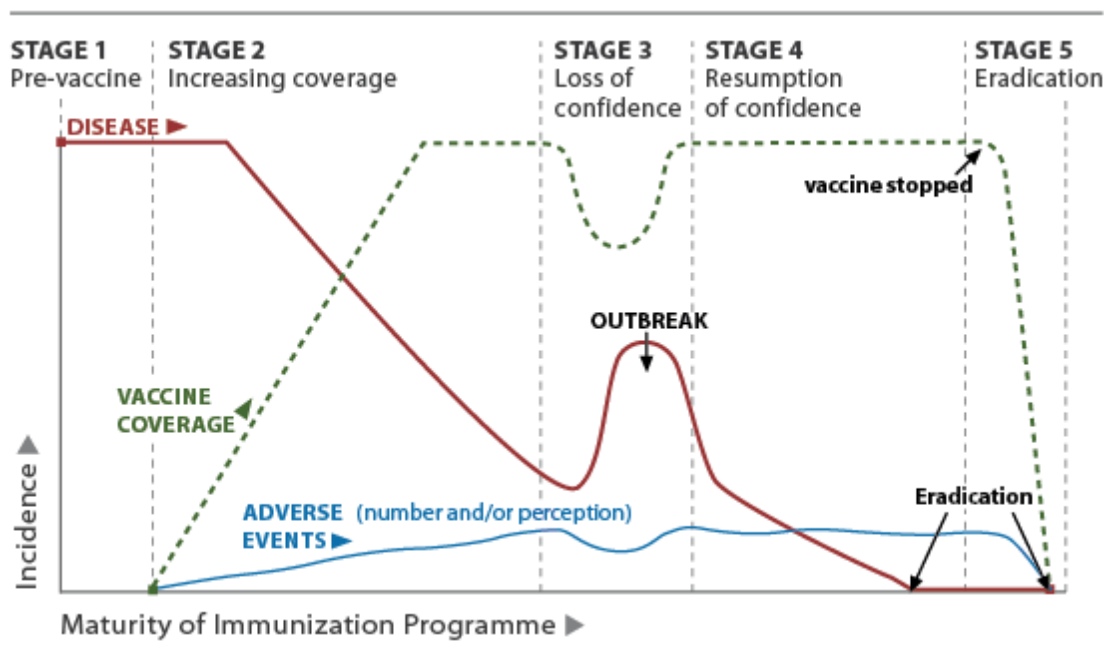


Figure 1. Diagram adapted from Chen RT et al. Vaccine Adverse Event Reporting System (VAERS). A passive surveillance system in the US intended to collect reports of reactions to vaccines. Under the aegis of the US Centers for Disease Control and Prevention and the US Food and Drug Administration. (VAERS). *Vaccine*, 1994; 12(6):542–550.

In Figure 1, we see potential stages in the evolution of an immunisation programme. In Stage1 (pre-vaccine), there is a high incidence of mortality and morbidity from infectious disease. In stage two, a vaccine is introduced, and as the coverage of the vaccine increases, the incidence of disease in the population decreases. In stage three, the benefits of the vaccine are most apparent and vaccine coverage is high: however, vaccine safety concerns increase in the population as the number of adverse events

increases with the higher number of vaccinated individuals. This results in a loss of confidence in the vaccine, a reduction in vaccine coverage and resurgence of the disease in the population. In stage four, the resurgence of disease (outbreaks) or availability of an alternative vaccine, for example, results in renewed public acceptance of vaccination. The coverage of vaccine increases once more and the incidence of disease in the population decreases. In stage five, vaccine-preventable diseases like smallpox that can be eradicated, vaccine use can be stopped, thereby removing the risk of adverse events. The aim of vaccination programmes today is to maintain high coverage of vaccines so that we remain in stage four and with certain diseases such as measles strive for eradication. This is only possible if enough people are vaccinated in the population and immune from disease (herd immunity).

Unfortunately, despite the obvious benefit of vaccination programmes, vaccines have become victims of their own success with an increasing number of people opting out of vaccination. Part of the problem is that before vaccinations were introduced, vaccine-preventable diseases were sufficiently common in the population that risks associated with the diseases were abundantly obvious. Conversely, in today's society, an increasing number of healthcare workers (HCWs) and the general public have never seen the diseases in real life and therefore base the decision to vaccinate on what they do know; which is often more focused on the side effects and pain associated with the vaccination itself. This has resulted in some scepticism regarding the importance of continued vaccination, particularly with an increasing number of new vaccines offered to children as part of a routine vaccination schedule [7, 8]. In addition, there is often a lack of knowledge regarding the risks and benefits of vaccination, which can lead to a significant number of parents having doubts about vaccination [7, 9-12]. A key determinant of whether a parent chooses to get their child vaccinated is HCWs, as they are considered a primary and trustworthy source of information into the benefit of vaccination and therefore their knowledge about vaccines are important in maintaining public confidence [7, 13-18].

Although the uptake of vaccinations is high in the Nordic countries, it is not uniformly so. Population-wide compliance for vaccination programmes is an extremely difficult task, but ensuring public acceptance and trust in vaccinations e.g. through good communication, transparency of information and trust in the healthcare

system and healthcare workers can go a long way to help ensure the uptake of vaccines remains high. The purpose of this thesis is to explore key factors like vaccine safety and effectiveness on vaccine uptake.

1.3 VACCINE EFFICACY AND EFFECTIVENESS

Vaccine efficacy is a measure of the difference in disease risk between vaccinated and unvaccinated individuals under ideal conditions. Randomised control trials (RCTs) are used to ascertain efficacy outcomes, whereby optimal conditions are maintained throughout the trial period. This means that the efficacy outcomes are not directly generalisable to the general population.

Vaccine effectiveness (VE) is a term used to reflect outcomes in a non-controlled environment and from a public health perspective, collecting data on vaccination individuals in the population is preferable to RCTs, as outcomes are more reflective of what is happening in the population where the environment is not controlled [19]. The Swedish healthcare registers provide the means for us to assess effectiveness in real-life settings and factor in access, distribution and detect changes in herd immunity [19, 20].

1.4 VACCINE SAFETY

The introduction of new vaccines (or medicines) follows extensive safety monitoring and for most vaccines included in the national programmes, there is data on the longer-term safety of these vaccines in the population. However, for annual vaccines like influenza – that alter each year depending on the circulating strains, longer-term information on their safety in a population is generally not available [21]. In these instances, very rare outcomes from the vaccination will only be discovered from post-vaccination surveillance in a larger population [21, 22]. A challenge with adverse events following vaccination (particularly for those that are rare) is identifying whether it was the vaccine itself that caused the outcome or just something that randomly occurred in that population [23].

2. BACKGROUND

2.1 STUDY I INVESTIGATING THE SIDE EFFECTS OF PANDEMIC INFLUENZA VACCINATION

Study I is a vaccine safety study looking at whether disease history is a risk factor for narcolepsy after vaccination with the pandemic influenza vaccination, Pandemrix, administered between 2009 and 2010.

2.1.1 Mass vaccination campaigns

During mass vaccination campaigns, large numbers of people are vaccinated over a relatively short period of time against a particular disease. The most widely accepted reason for doing this is to prevent an outbreak occurring in the population by rapidly increasing herd immunity and reducing the risk of complications from disease [24]. Examples of mass vaccination include meningococcal disease [25], Japanese Encephalitis [26], yellow fever [27] and influenza.

In June of 2009, in response to the global A(H1N1) influenza pandemic, four vaccines were manufactured for use in the European Union (EU), with three being authorised for use through the central European Medicines Agency (EMA) in the EU member states [22]. Influenza viruses are prone to antigenic shift and can cause pandemics with little warning, which can lead to a limited number of available doses of vaccine worldwide. Due to the severity of avian influenza strains specifically, the World Health Organization (WHO) encouraged the inclusion of adjuvants when the vaccines were being developed, as they have been shown to reduce the amount of antigen needed to provide a longer lasting protection against influenza [22]. Adjuvant AS03, in particular, has been shown to stimulate increased local or systemic reactions within three days of initial vaccination compared to vaccines that do not contain adjuvants; up to 2009 no major reactions were reported [22, 28, 29]. Due to the speed of the transmission of swine flu and there only being a small quantity of A(H1N1) vaccinations available, the immunisation strategy mimicked the annual influenza campaigns with the vulnerable being offered the vaccination first [22, 30]. In 2009-

2010 millions of individuals were vaccinated in Europe with one of the three H1N1 pandemic vaccines (Celvalpan, Focetrai and Pandemrix). According to estimates provided by the EMA by the 8th August 2010, at least 38.6 million individuals in EU/EEA countries had been vaccinated with one of the pandemic vaccines - Pandemrix being the most commonly used with <30.5 million individuals vaccinated [21, 31].

2.1.2 Adverse events following the pandemic influenza vaccination

In August 2010, the Swedish Medical Product Agency (MPA) and the Finnish National Institute reported abnormally large numbers of narcolepsy cases following vaccination with A(H1N1)pdm09 vaccination. In both Sweden and Finland, Pandemrix was the only pandemic influenza vaccine used, and in Sweden, 60% of the population had been vaccinated [32]. Similar associations between Pandemrix and narcolepsy were reported through studies conducted in other countries [33-36]. The European Centre for Disease Prevention and Control (ECDC) requested that the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium carry out a formal investigation. Several Nordic countries also carried out their own rapid assessment studies, particularly focussed on children and adolescents [32, 35, 37-40]. Several studies have investigated potential risk factors for the development of narcolepsy in conjunction with the pandemic vaccine, with some speculating that narcolepsy might be an autoimmune disease [41, 42], wild A(H1N1) pandemic influenza infection itself may play a role in narcolepsy development [43-46] or streptococcal infection is a trigger [43, 47], but as yet the actual trigger remains unknown [23].

2.1.3 Narcolepsy

Narcolepsy is one of the major sleep disorders characterised by excessive daytime sleepiness (EDS) and cataplexy [35]. There are two main types of narcolepsy, Type 1 (narcolepsy with cataplexy) and Type 2 (narcolepsy without cataplexy), these types were more clearly defined in 2017 based on research findings that had been carried out over the last five years. Narcolepsy has a strong association with the HLA-

DQB1*06:02 allele and that it is specifically the loss of hypothalamic hypocretin (orexin)-producing neurons that lead to the development of the disease [42, 48, 49].

2.1.4 Narcolepsy diagnosis

Narcolepsy is a chronic hypersomnia syndrome with an estimated incidence of 1 per 100,000 individuals annually [50]. It can take 10-15 years from first symptoms until diagnosis, with a peak of onset occurring during the second decade [50-53]. In addition, as its symptoms are similar to other illnesses e.g. depression, ADHD, sleep disorders and infections, this can contribute to the delay in diagnosis. There are seven diagnostic sleep centres and/or neurophysiology labs in Sweden, responsible for the investigating suspected sleep-related disorders, such as narcolepsy, as well as other nervous/neurological disorders. The centres receive referrals from General Practitioners (GPs) and specialists from healthcare centres all over Sweden when a disease such as narcolepsy is suspected. There are various tests that can be performed including; a Polysomnogram, a Multiple Sleep Latency Test (MSLT) and a hypocretin test.

- In a polysomnogram, the patient remains at the centre overnight and their brain activity is monitored along with heart rate, eye movements and blood pressure. This test determines typically how long it takes for the patient to fall asleep, whether rapid eye movement (REM) sleep occurs once a sleep, and how often the patient wakes during the night.
- An MSLT is carried out during the daytime and is a test for excessive daytime sleepiness. Brain activity is measured throughout, which basically measures how quickly the patient falls asleep, in a quiet location, during the daytime. It also determines whether REM sleep is achieved after falling asleep.
- A hypocretin test can also be used to measure the amount of hypocretin there is in the cerebrospinal fluid through performing a spinal tap. If a patient has narcolepsy, the level of hypocretin will be low.

2.2 STUDY II INVESTIGATING WHETHER A TWO-DOSE SCHEDULE IS AS EFFECTIVE AS A THREE-DOSE SCHEDULE AGAINST CONDYLOMA

Study II is a VE study looking at whether two doses of quadrivalent human papillomavirus (qHPV) vaccination is as effective as three doses, provided there is an optimal time between administration of dose one and two.

Papillomaviruses are an extensive family of viruses that can be found in most mammals and birds. Human papillomaviruses (HPV) are spread through skin-to-skin contact, typically during sexual activity and the risk of becoming infected with HPV is particularly high when the partner has had a large of sexual partners [54] and while most infections are asymptomatic, 75-80% of most women will have had an HPV infection at some point during their life. Infection with HPV is typically self-limiting, and 90% of cases will clear the infection within two years from initial infection [55]. To date, over 200 types of HPV have been identified [56, 57], roughly 40 of which can be transmitted sexually. According to the International Agency for Research on Cancer (IARC), there are 13 high-risk oncogenic HPV types [58] with types 16 and 18, which cause 70% of cervical cancer cases globally, being of specific interest in vaccine development [59]. Low-risk HPV types 6 and 11 are responsible for about 90% of condyloma cases [60].

Globally, cervical cancer is the fourth most common cancer to affect women during childbearing years [61]. In 2012, there were 528 000 new cases of cervical cancer diagnosed around the world, with 266 000 women succumbing to the disease, with 90% of deaths from cervical cancer occurring in less developed countries [62]. For countries with improving social and economic status e.g. Western Europe, Americas etc. the last 30 years have seen a noticeable reduction in cervical cancer incidence and mortality, coinciding with the successful implementation of secondary prevention efforts, notably screening and the subsequent early identification of cancer or pre-cancerous malignancies, diagnosis and treatment of cervical cancer [62].

2.2.1 Prophylactic HPV vaccines

HPV vaccines are subunit L1 virus-like particles (VLPs) vaccines and contain an adjuvant. An antibody response is triggered as a result of self-assembly of the L1 capsid protein into VLPs. There are three vaccines currently available:

- A bivalent HPV (bHPV) vaccine (CervarixTM; GlaxoSmithKline) was approved by the EMA in 2007 and two years later by the FDA [63, 64]. The bHPV vaccine provides protection against high-risk HPV types 16 and 18.
- The qHPV vaccine (GardasilTM; Merck), received marketing authorisation from the EMA and the Food and Drug Administration (FDA) in 2006 [65, 66]. The qHPV vaccine offers protection against high-risk HPV type 16 and 18 and low-risk HPV types 6 and 11. Gardasil has shown to have upwards of 99% efficacy against HPV 16 and 18 in HPV-negative women [67].
- A 9-valent HPV (pvHPV) vaccine (Gardasil 9TM; Merck) was approved by EMA and FDA in 2014 and 2015 respectively [68, 69]. This vaccine additionally provides protection against high-risk HPV types 31, 33, 45, 52 and 58 that are believed to cause roughly 20% of cervical cancers.

2.2.2 qHPV vaccination in Sweden

In 2007, an opportunistic qHPV vaccine was available at a subsidised price for girls aged 13-17 in Sweden, vaccines given to girls outside of this age range were paid for by the recipient. In 2012, qHPV vaccination became part of a routine school-based vaccination programme aimed at girls aged between 10 and 12, with a catch-up vaccination for girls aged between 13 and 18 years. Recommendations for the qHPV vaccine were for it to be administered as part of a 3-dose schedule given at 0, 2 and 6 months. In December 2014, the one-dose vaccination coverage for qHPV in the childhood vaccination programme was 82% and for subsidised and catch up vaccination nearly 60% [70, 71].

2.2.3 qHPV vaccine effectiveness

Nationwide VE studies are necessary to determine the public health impact of the qHPV vaccine on HPV-related outcomes in that country. Following the introduction of the qHPV vaccine, it was evident that the vaccine was not only effective in a population-based setting on condyloma and cervical abnormalities [72-76] but that there was a possible non-inferiority of two-doses compared to three-doses for young women [77]. In 2014, in accordance to the existing information, the EMA and World Health Organization Strategic Advisory Group of Experts (SAGE) recommended a two-dose HPV vaccination schedule for girls younger than 14 years of age, with 0-6 months between first and second dose of qHPV [78] and in January 2015, Sweden introduced a two-dose HPV vaccination programme for young girls [78, 79].

3. AIMS

Paper I: To investigate disease history before A(H1N1)pdm09 vaccination as a risk factor for narcolepsy.

Paper II: To assess incidence of condyloma after two doses of qHPV vaccine, by time since first dose, in girls and women initiating vaccination before age 20.

4. MATERIAL AND METHODS

4.1 DATA SOURCES AND COLLECTION

The studies in this thesis were granted ethical approval by the Regional Ethical Review Board in Stockholm. This chapter aims to provide information about data sources, exposures, outcomes and designs of the studies.

A personal identity number (PIN) is allocated to all individuals that are resident in Sweden, for at least one year [80]. Individual-level data can be obtained from the Swedish national health data registers and linked to other registers using the PIN. The responsibility for data linkages falls to the National Board of Health and Welfare and Statistics Sweden, who on completion replace the PIN by a de-identified study ID that cannot be traced back to the individual [80].

4.1.1 Swedish healthcare registers

Total Population Register, Migration Register, and Multigeneration Register

The Total Population Register (TPR) was established in 1968 and is held at Statistics Sweden. The TPR is a main source for demographic data that can be linked to other registers using in individuals PIN number [81]. The migration register was established in 1968 and contains information regarding immigration and emigration dates. The multigeneration register (MGR) was created in 1991 when the responsibility for registering addresses was taken over by the Swedish Tax authorities. This register contains a list of familial relations, including information on adoptive or biological parents. Both the Migration register and the MGR are both extracted from the TPR [82].

The National Patient Register (NPR)

In the 1960s the National Board of Health and Welfare established the NPR, at this time it only held information on region-specific inpatient coverage. The NPR gained national coverage in 1987 and in 1997 outpatient (day surgery) data was additionally added to the NPR. Outpatient data became systematically added to the NPR in 2001[81]. The International Classification of Diseases (ICD) with the 10th revision of ICD in use since 1997 [83] is used to report diagnoses to the NPR.

The National Causes of Death Register (CDR)

The CDR established by Statistics Sweden contains information on all deceased individuals residing in Sweden from 1952 onwards. It contains the date of death, the cause of death and information on deaths that occur abroad. In 1994, it was moved to the National Board of Health and Welfare [84].

The Prescribed Drug Register (PDR)

In July 2005, information on pharmacy-dispensed drug prescriptions became part of a newly automated register called the PDR. The PDR is held at the National Board of Health and Welfare and has had national coverage from the beginning. Drug and vaccine prescriptions are entered into the register using Anatomical Therapeutic Chemical (ATC) codes [85]. This register lacks information about school-based vaccinations and hospital administrated medications and prescriptions.

Swedish HPV Vaccination register (SVEVAC)

SVEVAC was originally created in 2002 for use in three counties as a voluntary system to register childhood vaccinations. In 2006, coinciding with the launch of the HPV vaccination in Sweden, SVEVAC was given nationwide coverage for registration of HPV vaccination specifically. In 2015 the responsibility of the register moved to the Swedish Association of Local Authorities and Regions (SKL).

Informed consent is needed from the parent or vaccinated individual. If informed consent is lacking, then the person is added anonymously (lacks a PIN), this means that any information obtained from SVEVAC cannot be linked to other registers. This means that it is not possible to identify whether the information is from one or more persons and, for example, whether someone receives one dose of the qHPV vaccine or multiple doses. In 2012, there was a change to the informed consent form on a municipality level (opt-out to opt-in), this led to a spike in anonymous registrations in a few counties in Sweden. It was later changed back to an opt-out information consent form.

4.2 STUDY DESIGN

4.3 STUDY I

A retrospective case-control design was used for study I, where cases of narcolepsy (outcome) were compared to controls without narcolepsy, to identify whether disease history was a risk factor for narcolepsy after A(H1N1)pdm09 vaccination.

4.3.1 Case and control identification

Six of the seven sleep centres in Sweden provided a list of potential cases (those referred for an MSLT between January 1st, 2009 and December 31st, 2010). There were 431 people who were referred for a possible sleep-related disorder, with 142 having a primary diagnosis by their referring clinician. These cases were contacted by Karolinska Institutet (KI) requesting permission to include them in the study. A case's referral date for an MSLT was defined as the index date in this study.

For each case four controls were randomly selected from TPR, matching on age, gender, county of residence and index date.

Case and control identification and reasons for not fulfilling inclusion criteria can be seen in Figure 2.

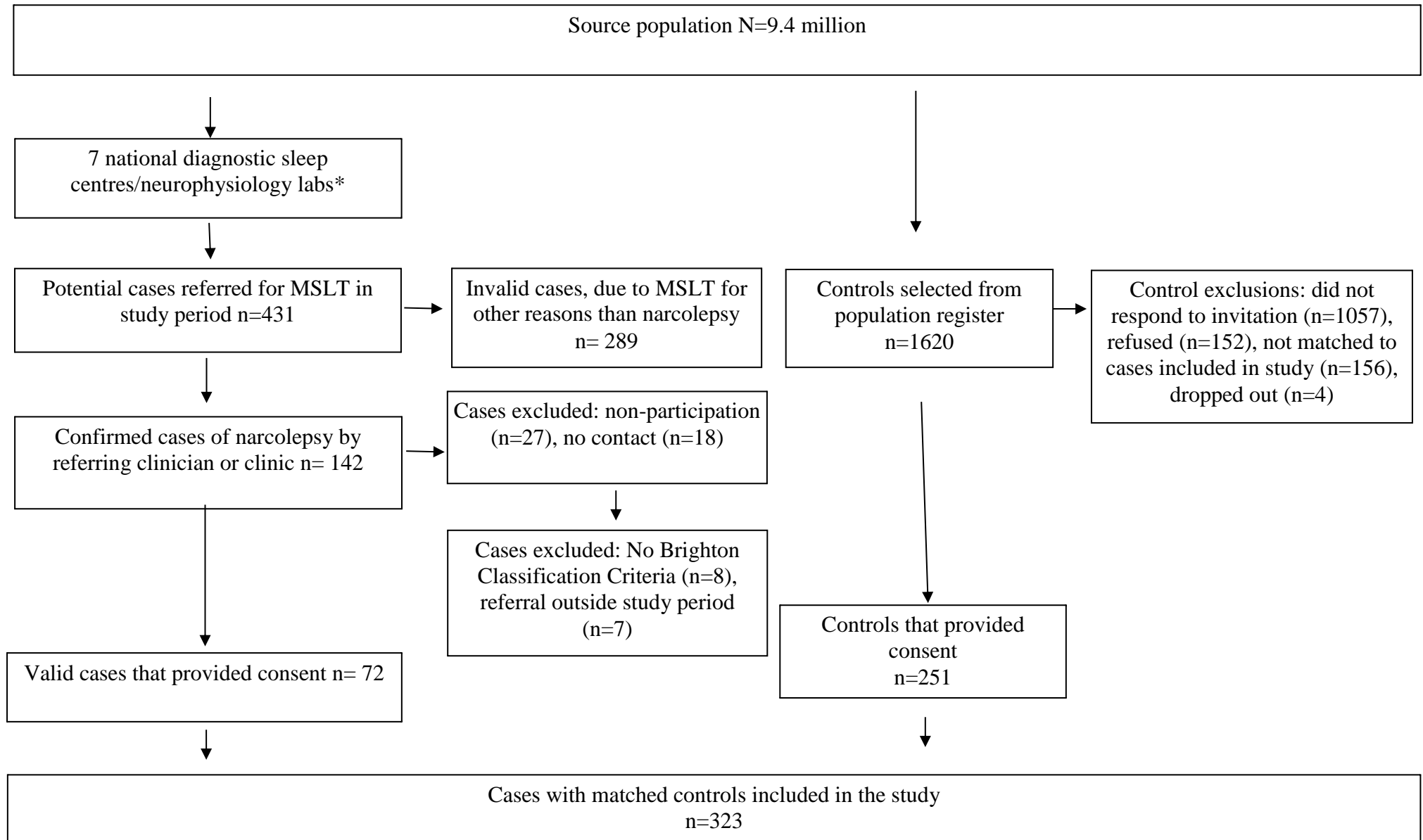


Figure 2. Flowchart to show case and control identification

* No response from one sleep centre, list of potential cases not provided.

4.3.2 A(H1N1)pdm09 vaccination

Information on A(H1N1)pdm09 vaccination was collected via telephone interview with cases and controls. Some dates were missing information e.g. day or month – as individuals were unable to recall the exact date of vaccination. In these instances, the day of the month was assigned to the 15th (middle of a standard month) with missing months in 2009 given November and in 2010 given January. These months represent the middle of October-December and middle of overall vaccination period of October 2009-March 2010 respectively.

4.3.3 Exposures

Disease history

Table 2. Information on disease history selected from the PDR and the NPR

Code	Disease	Source
ICD10		
G00-473, G475-99	Nervous system disorders	NPR
F00-99	Mental and behavioural disorders	NPR
A30-49	Bacterial diseases	NPR
C00-99	Neoplasms	NPR
J00-99	Respiratory diseases	NPR
A80-99	Viral infections of the CNS	NPR
B25-34	Other infections of the CNS	NPR
B95-99	Other bacterial, viral and other infectious agents	NPR
E10-14	Diabetes Mellitus	NPR
ATC*		
N	Nervous system disorders	PDR
R03	Obstructive airway diseases	PDR
J01	Antibacterial	PDR
J05	Antiviral	PDR

M01A	Anti-inflammatory/anti-rheumatic drugs, non-steroid	PDR
L04	Immunosuppressant	PDR
A10	Diabetes	PDR
N06BA01, N06BA03, N06BA04, N06BA07 and N06BA09	ADHD treatment and no tropics (proxy for ADHD diagnosis)	PDR

*Drugs used against listed diseases

Four combined exposure groups were also created a) nervous system disorders using ATC code N and/or ICD10 codes G00-473, 475-99 b) bacterial diseases using ATC code J01 and/or ICD10 A30-49 c) respiratory diseases using ATC code R03 and/or ICD10 J00-99 and d) viral diseases using ATC code J05 and/or ICD10 A80-99, B24. A multiple prescription/diagnosis variable was also created, taking into account that individuals could have received more than one prescription and/or diagnosis during the period of exposure in more of more categories.

Exposure windows

Disease history was studied as a risk factor for narcolepsy over three different exposure windows (Figure 3).



Figure 3. Exposure window: 1) Prescription (ATC) and diagnosis (ICD10) history before the index date (MSLT-referral date). Defined as after the first date in inpatient register (1987), outpatient register (2001) or PDR (2005) up until index date; 2) Prescription and diagnosis history during the vaccination period, defined as six month before to one month after vaccination date (specific to each case/control). For acute infections ATC J01 and J05, vaccination period was two weeks before to two weeks after vaccination; 3) Prescription and

diagnosis history before A(H1N1)pdm09 vaccination. Defined as after the first date in inpatient register (1987), outpatient register (2001) or PDR (2005) up until vaccination date.

4.4 STUDY II

A register-based cohort study design was used for study II. The effect of vaccination within the population was assessed among women aged 10-27 years who had received at least two doses of qHPV during the study period. These women were followed for HPV vaccination (exposure) and condyloma (outcome). All women who were diagnosed with condyloma before the study period were excluded.

4.4.1 Study population

In this study, we included women aged 10-27 years that lived in Sweden between 1st January 2006 and 31st December 2012. Girls entered the study cohort on the date of administration of the second dose of qHPV. They were followed for the first occurrence of condyloma. Women that had a history of condyloma i.e. had received a diagnosis prior to follow-up, were excluded, as were girls who emigrated, received the bivalent vaccine, initiated qHPV vaccination over the age of 20 or turned 27 before the start of follow up. Women were followed from their 10th birthday or start of follow-up until they were diagnosed with condyloma or one of the censoring criteria was met, i.e. death, emigration, bHPV, turned 27 or end of study period.

Details on study exclusions and the population that was analysed in this study can be seen in Figure 4.

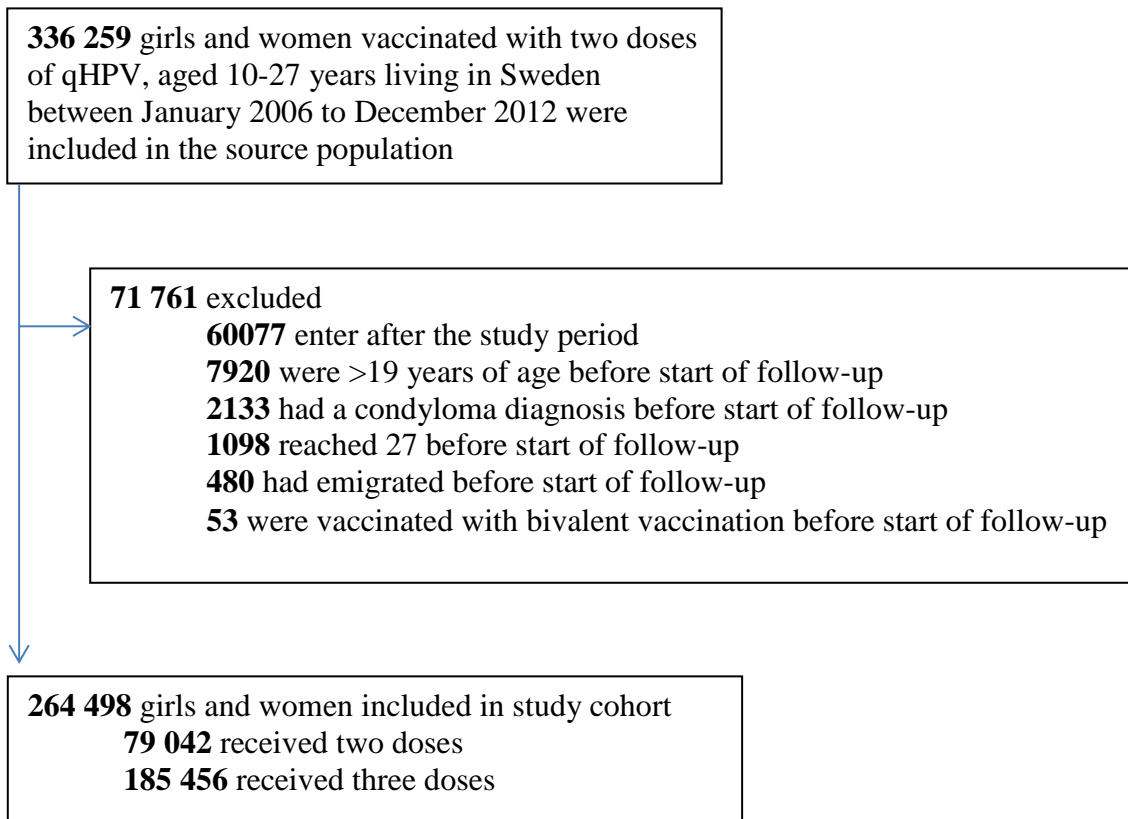


Figure 4. Details on study exclusions and the population analysed to investigate timing of two versus three doses of qHPV vaccine and associated effectiveness against condyloma.

4.4.2. Exposure

Between the years 2007 and 2011 (opportunistic vaccination period) vaccination were registered in SVEVAC. However, reimbursement for the vaccination was only possible if the vaccine doses were administered from a pharmacy during this period, and thus information regarding vaccinations could also be found in the PDR. School-based vaccinations (from 2012) are all registered in SVEVAC and from 2013 in National Vaccination Register (NVR). As there were incomplete vaccination records for doses one and two in SVEVAC during the course of the study, information was complemented with prescription data collected from the PDR, using ATC codes J07BM01 and J07BM02 respectively. Dispensation dates that occurred more than 14 days prior to or directly after the vaccination administration date were considered new doses [86].

4.4.3 Outcome

Condyloma cases were identified from the NPR using a unique identifying ICD10 code (A63.0). In addition, cases were identified from the PDR using ATC codes D06BB04 and D06BB10 (condyloma treatment podophyllotoxin and imiquimod respectively). While podophyllotoxin is used solely for the treatment of condyloma imiquimod can also be used to treat other conditions e.g. actinic keratosis. One episode of condyloma can have multiple entries in both the NPR and PDR and therefore subsequent cases of condyloma cannot be reliably identified

4.5 STATISTICAL ANALYSIS

4.5.1 Study I

In order to investigate whether disease history was a risk factor for narcolepsy, conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). As narcolepsy is a rare disease, the ORs were interpreted as the relative risk (RR) of narcolepsy.

In this study, three analyses were performed investigating disease history as a risk factor for narcolepsy:

1. A full data analysis, where all cases and controls were included, regardless of vaccination status (vaccinated or not) or timing of vaccination (before or after MSLT-referral date). In this analysis, we looked at disease history before the index date (exposure window 1, Figure 3).
2. Second, a vaccinated-only analysis was conducted where only cases/controls that received the vaccination before their index date were included - all exposure windows were of interest (Figure 3).
3. Third, a case-only analysis was carried out, which compared those vaccinated with an index date before vaccination, versus those with an index date after vaccination. The exposure windows of interest were 2 and 3 (Figure 3).

4.5.2 Study II

The incidence of condyloma was reported as crude incidence rates (IRs) per 100 000 person-years with 95% confidence intervals (CIs). These crude IRs were stratified by time between the first and second dose of qHPV (0-3, 4-7 or 8+ months) and calculated for two separate age-at-first vaccination categories (10-16 years and 17-19 years), reflecting median age for sexual debut in Sweden [87].

Poisson regression analysis was used to model IRs in relation to the time between the first and second dose of qHPV and age at first vaccination, adjusted for attained age. For individual follow-up, the underlying timescale was attained age, split into five categories (10-13, 14-16, 17-19, 20-21 and 22+ years) to reflect the risk of disease/infection with advancing age. Three versus two doses of qHPV was treated as a time-varying exposure, meaning that women could contribute person time to both dose groups. Incident rate ratios (IRRs) with 95% CIs were calculated from this model after two doses of qHPV relative to three different reference groups (all initiating vaccination at the same age):

- 1) Women who received three doses of qHPV according to the standard dosing schedule (0, 2, 6 months).
- 2) Women with three doses of qHPV with the same timing between first and second dose (two doses with 0-3 months between versus three doses with 0-3 months etc.).
- 3) Women who had received all three of the qHPV doses, with no restriction on the time between doses e.g. one to two and two to three.

IRs and IR differences (IRDs) and 95% CIs were predicted from the models (averaged across levels of attained age).

5. MAIN FINDINGS AND DISCUSSION

5.1 STUDY I

In study I disease history as a risk factor for narcolepsy after A(H1N1)pdm09 vaccination was estimated using conditional logistic regression. In total 72 cases and 251 controls were included in the study (range 3-69 years, mean 19 years).

In the full data analysis, including all cases and controls regardless of vaccination status or timing of vaccination (before or after MSLT referral), the risk of narcolepsy was increased in individuals with a disease history (prescription and/or diagnosis) of nervous system disorders (OR range 3.6-8.8), ADHD (OR=4.5 95% CI 1.4-14.7) and mental and behavioural disorders (and OR=3.8, 95% CI 1.6-8.8) before MSLT referral (See Table 6). It was speculated whether the increased risk we observed for ADHD could have been due to misdiagnosis, which would have also increased the risk we observed for nervous system disorders and mental and behavioural disorders.

Table 6. Full case-analysis showing association between disease history before index date on the risk of developing narcolepsy.

Full-case analysis*				
Characteristics	Cases N (%)	Controls N (%)	OR (95% CI)	P-value
ICD10*				
G00-473, 475-99	10 (13.89)	6 (2.40)	8.76 (2.68-28.61)	0.0003
F00-99	13 (18.06)	14 (5.58)	3.76 (1.60-8.81)	0.002
Multiple ICD10	31 (43.06)	71 (28.29)	2.39 (1.30-4.39)	0.005
ATC*				
N	21 (29.17)	30 (11.95)	3.55 (1.77-7.13)	0.0004
N06BA	7 (9.72)	5 (1.99)	4.49 (1.37-14.71)	0.01
R03	13 (18.05)	31 (12.35)	2.14 (1.00-4.57)	0.049
Multiple ATC	57 (79.17)	142 (56.57)	3.30 (1.72-6.33)	0.0003

*before MSLT referral. N.B Table 4 only shows significant results. Full table of results can be found in paper 1 at the back of the thesis.

It was possible to look at the case diagnoses ‘overall’ i.e. determine whether they were more likely to have received a diagnosis for other sleep-related disorders, which would support the hypothesis that early narcolepsy cases could have received an incorrect diagnosis in the beginning. We found evidence for this, with cases having more diagnoses for conditions like sleep apnoea and hypersomnia. Therefore, to explore this we performed a second analysis looking at vaccinated individuals only. In this analysis, we excluded cases/controls with an index date prior to vaccination. We found that nearly all the initially observed associations were no longer statistically significant and effect sizes were smaller (OR range=1.3-2.6) (Table 2 & 3 in Paper I).

However, as early cases (those that had an MSLT-referral before vaccination) had been excluded from the second analysis, it was hypothesised that it was actually these cases that were responsible for the associations observed in the full data analysis. This is assuming that these early cases received more prescriptions/diagnoses before vaccination (and thus during vaccination period and before the index date) than those who were referred after vaccination. It can also be speculated that cases resulting after vaccination, would have had a shorter diagnostic timeframe (fewer misdiagnoses) given the increased awareness surrounding narcolepsy.

To confirm if this and establish if there was a difference between these early cases and vaccine-associated cases, we performed a final analysis comparing cases referred before vaccination to those referred after. We only found large significant effects for prescriptions for nervous system disorders (OR=26.0 95% CI 4.0-170.2) and ADHD (OR=35.3 95% CI 3.4-369.9) during the vaccination period (See Table 4, in paper I) These findings supports the speculation that early cases were driving the associations found in the full data analysis and the significant effects were likely a result of confounding by indication and that disease history is not a risk factor for narcolepsy after A(H1N1)pdm09 vaccination.

5.2 STUDY II

In study II, the risk for condyloma after qHPV vaccination was estimated by including 264 498 girls, aged under 20 years, of whom 72 042 had received two doses

and 185 456 had received all three doses at the end of the study period. The majority of girls (83%) who were fully vaccinated had adhered to the recommended dosing schedule (0, 2, 6 months). The lowest rates of condyloma after two dose vaccination were observed in girls first initiation vaccination under the age of 17 years with 0-3 months between dose one and two (IR=84 95% CI 66-108) per 100 000 person-years. Conversely, The highest rates of condyloma after two-dose vaccination were observed in girls first initiating vaccination after the age of 17 years when there were 8+ months between dose one and two (IR= 603 95% CI 271-1343) per 100 000 person-years.

Comparing two doses versus standard three-dose schedule, we found that for girls first vaccinated before the age of 17 the IRR of condyloma after receipt of two doses with 0-3 months between dose one and two was 1.96 (95% CI 1.43-2.68) and for 4-7 months and 8+ months the IRR were 1.27 (95% CI 0.63-2.58) and 4.36 (95% CI 2.05-9.28) respectively. For girls initiating vaccination after the age of 17, a similar pattern was observed, with a higher risk for condyloma after two doses with 0-3 months between dose one and two and for 8+ months. However, we found no statistically significant association comparing two doses with 4-7 months in between versus the standard three doses (Table 7).

Table 7. IRR comparing two-dose versus three-dose vaccination by age at vaccination initiation and time between dose one and two, adjusted for attained age.

Age at first vaccination	Number of doses	Time between dose 1 and 2 (months)	IRR, 95%CI	P-value
≤16yr	3 doses	Standard dosing schedule (0, 2, 6)	Ref	Ref
	2 doses	0-3	1.96 (1.44; 2.68)	<0.001
		4-7	1.27 (0.63; 2.58)	0.506
		8+	4.36 (2.05; 9.28)	<0.001
17-19yr	3 doses	Standard dosing schedule (0, 2, 6)	Ref	Ref
	2 doses	0-3	2.12 (1.62; 2.77)	<0.001
		4-7	0.81 (0.36; 1.84)	0.615
		8+	3.16 (1.40; 7.14)	0.006

Comparing two-dose versus three-dose vaccination, where the time between doses was matched e.g. two doses with 0-3 months between doses versus three doses with 0-3 months between dose one and two, results remained much the same as above for both girls initiating vaccination before 17 years and those after. For 4-7 months and 8+ months, we found non-significant associations for girls initiating vaccination before 17 years with IRRs of 0.87 (95% CI 0.33-2.32) and 3.14 (95% CI 0.65-15.09) respectively. For girls initiating vaccination after 17 years, no association was found for 4-7 months between dose one and two (Table 3 in paper II).

The results from this study support the recommendations from EMA and SAGE and findings from immunogenicity trials. Evidently, reducing the number of required doses in the HPV vaccination schedule would be beneficial for a number of reasons: a) cost-effectiveness b) better compliance, c) better logistics in the programme. This study indicates that two doses is sufficient to confer protection provided that the timing between doses is optimal.

6. METHODOLOGICAL CONSIDERATIONS

6.1 SELECTION BIAS

In mass vaccination campaigns, such as those for pandemic influenza, the vaccine on offer is usually first targeted at higher risk individuals such as the elderly, pregnant woman, and children. However, the vaccination is not mandatory and thus individuals have to choose to be vaccinated. These people could, therefore, represent a more select group that somehow differ from those that choose not to be vaccinated - this is selection bias. Selection bias was a large problem in study I, not only did we have a select group of people choosing to receive the A(H1N1)pdm09 vaccine, but there also a large proportion of cases that did not want to participate in the study. It was not possible to ascertain any reason for refusal to participate and thus means to control for this selection bias.

Selection bias was also a problem in study II, as most of the girls were opportunistically vaccinated during the follow-up so the younger girls (13 to 17 years) were eligible for subsidised vaccination, but the remainder had to pay the entire cost of the vaccine. Thus, girls choosing to be vaccinated during this time period may represent a more select group – those willing to be vaccinated despite the cost. What is not known is whether other aspects, like education level, could have played a role in whether a girl chose to be vaccinated. This was less of a problem in study II, however, as girls entered the study following administration of dose two, therefore the ‘decision’ whether to receive the qHPV vaccination in the first place (dose one) has already occurred. In addition, individuals that choose to be vaccinated could be considered more health-conscious and adhere more to health-seeking behaviours than those that do not receive the vaccination. It has been shown previously that girls at greater risk of condyloma, over the age of 20, are more likely to seek out vaccination against HPV [88], it was possible, therefore, to limit the risk of self-selection bias by excluding women over the age of 20 years.

6.2 DIAGNOSTIC BIAS

In study I, diagnostic bias was a potential problem, as narcolepsy typically takes several years to develop and be diagnosed and in this lag time, misdiagnoses can occur. However, with the increased awareness of narcolepsy after the vaccination campaign, the time between symptom onset and diagnosis was shortened. To reduce the effects of diagnostic bias, we used the MSLT referral date (index date) and not the date of diagnosis as a proxy for diagnosis date. In addition, to account for the time between vaccination and diagnosis, we investigated several different exposure windows that were specific to each individual in the study based on their A(H1N1)pdm09 vaccination date and index date.

6.3 RECALL BIAS

In study I, the data was originally all self-reported. This led to a host of problems with data integrity, as many responses were missing or incomplete. We controlled for this by augmenting the self-reported data with exposure data from the Swedish healthcare registers, however, this was not possible for the date for A(H1N1)pdm09vaccination and this, therefore, remained the original self-reported response. Although we controlled for self-reported vaccination dates as best we could (by assigning 15th for missing dates, November for missing month in 2009 and January for missing month in 2010) we could not rule out recall bias – with cases being more likely to remember when and if they received the A(H1N1)pdm09 vaccination. This may have resulted in a potential overestimation of exposure in cases. However, as this study took place shortly after the vaccination campaign, we believe that the effects of recall bias would be very low as individuals are more likely to recall something that happened recently.

6.4 MISCLASSIFICATION OF EXPOSURE

In study II, there is possible misclassification of vaccination exposure, due to underreporting of HPV vaccinations in SVEAVAC. The impact of which would be girls considered falsely unvaccinated and therefore not enter the study at the administration of dose two. We did not consider this a big problem in our study,

however, as we additionally used dispensation dates (registered in PDR) to complement data from SVEAVAC, thus minimising risk of misclassification in our study.

6.5 ATTAINED AGE

In study II, the age at which an individual is vaccinated (age of vaccination initiation) does not change over time. However, during follow-up of a study an individual gets older i.e. they attain age. Therefore, age at vaccination initiation and attained age are two different things. To correct for effect modification by age at vaccination initiation, we grouped the girls into two age-at-first-vaccination categories and adjusted for attained age.

6.6 UNDERESTIMATION OF DISEASE EXPOSURE

In study I, we were unable to look at individual disease codes as part of the broader ATC and ICD10 categories as the study size was too small. It is also possible that less bacterial and viral infections were reported, as generally speaking individuals will only seek medical care for acute infections, resulting in an underestimation of disease exposure.

7. CONCLUSIONS

In study I, we found that disease history was not a risk factor for narcolepsy after A(H1N1)pdm09 vaccination. We found that there was potential for misdiagnosis in early cases i.e. those that presented with symptoms and were referred for an MSLT test before they were vaccinated with Pandemrix. This could mean that narcolepsy cases are being missed until later years and potentially increasing the incidence of other mental and behavioural disorders such as ADHD and depression.

In study II, we found that for women first vaccinated before the age of 20 years, a two-dose qHPV vaccination schedule, with 4-7 months between doses, may be as effective as the recommended three-dose schedule.

8. FUTURE DIRECTIONS

“The impact of vaccination on the health of the world’s people is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.”

Susan Plotkin and Stanley Plotkin. First Edition of ‘Vaccine’ [89]

While many public health successes can be attributed to vaccination, the future can present on-going challenges. There are, for example, still diseases for which there are no effective vaccines e.g. malaria and HIV, and locations around the world where there are limited resources or infrastructures for vaccinations if any exist at all. The success of vaccination depends on the continuance of effective medical research – with the development of highly effective vaccines (longer-lasting immune response), a minimal number of required doses (more cost-effective), hardy vaccines (will survive transport without cooling) and those that are simple to administer. In addition, focus to date has been placed on acute infectious diseases, but now with the development of an effective vaccine against cervical cancer, the focus could shift to prevention of chronic diseases such as TB, other cancers and Alzheimer’s disease.

Establishing the impact of the influenza vaccines following introduction into the population relies on repeated VE studies. However, before-after studies are difficult to conduct for influenza as VE is modest in comparison to other vaccines e.g. pneumococcal conjugate vaccine. In addition, seasonal influenza epidemics display considerable heterogeneity compounded by existing immunity within the population (prior vaccination or past exposure) and antigenic drift [90]. Influenza VE varies year to year as well, depending on the virus strains circulating and the degree of antigenic match between the influenza strain contained in the vaccine and the circulating strains in the population [90, 91]. Although the goal is to develop an effective universal vaccine that reduces the burden of disease, it is important to evaluate the economic impact of an influenza vaccination programme and this is something that the WHO is currently developing [92].

The HPV vaccines have been on the market for over a decade and the protective properties of the vaccines have been shown, for example, in Australia, the HPV rates dropped from 23% to 1% in women aged 18-24 years over the last 10 years [93]. However, the duration of protection following vaccination, against HPV infection and HPV related diseases is not known, therefore, continued monitoring with longer follow-up time is necessary. The 9-valent vaccine, which has been shown to have an increased impact in comparison to the qHPV vaccine [94] has also recently been approved for use, so we will not have any information about the long-term effects of the vaccine for some time to come.

It has been shown that males are protected against HPV-related cancers through herd effects when the vaccination coverage amongst girls is 80%, but also that including the boys into the HPV vaccination programmes could see a further reduction in the number of cancers in both sexes [95]. However, despite the obvious reductions in HPV related diseases and infections and the potential to include boys into the programme, girls are still at risk of cervical cancer and will require screening. Yet, we do not know the long-term difference in protection between the different vaccines and how this will affect their screening requirements nor how the screening requirement for these girls might differ from those who are not vaccinated. Therefore, future guidelines will need regular adaption to factor in differing screening requirements for these girls while achieving cost-effectiveness and maximum prevention of HPV-related infections and cancer.

Vaccine hesitancy also needs recognition as a changing global issue that threatens the success of vaccination programmes. The concept of vaccine hesitancy is complex and made up of many determinants that can vary depending on the setting. Different countries, for example, can have different magnitudes of vaccine hesitancy and the approach to dealing with the problem needs to be different. Countries must factor this in when developing a plan to measure and deal with vaccine hesitancy in their countries.

Duration of protection from vaccines administered as a child is also an important consideration for the future, as with people living longer additional booster shots may

be necessary. It is also something that individuals have to seek out for themselves, which not only requires the knowledge regarding the importance of vaccinations as an adult but the time commitment and ability to do so. One possible consideration is to make a life-long vaccination programme that is sustainable and standardised across Europe – a programme that an individual follows from birth until death. This programme could provide the means to develop new vaccines, improved accessibility, and new platforms with better information for risk-groups, travellers etc. and also focus on migrants that are entering into Sweden from countries with endemic, vaccine-preventable diseases. This idea has already been presented by the Swedish Public Health Agency [96] and could be a major break-through in ensuring a high uptake of vaccines and duration of protection in the population.

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*“We are not now that strength which in old days
Moved earth and heaven, that which we are, we are;
One equal temper of heroic hearts,
Made weak by time and fate, but strong in will
To strive, to seek, to find, and not to yield”*

Alfred Lord Tennyson, Ulysses, Line 65-70

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