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Newly introduced vaccines: effectiveness and determinants of acceptance

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Chapter 1. General introduction

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Since the beginning of the twentieth century, many infectious diseases have been controlled by large scale vaccination programs [1]. Due to herd effect, vaccination benefits extend beyond the vaccinated population. That is, when a sufficiently large proportion of the population is vaccinated, the unvaccinated segment of the population may also become protected against the spread of infection or the disease [2]. Hence, vaccination is referred to as one of the most cost-effective public health measures in preventing the burden of infectious diseases in deprived countries as is often made accessible to even the most hard-to-reach and vulnerable populations [3]. Nevertheless, current vaccination programs in Europe face challenges due to concerns regarding vaccine effectiveness and safety.

Vaccine effectiveness and its assessment

Population-based estimates of the effectiveness of vaccination programs can be obtained by experimental or observational studies using individual person follow-up data or the aggregated outcome data over a number of time points. An experimental randomized (placebo-) controlled trial (RCT) design is the preferred individual person or person cluster data driven study design, followed by a cohort and case-control observational design. However, an RCT is often not appropriate in assessing vaccine effectiveness, for example, if vaccination programs have already been introduced in the population. Also, implementation of the RCT is logistically challenging and costly. Therefore, evidence about vaccine effectiveness in targeted populations from national immunization programs is usually derived from observational studies. Such studies include the actual population that is targeted for vaccination, and this is a major advantage for policy making. However, observational studies can be susceptible to bias and confounding, and this needs to be taken into account in the design and analysis phase of the study. In order to validly synthesize evidence into a review or meta-analysis, data from high quality observational individual studies must be available. These limiting factors may in turn lead to uncertainty about the real effects of the studied vaccination programs, and therefore methodological challenges to assess vaccine effectiveness in observational studies as well as reviews and meta-analyses deserve special attention.

Another option than direct comparison between groups or individuals to assess large scale public health interventions is the use of time-series study designs. In time-series analyses, the aggregated outcome data over multiple and equally spaced time periods are used to estimate the effect of the intervention. This method can be used when there is a population-based intervention or multiple interventions occurring at known (different) time points instead of data on exposure status at the individual level. This is advantageous and resource saving as a means to assess the effect of large scale interventions on various outcomes without having to first combine the outcome data with exposure status.

Influenza, pneumococcal and Q-fever vaccination effectiveness assessments

Based on recommendations from the Health Council of the Netherlands, vaccines included in the National Immunization Program (NIP) should satisfy a number of objective criteria [4]. Among others, the vaccine has to be expected to considerably decrease the burden of disease within the population by preventing the disease or reducing its symptoms, and it must reach necessary vaccination rates [5]. Vaccinations within the NIP being considered to be effective, yet despite this, estimates of vaccine effectiveness in the targeted populations are not always as high as expected or lacking. This in turn can lead to discussion and negative attitudes towards vaccination in the public and among health professionals. For example, in the case of influenza vaccination, the populations at most risk to suffer from severe influenza complications are those who suffer from underlying medical conditions or have a hampered immune system. These groups are therefore targeted for annual influenza vaccinations, but influenza vaccine effectiveness is typically observed to be moderate in these groups [6]. This may be due to different formulation of the influenza vaccine every year, preferably in different population groups in order to determine true vaccine effectiveness.

In 2006, a 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the Netherlands and, was replaced in 2011 by a 10-valent (PCV10) vaccine [7]. It has been shown that the vaccine prevented the use of oral antibiotics in children [8], but no overall reduction in ear, nose and throat infections was found [9]. Although part of

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these findings could be explained by serotype replacement (a decrease of vaccine-serotype invasive pneumococcal disease (IPD) followed by an increase in IPD caused by non-vaccine serotypes [10,11]), the findings seem quite inconsistent. Additionally, there is no information on changes in antibiotic prescriptions that are usually used for acute otitis media and pneumonia, which are the most frequently prescribed antibiotics in young children in the Netherlands.

Although Q fever has been a mandatory notifiable disease in the Netherlands since 1975 [12], it only became a major, national concern in 2007. Between 2007 and 2009, a steep increase was seen in the number of notified human Q fever cases caused by *Coxiella burnetii* showed a steep increase, with 168 and 2357 new cases respectively [13]. There is only one vaccine against Q fever available for use in humans (Q-Vax, Commonwealth Serum Laboratories Limited). This vaccine is registered in Australia, where it is available and used to vaccinate individuals with high occupational risks to contract Q fever. In Europe including the Netherlands, the vaccine is not licensed, and therefore its use is limited. Regardless, evidence concerning Q fever vaccine effectiveness is needed because vaccination is considered to be an option to prevent symptomatic and asymptomatic cases of Q fever in the Netherlands.

Determinants of Human Papillomavirus vaccine acceptance

Vaccination coverage of most vaccines included in the national immunization schedules is usually very high [14]. Still, there are vaccines with suboptimal coverage. For example, in the Netherlands, the uptake rates of the vaccines administered as part of the Dutch NIP for infants and young children are well above 90% [15]. However, the Human Papillomavirus (HPV) vaccine is accepted by less than 50% of the target group of school-aged girls [15]. Surprisingly, in some developing countries HPV vaccination is much more accepted and reaches even up to and greater than 90% [16]. Determining which factors lead to such low vaccine acceptance in the Netherlands is necessary to be able to address these determinants in the future to increase the HPV vaccination rates.

Thesis objectives

The general objective of this thesis is to further advance research on newly introduced vaccines by assessing their effectiveness as well as the determinants of acceptance in different population groups. In this thesis, a number of literature studies and meta-analyses, observational cohort, case-control, time-series and questionnaire studies are presented and discussed.

Thesis outline

Chapter 2 is dedicated to A(H1N1)pdm09 pandemic and seasonal influenza. Influenza causes respiratory infections most commonly seen in young children but is also responsible for severe complications among elderly persons and patients with risk elevating chronic conditions. This thesis begins with an overview of the last five influenza seasons where the aim is to describe influenza seasons with regard to timing, duration, and geographical spread of influenza within the World Health Organization European Region (**Chapter 2.1**). This thesis continues with a review of cohort studies aiming to assess seasonal influenza vaccine effectiveness where a novel design method was used to adjust for biases (**Chapter 2.2**). Next, we proceed to observational studies assessing the effectiveness of different influenza vaccines. The first is a study of the pandemic influenza A(H1N1)pdm09 vaccine conducted in the Netherlands and offers evidence of vaccine effectiveness against influenza-like illness and laboratory-confirmed influenza in chronically ill and elderly individuals (**Chapter 2.3**). The second observational study presented was conducted in Lithuania and aims to assess 2012/2013 seasonal influenza vaccine effectiveness against laboratory confirmed influenza in the hospitalized population (**Chapter 2.4**). Next, we assess whether the predictors of the 2008/2009 seasonal and pandemic A(H1N1)pdm09 influenza seasons were similar and determine if influenza could be predicted from data routinely collected in general practice (**Chapter 2.5**). Finally, we provide evidence about the most important predictors that contribute to the acceptance of seasonal influenza vaccine among health care workers (**Chapter 2.6**).

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Chapter 3 discusses another important cause of respiratory diseases and its complications. *Streptococcus pneumoniae* is similar to seasonal influenza and mostly affects children and elderly individuals. A national vaccination campaign in the Netherlands with a 7-valent pneumococcal vaccine was introduced in 2006 and has been replaced with a 10-valent vaccine in 2011. In this chapter, we assess the effect of the Dutch national pneumococcal influenza campaign in children using a time-series design.

In **Chapter 4** we present evidence on Q fever vaccine effectiveness as well as bias assessments of the included individual studies.

In **Chapter 5** we provide evidence about the determinants of HPV vaccine acceptance. Considering the relatively low HPV vaccine uptake in the Netherlands, it is necessary to assess the factors leading to low vaccination uptake.

Finally, in **Chapter 6** we summarize the main findings of this thesis, discuss them in the relevant context and give perspectives for future research.

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***Chapter 2. Influenza: describing influenza seasons,
cases, vaccine acceptance and vaccine
effectiveness***

