Chapter 1

General Introduction

Influenza virology and epidemiology

There are three main types of influenza viruses: A, B and C. It is well known that influenza A and B are responsible for seasonal epidemics with a substantial public health impact on the human population [1]. Influenza A viruses are categorized into subtypes according to two proteins located on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Among all different influenza A subtypes, A(H3N2) and A(H1N1) have been commonly circulating in humans over the last 10 years [1]. Since 2009, a new strain of influenza A(H1N1) known as 2009 H1N1 or A(H1N1)pdm09 emerged which caused the 2009/2010 influenza pandemic [2]. Influenza B virus is not divided into subtypes, but since the 1970s has been diverged into two antigenically distinguishable lineages named B/Yamagata and B/Victoria [3].

One of the main characteristics of human influenza viruses is their ability to undergo antigenic mutations of two distinct types: a) antigenic drift, in which HA and NA gradually evolve and cause seasonal epidemics, and b) antigenic shift, in which influenza type A virus with a new gene segment(s) emerges and causes periodic pandemics [1].

In general, seasonal influenza viruses cause an acute respiratory disease with a short incubation period of 1 to 4 days (i.e. the infection usually starts 1 day before and infectiousness may last up to 3 days after symptom onset) with longer episodes if followed by a secondary bacterial infection or exacerbations of underlying disease. Typically, influenza infection starts with sudden onset of fever accompanied by systematic symptoms such as headache, myalgia and malaise as well as respiratory symptoms such as cough and sore throat [1]. Although, influenza infection occurs in all age groups, elderly people and people with chronic medical conditions are at higher risk of influenza and influenza-associated complications such as hospitalization and death [4,5].

Seasonal influenza vaccination

According to the World Health Organization (WHO), annual vaccination of high-risk populations (i.e. pregnant women, elderly, children aged 6-59 months,

individuals with specific chronic medical conditions and health-care workers) is the main strategy to prevent influenza and its severe complications [6]. Currently, trivalent inactivated influenza vaccines (TIV) containing two influenza A subtypes A(H1N1) and A(H3N2) and one influenza B virus (Victoria or Yamagata lineage) are commonly used worldwide.

Due to the changing nature of influenza viruses, influenza vaccine viral components should be updated annually. Therefore, twice a year WHO organizes consultations with an advisory group of experts to analyze the influenza surveillance and the antigenic characteristics data of circulating viruses in order to issue recommendation on the composition of the influenza vaccine for the following influenza season. These annual recommendations of the vaccine composition are then being released in February and September for the Northern and Southern hemispheres, respectively [7].

Since the influenza vaccine compositions are reformulated every year, influenza vaccine effectiveness (IVE), the ability of the vaccine to protect against influenza and influenza-related complications in a "real-world" situation, should be monitored annually. Additionally, IVE varies from season to season depending on multiple factors such as similarity between vaccine strains and the circulating viruses (also referred to as vaccine match) and individual characteristics of the vaccinated groups according to age and presence or absence of chronic medical conditions.

In order to monitor and estimate IVE for every influenza season, accurate and affordable observational assessment methods are required. Although conducting an experimental randomized (placebo-) controlled trial (RCT) is a preferable strategy, implementation of the RCT to assess IVE annually would be very costly and impractical. Furthermore, since the vaccination of high-risk populations such as elderly people is widely recommended, conducting RCT among these populations in many countries is not ethical [8]. Therefore, observational study designs, i.e. (variations on) cohort and case-control designs provide the main body of evidence on the IVE. Using these observational study designs a wide range of clinical outcomes such as influenza-like illness (ILI) as a less sever influenza-related complication to death as the most severe one could be monitored. In both retrospective and prospective cohort study designs, vaccinated and non-vaccinated individuals are followed up and incidence of influenza-related complications in

the vaccinated and non-vaccinated groups are compared. In a case-control study design, the prevalence of vaccination among cases and controls is compared.

Influenza vaccine effectiveness: an ongoing controversy

The largest and well-designed RCT study conducted by Govaert and colleagues showed 50% (95% CI 35–61%) efficacy for the inactivated influenza vaccine against serological influenza among elderly population during the influenza season 1991-1992 [9]. Importantly, in the same study after stratifying by age, influenza vaccine efficacy reduced to 23% (95% CI -51-61%) among the subgroup of persons aged 70 years or older, although power was low and 95% confidence intervals were largely overlapping [9]. The observed reduction in the influenza vaccine efficacy could in part be explained by immune senescence which is a decline in immune responsiveness with advancing age [10, 11].

As mentioned earlier, due to the scarcity of RCTs, observational studies play an important role in addressing seasonal IVE. However, since these studies are susceptible to different sources of biases, notably bias by differences in risk profiles between vaccinated and non-vaccinated persons, estimated IVE from such studies should be interpreted cautiously. Several studies gave evidence for presence of confounding bias in the cohort studies conducted between 1980 and 2001 assessing IVE against all-cause mortality among the elderly population [12,13]. It has been shown that estimated IVE against all-cause mortality in these cohort studies was highly overestimated due to the presence of confounding by indication or healthy user effect [14]. These results indicated that healthy older adults are more likely to be vaccinated and therefore have a different prognosis factors compared to the non-vaccinated frail elderly.

This problem was also highlighted in the 2010 Cochrane systematic review [15]. According to this review, due to the high level of heterogeneity between studies and likely presence of bias, drawing a clear conclusion about IVE among elderly population was stated to be implausible [5]. Furthermore, in the 2011 meta-analysis conducted by Osterholm et al., due to the lack of statistical power, pooled IVE against laboratory-confirmed influenza among elderly aged 65 years or older could not be estimated [16].

Multiple factors could contribute to the ongoing uncertainty about the IVE among community-dwelling elderly. Firstly, in most of the conducted cohort or case-control studies and meta-analyses based on such studies assessing IVE among community-dwelling elderly, the IVE estimates mainly pertained to non-specific endpoints, hospitalization and all-cause mortality, and not to specific laboratory-confirmed influenza outcomes. Therefore, the protective effect of influenza vaccination could be under(over)estimated. Secondly, variations between observational studies included in the meta-analyses could lead to high level of heterogeneity. For instance, differences between studies with regard to the target population (i.e. individuals aged 60 years or above, or 65 years or above etc.), inclusion and exclusion criteria, definition of influenza cases, and conducted statistical analyses could partly explain the high level of heterogeneity. Thirdly, pooling the estimates from the included studies in the meta-analysis without addressing the potential biases and adjusting for them could exacerbate the problem. In fact, more methodological challenges arise in meta-analysis of observational studies since treatment effects derived from such studies are more prone to bias [17,18]. Finally, in addition to variations in study design and statistical methods that are being used to estimate IVE, the unique year-to-year changing characteristics of the circulating influenza viruses make estimation of IVE challenging. For instance, several studies have shown that IVE differs per virus (sub)type/lineage and could vary depending on the circulating predominant virus(s) [19,20].

Thesis objectives

The general objective of this thesis is to provide more accurate estimates of IVE, particularly among the high-risk group of elderly population. In order to fill the essential gaps in the current scientific knowledge, in this thesis results from a number of novel systematic reviews and meta-analyses, a simulation study, and test-negative design case-control studies are presented and discussed.

Thesis outline

In **chapter 2** we present the results from two meta-analyses assessing IVE against laboratory-confirmed influenza, influenza-like illness, hospitalization from influenza and/or pneumonia and all-cause mortality among community-dwelling elderly. In this chapter, we first present results from a conventional meta-analysis of cohort studies. We then provide a novel bias-adjusted meta-analysis of the same studies. Finally we compare the performance of the two meta-analyses and discuss their advantages and disadvantages. In **Chapter 3** we elaborate on test-negative design case-control studies (TND) as a new and accurate observational study design to estimate IVE. In this chapter we present results from an aggregated-data meta-analysis of TND studies assessing IVE against laboratory-confirmed influenza among community-dwelling elderly. Additionally in this chapter we describe the applied generalized linear mixed model (GLMM), which is specifically adapted for TND studies. **Chapter 4** presents a simulation study which aims to compare the performance of the GLMM used in the aggregated-data meta-analyses with conventional meta-analysis methods such as DerSimonian and Laird random effects model and suggest the best method which could be applied to pool the estimates from TND studies. In **Chapter 5** we describe the results from an individual participant data meta-analysis of TND studies. In this chapter we present IVE estimates adjusted for the potential confounders i.e. age, gender, chronic medical condition, and smoking status. Additionally, we provide separate IVE estimates among the elderly sub-populations who suffer from respiratory disease, cardiovascular diseases, and diabetes. In **Chapter 6** we aim at estimating IVE over 11 influenza seasons, 2003/04 through 2013/14, using the Dutch Sentinel Practices of NIVEL Primary Care Database in the Netherlands. We further discuss the effect of circulating influenza virus type, subtype and lineages on IVE. In **Chapter 7** we provide evidence that depending on the type of control group which is used in TND studies, IVE estimates could vary. Additionally in this chapter we discuss the potential biases that could partially contribute to this variation. Finally, in **Chapter 8** we summarize the main findings of this thesis, discuss them in more details and provide suggestions for future research.

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