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An ecological study on influenza vaccination coverage and mortality in Europe

More uncertainty than certainty

- Bachelor Thesis -

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Your time is limited, so don't waste it living someone else's life. Don't be trapped by dogma — which is living with the results of other people's thinking. Don't let the noise of others' opinions drown out your own inner voice. And most important, have the courage to follow your heart and intuition. They somehow already know what you truly want to become. Everything else is secondary.

Steve Jobs (1955-2011), former CEO of Apple Inc.

Abstract

Background: Influenza viruses have been a threat to global public health for centuries. Millions of individuals are believed to suffer from influenza infection annually, of whom 250 000 to 500 000 die from the disease. Influenza is a vaccine preventable disease. Vaccination is recommended primarily in elderly individuals, despite great uncertainty of the benefits this prevention approach provides.

Study aim: The aim of this study is to analyze, if there is an association between influenza vaccination coverage rate (IVC) in the high-risk population ≥ 65 years old and mortality from all causes as well as influenza specific mortality in the elderly aged ≥ 65 years.

Methods: The study has an ecologic study design. It is based on annual national data from the European Union's statistical statistic office Eurostat and from the Organization for Economic Co-operation and Development. A descriptive data analysis was performed and correlations between IVC and mortality rates were assessed. Analyses were carried out on national-level and on above national-level.

Results: The study included nine European countries. Mortality rates from all causes as well as from influenza varied by country. IVC also differed in between countries. The majority of analyses on national-level resulted in a negative correlation between both variables, with a wide range in strengths of the association. Analyses above national-level showed a medium strong negative correlation for IVC and deaths from all causes, and correlations for the endpoint deaths from influenza were weak and did not indicate a generalizable direction of correlation.

Final statement: This study adds further uncertainty to the primarily vaccination of elderly individuals against influenza. It is strictly recommended to create an evidence base for influenza prevention with more powerful study designs and methods.

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Abbreviations

CI	Confidence Interval
EC	European Council of Ministers
EEA	European Economic Area
EEC	European Economic Community
HDI	Human Development Index
HMO	Health Maintenance Organization
IVC	Influenza vaccination coverage rate
OECD	Organization for Economic Co-operation and Development
OR	Odds-ratio
P&I	Pneumonia and Influenza
rho	Spearman's rank correlation coefficient
RR	Relative risk
UIIP	Universal influenza immunization program
U.S.A.	United States of America
WHO	World Health Organization

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1. Introduction

For centuries, influenza virus has been a threat to global public health (1). Every year, we can observe how the virus travels around the globe, causing seasonal epidemics, and sometimes even pandemics in the global population (2). Even though influenza is a vaccine preventable disease, it still causes viral infections in millions of people and deaths in hundreds of thousands of them each year (3). Thus, there has to be some kind of deficiency in dealing with this potentially lethal disease. Questions, which public health authorities should take into consideration are: Is the vaccine effective enough? Is the vaccination coverage rate in the population sufficient? Are we vaccinating the right individuals?

Immunization is probably one of the most effective interventions in preventive medicine. The World Health Organization (WHO) recommends annual influenza vaccination in nursing home residents, elderly individuals, individuals with chronic diseases, pregnant women, health care workers, individuals with essential functions in society, and children from the age of 6 month to 2 years (4). In other words, individuals who are most likely to experience a severe disease, and have the highest risk of death, should be vaccinated on annual basis, or in a pandemic situation prior to the rest of the population (3; 5).
In 2003, the World Health Assembly announced that an influenza vaccination coverage (IVC) of 75% in high-risk groups, should be achieved by 2010 (6). This objective was highlighted once more in a position paper from 2005 (6). In October 2009, the European Council of Ministers (EC) adopted this objective, and set the deadline for achievement to 2014/2015 (7).

Multiple studies have reported, that large-scale influenza vaccination programs in high-risk groups as well as in groups who are believed to be a major distributor of the virus throughout the community, could effectively lower the negative impact influenza has on public health (8; 9; 10; 11; 12; 13).

According to my current knowledge, the association of IVC and mortality on population level in Europe, is widely unknown.
Therefore, the aim of this study is to analyze, if there is an association between IVC in the high-risk population ≥ 65 years old and mortality from all causes as well as influenza specific mortality in the elderly aged ≥ 65 years.

The analysis is based on aggregate data from Eurostat and the Organization for Economical Co-operation and Development (OECD). Data, which political decisions are not uncommonly based on, despite their countless limitations.

2. Scientific Background

2.1. Influenza

Influenza is a viral respiratory disease, which is easily spread from human to human (3). Almost every region of the world is affected by influenza, whereas in temperate climates, influenza epidemics occur annually with peaks during the colder seasons of the year (3). Children are probably infected first, and afterwards spread the virus to the rest of the population (14). Even though influenza is preventable by vaccination, seasonal influenza epidemics are estimated to result in about three to five million individuals with severe illness, and about 250,000 to 500,000 deaths per year (3).

2.1.1. Influenza virus

There are three known subtypes of influenza viruses: type A, type B, and type C (15), whereby type A is likely to cause severe disease, and has pandemic potential (16).

Influenza viruses are distinguished by subtype, and appearance of their surface proteins hemagglutinin (HA) and neuraminidase (NA).

The surface protein HA plays a central role in the spread, and prevention of influenza. Immune systems are able to remember the appearance of a HA, and thereby protect individuals effectively against reinfection (2).

The problem is that replications of virions are often not very accurate, so HA and NA constantly change a little, which is called "antigenic drift" (15). The "antigenic drift" in HA however, allows influenza viruses to infect individuals multiple times because their immune system does not recognize the mutated HA protein (2).

Influenza type A viruses circulate in humans, swine, domestic poultry, migrating water birds, horses and other animals (15), though migrating water birds are believed to be the natural reservoir for influenza type A viruses (17).

The mutations, influenza viruses constantly go through, cause seasonal influenza epidemics, elevate the risk of influenza pandemics, and represent a potential threat to public health (3).

2.1.2. Epidemiology

In the past one hundred years, four influenza pandemics were documented. In 1918, the first pandemic of the last century occurred, caused by an influenza A(H1N1) virus which is known as "the mother of all pandemics" or "Spanish flu" pandemic (18). In 1957, a second pandemic occurred, known as the "Asian" influenza pandemic, caused by an influenza type A(H2N2) virus (19). In 1968, a third influenza pandemic occurred, known as the "Hong Kong"

influenza pandemic, caused by an influenza type A(H3N2) virus (16). In 2009, the latest influenza pandemic erupted, and is known as the "swine flu" pandemic, caused by an influenza A(H1N1) virus (20). All influenza pandemics were different in concern of virus structure, time, geography, epidemiology, and disease severity (16; 21).

Influenza affects all age groups (22). Generally, incidence rates are highest in children, and disease severity, hospitalizations as well as mortality are highest in the elderly (22).
Seasonal influenza outbreaks are subject to annual differences (22). They vary mainly in incidence, geographic distribution, disease severity, and dominant virus type (23). Incidence rates do not only vary in magnitude, they can also differ by gender and age annually (24). It is believed that young individuals are affected first, and then spread the virus to the rest of the population (14). Surveillance data for the 2009 A(H1N1) pandemic shows some resemblance in concern of age (20). At the beginning of the pandemic, the European Early Warning Response System (EWRS) collected case-based reports from 28 EU/EEA countries from 19 April 2009 (first validated case) to week 39/2009 (20). During that period 11,275 cases were reported of whom 99.4% or 11,207 were tested positive for pandemic A(H1N1)v (20). Years of age in the 11,207 laboratory-confirmed cases ranged from 0 to 90 years with a median age of 19 years (20). In this study population, 78% (n=11,207) of the cases were 30 years or younger, whereby 46.5% (n=11,207) were school-aged children from 5 to 19 years (20). Considering all cases, there were no differences in gender observable, but in younger individuals males were affected 20% more than females (20). The overall pandemic period lasted from week 18/2009 to week 35/2010, in which 925 861 cases of influenza-like-illness (ILI), and 7 202 014 cases of acute respiratory illness were reported by 27 countries in the European Union / European Economic Area (EU/EEA) (20).

Influenza incidence rates are subject to seasonal variations, whereby incidence rates are usually highest during the colder months of the year, and lowest during the warmer (22). Thus, in the northern hemisphere an increase in reported influenza cases can be observed from November to April, and in the southern hemisphere from May to September (22). In tropical regions such as the Philippines, Taiwan, or Thailand, circulation of influenza viruses is present throughout the whole year (22).

Influenza is a global disease, and therefore can be found in almost every place in the world, only at different times of the year (22). Antigenic and genetic analyzes of HA from A(H3N2) epidemics between 2002 and 2007 show, that annual differences in the HA protein seem to originate in East and Southeast Asia (25). High frequency of air travel as well as international

commerce from Asia to Europe, North America, and Australia, is hypothesized to enable the virus to spread to the rest of the world (25). In general, an epidemic virus strain is believed to emerge somewhere in East or Southeast Asia, and afterwards spreads to Europe, North America, and Australia (25). South America is affected sometime later probably because of limited direct travel from Asia (25).

Probably the most important factor for the severity of an influenza season is mutation of influenza viruses. An unfortunate mutation can provoke high attack and mortality rates across the world, due to low population immunity and ineffective vaccines.

2.1.3. Transmission

Influenza is transmitted via droplet infection from human to human (26). Infected individuals secrete viral particles through their respiratory tract, and while sneezing or coughing viral droplets become airborne (2; 26). Airborne droplets are absorbed by mucous membrane of one's mouth, nose, or lower respiratory tract, and can cause disease in susceptible individuals (2).

Overcrowded places, especially indoors, can lead to high attack rates in a short time, when there are a lot of non-immune individuals around an infected one (26).

Transmission by indirect contact via surfaces is also possible. Individuals' hands might come into contact with a contaminated surface, whereby these can become contaminated as well (2). As soon as they touch their face, virus material is enabled to reach mucous membrane, where it can cause disease (2).

2.1.4. Clinical aspects

Symptoms, incubation, and infectious period may vary by age, virus type, and individual features.

The incubation period of influenza is relatively short. In general, individuals develop symptoms in between 7 to 67 hours after infection (26). Median incubation time is longer for influenza type A with 34 hours, compared to type B with only 14 hours (26). In infected individuals, virus excretion is already present 24 hours before onset of symptoms, and therefore, they can infect others before even knowing that they are infected themselves (26). After 7 days virus excretion reduces to a minimum in adults (26). This might not be the case in children. In children, virus excretion can last up to 15 days, even when no clinical illness is present anymore (27).

Influenza infections are characterized by a sudden onset of high fever, shivers, and weaknesses (28). Individuals can experience multiple other symptoms, such as headache,

myalgia, anorexia, and diverse respiratory symptoms (28). Duration of disease takes mostly 2 to 7 days after onset of symptoms (26). A lot of complications during disease progression can arise. Patients can suffer from viral pneumonia, secondary bacterial pneumonia, myocarditis, encephalitis, or toxic shock syndrome (28). At highest risk for these complication are individuals with chronic medical conditions, for instance respiratory or cardiovascular diseases, and children <2 years old. Immunosuppressed patients, smokers, or pregnant women are also vulnerable groups for complications (26).
Virus type and strain also seem to play an important role for the clinical presentation of influenza patients. Influenza type A(H3N2) infections were reported to be clinically more severe than A(H1N1) and influenza B infections (8).

2.1.5. Influenza prevention

Influenza is a vaccine preventable disease, though vaccines are not 100% effective, and effectiveness is influenced by multiple factors.
WHO recommends annually influenza vaccination in nursing home residents, elderly individuals, individuals with chronic diseases, pregnant women, health care workers, individuals with essential functions in society, and children from the age of 6 month to 2 years (4). In other words, individuals who are most likely to experience a severe disease, and have the highest risk of death should be vaccinated every year, or in a pandemic situation prior to the rest of the population (3; 5).

In 2003, the World Health Assembly instructed all WHO member states with influenza vaccination recommendations in place, to achieve an influenza vaccination coverage of 75% in high-risk groups by 2010 (6). In 2005, WHO published a position paper on influenza vaccination, emphasizing their recommendations once again (6).
In October 2009, the European Council of Ministers finally adopted these recommendations, and advised their member states to reach a vaccination coverage of 75% not later than 2014 to 2015 (7). The adoption may be regarded as a reaction to the 2009 A(H1N1) pandemic.

A study group, of the Vaccine European New Integrated Collaboration Effort (VENICE) project, compared vaccine policies in the EU/EEA (29). In 2007, recommendations for influenza vaccination were present in all 27 EU member states (29). Nevertheless, recommendations varied by country. Austria and Estonia were the only countries, which recommended vaccination in all age groups (29). Slovakia recommended vaccination in individuals younger than 18 years, in addition to the elderly (29). All countries recommended vaccination in the elderly, with some age differences, for instance Germany recommends

vaccination in individuals 60 years and older, but France only in those 65 years and older (29). Despite Finland, no other country has included routine influenza vaccination for young children, though some recommend a vaccination (29). Vaccination of health care workers in stationary settings was recommended in 23 out of 27 countries, and in ambulatory settings in 22 out of 27 countries (29).

WHOs' recommendations, which are followed by a lot of countries, are based on the classic high-risk approach in preventive medicine. The high-risk approach aims at preventing individuals from a certain disease, who have the highest risk for medical complications, such as death (30). Individuals, who are at risk of developing a disease, but do not have a high-risk for severe outcomes, are not targeted by and do not benefit from this prevention approach (30). The opposite would be a preventive approach, which targets the whole population. Hereby, the whole population could benefit from a prevention program (30). In the case of influenza vaccination, high IVC in the whole population might protect unvaccinated individuals against infection as well, and limit the spread of influenza viruses.

Vaccination can be regarded as one of the most effective ways to prevent communicable diseases, as long as vaccine effectiveness is sufficient. In the case of influenza, vaccine effectiveness varies by virus strains included in the serum, age, and individual health conditions (31).
Every year, a new influenza vaccine is produced because of genetic and antigenic variations in circulating influenza viruses (32). Virologic surveillance is performed by WHO's Global Influenza Surveillance and Response System (GISRS), in collaboration with laboratories from around the world, to determine, which influenza virus subtypes and strains are circulating in the population (33). Based on GISRS's surveillance data, the Strategic Advisory Group of Experts on Immunization (SAGE), also run by WHO, publishes recommendations on composition of the annual influenza vaccine (34).

Another systematic review, reported vaccine effectiveness in nursing home facilities to be 23% against influenza-like illness (95% CI: 6%-36%), when vaccine was matched well to circulating virus strain (35). In community dwelling elderly, the study found no significant differences in effectiveness of protection against influenza (RR 0.19, CI: 0.02-2.01), influenza-like illness (RR 1.05, CI: 0.58-1.89), and pneumonia (RR 0.88, CI: 0.64-1.20) (35). A study from the Netherlands estimated vaccine effectiveness in individuals with high-risk medical conditions (36). The authors reported that 43% of GP visits (95% CI: 10%-64%) due to influenza, pneumonia, acute exacerbation of chronic lung disease, or acute otitis media had

been prevented in vaccinated high-risk children (36). Furthermore, in high-risk middle-aged individuals, 87% of hospitalizations (95% CI: 39%-97%), and 26% of GP consultations (95% CI: 7%-47%) had been prevented due to vaccination (36). Estimations for the elderly pointed out that 48% of hospitalizations (95% CI: 7%-71%), and 7% of GP visits (95% CI: 11%-23%) had been prevented in vaccinated individuals (36).

Age, and individual immunocompetence seem to play an important role in vaccine effectiveness. Nevertheless, it is not possible to find consistency in medical literature on effectiveness of influenza vaccinations.

A placebo controlled randomized trial reported that adverse effects after vaccination were present, but not severe (37). Out of 3 783 individuals, who received an influenza vaccination, 66% reported an adverse effect, whereby 44% of the 3 828, who received placebo, also reported an adverse effect ($p < 0.0001$) (37). In the active group, 51% reported pain or soreness at the injection site, compared to 14% in the placebo group, after solicitation (37). Overall, incidence of adverse effects was a little higher in the active group than in the placebo group, and was mostly caused by injection (37). The study showed that more severe adverse effects due to influenza vaccination are rare (37).

The current influenza prevention approach does not pursue the target to protect whole populations from the burden of influenza, it just aims at reducing severe outcomes in some individuals.
Despite some extremely limited behavioral measures, neuraminidase inhibitors could probably reduce the spread of influenza in a severe outbreak situation. This might work for a few days, until they are depleted (16).
Afterwards, the "ultima ratio" is closure of public infrastructure and quarantine of infected individuals to prevent further infections.

2.2. Influenza mortality

The severest complication of an influenza infection is death. WHO estimates that about 250,000 to 500,000 people die each year as a result of influenza infection (3).

The actual burden of influenza on mortality is not clearly identifiable. Influenza cases often die of secondary infection like pneumonia or of an underlying chronic medical condition, which is worsen by influenza infection (38). Death certificates mostly include only the clinical cause of death, for instance pneumonia or cardiac arrest, not what factor led to these complications, additionally influenza infections are rarely laboratory confirmed (39). A study

conducted in the United Kingdom after the 2009 A(H1N1) pandemic showed that the majority of deaths, with laboratory confirmed pandemic A(H1N1), suffered of a chronic medical condition in advance (38). Chronic neurological diseases, immunosuppression, chronic respiratory diseases, and heart diseases were marked on death certificates as a risk factor in the majority of all deaths (38). Comparison of the 2009 pandemic with data from past seasonal epidemics could not reveal a difference in distribution of risk factors among deceased persons (38). A possible explanation could be that influenza infection triggers an inflammatory process, which precipitates already present medical conditions (40).
Furthermore, influenza might be a trigger for acute myocardial infarction and cardiovascular death, as reported by systematic review, which compared 48 studies of different nature, published between 1932 and 2008 (41). A recently published study also provides evidence that influenza outbreaks are associated with an increase in hospitalizations and deaths from ischemic heart diseases (42). The study population consisted of all residence 50 years or older in the state of Maryland U.S.A., between 2001 and 2008 (42).

In general, newborns and seniors are at greatest risk of death during seasonal influenza epidemics, probably because newborns do not have enough immunocompetence yet, and elderly are more likely to have chronic medical conditions. Nevertheless, severe influenza epidemics or pandemics seem to cause an age shift towards younger individuals in the matter of death (40). A study, which analyzed the three influenza type A pandemics of the 20th century, showed remarkable differences in terms of age specific mortality (43). During all three pandemics, 1918/19 (A(H1N1)), 1957/57 (A(H2N2)), and 1968/69 (A(H3N2)), excess deaths in individuals <65 years old were proportionally very high, and leveled off steadily in post pandemic seasons (43). Furthermore, a UK study group showed that the majority of reported influenza deaths, during the 2009 A(H1N1) pandemic in the UK, were young and middle-aged adults with chronic medical conditions (38).

Predominant virus strain, also seems to contribute to the severity of an influenza season. The CDC estimated deaths associated with seasonal influenza in the US, between 1976 and 2007 (44). Estimations were calculated for deaths caused by pneumonia and influenza as well as respiratory and circulatory causes (44). For both endpoints, average mortality rates were 2.7 times higher during the 22 A(H3N2) seasons compared to the 9 none A(H3N2) (44).

In countries with temperate climates, death rates from all causes are highest during the colder seasons of the year (40). This excess in all-cause mortality has been suggested to be mainly

due to circulating influenza viruses, though there are also others, who oppose this hypothesis (40; 45).

Dushoff et. al. tried to estimate the burden of influenza on mortality in the United States from 1979 to 2001, with an annualized regression model (46). Results of this study pointed out that an average of 41 400 deaths per year (95% CI: 27 100 - 55 700), can be attributed to influenza (46). A study, conducted by Reichert et. al., assessed the winter increase in mortality in the United States, with standardized time series models from 1959 to 1999 (40). They created models for different mortality endpoints: all-causes, influenza and pneumonia, ischemic heart disease, cerebrovascular diseases, and diabetes (40). Mortality peaks for ischemic heart disease, cerebrovascular diseases, and diabetes were observed to be the same as for influenza and pneumonia mortality in about 85% of compared seasons (40). In seasons were mortality peaks differed, influenza and pneumonia mortality peaked about one month later than heart and cerebrovascular diseases, and diabetes (40). The authors hypothesized, that this is what can be expected when deaths are attributable to a single cause, because deaths from influenza and pneumonia are often delayed, but deaths due to vascular diseases occur immediately (40). Based on findings of this study, the authors assumed that influenza is causing the excess of mortality during the colder seasons of the year in the U.S.A. (40).

2.3. Influenza vaccination and mortality

The benefits of influenza vaccination are uncertain in concern of mortality, even though the actual goal of vaccination, is to prevent complications from influenza infection in high-risk groups. The current prevention approach in most European countries does not aim at reducing influenza associated morbidity in the whole population, it aims solely at protecting the most fragile from severe outcomes (47).

In 2007, a study was published which included 18 cohorts of community dwelling elderly, who were members of one U.S. health maintenance organization (HMO) (48). The Authors analyzed 10 influenza seasons, 1990/1991 to 1999/2000, and for the seasons 1997/1998 to 1999/2000, they also analyzed data from two other U.S. HMOs (48). The analysis included 298 623 unvaccinated individuals 65 years or older, and 415 249 vaccinated individuals 65 years or older (48). Logistic regression showed, when seasonal vaccine was matched poorly to circulating viruses, vaccination reduced the chance of death by 37% (OR 0.63, CI: 0.57-0.69), and in seasons for which the vaccine was matched well, the reduction was 52% (OR: 0.48, CI 0.46-0.51) (48).

Based on data of 33 influenza seasons in the U.S., the excess in all-cause mortality from December to March was about 5% on average, and in none of the examined seasons above 10% (49). Thus, it seems utopian to believe that influenza vaccination could reduce the risk of death from all-causes by 52% during influenza season. The only explanation is that either study is over- or underestimating the effects.

A study conducted by Simonson et. al. analyzed vaccination coverage in conjunction with excess pneumonia and influenza (P&I) as well as excess all-cause mortality for the years 1968 to 1999 (50). The authors reported that from the mid 1980s onwards, a steady increase in excess P&I mortality in individuals 65 years and older was observed, even though vaccination coverage increased from about 15% to 65% in those years (50). After adjusting their 3-year moving average for age and including only 18 A(H3N2) seasons, this increasing trend in excess mortality was gone (50). In an age-adjusted model for individuals 65 to 74 years old, excess P&I mortality rates reduced by 70% till about 1985, and remained steady afterwards (50). For individuals 85 years and older, the age-adjusted 3-year moving average showed a minimal reduction up to the 1980s, and remained steady afterwards (50).

Findings of cohort studies which show that influenza vaccination could reduce around 50% of the winter mortality in the U.S., seem to be affected by serious selection bias and confounding (51). Selection bias is induced into observational studies by disregard of the differences in individual health status inside the elderly population (52; 53).

A study showed that IVC in the medically unstable elderly population might not be as high as in the elderly population with stable health (54). The authors analyzed, whether the recommendation to vaccinate elderly hospitalized patients against influenza as well as pneumococci were implemented into practice (54). They included 41 488 discharged patients, who were U.S. Medicare members and aged 65 years or older, between October 1, 1998 and December 31, 1998 (54). Weighted proportions of patients vaccinated against influenza were 31.1% (95% CI: 30.7-31.6) prior to hospital admission, 1.5% (95% CI: 1.4-1.7) during admission, and 10.1% (95% CI: 10.3-10.9) after discharge, resulting in an overall weighted vaccination coverage rate of 42.7% (95% CI: 42.2-43.2) for this high risk population (54).

The most fragile elderly have a higher risk of death compared to their peers, due to unstable medical conditions. The risk is even elevated further, by missing influenza immunization. These differences, inside the elderly population, can serve as a confounding factor, and cause overestimation of vaccine effectiveness in observational studies (52). Further, an unspecific

endpoint, such as all-cause mortality, can amplify the overestimation of vaccine effectiveness (51).

Another critical point in the analysis of mortality benefits from influenza vaccination seems to be time (52). Jackson et. al. showed that vaccine effectiveness among vaccinated was highest before the actual beginning of seasonal influenza epidemics, and declined during as well as after the season (52). They studied 75 527 community dwelling seniors aged 65 and older, from the U.S. HMO cohort database (52). The study period ranged from September 1, 1995 to August 31, 2003, whereby beginning and end of influenza seasons were determined by national surveillance data (52). Primary endpoints were all-cause mortality, and hospitalization with a discharge diagnosis of P&I (52). Age, and sex adjusted relative risk for all-cause mortality in vaccinated seniors compared to unvaccinated was 0.39 (95% CI: 0.33-0.47) before influenza season, 0.56 (95% CI: 0.52-0.61) during the season, and 0.74 (95% CI: 0.67-0.80) after the season, across all study years (52). Corresponding relative risks for P&I hospitalization were 0.72 (95 % CI: 0.59-0.89), 0.82 (95 % CI: 0.75-0.89), and 0.95 (95 % CI: 0.85-1.07) (52). Additional adjustment for documented diseases in the 12 month prior to seasonal epidemics, reduced relative risks in all groups slightly (52). A secondary endpoint was hospitalization from injury or trauma, and influenza vaccination even had a preventive effect on these conditions (52). Corresponding RRs were 0.67 (95 % CI: 0.55-0.82) for before, 0.88 (95 % CI: 0.79-0.96) for during, and 0.85 (95 % CI: 0.77-0.94) for after the season (52). The study results show that influenza immunization seems to prevent severe outcomes at best before the seasonal epidemic has started, and reduces the risk for non-influenza associated hospitalizations (52). Jackson et. al. concluded that their data showed, how findings from observational studies are the result of bias, due to differences between vaccinated and unvaccinated individuals (52). Further, Jackson et. al. made an assumption on how findings without bias in a cohort study might be like. They assumed that influenza vaccination has 58% effectiveness in protecting against influenza infection, and that 10% of all winter deaths can be attributed to influenza. This would result in a reduction of 5.8% in all-cause mortality during influenza virus circulation, with a corresponding relative risk of about 0.94 (52).

2.4. Experiences from influenza prevention programs

In 1957, Japan was severely affected by the Asian influenza pandemic, which caused broad school closures, and attack rates of up to 60% in the population (19). After the pandemic, Japanese officials decided that schoolchildren should be vaccinated prior to the usual groups,

because they were the ones who spread influenza to the rest of the population (13). In 1977, the Japanese government made it obligatory for school-aged children to be vaccinated against influenza (13). Vaccination coverage among schoolchildren substantially increased, reaching up to 80% towards the mid-1980s (13). Public protest against vaccination grew, and effectiveness of the program was questioned (13). In 1987, it was permitted to refuse vaccination, which lead to a drop in administered influenza vaccines of about 50% between 1987 and 1990 (13). The Japanese government revoked the law in 1994, and distribution of vaccines became minimal (13).

There are multiple studies which tried to evaluate the Japanese mass vaccination program (8; 11; 13). Reichert et. al. compared excess deaths from all-causes, and excess P&I deaths in Japan with data from the U.S.A., between 1949 and 1998 (13). In Japan, the 5-year moving average of excess deaths decreased by about 50%, from 1962 to 1972. In the years 1972 to 1987, another decrease of 40% was achieved, after which rates were almost similar to those for the U.S. (13). Excess death rates for the U.S. did not change much during the study period (13). From 1987 onwards, excess death rates started to increase again, reaching the level observed before 1962 by 1994 (13). Reichert et. al. observed a reduction of 10 000 to 12 000 deaths attributable to P&I, and 37 000 to 49 000 deaths from all-causes annually, during the time the obligatory vaccination law was in place (13). They hypothesized that high vaccination rates among schoolchildren created a herd immunity for the elderly population (13).

A different study limited the analysis to excess P&I deaths in Japanese and U.S. seniors 65 years or older between 1978 and 2006 (8). The authors compared mortality pattern as the vaccination law was in place from 1978 to 1994, with the time after its repeal from 1995 to 2006 (8). Mortality data for U.S. seniors showed no differences before, and after 1994 (8). In Japanese seniors however, excess P&I deaths were elevated by 113% or 93 after the vaccination program was discontinued ($p<0.04$) (8). In comparison to the U.S., excess P&I mortality was lower in Japan ($p=0.001$) during mass vaccination of schoolchildren, and afterwards adapted to the level observed in the U.S. ($p=0.18$) (8). A negative binominal regression model was created, with adjustment for time period, predominant influenza subtype, and age (8). The model estimated a RR of 0.64 (95% CI: 0.49-0.83) for excess P&I deaths in Japanese seniors before discontinuation of schoolchildren vaccination (8). The RR of 0.64 corresponds to a prevention of 7.5 influenza-associated deaths per 100 000 (95% CI: 2.8-14.4) (8). No disparities between before and after 1994 were observed by applying the

same model to the U.S. population (8). These results indicate that high IVC in school-aged children, may reduce influenza-related deaths in the elderly population.

Another interesting influenza prevention program was carried out in the Canadian province of Ontario (10). In October 2000, the government of Ontario started its universal influenza immunization program (UIIP) which made a free influenza vaccination possible for every individual older than 6 month (10). Vaccinations were performed in physician offices, hospitals, schools, workplaces, pharmacies, community centers and shopping malls (10). For promotion of the free influenza vaccine, large-scale media campaigns were initiated to raise awareness, and compliance in the population (10). Kwong et. al. evaluated the consequences of the UIIP on population level (10). The study included hospitalizations, emergency department and physician office visits due to P&I, and all-cause mortality from August 1997 to August 2004 (10). Vaccination coverage was acquired from the National Population Health Survey 1996/1997, and the Canadian Community Health survey 2000/2001, 2003, and 2005, with response rates from 79% to 85% (10). Expected events for these influenza-related outcomes were assessed by Poisson regression, and afterwards compared to the observed events when the UIIP was in place (10). Data from Ontario, was compared to data from 9 other Canadian provinces, where the regular high-risk approach was in place for influenza prevention (10).

Overall IVC in Ontario was reported to be 18% (95% CI: 18%-19%) and 13% (95% CI: 12%-13%) for the other provinces, before the UIIP began (10). After the UIIP had been implemented, mean vaccination coverage in Ontario was 38% (95% CI: 37%-38%) and 24% (95% CI: 24%-24%) in the other provinces (10). In the elderly aged 65 and older, mean vaccination coverage ranged from 71% to 81% in Ontario and from 59% to 72% in the other provinces (10). Surprisingly, the percentage increase in vaccination status in the elderly was higher in the other provinces than in Ontario, but across all age groups, vaccination coverage was always highest in Ontario during the whole study period (10).

Statistical analysis showed an overall reduction of 74% (RR=0.26, 95% CI: 0.20-0.34) of influenza associated mortality for Ontario and 57% (RR=0.43, 95% CI: 0.37-0.50) for the other provinces, after the UIIP had been implemented (10). However, stratification for age pointed out, that the larger mortality benefits for Ontario were only statistical significant for individuals aged 85 or older (10). Regarding the whole population, the magnitude of all endpoints reduced more in Ontario than in other provinces (10). Nevertheless, age-specific analyses indicated that young and middle-aged individuals benefitted mostly from the UIIP,

and greater vaccine uptake in the elderly did not reduce influenza associated healthcare use or mortality in this population (10).
The authors concluded, that universal influenza immunization probably has more beneficial effects regarding the entire population than the high-risk approach currently in place in most countries (10).

In 1998, an influenza prevention program was initiated in Sao Paulo, Brazil (9). The public health program provided free influenza vaccination in public primary care facilities for all individuals aged 65 years and up, over a two week period prior to influenza season (9). In addition, the program was accompanied by large-scale media campaigns to raise public attention (9). Ferreira Antunes et. al. tried to assess the program's impact on influenza related mortality, by comparing P&I mortality data before implementation of the program from 1993 to 1997 with the period after onset of the program from 1998 to 2002 (9). They also analyzed socioeconomic differences, by assessing mortality on district level in combination with the human development index (HDI) as well as other measurements (9). Vaccination coverage in the elderly is believed to have been about 63% after 1998 (9). The authors estimated a reduction of 26.3% in P&I mortality after implementation of the vaccination program, which is equivalent to 1 341 prevented deaths in 5 years (9). Interestingly, districts with higher mortality levels prior to the intervention showed a higher reduction during intervention, and a lower HDI was correlated with a higher decrease in mortality (Spearman’s correlation coefficient = -0.32) (9). This study indicates that mass vaccination programs could have a positive effect on public health, and might help to reduce health inequalities (9).

3. Aim and study question

The aim of this study is to analyze, if there is an association between IVC in the high-risk population ≥ 65 years old and mortality from all causes as well as influenza specific mortality in the elderly aged ≥ 65 years.

4. Methods

For analysis of the study question, an ecological study design was chosen to evaluate the association between IVC and mortality on population level. The study focused solely on European countries. Influenza vaccination is generally recommended for individuals ≥ 65 years old, therefore solely the elderly population aged ≥ 65 years was included in this study. A second inclusion criteria for a country was data availability. For each country, annual

mortality data had to be available at least from 2005 to 2009, and annual IVC had to be available at least from 2004 to 2009. Percentage of population vaccinated against influenza was selected to be the independent variable, and deaths per 100 000 inhabitants was selected to be the dependent variable.

Data for statistical analyses were extracted from Eurostat, the statistical office of the EU and from the OECD. Eurostat served as the data source for mortality data, because all member states of the EU and European Economic Community (EEC) submit annual public health data to Eurostat, data can be found at (55; 56). Submission is based on a gentleman's agreement, which was established in the framework Eurostat's Working Group on "Public Health Statistics". As a data source for influenza vaccination coverage rates, the OECDs' key tables on health were used. All European countries, which were included in this study, had to be OECD member states, because no other data source on influenza vaccination coverage in such abundance was accessible.

Mortality data was expressed as standardized number of deaths per 100 000 inhabitants. Eurostat standardizes submitted numbers of deaths from EU/EEC member states for age. For the standardization procedure, the European standard population (defined by WHO) is used to calculate an age-specific death rate per 100 000 inhabitants. For the statistical analyses of this study, data for all causes of deaths (defined by the International Statistical Classification of Diseases and Related Health Problems (ICD) codes A00-Y89 excluding S00-T98) were extracted from Eurostat's database for each country and year. Deaths from all causes is a relatively unspecific endpoint to measure the probable impact of a vaccination against one disease. Thus, in addition to all causes of deaths, influenza specific deaths (defined by ICD codes J10_J11) were also extracted from the database. Data for causes of deaths were available till 2010.
Influenza vaccination coverage rates were expressed as percentage of the population ≥ 65 years old who received an annual influenza vaccination. The OECD calculates influenza vaccination coverage rates on basis of different data sources and programs from their member states. The final IVC in percent is calculated by number of persons ≥ 65 years old who received an annual vaccination, divided by the total number of inhabitants ≥ 65 years old. Data on influenza vaccination coverage was available from 2004 to 2011.

The study protocol involved no modification of the extracted data from Eurostat and the OECD. Mortality data was already standardized for differences in age distributions between countries, and given as a rate per 100 000 inhabitants, which accounts for differences in

population size. IVCs were available in percent, which is suitable to describe the distribution of a factor inside a population.

After data extraction from both online databanks, a spreadsheet was compiled in Microsoft Excel, which was used for data analysis and visual illustration of the study results.

For all bivariate analyses, vaccination data of a given year was analyzed in conjunction with mortality data of the following year, because vaccination against influenza is carried out regularly in the fall, and infection rates start to peak from January onwards. Comparison of IVC and mortality rates of the same year would disregard the seasonality of seasonal influenza. In other words, for analysis of the influenza season 2004/05, IVCs from 2004 and death rates from 2005 were used. European states only report annual mortality data to Eurostat.

All analyses were conducted separately for each country. For assessment of the relationship between IVC and mortality on a higher population level, all analyses were also carried out for an above national-level by combining data from all countries together. This higher level of aggregation was referred to as an annual European-level or above national-level. European-level did not refer to an actual level for all European countries, the term was just used for the purpose of simplicity.

At first, a descriptive data analysis was conducted by calculation of median values for both variables, and their corresponding 25th as well as 75th percentile, over the whole study period. Additionally, medians and percentiles were calculated across all countries for each year, which represented the European-level. A similar approach was used for the bivariate data analysis. Scatter plots were generated, whereby the x-axis represented the independent variable (IVC), and the y-axis represented the dependant variable (standardized deaths per 100 000 inhabitants). Scatter plots were created for each country, to assess the effect of IVC on mortality across the study period on national-level. Additionally, annual scatter plots combining all countries together were generated, to assess the effects on above national-level or European-level.

For estimation of the statistical relationship between both variables, non-parametric Spearman's rank correlation (rho) was chosen. This seemed to be the most suitable statistical test for not normally distributed aggregate data, which was used in this study (57). For each scatter plot, a corresponding rank correlation coefficient was calculated. A correlation coefficient between 0 and -1 indicated a negative correlation between the two variables, a correlation coefficient between 0 and 1 indicated a positive correlation, and a correlation

coefficient close to 0, in either direction, indicated that there was no correlation present. At last, essential study results were summarized in Figures and Tables.

5. Results

The analysis included nine European countries, which met the inclusion criteria: the Kingdom of Denmark (DEN), the Republic of Finland (FIN), the French Republic (FRA), the Republic of Ireland (IRE), the Grand of Duchy Luxembourg (LUX), the Netherlands (NLD), the Portuguese Republic (POR), the Kingdom of Spain (ESP), and the United Kingdom (GBR).

5.1. Descriptive analysis

5.1.1. National-level

Descriptive analysis pointed out differences between countries and years in standardized annual death rates for elderly individuals aged ≥ 65 years (**Table 1**).

Across the whole study period, the highest amount of deaths observed, was 4 623 per 100 000 (DEN 2004), and the lowest amount was 3 026 per 100 000 (FRA 2010). Throughout all studied years, the highest mortality rate was seen in DEN (4 253/100 000 to 4 520/100 000), and the lowest in FRA (3 026/100 000 to 3 483/100 000).

From 2005 to 2010, a reduction in death rates was observed in 89% (N=9) or 8 of the countries included in this study. The only exception, which did not follow this continuous trend, was ESP, due to an elevation in death rate from 2006 to 2007. In 55% (N=9) or 5 countries, an increase in deaths per 100 000 was observed from 2004 to 2005, in contrast to the general trend from 2005 onwards. The increase in mortality, from 2004 to 2005, ranged between 0,3% or 12 deaths (LUX) and 3,7% or 130 deaths (POR).

Table 1: Deaths from all causes (Deaths) per 100 000 inhabitants ≥ 65 years old and influenza vaccination coverage in percent (IVC), by year and country

Country	2004		2005		2006		2007		2008		2009		2010	
	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC
DEN	4623	31	4520	34	4479	33	4401	40	4293	51	4253	51	n.r.	46
FIN	3969	56	3845	52	3787	46	3752	48	3647	51	3641	46	3626	39
FRA	3456	68	3483	68	3271	68	3171	69	3139	70	3081	71	3026	66
IRE	4426	61	4442	63	4405	61	4067	62	3957	70	3906	54	3669	64
LUX	3905	51	3917	54	3882	51	3975	53	3621	53	3560	53	3520	47
NLD	4266	73	4184	77	4056	75	3893	78	3839	77	3720	74	3694	n.a.
POR	4349	39	4510	42	4139	50	4121	51	4074	53	3970	52	3946	n.a.
ESP	3680	69	3738	70	3462	68	3491	62	3400	65	3317	66	3208	57
GBR	4310	71	4227	75	3988	75	3918	74	3882	75	3675	73	3626	70

*n.r.: not reported; n.a.: not assessed

Descriptive analysis of standardized reported influenza specific deaths per 100 000 individuals ≥ 65 years old per year, also indicated variations between countries and years (**Table 2**).

Influenza mortality rates showed a wide range from 0 per 100 000 (LUX, 2006 and 2009) to 10,9 per 100 000 (NLD, 2005). In 71% (N=7) or 5 out of 7 years included in this study, NLD reported the highest influenza death rate. LUX reported twice (2006 and 2009) an influenza mortality rate of 0 per 100 000 elderly inhabitants. No other country reached this low level in any given year. In 67% (N=9) or 6 countries a strong increase in influenza death rates was observed for 2005 in comparison to 2004. From 2004 to 2005, reported influenza mortality increased in POR by 1 200%, in FRA by 517%, and in NLD by 132%. In the same time period, reported influenza deaths decreased in IRE by 83% and in FIN by 28%. In 2005, IRE reported an influenza death rate of 0,1 per 100 000, which is the lowest countable rate in this dataset. Over the whole study period, influenza specific mortality in the elderly never fell below 0,6 per 100 000 in NLD, and in GBR it never exceeded 0,5 per 100 000. On country level, reported influenza death rates show no decreasing or increasing trend over the years studied, it is more or less an up and down. In ESP, IRE, and GBR a relatively stable sideways trend is visible.

Table 2: Deaths from influenza (Deaths) per 100 000 inhabitants ≥ 65 years old and influenza vaccination coverage in percent (IVC), by year and country

Country	2004		2005		2006		2007		2008		2009		2010*	
	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC	Deaths	IVC
DEN	4,6	31	3,8	34	2	33	2	40	0,5	51	1,9	51	n.r.	46
FIN	4,2	56	3	52	1,2	46	1,4	48	0,8	51	1,4	46	0,4	39
FRA	1,2	68	7,4	68	0,8	68	1,5	69	1,2	70	2,3	71	0,5	66
IRE	0,6	61	0,1	63	0,4	61	0,3	62	0,5	70	0,3	54	0,1	64
LUX	1,6	51	6,6	54	0	51	5,8	53	1,3	53	0	53	1,2	47
NLD	4,7	73	10,9	77	2,7	75	2,6	78	1,3	77	3,4	74	0,6	n.a.
POR	0,2	39	2,6	42	0,6	50	0,9	51	0,7	53	1,5	52	0,3	n.a.
ESP	1	69	5,7	70	0,5	68	0,7	62	0,8	65	0,8	66	0,2	57
GBR	0,2	71	0,3	75	0,1	75	0,2	74	0,2	75	0,5	73	0,2	70

*n.r.: not reported

*n.a.: not assessed

Descriptive analysis of influenza vaccination coverage in percent of the elderly population aged ≥ 65 years also pointed out inter-country and annual differences (**Table 1, 2**).

Influenza vaccination coverage ranged from 31% (DEN, 2004) to 78% (NLD, 2007) across the whole study period. GBR and NLD, or 22% (N=9) of the countries studied, maintained a vaccination coverage in seniors of ≥ 70% from 2004 to 2010. A coverage rate of ≥ 60% was

observed in 55% (N=9) or 6 of the countries analyzed between 2004 and 2009. A reduction in influenza vaccination coverage was observed in 71% (n=7) or 5 countries from 2009 to 2010, whereby FIN showed proportionally the highest reduction with about 15% (46% to 39%), and ESP had the highest crude reduction of 9% (66 to 57). From 2004 and 2008, vaccination coverage rates were relatively stable in 66% (N=9) or 6 countries with no trends observable. In contrast, POR and DEN showed a slightly increasing trend, and coverage rates for FIN represented a constant up and down over the years.

The influenza vaccination coverage in NLD and GBR is almost identical, but the amount of reported influenza deaths per 100 000 inhabitants ≥ 65 years old varies greatly in between both nations. For the time period studied, rates for deaths from all causes were observed to be highest in DEN, and vaccination coverage in the elderly population was observed to be relatively low compared to the other countries.

5.1.2. Above national-level / European-level

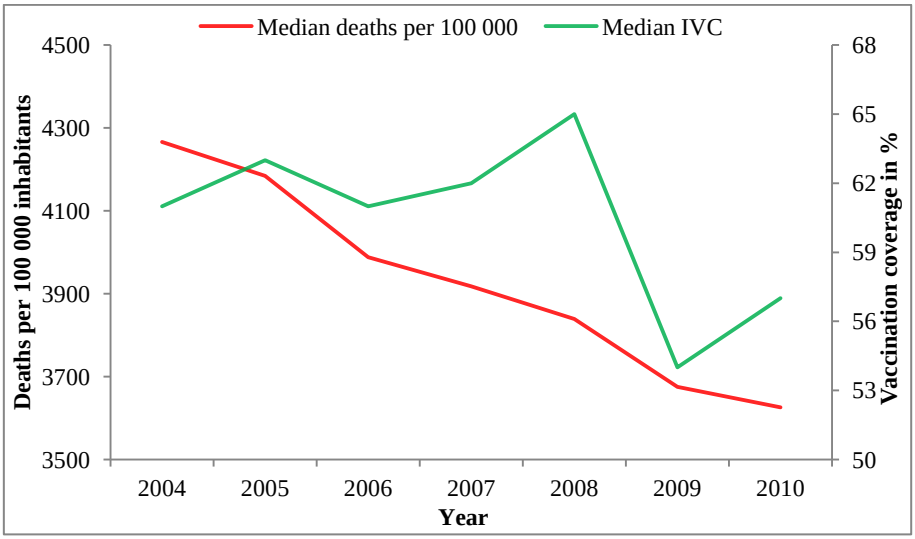
Considering combined data for all countries included in this study, median deaths per 100 000 inhabitants ≥ 65 years old showed a decreasing trend from 2004 to 2010 (**Table 3; Figure 1**). Median death rates decreased from year to year. Except from 2004 to 2005, 25th and 7th percentiles also decreased, undermining the observed trend in **Figure 1**. Between 2004 and 2005, the 25th percentile also showed a reduction, but this was not true for the 75th percentile . This indicates that not all countries shared the decreasing trend observed in median mortality rates. As described above, even 55% (N=9) of the nations studied did not share this trend from 2004 to 2005.

Table 3: Annual median deaths from all causes per 100 000 inhabitants ≥ 65 years old and annual median influenza vaccination coverage in the population ≥ 65 years old, across all countries per year

Year	Median deaths per 100 000 inhabitants ≥ 65 years old	Median vaccination coverage in % of population ≥ 65 years old
2004	4 266 (3 905; 4349)	61 (51; 69)
2005	4 184 (3 845; 4 442)	63 (52; 70)
2006	3 988 (3 787; 4 139)	61 (50; 68)
2007	3 918 (3 752; 4 067)	62 (51; 69)
2008	3 839 (3 621; 3 957)	65 (53; 70)
2009	3 675 (3 560; 3 906)	54 (52; 71)
2010*	3 626 (3 442; 3 675)	57 (46; 65)

*missing data for DEN, NLD, POR

Figure 1: **Annual median deaths from all causes per 100 000 inhabitants ≥ 65 years old and annual median influenza vaccination coverage in the population ≥ 65 years old, across all countries per year**



Median vaccination coverage the population aged ≥ 65 years, for all countries combined, did not show a clear trend over time (**Table 3; Figure 1**). From 2004 to 2007, a more or less sideways trend was observed in IVC, afterwards it decreased proportionally by 16% or 11% in crude rate, between 2008 and 2009. This decrease was only seen in median IVC, the 25th and 75th percentiles remained almost unchanged, indicating that still 50% of all countries had an IVC between 52% and 71%. After 2009, a slight upwards trend in median IVC was observed again, but this time the 25th and 75th percentiles showed a reduction, indicating that 50% or more countries had a decrease in IVC.

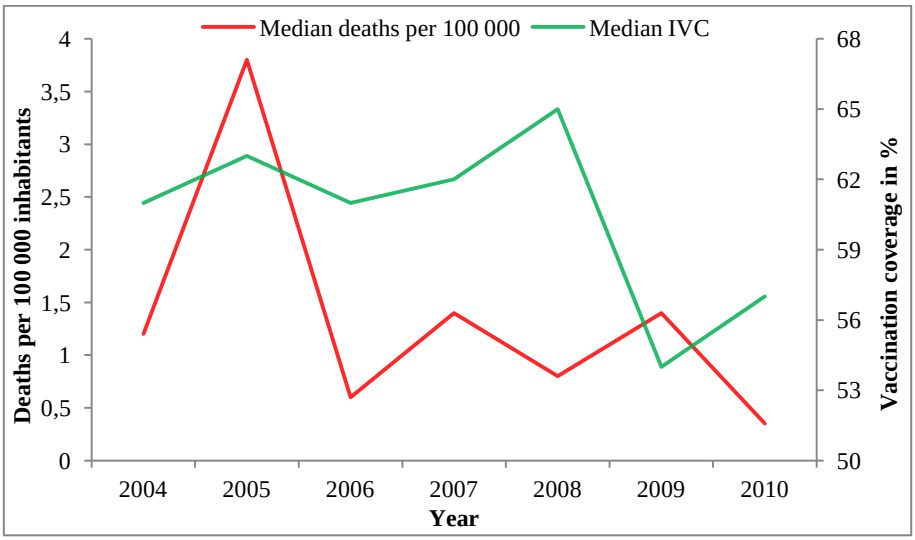
Combined data from all countries studied, showed no generalizable trend in reported influenza deaths per 100 000 inhabitants ≥ 65 years old (**Table 4; Figure 2**). The highest median mortality rate, in conjunction with the 25th and 75th percentile, was observed in 2005 (**Table 4**). This year also accounts for the highest peak in influenza death rates across the study period (**Figure 2**). Considering the whole study period, an up and down in median influenza death rates was observed. The lowest median influenza mortality rate was observed in 2010, which is also indicated by the 25th and 75 percentiles. The 25th and 75th percentiles for 2010, were both the lowest observed compared to all other years (25th: 0,2; 75th: 0,5). This indicated, that reported influenza deaths per 100 000 elderly inhabitants was lowest in at least 50% of the countries studied in 2010.

Table 4:Annual median deaths from influenza per 100 000 inhabitants ≥ 65 years old and annual median influenza vaccination coverage in the population ≥ 65 years old, across all countries per year

Year	Median influenza deaths per 100 000 inhabitants ≥ 65 years old	Median vaccination coverage in % of population ≥ 65 years old
2004	1,2 (0,6; 4,2)	61 (51; 69)
2005	3,8 (2,6; 6,6)	63 (52; 70)
2006	0,6 (0,4; 1,2)	61 (50; 68)
2007	1,4 (0,7; 2)	62 (51; 69)
2008	0,8 (0,5; 1,2)	65 (53; 70)
2009	1,4 (0,5; 1,9)	54 (52; 71)
2010*	0,4 (0,2; 0,5)	57 (46; 65)

*missing data for DEN, NLD, POR

Figure 2: **Annual median deaths from influenza per 100 000 inhabitants ≥ 65 years old and annual median influenza vaccination coverage in the population ≥ 65 years old, across all countries per year**



5.2. Bivariate analysis

For measurement of the statistical relationship between IVC and deaths from all causes, and influenza specific deaths, Spearman's rank correlation coefficients (rho) were calculated. In addition to the statistical approach, the relationship was analyzed visually in form of scatter plots. The analyses were carried out on country-level and on European-level, for which data from all countries was combined. Statistical results are displayed in tables and visual results are displayed in figures.

5.2.1. Country-level

Bivariate analysis resulted in different associations between IVC and deaths from all causes (**Table 5; Figure 3**).

Correlation coefficients indicated that the relationship between both variables differs by country (**Table 5**). A correlation coefficient can range between -1 and 1, this range was almost entirely covered in this analysis (-1 (POR) to 0,77 (FIN)). On country level, 56% (N=9) or 5 countries showed a distinct negative correlation between IVC and deaths from all causes, 22% or 2 countries showed almost no correlation, and 22% or 2 countries showed a distinct positive correlation.

Table 5: Spearman's rank correlation coefficient (rho) for influenza vaccination coverage in the population ≥ 65 years old and deaths from all causes per 100 000 inhabitants ≥ 65 years old, per country across all years

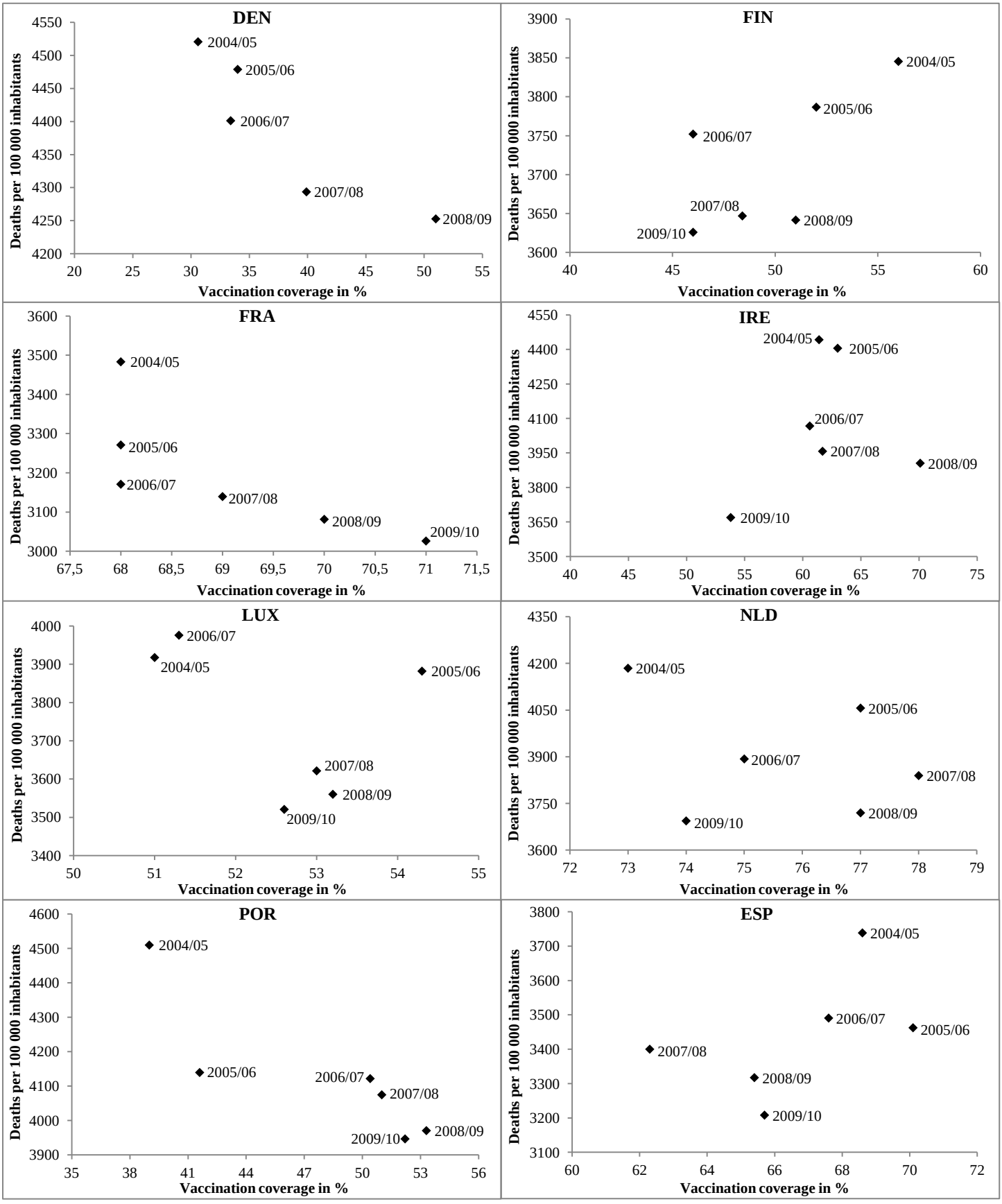
Country	rho
POR*	-1
DEN*	-0,9
FRA	-0,77
NLD*	-0,5
LUX	-0,43
GBR	-0,14
IRE	0,14
ESP	0,6
FIN	0,77

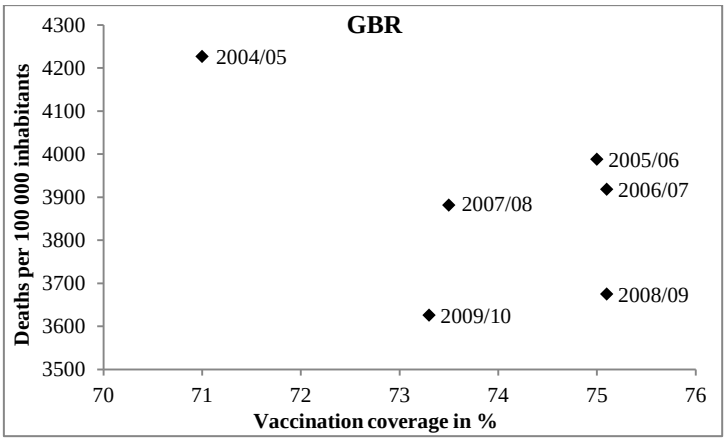
*missing data for 2010

The visual approach also illustrated that the association of IVC and deaths from all causes differs by country (**Figure 3**). In scatter plots for DEN and FRA, a negative correlation was observed, which indicated an almost linear relationship between both measurements. The plot for FIN showed exactly the opposite, it indicated a more or less positive linear correlation between IVC and deaths from all causes. In the diagram for ESP, also a negative correlation between both variables was visible, but here it illustrated more of a J-shape relationship than a linear. In visual analysis for IRE and NLD, no correlation between IVC and deaths from all causes was observable.

Overall, the visualized bivariate analysis did not show any generalizable pattern for the association of IVC and deaths from all causes (**Figure 3**). In every plot, there was always a point observed, which did not follow the overall relationship shown by the diagram, if one was shown.

Figure 3: Scatter plots for influenza vaccination coverage in the population ≥ 65 years old and deaths from all causes per 100 000 inhabitants ≥ 65 years old, per country across all years





Bivariate analysis of IVC and influenza specific deaths per 100 000 inhabitants ≥ 65 years old, resulted in different associations between both variables as well (**Table 6; Figure 4**).

The statistical analysis, for the endpoint of influenza specific mortality rates, showed a range of correlation coefficients from -0,89 (LUX) to 0,6 (FIN) (**Table 6**).

In 22% (N=9) or 2 countries a strong negative correlation between IVC and influenza death rate was observed, in 33% or 3 countries a weak negative correlation, in 22% or 2 countries a moderate positive correlation, in 11% or 1 country a weak positive correlation, and in 11% or 1 country almost no correlation was shown. This illustrates the differences in magnitude of the relationship between both variables and differences in direction of the correlation on country level. Overall, 55% or 5 countries showed a correlation coefficient between -0,3 and 0,3.

Table 6: Spearman's rank correlation coefficient (rho) for influenza vaccination coverage in the population ≥ 65 years old and deaths from influenza per 100 000 inhabitants ≥ 65 years old, per country across all years

Country	rho
LUX	-0,89
DEN*	-0,8
POR*	-0,26
NLD*	-0,2
ESP	-0,2
FRA	-0,14
GBR	0,26
IRE	0,49
FIN	0,6

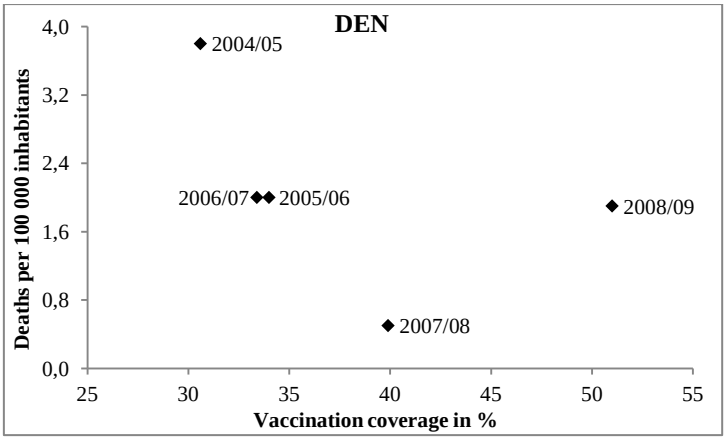
*missing data for 2010

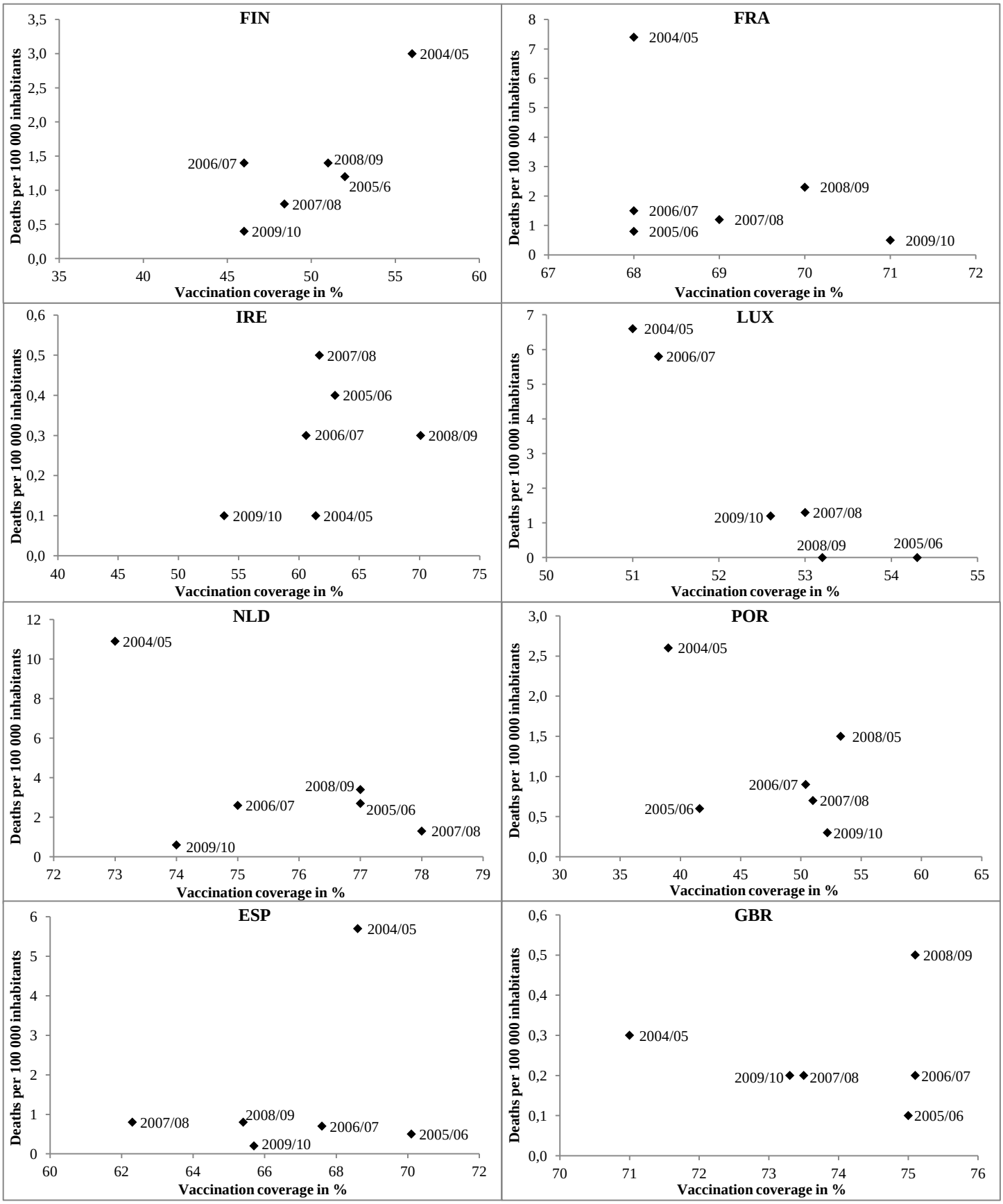
DEN and FIN were the only countries, for which correlation coefficients were almost similar for both outcome variables (**Table 6**). POR, which showed the strongest negative relationship between IVC and deaths from all causes, only showed a mild negative relationship for the

endpoint influenza specific deaths. FRA, for which a strong negative correlation was observed for the endpoint deaths from all causes, only showed a minimal negative correlation for the endpoint influenza deaths.

Visual bivariate analysis, of IVC in the elderly and influenza deaths per 100 000 elderly inhabitants, showed that the correlation between both variables differs by country (**Figure 4**). In the plots for FIN and IRE a strong positive correlation was observable, whereby in FIN the correlation seemed to be linear. The correlation coefficient did also indicate this positive relationship between IVC and influenza deaths (**Table 6**). Graphical illustration for LUX resulted in a strong negative correlation between both variables, this was also true for DEN, without consideration of an outlier (dot for 2008/09). Statistical results did also indicate the negative correlation for DEN and LUX (**Table 6**). In contrast, the correlation coefficient for GBR indicated a mild positive relationship, whereas visual analysis hinted a moderate negative correlation apart from one outlier (dot 2008/09) (**Table 6; Figure 4**). In the diagrams for FRA and NLD, it was not possible to observe, whether a negative, positive, or any relationship between IVC and influenza mortality was present. In almost all plots an outlier was present, which was observed to lie far away from all other points in the scatter plots. In 56% (N=9) or 5 of the countries the outlier represented the data for 2004/05, which showed a high influenza death rate in 2005, independent of IVC in the year before (Figure...). In the plots for DEN and GBR, one data point clearly did not follow the general relationship observed in the diagrams as well, in those cases, the point represented influenza mortality data for 2009 and IVC in 2008.

Figure 4: **Scatter plots for influenza vaccination coverage in the population ≥ 65 years old and deaths from influenza per 100 000 inhabitants ≥ 65 years old, per country across all years**




FIN
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2006/07
2008/09
2005/6
2007/08
2009/10
FRA
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2008/09
2006/07
2007/08
2005/06
2009/10
IRE
Deaths per 100 000 inhabitants
Vaccination coverage in %
2007/08
2005/06
2006/07
2008/09
2009/10
2004/05
LUX
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2006/07
2009/10
2007/08
2008/09
2005/06
NLD
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2008/09
2006/07
2005/06
2007/08
2009/10
POR
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2008/05
2006/07
2007/08
2005/06
2009/10
ESP
Deaths per 100 000 inhabitants
Vaccination coverage in %
2004/05
2007/08
2008/09
2006/07
2005/06
2009/10
GBR
Deaths per 100 000 inhabitants
Vaccination coverage in %
2008/09
2004/05
2009/10
2007/08
2006/07
2005/06

5.2.2. Above national-level / European-level

For assessment of the relationship between IVC and deaths from all causes as well as influenza specific deaths above nationa-level, data from all studied countries were combined. The statistical analysis was carried out by calculation of correlation coefficients for each year, and to visualize the relationship, scatter plots were generated.

The statistical analysis resulted in a range of correlation from -0,52 to -0,05 (**Table 7**). Correlation coefficients indicated a negative correlation between IVC and deaths from all causes per 100 000 elderly inhabitants aged ≥ 65 years from 2004/05 to 2007/08. From 2008/09 to 2009/10, which represented 33% (N=6) or 2 of the years analyzed, no correlation between both variables was observable anymore. A positive correlation coefficient was not shown in any year over the study period.

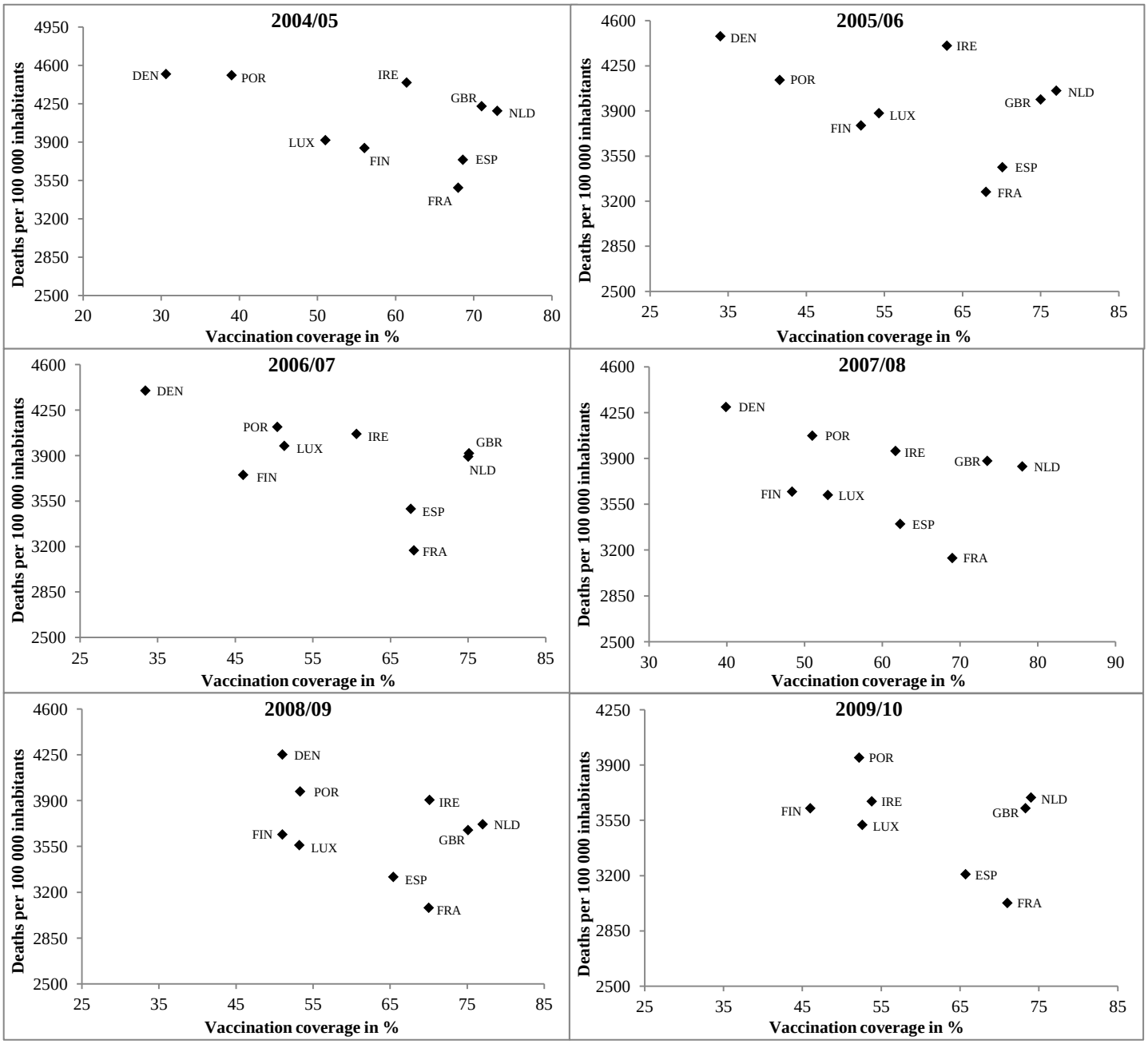
Table 7: Spearman's rank correlation coefficient (rho) for influenza vaccination coverage in the population ≥ 65 years old and deaths from all causes per 100 000 inhabitants ≥ 65 years old, across all countries per year

Year	rho
2004/05	-0,47
2005/06	-0,38
2006/07	-0,52
2007/08	-0,42
2008/09	-0,05
2009/10*	-0,05

* missing data DEN, NLD, POR

The visual analysis indicated a negative correlation between IVC and deaths from all causes (**Figure 5**). The negative relationship observable, between both variable, varied in magnitude from year to year. In the plot for 2007/08, a distinct negative correlation was shown, but this was not the case for 83% (N=6) or 5 of the other years studied. Except for 2007/08, there are always countries observable, which are not in line with the general relationship shown in the scatter plots. Data points for GBR, IRE, and NLD did not follow the general relationship, displayed by the rest of the countries, apart from the diagram for 2007/08. The correlations close to 0 for 2008/09 and 2009/10, shown by correlation coefficients, could not be observed in visual analysis (**Table 7; Figure 5**). For those two years, a negative relationship between IVC and mortality rate was observable in the visual analysis.

Figure 5: Scatter plots for influenza vaccination coverage in the population ≥ 65 years old and deaths from all causes per 100 000 inhabitants ≥ 65 years old, across all country per years



Results of the bivariate analysis for IVC and influenza specific death rates differed from those for mortality from all causes.

The statistical analysis showed a range of correlation coefficients from -0,28 to 0,25 (**Table 8**). The strongest negative correlation was calculated for 2006/07 and the strongest positive correlation for 2004/05. The years 2004/05 and 2006/07 were the only years, in which a moderate correlation was shown for IVC and deaths from influenza. In general, all years showed relatively weak correlation coefficients for the relationship between both variables.

Table 8: Spearman's rank correlation coefficient (rho) for influenza vaccination coverage in the population ≥ 65 years old and deaths from influenza per 100 000 inhabitants ≥ 65 years old, across all countries per year

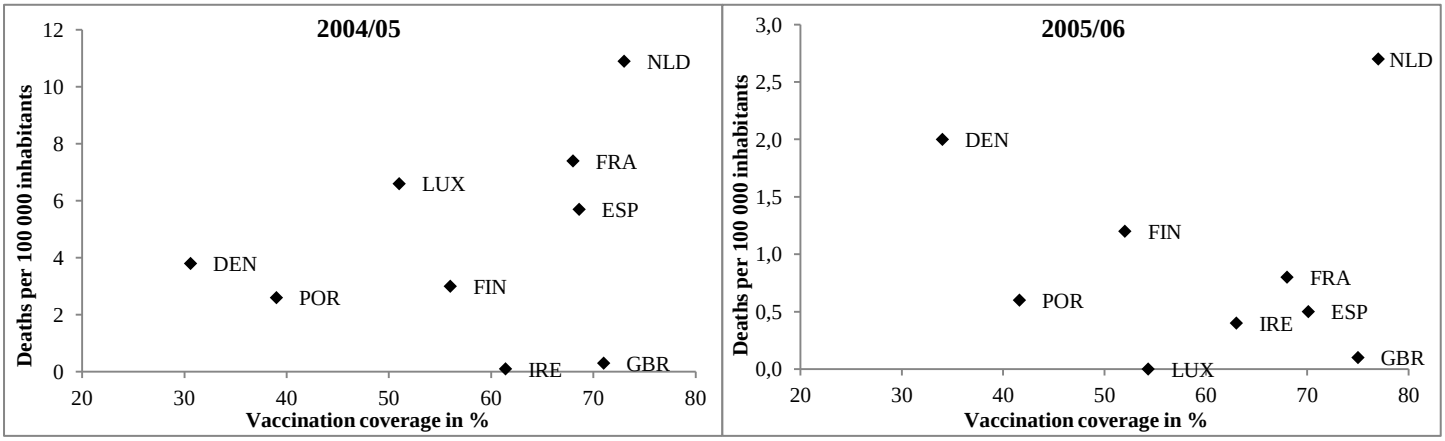
Year	rho
2004/5	0,25
2005/6	-0,1
2006/7	-0,28
2007/8	0,18
2008/9	0,13
2009/10*	0

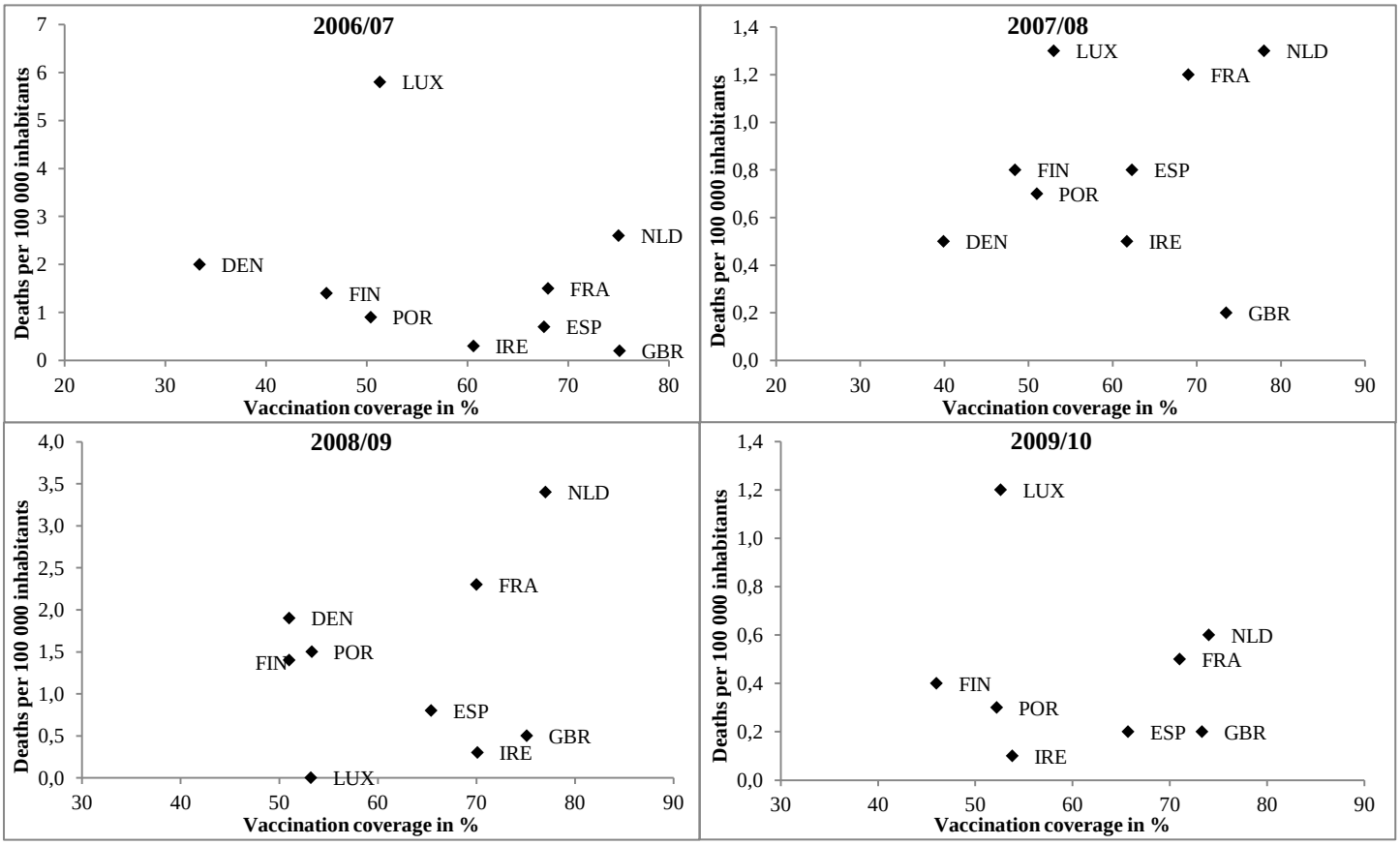
*missing data for DEN, NLD, POR

In 50% (N=6) or 3 of the studied years, almost no correlation between IVC and influenza mortality was indicated by the correlation coefficients. For 2009/10 the correlation coefficient was even 0. Without consideration of the magnitude of a correlation, for 50% (N=6) or 3 years a positive relationship, for 33% or 2 years a negative, and for 17% or 1 year no relationship at all was indicated between both measurements (**Table 8**).

Visual bivariate analysis of IVC and influenza specific mortality resulted in different relationships between both variables, and also in different observation than the correlation coefficients indicated (**Table 8; Figure 6**). For 50% (N=6) or 3 of the analyzed years, it was not observable, in which direction IVC and deaths from influenza might be correlated (**Figure 6**). The scatter plot for 2004/05 showed a slight positive relationship between both variables, whereby data points for GBR and IRE were not in line with this relationship. In the graphs for 2005/06 and 2008/09, a moderate negative correlation was observable, but also not all data points attributed to this relationship. In 2005/06 the data point for NLD was far away from all others, which indicated a negative correlation between both variable, and in 2008/09, it were data points for FRA and NLD, which did not follow the general relationship shown by the plot.

Figure 6: Scatter plots for influenza vaccination coverage in the population ≥ 65 years old and deaths from influenza per 100 000 inhabitants ≥ 65 years old, across all country per years





6. Discussion

6.1. Principal Findings

This study showed that deaths from all causes in the elderly population aged ≥ 65 years have been declining in nine European countries studied over time. Influenza specific deaths in the elderly were observed to decline and increase on annual basis. WHO's and EC's target, of an IVC of 75% or larger in the high-risk population of seniors ≥ 65 years old across Europe, has only been reached partly by GBR and NLD. Median IVC for nine European countries has been shown to decline rather than increase.

A negative correlation between IVC and deaths from all causes in the elderly was observed in the majority of times on national-level as well as on European-level. The correlation between IVC and influenza specific deaths was also observed to be negative in the majority of times on national-level, though the strength of the association was weaker, compared to deaths from all causes. On European-level, the direction of correlation between IVC and deaths from influenza remained uncertain.

6.2. Strengths and weaknesses of this study

The key strength of this study is its uniqueness, because based on personal research, no earlier study was found, which analyzed the relationship between IVC and mortality for multiple EU member states on national-level and above-level. Assessment of the effect on whole populations of a public health intervention, such as vaccination, is of great importance. By setting public health targets, like the target of a 75% IVC imposed by the EC in 2009, it is necessary to know, how this might influence the health of the EU's population. An additional strength of this study are its data sources. It is based on data from the European statistical office Eurostat and the OECD. The main function of Eurostat is "to provide the European Union with statistics at European level that enable comparisons between countries and regions", in other words, these are data used for central political decisions, which affect millions of people (58). One of OECD's main function is "drawing on facts and real-life experience, we recommend policies designed to make the lives of ordinary people better", by "facts" it can be implied that they mean their statistical database (59). Thus, all analyses in this study are based on data, which are commonly used for political decision making on highest level. A transparent analysis and critical questioning of the results can be regarded as a strength of this study.

Nevertheless, like every other study, this study also has a lot of weaknesses and limitations. The largest weakness of this is study lies in its study design. Ecologic studies are based on group characteristics, and not on individual characteristics. It is not assessable by any means, whether a vaccinated or unvaccinated individual died during the years studied. No individual data was included in the analysis. Data used in this study are aggregated on national-level, and only represent average values. As a result, this study does not allow conclusions to be drawn based on its results. Conclusions of any kind would probably represent an ecologic fallacy.

All analyses carried out in this study, solely included the two variables IVC and death rate. There was no multivariate analysis performed, which might have controlled for third variables influencing the association between IVC and mortality. There are multiple factors, which could have an influence on the association between both measurements included in this study. A few possible factors would be subsidy of influenza vaccination in a country, individual health conditions, vaccine match to predominant circulating virus strain.

Limitations also arise from both dependent variables. Deaths from all causes is an unspecific endpoint, because it includes almost all causes of deaths, except ICD-10 codes S00 to T98, which refer to "injury, poisoning and certain other consequences of external causes" (60).

Additionally, it has been documented that an unspecific endpoint, such as all-cause mortality, can amplify the overestimation of vaccine effectiveness (51). This probably what happened in all analysis for IVC and deaths from all causes. Even the dependent variable influenza specific deaths has enormous weakness. First of all, differences in influenza mortality rates shown in the descriptive analyses in **Table 1** are not plausible. NLD and GBR are both nations, which experience seasonal influenza outbreaks, have a high frequency of international travel, have reliable health systems, and have similar IVC rates. Thus, how can death rates from influenza be so different between those two nations. They are probably not, there are just differences in serological testing for influenza, differences in completion of death certificates, and differences in processing of the death certificates in national statistic offices (61). As a consequence, reported influenza specific deaths are presumably underestimated extensively. Other studies account for this underestimation by assessing the excess in all-cause mortality during influenza season, compared to a baseline value that would be expected without circulation of influenza viruses (44). This was not possible in this study, because countries only report annual mortality data to Eurostat, and not data on monthly or weekly bases.

In consideration of these major weaknesses, results of this study have to be interpreted with caution.

6.3. Relation of study results to previous studies

Comparison of the presented study results with other results from other studies, because no similar study was found.

Nevertheless, some of the strong negative correlations observed for the association between IVC and deaths from all causes (POR=-1, DEN=-0,9, FRA=-0,77) indicate that there is probably bias and/or confounding present. Based on findings from the U.S.A., influenza accounts for an average of 5% of all deaths during influenza season, thus such a strong correlation might not be true (49). In addition, it has been reported that findings of cohort studies, which estimated that influenza vaccination could result in a reduction of 50% in all-cause mortality during influenza season, seem to be affected by serious selection bias and confounding (51). As a consequence, this ecologic study might even be affected by additional bias and confounding, compared to the cohort studies conducted in the U.S.A., because there are no individual characteristics known.

Jackson et. al. proposed that a realistic finding in cohort studies would be a reduction of 5.8% for deaths from all causes during influenza season (52). Thus, a correlation coefficient would probably only show a weak to moderate negative relationship between IVC and all-cause

mortality. Surprisingly, it was shown in this study that IVC and influenza specific death rates have weak negative correlation in almost 50% (N=9) of the countries studied (**Table 6**). The results on above national-level in **Table 7** might overestimate the association between IVC and deaths from all causes as well from 2004/05 to 2007/08.

In consideration of a study, which showed that IVC in the medically unstable elderly population might not be as high as in the elderly population with stable health (54). NLD has a very high IVC compared to other countries, and has the highest influenza death rate from all countries in this study, so it could be believed that a similar situation is present in European countries. This raises the question, whether or not the current influenza prevention approach is sufficient.

6.4. .Meaning of the study results

The results of this study show that there probably is an association between IVC and deaths from all causes in the elderly. The problem is that on national-level a very large range of strengths of correlations was observed. Above national-level, for the first four years the strength of negative correlations was relatively stable in the medium range, and in the last two years of the study period, no correlation was observable any more. For IVC and influenza specific deaths, the relationship on national-level was almost similar to that for deaths from all causes, but above national-level it was very weak, without a distinct direction, and changing annually. Thus, any statement on strength of the association, would be pure speculation without any trustable data to support it.

The low level of IVC rates, in the actual target population for influenza prevention in multiple countries, should be alarming for physicians and public health professionals.

A positive result of this study is that death rates in the elderly population were observed to decline over the past years. Nevertheless, conducting reliable research with cause specific mortality for influenza across countries in the EU is not possible, due to probable underreporting of influenza specific deaths.

6.5. Unanswered questions and future research

Multiple questions remain unanswered. In the 2005 position paper, WHO stated that attack rates are highest in school-aged children, and that influenza imposes a substantial economical burden on societies, such as lost of productivity in educational or occupational settings, elevation of healthcare costs, and "social disruption" (6). Children two years or younger usually do not attend school, and seniors 65 years or older are mostly retired, thus it remains

unclear, how WHO's prevention approach is supposed to reduce these economical and social issues, which they are certainly aware of.

The true benefits of influenza vaccination in elderly individuals remain unclear, therefore additional research is necessary to evaluate the current influenza prevention approach. It is of great importance to know, how many deaths are actually caused by influenza each year. Further studies should be conducted, which try to analyze differences between elderly individuals who receive a vaccination and those who do not receive a vaccination, otherwise every study will have to deal with the issue of selection bias and confounding.

Finally, the issue of indirect benefits to the most fragile by vaccination of schoolchildren, has to be addressed by future prospective cohort studies.

7. Final statement

This study adds further uncertainty to the issue of primarily vaccinating elderly individuals against. Based on findings of this study, it is not possible to conclude, whether a high IVC is associated with reduced mortality in senior.

However, the results show that IVC needs to be increased in the elderly population, when the EC wants to achieve a 75% IVC across the EU until 2014/2015, especially because it has been shown that vaccination coverage decreased from 2009 to 2010 in 8 out of 9 nations.

A positive result is that death rates from all causes in individuals aged $\geq$ 65 years seem to be declining across all nine countries included in this study.

In consideration of previous research, it seems appropriate to ask the question: Are we doing enough to prevent the ancient public health problem influenza in the global population?

It is strictly recommended to create an evidence base for influenza prevention with more powerful study designs and methods, on which public health interventions can rely on.

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