The 2009 influenza pandemic in primary care. Clinical manifestations, attitudes and utilisation of services
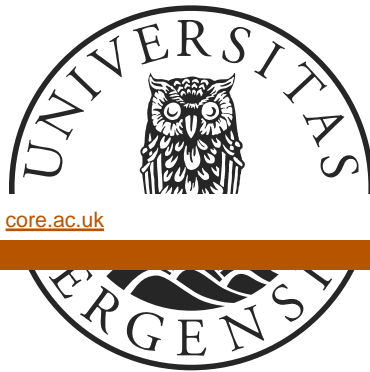
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"Running is one of the best solutions to clear the mind."

Sasha Azevedo

Acknowledgements

Introduction

Influenza viruses cause annual epidemics throughout the world and the majority of deaths are seen in the elderly and in those with pre-existing chronic conditions. Pandemics are characterised by a high attack rate, high virulence and by major changes in the genetic material of the virus so that a large percentage of the population will have no pre-existing immunity to the virus (Abramson 2011).

In the summer of 2009 it was clear that the novel influenza A/H1N1 virus spread rapidly between people. The immunity of the world's population was small and the risk of a pandemic was great. Norway had already experienced its first imported cases of the novel influenza virus, but so far below the epidemic threshold level.

As of September 2009, it appeared that the infectivity was great, but the illness in most cases relatively mild. However, cases of severe outcome in young, otherwise healthy people, as well as in pregnant women were reported, in addition to the usual risk groups with chronic illness (Dawood 2009, Jamieson 2009). Older people over 65 who are otherwise particularly susceptible to complications associated with influenza, appeared to be more protected (Dominguez-Cherit 2009, Louie 2009). The consequences in terms of morbidity and mortality of the new virus were unknown at this time, and there was a great need for more knowledge about the clinical course of the disease.

As part of preparations for a possible pandemic, mass vaccination of the entire Norwegian population was planned. There had been some discussion in the public about the appropriateness and potential risks of such a strategy. We wanted to explore opinions about risks and preventive measures among patients attending general practice with influenza.

Influenza epidemics put pressure on the primary care system. The regular GP scheme allows GPs to have very good overview of the chronically ill in their population. This means that Norwegian general practice would be an excellent "laboratory" for studying the disease and its consequences.

Abbreviations

BMI	Body mass index
GP	General practitioner
HA	Haemagglutinin
HELFO	Norwegian Health Economics Administration
ICPC-2	International Classification of Primary Care, second edition
ILI	Influenza-like illness
KUHR	Control and Payment of Reimbursement to Health Service Providers database (Kontroll og utbetaling av helserefusjon)
NA	Neuraminidase
OOH services	Out-of-hours services
RT-PCR	Reverse transcriptase polymerase chain reaction
WHO	World Health Organization

Abstract

Background: Primary care plays a major role in the response to a pandemic. The objectives of this thesis were to investigate the outbreak of the 2009 influenza pandemic from a primary care perspective with focus on clinical manifestations, behavioural measures and utilisation of services.

Methods: Cross-sectional questionnaire and clinical observational data from patients in general practice diagnosed with influenza-like illness, and nationwide registry-based studies based on claims data from general practice and out-of-hours services in Norway.

Results: Pandemic influenza in general practice was characterised by symptoms of fever, fatigue, cough and headache of 1 week duration. Hospitalisation was reported in 0.6% of cases and oseltamivir treatment in 39% of cases, but antiviral treatment did not affect the duration of illness. Women reported better adherence to personal protective measures and were more concerned about the side effects of the pandemic vaccine then men. The majority of influenza-like illness consultations took place in general practice as compared to out-of-hours services, however there was a 5.5-fold increase of influenza-like illness consultations in the out-of-hours services during the 2009 pandemic season in comparison to the 2008-9 season. General practice increased its capacity in response to the increased patient surge. Young age was associated with attending out-of-hours services for influenza-like illness as compared to attending the general practitioner. Pregnancy, diabetes and chronic lung disease were significant risk conditions for attending out-of-hours services among patients with influenza-like-illness during the pandemic. Contrary to this, having consultations with the general practitioner before the pandemic was associated with relatively lower use of out-of-hours services in the pandemic period.

List of publications

I. Simonsen KA, Hunskaar S, Wensaas KA, Rørtveit S, Cox R, Njolstad G, Rortveit G. Influenza-like illness in Norway: clinical course, attitudes towards vaccination and preventive measures during the 2009 pandemic. Fam Pract 2012;29:139-46.

II. Simonsen KA, Hunskaar S, Sandvik H, Rortveit G. Capacity and adaptations of general practice during an influenza pandemic. Plos One 2013;8:e69408.

III. Simonsen KA, Hunskaar S, Sandvik H, Rortveit G. Primary care utilisation among patients with influenza during the 2009 pandemic. Does risk for severe influenza disease or prior contact with the general practitioner have any influence? Fam Pract 2014;doi: 10.1093/fampra/cmu072.

Contents

1. Background

1.1 Influenza pandemics in history

> *I incline to the belief that influenza is not infectious but due to some impurity, probably chemical, in the air, which appears to affect the nervous system most powerfully (...) but the whole question of the etiology of influenza and the mode in which it spreads is still a mystery, and we can only hope some light may ere long illumine the darkness that enshrouds it.* (Nicholson 1891)

Influenza epidemics have been documented by written sources for several hundred years, but there are written reports on possible influenza dating back to 412 BC (Potter 2001). Pandemics occur at an interval of 10 to 50 years and arise when a novel avian influenza heamagglutinin (HA) or/and neuraminidase (NA) mixes through reassortment with pre-existing human influenza viruses or by an avian virus that adapt to effective human transmission. It is believed that pigs can serve as mixing vessels as they have receptors for both human and avian viruses in their epithelial cells (Peiris 2009). Three influenza pandemics were recognised in the 20th century: in 1918–19, 1957 and 1968. The H1N1 influenza pandemic in 1918-19, also called the "Spanish flu" had a fatality rate of 2-3%, and caused between 40 and 50 millions deaths due to the high number of infected (Potter 2001). Nearly half of influenza-related deaths during the Spanish flu were in age group 20-40 years and among otherwise healthy individuals (Simonsen 1998). The reason for the high mortality in the young is not fully understood. The shift in mortality rates towards younger age in pandemics compared to seasonal epidemics is suggested to be due to exposure to related viruses in previous pandemics thus sparing those at older age (Miller 2009). It is estimated that up to 50% of the world's population was infected during the "Spanish flu" (Potter 2001). The "Asian flu" in 1957-58 was of H2N2 subtype, and mostly affecting children. A fatality rate at <0.2% (1-4 million deaths) has been calculated. However, elevated mortality rates in children did not occur (Webster 2013). The pandemic in 1968-69, the "Hong Kong flu" was of H3N2 subtype and affected all age groups (WHO 2011a). The 1968 pandemic was relatively mild probably due to pre-existing antibodies of the H2N2 seasonal strain that gave some protection in the elderly

(Webster 2013). The re-emergence of the A(HIN1) virus in 1977 to cause the "Russian flu", has not been considered to be a true pandemic, as the virus probably was introduced to the population from a laboratory stock (Webster 2013).

1.2 Influenza viruses

There are three types of influenza virus: A, B and C. They all belong to the *Orthomyxoviridae* family of viruses. Influenza C rarely causes disease in man. Influenza A and B are considered to be the major human pathogens responsible for seasonal influenza. While type B causes occasional outbreaks and seasonal epidemics, type A is the only type of virus associated with pandemic influenza. Influenza virus A is the most important of all influenza types and it is found in a large range of animal species (birds, pigs, horses, mink, seals, whales). The type A is divided into several subtypes based on the properties of the surface proteins HA and NA. The HA is responsible for binding and entry into host epithelial cells while the NA is involved in the process of new viral particles budding out of host cells. Birds form the natural reservoir for all known influenza A subtypes (Abramson 2011).

There are 18 HA subtypes and 11 NA subtypes known to date (Freidl 2014). Only H1, H2 and H3 heamagglutinins and N1 and N2 neuraminidases subtypes are known to have caused pandemic human disease. Avian subtypes H5, H7 and H9 can sporadically infect humans and cause disease (Broberg 2014, Freidl 2014, Van-Tam 2009). The HA and NA surface proteins are genetically unstable and cause changes in the virus over time.

"Antigentic drift" is the term used to describe point mutations that lead to small variations in the HA and NA proteins. Antigenic drift results in sporadic outbreaks and seasonal epidemics due to partial escape in host immunity. The HA and NA proteins are closely related to previous circulating seasonal influenza virus, but as the surface proteins change slightly over time by antigenic drift previously acquired immunity does not work, making the population more prone to infection; hence the need for updating the influenza vaccine at a yearly basis (Temte 2010). "Antigenic shift" is

used to describe recombinant genetic changes in the surface proteins HA and NA that lead to production of a new strain, i.e. a new genetic variant of the virus. Antigenic shifts cause more widespread epidemics and pandemics due to lack of immunity in a large percentage of the population (Abramson 2011).

Influenza viruses spread by droplets from the airways of an infected individual, but there is also evidence that influenza can spread by contact with body fluids such as blood, faeces and vomit or by touching contaminated surfaces (Arena 2012, Webster 2013). The incubation period from infection to first appearance of symptoms varies from 1-4 days. The illness usually lasts less then one week. Children are more likely to transmit the virus due to higher levels of virus load in their respiratory tract and lower adherence to personal hygienic measures. Also, they are often in crowded kindergartens and schools that make the transmissibility easier. The virulence is highest during the febrile phase of disease and subsides steadily over 5-7 days (longer in children). Most cases of influenza are self-limited and patients normally recover without sequelae. Complications, such as pneumonia, bronchitis, otitis media and other secondary bacterial infections are more common in people with underlying co-morbidity, in children and among the elderly (Meier 2000, Webster 2013).

1.2.1 Epidemiology

The virologic basis for recurrent epidemics is a continual process of antigenic drift among circulating influenza viruses occurring annually in temperate regions (Simonsen 1998). Usually one influenza A virus (H1N1 or H3N2 since 1977) or influenza B virus will dominate each winter season, but mixed epidemics do occur (Simonsen 1997). Influenza epidemics are remarkably seasonal in character. Most epidemics in the southern hemisphere peak at local mid-winter (May-September) and correspondingly epidemics in the northern hemisphere peak around winter (November-March). The influenza activity around tropical zones is more diverse (Hope-Simpson 1981). Low temperature and low absolute humidity are factors that are identified to explain the seasonality of influenza epidemics in temperate areas (Lowen 2014, van Noort 2012). Low absolute humidity is found to be associated with

increased influenza mortality, also after controlling for low temperature (Barreca 2012). There is scarce data on the effect of weather in tropical and subtropical countries. One report found a temporal association between low temperature and high level of influenza-like illness (ILI) cases in Niger (Jusot 2012). Epidemics tend to start in the eastern or southern hemispheres and then spread to Europe and North America. Pandemics however do not follow the rule of seasonality. The 1918, 1957 and 2009 pandemics started in spring, had several waves and spread globally. High influenza activity was observed year-around (Potter 2001). The *Textbook of Influenza* characterises a pandemic virus as a novel influenza A virus with animal origin that causes human disease with sustained human-to-human transmission, to which most or all of the population lack immunity (Webster 2013).

Influenza mortality is difficult to estimate based on influenza-specific diagnoses alone, as this will certainly underestimate the true burden of influenza. Mortality due to secondary complications such as bacterial infection and exacerbations of chronic diseases succeeding the influenza infection should be taken in to account when estimating influenza mortality. Therefore influenza mortality traditionally has been estimated through an excess mortality approach (Webster 2013). The estimated influenza-related excess mortality in Norway for the influenza seasons from 1976 to 2004 varied from 217 to 1802 deaths, which corresponds to a mean estimated excess influenza-related mortality of 910 deaths per season, or 2.1% of all deaths per year (Gran 2010). In the USA, the estimated excess mortality due to influenza during seasons 1972-2002 was 21,000 deaths per year on average (Simonsen 1997). Highest mortality was seen in persons >65 years and in seasons where influenza A/H3N2 was the dominating virus had the highest mortality. The reason for this severe impact on mortality when the A/H3N2 virus was the dominating seasonal strain is believed to be because this virus type have been resulted from major drifts thus making a larger proportion of the population without pre-existing immunity (Simonsen 1998, Webster 2013).

The 2009 influenza pandemic

Influenza pandemics occur when an influenza virus with a novel HA, against which there is little or no existing immunity, emerges in the human population and efficiently transmits from human-to-human (Garten 2009). The A(H1N1)pdm09 virus is a quadruple reassortant virus containing genetic materials from human, avian and swine influenza viruses with genetic segments from the Eurasian swine linage, classic swine H1N1 lineage, human H3N2 lineage and avian lineage (Dawood 2009). The first cases of human infection were detected in Mexico in March 2009 (WHO 2009a). On 11 June 2009, WHO raised the level of pandemic alert from phase 5 to phase 6 (highest level), indicating that the first influenza pandemic in the 21st century was under way (WHO 2009b). At this point 74 countries had reported 28,774 cases of laboratory confirmed pandemic influenza, including 144 deaths. In total, 18,500 deaths were registered during the pandemic due to A(H1N1)pdm09. The true burden of the pandemic is difficult to interpret, as many cases are not confirmed by laboratory tests or in death certificates. The highest attack rates were seen in children and young adults, and only 2% of the confirmed cases were in the age group ≥65 years of age (Devaux 2010, Waalen 2010). It is presumed that the immunity among older age groups was related to pre-existing antibodies as a result of previous exposure to genetically related H1N1 viruses (Miller 2010, Waalen 2010).

During the 2009 pandemic, the estimated excess influenza mortality in the USA was 12,500 deaths from April 2009-April 2010, and 87% of deaths were in the age group below 65 years of age (Shrestha 2011). Estimated excess deaths during the 2009 pandemic in Denmark range from 30 to 312 (0.5–5.7 per 100,000 population) (Molbak 2011). Globally, it was estimated that 151,700–575,400 respiratory and cardiovascular deaths were associated with the 2009 influenza pandemic (Dawood 2012). In Norway, the pandemic influenza mortality was 56-96 excess deaths depending on the method applied. Most of excess deaths were observed in age group +65 years (Gran 2013).

The first two cases of confirmed influenza in Norway were detected 9 May 2009, both cases infected during a stay in Mexico. The health authorities in Norway have estimated that 900,000 individuals were infected during the pandemic in Norway

(Kacelnik 2011). There were 12,513 laboratory confirmed cases and 32 deaths in the country. The majority of fatal cases had underlying co-morbidity (Kacelnik 2011). Among hospitalised patients to a Norwegian university hospital, 86% had underlying co-morbidity (Brandsaeter 2011). Norway had two waves of ILI. A minor epidemic occurred in July-August, were rhinoviruses co-circulated together with influenza, causing the small summer wave (Anestad 2011, Waalen 2010). The main wave occurred in October-November and the peak was observed in week 45, 2009 (Blasio 2012, Waalen 2010). This two-wave pattern was seen in many European countries (Keramarou 2011, Molbak 2011).

In preparation for a pandemic, the Norwegian Medical Association and the Norwegian Directorate of Health in a joint press release on 9th of September 2009, suggested a number of measures to make the health care services better able to meet the increased demand for medical services and mass vaccination. Among these proposed measures were extended opening hours for GPs, opportunities for recruitment of additional personnel, increased use of self sickness-certification and reprioritisation of doctor's appointments (Braaten 2009, Helsedirektoratet 2009). The specific measures were authorised by the Norwegian Directorate of Health at the following dates: The sick leave self-certification was extended from 3 to 8 days and launched on 23rd of October 2009. On the 5th of November 2009 oseltamivir and zanamivir were released as over-the-counter drug without doctor's prescription to ease the pressure on the primary care services (Blasio 2012).

1.2.2 Nomenclature

The nomenclature designates the type/animal host/geographical place of isolation/strain number/year of isolation (two of four digits), and if type A, followed by bracket with H and N subtypes (Van-Tam 2009). The pandemic influenza virus that caused the 2009 pandemic was isolated in California and had the following nomenclature: A/swine/California/7/2009 (H1N1). In 2011 the official name for the pandemic strain was changed to A(H1N1)pdm09 (WHO 2011b).

1.2.3 Clinical signs and symptoms

Seasonal influenza presents as an acute illness characterised predominantly by cough, malaise and fever. Other common symptoms are chills, headache, anorexia, rhinitis and sore throat (50-79% of confirmed cases), sputum, dizziness, hoarseness and chest pain (<50% of confirmed cases) and gastrointestinal symptoms (vomiting, diarrhoea, nausea, stomach pain) (<10% of confirmed cases) (Van-Tam 2009). The clinical signs and symptoms of pandemic influenza were found to be similar to previous seasonal influenza epidemics except that children and young adults were disproportionately affected by the A(H1N1)pdm09 as only 2% of laboratory-confirmed cases were <65 years of age (Belongia 2010, Ong 2009). Studies from the first cases of pandemic influenza in the USA, United Kingdom and surveillance data from the first wave in Europe, reported that up to 1/4 of patients with confirmed influenza had gastrointestinal symptoms (diarrhoea, vomiting, stomach aches and nausea), especially among young children (Dawood 2009, Devaux 2010, McLean 2010). Other reports did not confirm these results (Cao 2009, Chan 2010, Ong 2009).

1.2.4 Diagnosis of influenza

Laboratory diagnosis

The viral load in the respiratory tract is highest during the acute phase of the influenza disease. For seasonal influenza A and B and A(H1N1)pdm09, viral shedding peaks within days of the onset of the illness. Figure 1 illustrates the clinical phases of influenza and eligible diagnostic tests according to time of illness. Specimens intended for virus isolation and for viral genome detection should be collected as soon as possible after the onset of symptoms when the viral load is highest. Laboratory tests for diagnosis of acute phase illness include reverse transcriptase polymerase chain reaction (RT-PCR) assay, viral culture, enzyme-linked immunoassay (EIA), immunofluorescence (IF) and point of care test (PoCT) (Webster 2013).
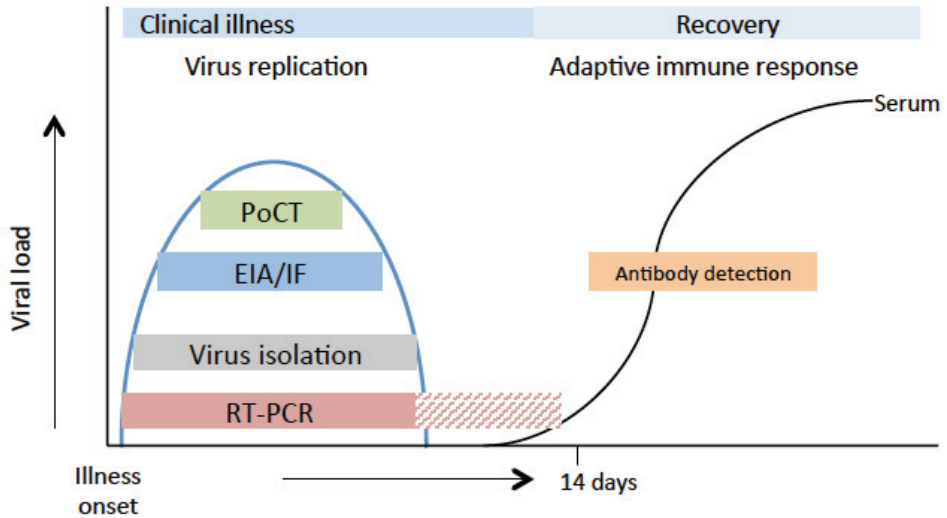
Figure 1. Influenza detection according to phases of illness using different diagnostic tests: Reverse transcriptase polymerase chain reaction (RT-PCR) assay, virus isolation, enzyme-linked immunoassay (EIA), immunofluorescence (IF), point-of-care test (PoCT) and antibody detection (Webster 2013).

The WHO recommended molecular diagnostics (RT-PCR) to be the "gold standard" for diagnosing A(H1N1)pdm09 (WHO 2009c). The RT-PCR test can distinguish between different subtypes of influenza and the test result is usually ready in 1-2 days depending on the capacity of the laboratory, logistics and transport. Point-of-care tests (rapid influenza antigen immunoassay) have also been developed, but the usefulness of those test kits is questionable as the sensitivity is low (Poeppl 2011).

Serologic tests rely on the detection of antibody immune response to the influenza infection. Serological testing is not useful in a clinical setting as it is necessary to obtain sera in the acute phase of the disease (baseline level) and 10-14 days post illness onset to be able to detect raise in titre (Hobson 1972). However, it is useful for population studies and to evaluate vaccine efficacy (Madhun 2010). When a novel influenza A virus arise in the community (i.e. a pandemic strain) in which a large part of the population has little or no previous immunity to the new strain, a single blood sample is sufficient to detect rise in titre level as evidence of recent infection to that

virus. The hemagglutination inhibition (HI) antibody tests can detect strain-specific serum IgG HI titres. Titres ≥40 are considered 50% protective and titres ≥10 as seropositive (Morner 2012).

Clinical diagnosis

Different diagnostic criteria have been developed to identify influenza on a clinical basis. Clinical diagnosis of influenza is challenging, however, because these symptoms are shared with many other common respiratory tract infections (van Elden 2001). The presence of fever (> 38°C) and cough when the prevalence of influenza is high in the community has been shown to give the best prediction of influenza, with a positive predictive value of 30-80% for influenza diagnosis (Govaert 1998, Michiels 2011, Monto 2000, van Elden 2001). Outside the influenza season, the absence of cough and fever makes the diagnosis very unlikely (Michiels 2011).

1.2.5 Clinical risk groups and vaccine recommendation

Yearly influenza vaccination to high-risk groups and the elderly has been recommended for decades in the United States and many other countries (Couch 2000). There is remarkable consistency internationally concerning targeted risk groups and vaccine recommendations (Mereckiene 2014). Most countries recommend vaccination for all individuals ≥65 years of age (some countries at age 50, 55 or 60 years of age). The Norwegian recommendation is given in Table 1.

Table 1. Seasonal influenza vaccine recommendation in Norway – season 2013-4

Everyone aged 65 years and over

Residents in nursing homes and sheltered accommodation

Pregnant women after week 12 of pregnancy (2nd and 3rd trimester)

Children and adults with:

> diabetes mellitus, type 1 or 2
>
> chronic respiratory disease
>
> chronic cardiovascular disease
>
> chronic liver failure
>
> chronic renal failure
>
> chronic neurological disease or injury
>
> impaired immunity against infection
>
> severe obesity (BMI over 40)
>
> other severe or chronic illness evaluated on an individual basis by a doctor

Health professional with patient contact

Pig farmers and others who have regular contacts with live pigs

Household contacts of highly immunosuppressed patients should consider vaccination against influenza to protect the patient

(Norwegian Institute of Public Health 2014a)

Vaccine efficacy

The evidence of effectiveness of seasonal influenza vaccination derives mainly from observational studies as few clinical studies and randomised control trials have been performed to evaluate this (Govaert 1994, Vist 2009). In a multicentre case-control study performed in the 2012-3 season to measure the effect of the seasonal vaccine, the effectiveness for preventing medically attended laboratory-confirmed influenza was below 70% (Kissling 2014). The Norwegian Knowledge Centre for the Health Services concluded in a review in 2009 that the seasonal influenza vaccine may possible reduce the risk of ILI in the elderly, however the documentation was scarce and affected with high risk of bias (Vist 2009). In a bias-adjusted meta-analysis of 14 cohort studies, influenza vaccination of community-dwelling persons ≥60 years, showed statistically significant effectiveness against hospitalisation from influenza and/or pneumonia and all-cause mortality, but not against influenza and ILI (Darvishian 2014). In a population-based cohort study from Sweden, the vaccine effectiveness in terms of reducing all-cause mortality in three influenza seasons was 1-19% (Ortqvist 2007). A study from Korea with a retrospective case-control design found a vaccine effectiveness of 32.5% in preventing hospitalisations, but the effectiveness rose to 72.6% among patients ≥65 years with chronic heart disease (Seo 2013). Influenza vaccination in healthy adults seems to have no effect on reducing hospitalisation or complications such as pneumonia, and only modest effect on reducing influenza symptoms (Demicheli 2014).

Influenza vaccination and clinical risk groups

Patients with diabetes have increased risk of influenza-related complications and the increased risk is explained by abnormal glucose metabolism (Frasca 2013, Wang 2013). Lau et al. found a reduction of 43% of pneumonia and influenza-related hospitalisations in adult diabetic patients after influenza vaccination compared to unvaccinated matched controls (Lau 2013). Influenza vaccination is reducing hospitalisations and mortality among patients with cardiovascular diseases and chronic lung diseases (Nichol 2003, Simpson 2010). Morbid obesity (BMI≥40) has been detected as a novel risk factor for severe influenza outcome after infection with

A(H1N1)pdm09 (Schreter 2011, Yu 2011). The increased risk among obese is related to impairment of the immune system due to defects in T cell function (Paich 2013). Pregnant women also had increased risk of influenza-related complication after infection with A(H1N1)pdm09, probably due to altered immunity and physical adaptation during pregnancy (Jamieson 2009, Lim 2011). A(H1N1)pdm09 infection in pregnancy was associated with increased risk of foetal death (Haberg 2013) and maternal immunization has been proven effective in reducing influenza-related complications in the offspring (Zaman 2008) but no effect on reducing abortion or foetal death (Demicheli 2014).

Influenza vaccines

The seasonal influenza vaccine nowadays usually contains inactivated surface antigens of HA and NA for the three seasonal circulating strains. An increase of serum concentration of antibodies to one subtype of HA is used as a measure of the protection offered against viruses of the same subtype. Cellular immunity is also contributing to the immune responses against influenza, and it is speculated that those who are vaccinated have less cytotoxic T-cell activity than those who are naturally infected by influenza viruses. For this reason is it debated whether healthy individuals and health care workers should be targeted groups for annual influenza vaccination (Haneberg 2013).

The influenza vaccine is updated on a yearly basis based on circulating strains. Antibodies against the surface protein HA are of major importance for protection against infection, and the HA is the primary component of the currently licensed influenza virus vaccines (Garten 2009). The 2014-5 seasonal influenza vaccine (northern hemisphere) contains HA surface antigens of influenza A/H1N1, influenza B, and influenza A/H3N2. For the 2013-4 season the vaccine effectiveness has been reported to be 40-73% in preventing H1N1 influenza (Andrews 2014, Castilla 2014). The pandemic vaccine was however produced as a monovalent split virus vaccine containing HA of A/California/7/2009-like virus (H1N1). The two pandemic vaccines available (Pandemrix® and Arepanrix®) contained adjuvans (proprietary oil-in-water emulsion system) called AS03 to induce effective immune responses (Madhun 2010).

In Norway a mass vaccination campaign started in October 2009, and 40-45 % of the population was vaccinated with Pandemrix® (Blasio 2012, Waalen 2010). The effectiveness of the pandemic vaccine, measured as preventing medically attended, laboratory confirmed A(H1N1)pdm09 illness was 93% in a Canadian case control study (Skowronski 2011). In a Norwegian university hospital, 98% of health care workers had protective titers 2-3 weeks after vaccination with Pandemrix® (Madhun 2010).

There are concerns about serious side effects of the pandemic vaccine. A sudden increase in the rare neurological disease narcolepsy has been observed in several countries among children and young adults after the pandemic (Heier 2013, Miller 2013). It is suggested that this condition was associated with Pandemrix® vaccination. The Pandemrix® vaccine-associated risk of narcolepsy in children and adolescents has been reported to be four to 13-fold compared to unvaccinated individuals (Partinen 2014). The mechanism behind the increased risk of narcolepsy after vaccination with the AS03 adjuvant pandemic vaccine is not fully understood. It is suggested that the combination of viral particles and the adjuvant may have elicited an autoimmune reaction in susceptible individuals (Heier 2013).

1.2.6 Antiviral treatment

The neuraminidase inhibitors oseltamivir and zanamivir are commonly used drugs against seasonal and pandemic influenza. They work by interfering with the release of viral particles from the surface of epithelial cells in the respiratory tract (Abramson 2011).

Oseltamivir was first approved in USA in 1999 and then in Europe in 2003. Kaiser et al. published a paper on the treatment effects of oseltamivir in 2003 based on the 10 randomised control studies in the oseltamivir trial. This study showed that oseltamivir reduced hospitalisation by 59%, reduced antibiotic use by 27% and lowered the risk of respiratory tract infections by 55% in healthy adults and in high-risk patients (Kaiser 2003). Since that time oseltamivir has been stockpiled in many countries world wide

in the preparedness for a pandemic. It was also put on the WHO's list of essential drugs (and still is) and oseltamivir was recommended for both prophylactic use and treatment of influenza (Jefferson 2014a). In 2009, in the light of the emerging pandemic, the Cochrane group attempted to make an updated review on anti-influenza drugs. It then became evident that the Kaiser study had serious shortcomings including high risk of bias, missing data and insufficient information on inclusion and exclusion criteria (Cohen 2009). After more than 3 years, the pharmaceutical company Roche finally released the full clinical data material on the oseltamivir trial to be analysed by the Cochrane group. After receiving the full study protocol from the Tamiflu® (oseltamivir) clinical trials, the Cochrane review was updated. Jeffersen et al. found a high level of bias in those industry-funded studies (Jefferson 2014c). According to this updated review, the potential benefit of oseltamivir is probably limited to a symptom-reducing drug (Jefferson 2014b). Hsu et al. performed a systematic review of observational studies on treatment effects of anti-influenza drugs in 2012. They found that oseltamivir and zanamivir may reduce symptom duration by 33 and 23 hours respectively, but as seen with the randomised control trials, the evidence was limited due to bias (Hsu 2012). Another systematic review could not find additional treatment effects for zanamivir (Michiels 2014).

In Norway, oseltamivir is approved for children and adults and zanamivir for persons ≥5 years of age. Oseltamivir is given orally and zanamivir as an inhaled powder-formulation. In the national guidelines from Norwegian Institute of Public Health it is recommended that the antivirals are to be taken within 48 hours after debut of influenza symptoms, but should also be considered for patients with symptoms of >48 hours duration when there is risk of severe complications and for patients hospitalised with influenza. Elderly (≥65 years) and individuals with risk of severe outcomes or belonging to a clinical risk group are targeted groups for antiviral treatment. Prophylactic treatment with oseltamivir is indicated for unvaccinated close contacts belonging to risk groups for complications.

1.2.7 Influenza surveillance

Most developing countries have a surveillance system for influenza. In Europe, (among them, Norway) give annual reports on epidemiology of communicable diseases of public health significance to the European Surveillance System. Influenza epidemiology (virological data and ILI consultations from primary care) is monitored through the European Surveillance Influenza Network (Amato-Gauci 2011). In Norway, the Norwegian Institute of Public Health organises this surveillance by the means of the Norwegian Notification System for Infectious Diseases. Selected GP practices have for many years been reporting the numbers of ILI to this system. From 1998, a system of 201 sentinel GP practices was established, with weekly reporting of the number of ILI. These practices comprised about 10 % of all general practices of the former reporting system but about 25 % of the reported volume of ILI. The sentinels report weekly, from week 40 in autumn to week 20 in spring, the number of ILI using the case definition of "R80 Influenza" from the ICPC-2 (Gran 2010). During the pandemic season in 2009, this sentinel surveillance of ILI was extended to year-around reporting. From 2014, this will be replaced by a new primary care surveillance system, called the "Disease pulse". In this system, all consultations on a national level containing diagnosis "R80" from both general practice and OOH services will be registered in a weekly report (Norwegian Institute of Public Health 2014b). Virological surveillance of influenza is also performed by another system of selected GPs ("lighthouse GPs") collecting nasopharyngeal swabs from ILI patients to the regional microbiological laboratories that in turn report to Norwegian Institute of Public Health. Sentinel GP surveillance system are common in many countries in Europe (Vega 2013). In the USA, claims data has been shown to follow the same trends in influenza activity as the official sentinel practices (Viboud 2014). There are also promising results concerning the use of medical records from OOH services for surveillance of influenza activity. A study from Ireland showed that ILI activity at OOH services peaked one week before the national rates (Brabazon 2010).

1.2.8 Personal protective measures to prevent influenza virus spreading

Personal protective measures include improved personal hygiene (frequent hand washing, cover sneezes and coughs), physical protective measures (use of gloves, face masks and mechanical filter respirators) and social distancing (avoiding public transportation, crowds and work place). Adherence to personal protective measures has been associated with female gender (Lin 2011, Timpka 2014, Wong 2011) and older age groups (Bults 2011, Kiviniemi 2011, Lin 2011). Increased attention to hand washing was the most commonly protective measure reported during the pandemic, while use of face masks was the least commonly reported measures across different populations (Kiviniemi 2011). The evidence for face masks being protective in reducing influenza virus spread is limited (Cowling 2010b). In Norway, there was a decrease in cases of several types of infectious diseases attending the OOH services after the main pandemic wave succeeding the Norwegian health authorities' campaign for better hygiene (Sandvik 2011). The hygiene campaign may have contributed to this. A population-based survey from Norway in 2007 showed that 80% of the respondents would take precautions concerning personal hygiene if a pandemic occurs in the future (Kristiansen 2007). The evidence that hand washing reduces the spread of infectious diseases is solid (Jefferson 2011).

1.2.9 Attitudes towards influenza vaccination and influenza disease

Targeted groups for influenza vaccine are people belonging to a clinical risk group, elderly, pregnant women and health care workers (Mereckiene 2014). Attitudes towards influenza vaccination vary among different populations, with age, gender and education level, with previous influenza vaccination uptake as well as other patient's characteristics (Peretti-Watel 2013). Variation in attitudes towards vaccination is also seen among different types of health care workers (Fatiregun 2012, Kissin 2011, Mak 2013). Having received the seasonal influenza vaccination in the 2008-9 season was the strongest predictor to receive pandemic influenza vaccination among health care workers (Hothersall 2012, Kaboli 2010, Toh 2012, Virseda 2010, Wong 2010). A

positive attitude to receive pandemic influenza vaccination is more likely among doctors than nurses (Arda 2011, Kaboli 2010, Toh 2012). Worries about side effects of the pandemic vaccine are high among health care workers in general and specifically among nurses (Arda 2011, Kaboli 2010, Savas 2010). The vaccination coverage among students is low and female gender is associated with higher perceived risk of getting influenza and they also show a more positive attitude towards vaccination (Park 2010, Suresh 2011). In the general population, factors that are associated with willingness to take the pandemic influenza vaccine are high perceived risk of getting ill and a positive attitude towards vaccine safety (Lin 2011, Naing 2012). Among pregnant women, pandemic vaccine receipt was associated with previous seasonal influenza uptake, perceived risk of getting ill and correct knowledge about the influenza pandemic (Eppes 2013). A major reason for declined vaccination in pregnancy was concerns about vaccine safety (Ding 2014, White 2010). GPs in an Australian study demonstrated low level of confidence to give the pandemic influenza vaccine to pregnant women due to precautions about vaccine safety (Maher 2014).

1.3 The Norwegian primary health care system

1.3.1 Organisation

The municipalities organise general practice and OOH services in Norway. Every citizen has the right to be registered with a specific GP. The list system was established in 2001, but there has been a long tradition for personal doctoring in Norway (Hjortdahl 1989). 99.6% of the population has a designated GP (The Norwegian Directorate of Health 2014). The average list length was 1180 in 2009 and typical GP worked 4 days a week (30 hours) with direct patient contact (Hetlevik 2012). Average waiting time was 6 working days in 2004 (Hetlevik 2004). GPs generally pre-book appointments and have a few slots available for new or urgent illnesses each day. The accessibility for urgent calls and emergency visits is challenged by a large variation between practices (Sandvik 2012a). GPs are responsible for primary care emergency services during office hours, but in the larger cities separate institutions of emergency services also operate at office hours. Primary

care physicians staff these services. The OOH services are organised with GPs in rotas. OOH services are operating evenings, nights, weekends and holidays. Several OOH services are organised in large inter-municipal collaborations. Only half of GPs working in the regular GP scheme in Norway are doing OOH work (Sandvik 2012b). The diagnosis system in Norwegian primary care is ICPC-2 (Brage 1996).

1.3.2 Financing of primary care services

GPs are paid by a combination of fixed capitation and fee-for-services. Patients pay a user fee for each consultation or service at the GP office. Once the patients have paid a certain amount in user fees, they are entitled to a healthcare exemption card. This amount was 2105 NOK in 2014. The fees are regulated at a yearly basis. The income for doctors at OOH services is by fee-for-services solely. The municipalities cover all other costs (ancillary staff, housing, medical equipment) at the OOH services. All primary care doctors working in general practice or at OOH services are obliged to deliver electronic billing claims to the Norwegian Health Economics Administration (HELFO) for reimbursement. The claims contain diagnoses according to ICPC-2, date/time of contact, patient's variables, and the fees.

1.3.3 The GP as a the primary source of medical care

Primary care is characterised by being comprehensive, patient focused, coordinated and first contact access for each new need (Starfield 2005). Referral from primary care (both in-hospital and ambulatory specialist care) is mandatory in Norway to get to secondary care. Hence, GPs in Norway act as gatekeepers and coordinate access to more advanced care. Unlike many other countries, GPs in Norway also have an important role in initial care for emergency patients (Lillebo 2013). Continuity of care in general practice, which implies that individuals use their GP as the primary source of care over time for most of their health care needs, is associated with greater satisfaction, better compliance, and lower hospitalisation and OOH services use (Hjortdahl 1992, Starfield 2005). These core concepts of primary care are highly appreciated by GPs in different countries (Stokes 2005). A recent study from Norway

found that continuity of care was associated with reduced hospitalisations and use of specialist services (Hansen 2013). In the USA, continuity of care was associated with reduced cost, reduced hospitalisation rate and less adverse effect for patients with diabetes, heart disease and obstructive lung disease (Hussey 2014). The mean annual consultation rate is 2.52 in Norway (2009) and 78% of patients had at least one annual consultation with their regular GP (Hetlevik 2012).

Care for people with chronic disease

GPs are important in providing care for people with chronic diseases. Multimorbidity maybe defined as two or more chronic diseases or chronic conditions (Barnett 2012). The prevalence of patients with multimorbidity was 23% in a large study from primary care practices in Scotland (Barnett 2012). Prevalence figures from primary care in Spain was 47% (Foguet-Boreu 2014) and 32% in Denmark (Moth 2012) but the prevalence of multimorbidity was 66% among primary care patients >55 years in Ireland (Glynn 2011). Regular contact and scheduled follow up appointments with the GP can be preventive as early disease exacerbations can be recognised and adequate treatment given. Disease exacerbations among persons with cardiovascular diseases, chronic lung diseases, and conditions where immunodeficiency may be a part (diabetes, liver disease, cancer) are sensitive to exposures to infectious diseases, such as influenza. People with chronic respiratory diseases are frequent attenders of primary care (Santus 2012). Glynn et al. found significantly increased health care utilisation among patients with multimorbidity (Glynn 2011). A study from Australia found regular GP contact to be associated with reduced mortality and hospitalisation in patients with chronic lung diseases (Einarsdottir 2010). People with chronic diseases also are heavy users of the OOH services, either due to exacerbation of the chronic disease or due to a new unrelated event (Flarup 2014).

The role of GPs in influenza epidemics

In countries with a primary care system, GPs take a great responsibility during influenza epidemics (Bocquet 2010, Sauro 2006). GPs play a key role in the preparedness to an influenza epidemic as they have information about patients belonging to a clinical risk group and to whom influenza vaccination should be offered

(Collins 2008). Vaccination to people at risk can reduce the pressure on the primary care system in terms of reduced consultation rates (Tacken 2004). The 2009 pandemic caused an increase in workload for GPs; A 58% increase in consultations to primary care services due to influenza was reported in a region in Spain (Aldaz 2011). As most cases of influenza are self-limited and treated only by GPs, they play an important role for the vast majority of patients during outbreaks. Few patients are in need of hospital care. Furthermore, GPs are also important gatekeepers when patients are in need for more advanced care, i.e. hospitalisation or to whom a thoroughly follow up approach should be delivered (Lee 2010). GPs are important health counsellors, as most people get the usual care from a GP. An important task for GPs is also to explain to people the benefits of the vaccine. Scheduled meetings between the GP and the patient can offer a good opportunity to raise questions about vaccine recommendation and safety issues in a trustful manner (Kunin 2013).

Pandemic preparedness plan – the role of the municipalities

Every municipality in Norway has a Chief Municipal Medical Officer who is in charge of the community health services. In addition there may be a designated Chief Infection and Control Doctor who is given responsibility for surveillance of communicable diseases and vaccination issues. Contingency plan for mass vaccination in municipalities is rooted in the Act relating to the municipal health services, Act relating to control of communicable diseases and Act on health and social preparedness and associated regulations (Folkehelseinstituttet 2008). The Ministry of Health and Care Services is the supreme responsible organ in Norway for the plan for mass vaccination against pandemic influenza in municipalities together with The Norwegian Institute of Public Health. All municipalities in Norway are obliged to have a local plan for mass vaccination in preparedness for influenza pandemic. Planning for a pandemic is based on experience with yearly influenza vaccination. The GPs have a central role in the process of vaccination, as they possess the best information about those patients belonging to a clinical risk group (Johannessen 2009). The plan regulates all logistics issues concerning distribution, storing, delivery and registration of the vaccines. The plan should also give detailed information about how a mass vaccination should be organised at the community level. Small municipalities may

choose to organise this solely at the GPs' offices, others by invitation in local media for mass vaccination in local premises such as health centres, sport halls, premises used for elections and so on (Rørtveit 2011). Health care workers who have direct patient-contact are prioritised first for pandemic influenza vaccination according to the national pandemic plan.

2. Aims

The aim of the present thesis was to investigate the outbreak of pandemic influenza from a primary care perspective with focus on clinical manifestations, behavioural measures and utilisation of services. The three studies conducted had the following specific aims:

Study I: (i) to investigate symptoms and clinical course among patients diagnosed with ILI in general practice; (ii) to explore whether symptoms could be differentiated between serologically negative and positive cases; and (iii) to investigate patients' attitudes towards vaccination and their use of health preventive measures (**Paper I**).

Study II: (i) to investigate how and to what extent general practice and OOH services were used during the 2009 pandemic in Norway; (ii) to investigate the impact of the pandemic on primary care services in comparison to a normal influenza season; and (iii) to investigate whether there were socio-demographical differences between patients with ILI treated in general practice and OOH services during a pandemic (**Paper II**).

Study III: (i) to explore how patients at risk for severe influenza used primary care services for ILI during the pandemic in comparison to low risk patients; and (ii) to investigate how patients with prior consultations with their GP used primary care services for ILI in comparison to patients who had no such consultations before the pandemic (**Paper III**).

The published papers (**Paper I**, **II** and **III**) are later on referred to by their Roman numerals.

3. Materials and methods

3.1 Design

Study I is a cross-sectional study with patients in a general practice setting (**Paper I**). In collaboration with the research group, the chief municipal medical officer of each municipality mailed a letter to all GPs prior to the study, and they were requested to use ICPC-2 code "R80 Influenza-like illness" in their medical records when diagnosing a patient with influenza or ILI. For all other influenza-related contacts and questions to GPs' offices, they were encouraged to use other diagnostic codes. GPs were asked to diagnose influenza in line with clinical recommendations and these were sent out. I visited all participating GP practices to ensure that the participating GPs comprehended in line with the study protocol. In addition, a paper with the diagnostic criteria of ILI was given in person to all participating GPs at the start of the study. A sample of the study participants (restricted to patients >18 years) who responded to a questionnaire were further included with data from a blood sample.

Study II and III are based on observational data from a national registry of billing claims (KUHR database; se below) (**Paper II and III**). Study II has a cross-sectional design. The design of the study reported in **Paper III** may be defined as a historical cohort because the exposure status of interest was recorded in the past and the outcome measured at a given time period later. The data in Study II and III were recorded prospectively, in real-time by the primary care doctors as a part of regular clinical work, and collected retrospectively by the researchers for analyses.

3.2 Data sources

Questionnares
The data source in Study I was questionnaires from patients attending their GP and had an influenza diagnosis (ICPC-2 R80) in the period of October 26 to December 31 2009.

The KUHR database

The data source for Study II and III was the KUHR database with information extracted from billing claims from primary care doctors in Norway.

All GPs in the regular GP scheme and all doctors at OOH services send electronic billing claims to HELFO for each patient contact to claim fee-for-services. Doctors working temporarily in the regular GP scheme or in OOH services are also obliged to send billing claims. The claims are registered in the KUHR database. The Norwegian Directorate of Health is responsible for KUHR. Claims that are paper-based are not included in this database. However, the KUHR database contains >95% of all claims for 2008 and 2009 (Nydal 2010).

Variables in the data received from KUHR include:

- Physician variables: person identifier, municipality, practice type.

- Patient variables: person identifier, municipality, age, gender.

- Date and time of contact.

- Fees

    o Fees according to type of contact (consultation, home visit, telephone contact, multidisciplinary meeting).

    o Fees for diagnostic procedures, laboratory tests and other additional fees.

- Diagnosis according to ICPC-2 (up to two diagnoses are recorded).

3.3 Participants

Study I (**Paper I**): GPs in the municipalities of Bergen (256,600 inhabitants), Austevoll (4,571 inhabitants), Lindås (14,286 inhabitants), Meland (6,631 inhabitants) and Kvam (8,360 inhabitants) were invited to participate in this study. In Bergen, we restricted the invitation to larger practices with three or more GPs due to logistical

reasons. In the other municipalities, we invited all GPs. Eligible patients were all individuals with the ICPC-2 diagnosis code "R80 Influenza/influenza-like illness", identified from the primary care records of participating GPs in the study period (Figure 2).
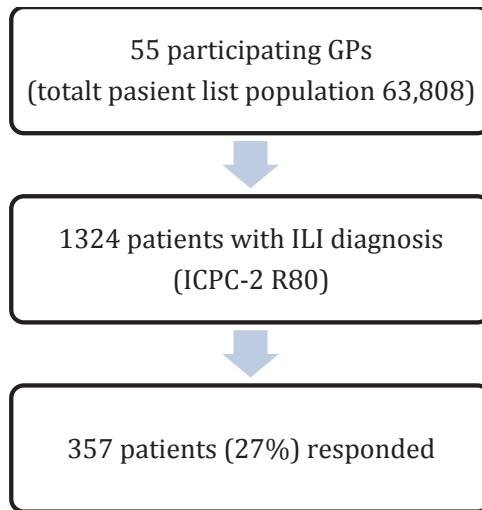
Figure 2. Flow chart of inclusion process of GPs and patients.

All patients given an ILI diagnosis were sent a questionnaire 2-4 weeks after the first encounter with the GP's office. After the study was finished, a manual search was performed in 15 of 55 GPs' medical records to investigate the accuracy of the diagnostic procedures. This procedure revealed that 4 of these 15 GPs had applied the influenza diagnosis code (R80) inappropriately for the purpose of this study. Consequently, some individuals who did not have ILI received our questionnaire. The magnitude of this inaccuracy is difficult to decide.

All patients >18 years of age receiving the questionnaire were also asked to volunteer to give a blood sample to measure serological response to A(H1N1)pdm09. Among all responders >18 years of age (251 patients; 70%), 186 patients volunteered for a blood test. If the patient did not give information about the date of sickness or did not donate a blood sample in the appropriate time window, then the patient was rejected from the

serology study (n=17). Flow chart for the inclusion process of the serology part of the study is given in Figure 3.
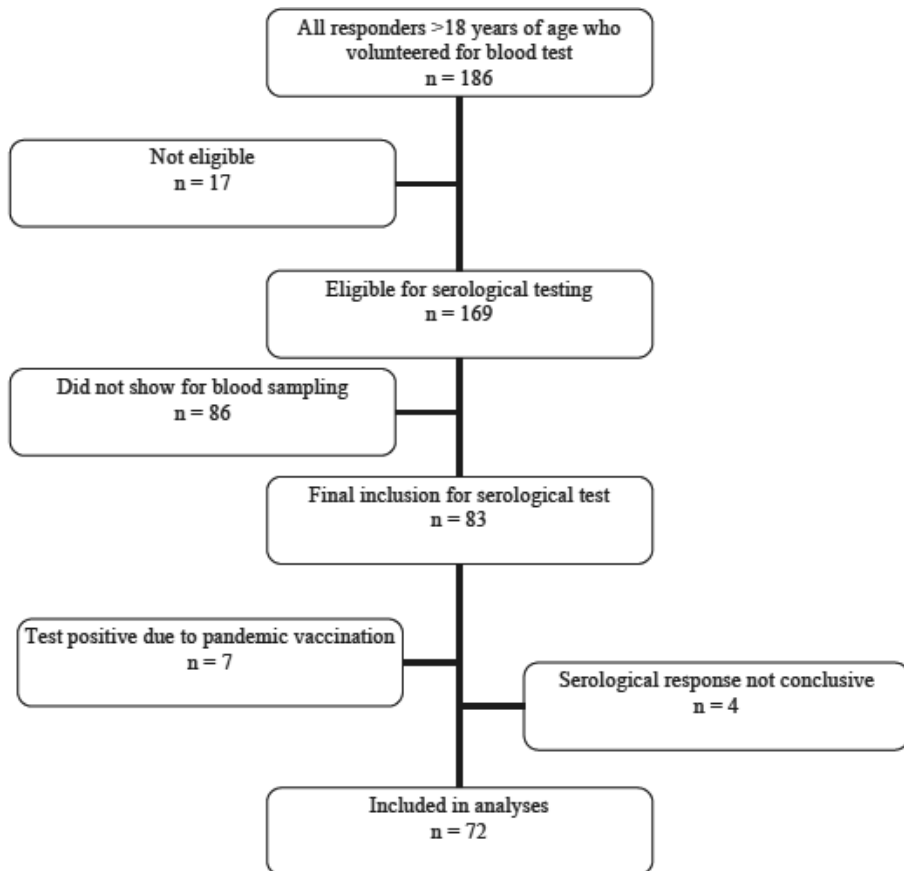
Figure 3. Flow chart of cases with serological test; 72 cases were included for final statistical analyses.

Study II (**Paper II**): All patient consultations registered in the KUHR database from two consecutive influenza seasons were included in the study. The threshold for influenza season, as defined by the Norwegian Institute of Public Health, is 1.4% ILI consultations per week. For the 2008-9 influenza season, this corresponds to week 1–9 in 2009, and for the pandemic influenza season this corresponds to week 30–51 in 2009.

Study III (**Paper III**): All patient consultations registered in the KUHR database from
1 January 2008 – 31 December 2009 were included.

3.4 Variables

Study I

In Study I, all patients where the diagnosis R80 was given in the GPs' medical records,
were eligible for the study and these were mailed the questionnaire, by the doctor or
local secretary.

The questionnaire (Appendix 1) was 4 pages long and was divided into the following
sections: (i) self-reported symptoms of influenza including duration of symptoms; (ii)
information about treatment, type of consultation and frequency of visit to health care
providers as well as advice and preventive measures taken during the pandemic; (iii)
history of seasonal and pandemic vaccination; statements concerning vaccination and
influenza disease (pre-formulated motives/barriers) and (iv) demographics (age,
gender, body weight in kg, height in cm, smoking habits, level of education,
professional position, co-morbidities (cardiovascular disease, lung disease, diabetes,
chronic renal disease, immunodeficiency, neurological disease) and for women;
statement of pregnancy (yes/no).

The research group, who has long combined experience with seasonal influenza from
clinical work as GPs, developed the variables in the questionnaire. We listed
symptoms of influenza to allow the patients to answer from the full panorama of
possible symptoms.

Eligible patients >18 years of age who volunteered to give a blood sample were
included in the serology study. The blood sample was collected at the GP's practice
and sent to the Influenza Centre at the University of Bergen for analyses. The blood
sample was collected 4–10 weeks after the first contact and analysed by the
haemagglutination inhibition assay (HAI), which measures the specific serological
A(H1N1)pmd09 response (Madhun 2010). The geometric mean haemagglutination
inhibition titre was calculated for each subject and titres <10 were assigned a value of

5 for calculation purposes and considered negative. Samples with HAI titres ≥40 were considered seropositive and deemed protective. Titres of 10-39 were considered possible A(H1N1)pdm09 and excluded in statistical analyses.

Study II and III

In Study II and III the following HELFO variables were used: Patient's age and gender, date of contact, type of contact (only claims containing a consultation were used) and diagnosis according to ICPC-2. In addition, the centrality of the patient's municipality was recorded. Centrality was defined as a municipality's geographical location in relation to a centre where there are important central functions and is measured on a scale of 0 to 3 where 0 is the least and 3 is the most central.

In Study III we also included a person identifier (from KUHR database) allowing the utilisation of general practice and OOH services to be linked on the individual level. Patients belonging to a clinical risk group were defined in accordance to WHO definitions and are in line with national guidelines. In **Paper III** a clinical risk patient was defined if the patient had at least one consultation with the GP (in general practice) coded with the relevant and specific ICPC-2 codes at least one time in the pre-pandemic period (Week 1 2008 – Week 29 2009). Pregnancy was defined as having at least one consultation with the GP in the pandemic period (Week 30-51 2009) with pregnancy specific ICPC-2 codes. Chronic renal disease was omitted due to lack of specific and relevant ICPC-2 codes to recognise such conditions (O'Halloran 2004). The number of GP visits before the pandemic was categorised as 0,1,2,3,4-7 or ≥ 8 consultations in the pre-pandemic period with the patients GP.

3.4.2 Outcome variables

Outcome variables in **Paper I** were self-reported duration and symptoms of influenza, treatment and hospitalisation (Appendix 1). Additional outcome variables in **Paper I** were statements about vaccination and influenza disease and adherence to personal protective measures. A sample of eligible patients was characterised according to results of serological testing. The outcome variable in **Paper II and III** was use of OOH services, with use of general practice as reference category.

3.4.3 Exposure variables

Paper I: Exploration of symptoms among influenza patients without a specific exposure. For the subsample of patients with serology results, the exposure variable was ILI (ICPC-2 "R80").

In **Paper II** the exposure variable was having had a consultation with influenza diagnosis (ICPC-2 "R80") as the result.

In **Paper III** the exposure variables were 1) risk factors for severe influenza outcome and 2) the number of consultations with the GP in the pre-pandemic period among those patients diagnosed with ILI as the result.

3.4.4 Confounding variables

Confounding was not evaluated in **Paper I** per se, but results were given in strata to control for age and gender. In **Paper II and III**, potential confounding variables were age, gender and centrality.

Age

In **Paper I**, 82 out of 1324 invited patients and 2 out of 357 responders had missing information about. Age was presented in three groups: 0-17, 18-40 and >40 years based on the age span of the participants. Age was also dichotomised at 40 years of age based on the results of preliminary analyses. In **Paper II**, age was dichotomised to the age groups 0–20 years and >20 years in the frequency tables, based on the results of preliminary analyses. In the multivariate analyses, age was divided in three strata (0–20, 21–49 and 50 years and above) for testing of effect modification of age. In **Paper III**, age was divided into eight strata (0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49 and ≥ 50 years of age) in the frequency tables. In the multivariate analyses, age was divided in five-year strata for testing of modification of age. All data included in **Paper II and III** contained valid information about age.

Gender

In **Paper I**, 82 out of 1324 invited patients and 1 out of 357 responders had missing information about gender. All data included in **Paper II and III** contained valid information about gender. Gender was tested as an effect modifier in **Paper II and III**.

Centrality

In **Paper II** centrality were dichotomised to rural (centrality categories 0, 1 and 2) and urban (centrality category 3). In **Paper III** all categories of the centrality variable were included in the analyses. Effect modification was tested for this variable in **Paper II and III**.

3.5 Analyses and statistical methods

Both univariate and bivariate statistics were used to characterise the samples in all studies as well as stratified analyses where relevant. Chi-square tests were used to check for differences between groups. Effect modification was tested by the Breslow–Day test for homogeneity between odds ratios (OR) after stratified analyses (**Paper II and III**). Confounding was evaluated by Mantel–Haenszel common odds ratios and logistic regression analyses (**Paper II and III**). Multivariate logistic regression analyses were performed to adjust for the confounders (**Paper II and III**).

All tests were two-sided. P-values <0.05 were considered statistically significant in all analyses. ORs were presented with 95% confidence interval (CI).

The statistical analyses were performed using SPSS Software version 17 (**Paper I**), version 19 (**Paper II**) and version 21 (**Paper III**).

3.6 Ethics

Study I (**Paper I**) was approved by Regional Committee for Medical Research Ethics (project number 2009/1334). All patients who responded on the questionnaires provided written informed consent. For those below 18 years of age a guardian gave a written consent.

The Norwegian Social Science Data Services approved the studies presented in **Paper II and III**, stating that the project was based on registry data from HELFO (project number 25159). The data that was delivered from HELFO was anonymous, and approval from the Regional Committee for Medical Research Ethics was not required.

4. Results

4.1 Paper I

Influenza-like illness in Norway: clinical course, attitudes towards vaccination and preventive measures during the 2009 pandemic

The first study was a cross-sectional study in general practice based on patients with ILI during the peak of the influenza pandemic in Norway.

Out of a list population of 63,808 (55 GPs), a total of 1324 patients were diagnosed with ILI in the 10-week-study period. Of these, 357 (27%) patients responded on the questionnaire. Median age was 32 years and 59% were females. Fatigue (94%), headache (79%), cough (77%) and myalgia/arthralgia (76%) were the most commonly reported symptoms among all participants. Fever and/or feverishness were reported in 94% of patients, whereas fever alone (elevated temperature to >38°C) was reported by only 61%. The median duration of illness was 7 days; the median duration of specific symptoms varied from 2 to 8 days.

Serological testing was performed in 83 patients (72 eligible for final analysis); 34 confirmed positive and 38 confirmed negative for the A(H1N1)pdm09 virus. The most common symptoms for patients with confirmed H1N1 were fatigue (94%), cough (82%) and headache (76%). There were no statistically significant differences in symptoms between negative and positive A(H1N1)pdm09 groups.

Women reported more use of cough hygiene (64% versus 51%, P = 0.015), hand washing (87% versus 73%, P < 0.01) and use of paper tissue (55% versus 34%, P < 0.01) than men. Women were also more concerned about possible adverse effect of the vaccine than men (64% versus 45%, P < 0.01).

Conclusions: Clinical symptoms of A(H1N1)pdm09 influenza were similar to seasonal influenza and difficult to discriminate from other upper respiratory tract infections.

Women reported better adherence to personal protective measures than men and were also more concerned about possible side effects of the pandemic vaccine.

4.2 Paper II

Capacity and adaptations of general practice during an influenza pandemic

This study was a registry-based study of all ILI consultations from primary care in Norway during the 2009 pandemic. The 2008-9 influenza season was selected for comparison (baseline season). Data was extracted from electronic billing claims from primary care doctors in general practice and OOH services.

During the pandemic period 152,969 and 29,403 were consultations for ILI in general practice and OOH services, respectively. This constitutes a 3.3-fold increase of total ILI consultations compared to the 2008-9 influenza season. Younger age was associated with higher use of OOH services (26.1% in age group ≥20 years and 13.5% in age group <20 years). The pandemic period peaked in week 40 with 25% of all ILI consultations taking place in OOH services. This was in contrast to the 2008-9 season where only 10% of ILI consultations were conducted in OOH services.

Conclusions: Most of the ILI consultations took place in general practice during the 2009 pandemic; however, there was a 5.5-fold increase of ILI consultations in the OOH services during the 2009 pandemic season in comparison to the 2008-9 season. Low age was associated with the use of OOH services compared to general practice. GPs in Norway showed an ability to increase capacity during a pandemic.

4.3 Paper III

Primary care utilisation among patients with influenza during the 2009 pandemic. Does risk for severe influenza disease or prior contact with the general practitioner have any influence?

This study was a registry-based study of all patients diagnosed with ILI during the 2009 pandemic in Norway. Patients belonging to risk groups were identified during an 18-months period by diagnoses from GPs' billing claims.

Of 12,691 ILI patients in general practice and 2480 ILI patients in OOH services with clinical risk factors, patients with chronic lung disease and pregnancy comprised the largest risk groups. Being an ILI patient with at least one risk factor was associated with higher risk of attending OOH services (OR 1.50, 95% CI 1.42, 1.57). Pregnancy (OR 1.70, 95% CI 1.52, 1.89), diabetes mellitus (OR 1.68, 95% CI 1.49, 1.89), chronic lung disease (OR 1.44, 95% CI 1.34, 1.55) and cardiovascular disease (OR 1.42, 95% CI 1.23, 1.63) were risk markers associated with attending OOH services for ILI.

Having any number of GP visits in the period before the pandemic (OR 0.84, 95% CI 0.79, 0.90 for 1 consultation with the GP) was associated with a lower risk of attending OOH services for ILI during the pandemic.

Conclusions: Pregnancy, diabetes and chronic lung disease were significant risk conditions for attending OOH services among patients with ILI during the pandemic. Contrary to this, having visited the GP before the pandemic was associated with lower use of OOH services.

5. Discussion

5.1 Methodological considerations

5.1.1 The design

Paper I

A major problem for studies on disease outbreaks is to obtain data prospectively as the outbreak emerges in the population. We managed to establish the research group and design for the first study before the pandemic reached epidemic threshold levels in Norway. Recruitment of GPs for the study was finalised at the time where the main pandemic wave began in Norway. Questionnaires were sent to eligible patients only a short time after contact with their GPs. This approach reduced the possibility of recall bias. For reasons due to logistics, time for planning, ethics approval and the recruitment process a cross-sectional design was decided for in **Paper I**. Due to lack of time it was not possible to do a pilot study or to validate the questionnaire used in **Paper I**. A major limitation with the design in this study was how the patients were included for the study. Eligible patients were those in whom the influenza diagnosis R80 was given in the medical records whether the influenza diagnosis was set during a simple contact with the office or during a consultation with the GP. This approach may have reduced the accuracy of the diagnosis. This was further confirmed by the manual search in GPs' records where 4 out of 15 GPs (or, in many cases, their secretaries) had applied the diagnosis incorrect for our purpose. The diagnosis was used for situations such as influenza in the family, concerns about vaccination, etc. as well as own influenza symptoms. The inclusion process may have affected the response rate of the study in a negative direction, as some patients who did not have influenza, incorrectly received the questionnaire. For this reason, it is assumed that the true response rate among patients with influenza probably was higher than recorded.

Paper II and III

For **Paper II and III** we used national data from the KUHR database, which has considerable limitations with respect to the quality of the data material for research

purposes. Routinely collected claims data are not designed for research purposes. It contains no clinical data other than diagnoses. GPs and OOH services doctors generally send billing claims to HELFO to get paid. The economical motivation to send billing claims from patient activities in primary care is of course very strong and thus it is unlikely that doctors fail to report to HELFO. The KUHR database is very complete in documenting that a contact or consultation between a doctor and a patient has actually taken place and selection bias is thus unlikely to occur. A major concern with respect to data quality and accuracy is how diagnoses are reported. Specifically there is reason to be concerned about how simple contacts (not including a doctor) are reported. Claims from patient activities where the doctor has not been directly involved with the patients in his office (telephone calls to patients, letters or laboratory contacts without seeing a doctor) are omitted in **Paper II and III** because the chance of reporting inaccurate diagnoses is much more likely in such circumstances. When the doctor interacts with the patient in a face-to face consultation a medical history and regularly physical examination will be performed and hence the diagnosis has higher accuracy of describing the actual problem encountered. However, HELFO only record up to two diagnoses in the claims, and the majority of claims obtained for these studies (**Paper II and III**) contain only one diagnosis, thus reduced the possibilities to capture the full diagnostic works that is going on in the consultations. For example a patient can have both pneumonia and influenza, but only one of these diagnoses recorded in the claim.

Observational studies are affected with limitations. The study design in **Paper I and II** was cross-sectional. Generally, caution should be made to interpret associations as causal relationship because exposure and outcome variables are recorded at the same time. **Paper III** was a historical cohort study, and because the exposures were recorded before the outcome, the temporal relationship may allow interpretations about causality, although other criteria for causality may not be fulfilled.

5.1.2 Risk of misclassification

In epidemiology we recognise two different types of misclassification: differential and non-differential misclassification. Exposure, outcome and confounding variables are subject to risk of misclassification errors. For the outcome this may mean that a person who is classified with disease is incorrectly classified as without disease, and vice versa. The same counts for exposure and confounding variables. The correct classification depends on the accuracy of the measurement methods, i.e. the sensitivity and specificity of the diagnostic tool and the lack of information bias. Bias in estimating an effect can be caused by measurement errors in the needed information. Such a bias is called information bias (Rothman 2012a).

One strength in this thesis is the low risk of recall bias: Participants in **Paper I** were given the questionnaires shortly after the contact with the GPs. Data used in **Paper II and III** were recorded prospectively in real-time by primary care doctors as a part of regular clinical work.

Differential misclassification

With differential misclassification, the misclassification differs according to the value of other study variables (Rothman 2012b). It means that the exposure variable relies on the level of the outcome variables or vice versa. It is possible that patients with a risk factor for severe influenza outcome (**Paper III**) had a higher chance of getting the ILI diagnosis than those without a risk factor. Risk patients who presented to primary care services with ILI symptoms were more likely to be prioritised to see with a doctor than low-risk patients, in line with the health authorities' recommendations. Accordingly, differential misclassification of the disease (influenza) on the basis of exposure status (risk group) was probably present in **Paper III**. Reversely, there was no differential misclassification of the exposure on the basis of the disease. Exposure variables (clinical risk group and number of consultations in the pre-pandemic period) were recorded prospectively before the primary care doctor diagnosed ILI and no recall bias was likely to be present. Differential misclassification was probably not

present in **Paper II**, because we used practice type as outcome variable and ILI diagnosis as exposure variable.

Nondifferential misclassification

Nondifferential misclassification is misclassification that is unrelated to other study variables. The level of nondifferential misclassification of the disease depends on the diagnostic test's sensitivity and specificity (Rothman 2012a). In the case of influenza, laboratory confirmation is the gold standard. This was performed for a subsample of patients who responded on the questionnaire in Study I. Cases of influenza were collected from GPs' records (**Paper I**) and from claims data (**Paper II and III**). The clinical diagnosis of influenza has been found to have a sensitivity of 0.88 and specificity of 0.42 when the prevalence of influenza was high in the community (Michiels 2011). The clinical diagnosis of influenza reflects the reality of imperfect diagnostic capability and thus represents a potential source of misclassification. On a national level, it is difficult to know how primary care doctors used the influenza diagnosis (R80) when seeing a patient presenting with ILI. Alternative diagnoses such as "fever", "upper respiratory tract infection" and "pneumonia" could also have been used as possible diagnoses when suspecting influenza. If this practice differs among primary care doctors in Norway, misclassification will be present. There is also a possible misclassification the other way around. ILI during the first wave of the pandemic was mainly due to rhinoviruses (Anestad 2011).

Nondifferential misclassification of the exposure variables is a problem in **Paper III**. The clinical risk groups for severe influenza outcomes are well defined by the WHO and in national guidelines. We used a pragmatic search based on diagnoses from consultations with the GPs in the pre-pandemic period. The use of ICPC-2 from primary care records is a relevant proxy for defining chronic conditions (O'Halloran 2004). Because we used routine data, our study shares the limitations of other studies using routine data, particularly reliance on the quality of clinical data and specifically diagnoses. Some risk groups are probably underreported. For example if some patients had their regular care supplied from specialists in the inclusion period, they are not identified as a risk patients during the pandemic period. They will then be falsely

categorised as non-risk patients. The problem with underreporting cases in clinical risk groups is that it may affect the associations found in the study. If underreporting has occurred, the associations reported will probably be weaker than reality. People with chronic diseases are frequent users of OOH services, and this is specifically so for those patients who are not familiar with their GP (Flarup 2014). We found that 14% of the patients with ILI who attended the primary care services were from risk groups. The number should be higher if underreporting has occurred. However, the problem with underreporting is probably limited due to the long inclusion period of 18 months. More than 67% of patients in Norway had at least one consultation with their GP in 2009, and the number was even higher for older patients and those with chronic conditions (Hetlevik 2012).

Some diseases are better defined in the ICPC-2 chapters than others. Cardiovascular diseases, chronic lung diseases (asthma and chronic obstructive pulmonary disease), diabetes, cancers, and several liver diseases and neurological diseases have specific diagnosis codes that are easy to identify in the primary care records. It is hard to believe that GPs give those diagnoses of chronic diseases by random or false grounds. Undiagnosed patients will of course not be detected, for example a person with recurrent coughs, wheezes and pneumonias who if tested by spirometry would have been diagnosed with an obstructive lung disease. Even though chronic renal failure is identified as a risk factor for severe influenza outcome, there exists no specific or generic ICPC-2 code to identify that condition (Barnett 2012). For that reason this risk factor was omitted in **Paper III**.

Women who were pregnant during the pandemic period could have been detected with high accuracy if linking to the birth registry was available for the researchers. To come around that problem, we defined pregnancy when at least one ICPC-2 code specific for pregnancy was given by the GP in the pandemic period. Most women in Norway consult their GP several times during the pregnancy. Also, specific fees exist for prenatal consultations that increase the sensitivity of the diagnosis. Women who gave birth before they had the ILI diagnosis will be misclassified as belonging to a risk group in our study. Reversely, there is no reason to suspect that a high percentage of

women have been misclassified as non-pregnant by this inclusion method, due to the universal care delivered by GPs during pregnancy. So, the misclassification in this case would go in one direction. It means that associations concerning pregnancy as a risk factor for OOH services attendance may be weaker than reported in this study.

Morbid obesity, defined as BMI≥40, was identified as a new risk factor for severe influenza outcome during the pandemic (Louie 2011). Persons with overweight (BMI 25.0-29.9), or obesity (BMI ≥30.0) are found to have impaired immunity to influenza in experimental studies, thus posing a potential risk for severe influenza outcome in those individuals (Paich 2013). The two ICPC-2 codes used to identify obesity as a risk factor in **Paper III** do not correlate to a specific BMI-class. Also, persons with overweight and obesity are poorly documented and diagnosed in primary care records (Baer 2013). It is reason to believe that obesity as a risk factor is subject to nondifferential misclassification in one direction in this study. Due to underreporting of BMI and diagnosis of obesity in primary care medical record, the association reported will be diluted, i.e. the association in the population will be stronger than our reports.

5.1.3 Selection bias

Selection bias is a systematic error in a study that stems from the procedures used to select participants, which may influence study participation in a systematic way. This occurs when the association between exposure and the outcome differs for those who participate and those who do not participate in the study (Rothman 2012b). Participants were included based on contact with the GPs' office (**Paper I**) or attendance at the GPs' office and/or OOH services (**Paper II and III**). The composition of the study groups will depend on individuals' health seeking behaviour and the information recorded in the primary care records. Individuals with minor symptoms are less likely to seek medical help and a selection bias according to severity is reasonable to suspect (Bilcke 2014). Firstly, not all cases that were infected with influenza develop symptoms of disease. Secondly, not all with symptoms of influenza seek medical care. And thirdly, not all who seek medical care see a doctor

and eventually receive the influenza diagnosis. During the pandemic, different measures were addressed to the public to avoid pressure on the primary care services. These included the use of extended self-certification of sick leave and the release of oseltamivir as over-the-counter drug. And finally, the risk of getting the influenza diagnosis by a primary care doctor depends on the capacity of primary care services to admit new patients who seek medical care during an outbreak. Almost 75% of all contacts in Norwegian OOH services ended without a consultation with a doctor (Press 2010). Those who are otherwise healthy (including young persons) and people with no underlying clinical risk group are possibly underestimated when only those who attended primary care services are counted (Sauro 2006). And opposite, people with a clinical risk factor, the elderly, and especially those who regularly attend primary care, as well as those with moderate to severe symptoms are more likely to consult a doctor (Bilcke 2014).

The composition of included participants will be influenced by the response on the questionnaire (**Paper I**). Among all invited participants in the study reported in **Paper I**, only 27% responded. We did not have information about non-responders, so it is difficult to say if the groups of responders and non-responders differ in any respect. A selection bias according to age is suspected in **Paper I** because of skewed age distribution towards older age in our study compared to laboratory-confirmed cases of influenza in Norway (Norwegian Institute of Public Health 2009b). Children are less likely to respond to questionnaire studies if not assisted by an adult. Also, it is difficult to report symptoms from the youngest ones. In **Paper II and III** all cases were included and selection bias on this level was not a problem.

5.1.4 Internal validity and generalisability

The validity of a study is usually divided into two components: Internal and external validity. Internal validity is sensitive to systematic bias, such as confounding, selection bias and information bias. Strong internal validity is lack of systemic errors and is a prerequisite for external validity and for the results to be generalisable outside the source population (Rothman 2012a). In **Paper I**, the low response rate and hence

possible selection bias threatens the internal validity and thus pose a problem with generalisability. Due to aforementioned concerns, the ability to use the study as a prevalence study is thus also weakened. Information bias is probably also present due to misclassification of the disease (influenza). In the case of the serology part, eligible patients were tested with a gold standard influenza test and information bias was probably not present. We interpret that the internal validity of describing symptoms of patients from general practice with a confirmed influenza diagnosis as strong.

Paper II and III are both subject to misclassification errors, however selection bias was not present in those studies and plausible confounding was controlled for by multivariate regression analyses. The data are very complete on a national level and the representativeness is high. Results from studies reported in **Paper II and III** are generalisible to countries with a similar primary care system as Norway. They cannot be generalised to countries with a very different health care system where specialist services take a more central place, or in health care systems where referrals are not mandatory.

5.1.5 Effect modification

Effect modification refers to a situation in which a measure of effect changes over the value of some other variable (Rothman 2012b). In **Paper II** we found a significant effect modification for age and gender on the effect of diagnosis on practice type, as significantly higher ORs for ILI diagnosis were found for males and age group >50 years for these exposures. When effect modification is present, results should be given in strata. Men and younger people were significantly more often attended OOH services during the pandemic compared to women and those in age group ≥50 years. In **Paper III**, effect modification was statistically significant for centrality on the association between three risk factors (chronic lung disease, diabetes mellitus and "any risk factor") on the use of OOH services, as significantly higher ORs were found for these three exposures in more central areas than in rural areas.

5.2 Discussion of the results

5.2.1 Influenza attack rates

The influenza pandemic caused a substantial demand on the primary care services in Norway. Out of a population of 4.8 millions inhabitants (2009), ~2% received an ILI diagnosis in general practice during the pandemic (Table 2).

Table 2. Proportion of ILI in general practice in Norway during the 2009 pandemic

Source	Type of cases	§Source population (N)	ILI cases (n)	Proportion (%)
Paper I	ILI contacts	63,808	1,324	2.1
Paper II	ILI consultations	5,442,624	104,168	1.9
Paper III	ILI patients	4,799,252	94,404	2.0

§Source population is defined as the total number of ILI in general practice for the three respective studies. Paper III: Population in Norway per 1.1.2009

Corresponding number for OOH services is given in Table 3. ILI consultation rate was 4.6% and 0.4% of the population had a consultation in the OOH services due to ILI.

Table 3. Proportion of ILI in OOH services in Norway during the 2009 pandemic

Source	Type of cases	§Source population (N)	ILI cases (n)	Proportion (%)
Paper II	ILI consultations	496,529	22,632	4.6
Paper III	ILI patients	4,799,252	17,738	0.4

§Source population is defined as the total number of ILI consultations in OOH services and for Paper III: Population in Norway per 1.1.2009

For the 2008-9 season, the ILI consultation rate was 1.5% in general practice and 1.9% in OOH services respectively (**Paper II**).

The Norwegian Institute of Public Health has estimated that 900,000 individuals were infected during the 2009 pandemic in Norway, which gives a national infection rate of 19% (Kacelnik 2011). This gives consultation incidence rates among the infected of

10.5% in general practice and 2.0% in OOH services, when using the national estimate as the denominator. As of January 2010, 59% of a representative population sample had detectable antibodies to the A(H1N1)pdm09 virus either due to infection or immunisation and 44.9% of the sample had protective values (HI titre ≥40) (Waalen 2010). The sentinel GPs in Norway reported an average ILI consultation rate of 4.5% in the pandemic period (week 30-51 2009) (Norwegian Institute of Public Health 2009a). This number is higher than we found (Table 1). A possible explanation of this inconsistency in figures could be due to more precise definition of ILI among sentinels GPs. Sentinel GPs have years of experience with reporting ILI and are encouraged to use the ICPC-2 code "R80" restricted for cases of clinical influenza (Gran 2010). So, there are reasons to believe that GPs on a national level report ILI in their billing claims using several different diagnoses from the ICPC-2 chapters, for example "A03 Fever", "R78 Upper respiratory tract infection" and more. When we take a look at all GP consultations from the peak of the main pandemic wave, but exclude the consultations with diagnosis R80 (Figure 4) we observe a peak in week 44 that corresponds well to the peak of ILI in Norway. Such a peak is not observed in the same weeks for 2008 (data not shown). This gives evidence to our concerns about the method of identifying ILI cases from billing claims. An alternative interpretation of the peak observed in Figure 4 could represent a true increase in non-influenza consultations in general practice. This is supported by the fact that our method of identification of ILI, in line with the new primary care influenza surveillance based on claims data seems to follow the same patterns as the current sentinel GP surveillance system (Hauge 2014). Also, claims-based ILI is found reliable in USA for capturing influenza activity in the population (Viboud 2014).
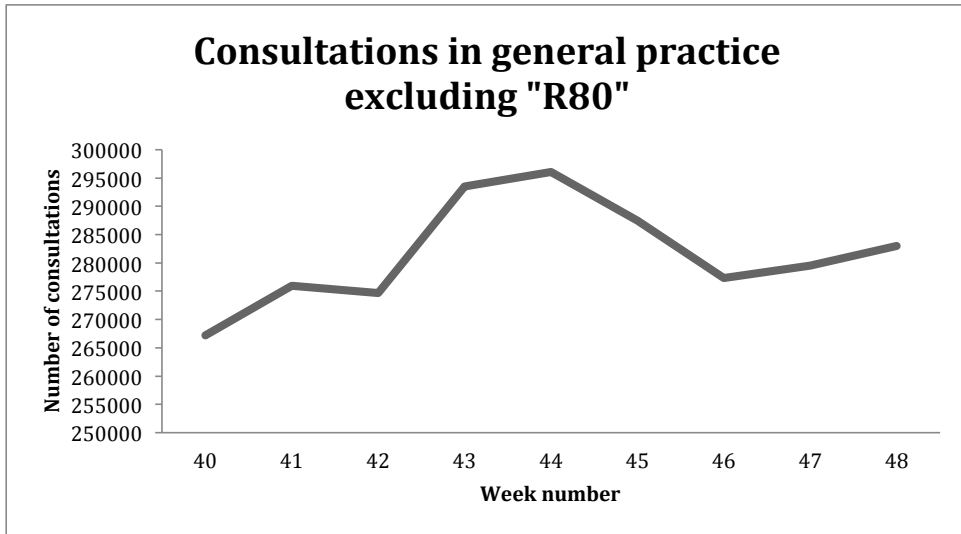
Consultations in general practice excluding "R80"

Figure 4. Consultations per week in general practice in Norway during week 40-48 2009 excluding diagnoses with ICPC-2 code "R80 influenza".

In China the annual incidence rate of outpatients ILI was 19.2 per 1000 population in 2009 (Guo 2012). The clinical attack rate in USA was 20% (Shrestha 2011) and only 5% in Denmark (Molbak 2011). In contrast to many countries in Europe, Norway experienced much higher number of ILI cases during the pandemic compared with the preceding epidemic seasons (Meeyai 2013). Reasons for this heterogeneity in number of ILI cases and high number of ILI cases in several countries are not known. It is discussed by Meeyai et al. that countries with improved public communication systems encouraged possible cases to seek medical attention thus explaining the higher ILI rates in some countries, including Norway.

5.2.2 Primary care utilisation

Utilisation according to age (Paper II and III)
The first papers on the novel influenza virus reported a skewed age distribution towards younger age compared with seasonal influenza, where mostly elderly is infected (Cao 2009, Dawood 2009, Dominguez-Cherit 2009, Kumar 2009). The median age was 20-44 years in those aforementioned papers. We found a median age

of 29.4 years during the pandemic period and a median age of 36.5 years in ILI patients in the 2008-9 season (**Paper II**). During the pandemic, 43.9% of ILI patients were below 20 years of age, and only 10.4% were ≥50 years of age. In general practice, 29.0% were below 20 years of age and 15.9% were ≥50 years of age (**Paper III**). Among all ILI patients, there was a tendency for the youngest ILI patients to use OOH services more than their older counterparts (26.1% in age group ≤20 years and 13.5% in age group >20 years) (**Paper II**). The high utilisation of OOH services among young patients during the pandemic was expected as young children (0-9 years) have the highest contact rates in Norwegian OOH services (Hansen 2009). Also, the clinical attack rates were highest among children and young adults due to no previous immunity to the A(H1N1)-like viruses (Miller 2010, Waalen 2010). According to Poehling et al., children (0-5 years) had 10-250 times as many influenza-related outpatient consultations than hospitalisations during two consecutive influenza seasons thus representing a major burden on the primary care services (Poehling 2006).

To further evaluate young age as an independent risk factor for attending OOH services with ILI during the pandemic, I performed additional multivariate regression analyses with practice type as outcome variable (reference variable: general practice) and age dichotomized at 20 years of age as exposure variable (reference variable: ≥20 years of age). This gave an unadjusted OR = 1.91 (95% CI 1.85, 2.00) and an adjusted OR = 1.45 (95% CI 1.41, 1.56) when controlling for gender, centrality and clinical risk groups ("any risk"). In conclusion, young age (<20 years) was an independent risk factor for attending OOH services compared to general practice for ILI during the pandemic.

Utilisation according to risk groups (Paper III)

We found that pregnancy, diabetes, chronic lung disease, and cardiovascular disease were risk factors that were statistically significantly associated with attending the OOH services among patients with ILI. Also ILI patients with neurological disease and conditions associated with immune deficiency (including cancers) had increased risk of attending OOH services. However, the associations found were weak. The

increased risk of attending OOH services may reflect a real increased risk among those belonging to a risk group. Alternatively, it may reflect a higher likelihood of getting an influenza diagnosis recorded because such patients are more likely to use the OOH services on a regular basis or because they are more careful about their health and more likely to report fever and other flu symptoms to the doctor. In a British study, factors like fear, anxiety or if the condition was felt urgent were associated with increased OOH service use (Drummond 2000). The increased attention in national newspapers about the pandemic and its possible serious consequences could have led to higher OOH utilisation among people at risk (Lundh 2009) and especially for those who were pregnant during the pandemic (Fjellheim 2009). People with chronic diseases are frequent attenders both in general practice and OOH services, and they have higher rates of hospitalisation (Glynn 2011). A large cross sectional study from Danish OOH services found that 30% of adult patients contacting OOH services were by people with chronic diseases, in which cardiovascular disease, diabetes and cancer constituted the largest groups. People with chronic diseases were more likely to receive a face-to-face consultation (Flarup 2014). In light of the advice from the Norwegian health authorities where patients at increased risk of severe outcomes should be prioritised in primary care services, we can conclude that the OOH services seemed to prioritise in accordance with the advice.

Utilisation according to number of consultations with the GP in the pre-pandemic period (Paper III)

One of the aims was to investigate the relationship between GP visits before the pandemic and utilisation of primary care during the pandemic. This study tests the hypothesis that continuity of GP care protects against using the OOH services for an acute illness such as influenza. Our study showed that having at least one consultation prior to the pandemic was associated with lower risk of attending OOH services for ILI as compared to attending the GP. Reversely, no GP consultation history was associated with OOH service utilisation for ILI during the pandemic. Continuity of care has two important dimensions; longitudinality and intensity (Hansen 2013). The former is describing the duration of doctor-patient relationship and the latter is describing intensity of visits. According to two studies from Norwegian general

practice, only longitudinality was associated with reduced specialist care and higher patient satisfaction. High frequency of visits was associated with presence of chronic diseases and with increased probability of specialist use (Hansen 2013, Hjortdahl 1992). In our study, the exposure variable was number of consultation with the GP in an 18-months period prior to the pandemic. Whether this approach was a good surrogate for longitudinality of care or intensity of care, or perhaps a mixture of both, can be discussed. Our results suggest that continuity of care could possibly reduce the use of OOH services during a pandemic.

5.2.3 Primary care capacity (Paper II)

The capacity of a primary care system depends on several factors including available doctors in general practice and OOH services, total hours available for patient appointments, waiting time and booking preferences.

Influenza epidemics are expected to put extra pressure on the primary care services (Bocquet 2010, Pitman 2007). In **Paper II** we compared the 2008-9 influenza epidemic to the 2009 pandemic in terms of consultations volume during both influenza periods. Respectively, 10.7% of ILI consultations in the 2008-9 season and 17.8% ILI consultations in the pandemic period were conducted in the OOH services. This constituted a 5.5-fold increase of ILI consultations in the OOH services during the 2009 pandemic season. Comparing the utilising pattern of these two periods sheds new light on the interaction between OOH services and general practice during a period with increased patient load. The pandemic period looked quite similar in the start of the 2008-9 season: About 1/10 of ILI consultations were conducted in the OOH services. This proportion held through the whole 2008-9 season. When the pressure on the primary care increased during the pandemic autumn wave, the ILI consultation proportion changed substantially towards a higher proportion of OOH service consultations. At the peak, 25% of all ILI consultations were conducted in OOH services, compared to 10% on average during a regular season. This change in proportion between primary care services can be expressed as a mechanism of

adaptation in which OOH services adapted by increasing the capacity for ILI to the benefit of other encounters (Figure 5).
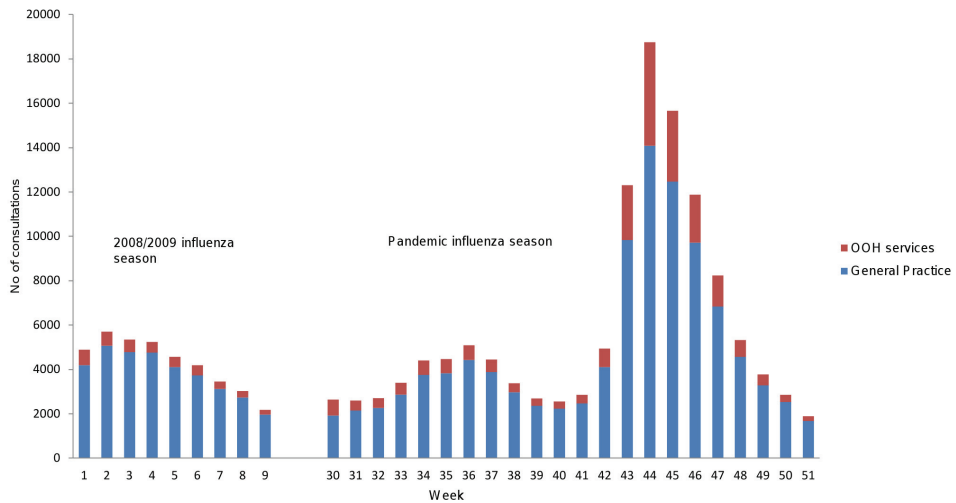
*Figure 5. ILI consultations in general practice and OOH services during 2008-9 influenza season (week 1–9 2009) and pandemic influenza season (week 30–51 2009)(**Paper II**).*

In absolute numbers, however, general practice had the largest capacity due to substantially more doctors working compared to the OOH services. Additionally, the capacity for non-influenza consultations was increased in general practice during the autumn pandemic wave (Figure 4) so that the total capacity for consultations increased. In the OOH services the total capacity was unchanged compared to pre-pandemic phase so that non-influenza consultations decreased to the benefit for influenza patients. Increasing the primary care capacity during outbreaks of emerging infectious diseases is an important step in first line preparedness and may prevent unnecessary hospital admissions (Bocquet 2010, Lurie 2009).

5.2.4 Clinical characteristics of influenza-like illness (Paper I)

There are few published papers on the clinical characteristics of influenza from patients consulted in general practice (Michiels 2011, Sessa 2001, van Elden 2001). Regarding pandemic influenza, two reports from general practice were restricted to children and teenagers (Hawkes 2011, Nitsch-Osuch 2010) and only one study described clinical features of patients with influenza from a primary care setting during the pandemic without restriction to a specific age group (Duque 2011). Among the laboratory confirmed influenza cases in **Paper I**, fatigue (94%), cough (82%), headache (76%) and fever (56%), were the most common symptoms. This is comparable with the results from Nitsch-Osuch et al. and Dugue et al. except that fever was reported in a lower percentage among our cases. However, 97% of confirmed cases reported fever and/or feverishness in our study. Also, longer periods of cough and illness duration (median length 9 days) were reported among confirmed cases compared to those with negative tests (**Paper I**).

Treatment with oseltamivir was reported in 140 patients (39%) in **Paper I**, and was significantly associated with the age group ≤40 years. However, this treatment did not affect the duration of symptoms of influenza disease compared to patients not reporting such treatment. In a recent systematic review on oseltamivir treatment, this was found to reduce symptoms in adults by 16.7 hours (Jefferson 2014b). Only two patients in our study reported hospitalisation, both patients belonging to a clinical risk group, thus reflecting the mild appearance of the A(H1N1)pdm09 virus. To conclude, symptoms of pandemic influenza were similar to seasonal influenza symptoms, findings in line with others (Belongia 2010, Shiley 2010).

5.2.5 Self-reported adherence to precautionary behaviours (Paper I)

Participants in **Paper I** reported high level of adherence to personal protective measures. This study was conducted when the pandemic peaked in Norway and simultaneously with the campaign launched by the health authorities for better hygiene. The campaign focused on cough and hand hygiene as an infection preventive measures against influenza. In the same period there were reduced contact rates for infectious diseases to OOH services (Sandvik 2011). The results suggest that the campaign was effective (**Paper I**, Sandvik 2011). We found a strong correlation of adherence to advice with female gender. Women were more likely to adhere to cough etiquette and applied hand washing more often than men. We found no gender differences concerning social distancing or use of hand disinfectant and the use of face masks. Also, there were no differences in preventive measures according to age. Frequent hand washing was associated with female gender among health care workers (La Torre 2009, Savas 2010) and in the general population in Hong Kong (Cowling 2010a, Lau 2010) and China (Lin 2011). A study from a primary care clinic in Malaysia did not find gender differences in practices regarding hand washing and similar measures; however a positive attitude towards preventive measures was significantly associated with female gender (Latiff 2012).

5.2.6 Attitudes towards influenza vaccination and disease (Paper I)

A positive attitude to vaccination of the whole population against A(H1N1)pdm09 was reported by the majority of participants in **Paper I**. The perceived risk of getting influenza was, however very low. This finding is puzzling as the responders' were selected from patients who had recently experienced influenza. Only ¼ of responders would consider influenza vaccination the succeeding year. A negative attitude towards the influenza vaccine in general and regarding the pandemic vaccine was associated with female gender and age >40 years (**Paper I**). Toh et al. reported similar findings concerning attitudes towards pandemic vaccination among health care workers in primary care clinics in Singapore (Toh 2012). Concerns about pandemic vaccine side effects were also associated with female gender but with age ≤40 years. Fewer

concerns were reported for the seasonal vaccine than for the pandemic vaccine. Our study suggests that there were some misunderstandings in the public concerning risk and safety of influenza vaccine and influenza disease. More effort from the health authorities should be taken in order to improve communication about vaccine safety and risk as well as the general knowledge about influenza (Dedoukou 2010, Aavitsland 2014).

6. Conclusions

This thesis contributes to the present knowledge about the 2009 influenza pandemic viewed from a primary care perspective.

We found that clinical characteristics of the novel A(H1N1)pdm09 influenza were similar to seasonal influenza except for a skewed age curve towards younger people.

Women reported better adherence to precautionary behaviour during the pandemic than men and were more concerned about side effects of the pandemic vaccine.

The primary care services were exposed to a significant increase in the number of consultations during the pandemic as compared to a seasonal influenza epidemic. Primary care services in Norway showed the ability to increase capacity and prioritise, according to authority advice during a period of increased patient surge. Young age was associated with increased risk of attending OOH services.

Clinical risk groups for severe influenza outcome, and especially those being pregnant during the pandemic or suffering from diabetes, chronic lung diseases or cardiovascular diseases, had an increased risk of attending OOH services with ILI.

Continuity of GP care in terms of having had consultations prior to the pandemic was associated with lesser risk of attending OOH services with ILI during the pandemic.

7. Future research

During the last decade we have witnessed outbreaks of avian influenza, Severe
Acquired Respiratory Distress (SARS), Middle East Respiratory Syndrome (MERS)
and currently the devastating Ebola outbreak in Africa, all showing that surveillance,
research and global action are needed to control infectious diseases.

Influenza viruses are driven by continuous change in its genetic material to cause
seasonal epidemics and occasional pandemics. Primary and community health care
services are in most countries the first line of care for people suffering from influenza.
Substantially fewer are in need of hospital care. However, much of the current
knowledge about influenza is derived from hospital and experimental research.

Primary care is a field where knowledge is highly needed and still lacking the most.
More efforts should be done to study the clinical features of influenza in patients
seeking primary care, and specifically for those belonging to a risk group.

Clinical research in general practice is difficult with respect to logistics, especially
with regard to the process of recruitment of doctors and patients at a time when things
must happen quickly such as during epidemics. Primary care research networks may
be a step to change this situation (Rortveit 2014).

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