Diplomarbeit

Prevalence of vaccination against pneumococcal infection, influenza and pertussis in hospitalized cardiologic and pneumologic patients at the University Hospital LKH Graz

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Graz, am 03.07.2018 *Tanja Röblreiter eh*

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1 Abstract

1.1 Aim

According to the “Impfplan Österreich 2017” created by the Austrian federal ministry of health and the S3 Guidelines for prevention of pneumonia vaccination against influenza, pertussis and pneumococcal infection is recommended for all cardiologic and pneumologic patients (1,2). As a result of the vaccinations these vulnerable group of patients should be protected from exacerbation of their underlying chronic diseases and from the increased mortality related to infections. However, research data about the prevalence of pneumococcal, influenza and pertussis vaccination within cardiologic and pneumologic patient groups from German speaking area and especially Austria are not available and our study gives insight into possible vaccination gaps. These vaccination gaps in hospitalized pneumologic and cardiologic patients can be anticipated, based on an US American study from 2005 stating that only one out of three patients with a chronic cardiovascular disease is vaccinated against influenza despite the recommendation for annual vaccination by the American Heart Association (AHA) and American College of Cardiology (ACC) (3).

1.2 Methods

We analysed data of 200 cardiologic and pneumologic patients hospitalized between 1st and 31st of April 2017 at the University Hospital Graz (department of pneumology or cardiology) with a questionnaire and a MEDOCS research. We collected the following information: age, gender, underlying diseases and relevant medication; Table 1 and Table 2 illustrate the collected clinical data in detail.

1.3 Results

We analysed data of 200 patients, 133 male (66.5%) and 67 female (33.5%). Of these, 148 (74.0%) were cardiologic patients and 52 (26.0%) pneumologic patients with a median age of 68 and an average age of 66.2 years (±SD 14.7 years). Out

of the 200 included patients only 17.5% were vaccinated against influenza, 11.5% against pertussis and 18.5% against pneumococcal infection. 30.3% of the influenza unvaccinated patients but only 17.1% of the vaccinated patients suffered from acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017. Vaccinated patients also suffered less from respiratory tract infections in this period (28.6% vaccinated versus 43.0% not vaccinated). The other vaccinations did not show such big differences in the appearance of acute rhinopharyngitis (30.4% vaccinated against pertussis versus 27.7% not vaccinated; 32.4% vaccinated against pneumococcal infection versus 27.0% not vaccinated) and respiratory tract infections (47.8% vaccinated against pertussis versus 39.6% not vaccinated; 37.8% vaccinated against pneumococcal infection versus 41.1% not vaccinated). Furthermore, it was noticeable that patients who had had no contact to a doctor between 1st of December 2016 and 31st of March 2017 were vaccinated less than patients that were in contact with doctors in this period (5.7% of patients vaccinated against influenza versus 9.7% of patients not vaccinated had no contact, 4.4% in patients vaccinated against pertussis versus 9.6% of patients not vaccinated, 2.7% of patients vaccinated against pneumococcal infection versus 10.4% of patients not vaccinated).

1.4 Conclusions

The presented results are the first data from hospitalized pneumologic and cardiologic Austrian patients regarding the prevalence of influenza, pertussis and pneumococcal immunization. In hard contrast to guidelines, official recommendations and the broad scientific evidence about the benefit of vaccination in high risk groups, the overall vaccination rate for influenza, pertussis and pneumococcal immunization was in our cohort remarkable low (17.5% influenza vaccination, 11.5% pertussis vaccination and 18.5% pneumococcal vaccination). These findings show that many patients that would actually benefit from these vaccinations are in a large part not convinced of the advantages or rather not enlightened about the exact effects of the vaccinations. All in all, the results underline the urgent need to improve and increase the immunization coverage of cardiologic and pneumologic patients and to strengthen their

awareness of the significance of the vaccinations to protect them from infection related complications and the deterioration of their underlying diseases.

2 Zusammenfassung

2.1 Zielsetzung

Für alle Patienten/Patientinnen mit kardialen oder pulmonalen Grunderkrankungen ist entsprechend dem österreichischen Impfplan 2017 des Bundesministerium für Gesundheit und der S3-Leitlinie zur Pneumonie-Prävention von 2016 die Influenza-, Pneumokokken- und Pertussis-Impfung empfohlen (1,2). Dadurch sollen diese vulnerablen Patientengruppen vor entsprechenden Infektionen und deren negativen Folgen auf die kardiopulmonalen Grunderkrankungen geschützt werden. Da im deutschsprachigen Raum und im speziellen Österreich keine Impfprävalenz-Daten für kardio- pulmonal vorerkrankte Patienten/Patientinnen bekannt sind, gibt unsere Studie daher erstmals Einblick in mögliche Behandlungsdefizite. Diese sind anzunehmen, da eine US amerikanischen Studie bereits 2005 zeigen konnte, dass trotz der AHA und ACC Empfehlung zur jährlichen Influenza-Impfung nur einer von drei Patienten/Patientinnen mit chronischer Herz-Kreislauf-Erkrankung gegen Influenza geimpft war (3).

2.2 Methoden

Es wurden 200 kardial oder pulmonal erkrankte Patienten/Patientinnen eingeschlossen, die zwischen dem 1. und dem 31. April 2017 in der Abteilung für Kardiologie oder Pneumologie des LKH Graz stationäre behandelt wurden. Mit Hilfe eines Patientenfragebogens wurden impfrelevante Daten erhoben. Zusätzlich wurden folgende klinische und epidemiologische Daten durch eine MEDOCS Recherche erfasst: Alter, Geschlecht, Grunderkrankung und relevante Medikation; Tabelle 1 und Tabelle 3 zeigen die gesammelten klinischen Daten im Detail.

2.3 Resultate

Wir haben die Daten von 200 Patienten/Patientinnen analysiert. Von diesen waren 133 (66,5%) männlich und 67 (33,5%) weiblich; 148 (74,0%) waren kardiologische Patienten/ Patientinnen und 52 (26,0%) pulmologisch erkrankte

Patienten/Patientinnen. Der Altersmedian lag bei 68 Jahre und der Mittelwert des Alters bei 66,2 Jahre (±SD 14,7 Jahre). Von den eingeschlossenen 200 Patienten/Patientinnen waren nur 17,5% gegen Influenza geimpft, 11,5% gegen Pertussis und 18,5% gegen Pneumokokken. 30,3% der nicht gegen Influenza geimpften Patienten/Patientinnen und 17,1% der geimpften Patienten/Patientinnen hatten zwischen dem 1. Dezember 2016 und dem 31. März 2017 einen grippalen Infekt. Geimpfte Patienten/Patientinnen hatten zusätzlich weniger Atemwegsinfekte in dieser Zeit (28,6% der geimpften versus 43,0% der nicht geimpften Patienten/Patientinnen). 30,4% der gegen Pertussis geimpften Patienten/Patientinnen hatten einen grippalen Infekt und 27,7% der nicht geimpften; 47,9% der geimpften Patienten/Patientinnen hatten einen Atemwegsinfekt und 39,6% der nicht geimpften. Weiters hatten 32,4% der gegen Pneumokokken geimpften Patienten/Patientinnen einen grippalen Infekt und 27,0% der nicht geimpften; 37,8% der geimpften Patienten und 41,1% der nicht geimpften hatten einen Atemwegsinfekt. Außerdem konnten wir sehen, dass Patienten/Patientinnen, die zwischen dem 1. Dezember 2016 und dem 31. März 2017 keinen Kontakt zu Ärzten hatten, unzureichender geimpft waren als Patienten/Patientinnen, die in dieser Zeit Kontakt hatte (5,7% der gegen Influenza geimpften Patienten/Patientinnen versus 9,7% der nicht geimpften hatten keinen Kontakt, 4,4% der gegen Pertussis geimpften Patienten/Patientinnen versus 9,6% der nicht geimpften, 2,7% der gegen Pneumokokken geimpften Patienten/Patientinnen versus 10,4% der nicht geimpften).

2.4 Schlussfolgerungen

Respiratorische Infektionen können bei kardiopulmonal vorerkrankten Patienten/Patientinnen häufig zu einer akuten Verschlechterung ihrer Grunderkrankung führen. Die Prävention von respiratorischen Infektionen hat daher bei diesen Risikopatienten/Risikopatientinnen einen hohen Stellenwert. Unsere Resultate sind die ersten österreichischen Daten zur Impfprävalenz von Influenza-, Pertussis- und Pneumokokken-Impfungen bei kardial oder pulmonal erkrankten Patienten/Patientinnen. Die festgestellte sehr niedrige Impfrate von 17,5% (Influenza-Impfung), 11,5% (Pertussis-Impfung) und 18,5%

(Pneumokokken-Impfung) steht in klarem Widerspruch zu internationalen kardiovaskulären und pneumologischen Leitlinien und nationalen Impfempfehlungen. Die Ergebnisse zeigen, dass viele der von uns befragten Risikopatienten/Risikopatientinnen, die eigentlich von diesen Impfungen profitieren würden, entweder nicht von der protektiven Wirkung der Impfungen überzeugt sind oder bisher nicht ausreichend über den Nutzen der Impfungen aufgeklärt wurden. Mit Bezug auf die oben genannten klar indizierten und empfohlenen Impfungen kann zusammenfassend gesagt werden, dass eine erhebliche Unterversorgung kardiologisch und pulmologisch erkrankter Patienten/Patientinnen vorliegt; die Impfprävalenz muss in diesen Patientengruppen dringlich verbessert werden. Die aktuell verwendeten Strategien zur Verbesserung der Impfraten sind nicht effektiv und müssen reevaluiert werden.

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List of abbreviations

(AE-)COPD – (acute exacerbation of) chronic obstructive pulmonary disease

ACC – American College of Cardiology

ACE-I – angiotensin converting enzyme inhibitor

AHA – American Heart Association

ARDS – acute respiratory distress syndrome

BMI – body mass index

CAP – community acquired pneumonia

CDC – The United States Centers for Disease Control and Prevention

CHD – coronary heart disease

COPD - chronic obstructive pulmonary disease

CVD – cardiovascular disease

DTaP – diphtheria, tetanus and acellular pertussis vaccine

H – hemagglutinin

ICD – International Classification of Diseases

ICS – inhalative corticosteroid

IIV – inactivated influenza vaccine

IPD – invasive pneumococcal disease

KHK – koronare Herzkrankheit

LABA – long acting beta agonist

LAIV – live attenuated influenza vaccine

LAMA – long acting muscarinic antagonist

LDL – low density lipopolysaccharide

N – neuraminidase

PCV – pneumococcal conjugated vaccine

PPI – proton pump inhibitor

PPV – pneumococcal polysaccharide vaccine

SD – Standard deviation

Tdap – tetanus, diphtheria and acellular pertussis vaccine

3 Introduction

3.1 Influenza

3.1.1 Epidemiology and pathogenesis

The influenza virus, a RNA virus belonging to the family of Orthomyxoviruses, is one of most widely spread human pathogens and causes feverish infections in 20.0% of all children and 5.0% of all adults. During the winter months in Austria there are approximately 380 000 people affected by the infection annually (4). The virus spreads mainly by droplet and aerosol transmission of infected respiratory secretions. Influenza diseases in humans are mostly caused by the types A and B, but in sporadic cases it is also caused by the less common type C (5). The influenza A virus is further divided into different subtypes, specified by the surface antigens hemagglutinin (H) and neuraminidase (N). Because of frequent mutations and antigenic shifts, which are a result of the numerous virus replications, there are many different strains with varying antigens. These antigenic shifts occur more often in influenza A than in influenza B (6). Because one specific antibody only protects from one particular antigen, it provides no immunity against different influenza subtypes. Therefore it is necessary to vary the vaccines against influenza once or twice a year and furthermore to vaccinate once every year, to provide the best protection against currently circulating or new subtypes (7).

3.1.2 Clinical manifestation

After an incubation period of a few hours to a few days, the infection leads to different symptoms depending on immunologic, virus specific and individual characteristics. Typical symptoms are myalgia, high fever, headache, sore throat, cough, and a general feeling of strong discomfort, but sometimes there are atypical courses with diarrhoea, rhinitis and nausea (2,7). Elderly people above 65 years, children less than two years and people with chronic diseases or reduced immunity have a higher risk of influenza related morbidity and mortality.

Preexisting comorbidities like chronic obstructive pulmonary disease (COPD) or cardiovascular diseases (CVD) frequently deteriorate during influenza infections. Moreover, the infection can lead to severe pneumonia or myocarditis (8,9). In case of influenza-associated pneumonia, bacterial superinfections with *Staphylococcus aureus* or *Streptococcus pneumoniae* are common and severe. *Streptococcus pneumoniae* superinfections are preventable by pneumococcal vaccination (9).

3.1.3 Treatment

In otherwise healthy persons influenza infections are usually non-severe and do not require antiviral or other specific treatment.

However, in comorbid patients (e.g. known CVD, neurological diseases, chronic pulmonary diseases, severe obesity, diabetic mellitus, pregnant woman) influenza infections can be severe or are able to trigger life-threatening exacerbations of the underlying disease. In these high-risk patients, antiviral therapy should be started within the first 48 hours after onset of symptoms. There are two classes of antiviral drugs for the treatment of influenza (9):

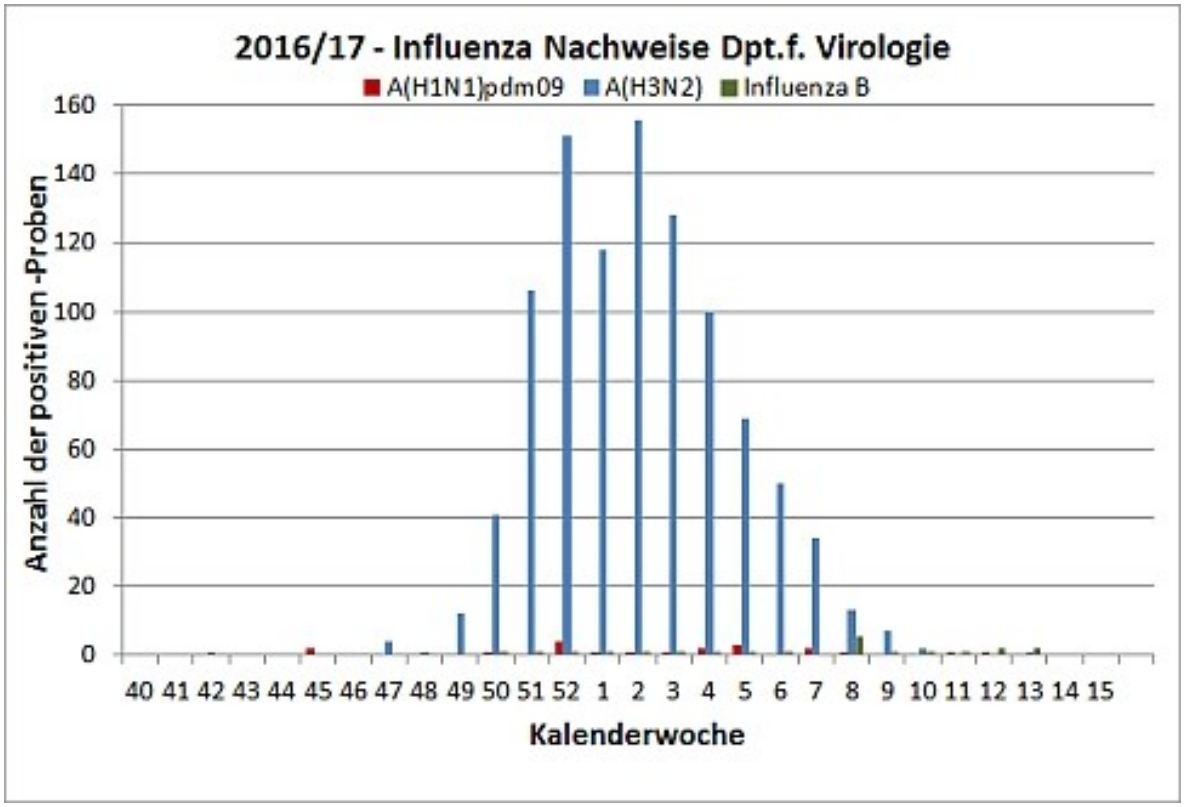
Adamantanes (amantadine and rimantadine) are M2 proton channel blockers and thus prevent the uncoating of the virus and the release of viral RNA in the cytoplasm of infected cells. They are only effective against influenza A and since a high number of virus strains have a documented resistance for adamantanes, amantadine and rimantadine are currently not recommended for the prophylaxis and the treatment of influenza (9,10).

Neuraminidase inhibitors prevent the release of viral particles from infected epithelial cells and thereby further expansion in the respiratory tract. They are active for the treatment and the prophylaxis of Influenza A and B virus. In clinical settings only two neuraminidase inhibitors are used and relevant: oseltamivir, an oral capsule administered orally, and zanamivir, a dry powder administered by inhalation (9,10).

3.1.4 Season

In the northern hemisphere the influenza season lasts from November till April, on the southern hemisphere from May till October and in tropical regions it lasts the whole year. In Austria, the start of the influenza season 2016/2017 was in calendar week 49/2016 with an increase in the morbidity rate, although sporadic cases of infections were also reported since calendar week 42/2016. Thereby, in this season the flu epidemic did start about four to six weeks earlier than usual in Austria. The peak was reached between calendar week 52/2016 and 2/2017, and after that the activity of the virus continuously decreased and ended in calendar week 9/2017. After that only sporadic influenza infections were reported until calendar week 13/2017 (11).

Figure 1 Influenza season 2016/2017 in Austria (adapted from (11)*)*



3.1.5 Recommendations for vaccination

The WHO recommends vaccinating once a year (except for children who are vaccinated the first time before the age of eight, in this case two vaccinations in distance of four weeks are recommended (6)) before but also during the influenza

season, because of the high mutation rate of the virus and the great variety of strains and subtypes (7). The immunization is recommended for every person who would like to protect him- or herself, but it is especially recommended for children from the age of six months and people at high risk for influenza infection. This includes people who suffer from chronic diseases like COPD, cardiovascular diseases (except arterial hypertension), neurologic conditions, renal and metabolic diseases, people who have close contact with infants and people with chronic diseases, women who are pregnant or are planning to become pregnant in the influenza season, morbidly obese people with a BMI over 40, people older than 50 years and healthcare workers (2,8,13).

3.1.6 Vaccines

There are two types of influenza vaccine available, the inactivated influenza vaccine (IIV) that is administered intramuscularly or intradermally and the live attenuated influenza vaccine (LAIV) that is administered intranasally. The immunity after IIV vaccination only persists for less than one year due to the continuous antigenic shift of influenza viruses, therefore it is necessary to change the vaccine each year. (9). For example, since influenza A (H1N1)pdm09, A (H3N2) and influenza B were the most common subtypes in season 2015/16 (12), it was advised that trivalent vaccines contain an A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus and a B/Phuket/3073/2013-like virus; quadrivalent vaccines in addition should contain an B/Brisbane/60/2008-like virus (14).

Another reason for the short duration of the protection provided by the vaccine is the steady decrease in the number of IIV induced antibody. Nonetheless the immunization provides a 60.0% protection against influenza among healthy people younger than 65 years, a 50.0% to 60.0% effectiveness in preventing hospitalization and an 80.0% effectiveness in preventing death among elderly people. LAIV is only approved for the immunization of healthy, non-pregnant people between two and 49 years and provides sufficient protection in this age group (9).

3.1.7 Influenza and chronic diseases

The general mortality risk in community-dwelling elderly persons above 65 decreases by 10.0% after the first influenza immunization and by 24.0% after the revaccination (15).

CAP is caused by a viral infection in up to 22.0% (in 9.0% by an influenza virus) (1). Although there is little evidence that influenza vaccination prevents CAP in healthy adults above 65 and no evidence that it prevents CAP in adults above 65 with comorbidities and in adults who suffer from COPD, influenza immunization is highly recommended in international CAP guidelines, because well proven evidence of above mentioned positive effects on general morbidity and mortality and because the highly increased mortality in CAP caused by an influenza infection and following bacterial superinfection (16,17).

Moreover, influenza vaccination provides an impressive reduction of cardiovascular mortality because acute influenza diseases increase significantly complications like myocardial infarction or acute coronary syndrome. These complications result from infection-associated cardiovascular stress (fever, dehydration, hypotension and tachycardia) but also from inflammation-triggered atherosclerotic plaque destabilisation and ruptures (18). Therefore, the AHA/ACCF Guideline for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommended 2011 that all patients should be vaccinated annually (19,20). Strong evidence for this recommendation provided the FLUVACS trial, a randomized, controlled study regarding the benefit of the influenza vaccination on patients with acute coronary syndrome and planned interventions. The trial included 200 myocardial infarction patients and 101 patients with planned angioplasty/stenting and the patients were randomly assigned to receive influenza vaccination or to remain unvaccinated. After one year cardiovascular death was considerably higher among unvaccinated patients (17.0%), than in vaccinated patients (6.0%), and the relative risk was 0.34 as compared to controls. Patients who had suffered from acute myocardial infarction also strongly profited of the vaccination (four events in vaccinated participant versus 21 events in the unvaccinated) (21).

Regarding AECOPD, up to 36.0% of all cases are caused by proven influenza A or B virus infections, and therefore it is clearly recommended to vaccinate all COPD patients once a year (2,22). The occurrence of AECOPD significantly decreased in patients vaccinated against influenza compared to those treated with a placebo and beyond that the mortality in patients with COPD was also reduced (16,17). In general, patients with chronic lung disease benefit from influenza vaccination, leading to fewer hospitalizations and reduced mortality during the influenza season (23).

3.2 Pertussis

3.2.1 Epidemiology and pathogenesis

Pertussis, commonly also known as whooping cough, is a highly infectious acute disease that affects approximately 60 million people each year, whereas most cases occur in developing nations with low immunization coverage (24). In Austria there were 1208 reported cases in 2016 (2). It is caused by the gram negative, aerobe and rod-shaped bacterium *Bordetella pertussis* (9). The bacterium is mostly transmitted by droplets of infected human respiratory secretions (25). The bacteria attaches to epithelial cilia of the upper respiratory tract and produces toxins and mediators like pertussis toxin, tracheal cytotoxin, filamentous hemagglutinin (FHA), agglutinogens, adenylate cyclase and pertactin, which harm the respiratory epithelia, promote lymphocytosis and are therefore responsible for the secondary immune system triggered inflammatory response, which causes even more epithelial damage and associated symptoms in the upper respiratory tract (9,26).

The number of people who suffer from pulmonary complications due to an infection with *Bordetella pertussis* increased in Austria from 569 registered cases in 2015 to 1208 registered cases (1122 cases confirmed) in 2016. The largest increase in infections was noticeable in adults aged 40 to 45, but also in the age groups from 65 to 70 and from 15 to 20. This can among other things be explained

by the low revaccination rate in adults and the loss of seroprotection five to eight years after vaccination (2).

3.2.2 Clinical manifestation

After an incubation period of commonly seven to ten days, *Bordetella pertussis* infection manifests in three clinical stages (9). The first stage is called the catarrhal stage and is very similar to the common cold, with symptoms like low grade fever, non-purulent rhinitis and dry cough. After one to two weeks the cough progressively evolves into intense coughing fits and the second stage, the paroxysmal stage, begins (9,25).

At the end of a paroxysmal cough which also appears more often at night, the patient often has difficulty with drawing breath, which appears as “whoop”, therefore the name “whooping cough”. The coughing fits may also end with cyanosis, fatigue and vomiting due to the severe exspiratory effort (25,27).

In the third stage, the convalescent stage, the coughing fits slowly decrease over weeks, but may also reappear accompanied by respiratory infections months after the beginning of the *Bordetella pertussis* infection (9). In children severe complications during the infection include hypoxia, secondary bacterial pneumonia and ARDS, malnutrition due to the vomiting, encephalopathy, seizures and pneumothorax. Due to larger airways, live threatening complications are less frequent in adults, but syncopes, hernia, fracture of the thoracic cage and stress incontinence can occur in adult patients (2,9,25). Nonetheless, according to a Canadian study pertussis related complications are more frequent in vaccinated adults than in vaccinated adolescents (28.0% of adults but only 16.0% of adolescents suffered from complications) (28). Adults with co-morbidities like COPD or congestive heart failure might also be at higher risk for suffering pertussis related complications or a severe pertussis infection, although there are no studies that provide evidence for it (26,29).

3.2.3 Treatment

Antibiotics given very early during the catarrhal stage may reduce the severity of coughing fits, the duration of other symptoms and the time of bacterial shedding. In general, pertussis is a self-limiting disease. Even without antibiotic treatment, *Bordetella pertussis* is rapidly cleared from the upper respiratory tract. After three to four weeks of symptomatic disease the bacterium is no longer shaded and most people seem to overcome the infection without antibiotics within six weeks (30). Antibiotics given in the paroxysmal stage frequently do not shorten or reduce the symptoms but may have still a positive effect on transmission. Therefore, for pregnant women, health care workers and people who work in the surrounding of an infant, antibiotic treatment is recommended by the CDC for those who suffer from persistent cough for up to six weeks, to reduce the likelihood of transmission of the infection (31). Furthermore, the CDC recommends an antibiotics treatment with the macrolides Clarithromycin for seven days or Azithromycin for five days, because these macrolides are highly effective in the eradication of the bacteria *Bordetella pertussis* and cause less gastrointestinal adverse effects as for example Erythromycin (31).

Unfortunately to this day there is no proven effective treatment for the coughing fits, a study from 2014 found insufficient evidence to rate the effectiveness of corticosteroids, beta2- agonists, pertussis-specific immunoglobulin, antihistamines and leukotriene receptor antagonists (32).

3.2.4 Recommendations for vaccination

The vaccination against pertussis is included in the free immunization program in Austria. Because of the commonly occurrence and the severe clinical course of pertussis infections in infancy, it is recommended to vaccinate children after they reach the age of two months following a 2 + 1 schema (vaccinations at third, fifth and twelfth month of life). To complete the initial immunization the children get vaccinated with a combination vaccine containing diphtheria, pertussis, polio and tetanus at the age of seven to nine. After that a booster injection with this combination vaccine is recommended every ten years till the age of 60 and afterwards every five years. The immunization against pertussis is recommended

for everyone but is especially important for following groups: women who are planning on getting pregnant, pregnant women (but only between the 27th to 36th week of pregnancy), people in the surrounding of an infant that is too young to be vaccinated (adults can infect infants and children, who are more likely to suffer more severe infections and who have also a higher mortality), health care workers, people over the age of 60, smokers and people at a higher risk resulting from an underlying disease (for example COPD, a chronic cardiologic or pulmonary disease or permanent immunosuppression) (2).

3.2.5 Vaccines

The first pertussis vaccine was available in 1948 in the United States and was a whole cell vaccine, containing inactivated *Bordetella pertussis* cells. Effectiveness of the vaccination was 70.0% to 90.0%, but decreased rapidly after five to ten years until it offered only very little protection. Because of common side effects after the vaccination, like fever or local reactions such as swelling or pain, the safety of the vaccine was questioned and new purified acellular pertussis vaccines that vary in its composition (the concentration of the pertussis cells) for the different age groups were developed. The acellular vaccines are like the whole cell vaccines only available in combination with diphtheria and tetanus toxoids. There are two vaccines available for children (DTaP) from the age of six months to seven years, Infanrix® and Daptacel®, and two for adults (Tdap), Boostrix® and Adacel®. Both adult vaccines contain less diphtheria toxoid than the paediatric version and are approved for people from the age of ten (Boostrix®) or eleven (Adacel®) to the age of 64 (9). Studies showed that the paediatric acellular pertussis vaccines were more effective (efficiency was 80.0% to 85.0%) and local and systemic adverse effects occurred less often than in than the whole cell vaccines. Furthermore, it showed that adult acellular vaccines provided the same protection as the paediatric version, compared to the resembling antibody level triggered by the different vaccines (9).

3.2.6 Pertussis and chronic diseases

To this day there are no studies that prove the positive effect of the pertussis vaccination on patients with COPD. However, because of the fact that *Bordetella pertussis* has been shown to play a role in acute exacerbation it can be assumed that the immunization may be advantageous for patients with COPD (33).

3.3 Pneumococcal Infection

3.3.1 Epidemiology and pathogenesis

Pneumococcal infection is a highly contagious disease caused by the gram-positive, alpha-hemolytic, encapsulated bacterium *Streptococcus pneumoniae,* commonly also called pneumococcus. Over 90 serotypes of this bacterium are known, differing in the composition of the capsules, which also trigger the virulence (34). Pneumococci can colonise the oro-/nasopharynx without causing relevant infections (facultative pathogenic). However, depending of the individual immune status, previous pneumococcal vaccinations, and the pneumococcal serotype severe infections can occur. Pneumococcal infections can be divided in local infections (sinusitis, bronchitis, peribronchial pneumonia and otitis media) and invasive infections (sepsis, parenchymal pneumonia, meningitis and others). Invasive infections are subsumed as invasive pneumococcal diseases (IPD) and secondary bacterial spread due to bacteraemia. Furthermore, an invasive pneumococcal infection is confirmed by isolation of the bacterium from a normally sterile site. Bacterial pneumolysin, a cytotoxin secreted by *Streptococcus pneumoniae*, plays a crucial role in the development of pneumococcal bacteraemia. It destroys endothelial cells by forming pores in membranes, supresses the host immune system, facilitates intra-alveolar replication of pneumococci and the penetration and spread of pneumococci from the alveoli into the interstitial space and therefore into the bloodstream. (2,34,35).

Through aspiration *Streptococcus pneumoniae* causes pneumonia and by continuous spread the less severe and more common diseases otitis media and

sinusitis (2,35). The infection is transmitted by droplets of infected respiratory secrets. The colonization of the nasopharynx in adults is mostly a result of close contact with colonized small children or people from the surrounding of small children. Because of that it is important to vaccinate young children to protect the elderly from serious respiratory diseases and pneumonia (2).

In Austria there were 438 reported cases of invasive pneumococcal infection in 2016 and the resulting incidence was 5.03 / 100 000 (36). This is a small but certain increase of infections as there were 422 reported cases in 2015 and only 322 reported cases in 2014 (37,38). However, this might be underestimated, as in clinical practice pneumococcal-specific diagnostic test are frequently not applied. The most common serotypes were 3 (25.9%), 19A (7.8%), 22F (6.7%) and 8 (4.9%). Of the IPD cases with known clinical presentation (63.5%), 79.1% manifested in pneumonia, 11.9% in meningitis, 7.6% in sepsis and 1.4% had other clinical presentations (36).

3.3.2 Clinical manifestation

The clinical manifestation varies in its symptoms depending on the infected organ system (9).

Sinusitis and otitis media are the most common types of pneumococcal infection and are usually less severe than the other manifestations, including symptoms like fever, headache, ear pain and sleepiness. Only in rare cases the bacteria may extend from the sinus frontalis or ethmoidales or the middle ear to the subarachnoid space to cause cerebral abscesses or secondary meningitis (9,35,39).

A more severe form of pneumococcal disease is the pneumococcal pneumonia. The infection starts frequently with some fever and chills and progresses with productive cough, dyspnea, hypoxia and pleuritic chest pain (9,35). Inflammatory neutrophilic cells infiltrate the lung parenchyma (visible on X-ray) and bacteria may spread into the bloodstream causing life-threatening pneumogenic sepsis (35). Without early appropriate therapy complications like sever pneumonia including ARDS, pleural empyema, pericarditis, airway obstruction with atelectasis and lung

abscess formation might occur and worsen overall survival (9). The mortality and incidence of pneumonia severely increase after 50 years, despite the fact that the disease occurs in every age group (35).

In primary pneumococcal bacteraemia, the bacterium invades the bloodstream early without causing obvious pneumonia or other organ-specific infection. The patient may only suffer from fever, chills, low alertness and symptoms of sepsis like hypotension, tachycardia and tachypnoea. However, the bacteraemia may cause secondary pneumococcal peritonitis, therefore it is important to treat patient with therapy-refractory ascites with prophylactic antibiotics to prevent this complication (35,39,40). In some fulminant cases disseminated intravascular coagulation appears which can be explained by the pneumolysin triggered activation of cloth factors (35).

Primary acute purulent meningitis is the most serious type of invasive pneumococcal infection. It appears without a preceding extracerebral infection. Less frequent, secondary pneumococcal meningitis may occur as secondary complication of an extracerebral pneumococcal infection or even after a cranial trauma (9,35). The symptoms of pneumococcal meningitis include photophobia, cranial nerve signs, nausea, emesis, high fever, disorientation, headache and meningism (9). Furthermore, there is the risk that intracranial complications like brain edema and spontaneous intracranial haemorrhages associated with vasculitis may develop (41). The mortality rate of pneumococcal meningitis is around 15.0 to 60.0% and rapidly increases after the age of 60 (41,42).

3.3.3 Treatment

Penicillin is the antibiotic of choice in most cases of pneumococcal infection, but because of a high rate of antibiotic resistance ranging from 10.0% to 30.0% in some countries it may be necessary to treat the infections with glycopeptide antibiotics like vancomycin, quinolones and high dose cephalosporins if they are susceptible (35). The antibiotic resistance is different depending on the area, the strain and the serotypes (34,35). In 2016 in Austria, the National Comittey fur Oneumococci tested a 9.8% erythromycin, a 6.4% clindamycin and a 7.0%

tetracycline in vitro resistance in 388 isolates, 92.0% of all isolates were fully susceptible to penicillin (36).

3.3.4 Recommendations for vaccination

The vaccination is included in the free immunization program in Austria and is available for children younger than two years and for children at a high risk younger than five years. It is recommended to vaccinate with a conjugated vaccine following a 2 + 1 scheme at the third, fifth and twelfth month of life. For children a ten valent conjugated vaccine (Synflorix®, PCV10), which is included in the free vaccination program, and a 13 valent conjugated vaccine (Prevenar 13®, PCV13) are approved and it is recommended to complete the vaccination course with the same vaccine that was used at the beginning. After initial immunization in infancy/childhood no booster injection is necessary for adults with normal risk below the age of 50. Because the morbidity of pneumococcal infection rapidly increases after the completed 50th year of life, vaccination against pneumococcal infection should be refreshed at this age. Furthermore, the immunization is highly recommended for people at a high risk to contract the infection, or for people with comorbidities and therefore at a higher risk for a more serious course of the disease. This includes people with functional or anatomical asplenia, congenital or acquired immunodeficiency, nephrotic syndrome, renal insufficiency, a chronic pulmonary disease, a cardiovascular disease, diabetes mellitus, alcoholics and children with weight faltering or neurological diseases.

For people above the age of 50 who are not vaccinated it is recommended to use the PCV13 vaccine first and complete the vaccination course after one year with the 23 valent polysaccharide vaccine (Pneumovax 23®, PPV23). Adults above the age of 50 who were previously inoculated with a PPV23 vaccine should get a booster injection after one year with a PCV13 vaccine (2).

3.3.5 Vaccines

Pneumococcal polysaccharide vaccines consist of purified capsular polysaccharide antigen. When it was first licensed in 1977 it contained 14 different types of pneumococcal antigen but in 1983 a new vaccine containing 23 different types of pneumococcal bacteria, responsible for 60% to 76% of pneumococcal infections, was licensed and took over the place of the 14-valent vaccine. In 2000 the first conjugated vaccine was approved. It consists of purified polysaccharide antigen as well (the first PCV contained antigen of seven different bacteria) but contrary to the PPV the antigen is conjugated to the nontoxic variant of diphtheria toxin CRM197. In 2010 the currently most widely used PCV was licensed containing the antigen of 13 different bacteria which were responsible for a larger variety of diseases than the antigen included in PCV7 (9).

The immune protection of PPV23 in healthy adults usually starts two to three weeks after vaccination but may delay in the elderly and people with immunodeficiency like for example asplenia or in people with chronic diseases. Furthermore it provides no immune protection in children under the age of two because the immune system of these children does not react to the capsular polysaccharide antigen of the vaccine yet. Because of that a PCV is used for vaccinating children under the age of two and people with immunodeficiency (9).

PPV23 has 60.0% to 70.0% effectiveness in preventing invasive infections induced by serotypes contained in the vaccine and provides protection for five years in healthy grown-ups (9).

PCV7 provides a 90.0% protection against vaccine-type invasive infection in children; in addition there were also fewer incidents of pneumonia and otitis media. PCV13 on the other hand provides a 45.0% effective protection against non-invasive pneumococcal pneumonia caused by vaccine serotypes and a 75.0% effective protection against vaccine-type invasive infection in adults older than 65 years (9).

3.3.6 Pneumococcal infection and chronic diseases

In Europe approximately 30.0% to 50.0% of all CAP are caused by *Streptococcus pneumoniae* (34). There is no sufficient evidence for PPV23 having a protective effect against non-invasive community acquired pneumococcal pneumonia, although it provides sufficing protection against invasive pneumococcal infections (1). PCV13 on the other hand reduces pneumonia by 45.0% and invasive infections by 75.0% and provides sufficient and steady protection, even years after the vaccination; however it has no significant effect on the overall incidence of CAP (43). Therefore PCV13 should be favoured as standard immunization for people above the age of 60 and as indication immunization for risk groups, but it is necessary to continuously reevaluate the serotype-shift and the associated impact on this recommendation (1).

Furthermore, to this day there is no study that proves the decrease of AECOPD prevalence by vaccinating against pneumococcal infection with PPV23 and there is no data regarding PCV13, although *Streptococcus pneumoniae* does play a role in the acute exacerbation of COPD (44,45).

In addition PPV is associated with decreased events of acute coronary syndrome in people from the age of 65 onwards. This could be explained by the PPV induced formation of antibodies against oxidised LDL, which is responsible for arteriosclerosis. The reduction of LDL was only shown in murine models until today, but it may imply that pneumococcal immunization also has a protective effect against arteriosclerosis in humans (46). Since patients with heart disease are at a higher risk for invasive pneumococcal infection, pneumococcal vaccination is recommended anyway (47).

4 Material and Methods

4.1 Objectives

Our objective was to evaluate the number of cardiologic and pneumologic patients vaccinated against influenza, pneumococcal infection and pertussis. Furthermore, we wanted to find out about potential differences in the clinical outcome and possible worsening of underlying diseases of hospitalized pneumologic and cardiologic patients vaccinated and not vaccinated against influenza, pneumococcal infection and pertussis.

4.2 Study design

This study was performed as a questionnaire study of hospitalized pneumologic and cardiologic patients. In total, 200 patients were questioned between the 1st of April 2017 and 31th of April 2017 in the clinical division for lung diseases and the clinical division for heart diseases at the University Hospital Graz. Furthermore, all patients received a consent (to read and sign), which explained the character of the study. Given that it was a questionnaire study without any kind of intervention, no side effects were possible.

In addition to the data and information from the questionnaire further data was collected by reviewing the medical reports of the last year in the electronic Styrian Hospital Network, the MEDOCS database. After the survey, collected data was analysed with “Microsoft Excel 2010” and “IBM SPSS Statistics”. Data was compared using Chi-squared test and cross tabulation. Statistically significant data was considered a p-value less than 0.05.

For this master thesis, relevant publications were found using “PubMed Advanced Search Builder” and “snowball sampling”; I searched for selected topics in “Up to date”, surveyed the list of references for publications relevant for my thesis and reviewed them via “Pubmed”. Further important sources were websites that engage with the current development of infections like the website of the WHO, the CDC and the Medical University of Vienna.

The study was granted approval by the ethics committee of the Medical University Graz on February 10th, 2017.

4.3 Patient definition

4.3.1 Inclusion criteria

All patients that were hospitalized at the division of cardiology or the division of pulmonology at the University Hospital Graz between the 1st of April 2017 and the 31st of April 2017 were considered for the study. Overall, 200 patients (133 male (66.5%) and 67 female (33.5%)) were included in the analysis. 148 patients were enrolled at the division of cardiology (74.0%) and 52 patients at the division of pulmonology (26.0%). Their mean age was 66.2 years (±SD 14.7 years) and their median age was 68 years; the youngest patient was 21 and the oldest patient was 92 years old. 80 (40.0%) of these patients were smokers, 25 (12.5%) were non-smokers and 95 (47.5%) of them were former smokers.

4.3.2 Exclusion criteria

We had to exclude patients that were not able to communicate or understand the questions asked because of the severity of their underlying disease or because of old age, patients who did not want to participate in the study and aside from that, patients under the age of 18.

4.4 Data collection

4.4.1 Questionnaire for patients (for the original questionnaire look at page 65)

The questionnaire for the patients included:

Table 1 Data gathered in the questionnaire for patients

Age
Gender
Enrolment site (division of pulmonology or cardiology)
Smoking habits
Immunization status regarding the influenza vaccination
Immunization status regarding the vaccination against pneumococcal infection
Immunization status regarding pertussis vaccination
The reason why the patient is not vaccinated (The vaccination was not recommended, the patient forgot about it, the patient had not time, the patient was not convinced of the benefit, the patient was scared of adverse drug effects, the patient has experienced adverse drug effects in the past, the patient was advised against the vaccination by family, friends or doctors)
Which vaccine was used for vaccination against pneumococcal infection
Date of the last vaccination if the patient was vaccinated against pneumococcal infection or pertussis
Acute rhinopharingitis between the 1st of December 2016 and 31st of March 2017
Respiratory tract infection between 1st of December 2016 and 31st of March 2017
If the patient suffers from COPD
In patients with COPD if they had an AECOPD (with increasing dyspnoea, more severe cough with increasing frequency, more and purulent mucus in the bronchial tubes, wheezing breathing sounds or edema of the legs) between the 1st of December 2016 and 31st of March 2017
Hospitalization or non-hospital treatment and therefor contact with a doctor between the 1st of December 2016 and 31st of March 2017

4.4.2 Data not covered by the questionnaire

The following data was not included in the questionnaire for patients and therefore researched by a MEDOCS database search:

Table 2 Data gathered by a MEDOCS database search

Admission diagnosis
Underlying diseases
In patients with COPD: GOLD stages and the best FEV1 of the last two years
Patients with coronary artery disease
Stage of CHD and interventions in the past
Medication (in particular ACE-inhibitors, proton pump inhibitors (PPIs), immunosuppressive and chemotherapeutical drugs during the last twelve months, beta blocking agents, oral anticoagulants, heparin, inhibitors of platelet aggregation, long acting beta agonists (LABA), long acting muscarinic antagonist (LAMA) and inhalative corticosteroids (ICS), calcium, sodium and potassium channel blockers, digitalis, diuretics, AT1 antagonists and aldosterone antagonists.

5 Results

5.1 Vaccination against influenza

5.1.1 Prevalence of influenza vaccination

Out of 200 patients asked, 35 (17.5%) were vaccinated and 165 (82.5%) were not vaccinated against the influenza virus. Of these 165 unvaccinated patients, 120 were hospitalized at the division of cardiology and 45 patients were hospitalized at the division of pneumology. Out of the 35 vaccinated patients, 28 were hospitalized at the division of cardiology and seven at the division of pneumology.

Figure 2 Patients vaccinated against influenza

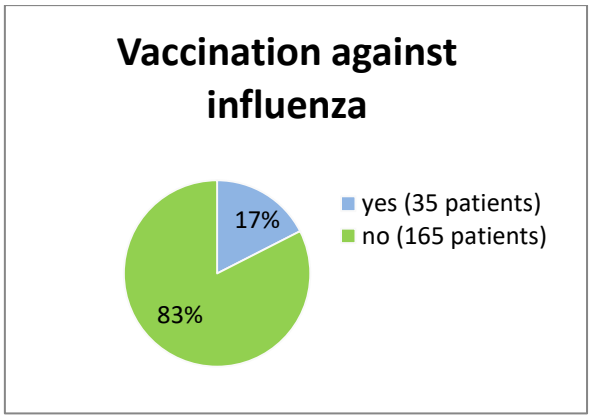
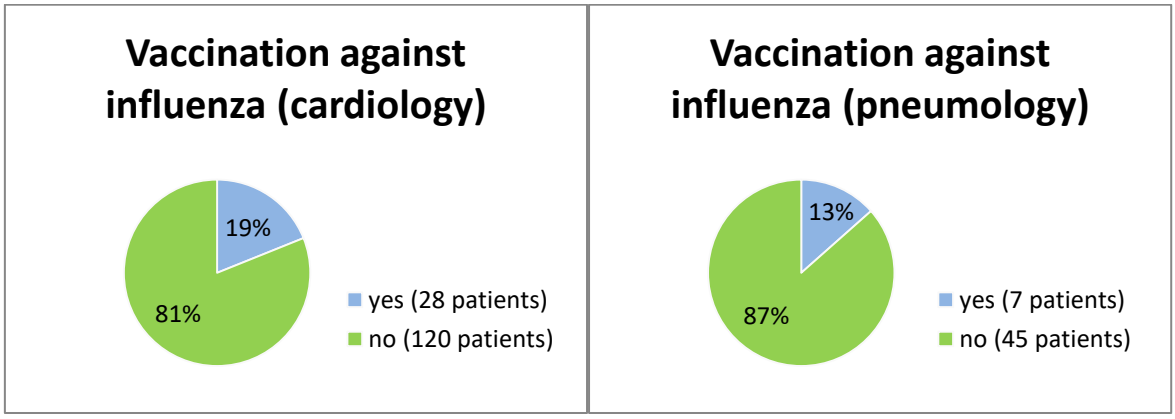


Figure 3 Patients vaccinated against influenza at the division of pneumology and cardiology



The following table shows which specific factor was the reason for vaccination recommendation of the patient, the respective number of patients for each reason and how many patients were or were not vaccinated in each group.

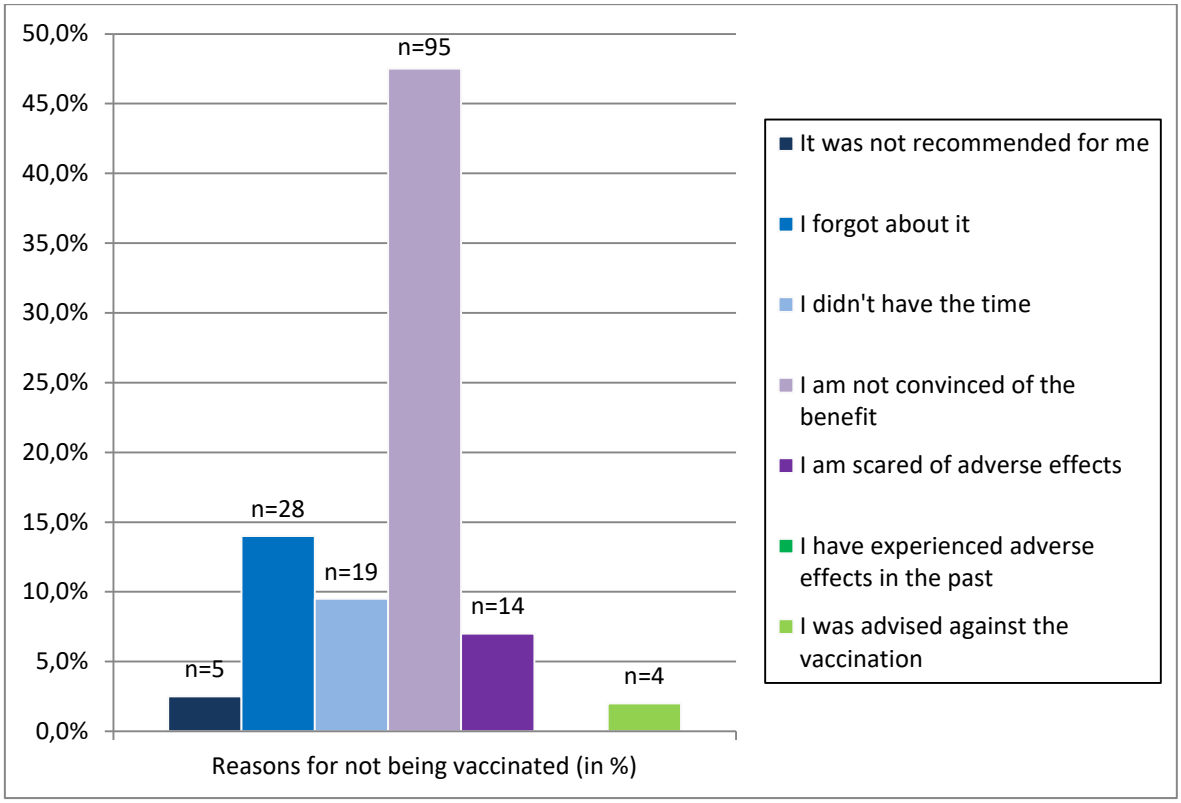
Table 3 Indications for influenza vaccination

Influenza vaccination recommended because of:	Number of patients (out of 200)	Patients vaccinated	Patients not vaccinated
Age *(older than 50 years)*	176	34 (19.3%)	142 (80.7%)
Underlying disease *(total)*	187	33 (17.7%)	154 (82.4%)
-CVD *(by definition of the ICD* (48)*)*	182	32 (17.6%)	150 (82.4%)
-COPD	36	9 (25.0%)	27 (75.0%)
-CHD	92	16 (17.4%)	76 (82.6%)
immunosupression *(medicinal)*	16	1 (6.3%)	15 (93.8%)
Smoking *(smokers + former smokers)*	120	17 (14.2%)	103 (85.8%)
Not necessarily recommended	6	0 (0.0%)	6 (100.0%)

5.1.2 Reasons for not being vaccinated

Reasons for not being vaccinated against influenza were variable: Out of 200 patients 95 (47.5%) were not convinced of the benefit of influenza vaccination, 28 (14.0%) forgot about it, 19 (9.5%) did not have the time for influenza vaccination, 14 (7.0%) had concerns about possible adverse side effects, and four (2.0%) declined influenza vaccination after being advised against the vaccination (one patient was advised against the vaccination by an acquaintance, three patients by their general practitioner). In only five cases (2.5%) influenza vaccination was just not recommended and in no case vaccination was declined due to previous personal negative experiences with the influenza vaccination (see Figure 4).

Figure 4 Reasons of all the patients for not being vaccinated against influenza



Comparing cardiologic and pneumologic patients, cardiologic patients were more frequently not convinced of the benefit of influenza vaccination than pneumologic patients (49.3% versus 42.3%) or were scared of possible adverse side effects (8.8% versus 1.9%). On the other hand, pneumologic patients stated more often that they forgot about it (26.9% versus 9.5%) or did not have the time (11.5% versus 8.8%). Nearly the same percentage of patients did not vaccinate because it was not recommended for them (2.7% cardiologic versus 1.9% pneumologic patients) or because they were advised against the vaccination (2.0% cardiologic versus 1.9% pneumologic patients) and neither cardiologic nor pneumologic patients did experience adverse side effects in the past (see Figure 5 and 6).

Figure 5 Reasons of cardiologic patients for not being vaccinated against influenza

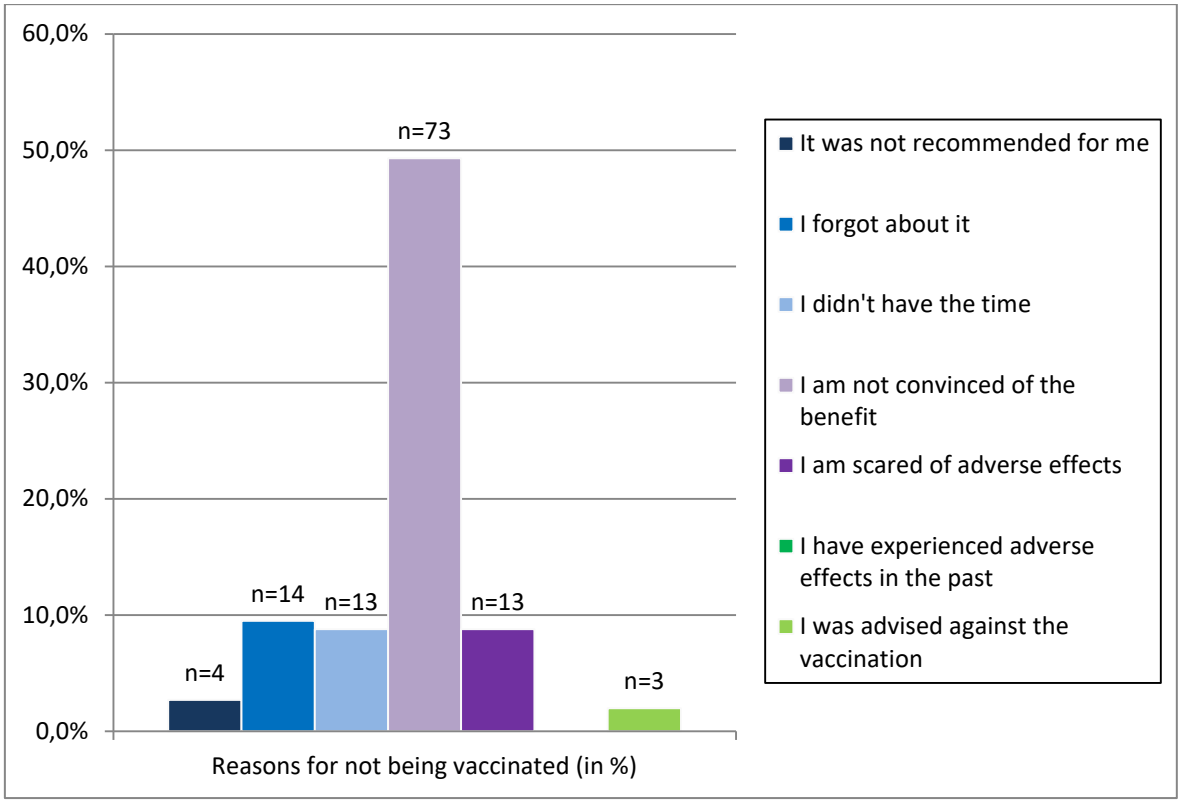
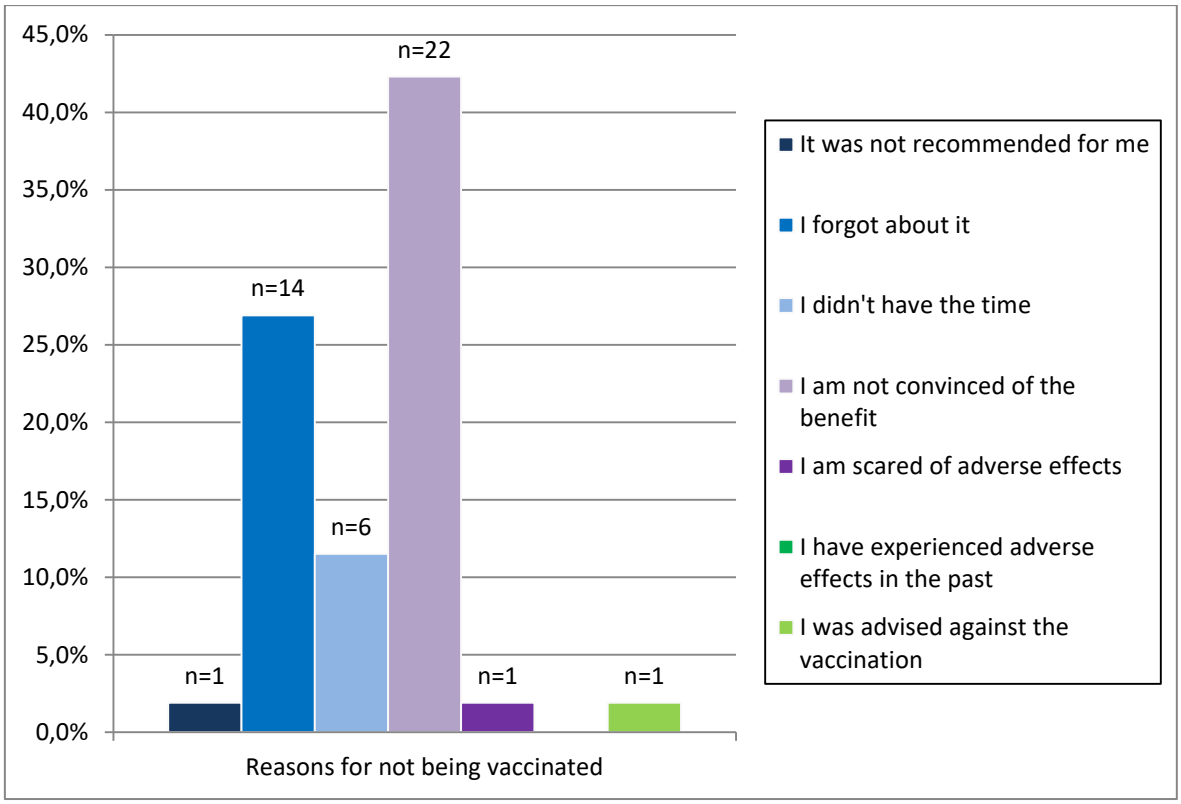


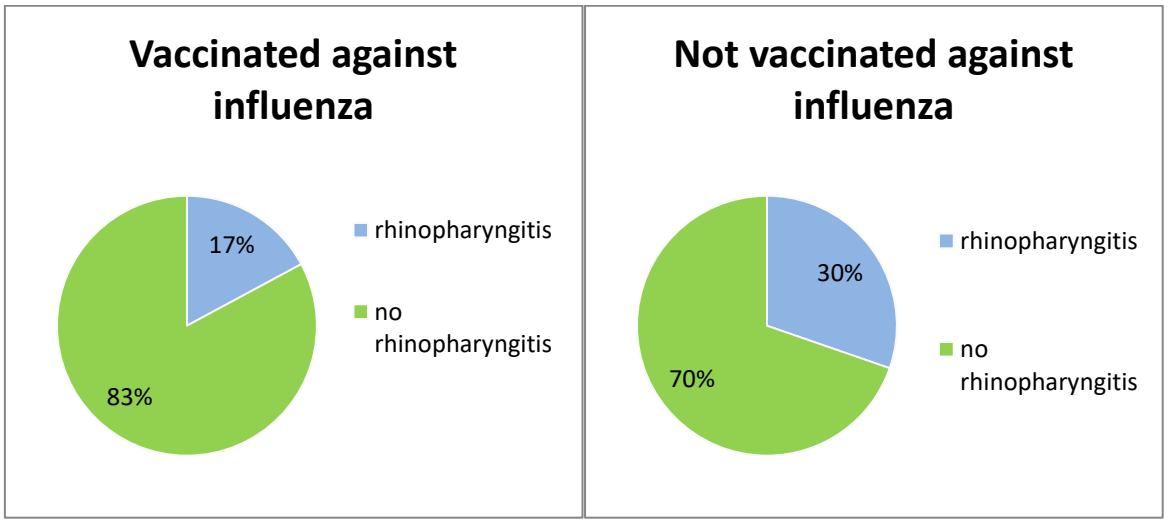
Figure 6 Reasons of pneumologic patients for not being vaccinated against influenza



5.1.3 Impact of influenza vaccination on acute rhinopharyngitis

Out of the 35 patients vaccinated against influenza, six (17.1%) suffered from acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 29 (82.9%) did not. On the other hand 50 (30.3%) out of the 165 patients not vaccinated reported that they had an acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 115 (69.7%) did not.

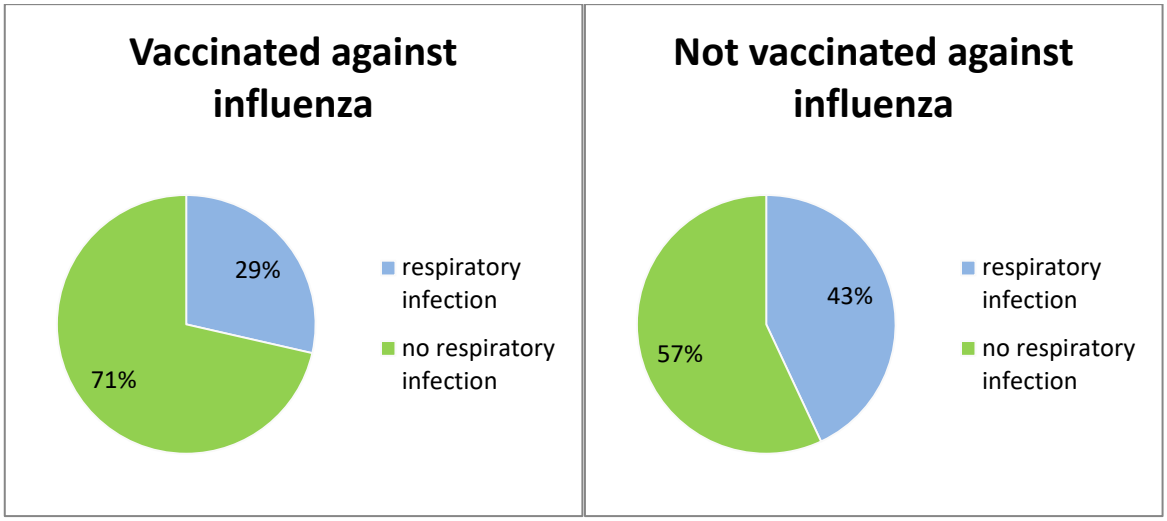
Figure 7 Acute rhinopharyngitis in patients vaccinated and not vaccinated against influenza



5.1.4 Impact of influenza vaccination on respiratory tract infections

Out of the 35 patients vaccinated against influenza, ten (28.6%) suffered from respiratory tract infection between 1st of December 2016 and 31st of March 2017 and 25 (71.4%) did not. On the other hand 71 (43.0%) out of the 165 patients not vaccinated reported that they had a respiratory tract infection between 1st of December 2016 and 31st of March 2017 and 94 (57.0%) did not.

Figure 8 Respiratory infections in patients vaccinated and not vaccinated against influenza



5.2 Vaccination against pertussis

5.2.1 Prevalence of pertussis vaccination

Out of 200 patients asked, 23 (11.5%) were vaccinated and 177 (88.5%) were not vaccinated against pertussis. Of these 177 unvaccinated patients, 131 were hospitalized at the division of cardiology and 46 patients were hospitalized at the division of pneumology. Out of the 23 vaccinated patients, 17 were hospitalized at the division of cardiology and six at the division of pneumology.

Figure 9 Patients vaccinated against pertussis

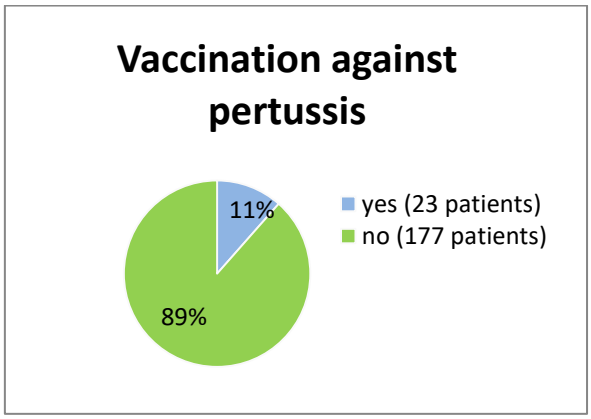
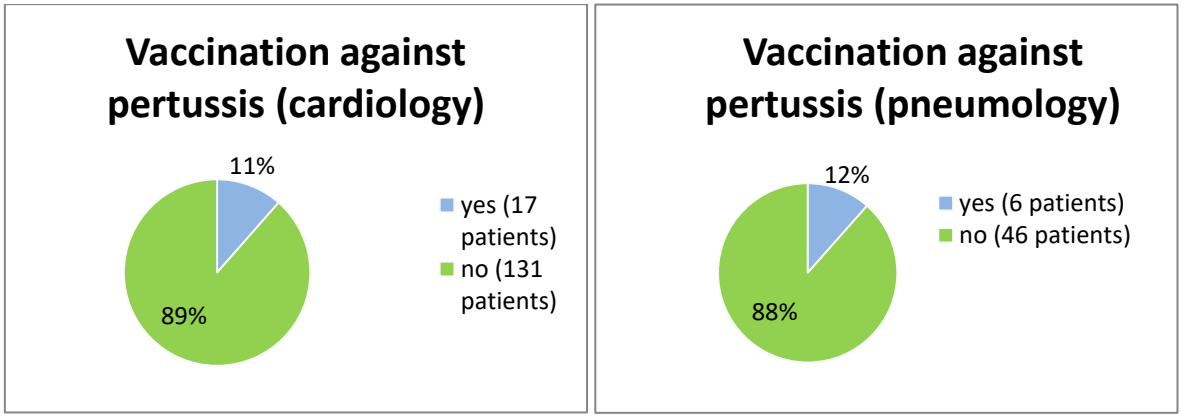


Figure 10 Patients vaccinated against pertussis at the division of pneumology and cardiology



The following table shows each specific reason for vaccination recommendation, the respective number of patients and how many patients were or were not vaccinated in each group.

Table 4 Indications for pertussis vaccination

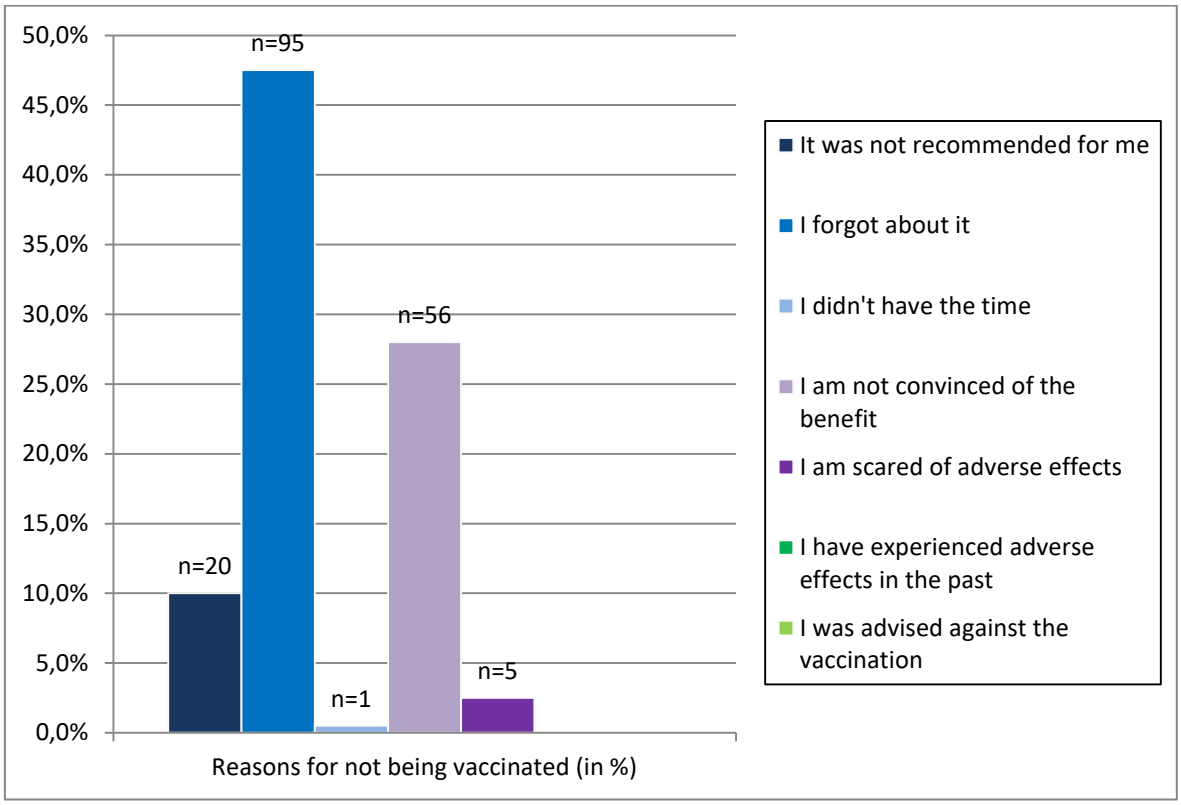
Pertussis vaccination recommended because of:	Number of patients	Patients vaccinated	Patients not vaccinated
Age *(older than 60 years)*	145	12 (8.3%)	133 (91.7%)
Underlying disease	187	22 (11.8%)	165 (88.2%)
-CVD *(by definition of the ICD* (48)*)*	182	21 (11.5%)	161 (88.5%)
-COPD	36	5 (13.9%)	31 (86.1%)
-CHD	92	10 (10.9%)	82 (89.1%)
immunosupression *(medicinal)*	16	3 (18.8%)	13 (81.3%)
Smoking *(smokers + former smokers)*	120	15 (12.5%)	105 (87.5%)
Not necessarily recommended	7	1 (14.3%)	6 (85.7%)

5.2.2 Reasons for not being vaccinated

Reasons for not being vaccinated against pertussis were variable: Out of 200 patients 95 (47.5%) forgot about it, 56 (28.0%) were not convinced of the benefit of pertussis vaccination, 20 (10.0%) never were recommended to get vaccinated, five (2.5%) had concerns about possible adverse side effects and none declined pertussis vaccination after being advised against the vaccination. In only one case (0.5%) the patient just did not have the time for pertussis vaccination and in no

case vaccination was declined due to previous personal negative experiences with the pertussis vaccination (see Figure 11).

Figure 11 Reasons of patients (n=) in general for not being vaccinated against pertussis



Comparing cardiologic and pneumologic patients, cardiologic patients were more frequently not convinced of the benefit of pertussis vaccination than pneumologic patients (31.1% versus 19.2%). On the other hand, pneumologic patients stated more often that they forgot about the vaccination (61.5% versus 42.6%).

Apart from that, nearly the same number of patients said that they did not get vaccinated because it was not recommended for them (10.8% cardiologic versus 7.7% pneumologic patients), that they were scared of possible adverse side effects (3.4% cardiologic versus 0.0% pneumologic patients) or that they did not have the time to get the vaccination (0.7% cardiologic versus 0.0% pneumologic patients). Neither cardiologic nor pneumologic patients were advised against pertussis vaccination or did experience adverse side effects in the past (see Figure 12 and 13).

Figure 12 Reasons of cardiologic patients (n=) for not being vaccinated against pertussis

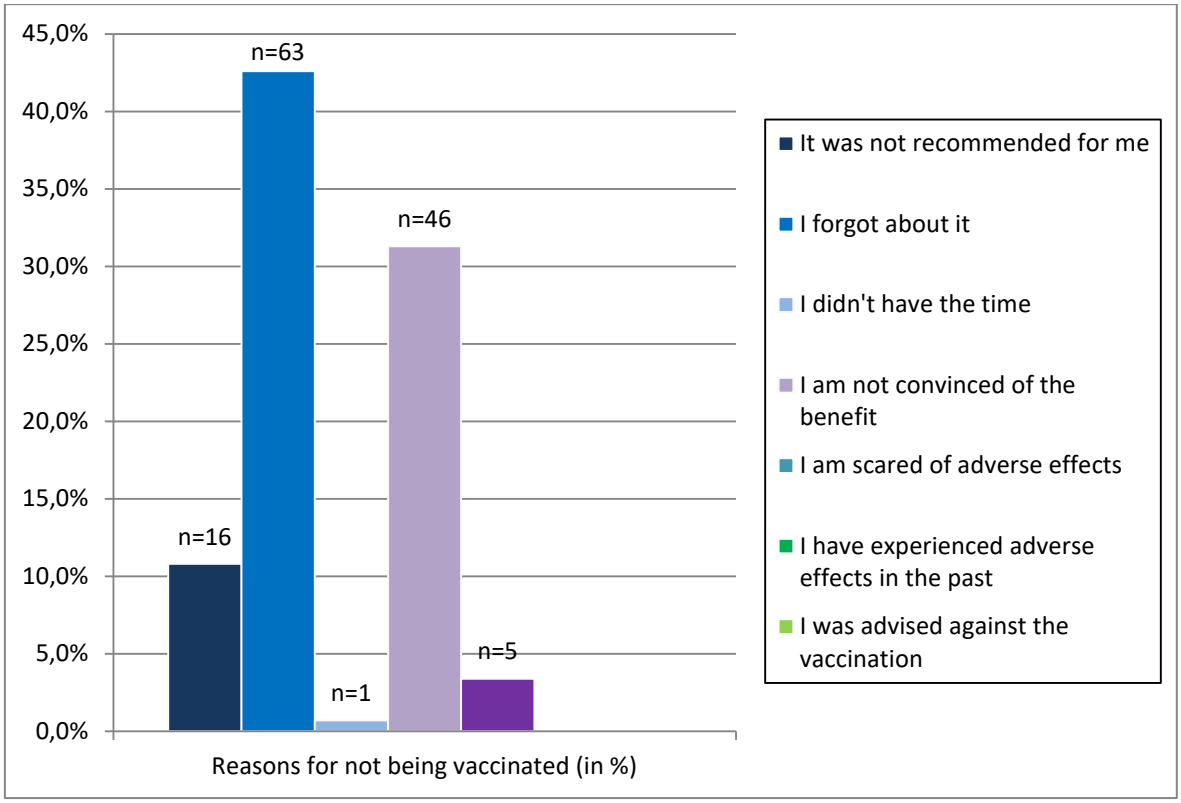
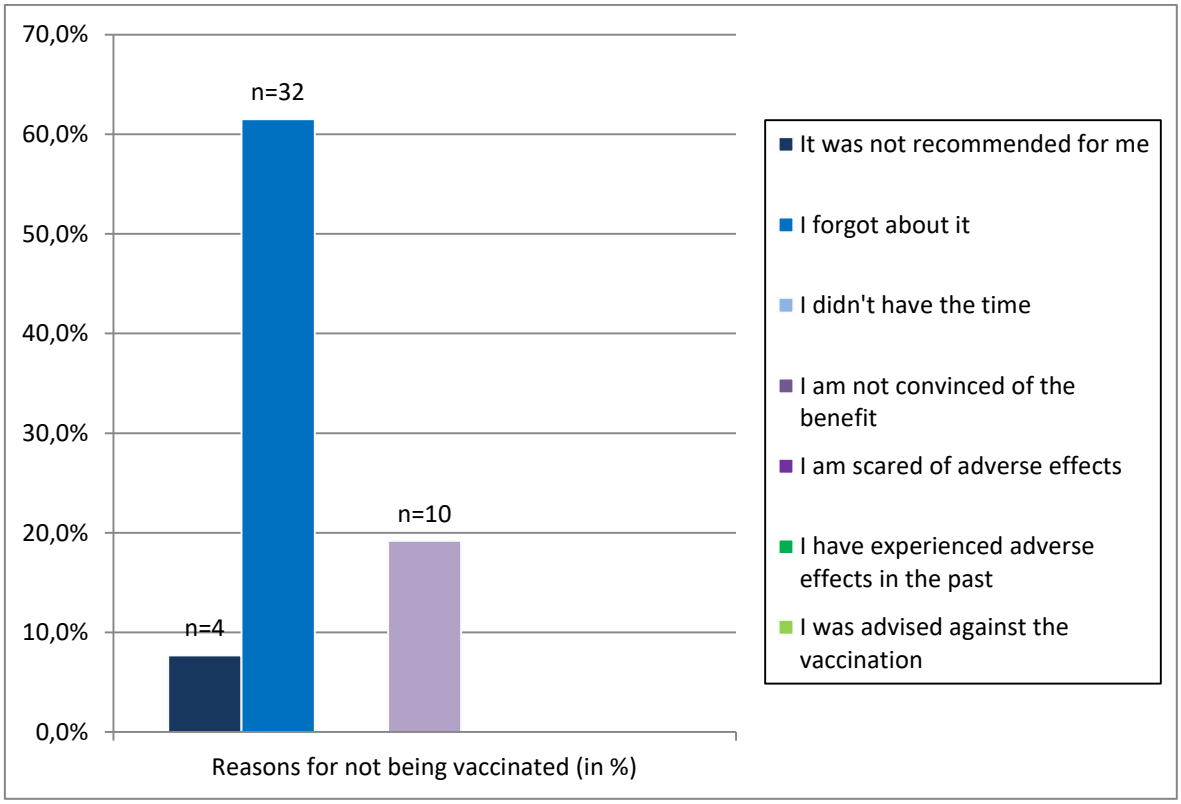


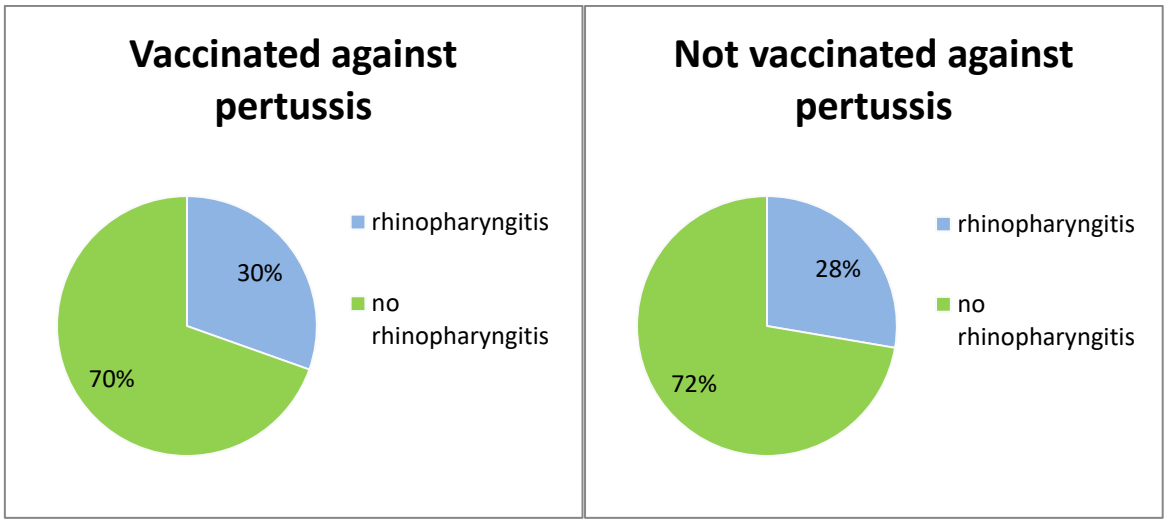
Figure 13 Reasons of pneumologic patients (n=) for not being vaccinated against pertussis



5.2.3 Impact of pertussis vaccination on acute rhinopharyngitis

Out of the 23 patients vaccinated against pertussis, seven (30.4%) suffered from acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 16 (69.6%) did not. On the other hand 49 (27.7%) out of the 177 patients not vaccinated reported that they had an acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 128 (72.3%) did not.

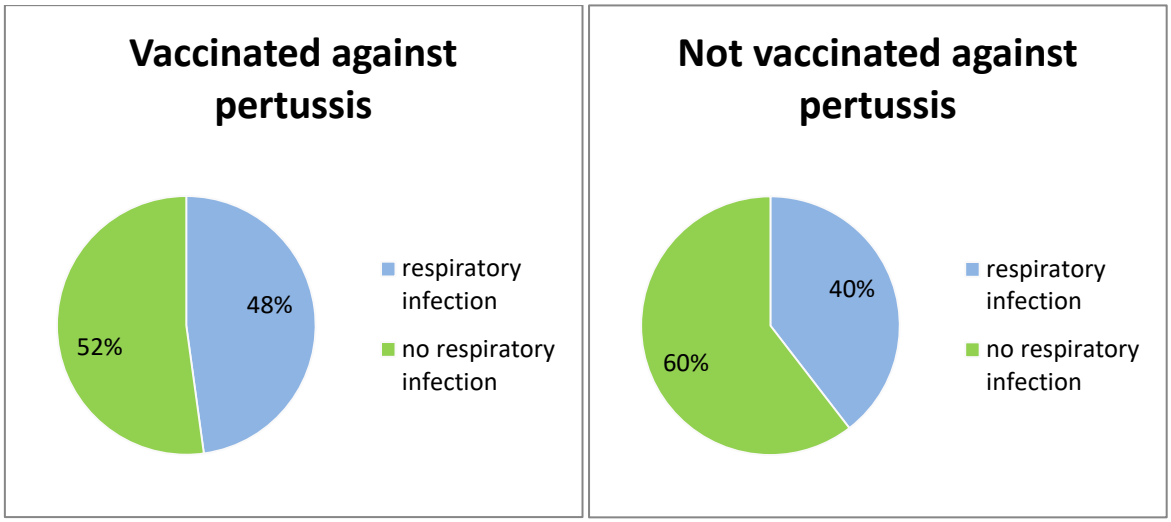
Figure 14 Acute rhinopharyngitis in patients vaccinated and not vaccinated against pertussis



5.2.4 Impact of pertussis vaccination on respiratory tract infections

Out of the 23 patients vaccinated against pertussis, eleven (47.8%) suffered from respiratory tract infection between 1st of December 2016 and 31st of March 2017 and twelve (52.2%) did not. On the other hand 70 (39.6%) out of the 177 patients not vaccinated reported that they had a respiratory tract infection between 1st of December 2016 and 31st of March 2017 and 107 (60.5%) did not.

Figure 15 Respiratory tract infections in patients vaccinated and not vaccinated against pertussis



5.3 Vaccination against pneumococcal infection

5.3.1 Prevalence of vaccination against pneumococcal infection

Out of 200 patients asked, 37 (18.5%) were vaccinated and 163 (81.5%) were not vaccinated against pneumococcal infection. Of these 163 unvaccinated patients, 122 were hospitalized at the division of cardiology and 41 patients were hospitalized at the division of pneumology. Out of the 37 vaccinated patients, 26 were hospitalized at the division of cardiology and eleven at the division of pneumology.

Figure 16 Patients vaccinated against pneumococcal infection

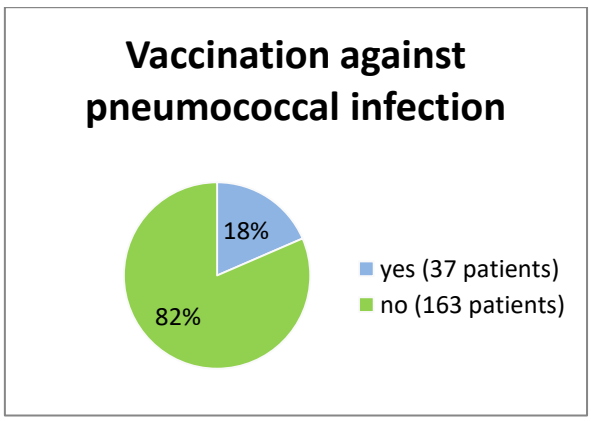
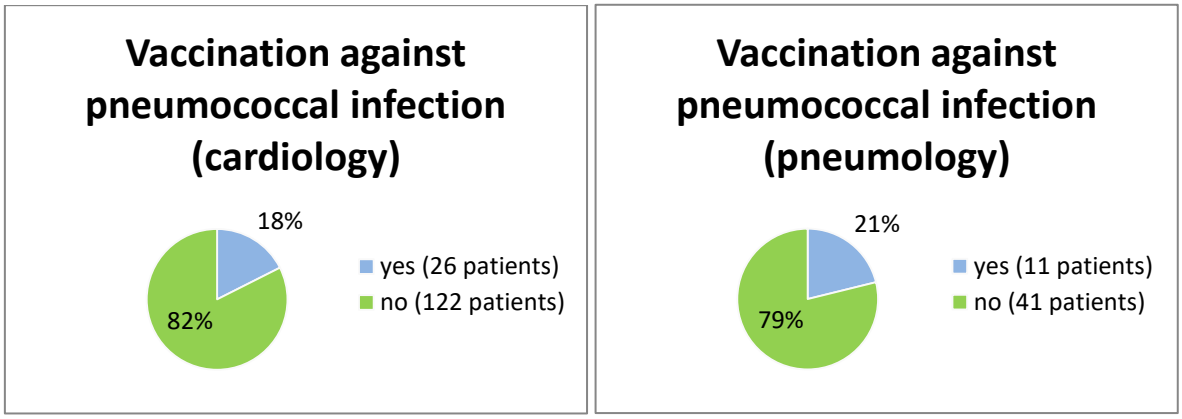


Figure 17 Patients vaccinated against pneumococcal infection at the division of pneumology and cardiology



The following table shows each specific reason for vaccination recommendation, the respective number of patients and how many patients were or were not vaccinated in each group.

Table 5 Indications for pneumococcal vaccination

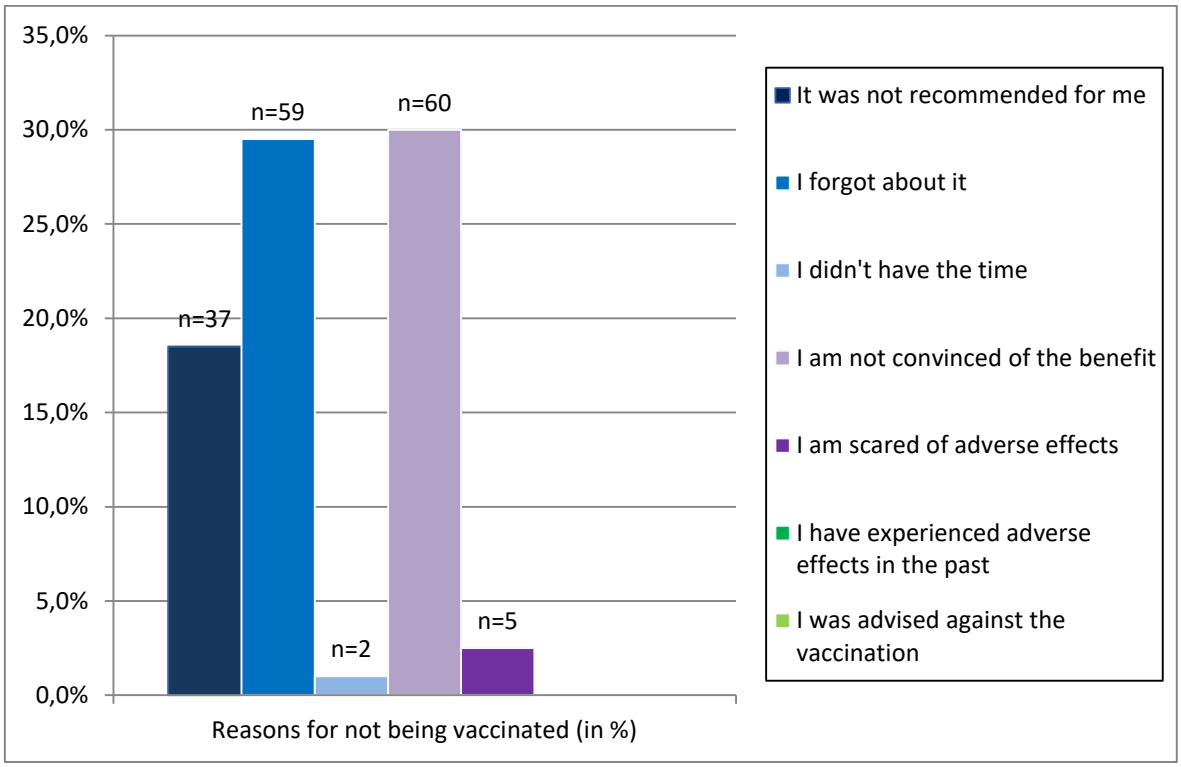
Vaccination against pneumococcal infection recommended because of:	Number of patients	Patients vaccinated	Patients not vaccinated
Age *(older than 50 years)*	176	36 (20.5%)	140 (79.6%)
Underlying disease	187	35 (18.7%)	152 (81.3%)
-CVD *(by definition of the ICD* (48)*)*	182	32 (17.6%)	150 (82.4%)
-COPD	36	13 (36.1%)	23 (63.9%)
-CHD	92	15 (16.3%)	77 (83.7%)
immunosupression *(medicinal)*	16	4 (25.0%)	12 (75.0%)
Smoking *(smokers + former smokers)*	120	22 (18.3%)	98 (81.7%)
Not necessarily recommended	6	1 (16.7%)	5 (83.3%)

5.3.2 Reasons for not being vaccinated

Reasons for not being vaccinated against pneumococcal infection were variable: Out of 200 patients 60 (30.0%) were not convinced of the benefit of pneumococcal vaccination, 59 (29.5%) forgot about it, 37 cases (18.5%) pneumococcal vaccination was just not recommended, five (2.5%) had concerns about possible adverse side effects and two (1.0%) did not have the time for the vaccination.

None declined pneumococcal vaccination after being advised against it and in no case vaccination was declined due to previous personal negative experiences with vaccination against pneumococcal infection (see Figure 18).

Figure 18 Reasons of patients (n=) in general for not being vaccinated against pneumococcal infection



Comparing cardiologic and pneumologic patients, cardiologic patients were more frequently not convinced of the benefit of pneumococcal vaccination than pneumologic patients (32.4% versus 23.1%) and also stated more often that they did not get vaccinated because the vaccination never was recommended for them (20.3% versus 13.5%). On the other hand, pneumologic patients declared more often that they just forgot about the vaccination (40.4% versus 25.7%).

Apart from that, nearly the same number of patients said that they were scared of possible adverse side effects (3.4% cardiologic versus 0.0% pneumologic patients) or that they did not have the time to get the vaccination (0.7% cardiologic versus 1.9% pneumologic patients). Neither cardiologic nor pneumologic patients were advised against pneumococcal vaccination or did experience adverse side effects in the past (see Figure 19 and 20).

Figure 19 Reasons of cardiologic patients (n=) for not being vaccinated against pneumococcal infection

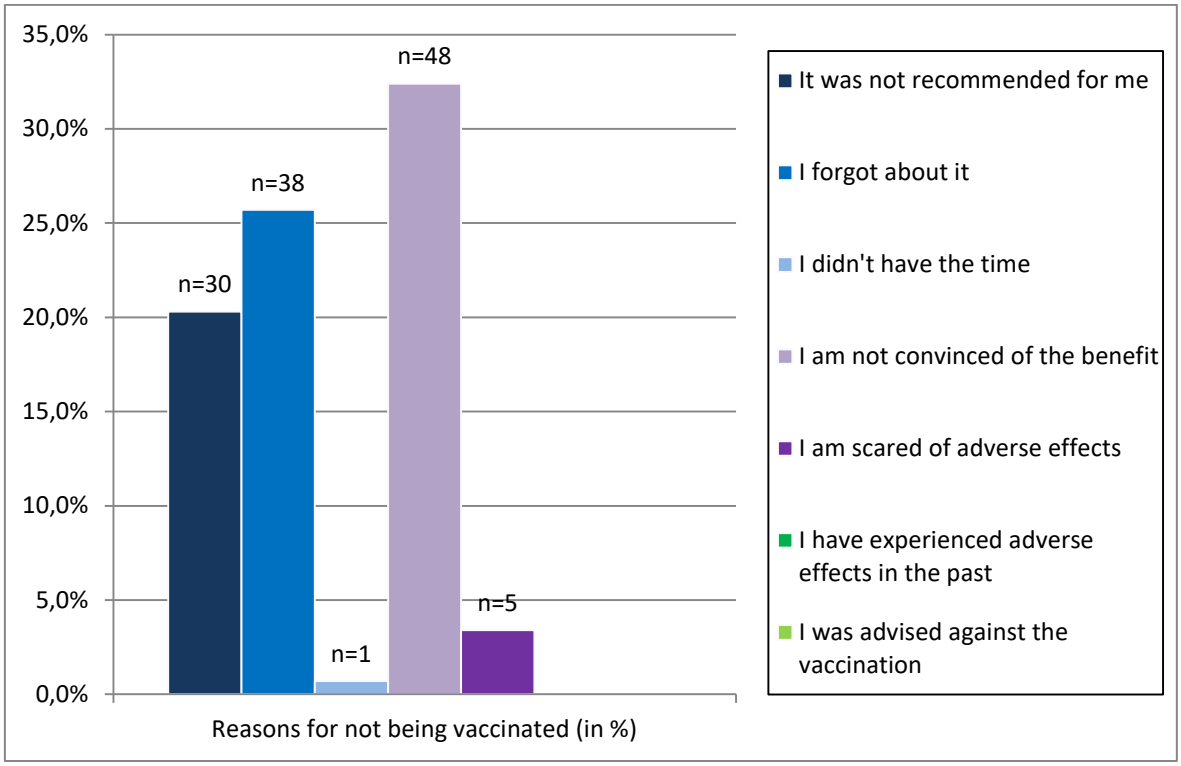
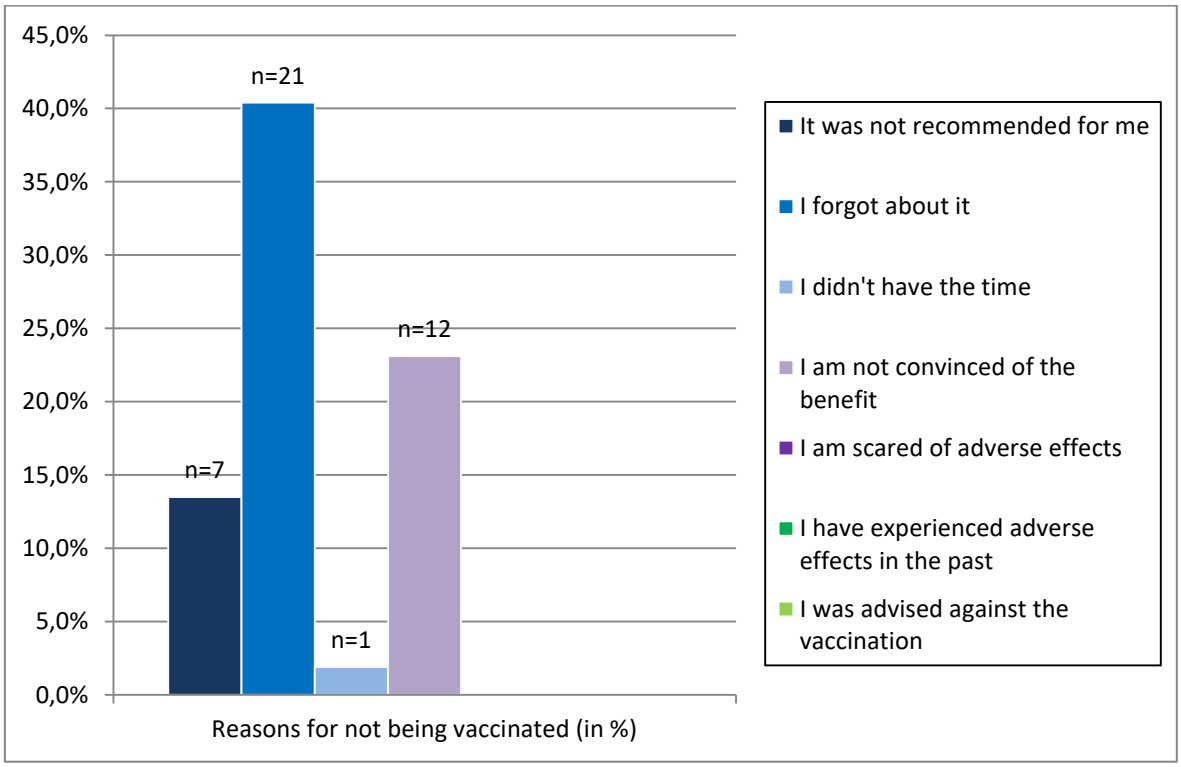


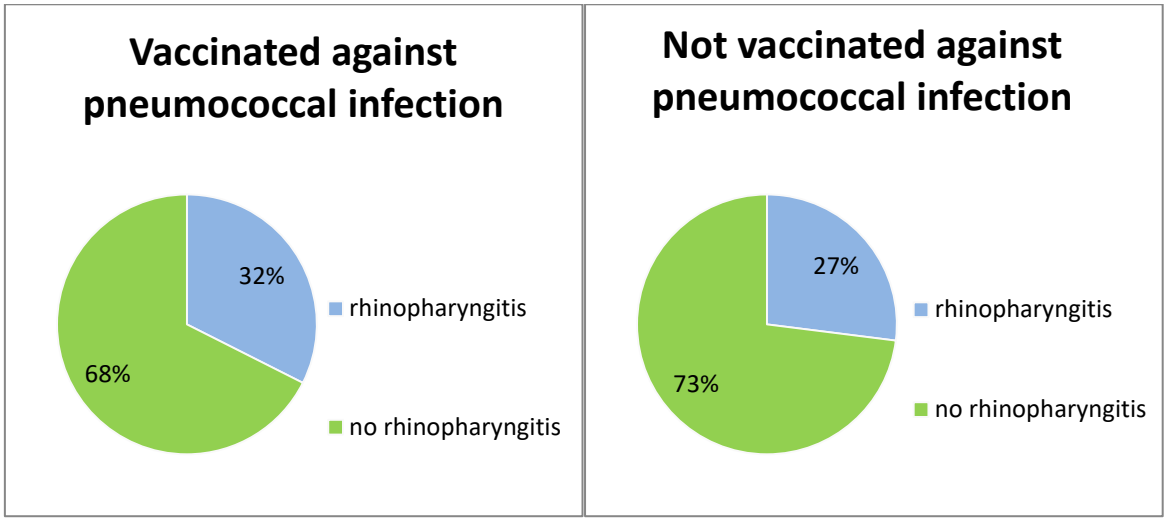
Figure 20 Reasons of pneumologic patients (n=) for not being vaccinated against pneumococcal infection



5.3.3 Impact of vaccination against pneumococcal infection on acute rhinopharyngitis

Out of the 37 patients vaccinated against pneumococcal infection, twelve (32.4%) suffered from acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 25 (67.6%) did not. On the other hand 44 (27.0%) out of the 163 patients not vaccinated reported that they had an acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017 and 119 (73.0%) did not.

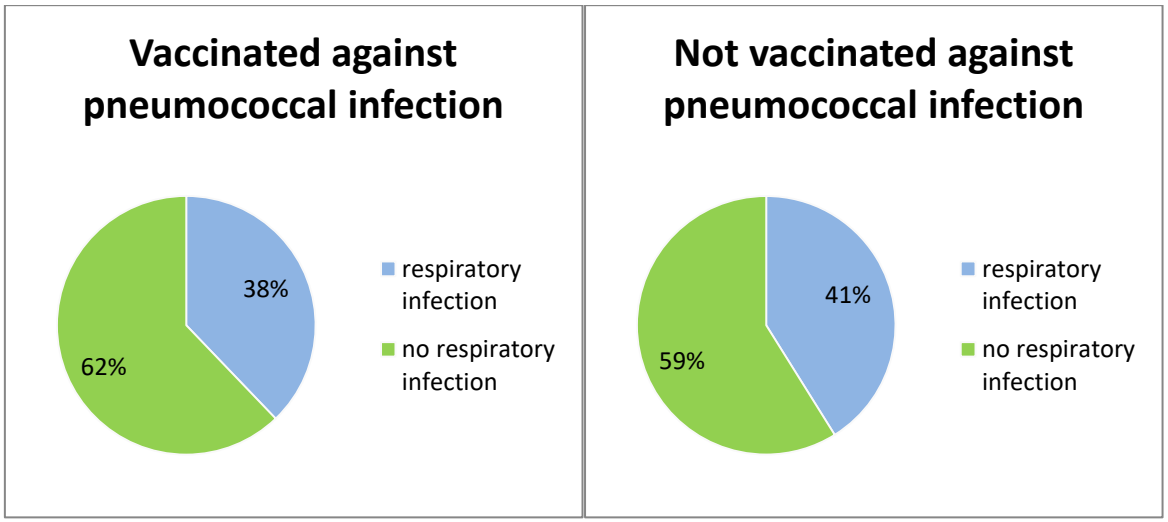
Figure 21 Acute rhinopharyngitis in patients vaccinated and not vaccinated against pneumococcal infection



5.3.4 Impact of vaccination against pneumococcal infection on respiratory tract infections

Out of the 37 patients vaccinated against pneumococcal infection, 14 (37.8%) suffered from respiratory tract infection between 1st of December 2016 and 31st of March 2017 and 23 (62.2%) did not. On the other hand 67 (41.1%) out of the 163 patients not vaccinated reported that they had a respiratory tract infection between 1st of December 2016 and 31st of March 2017 and 96 (58.9%) did not.

Figure 22 Respiratory tract infections in patients vaccinated and not vaccinated against pneumococcal infection



5.4 Patients with (AE-)COPD or asthma

34 Patients with COPD and two patients with asthma were interviewed. Nine (25%) were vaccinated against influenza, 13 (36.1%) were vaccinated against pneumococcal infection and five (13.9%) were vaccinated against pertussis. This concludes that patients who suffered from COPD or asthma were by trend more often vaccinated against influenza ($p>0.05$; not statistically significant) and pneumococcal infection (statistically significant with $p=0.003$) than non COPD/asthma patients.

Moreover, five (14.7%) of the 34 COPD patients suffered from an acute exacerbation of COPD. Out of these five patients one was vaccinated against influenza, two were vaccinated against pneumococcal infection, and none was vaccinated against pertussis.

5.5 Patients with pneumonia

This study also included 17 patients who suffered from pneumonia, one with proven pneumococcal pneumonia and one with verified influenza pneumonia. Out of the 17 patients one was vaccinated against influenza, three were vaccinated against pneumococcal infection, and two were vaccinated against pertussis.

5.6 Patient with pertussis infection

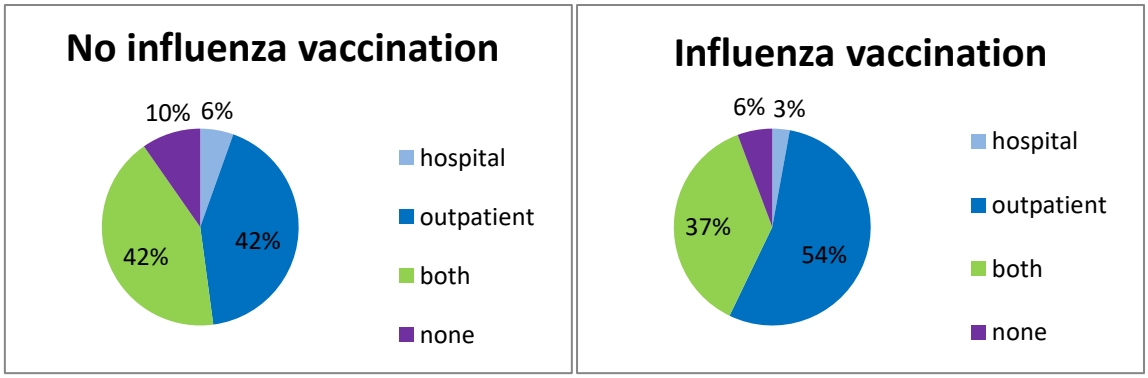
As a part of this questionnaire study one patient who suffered from pertussis infection in the winter 2016/17 was questioned and this patient was immunized against influenza, but not against pneumococcal infection and pertussis.

5.7 Contact with doctors between 1st of December 2016 and 31st of March 2017

5.7.1 Influenza vaccination

Out of the 35 patients vaccinated against influenza one patient (2.9%) was only in hospital, 19 (54.3%) were only in non-hospital treatment, 13 (37.1%) were both in hospital and in non-hospital treatment and two patients (5.7%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.
On the other hand, out of the 165 patients not vaccinated against influenza, nine (5.5%) were only in hospital, 70 (42.4%) were in only in non-hospital treatment, 70 (42.4%) were both in hospital and in non-hospital treatment and 16 (9.7%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.

Figure 23 Contact with doctors between 1st of December 2016 and 31st of March 2017 of patients vaccinated and not vaccinated against influenza

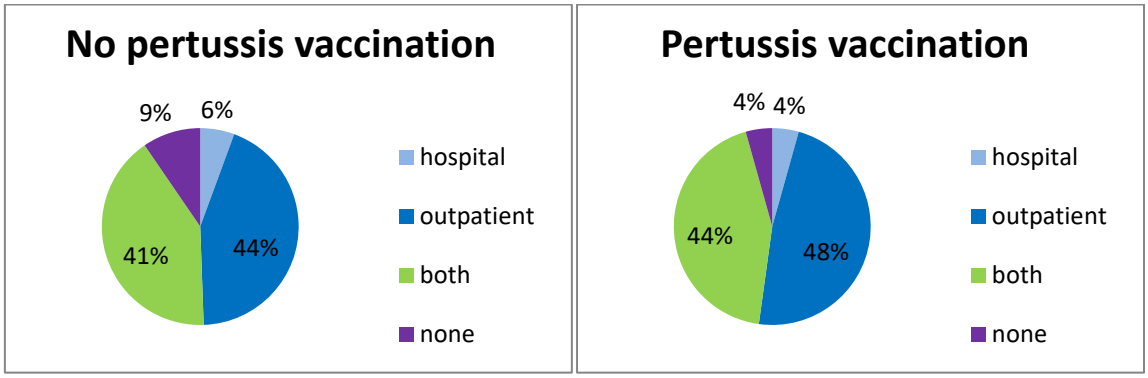


5.7.2 Pertussis vaccination

Out of the 23 patients vaccinated against pertussis one patient (4.4%) was only in hospital, eleven (47.8%) were only in non-hospital treatment, ten (43.5%) were

both in hospital and in non-hospital treatment and one person (4.4%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.
On the other hand, out of the 177 patients not vaccinated against pertussis, ten (5.7%) were only in hospital, 78 (44.1%) were only in non-hospital treatment, 73 (41.2%) were both in hospital and in non-hospital treatment and 17 (9.6%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.

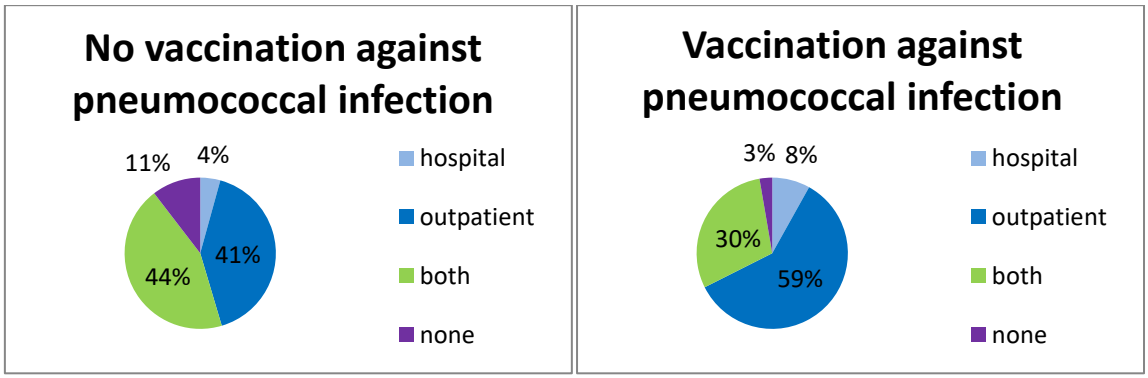
Figure 24 Contact with doctors between 1st of December 2016 and 31st of March 2017 of patients vaccinated and not vaccinated against pertussis



5.7.3 Vaccination against pneumococcal infection

Out of the 37 patients vaccinated against pneumococcal infection three patients (8.1%) were only in hospital, 22 (59.5%) were only in non-hospital treatment, eleven (29.7%) were both in hospital and in non-hospital treatment and one person (2.7%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.
On the other hand, out of the 163 patients not vaccinated against pneumococcal infection, seven (4.3%) were only in hospital, 67 (41.1%) were only in non-hospital treatment, 72 (44.2%) were both in hospital and in non-hospital treatment and 17 (10.4%) had no contact to doctors at all between 1st of December 2016 and 31st of March 2017.

Figure 25 Contact with doctors between 1st of December 2016 and 31st of March 2017 of patients vaccinated and not vaccinated against pneumococcal infection



6 Discussion

Influenza, pertussis and pneumococcal infection immunization are highly recommended for people with underlying chronic diseases (except arterial hypertension) to protect them from deterioration of their diseases (2).

The aim of this study was to evaluate the prevalence of influenza, pertussis and pneumococcal infection vaccination in hospitalized cardiologic and pneumologic patients. Furthermore, we wanted to detect differences in the outcome, in the perception of usefulness of vaccination and possible worsening of underlying diseases in vaccinated and non-vaccinated patients.

We analysed data of 200 patients (133 male (66.5%) and 67 female (33.5%); 148 (74.0%) cardiologic patients and 52 (26.0%) pneumologic patients) with a median age of 68 years collected through a questionnaire search and a MEDOCS database research. Of these 200 patients only 17.5% were vaccinated against influenza, 11.5% against pertussis and 18.5% against pneumococcal infection. It is possible that these results may differ because of the fact that only the minority of patients had their vaccination record with them in hospital and we cannot be certain that every patient remembered his immunization history properly.

Patients who suffered from COPD/asthma were by trend more often vaccinated against influenza (not statistically significant) and pneumococcal infection (statistically significant with $p<0.05$) than non COPD/asthma patients.

Additionally, the group of patients to whom vaccination against influenza was recommended due to COPD was the group with the highest immunization rate (25.0% vaccinated). Patients on the other hand who were not highly recommended to vaccinate were the group least vaccinated (0.0%), closely followed by the group of patients with immunosuppression (6.3%). It was remarkable that only 17.6% of patients with CVD were vaccinated; a result even lower than the immunization rate of 34.0% detected 2005 through the Behavioral Risk Factor Surveillance System, a system of health-related telephone surveys of the CDC, in the United States (3).

The group of patients to whom vaccination against pertussis was recommended due to immunosuppression was the group with the highest immunization rate (18.8% vaccinated), patients on the other hand who were recommended to

vaccinate because they reached the age of 60 years were the group least vaccinated (8.3%).

Furthermore, the group of patients to whom vaccination against pneumococcal infection was recommended due to COPD was the group with the highest immunization rate (36.1% vaccinated), patients on the other hand who were recommended to vaccinate because of CHD were the group least vaccinated (16.3%).

The reasons mostly mentioned for not being vaccinated were that the patient was not convinced of the benefit of the immunization (in vaccination against pneumococcal infection and influenza) and that the patient forgot about it (in vaccination against pertussis). In particular it was noticeable that many patients have very low confidence in the influenza vaccination and do not consider it necessary. Especially cardiologic patients were by a high percentage not convinced of the benefit of vaccination against influenza (49.3% versus 42.3% of pneumologic patients). Perhaps this is a result of many doctors being unaware of the fact that influenza immunization should be considered a cardioprotective drug and therefore not advising their patients to get vaccinated. On the other hand it was astonishing that many patients evidently have never heard of the vaccination against pneumococcal infection even though it would be highly recommended for them.

It was interesting that 30.3% of the patients not vaccinated but only 17.1% of the patients that were vaccinated against influenza suffered from acute rhinopharyngitis between 1st of December 2016 and 31st of March 2017. Vaccinated patients also suffered less from respiratory tract infections in this period (28.6% of all vaccinated patients versus 43.0% not vaccinated patients); this may indicate that influenza immunization encourages decrease of the incidence of acute rhinopharyngitis and respiratory tract infections. Thus it can be concluded that there is a trend showing that acute rhinopharyngitis and respiratory tract infections did occur less in patients who were vaccinated against influenza, but this is not statistically significant, which can be explained by our relatively small number of patients.

The other vaccinations did not show such big differences in the appearance of acute rhinopharyngitis (30.4% of all patients vaccinated against pertussis versus 27.7% of all patients not vaccinated; 32.4% of all patients vaccinated against

pneumococcal infection versus 27.0% of all patients not vaccinated) and respiratory tract infections (47.8% of all patients vaccinated against pertussis versus 39.6% of all patients not vaccinated; 37.8% of all patients vaccinated against pneumococcal infection versus 41.1% of all patients not vaccinated). This ineffectiveness of pertussis and pneumococcal vaccination regarding prevention of rhinopharyngitis and unspecific respiratory tract infection is not surprising as 1.) Pertussis is not causing pharyngitis und is not a frequent cause of respiratory tract infection, 2.) *Streptococcus pneumoniae* is not causing rhinopharyngitis and 3.) Pneumococcal vaccination is not reducing the overall incidence of community acquired pneumonia as it was shown in the CAPITA trial (43).

Moreover, there could be a bias in our data because patients at a worse general health status consult doctors more frequently and are thus more likely to be recommended vaccination. These patients are naturally at a higher risk for respiratory tract infections, regardless of vaccination status.

Furthermore, it was noticeable that patients who had had no contact to a doctor between 1st of December 2016 and 31st of March 2017 were vaccinated less than patients that were in contact with doctors in the same period (5.7% of all patients vaccinated against influenza versus 9.7% of all patients not vaccinated had no contact, 4.4% in patients vaccinated against pertussis versus 9.6% of patients not vaccinated, 2.7% of all patients vaccinated against pneumococcal infection versus 10.4% of all patients not vaccinated). This may be explained by the fact that patients that were not in hospital or in outpatient care did probably not receive the information and medical reconnaissance provided by doctors regarding the recommended vaccinations.

However, even in patients who were seen by physicians in the previous months (in hospital or in outpatient care) the general vaccination rate was disappointing low. So we conclude that physicians do not adequately discuss and promote recommended vaccinations with their patients. This severe deficit might be explained due to different factors (e.g. lacking awareness of guidelines and vaccine recommendations or just missing time in the daily routine to discuss the benefits of vaccines with the patients), which should be addressed in a further study involving physicians.

Another factor may be that the process of getting vaccinated in adulthood as it is now is rather impractical and uncomfortable. For example, it would be far more

convenient if general practitioners had the vaccine in stock and could apply it right after recommending an immunization and after informing about its benefits.

Taken together, a target for the future could be to repeat the study with a larger group of patients from different hospital divisions to get larger amount of data and thereby more accurate results. Moreover, it would also be interesting to perform an additional questionnaire study with the aim of asking the doctors if they are vaccinated themselves and if they are sufficiently informed about the recommendations regarding vaccinations for people with chronic diseases.

In conclusion, to the best of our knowledge the presented results are the first data regarding the influenza, pertussis and pneumococcal infection immunization coverage in Austria. Overall vaccination rates with the percentages of 17.5% (influenza vaccination), 11.5% (pertussis vaccination) and 18.5% (pneumococcal infection vaccination) are rather low. The findings show that many patients that would actually benefit from these vaccinations are at a large part not convinced or rather not enlightened about the advantages and exact effects of the vaccinations. Obviously, official recommendations alone are insufficient to implement important vaccinations and additional strategies are needed to improve the immunization rate.

All in all, the results may help to improve and increase the immunization rate of cardiologic and pneumologic patients and to strengthen the awareness of people regarding the significance of vaccinating properly to protect them from infection related complications and the deterioration of their underlying diseases.

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Fragebogen zur Impfprävalenz

Patienten-Nummer:

Angaben zur Person:

*Alter (in Jahren)*_____

*Station*_____

Ich bin **MÄNNLICH** **WEIBLICH**

☐ ☐

Ich bin **RAUCHER** **NICHTRAUCHER** **EX-RAUCHER**

☐ ☐ ☐

Ich leide an chronischer obstruktiver Lungenkrankheit (COPD) oder Asthma. **JA** ☐ **NEIN** ☐

Wurden Sie im Zeitraum von September 2016 bis Februar 2017 gegen Influenza (Grippe) geimpft? **JA** □ **NEIN** □

Wenn Sie nicht geimpft sind: Weshalb erfolgte die Impfung nicht?

□wurde mir nicht empfohlen
□habe ich vergessen
□habe keine Zeit gehabt
□bin nicht überzeugt vom Nutzen der Impfung
□habe Angst vor Nebenwirkungen
□habe bei Impfungen in der Vergangenheit Nebenwirkungen gehabt

□mir wurde davon abgeraten

wenn ja: von wem wurde Ihnen abgeraten?

FAMILIE **BEKANNTE/FREUNDE** **ÄRZTE** **KRANKENSCHWESTER/-PFLEGER BZW. MEDIZINISCHES FACHPERSONAL**

□ □ □ □

JA **NEIN**

Sind Sie gegen Pneumokokken (Lungenentzündung) geimpft? □ □

Wenn ja, wann erfolgte diese Impfung zuletzt? _____

Was für ein Impfstoff (Pneumovax, Prevenar 13) wurde verwendet? _____

Wenn Sie nicht geimpft sind: Weshalb erfolgte die Impfung nicht?

□wurde mir nicht empfohlen
□habe ich vergessen
□habe keine Zeit gehabt
□bin nicht überzeugt vom Nutzen der Impfung
□habe Angst vor Nebenwirkungen
□habe bei Impfungen in der Vergangenheit Nebenwirkungen gehabt

□mir wurde davon abgeraten

wenn ja: von wem wurde Ihnen abgeraten?

FAMILIE	BEKANNTE/FREUNDE	ÄRZTE	KRANKENSCHWESTER/-PFLEGER BZW. MEDIZINISCHES FACHPERSONAL
□	□	□	□

	JA	NEIN
Sind Sie gegen Pertussis (Keuchhusten) geimpft?	□	□

Wenn ja, wann erfolgte diese Impfung zuletzt? _____

Wenn Sie nicht geimpft sind: Weshalb erfolgte die Impfung nicht?

□wurde mir nicht empfohlen
□habe ich vergessen
□habe keine Zeit gehabt
□bin nicht überzeugt vom Nutzen der Impfung
□habe Angst vor Nebenwirkungen
□habe bei Impfungen in der Vergangenheit Nebenwirkungen gehabt

□mir wurde davon abgeraten

wenn ja: von wem wurde Ihnen abgeraten?

FAMILIE	BEKANNTE/FREUNDE	ÄRZTE	KRANKENSCHWESTER/-PFLEGER BZW. MEDIZINISCHES FACHPERSONAL
□	□	□	□

In der Zeit von 01. Dezember 2016 bis 31. März 2017 hatte ich

□einen Atemwegsinfekt (Husten)
□einen grippalen Infekt

In der Zeit von 01. Dezember 2016 bis 31. März 2017

□war ich stationär im Krankenhaus

□hatte ich eine ambulante Behandlung / musste einen Arzt aufsuchen

<u>Zusatzfragen für Patienten, die an COPD oder Asthma leiden:</u>

In der Zeit von 01. Dezember 2016 bis 31. März 2017 hatte ich folgende Beschwerden:

☐ zunehmende Atemnot

☐häufigerer und stärkerer Husten

☐vermehrte zähe Schleimbildung in den Bronchien

☐gelb-grünliche Verfärbung des Schleims (Eiterbildung)

☐ein pfeifendes Atemgeräusch

☐zunehmende Schwellung der Beine / Wassereinlagerungen

	JA	**NEIN**
Aufgrund dieser Beschwerden war ein Krankenhausaufenthalt notwendig.	☐	☐