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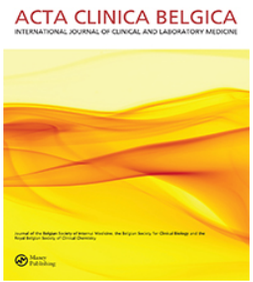

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The incidence of lower respiratory tract infections and pneumococcal vaccination status in adults in flemish primary care

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ABSTRACT

Pneumococcal vaccination coverage of adults at risk for pneumococcal disease is below recommended levels. There is no observational data on pneumococcal vaccination and the incidence of lower respiratory tract infections in a general adult population. The current study had the objective to explore the incidence of lower respiratory tract infections and the pneumococcal vaccine coverage in function of age, influenza vaccination status and risk status, in Flanders, Belgium. We used data from Intego, ageneral practice-based morbidity registration network in Flanders (Belgium). We gathered data on pneumococcal vaccinations, influenza vaccination (in 2014) and ICPC2-coded diagnoses of pneumonia and acute bronchitis (2015). First, we divided the population into three groups along the risk status for developing apneumococcal infection according to the recommendations for pneumococcal vaccination in adults by the Belgian High Council of Health. 28.6% from our total adult study population are considered the target group for vaccination. Second, we found that the average pneumococcal vaccination coverage in this targeted population was 18.7%. Third, we found asignificantly higher incidence of LRTI in patients previously vaccinated against pneumococcal disease and/or influenza across the majority of subgroups. Pneumococcal vaccination coverage in Flanders is quantitatively low but observed to be qualitatively high in terms of reaching the most at risk population. Our findings are likely to be highly relevant to addressing future vaccination strategies in Flanders.

KEYWORDS

Lower respiratory tract infections; pneumonia; bronchitis; pneumococcal vaccination

Background

Acute lower respiratory tract infections (LRTI), usually divided into pneumonia and acute bronchitis, are a major cause of morbidity and mortality worldwide, accounting for 4.8% of all deaths in 2013 [1]. LRTIs can be caused by a variety of pathogens, either viral (like influenza) or bacterial.

Streptococcus pneumoniae (SP) is the most frequently isolated pathogen in LRTI [2] and the most prevalent bacterial etiology of community-acquired pneumonia (CAP) in the European adult population [3,4]. In the Belgian adult population, SP was found to be responsible for approximately 5% of serious LRTIs observed in primary care [5]. Furthermore, SP is responsible for approximately one-fifth of the fatal LRTI cases [3]. Pneumococcal pneumonia is estimated to be the cause of over one million deaths annually [6], granting it the highest mortality from all vaccine-preventable infectious diseases [7]. Up to a third of community-acquired pneumonia may be influenza related, due to bacterial coinfection or secondary bacterial pneumonia [8].

To prevent pneumococcal diseases in adults, two types of vaccines are available: the 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). Although proven effective in children, the efficacy of these vaccines in the prevention of pneumococcal pneumonia in adults is up until now the subject of debate [9,10]. However, a recent meta-analysis proved PPV23 effectiveness against invasive pneumococcal disease (IPD) and pneumococcal pneumonia [11]. Furthermore, results of CAPiTA, a randomized, double-blind, placebo-controlled trial in >84,000 older adults aged ≥65 years, showed that the PCV13 was effective in preventing vaccine-type pneumococcal CAP, vaccine-type pneumococcal non-bacteremic (noninvasive) CAP and vaccine-type IPD [12].

The availability of this study has prompted some recommending bodies to adapt recommendations for pneumococcal vaccination in adults to include PCV13 into the adult vaccination recommendations. Therefore, in Belgium, the High Council of Health recommends since 2014 to vaccinate adults aged 50 years or older with an increased risk of pneumococcal infection with PCV13 followed by PPV23 with an interval of at least 8 weeks. Generally, the population is divided into a 'median risk' and a 'high risk' group, based on age and other host or environmental factors

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[13–15]. Furthermore, the High Council of Health also recommends vaccinating all adults between 65 and 85 years old [16]. However, in daily practice, and in contrast to routine childhood immunization, adult vaccination rates turn out to be low- [17–19] and high-quality evidence of effectiveness of this strategy in the targeted population remains limited to the prevention of IPD and pneumonia in select patient groups [20–25].

In Belgium data on pneumococcal vaccination coverage are scarcely available and not of recent date. Moreover, the available data do not allow to assess to what extent the population at high risk for pneumococcal infection is reached. In addition, population-based data with regards to the incidence of LRTI are lacking. Therefore, it is not possible to estimate whether the defined risk groups indeed represent individuals at highest risk for LRTI.

Therefore, the current study had the objective to explore the incidence of LRTI and the pneumococcal vaccine coverage in function of age, influenza vaccination status and risk status, in Flanders, Belgium. A second objective was to explore if the persons that are identified as being at risk by the actual recommendations, really develop most LRTI's.

Methods

General methods of Intego

Data were obtained from Intego, a Flemish general practice-based morbidity registration network, based at the Academic Centre for General Practice at the University of Leuven [26]. All the information is routinely collected in the electronic health records by the general practitioner (GP) during daily practice. Currently, 111 GPs, all using the medical software program Medidoc®, are collaborating in the Intego project. These GPs work in 49 practices evenly spread throughout Flanders, the northern part of Belgium. Patients in this registration network cover about 2% of the Flemish population. The Intego GPs prospectively and continuously register all new diagnoses together with new drug prescriptions, laboratory test results, vaccinations, and some background information (including sex and year of birth) using computer-generated keywords linked to codes. Using specially framed extraction software, new data were collected on a yearly basis from the computers of the participating GPs by a trusted third party and entered into a central database. Registered data were continuously updated, accumulating a history for each patient.

Data selection

For this study, we included all patients aged 18 years or older and used available data until 31 December 2015.

Pneumococcal vaccination status (ATC code J07AL01, J07AL02, J07AL52) was recorded. The date of the last vaccination was recorded as well. The years since the last vaccination were calculated as follows: day event – day last vaccination for people with an event in 2015 or 31/12/2015 – day last vaccination for people with no event in 2015. Flu vaccination status (ATC code J07BB) was recorded for the previous year (2014).

The incidence and relative rates of acute pneumonia (ICPC2 code R81) and acute bronchitis (ICPC2 R78) and pneumococcal vaccination status were calculated for 2015. Data regarding relevant morbidities of the patients included in Intego were extracted out of the Intego database using ICPC2 codes. Using these data, patients were categorized into 3 categories according to the Belgian High Council of Health: high-risk patients for developing a pneumococcal infection (immunocompromising conditions; including HIV, hematologic malignancies, and the use of glucocorticoids or immunosuppressants), median risk patients (immunocompetent patients with a history of chronic respiratory or cardiovascular disease, chronic liver disease, chronic kidney disease or chronic alcohol abuse) and low-risk patients (all the other patients in the yearly contact group of 2015). The yearly contact group is defined as all patients who contacted their GP at least once in that year, and as a consequence patients of which we have data. This is in contrast to the practice population, which also contains patients who did not contact the GP in that year. This is explained earlier [27].ICPC2 codes for the comorbidities are displayed in Appendix A.

Statistical analysis

Data were presented as numbers and percentages. RRs (risk ratios) were calculated by using univariate and multivariate log-binomial regression. Adjusted risk ratios (aRR) and corresponding 95% confidence interval (95% CI) were calculated using R software version 3.1.3.

Results

Population at risk for pneumococcal infection

From a total study population of 100,484, more than a quarter of the adult population and almost half of the patients aged 65 or older met at least one criterion for being considered at median risk for developing a pneumococcal infection (48.5%) while 3.7% were considered to be at high risk (Table 1). In total, 28.6% of the adult study population belonged to the target group for vaccination according to the Belgian High Council of Health (Table 1). Older people tended to have more risk factors for developing a pneumococcal infection in both the medium- and high-risk groups,

Table 1. Proportion of adult patients at risk in 2015 and age group (4 age groups) (N = 100,484).

Risk group	Total population	18-49 years	50-64 years	65-84 years	85+ years
High risk group, n	2089	636	663	707	83
Number of high risk group comorbidities					
1	2006 (96.0)	620 (97.5)	633 (95.5)	672 (95.0)	81 (97.6)
≥2	83 (4.0)	16 (2.5)	30 (4.5)	35 (5.0)	2 (2.4)
Number of high and median risk group comorbidities					
1	1062 (50.8)	461 (72.5)	345 (52.0)	237 (33.5)	19 (22.9)
2	559 (26.8)	145 (22.8)	190 (28.7)	204 (28.9)	20 (24.1)
≥3	468 (22.4)	30 (4.7)	128 (19.3)	266 (37.6)	44 (53.0)
Median risk group, n	23,916	6983	6440	8272	2221
Number of median risk group comorbidities					
1	16,746 (70.0)	6247 (89.5)	4731 (73.5)	4733 (57.2)	1035 (46.6)
2	4440 (18.6)	618 (8.9)	1218 (18.9)	2037 (24.6)	567 (25.5)
≥3	2730 (11.4)	118 (1.7)	491 (7.6)	1502 (18.2)	619 (27.9)
Low risk patients, n	74,479	45,205	17,152	6377	3953

n = number of participants.

although this was more pronounced in the high-risk group. The majority of the 85+ group with high risk for developing a pneumococcal infection had even 3 or more morbidities that were considered as risk factors for developing a pneumococcal infection (Table 1).

The presence of a cardiovascular disease or cardiovascular complaint was the most prevalent morbidity in adults aged 65 or older in the medium-risk group (Appendix B). On the other hand, in the study population up until 64 years, respiratory illnesses were the main morbidity in the medium-risk group (Appendix B). The dominant reason for being a high-risk patient was the same in both age groups; the prescription of glucocorticoids or other immunosuppressants (Appendix B).

Vaccination coverage

In total, 5162 patients (5.1% of the study population) received a previous pneumococcal vaccination with the polysaccharide vaccine (PPV23) and 598 patients received the conjugated vaccine (PCV13) (0.6%) (data not shown). According to the recommendations of the Belgian High Council of Health, 18.7% of the targeted population was previously vaccinated while the vaccination coverage was 0.9% in the non-target population (all patients aged 18–49 and low-risk patients aged 50–65) (Table 2).

In the 50–64 year olds, the vaccination coverage ranged from 5.6% in the medium-risk group to 17.8% in the high-risk group. Whereas in the 65–84 year olds, vaccination coverage ranged from 26.5% to 34.0% in the medium and high-risk group, respectively. Within each risk group, the vaccination coverage increased with increasing number of morbidities (Table 2). In the oldest group, the number of years since the last pneumococcal vaccination was higher compared to younger age groups. The overall rate of previous influenza vaccination in 2014 in our database was 17.2%. In our study population, vaccination coverage increased with increasing age and/or risk status. In each subgroup, more people were vaccinated against flu as compared to pneumococcal vaccination (Table 2).

Incidence of LRTI

In 2015, the incidence of LRTI in the total adult population increased with age and risk status (32.2‰, 76.1‰ and 142.2‰ for low-, medium- and high-risk groups, respectively) (Table 3). Even more, the incidence of LRTI increased with the number of morbidities within each age and risk group (Table 3). The same results were found both for acute bronchitis and pneumonia (Figure 1).

A seasonal trend was observed in the number of people with a diagnosis of LRTI. The risk of developing LRTI increased in fall and winter, i.e., from September to February. The same trend was seen for the incidence of acute bronchitis, but for pneumonia, this trend was less pronounced (Figure 2).

Incidence of LRTI according to pneumococcal vaccination status

A difference was observed in LRTI incidence between people who were vaccinated for pneumococcal disease (120.2‰ – overall medium-risk group; 218.4‰ – overall high-risk group) and those who did not receive a pneumococcal vaccination (69.5‰ – overall medium-risk group; 124‰ – overall high-risk group) (data not shown).

The incidence of LRTI was higher in all low-, medium- and high-risk groups of people vaccinated in the last 5 years, compared to the non-vaccinated people (Table 3). The opposite (more LRTI in the non-vaccinated people) was observed in a few subgroups based on the number of comorbidities (50-64y high-risk group with 1 or 2 high or medium-risk factors; 65-84y high-risk group with one high or medium-risk factor; ≥85y medium-risk group with just one comorbidity). However, these differences were less pronounced compared to the total risk groups.

Table 2. Proportion of adult patients with a previous registered pneumococcal vaccination per age and risk group in 2015 (N = 100,484) (4 age groups).

	Previous pneumococcal vaccination n (%)				
Age and risk groups	PPV	PCV	Years since the last pneumococcal vaccination Median [P_{25}; P_{75}]	>1 previous vaccination n (%)	Flu vaccination in 2014 n (%)
50–64 years					
Low risk (N = 17,152)	263 (1.53)	47 (0.27)	3.3 [1.3; 5.2]	69 (0.40)	2020 (11.78)
Median risk (N = 6440)	309 (4.80)	52 (0.81)	3.2 [1.2; 5.1]	94 (1.46)	1622 (25.19)
Number of median risk group comorbidities					
1	181 (3.83)	30 (0.63)	3.2 [1.4; 5.1]	52 (1.10)	1049 (22.17)
2	80 (6.57)	17 (1.40)	3.2 [1.1; 5.1]	23 (1.89)	371 (30.46)
≥3	48 (9.78)	5 (1.02)	2.9 [1.2; 4.4]	19 (3.87)	202 (41.14)
High risk (N = 663)	89 (13.42)	29 (4.37)	1.6 [0.8; 4.0]	25 (3.77)	218 (32.88)
Number of high risk group comorbidities					
1	79 (12.48)	26 (4.11)	1.6 [0.8; 4.0]	22 (3.48)	204 (32.23)
≥2	10 (33.33)	3 (10.00)	2.0 [0.4; 3.1]	3 (10.00)	14 (46.67)
Number of high and median risk group comorbidities					
1	30 (8.70)	9 (2.61)	1.6 [1.0; 4.0]	4 (1.16)	93 (26.96)
2	32 (16.84)	10 (5.26)	1.8 [0.7; 4.2]	14 (7.37)	62 (32.63)
≥3	27 (21.09)	10 (7.81)	1.2 [0.8; 3.3]	7 (5.47)	63 (49.22)
65-84 years					
Low risk (N = 6377)	1180 (11.42)	118 (1.14)	3.3 [1.4; 5.2]	490 (4.74)	4055 (39.25)
Median risk (N = 8272)	1951 (23.59)	237 (2.87)	3.3 [1.2; 5.3]	827 (10.00)	5137 (62.10)
Number of median risk group comorbidities					
1	965 (20.39)	101 (2.13)	3.2 [1.2; 5.2]	416 (8.79)	2732 (57.72)
2	498 (24.45)	72 (3.53)	3.3 [1.2; 5.2]	202 (9.92)	1327 (65.14)
≥3	488 (32.49)	64 (4.26)	3.3 [1.2; 5.9]	209 (13.91)	1078 (71.77)
High risk (N = 707)	219 (30.98)	21 (2.97)	3.1 [1.2; 4.5]	104 (14.71)	488 (69.02)
Number of high risk group comorbidities					
1	206 (30.65)	19 (2.83)	3.2 [1.2; 4.5]	98 (14.58)	462 (68.75)
≥2	13 (37.14)	2 (5.71)	1.2 [0.7; 3.1]	6 (17.14)	26 (74.29)
Number of high and median risk group comorbidities					
1	61 (25.74)	5 (2.11)	3.2 [1.2; 4.1]	25 (10.55)	147 (62.03)
2	56 (27.45)	6 (2.94)	2.3 [1.0; 3.4]	32 (15.69)	138 (67.65)
≥3	102 (38.35)	10 (3.76)	3.2 [1.5; 5.2]	47 (17.67)	203 (76.32)
≥85 years					
Low risk (N = 3953)	229 (12.78)	2 (0.11)	4.2 [2.3; 8.1]	116 (6.47)	485 (27.06)
Median risk (N = 2221)	659 (29.67)	20 (0.90)	4.3 [3.1; 8.1]	320 (14.41)	1227 (55.25)
High risk (N = 83)	25 (30.12)	1 (1.20)	4.1 [2.2; 6.7]	15 (18.07)	55 (66.27)

n = number of participants; PPV = pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugated vaccine.

Incidence of lower respiratory tract infections according to influenza vaccination status

Irrespective of pneumococcal vaccination status, having received an influenza vaccination was associated with a higher chance of developing an LRTI. In the non-vaccinated people against influenza aged ≥85 years, we noticed no clear pattern between the vaccinated and non-vaccinated people for pneumococcal infection (Table 4).

Discussion

Main findings

This large observational population-based study of an adult primary care population aimed to provide insights into the size of the population considered at risk for pneumococcal disease according to the Belgian recommendations, their vaccination coverage, and relative incidences of LRTI. First, 28.6% of our total adult study population was considered the target group for vaccination. Second, the average pneumococcal vaccination coverage in the target population was 18.7% and increased with age and risk status. Influenza vaccination coverage was more than five times as high in some risk and age groups. On the other hand, only 0.9% of the non-target population was vaccinated against pneumococcal diseases. Third, a significantly higher incidence of LRTI was found in previously vaccinated (pneumococcal and/or influenza) patients across the majority of subgroups.

Comparison of findings to literature

Vaccination coverage

In 2005, the pneumococcal vaccination coverage in the Belgian older population was estimated to be 30% [28], compared to our 21.5% coverage of the 65 + population (Table 2). More recently, data from

Table 3. Incidence and relative risk of LRTI per age and risk group in 2015 according to pneumococcal vaccination status (N = 100,484).

	Incidence of LRTI (acute bronchitis or pneumonia)			
Age and risk groups	aRR [95%CI]	No vacc. ‰	Vacc. ‰	Total ‰
18-49 years				
Low risk (N = 45,205)	0.36 (0.20; 0.74)	23.7	65.7	23.8
All people				
Median risk (N = 6983)				
All people	0.28 (0.18; 0.46)	46.0	66.7	47.7
High risk (N = 636)				
All people	0.94 (0.40; 3.02)	75.1	80.0	75.5
50-64 years				
Low risk (N = 17,152)				
All people	0.45 (0.32; 0.67)	40.0	88.7	40.8
Median risk (N = 6440)				
All people	0.48 (0.37; 0.64)	71.4	147.6	75.3
Number of comorbidities				
1	0.54 (0.37; 0.81)	65.9	123.1	68.3
2	0.42 (0.27; 0.69)	81.3	195.4	89.5
≥3	0.64 (0.34; 1.39)	102.0	160.0	107.9
High risk (N = 663)				
All people	0.79 (0.51; 1.28)	147.7	188.1	153.8
Number comorbidities				
1	0.79 (0.51; 1.32)	147.6	186.8	153.2
≥2	0.75 (0.14; 5.03)	150.0	200.0	166.7
Number of high and median risk group comorbidities				
1	1.17 (0.45; 4.68)	102.9	88.2	101.4
2	1.04 (0.53; 2.39)	201.3	194.4	200.0
≥3	0.71 (0.37; 1.49)	206.2	290.3	226.6
65-84 years				
Low risk (N = 6377)				
All people	0.81 (0.65; 1.04)	52.0	63.9	53.4
Median risk (N = 8272)				
All people	0.73 (0.64; 0.85)	87.0	118.5	94.8
Number of comorbidities				
1	0.72 (0.59; 0.90)	76.6	106.1	82.8
2	0.91 (0.68; 1.23)	96.7	106.3	99.2
≥3	0.72 (0.55; 0.94)	111.7	155.5	126.5
High risk (N = 707)				
All people	0.63 (0.46; 0.87)	147.6	234.5	175.4
Number of comorbidities				
1	0.64 (0.46; 0.90)	145.7	226.4	171.1
≥2	0.53 (0.15; 1.69)	190.5	357.1	257.1
Number of high and median risk group comorbidities				
1	1.06 (0.53; 2.41)	137.1	129.0	135.0
2	0.38 (0.19; 0.74)	96.6	254.2	142.2
≥3	0.72 (0.47; 1.11)	205.0	285.7	236.8
≥85 years				
Low risk (N = 3953)				
All people	0.75 (0.43; 1.45)	39.1	51.9	40.7
Median risk (N = 2221)				
All people	0.91 (0.70; 1.2)	95.8	105.3	98.6
Number of comorbidities				
1	1.13 (0.71; 1.91)	80.7	71.2	78.3
2	0.81 (0.48; 1.40)	86.8	107.0	93.5
≥3	0.90 (0.6; 1.37)	132.4	146.9	137.3
High risk (N = 83)				
All people	0.42 (0.21; 0.83)	193.0	461.5	277.1
Number of comorbidities				
1	0.43 (0.21; 0.85)	200.0	461.5	284.0
≥2	NA	0.0	NA	0.0
Number of high and median risk group comorbidities				
1	NA	0.0	250.0	52.6
2	NA	176.5	333.3	200.0
≥3	0.61 (0.28; 1.24)	320.0	526.3	409.1

n = number of participants; PPV = Pneumococcal polysaccharide vaccine; PCV: Pneumococcal conjugated vaccine: aRR (95%CI) = adjusted risk ratio (95% confidence interval); vacc = vaccination; NA = Not applicable.

a Belgian survey in the same region and year as our study reported a much lower pneumococcal vaccination coverage in the population at risk (8.0%), but also observed a much higher influenza vaccination coverage (29%) [29]. This was a survey in the general population based on self-reported data. The Intego database is based on patient records completed by the physician. Surveys are more prone to non-responder bias and errors because some people are not aware of which type of vaccine they received. The latter being a general concern in survey-based estimates of vaccination coverage. Therefore, the use of

Table 4. Incidence and relative risk of LRTIs per age and risk group in 2015 according to pneumococcal vaccination status for people who had (no) influenza vaccination in 2014 (N = 83,247).

	Incidence of LRTI (acute bronchitis or pneumonia) For people without influenza vaccination in 2014				Incidence of LRTI (acute bronchitis or pneumonia) For people with influenza vaccination in 2014			
Age and risk groups	aRR [95%CI]	No pneumo vacc. ‰	Pneumo vacc. ‰	Total ‰	aRR [95%CI]	No pneumo vacc. ‰	Pneumo vacc. ‰	Total ‰
50-64 years								
Low risk (N = 17,152)								
All people	1.24 (0.54; 3.96)	38.5	31.0	38.4	0.39 (0.26; 0.62)	52.3	134.1	58.9
Median risk (N = 6440)								
All people	0.37 (0.25; 0.59)	63.9	173.1	66.2	0.71 (0.50; 1.05)	96.8	136.0	102.3
Number of median risk group comorbidities								
1	0.44 (0.25; 0.89)	61.1	138.5	62.5	0.74 (0.45; 1.29)	84.9	115.4	88.7
2	0.30 (0.15; 0.71)	68.2	230.8	73.2	0.64 (0.36; 1.26)	116.1	180.3	126.7
≥3	0.38 (0.16; 1.44)	87.0	230.8	93.4	0.94 (0.41; 2.68)	127.3	135.1	128.7
High risk (N = 663)								
All people	0.44 (0.24; 1.05)	120.6	272.7	128.1	1.4 (0.80; 2.61)	230.2	164.6	206.4
Number of high risk group comorbidities								
1	0.39 (0.21; 0.92)	117.4	300.0	125.9	1.55 (0.87; 3.05)	240.6	154.9	210.8
≥2	NA	214.3	0.0	187.5	NA	0.0	250.0	142.9
Number of high and median risk group comorbidities								
1	0.36 (0.13; 2.00)	90.2	250.0	95.2	3.88 (0.8; 69.45)	149.3	38.5	118.3
2	0.48 (0.21; 1.76)	159.7	333.3	171.9	2.31 (0.92; 7.57)	342.9	148.1	258.1
≥3	0.83 (0.21; 13.72)	166.7	200.0	6169.2	0.88 (0.40; 2.01)	270.3	307.7	285.7
65-84 years								
Low risk (N = 6377)								
All people	0.86 (0.51; 1.61)	42.8	49.6	43.0	1.04 (0.80; 1.37)	70.2	67.4	69.5
Median risk (N = 8272)								
All people	0.65 (0.48; 0.91)	73.7	113.3	78.1	0.82 (0.69; 0.97)	97.8	119.6	104.9
Number of median risk group comorbidities								
1	0.55 (0.37; 0.86)	65.3	119.2	70.5	0.85 (0.66; 1.09)	87.2	103.0	91.9
2	0.66 (0.37; 1.29)	83.5	126.4	88.7	1.04 (0.75; 1.46)	106.0	102.3	104.7
≥3	1.21 (0.57; 3.11)	99.7	82.2	96.7	0.70 (0.52; 0.95)	118.2	167.8	138.2
High risk (N = 707)								
All people	0.25 (0.12; 0.55)	86.7	347.8	114.2	0.85 (0.60; 1.22)	189.5	221.7	202.9
Number of high risk group comorbidities								
1	0.28 (0.14; 0.66)	90.4	318.2	114.3	0.85 (0.59; 1.24)	183.8	215.8	197.0
≥2	NA	0.0	1000.0	111.1	1.00 (0.29; 3.46)	307.7	307.7	307.7
Number of high and median risk group comorbidities								
1	NA	132.5	0.0	122.2	0.97 (0.44; 2.31)	141.3	145.5	142.9
2	NA	32.3	500.0	60.6	0.61 (0.30; 1.25)	144.6	236.4	181.2
≥3	0.16 (0.05; 0.46)	78.4	500.0	158.7	1.02 (0.64; 1.64)	263.6	258.1	261.1
≥85 years								
Low risk (N = 3953)								
All people	1.02 (0.32; 6.26)	25.3	24.7	25.2	1.34 (0.70; 2.83)	89.6	66.7	82.5
Median risk (N = 2221)								
All people	1.13 (0.60; 2.35)	53.6	47.4	52.3	1.05 (0.78; 1.41)	138.4	132.2	136.1
Number of median risk group comorbidities								
1	1.14 (0.45; 3.80)	55.6	48.8	54.5	1.39 (0.81; 2.55)	113.1	81.1	101.7
2	0.64 (0.20; 2.40)	38.5	59.7	44.2	0.98 (0.56; 1.80)	131.3	133.3	132.1
≥3	2.02 (0.56; 12.81)	65.1	32.3	56.3	0.92 (0.61; 1.43)	179.9	194.6	185.6
High risk (N = 83)								
All people	0.37 (0.06; 1.89)	111.1	300.0	178.6	0.41 (0.19; 0.86)	230.8	562.5	327.3
Number of high risk group comorbidities								
1	0.37 (0.06; 1.89)	111.1	300.0	178.6	0.43 (0.20; 0.90)	243.2	562.5	339.6
≥2	NA	NA	NA	NA	NA	0.0	NA	0.0
Number of high and median risk group comorbidities								
1	NA	0.0	NA	0.0	NA	0.0	250.0	100.0
2	NA	200.0	NA	200.0	NA	166.7	333.3	200.0
≥3	0.83 (0.05; 4.70)	250.0	300.0	285.7	NA	333.3	777.8	466.7

n = number of participants; PPV = pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugated vaccine: aRR (95%CI) = adjusted risk ratio (95% confidence interval); vacc = vaccination; NA = not applicable.

medical record data was put forward as the golden standard [30–34].

While studies on pneumococcal vaccination rates in other Western countries also reported a low coverage of their targeted adult populations, they generally reported higher rates than our findings. Marked international differences, even within Europe, are attributable to the heterogeneity in guidelines defining different risk groups based on other criteria [35] or severity cut-off points [36], and their complex conjunction with vaccine uptake

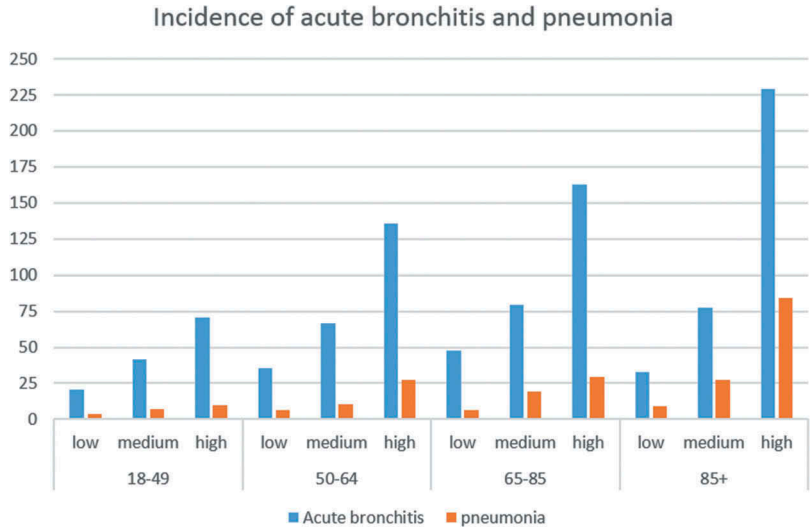

Figure 1. Incidence of acute bronchitis of pneumonia per age and risk group in 2015 (N = 100,484). Legend: Incidence of acute bronchitis of pneumonia in ‰ per age and risk group in 2015. 4 age groups were used 18–49 years; 50–64 years; 65–85 years and ≥85 year and 3 risk groups were used according to the recommendations of the Belgian high council of health. Figures were displayed in blue for acute bronchitis and orange for pneumonia.

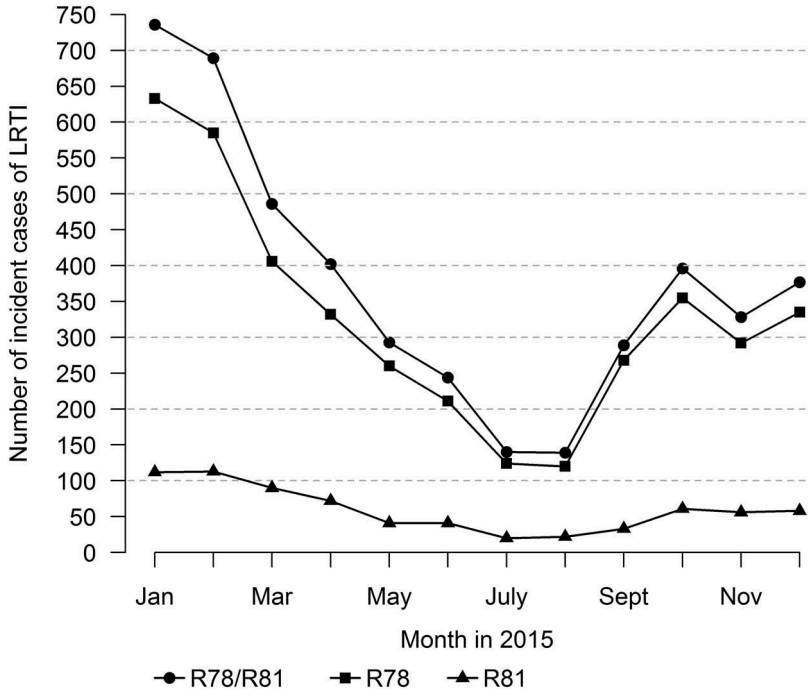

Figure 2. Number of people with a diagnosis of a lower respiratory tract infection in 2015 per month. Legend: Number of people with a diagnosis of a lower respiratory tract infection (circles), bronchitis (rectangles) of pneumonia (triangles) in 2015 were displayed per month.

influencing factors such as vaccination programs and affordability or reimbursement [37].

The incidence of LRTI

Other large population-based observational studies of primary care records in different regions, also reported a higher incidence of LRTI according to predefined risk criteria. For example, in the Dutch population selected underlying conditions were related to a twofold increase in incidence of LRTI [38] which was much similar to our findings, and a threefold increase in risk for CAP in the U.S. population [15]. A population-based study in the U.K. confirmed our finding of an increased incidence of LRTI with age to be most noticeably for pneumonia [39]. We found an overall incidence of pneumonia in the Flemish population of 5.8/1000py, which seems fairly low according to reported incidences of 9.7/1000py in Germany [40] and 10.6/1000py in subjects

aged 18–64 years in the USA [41]. However, a summary of other research in Europe also showed a variety of incidence estimates [42].

Effectiveness of pneumococcal/influenza vaccines

While the incidence of LRTI significantly increased with risk (comorbidities) and to lesser extent with age, we found a significantly higher incidence of LRTI in previously vaccinated patients with a pneumococcal and/or influenza vaccine across the majority of subgroups. Based on these results, the vaccine apparently seemed inefficient. However, several remarks should be made in this context. The vaccine effectiveness (VE) should be monitored in observational cohort studies when the vaccine is already available in practice. However, multiple forms of bias/confounding have been described in observational cohort studies. Confounding by indication is likely to be present if patients with underlying chronic diseases are more likely to be vaccinated than healthy study participants. This leads to an underestimation of VE since the less healthy population is at higher risk of adverse health outcomes. This automatically implies a high risk of confounding by indication [43,44]. Furthermore, although SP is the most frequently isolated pathogen in LRTIs, only a limited proportion of 5% of the LRTIs is caused by pneumococcal infections. Third, along the recommendations, only adults from 50 years or more with comorbidities are advised to be vaccinated against pneumococcal disease. This may imply that, due to immunosenescence, there might be a lower uptake of the vaccine with increasing risk and/or age. For all these reasons we cannot make any conclusions on vaccine effectiveness.

Strength and weaknesses

Our study has important strengths, being a large, population-based study of 100,484 primary care records, covering approximately 2% of all adults spread throughout Flanders. Without the bias of non-responders and questionable accuracy of self-reported vaccination status, we were able to provide a more accurate estimate of vaccination coverage in the adult Flemish population than the current survey-based results [29].

While GPs in Flanders often diagnose pneumonia without radiological confirmation, we realize some diagnoses could be missed or false [45]. However, we argue to have substantially reduced this limitation by focusing on all LRTI; thus, still capturing diagnoses that could have switched after technical investigation. Registration of smoking status in the Intego database is inadequate. Therefore, we could not use this important risk factor correctly in risk assessment [46]. However, as this would only rule out 'healthy smokers' because we would have detected smokers as soon as secondary pulmonary or cardiovascular conditions emerge. For the same reason, we could not adjust for socioeconomic factors, but these were shown to be of limited influence in the Belgian elderly population [47]. Gender is also known to be a potential risk factor [21] but again not of the utmost importance to our general study objective.

Clinical impact

We observed low vaccination coverage. The confirmation of a higher incidence according to risk and age supports the need for efforts to increase vaccination coverage in the target population. We suggest it could be pragmatically doubled through seasonal co-administration with the influenza vaccine, since influenza vaccination coverage was much higher in the target group.

On the other hand, we observed very low vaccination coverage of the non-target group. We can conclude that GPs in that respect comply with the guidelines. We observed a higher incidence of LRTI in the most vulnerable population who was already vaccinated. With this in mind, we observe that GPs can assign the most vulnerable people by using the guidelines. For this, we would not recommend to redefine the target group for vaccination.

Conclusion

This observational study of 100,484 primary care records was the first to explore the incidence of LRTI and the pneumococcal vaccination coverage in the general Flemish adult population according to age and risk criteria. From the perspective of not seeing a lower incidence of LRTI in vaccinated patients, we argue that – in line with findings in clinical trials – the protective effect of the pneumococcal vaccine in adults would be small at best in our observations. The results on vaccination coverage and incidence of LRTI according to risk and age might indicate the presence of a bias by indication, as seen in similar observational studies in other regions. The confirmation of a higher incidence according to risk and age supports the need for efforts to increase vaccination coverage in the target population.

Availability of data

Intego has no permission form the ethical review board to publish the full database.

Consent for publication

Patients are well informed about Intego through posters in the waiting room of the GP's. They do not sign an informed consent but can use the opt-out option that is incorporated in the EHR of the GP. Data are pseudonymised and by no means have researchers access to names or contact details of the patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Ethics approval and consent to participate

Data were collected from the computers of the participating GPs by a trusted third party. The scientific and ethical review board assesses whether the questions are ethically correct (Ethics Board) and scientifically sound (Scientific Board). They have an advisory function, comparable to a Data Safety Monitoring Board in clinical trials. By this, our procedures are compliant with the law confirmed by decision n° 13.026 of March 19th, 2013 of the Sectoral Committee of Social Security and Health (www.privacycommission.be). The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no ML 1723).

Authors' Contributions

BVB, GVP and CM conceived the study idea, SH was responsible for statistical analyses, TDB and BV took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

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Appendices

Appendix A. ICPC codes used for comorbidities

High risk patients	AIDS (B90)	Ever diagnosed before 31/12/2015
	Lymphoma (B72)	diagnosed between 01/01/2010 and 31/12/2014 (5 years)
	Leukemia (B73)	diagnosed between 01/01/2010 and 31/12/2014 (5 years)
	Malignant neoplasm (B74)	diagnosed between 01/01/2010 and 31/12/2014 (5 years)
	Immunosuppressant (ATC L04)	in 2014 or in 2015
	Glucocorticoids (ATC H02AB)	at least 2x in 2015
Median risk patients	Chronic bronchitis (R79):	Ever diagnosed before 31/12/2015
	Congenital respiratory anomaly (R89):	Ever diagnosed before 31/12/2015
	COPD (R95):	Ever diagnosed before 31/12/2015
	Asthma (R96):	Ever diagnosed before 31/12/2015
	Congenital cardiovascular anomaly (K73):	Ever diagnosed before 31/12/2015
	Angina pectoris (K74):	Diagnosed in 2014 or in 2015
	Acute myocardial infarction (K75):	Ever diagnosed before 31/12/2015
	Chronic ischemic heart disease (K76	Ever diagnosed before 31/12/2015
	Heart failure (K77):	Ever diagnosed before 31/12/2015
	Atrial fibrillation (K78	Ever diagnosed before 31/12/2015
	Pulmonary heart disease (K82):	Ever diagnosed before 31/12/2015
	Heart valve disease (K83):	Ever diagnosed before 31/12/2015
	TIA (K89):	Ever diagnosed before 31/12/2015
	CVA (K90):	Ever diagnosed before 31/12/2015
	Peripheral arterial disease (K92):	Ever diagnosed before 31/12/2015
	Chronic liver disease (D97):	Ever diagnosed before 31/12/2015
	Chronic kidney disease eGFR<60 mL/min:	One measure <60 in 2013 or 2014
	*Chronic alcohol abuse (P15)	Ever diagnosed before 31/12/2015
Low risk patients	All the other patients in the yearly contact group 2015	

Appendix B. Proportion of adult patients at risk in 2015 and age group (4 age groups) (N = 100,484)

Risk group	Total population	18–49 years	50–64 years	65–84 years	85+ years
High risk group, n	**2089**	**636**	**663**	**707**	**83**
Aids, n (%)	105 (5.0)	78 (12.3)	26 (3.9)	1 (0.1)	0 (0.0)
Lymphoma, n (%)	141 (6.7)	46 (7.2)	36 (5.4)	51 (7.2)	8 (9.6)
Leukemia, n (%)	133 (6.4)	49 (7.7)	48 (7.2)	32 (4.5)	4 (4.8)
Malignant neoplasm blood other, n (%)	55 (2.6)	7 (1.1)	20 (3.0)	22 (3.1)	6 (7.2)
Immunosuppressant, n (%)	488 (23.4)	191 (30.0)	169 (25.5)	122 (17.3)	6 (7.2)
Glucocorticoids, n (%)	1251 (59.9)	281 (44.2)	395 (59.6)	514 (72.7)	61 (73.5)
Median risk group, n	**23,916**	**6983**	**6440**	**8272**	**2221**
Chronic bronchitis, n (%)	852 (3.6)	232 (3.3)	224 (3.5)	326 (3.9)	70 (3.2)
Congenital respiratory anomaly, n (%)	18 (0.1)	7 (0.1)	3 (0.0)	8 (0.1)	0 (0.0)
COPD, n (%)	2438 (10.2)	260 (3.7)	760 (11.8)	1162 (14.0)	256 (11.5)
Asthma, n (%)	9894 (41.4)	4598 (65.8)	2751 (42.7)	2252 (27.2)	293 (13.2)
Congenital cardiovascular anomaly, n (%)	295 (1.2)	167 (2.4)	61 (0.9)	58 (0.7)	9 (0.4)
Angina pectoris, n (%)	242 (1.0)	27 (0.4)	68 (1.1)	122 (1.5)	25 (1.1)
Acute myocardial infarction, n (%)	2288 (9.6)	393 (5.6)	711 (11)	945 (11.4)	239 (10.8)
Chronic ischemic heart disease, n (%)	1459 (6.1)	116 (1.7)	354 (5.5)	785 (9.5)	204 (9.2)
Heart failure, n (%)	971 (4.1)	37 (0.5)	98 (1.5)	481 (5.8)	355 (16.0)
Atrial fibrillation, n (%)	2466 (10.3)	99 (1.4)	326 (5.1)	1400 (16.9)	641 (28.9)
Pulmonary heart disease, n (%)	203 (0.8)	10 (0.1)	17 (0.3)	120 (1.5)	56 (2.5)
Heart valve disease, n (%)	1778 (7.4)	204 (2.9)	358 (5.6)	894 (10.8)	322 (14.5)
TIA, n (%)	1008 (4.2)	37 (0.5)	145 (2.3)	547 (6.6)	279 (12.6)
CVA, n (%)	1996 (8.3)	270 (3.9)	505 (7.8)	858 (10.4)	363 (16.3)
Peripheral arterial disease, n (%)	1926 (8.1)	243 (3.5)	454 (7.0)	969 (11.7)	260 (11.7)
Chronic liver disease, n (%)	2055 (8.6)	373 (5.3)	731 (11.4)	818 (9.9)	133 (6.0)
Chronic kidney disease, n (%)	3786 (15.8)	113 (1.6)	493 (7.7)	2192 (26.5)	988 (44.5)
Chronic alcohol abuse, n (%)	1905 (8.0)	671 (9.6)	766 (11.9)	442 (5.3)	26 (1.2)
Low risk patients, n	**74,479**	**45,205**	**17,152**	**6377**	**3953**