PNEUMOCOCCAL VACCINATION AND THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS IN ADULTS IN FLEMISH PRIMARY CARE

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ABSTRACT

ACHTERGROND Bij volwassenen met verhoogd risico is de dekking met het pneumokokkenvaccin (PV) nog vaak laag. Er zijn nog geen globale observationele gegevens over de associatie tussen PV en de incidentie van lage luchtweginfecties (LLWI). **ONDERZOEKSVRAAG** De volwassen PV-dekking schatten volgens leeftijd en risico's, en de relatieve ratio's bekijken van de incidentie van LLWI bij gevaccineerde en niet-gevaccineerde volwassenen. **METHODE** Met gegevens van Intego, een Vlaams huisartsen-registratienetwerk, werden 95,508 volwassenen ingedeeld in drie risicogroepen, met als niet-doelgroep de laag-risico volwassenen <65j. We verzamelden data over PV, griepvaccinatie (2012) en ICPC2-gecodeerde diagnosen van longontsteking en acute bronchitis (2013). **RESULTATEN** De vaccinatiegraad was globaal laag (6,4% vs pneumokokken, 12% vs influenza), maar nam toe met leeftijd en risico. De incidentie van LLWI (45/1000 patiëntenjaren) nam ook toe volgens leeftijd en risico, en was significant hoger in de gevaccineerde groepen, ook bij vergelijking van de gevaccineerde niet-doelpopulatie met de niet-gevaccineerde doelgroep (104 vs 61/1000pj). **DISCUSSIE** Wat LLWI betreft, wordt in de dagelijkse praktijk de accuraatheid van richtlijnen overtroffen door klinische inschatting om de bevolking met het "echt hoogste risico" te vinden, zichtbaar doordat relatieve risicoverschillen groter zijn dan een mogelijke bescherming door het vaccin. We vonden ook dat co-administratie met het griepvaccin de huidige pneumokokkenvaccinatiegraad kan verdubbelen. **CONCLUSIE** DE PV-dekking in Vlaanderen is kwantitatief laag maar kwalitatief hoog in het bereiken van de hoogste risicopopulatie. Onze bevindingen kunnen relevant zijn voor toekomstige vaccinatiestrategieën in Vlaanderen. In afwachting van meer bewijs van de effectiviteit van het vaccin, kunnen andere regio's met een lage vaccinatiegraad onze benadering gebruiken om de efficiëntie van de selectie van hun ware PV-doelgroep te evalueren.

ABSTRACT

BACKGROUND Pneumococcal vaccination (PV) coverage of adults at risk for pneumococcal disease is below recommended levels. There is no observational data on the association of pneumococcal vaccination and the incidence of lower respiratory tract infections (LRTI) in a general adult population. **STUDY OBJECTIVE** Estimating pneumococcal vaccination coverage in Flemish adults according to age and risk, and exploring the relative rates of incidence of LRTI in vaccinated vs non-vaccinated adults. **METHODS** We used data from Intego, a general practice-based morbidity registration network in Flanders (Belgium). According to relevant morbidities, 95,508 adults were categorized in three risk groups, with low risk adults <65y being the non-target population. We gathered data on PV, influenza vaccination (in 2012) and ICPC2-coded diagnoses of pneumonia and acute bronchitis from 2013. **RESULTS** Vaccination coverage was generally low (6.4% vs pneumococcus; 12% vs influenza) but increased with age and risk. The incidence of LRTI (45/1000 patient years) also increased with age and risk but was significantly higher in the vaccinated parts, also when comparing the vaccinated non-target population to the non-vaccinated target population (104 vs 61 /1000py). **DISCUSSION** We argue that in terms of incidence of LRTI, clinical judgement transcends the accuracy of guidelines in selecting the "truly most at risk" population, observable because of relative risk differences being greater than a potential protection from the vaccine. We also found co-administration with the influenza vaccine could double current coverage. **CONCLUSION** PV coverage in Flanders is quantitatively low but qualitatively high in terms of reaching the population most at risk for LRTI. Our findings are likely to be highly relevant to addressing future vaccination strategies in Flanders. Awaiting more evidence of vaccine effectiveness, other regions with low vaccination coverage can use our approach to assess vaccine target selection efficiency in their adult population.

INTRODUCTION

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). Streptococcus pneumoniae is the most frequently isolated pathogen in community-acquired pneumonia (CAP) in the European adult population (2, 3) and the most prevalent bacterial etiology of acute bronchitis (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 (2). 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).

To prevent pneumococcal diseases, two types of pneumococcal vaccine (PV) are available: the pneumococcal polysaccharide vaccine (PPV23) and the pneumococcal conjugate vaccine (PCV7, PCV10 and PCV13). Childhood immunization has become routine practice for all children in many countries, as it is supported by evidence of vaccine effectiveness in preventing invasive pneumococcal disease (IPD), otitis and pneumonia (8). PV programs for adults mainly target those known to be at greater risk for pneumococcal pneumonia and IPD, generally dividing this population in a ‘median risk’ and a ‘high risk’ group, based on age and other host or environmental factors (9-11). In daily practice however, and in contrast to routine childhood immunization, adult vaccination rates turn out to be low (12-14) and high quality evidence of effectiveness of this strategy remains limited. (15-20).

Several observational studies in different countries monitor adult PV coverage or provide large population based estimates of the incidence of LRTI. To date, no large-scale observational studies explored the association of previous PV status with the incidence of LRTI in the general adult population.

Therefore, the current study had two main objectives. First, to explore the PV coverage in adults according to age and risk status. Second, to investigate whether there is a different incidence of LRTI in vaccinated and non-vaccinated patients.

METHODS

GENERAL METHODS OF INTEGO

Data were obtained from Intego, a Flemish general practice-based morbidity registration network based in the Department of General Practice at the Catholic University of Leuven. Currently ninety General Practitioners (GP), all using the medical software program Medidoc®, are collaborating in the Intego project. These GPs work in 55 practices evenly spread throughout Flanders, the northern part of Belgium. The GP's data were checked on their quality before inclusion in the database. The participating GPs receive yearly quality checks based on peer comparison and feedback on the quality of their data. 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 from the computers of the participating GPs and entered into a central database. Registered data were continuously updated, accumulating a history for each patient.

DATA SELECTION

Status for PV (ATC code J07AL) was checked and the incidence and relative rates of acute pneumonia (ICPC2 code R81) and acute bronchitis (ICPC2 R78) and admission of influenza and pneumococcal vaccines were calculated for 2013. 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: high risk patients (immunocompromising conditions; including AIDS, 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 2013)

RESULTS

From a total population of 95,508, half of the patients aged ≥65y met at least one median or high risk criterion (50.6%), with cardiovascular disease being the most prevalent risk factor (29.3% of ≥65y) (Table 1). Respiratory illnesses were the main risk factor in the youngest adults (9.3% of 18-49y). The dominant reason for being a high-risk patient was the same in every age group; the prescription of glucocorticoids or other immunosuppressants.

Table 1. Proportion of patients at risk in 2013 (Total population, n = 95,508)

	Total population	Age strata				
		18 – 49 (n = 50518)	50 – 64 (n = 22702)	65 – 74 (n = 10256)	75 – 84 (n = 7960)	+85 (n = 4072)
High risk group, n	**2287**	**686**	**729**	**435**	**342**	**95**
Aids, n (%)	91 (4.0)	68 (2,97)	21 (0,92)	2 (0,09)	(0)	(0)
Lymphoma, n (%)	126 (5.5)	44 (1,92)	33 (1,44)	33 (1,44)	13 (0,57)	3 (0,13)
Leukemia, n (%)	147 (6.4)	48 (2,1)	48 (2,1)	23 (1,01)	22 (0,96)	6 (0,26)
Malignant neoplasm blood other, n (%)	55 (2.4)	8 (0,35)	14 (0,61)	18 (0,79)	12 (0,52)	3 (0,13)
Immunosuppressant, n (%)	650 (28)	203 (8,88)	229 (10,01)	123 (5,38)	84 (3,67)	11 (0,48)
Glucocorticoids, n (%)	1315 (57)	334 (14,6)	417 (18,23)	255 (11,15)	232 (10,14)	77 (3,37)
Median risk group, n	**22889**	**6476**	**6004**	**4105**	**4092**	**2212**
Chronic bronchitis, n (%)	907 (3.9)	244 (1,1)	231 (1,0)	184 (0,8)	165 (0,72)	83 (0,36)
Congenital respiratory anomaly, n (%)	18 (0.08)	6 (0,026)	5 (0,022)	2 (0,009)	5 (0,022)	0 (0)
COPD, n (%)	2370 (10)	274 (1,2)	750 (3,3)	570 (2,5)	535 (2,3)	241 (1,1)
Asthma, n (%)	9061 (40)	4238 (18,5)	2540 (11,1)	1227 (5,37)	815 (3,56)	241 (1,05)
Congenital cardiovascular anomaly, n (%)	244 (1.1)	121 (0,53)	62 (0,27)	32 (0,14)	22 (0,096)	7 (0,031)
Angina pectoris, n (%)	253 (1.1)	33 (0,14)	71 (0,31)	57 (0,25)	68 (0,30)	24 (0,11)
Acute myocardial infarction, n (%)	1910 (8.3)	352 (1,54)	576 (2,52)	399 (1,75)	386 (1,69)	197 (0,86)
Chronic ischemic heart disease, n (%)	1236 (5.4)	86 (0,38)	281 (1,23)	319 (1,4)	376 (1,64)	174 (0,76)
Heart failure, n (%)	957 (4.2)	34 (0,15)	92 (0,4)	143 (0,63)	322 (1,41)	366 (1,6)
Atrial fibrillation, n (%)	2147 (9.4)	91 (0,4)	286 (1,25)	489 (2,14)	745 (3,26)	536 (2,34)
Pulmonary heart disease, n (%)	173 (0.76)	7 (0,031)	11 (0,048)	36 (0,16)	72 (0,32)	47 (0,21)
Heart valve disease, n (%)	1446 (6.3)	168 (0,74)	302 (1,32)	298 (1,3)	422 (1,85)	256 (1,12)
TIA, n (%)	990 (4.3)	31 (0,14)	129 (0,56)	218 (0,95)	310 (1,35)	302 (1,32)
CVA, n (%)	1778 (7.8)	233 (1,02)	410 (1,79)	352 (1,54)	436 (1,9)	347 (1,51)
Peripheral arterial disease, n (%)	1895 (8.3)	243 (1,06)	421 (1,84)	418 (1,83)	539 (2,35)	274 (1,2)
Chronic liver disease, n (%)	1705 (7.4)	329 (1,44)	628 (2,74)	358 (1,56)	292 (1,27)	98 (0,43)
Chronic kidney disease, n (%)	5421 (24)	210 (0,92)	820 (3,58)	1211 (5,29)	1951 (8,53)	1229 (5,37)
Chronic alcohol abuse, n (%)	1652 (7.2)	619 (2,7)	634 (2,77)	263 (1,15)	107 (0,47)	29 (0,12)
Low risk patients, n	**70332**	**43356**	**15969**	**5716**	**3526**	**1765**

Table legend: COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; CVA: cerebrovascular accident.

Percentages are calculated for the total risk group (high, median or low).

Table 2. Proportion of patients with a previous registered pneumococcal vaccination per age and risk group in 2013

Age (years) / Risk		Previous pneumococcal vaccination, n (%)		>1 previous vaccination, n (%)	Flu vaccination in 2012, n (%)	Flu vacc + previous pneumococcal vaccination, n
		PNEUMO 23 (ATC J07AL01)	Conjugated vaccine (ATC J07AL02)			
Total population						
	Low risk	1969 (2,8)	10 (0,01)	682 (0,97)	4775 (6,79)	1190
	Median risk	3761 (16,43)	9 (0,04)	1646 (7,19)	5962 (26,05)	2331
	High risk	428 (18,71)	1 (0,04)	158 (6,91)	734 (32,08)	298
18 - 49						
	Low risk	123 (0,28)	3 (0,01)	22 (0,05)	640 (1,48)	30
	Median risk	77 (1,19)	1 (0,02)	14 (0,22)	255 (3,94)	27
	High risk	31 (4,52)	0 (0)	2 (0,29)	67 (9,77)	10
50 – 64						
	Low risk	260 (1,63)	1 (0,01)	60 (0,38)	1339 (8,38)	126
	Median risk	343 (5,71)	2 (0,03)	84 (1,4)	1086 (18,09)	186
	High risk	92 (12,62)	0 (0)	17 (2,33)	195 (26,75)	61
65 – 74						
	Low risk	587 (10,27)	0 (0)	139 (2,43)	1513 (26,47)	414
	Median risk	878 (21,39)	0 (0)	282 (6,87)	1738 (42,34)	583
	High risk	120 (27,59)	0 (0)	41 (9,43)	214 (49,2)	88
75 – 84						
	Low risk	695 (19,71)	1 (0,03)	329 (9,33)	997 (28,28)	463
	Median risk	1592 (38,91)	3 (0,07)	817 (19,97)	2005 (49)	1064
	High risk	144 (42,11)	0 (0)	70 (20,47)	198 (57,89)	107
85+						
	Low risk	301 (17,05)	2 (0,11)	129 (7,31)	283 (16,03)	157
	Median risk	869 (39,29)	1 (0,05)	447 (20,21)	876 (39,6)	471
	High risk	40 (42,11)	0 (0)	27 (28,42)	59 (62,11)	32

Table 3. Incidence and relative rate of lower respiratory tract infections per age and risk group in 2013 according to pneumococcal vaccination status

Age (years) / Risk		Incidence LRTI (acute bronchitis or pneumonia) (/1000 patient years)						Incidence acute bronchitis (/1000 patient years)						Incidence pneumonia (/1000 patient years)					
Total population		Relative rate, 95% CI			no vacc	vaccinated	total	Relative rate, 95% CI			no vacc	vaccinated	total	Relative rate, 95% CI			no vacc	vaccinated	total
	low risk	0,45	0,39	0,54	32,56	71,61	**33,65**	0,44	0,37	0,52	29,43	66,53	**30,47**	0,41	0,25	0,67	3,54	8,63	**3,68**
	median	0,60	0,54	0,66	64,30	107,95	**71,48**	0,60	0,54	0,67	56,88	94,66	**63,09**	0,56	0,42	0,75	9,46	16,75	**10,66**
	high	0,65	0,52	0,81	131,79	203,27	**145,17**	0,58	0,46	0,73	111,89	193,93	**127,24**	1,01	0,51	2,00	23,67	23,36	**23,61**
18-49																			
	low risk	0,40	0,20	0,78	25,74	65,04	**25,86**	0,40	0,20	0,83	22,92	56,91	**23,02**	0,38	0,05	2,68	3,08	8,13	**3,09**
	median	0,35	0,20	0,62	50,48	142,86	**51,58**	0,39	0,21	0,72	45,01	116,88	**45,86**	0,28	0,07	1,12	7,19	25,97	**7,41**
	high	3,12	0,45	21,77	100,76	32,26	**97,67**	2,65	0,38	18,52	85,50	32,26	**83,09**	/	/	/	16,79	0,00	**16,03**
50-64																			
	low risk	0,38	0,27	0,53	46,60	123,08	**47,84**	0,38	0,27	0,53	43,35	115,38	**44,52**	0,34	0,11	1,08	3,95	11,54	**4,07**
	median	0,45	0,34	0,58	70,31	157,43	**75,28**	0,44	0,34	0,59	62,18	139,94	**66,62**	0,55	0,25	1,18	11,13	20,41	**11,66**
	high	0,71	0,45	1,10	146,00	206,52	**153,64**	0,75	0,46	1,22	130,30	173,91	**135,80**	0,58	0,17	2,01	18,84	32,61	**20,58**
65-74																			
	low risk	0,68	0,48	0,95	42,70	63,03	**44,79**	0,63	0,44	0,88	38,41	61,33	**40,76**	1,32	0,31	5,57	4,48	3,41	**4,37**
	median	0,63	0,50	0,78	72,20	115,03	**81,36**	0,60	0,48	0,76	64,15	107,06	**73,33**	0,95	0,44	2,08	8,68	9,11	**8,77**
	high	0,80	0,50	1,26	146,03	183,33	**156,32**	0,69	0,42	1,12	120,63	175,00	**135,63**	1,52	0,33	7,07	25,40	16,67	**22,99**
75-84																			
	low risk	0,63	0,45	0,87	42,39	67,63	**47,36**	0,61	0,44	0,86	38,86	63,31	**43,68**	0,59	0,21	1,67	4,24	7,19	**4,82**
	median	0,75	0,61	0,91	76,80	103,02	**87,00**	0,77	0,62	0,95	70,00	91,08	**78,20**	0,61	0,35	1,06	10,00	16,33	**12,46**
	high	0,64	0,40	1,01	141,41	222,22	**175,44**	0,45	0,27	0,76	101,01	222,22	**152,05**	2,42	0,68	8,65	50,51	20,83	**38,01**
85+																			
	low risk	0,51	0,29	0,88	28,69	56,48	**33,43**	0,48	0,26	0,89	22,54	46,51	**26,63**	0,62	0,17	2,26	6,15	9,97	**6,80**
	median	**0,72**	0,53	0,96	62,55	87,46	**72,33**	**0,71**	0,51	1,00	49,14	69,04	**56,96**	**0,61**	0,33	1,15	14,15	23,01	**17,63**
	high	**0,67**	0,34	1,31	218,18	325,00	**263,16**	**0,62**	0,31	1,23	200,00	325,00	**252,63**	**1,09**	0,19	6,23	54,55	50,00	**52,63**

VACCINATION COVERAGE

In total, 6158 patients (6.45% of the study population) received a previous pneumococcal vaccination with the polysaccharide vaccine (PPV23), including 20 patients who also received the conjugated vaccine (PCV) (0.02%) (Table 2). Overall, the vaccination coverage increased with age and risk; ranging from less than 0.3% in the youngest low-risk patients to over 40% in the oldest high-risk patients. Of the targeted population, 16% was previously vaccinated. In the non-target population (low risk patients aged 18-64), vaccination coverage was 0.6%, accounting for 41% of the administered vaccinations in the age range 18-64 or 6.2% of all registered vaccines. (data not shown).

The overall rate of previous influenza vaccination (IV) in 2012 was 12% (Table 2). In the population with a previous PV, concomitant IV coverage was 62%, with little variability between subgroups except for the youngest age group in which double coverage rate was low (29%). In the non-pneumococcal-vaccinated population, influenza vaccination uptake was generally lower but increased with age and risk from 1.4% in the youngest low risk group to 49% in the oldest high risk. In total, 19% of the non-vaccinated, but targeted population for PV was covered with IV. (data not shown).

INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS ACCORDING TO AGE AND RISK

In 2013, the overall incidence of LRTI was 45 per 1000 patient years (table 3). We found the incidence of LRTI to increase significantly with risk status, with a relative rate (RR) of 2, doubling the incidence from low to median risk (RR 2.12, 95% CI [2.00-2.26]) and from median to high risk (RR 2.03, 95% CI [1.82-2.27]). (data not shown). The incidence of pneumonia was shown to

increase more rapidly according to risk status, resulting in an up to threefold higher incidence between several adjacent risk groups, hence also becoming a larger part of the LRTI diagnoses in high risk groups (21%, vs 12% in low risk groups). (data not shown). When compared to risk groups in the total working-age population (age range 18-64), the incidence of LRTI was higher in all corresponding risk groups in the older part of the population (≥65y). (table 3).

RELATIVE RATE OF LOWER RESPIRATORY TRACT INFECTIONS ACCORDING TO PNEUMOCOCCAL VACCINATION STATUS

In the general adult population, the incidences of LRTI, as well as the incidence of acute bronchitis and pneumonia separately, were found to be significantly higher in vaccinated patients (table 3). The RRs of LRTI incidence were significant in all age groups and in low and median risk subgroups. In high-risk subgroups, only the incidence of acute bronchitis was significantly higher in vaccinated patients aged 75-84 years. The incidence of pneumonia was found to be significantly higher in the vaccinated part of the low and median risk populations, as well as in every age subgroup except for age range 65-74 years. (data not shown). Further assessment of relative rates according to vaccination status between different risk groups within same age groups showed a significantly higher incidence of LRTI in the vaccinated low risk patients aged 50 to 64 years old compared to the non-vaccinated median and high risk patients in this age group (RR 0.63, 95% CI [0.45-0.89]). Moreover, the incidence of LRTI in the vaccinated part of the non-targeted population (low risk working-age adults) was found to be significantly higher than the incidence in the non-vaccinated part of the targeted population (all adults at median or high risk or aged 65 or older) (RR 0.58, 95% CI [0.43-0.79]). (data not shown).

DISCUSSION

This large population-based study aimed to provide on-field insights in the risk distribution, PV coverage and associated RRs of incidence of LRTI in a general adult population. First, we found the PV coverage to be higher in targeted risk groups and older patients, but very low in general and partly aimed at patients out of the scope of our criteria. IV coverage is almost twice as high and overlaps with more than half of the PV coverage. Second, while the incidence of LRTI significantly increased with risk and to lesser extent with age, we found a significantly higher incidence of LRTI in previously vaccinated patients across the majority of subgroups. Moreover, the incidence of LRTI in the low risk patients vaccinated outside our criteria was significantly higher than the incidence in the non-vaccinated target population.

COMPARISON OF FINDINGS TO LITERATURE

VACCINATION COVERAGE

In 2005, the PV coverage in the Belgian elderly was estimated to be 30% (21), much similar to our 30.3% coverage of the ≥75y population (table 2). Data from a Belgian survey in the same region and year as our study reported a much lower pneumococcal vaccination coverage in the population at risk of 8% compared to our 16%, but also observed a much higher IV coverage of 29% compared to our 12% (22). Several potential confounders could be responsible for these discrepancies; as they only took into account vaccines administered in the past 5 years, used another definition of “at risk” and are more prone to non-responder bias. The latter being a general concern in survey based estimates of vaccination coverage. Therefore, the use of medical record data was put forward as the golden standard (23-27).

While studies on PV coverage in other Western countries also reported a low coverage of their targeted adult populations, they generally report higher rates than our findings. PV (an IV) coverage in the overall German adult population was estimated to be 3.8% (and 8.8%) in the age range 18-59 years and 50.9% (and 41.2%) in the population of ≥60y (12). In Ireland, IV and PV coverage in individuals at risk was 28% and 11% in the age group 18-64y, and 69% and 41% in the ≥65y population (28). In Spain, PV coverage in Catalonians raised to 53% in 2003 after implementing free systematic PV for the elderly (29) and was recently assessed to cover 79.5% of ≥80y (30). In 2010, the overall PV coverage of COPD patients in Madrid was 65.5% (31) and in Stockholm, over a study period of 3 years, 50% of respondents aged ≥65y received at least one PV and 66% at least one IV (32).

In the U.S., PV coverage of 60% of the ≥65y population was reported in 2008 (33), followed by a drastic decline caused by the addition of smoking and asthma as high risk factors (34) (14). In Canada, PV coverage of the at-risk population was estimated to be 14% in the adults younger than 65 years of age, 39% in healthy elderly and 49% in at-risk elderly (37).

These marked international differences, even within Europe, are attributable to the heterogeneity in guidelines; defining different risk groups based on other criteria (38) or severity cut-off points (39), and their complex conjunction with vaccine uptake influencing factors (40).

In regard to concomitant IV coverage, similar overlap rates (61%) were reported in England and Wales in 2012, where the authors also found pregnancy to be the cause of the relatively lower co-administration in the youngest part of the population (39).

THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS

Other large population-based observational studies of primary care records in different regions, also report a higher incidence of LRTI according to predefined risk criteria. Much similar to our findings, selected underlying conditions were related to a twofold increase in incidence of LRTI in the Dutch population (41) and a threefold increase in risk for CAP in the U.S. population (11). A population-based study in the U.K. confirmed our finding of an increased incidence of LRTI with age to be most notable for pneumonia (42). 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 (43) and 10.6/1000py in subjects aged 18-64y in the U.S. (44). However, a summary of other research in Europe also showed lower and even much higher incidence estimates (45).

RELATIVE RATES OF INCIDENCE

While a large number of clinical trials reported relative rates of incidence of pneumonia according to PV status, we had no validly comparable data at our disposal, as we didn't find reported results on relative rates of incidence of LRTI in a general adult population according to vaccination status through a similar observational approach.

POTENTIAL CAUSES OF HIGHER INCIDENCE OF LRTI IN VACCINATED PATIENTS

CLINICAL TRIALS AND CURRENT EVIDENCE OF PPV23 EFFECTIVENESS

In the wake of newly found evidence of vaccine effectiveness of PCV in adults (19), we found three recent meta-analyses studying similar effectiveness of PPV23 (17, 18, 46) beyond the scope of demonstrated protection against IPD (40, 47).

A meta-analysis by Kraicer-Melamed and colleagues stated their results are suggestive (but non-significant) for a protective effect of PPV23 against all-cause pneumonia (18), but had

to withdraw this conclusion after correcting their calculations for an error in the interpretation of data from one of the included trials (48, 49). Schiffner-Rohe and colleagues arrived at the same conclusion with a meta-analysis focusing on the prevention of pneumococcal CAP (pCAP) in adults ≥60y (17). A meta-analysis by Wen-qi Diao and colleagues including immunocompetent adults of all ages, confirmed the lack of significant evidence on the prevention of pCAP but also concluded that PPV23 weakly protects against all-cause pneumonia in this population, but not when a stratified analysis based on study setting excluded the Japanese population (46). Supported by evidence of ethnic influence on morbidity from LRTI (50), we conclude that to date, no high quality evidence of a protective effect of PPV against all-cause pneumonia is shown in a general adult European or American population. However, further research is encouraged by the accumulation of results that do suggest a protective effect.

COUNTER-INTUITIVE ADDITION TO RECOGNIZABLE OBSERVATIONS

The results on vaccination coverage and incidence of LRTI according to risk and age, could bring us to the same conclusions as similar observational studies in other regions; confirmation of a higher incidence according to risk and age, supporting the need for efforts to increase PV coverage in the target population.

However, to add new perspective to this kind of observational studies, we also explored the influence of PV coverage on the incidence of LRTI. From the perspective of a vaccine being protective against disease, observations could be interpreted as PV not being fit for this purpose and warrant further research to rule out an even adverse effect of the vaccine, as we found significantly higher incidences of LRTI in the vaccinated population.

This would be a counter-intuitive finding from a trial minded point of view, moreover as we did divide the population into groups with a similar risk status. However the selection of patients that were vaccinated in these groups was not made randomly. Therefore, such as it is the intention of observational studies, we search for possible explanations and corresponding implications.

HYPOTHESES

Several factors are known to play a role in generally low vaccination coverage, including patient and doctor awareness and attitude, availability of the vaccine, public campaigns and reimbursement policies (51). Factors that support the increase of incidence of LRTI with age and risk are also well addressed in literature. While these factors certainly play a role in the vaccination coverage in Flemish adults, we focus on factors that may explain our new observation of a higher incidence of LRTI in the vaccinated patients.

From the perspective of not seeing a lower incidence of LRTI in vaccinated patients, we argue that the protective effect of PV in would be small at best in our observations. A study estimated that only 5% of serious LRTI in Belgian adults is caused by streptococcus pneumoniae (5). While carriers of Streptococcus have a higher risk for LRTI from other pathogens as well, the scope of the vaccine may be wider through reducing colonization rates, especially in the elderly (52-54). The protection level in our studied population is also reduced by the potentially long periods since last PV.

While arguments for a lesser impact of the vaccine can play a role, there must be factors that at least overrule this protective effect to explain the higher incidence. Within every risk subgroup, there will still be differences between patients, as further subdivision is possible on

basis of severity of disease and multi-morbidity. A study in young adults aged 18-49 with an underlying condition, found that the risk for pneumonia raised from 2.5% to 6.2% when they had a second risk factor, and increased to 15.6% in those with three conditions (11). This means we could have a six fold difference in incidence of LRTI within the same age and risk group. Health care providers can use guidelines to assess a certain degree of risk, but these factors are not extensively addressed in most guidelines since they already recommend to vaccinate the entire group. In daily practice with low vaccination coverage however, this could mean that health care providers are actively targeting the "most at risk" patients within a subgroup. There were also known risk factors that are not taken into account in our criteria, such as auto-immune diseases, several neurologic conditions (e.g. Parkinson's disease, multiple sclerosis and dementia), being underweight, socio-economic factors and psychiatric disorders (including but not limited to drug abuse) (3, 11, 55, 56). Without other conditions, these patients would be allocated in a low risk group. If they were detected in daily practice however, this would explain the relatively higher incidence of LRTI in the vaccinated non-target population of low risk patients aged 18-64y.

IMPLICATIONS

Following this reasoning, we could state that our finding of a higher incidence of LRTI in vaccinated adults may be attributable to a successful sub-selection of the "most at risk" patients within a risk group. Moreover, we also found several significantly higher rates in vaccinated patients from one subgroup versus non-vaccinated patients from a higher risk or age group. Most interestingly, we found a significantly higher rate in the total vaccinated non-target population versus the non-vaccinated target population. This could mean that, in daily practice, clinical judgement transcends the accuracy of risk criteria in selecting the "most at risk" population. In Belgium, the importance of clinical judgement was addressed by the High Council for Public

Health in 2005, supporting this approach by including it in an update of the Belgian recommendations for pneumococcal vaccination in 2005 (57). While it is unclear how much these changed recommendations influenced daily practice, our observations seemed to acknowledge the presence as well as the relevance of clinical judgement in following guidelines as it successfully contributes to targeting the most at risk Flemish adults.

Awaiting further evidence in support of more global targeting of the adult population, other regions struggling with low vaccination coverage could use our approach to assess "vaccine target selection effectiveness"; potentially observing blind spots or false focuses. This way, more important quality issues can be addressed first, followed by thought-out directions for quantity improvement. To that latter purpose, we also advocate the use of seasonal co-administration with currently observed IV practice. As the targeted populations of both vaccines are very similar and co-administration of PPV23 with IV is known to be safe (58), we calculated that by fully using this field of opportunity, PV coverage in the target population could be increased by 100%. (data not shown).

In general, we should keep monitoring the on-field evolution of the incidence of LRTI in association with pneumococcal vaccination, as the implementation of vaccination strategies itself, changes the very nature of the factors on which they were based through complex interaction of mechanisms as indirect childhood immunization effects, herd immunity and serotype replacement. While these mechanisms are studied, they are still highly unpredictable. Therefore, continuous vigilance is required in order to keep appropriately adapting and implementing regional immunization strategies.

STRENGTHS AND LIMITATIONS

Our study has important strengths, being a large, population-based study of 95,508 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 current survey based results (22). However, we didn't exclude vaccinations older than five years, since the identification of even the poorly targeted population was more relevant to our study objective than the actual level of protection (47, 60).

Because general practitioners in Flanders often diagnose pneumonia without radiological confirmation, we realize some diagnoses could be missed or false (64). However, we argue to have substantially reduced this limitation by focusing on all LRTI, thus still capturing diagnoses that should be switched after technical investigation. Registration of smoking status in the Intego database is inadequate. Therefore we could not use this considerably important risk factor in risk assessment (65). However, this would only rule out "healthy smokers" as we would have detected smokers as soon as secondary pulmonary or cardiovascular conditions emerged. For the same reason, we couldn't adjust for socio-economic factors, but these were shown to be of limited influence in the Belgian elderly population (66). Gender is also known to be a potential risk factor (16) but again less important to our general study objective.

CONCLUSION

This observational study of 95,508 primary care records, was the first to explore the association of PV coverage and the incidence of LRTI in the general Flemish adult population according to age and risk criteria. We observed a low PV coverage, and suggested it could to be

pragmatically doubled through seasonal co-administration with IV. We found a significantly higher incidence of LRTI in vaccinated patients. We argue this could be a sign of clinical judgement leading to a more accurate selection, within and beyond current risk criteria, of the truly most at risk adults for LRTI. As further research may validate our findings, we consider our approach to be highly relevant for assessing “vaccination target selection efficiency” in regions with low vaccination coverage.

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Bijlage 1: gunstig advies ethisch comité

Betreft uw aanvraag Ethische begeleiding masterproeven met titel "PNEUMONOCCOCAL VACCINATION AND THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS IN ADULTS IN FLEMISH PRIMARY CARE" (mp12673)

English version below

Geachte Heer/Mevrouw

De Opleidingspecifieke Ethische Begeleidingscommissie van de opleiding "Master in de huisartsgeneeskunde (Leuven e.a.)" heeft uw voorstel tot Masterproef "PNEUMONOCCOCAL VACCINATION AND THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS IN ADULTS IN FLEMISH PRIMARY CARE" onderzocht en gunstig geadviseerd. Dit betekent dat de commissie van oordeel is dat de studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Dit gunstig advies van de commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor zelf verantwoordelijk. Indien u van plan bent uw masterproef te publiceren kan deze e-mail dienen als bewijs van goedkeuring.

Dear Mr/Ms

The Supervisory Committee on Medical ethics of the "Master in de huisartsgeneeskunde (Leuven e.a.)" programme has reviewed your master's thesis project proposal "PNEUMONOCCOCAL VACCINATION AND THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS IN ADULTS IN FLEMISH PRIMARY CARE" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent.

De OBC meent dat de aanvraag in orde is op ethisch vlak, maar ziet op methologisch en wetenschappelijk vlak nog heel wat tekortkomingen.

Met vriendelijke groeten

Opleidingsspecifieke begeleidingscommissie van de opleiding Master in de huisartsgeneeskunde (Leuven e.a.)

Bijlage 2: goedgekeurd protocol

VERZOEK TOT ADVIES VAN HET ETHISCH COMITE BETREFFENDE EEN ONDERZOEKSPROJECT BIJ DE MENS

IN HET KADER VAN DE MASTER-NA-MASTER HUISARTSGENEESKUNDE

1. TITEL VAN HET ONDERZOEK

PNEUMONOCCOCAL VACCINATION AND THE INCIDENCE OF LOWER RESPIRATORY TRACT INFECTIONS IN ADULTS IN FLEMISCH PRIMARY CARE

2. GEGEVENS VAN DE BEGELEIDENDE EN SUPERVISERENDE ONDERZOEKER(S)

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5. INDIEN HET MASTERPROJECT AANSLUIT BIJ EEN LOPEND ONDERZOEK

ZIE BIJLAGE 1: GOEDKEURING LOPEND ONDERZOEK

6. Periode (begin- en einddatum maand/jaar)

- START/EINDE ONDERZOEK:
  ALS CONTINU MORBIDITEIT REGISTRATIENETWERK IS INTEGO GESTART IN 1994 EN LOOPT ANNO 2016 NOG STEEDS DOOR. VOOR HET HUIDIGE ONDERZOEK WORDT GEKEKEN NAAR 2013 EN GEGEVENS UIT DE VOORGAANDE JAREN.

7. Soort onderzoek

RETROSPECTIEF OBSERVATIONEEL ONDERZOEK: GEGEVENSVERZAMELING VAN PATIËNTEN UIT ANDERE DATABANK (INTEGO)

8. Geef een Korte samenvatting van het protocol (minimum 30 zinnen/ een halve pagina en maximum één pagina), verstaanbaar voor mensen niet gespecialiseerd in de materie, verwijs niet alleen naar een bijgevoegd protocol.

INTEGO DATABANK

ER WORDT GEWERKT MET GEGEVENS UIT DE DATABANK VAN INTEGO. INTEGO STAAT VOOR "GEÏNTEGREERD COMPUTERNETWERK" EN IS EEN VLAAMS REGISTRATIENETWERK VAN HUISARTSEN OPGESTART VANUIT HET ACADEMISCH CENTRUM HUISARTSENGENEESKUNDE VAN DE KU LEUVEN. DE OPZET VAN DIT PROJECT IS OM EEN GROTE DATABASE OP TE BOUWEN OVER MORBIDITEIT IN DE EERSTELIJNSZORG. MOMENTEEL WERKEN 90 HUISARTSEN, VERSPREID OVER 55 PRAKTIJKEN, MEE AAN HET INTEGO PROJECT. ZIJ REGISTREREN ALLE NIEUWE DIAGNOSES, MEDICATIEVOORSCHRIFTEN, RESULTATEN VAN LABORATORIUMONDERZOEKEN, VACCINATIES EN BEPAALDE ACHTERGRONDINFORMATIE VAN DE PATIËNTEN. DE VERZAMELDE DATA ZIJN EEN WAARDEVOLLE BRON VOOR VERDER ONDERZOEK.

OPGEHAALDE GEGEVENS

VOOR DIT ONDERZOEK WORDEN UIT DE INTEGO DATABANK ALLE PATIËNTEN VERZAMELD DIE IN 2013 ACHTTIEN JAAR OF OUDER WAREN. VAN DEZE PATIËNTEN WORDT BEKEKEN OF ZE EEN VACCINATIE TEGEN PNEUMOKOKKEN HEBBEN GEKREGEN, OF ZE EEN GRIEPVACCIN HEBBEN GEKREGEN IN 2012 EN WELKE AANDOENINGEN ZE HEBBEN DIE RELEVANT ZIJN OM HUN RISICO OP EEN LAGE LUCHTWEGINFECTIE IN TE SCHATTEN. TOT SLOT WORDT UIT DE DATABANK VOOR DEZE POPULATIE OOK DE INCIDENTIE VAN LAGE

LUCHTWEGINFECTIES IN 2013 GEHAALD, MET NAME DE DIAGNOSES "ACUTE BRONCHITIS" EN "ACUTE PNEUMONIE", VOLGENS DE 'INTERNATIONAL CLASSIFICATION OF PRIMARY CARE, 2ND EDITION' (ICPC2) GECODEERD ALS RESPECTIEVELIJK R78 EN R81.

RISICOGROEPEN

OP BASIS VAN HUN RISICOFACTOREN WORDEN DE PATIËNTEN IN DRIE CATEGORIEËN INGEDEELD: HOOG RISICO-PATIËNTEN, MIDDELMATIG RISICO-PATIËNTEN EN LAAG RISICO-PATIËNTEN. INCLUSIECRITERIA OM ALS HOOG RISICO TE WORDEN GECLASSIFICEERD ZIJN IMMUNOLOGISHE PROBLEMEN DOOR BEHANDELINGEN MET CORTICOSTEROÏDEN OF IMMUNOSUPPRESSIVA OF DOOR AANDOENINGEN ALS AIDS, LYMFOOM, LEUKEMIE EN ANDERE HEMATOLOGISCHE MALIGNITEITEN. DE GEMIDDELDE RISICO-PATIËNTEN ZIJN MENSEN MET AANDOENINGEN VAN HET ADEMHALINGSSTELSEL (CRHONISCHE BRONCHITIS, AANGEBOREN AFWIJKINGEN VAN HET ADEMHALINGSSTELSEL, COPD EN ASTMA), CARDIOVASCULAIRE PROBLEMEN (AANGEBOREN HART- OF BLOEDVATAFWIJKINGEN, ANGINA PECTORIS, EEN VOORGESCHIEDENIS MET MYOCARDINFARCT, CHRONISCHE ISCHEMISCHE HARTZIEKTEN, HARTFALEN, VOORKAMERFIBRILLATIE, PULMONALE HYPERTENSIE, HARTKLEPAANDOENINGEN, BEROERTE EN PERIFEER VAATLIJDEN), CHRONISCHE LEVERZIEKTE, CHRONISCH NIERFALEN EN ALCOHOLMISBRUIK. ALLE PATIËNTEN WAARBIJ IN HET DOSSIER GEEN ENKELE VAN DE HIERBOVEN OPGESOMDE RISICOFACTOREN GECODEERD WERD OPGESLAGEN, WORDEN GECLASSIFICEERD ALS LAAG RISICO-PATIËNTEN.

ANALYSE

DEZE GEGEVENS WORDEN GEANALYSEERD OM TE BEKIJKEN HOE GROOT DE RISICOGROEPEN ZIJN, HOE GROOT HET AANDEEL VAN VERSCHILLENDE LEEFTIJDSCATEGORIEËN IS, HOEVEEL PATIËNTEN ER PER LEEFTIJDSGROEP EN PER RISICOGROEP GEVACCINEERD WERDEN EN HOE VAAK IN DEZE VERSCHILLENDE GROEPEN IN 2013 EEN LAGE LUCHTWEGINFECTIE WERD GEDIAGNOSTICEERD. OP DEZE MANIER KAN EEN VERGELIJKING GEMAAKT WORDEN TUSSEN DE INCIDENTIE VAN LAGE LUCHTWEGINFECTIES BIJ PATIËNTEN DIE WEL OF NIET WERDEN GEVACCINEERD. TEVENS KAN BEKEKEN WORDEN OF DE RELATIEVE RATIO VAN DEZE INCIDENTIES ANDERS IS WANNEER PATIËNTEN MET EN ZONDER VOORAFGAAND GRIEPVACCIN WORDEN VERGELEKEN.

9. HET ONDERZOEK IS

EPIDEMIOLOGISCH

10. ZIJN ER ZIEKENHUISDIENSTEN BETROKKEN?

NEEN

11. WIE IS DE OPDRACHTGEVER VAN DE NIET INDUSTRIE GESPONSORDE STUDIE

FACULTEIT GENEESKUNDE KU LEUVEN

12. KEUZE VAN DE PROEFPERSONEN :

A. GEZONDE PROEFPERSONEN ?

ALLE PERSONEN VANAF 18 JAAR IN DE INTEGO DATABANK IN 2013

B. ZWANGERE VROUWEN OF VROUWEN DIE TIJDENS HET ONDERZOEK ZWANGER KUNNEN WORDEN ?

JA

C. AANTAL PROEFPERSONEN: 95.508

D. LEEFTIJD : 18 JAAR EN OUDER

E. GESLACHT : M/V

F. HOE WORDEN ZE GEREKRUTEERD?

DATABANK VAN INTEGO

13-15. INFORMATIE EN TOESTEMMING VAN DE PROEFPERSONEN

DE INTEGO-DATABANK BEVAT DE GEGEVENS VAN DE PATIËNTEN VAN 90 HUISARTSEN IN 55 HUISARTSENPRAKTIJKEN. HET GAAT HIER ZOWEL OM VOLWASSENEN ALS MINDERJARIGEN. DE GEGEVENS WORDEN ANONIEM GEREGISTREERD EN DE TOESTEMMING VAN DEZE PATIËNTEN WORDT BEKOMEN DOOR INFORMATIE TE GEVEN OVER EEN UITSTAPMOGELIJKHEID (OPT-OUT STRATEGIE) VOOR WIE NIET IN DE DATABANK WENST OPGENOMEN TE WORDEN. PATIËNTEN DIE GEEN ACTIE ONDERNEMEN, WORDEN OP DIE MANIER BESCHOUWD ALS PATIËNTEN DIE TOESTEMMING HEBBEN GEGEVEN. DE GEDETAILLEERDE BESCHRIJVING VAN DEZE PROCEDURE IS TERUG TE VINDEN IN HET PROEFSCHRIFT VAN CARLA TRUYERS (1).

1. TRUYERS C. THE USE OF GENERAL PRACTICE CONTINUOUS MORBIDITY REGISTRATION SYSTEMS FOR PUBLIC HEALTH SURVEILLANCE. 2011.

16. VERZEKERING

IN PRINCIPE IS HET DE VERZEKERING VAN DE UNIVERSITEIT WAARAAN UW PROMOTOR VERBONDEN IS WAARDOOR U GEDEKT BENT.

WANNEER U EN/OF UW PROMOTOR EEN ANDERE VERZEKERING HEBBEN AFGESLOTEN, GELIEVE DAN DE VERZEKERINGSPOLIS BIJ TE VOEGEN.

17. WERD EEN ANALOOG ONDERZOEK REEDS ELDERS UITGEVOERD, HETZIJ IN ZIJN GEHEEL, HETZIJ GEDEELTELIJK ?

ER WERD VOORHEEN IN VERSCHILLENDE LANDEN NOG RETROSPECTIEF OBSERVATIONEEL ONDERZOEK UITGEVOERD MET GELIJKAARDIGE ONDERZOEKSVRAAG, ECHTER MEESTAL GERICHT OP DE INCIDENTIE VAN PNEUMONIE EN INVASIEVE PNEUMOKOKKENZIEKTE. RESULTATEN HIERVAN ZIJN VERSCHILLEND NAARGELANG DE STUDIE-OPZET. IN DEZE STUDIE WORDT SPECIFIEK GEKEKEN NAAR ALLE IN EERSTE LIJN GEDIAGNOSTICEERDE LAGE LUCHTWEGINFECTIES, NIET ENKEL DE BEVESTIGDE DOOR PNEUMOKOKKEN VERWEKTE INFECTIES.

18. WANNEER VERWACHT MEN VOORDEEL VOOR DE DEELNEMER

A. HEEFT HET EXPERIMENT EEN DIAGNOSTISCH OF THERAPEUTISCH DOEL DAT ONMIDDELLIJK VOORDEEL AAN DE ONDERZOCHTE ZAL BRENGEN ?

NEEN

B. MAAKT HET EXPERIMENT DEEL UIT VAN EEN DIAGNOSTISCH EN THERAPEUTISCH PLAN WAARVAN MEN MAG VERWACHTEN DAT DE RESULTATEN BINNEN AFZIENBARE TIJD VOOR ANDERE ZIEKEN NUTTIG ZULLEN ZIJN ?

NEEN

C. MAAKT HET EXPERIMENT DEEL UIT VAN EEN GEHEEL VAN ONDERZOEKEN WAARVAN HET DIAGNOSTISCH OF THERAPEUTISCH BELANG NIET ONMIDDELLIJK DUIDELIJK IS, MAAR WAARVAN MAG WORDEN VERWACHT DAT DE RESULTATEN LATER TOT DIAGNOSTISCHE OF THERAPEUTISCHE TOEPASSINGEN OF TOT EEN BETERE KENNIS VAN DE FYSIOPATHOLOGISCHE MECHANISMEN ZULLEN LEIDEN ?

JA

19. REKENING HOUDEND MET DE HUIDIGE STAND VAN ZAKEN VAN DE WETENSCHAP:

A. MEENT U DAT DEZE STUDIE:

WAARSCHIJNLIJK GEEN ENKEL RISICO INHOUDT

20. ZULLEN DE PERSONEN IN DE LOOP VAN DEZE STUDIE VOORTDUREND ONDER MEDISCH TOEZICHT STAAN

NEEN

21-24. NIET VAN TOEPASSING

25 . FINANCIËLE OVEREENKOMST

(INDIEN EEN DEFINITIEVE FINANCIËLE OVEREENKOMST NOG NIET BESCHIKBAAR IS, DAN KAN EEN BUDGET PROPOSAL DAT TEGENGETEKEND IS DOOR EEN VERTEGENWOORDIGER VAN DE FINANCIERDER + ONDERZOEKER VOLSTAAN) INDIEN HET BEDRAG VAN DE DEFINITIEVE FINANCIËLE OVEREENKOMST HOGER IS DAN HET INGEDIENDE "BUDGET PROPOSAL", MOET DEZE DEFINITIEVE FINANCIËLE OVEREENKOMST ALSNOG TER GOEDKEURING VOORGELEGD WORDEN AAN HET ETHISCH COMITÉ)

NIET VAN TOEPASSING

IK VERKLAAR DE GEHELE VERANTWOORDELIJKHEID VAN HET HIERBOVEN VERMELD PROJECT OP MIJ TE NEMEN EN BEVESTIG DAT VOOR ZOVER DE HUIDIGE KENNIS HET TOELAAT, DE GEGEVEN INLICHTINGEN MET DE WERKELIJKHEID OVEREENSTEMMEN.

HUISARTS-IN-OPLEIDING

DATUM : 15/06/2016
NAAM : BART VERBOVEN
HANDTEKENING :



PRAKTIJKOPLEIDER

DATUM : 3/7/16
NAAM : STEFAAN VINCK
HANDTEKENING :



PROMOTOR

DATUM :

NAAM : GIJS VAN POTTELBERGH

HANDTEKENING :

CO-PROMOTOR

DATUM :

NAAM : BERT VAES

HANDTEKENING :

DIENSTHOOFD VAKGROEP HUISARTSGENEESKUNDE UNIVERSITEIT WAARAAN PROMOTOR VERBONDEN (VOOR AKKOORD)

DATUM :

NAAM : BERT AERTGEERTS

HANDTEKENING :

BIJLAGE 1: GOEDKEURING LOPEND ONDERZOEK

Kopie 35

FACULTEIT GENEESKUNDE
COMMISSIE VOOR MEDISCHE ETHIEK/KLINISCH ONDERZOEK
U.Z. GASTHUISBERG E322
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Prof. F. Buntinx
Huisartsgeneeskunde

KATHOLIEKE
UNIVERSITEIT
LEUVEN

ONS KENMERK ML1723
LEUVEN, 01-11-20

Intego, een netwerk van geïnformatiseerde huisartspraktijken voor morbiditeits-registratie : consolidatie, continue kwaliteitsverbetering, en aanvulling met gegevens rond diagnostiek.

Geachte Collega,

In antwoord op uw brief van 25 oktober 2001 en na inzage van het bijgevoegd dossier meent de Commissie voor Medische Ethiek van de Faculteit Geneeskunde dat het voorgenomen onderzoek ethisch verantwoord is. De Commissie neemt hierbij nota van uw verklaring dat de patiëntgegevens enkel in geanonimiseerde vorm worden doorgegeven, zodat de privacy van de patiënten niet in het gedrang komt.

Met de meeste hoogachting,

Prof. Dr. P. De Schepper
Voorzitter
Commissie voor Medische Ethiek/ Klinisch Onderzoek

Prof. Dr. W. Heyns
Secretaris

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