

SEASONAL INFLUENZA VACCINATION: PRIORITIZING CHILDREN OR OTHER TARGET GROUPS?

PART II: COST-EFFECTIVENESS ANALYSIS – SUPPLEMENT 1.1



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■ SUPPLEMENT REPORT

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1. REVIEW DETAILS OF EFFICACY AND EFFECTIVENESS STUDIES

1.1. Influenza vaccine efficacy in children

The use of influenza vaccines in the European Union (EU) is not harmonized, probably due to the sparseness of irrefutable data. Following the European Summary of Product Characteristics (SPC) of the Trivalent Inactivated Influenza Vaccines (TIV), these vaccines can be used in children from 6 months onwards.¹⁻³ However, this assessment is given with a warning, because the data on the use of TIV in children remain sparse. On the other hand, one Live Attenuated Influenza Vaccine (LAIV) formulation ("FLUENZ") has been granted a license for children only, and in contrast to TIV, the use of this LAIV in children has been discussed explicitly in these public EC documents.^{4, 5}

1.1.1. Live Attenuated Influenza Vaccine (LAIV) studies in children based on EPAR

Table 1 – Overview of Randomised Double Blind Clinical Trials involving LAIV in children

Study number, location/date	Design and objectives	Test products	Number of subjects randomized	Age of subjects
<i>TIV controlled</i>				
MI-CP111 USA Asia Europe Middle East 2004-05	Randomized, double blind, active controlled One or two dose regimen Primary efficacy objective: To estimate the relative efficacy and assess the safety of FLUENZ compared to TIV on incidence of culture-confirmed CDC-Influenza-Like illness caused by matched strains Secondary objectives: - To estimate the relative effectiveness of R-FLUENZ compared to TIV. - To assess the tolerability of FLUENZ compared to TIV.	Refrigerated FLUENZ 0.2 ml TIV 6-35 months: 0.25 ml >35 months: 0.5 ml	Total: 8475 4243 4232	6-59 months
<i>Placebo controlled</i>				
AV006 Y1 USA/1996-97	Randomized, double blind, placebo controlled One or two-dose regimen Primary objective (revised): To demonstrate that children receiving a two-dose primary vaccination regimen of FLUENZ are protected from cultured-confirmed influenza illness (CCII) caused by community-acquired subtypes antigenically similar to those contained in the vaccine. Secondary objectives (revised) (ITT): - Two-dose regimen, as randomized. To demonstrate that children enrolled in a two-dose primary vaccination regimen of FLUENZ are	Frozen FLUENZ Placebo 0.5 ml	Total: 1602 1070 532	15-71 months



	protected from CCII. - Core efficacy study cohort. To demonstrate the efficacy of either a one- or two-dose primary vaccination regimen of FLUENZ to protect children against CCII. - One-dose regimen. To estimate the efficacy of a one-dose primary vaccination regimen of FLUENZ to protect children against CCII. - Follow-on study cohort. To demonstrate the efficacy of a second year's single dose of FLUENZ to protect children who received a one- or two-dose primary vaccination in the previous year against CCII.			
AV006 Y2 USA/1997-98	Randomized, double blind, placebo controlled Re-vaccination in children enrolled in AV006 Y1 One dose regimen Primary efficacy objective: Efficacy of a second year's single re-vaccinating dose of FLUENZ against CCII caused by subtypes antigenically similar to those contained in the vaccine in children who received a one- or two-dose primary vaccination regimen in the previous year Secondary efficacy objectives: - Protection of children enrolled in the two-dose regimen in the first year re-vaccinated in Year Two. - Protection of children enrolled in the one-dose regimen in the first year re-vaccinated in Year Two. - Protection against all community-acquired viral subtypes.	Frozen FLUENZ Placebo	Total: 1358 917 441	26-85 months
D153-P501 China Taiwan India Southeast Asia 2000-2002	Year 1: randomized, double blind, placebo controlled Two dose regimen Year 2 : randomized One dose regimen Primary Efficacy Objective: Efficacy over one season against CCII caused by community-acquired subtypes antigenically similar to those contained in the vaccine Secondary Efficacy Objectives (cfr. narratives).	Refrigerated FLUENZ Placebo Refrigerated FLUENZ Placebo 0.2 ml	Total Year 1: 3174 1900 1274 Total Year 2: 2947 1477 1470	>12-<36 months
D153-P502 EU Israel 2000-2002	Randomized, double blind, placebo controlled Two dose regimen in Year 1, one dose regimen in Year 2 Primary efficacy objective: Efficacy over one season against CCII caused by community-acquired subtypes antigenically similar to those contained in the vaccine Secondary Efficacy Objectives (cf narratives)	Refrigerated FLUENZ Placebo Refrigerated FLUENZ Placebo 0.2 ml	Total Year 1: 1784 1059 725 Total Year 2: 1119 658 461	6-<36 months
D153-P504 South Africa	Randomized, double blind, placebo controlled One or two dose regimen in Year 1, one dose regimen in Year 2	Refrigerated FLUENZ (2 doses) Refrigerated FLUENZ (1 dose)	Total Year 1: 3200 1064	6-<36 months



Brazil Argentina 2001-2002	Primary efficacy objective: Efficacy over first season against CCII caused by community-acquired subtypes antigenically similar to those contained in the vaccine: - Whether administration of 1 dose of FLUENZ resulted in superior efficacy compared to the placebo - Whether administration of 2 doses of FLUENZ resulted in superior efficacy compared to the placebo Secondary efficacy objectives: - Efficacy over first season against CCII caused by any community-acquired subtypes - Efficacy over 2nd season against CCII caused by community-acquired subtypes antigenically similar to those contained in the vaccine - Efficacy over 2nd season against CCII caused by any community-acquired subtypes - Efficacy in the 1st and 2d seasons, against AOM, febrile OM, and influenza-associated OM - Efficacy against hospitalization and pneumonia	Excipient Placebo Saline Placebo Refrigerated FLUENZ Refrigerated FLUENZ Placebo Placebo 0.2 ml	1067 543 526 Total Year 2: 2202 735 732 365 370	
D153-P522 Europe Southeast Asia Hong Kong Mexico Bangladesh 2002-03	Randomized, double blind, placebo controlled Two dose regimen Primary efficacy objective: To determine if R-FLUENZ interferes with the immune response to MMR vaccine administered concomitantly Secondary Efficacy Objectives - Efficacy over one season against CCII caused by community-acquired subtypes antigenically similar to those contained in the vaccine - Efficacy over one season against CCII caused by any community-acquired subtypes - Efficacy against AOM, febrile OM, and influenza-associated OM	Refrigerated FLUENZ (0.2 ml)+MMR Placebo (0.2 ml)+MMR	Total: 1233 819 414	11-<24 months

Source: European Commission, EPAR LAIV, 2011.⁵

**Active controlled trial, MI-CP111**

MI-CP111 was a phase III, refrigerated FLUENZ versus TIV randomized, double-blind, active-comparator, multinational trial, enrolling children aged 6 months to 59 months.

A total of 8475 subjects were randomized 1:1 with 4243 subjects in the FLUENZ group and 4232 subjects in the TIV group. Randomization was stratified by age, country, history of prior influenza vaccination, and history of wheezing (defined as ≥ 3 wheezing illness episodes requiring medical follow-up or hospitalization).

Subjects were randomized at 249 sites in the U.S. and 15 countries in Asia and Europe/Middle East: 4117 subjects (48.6%) were randomized in the U.S. (133 sites), 542 (6.4%) in Asia (3 countries, 15 sites), and 3816 (45.0%) in Europe/Middle East (12 countries, 101 sites). After the U.S., the countries with the highest number of randomized subjects were Finland (725 subjects, 8.6%), Israel (653 subjects, 7.7%), the United Kingdom (563 subjects, 6.6%), and Belgium (459 subjects, 5.4%).

The following vaccine formulations were compared:

- (A) Liquid formulation vaccine (Refrigerated FLUENZ, henceforth: R-FLUENZ): dosage strength/strain: 107 ± 0.5 FFU of A/NewCaledonia/20/99 (H1N1), A/Wyoming/03/2003(H3N2) and B/Jilin/20/2003 [B/Shangai/361/2002-like] given intranasally at a total dose volume of 0.2 ml.
- (B) Commercial TIV vaccine: dosage strength /strains/0.25 ml or 0.5ml: 7.5 μ g or 15 μ g each of HA of A/NewCaledonia/20/99 (H1N1), A/Wyoming/03/2003 (H3N2), B/Jiangsu/10/2003 [B/Shanghai/361/2002-like] (2004-2005 formula), depending on subject age.

Children who were previously vaccinated were to receive one dose of vaccine or placebo, whereas those who were not previously vaccinated received 2 doses of vaccine or placebo. Children receiving two doses were given each vaccination 28-42 days apart. All doses were administered prior to the influenza season. The age distribution of the subjects was similar between the two trial groups (about 48% in 6-23 months; 33% in 24-35 months; 20% 36-59 months). The distribution of underlying medical conditions at baseline was similar between the R-FLUENZ and TIV treatment groups. Up to 9% of subjects had an underlying medical condition and 76% of all the underlying medical conditions identified were chronic lung disease.

The distribution of subjects by wheeze/asthma history was similar between treatment groups and among the ATP, ITT, and Safety populations. Approximately 21% were identified as having a past medical history of wheezing, 6% had a history of >3 wheezing illnesses that required medical follow-up or hospitalization, 4% had a medical diagnosis of asthma prior to the trial, 2% had a history of persistent cough related to asthma, and 18% had previously received medication for wheezing, asthma, or persistent cough related to asthma.

Administration of the FLUENZ vaccine resulted in a 44.5% (95%CI 22.4–60.6) reduction in culture-confirmed influenza illness caused by virus strains antigenically matched to those used in the vaccine blend compared to TIV. The incidence of illness due to all possible strains showed a 54.9% reduction (95%CI 45.4–62.9), whereas the efficacy against mismatched strains showed a 58.2% reduction (95%CI 47.4–67.0). Results were driven by the relative efficacy for FLUENZ compared to TIV for circulating A/H1N1 strains (relative efficacy for B strains was not statistically significant in this study; no matched H3N2 strains were isolated in this study).

Relative efficacy of FLUENZ was also demonstrated against the symptomatic influenza infection (due to matched strains, mismatched strains, and all strains regardless of antigenic match) and against the endpoints of acute otitis media (AOM) and lower respiratory illness (LRI) associated with positive nasal cultures for influenza.



Table 2 – Stratified efficacy analyses of the primary endpoint of MI-CP111 (According to protocol)

	CAIV-T (N=3893)		TIV (N=3943)		Relative efficacy ^a		95% exact CI for relative efficacy ^a
	N	# culture-confirmed cases	Crude attack rate (cases/N)	N	# of cases	Crude attack rate (cases/N)	
AGE	23		1.30%	1852	32	1.70%	
- 6-23 months	1834	17	1.30%	1301	24	1.80%	29.10%
- 24-35 months	1311	13	1.70%	783	37	4.70%	32.60%
- 36-59 months^b	771	13	1.70%	783	37	4.70%	65.60%
PRIOR INFLUENZA VACCINATION^c	18		1.90%	937	29		3.10%
- Yes	929	35	1.20%	2999	64	2.10%	39.30%
- No	2987	35	1.20%	2999	64	2.10%	46.90%
WHEEZING HISTORY^d		8	3.30%	216	9	4.20%	
- Yes	246	45	1.20%	3720	84	2.30%	24.00%
- No	3670	45	1.20%	3720	84	2.30%	46.90%
GENDER		24	1.20%	2017	43	2.10%	
- Male	2008	29	1.50%	1919	50	2.60%	49.80%
- Female	1908	29	1.50%	1919	50	2.60%	44.80%
RACE		49	1.50%	3184	80	2.50%	
- White/Non-Hispanic	3168	4	0.50%	752	13	1.70%	40.30%
- Non-White	748	2	1.30%	140	2	1.40%	64.80%
- Black	156	0	0.00%	243	3	1.20%	-124.70%
- Hispanic	225	1	0.30%	297	5	1.70%	100%
- Asian	290	1	1.30%	72	3	4.20%	69.40%
- Other	77						45.60%

a. Relative efficacy was adjusted for country, age, prior vaccination status, and wheezing history status. b. One 60-month-old subject was counted in the 36-59 month stratum. c. Subjects with an unknown vaccine history were counted as not having received prior influenza vaccination. d. Positive wheezing history was defined as a history of ≥ 3 wheezing illness requiring medical follow-up or hospitalization. Subjects with an unknown wheezing history were counted as having a negative wheezing history. Source: adapted from European Commission, EPAR LAIV, 2011.⁵

**Placebo controlled RCT, AV006 Y1**

This was a randomized, double-blind, placebo controlled, multi-centre trial in US children aged 15 months to 71 months. The study was designed as a two-year study (1996-1997) with a single cohort recruited in year one, to be re-vaccinated without re-randomization in year two. Eligible participants were subjects not previously vaccinated against influenza. A total of 1602 subjects were enrolled and randomized 2:1 to receive either frozen FLUENZ (N = 1070) or placebo (N = 532) in year 1. Furthermore, subjects were enrolled to receive either a 2-dose (N = 1314) or 1-dose (N = 288) primary vaccination regimen of either FLUENZ or placebo in year 1. No randomization according to number of doses took place. Children were vaccinated in the two-dose schedule and received their second dose administered 46 to 74 days after dose one.

In subjects who underwent a 2 dose regime, the efficacy of FLUENZ was estimated to be 93.4% (95%CI 87.5–96.5) for any strain, 96.0% (95%CI 89.4–98.5) for A/H3N2, and 90.5% (95%CI 78.0–95.9) for B (No A/H1N1 influenza strain circulated that season). Efficacy in protecting against culture-confirmed influenza caused by any strain among subjects enrolled to receive 1 dose was estimated to be 88.8% (95%CI 64.5–96.5). FLUENZ also significantly reduced the occurrence of febrile illness and otitis media associated with culture-confirmed influenza [95.0% (95%CI 90.0–97.5) and 97.5% (95%CI 85.5–99.6) respectively].

Placebo controlled RCT, AV006 Y2

This trial is the second part of the AV006 study, covering the second year (September 1997-March 1998). All subjects who completed the year 1 part of the study were encouraged to participate in the second part. Subjects received a single dose of the same treatment (FLUENZ or placebo) according to their randomization in Year 1. The population was made up of returning subjects, who remained in the same treatment group, FLUENZ (N = 917) or placebo (N = 441), to which they had been randomized in a 2:1 ratio in the prior year. Efficacy of FLUENZ after revaccination in the 2nd year was 100% (95%CI 63.1–100) against antigenically matched strains and 87.1% (95%CI 77.7–92.6) against all strains (nearly all, 66 of 71, of the wild-type strains isolated were an antigenically drifted A/H3N2 strain mismatched to the vaccine strain).

Placebo controlled RCT, D153-P501

This was a randomized, double-blind, placebo-controlled, two year crossover study designed to determine safety and efficacy of the refrigerated formulation of FLUENZ (R-FLUENZ) in children aged 12 months to <36 months of age. Study centres: China, Hong Kong, India, Malaysia, the Philippines, Singapore and Thailand (study periods: September 2000–October 2002).

During the first year, 3174 subjects were randomized at a 3:2 ratio to receive 2 doses of either refrigerated vaccine or placebo, separated by 28–56 days. In the 2nd year, 2947 were randomized again at a 1:1 ratio to receive a single dose of vaccine or placebo, irrespective of their year 1 treatment. The crossover design resulted in 4 treatment groups (year 1/year 2 = FLUENZ/FLUENZ, FLUENZ/Placebo, Placebo/FLUENZ, and Placebo/Placebo).

In Year 1, of 3174 randomized subjects, a total of 2764 subjects were included in the per protocol population (87.0% R-FLUENZ, 87.2% placebo). The main reason for exclusion from the per protocol population was “No second vaccination in year 1” (4.7% Indian sites, 7.2% non-Indian sites). In Year 2, of 2947 subjects randomized, a total of 2731 (92.7%) were included in the per protocol population in year 1 and 2527 (85.7%) were included in year 2. The main reasons for exclusion from the per protocol population in year 2 were no vaccination in year 2 (8.6%) or a major protocol violation in year 1 (7.3%).

The overall efficacy against culture-confirmed influenza-illness of 2 vaccine doses administered in the first year was 70.1% (95%CI 60.9–77.3%) in per- protocol and 67.8% (95%CI 58.8–74.9%) in intent-to-treat analysis against any influenza strain. Efficacy against matched strains was 72.9% (95%CI 62.8–80.5), based on an efficacy of 80.9% (95%CI 69.4–88.5) and 90.0% (95%CI 71.4–97.5) versus A/H1 and A/H3 strains respectively. Against the B vaccine strain, efficacy was found to be 44.3% (95%CI 6.2–67.2).



The overall efficacy in year 2 of a primary series of two doses of FLUENZ in year 1 (FLUENZ/Placebo treatment group) against any strain was 64.2% (95%CI 44.2–77.3%) and against viral subtypes antigenically similar to those in the vaccine compared to Placebo/placebo was 56.2% (95%CI 30.5–72.7). Efficacy against the A/H3 strain was 61.3% (95%CI 34.9–77.4). Efficacy assessment was not possible against the A/H1 and B strains, 83.7% (95%CI -64.4–99.7) and 8.9% (95%CI -264.1–75.1) respectively, due to an inadequate number of isolates.

Efficacy in the second year of the study in the FLUENZ/FLUENZ vs. FLUENZ/ Placebo treatment (i.e. two doses in year 1 and one dose in year 2 vs. two doses in year 1) showed an overall estimate of efficacy against any influenza strain of 35% (95%CI -2.9–59.5%) and against any influenza subtype antigenically similar to those in the vaccine of 64.2% (95%CI 28.9–83.2). Although positive estimates of efficacy were reported for each strain, the number of cases reported for A/H1 and B were insufficient to draw any conclusion. The estimate of efficacy against antigenically similar A/H3 subtypes was 64.6% (95%CI 21.5–85.4).

In year 2 of the study, efficacy comparison in the FLUENZ/FLUENZ (i.e. two doses in year 1 and one dose in year 2) vs. Placebo/Placebo treatment groups provided an evaluation of efficacy in a fully vaccinated population compared to an unvaccinated population. The overall estimate of efficacy against any strain and against viral subtypes similar to those in the vaccine was 64.2% (95%CI 44.2–77.3%) and 84.3% (95%CI 70.1–92.4), respectively. While the individual efficacy estimates were positive for each of the influenza strains, there were insufficient cases to accurately assess efficacy against antigenically similar A/H1 and B subtypes, 100.0% (95%CI 2.9–100.0) and 61.6% (95%CI -97.6–94.0), respectively. The estimate of efficacy for antigenically similar A/H3 subtypes was 86.3% (95%CI 71.4–94.1).

Analysis of efficacy in the second year of the study in the FLUENZ/FLUENZ vs. Placebo/FLUENZ treatment groups (i.e. two doses in year 1 and one dose in year 2 vs. one dose in year 2) revealed an overall efficacy against any strain and against subtypes antigenically similar to those in the vaccine of 17.2% (95%CI -44.2–52.0%) and 60.9% (95%CI 15.9–82.6), respectively. Due to insufficient numbers of culture positive cases of antigenically similar A/H1 or B subtypes, an accurate assessment of efficacy could not be determined. The estimate of efficacy against antigenically similar A/H3 subtype was 67.4% (95%CI 23.5–87.1).

Due to the paucity of episodes, no conclusions of efficacy against AOM (acute otitis media) could be drawn.

Placebo controlled RCT, D153-P502

This was a randomized, double-blind, placebo controlled, multi-centre trial in children aged 6 months to <36 months in Europe (Belgium, Finland, Israel, Spain and the United Kingdom). Study period: October 2000- May 2002. A total of 1,784 subjects were randomized in a 3:2 ratio to receive 2 doses in the 1st year, 35 ± 7 days apart, and a single dose in the 2nd year of either FLUENZ vaccine or placebo. In year 2, subjects received the same treatment they had received in the first year. A total of 1616 (90.6%) subjects [951 (89.8%) FLUENZ subjects and 665 (91.7%) placebo subjects] were included in per protocol population in the first season. Over two thirds [1090 in total; 640 (97.3%) FLUENZ subjects and 450 (97.6%) placebo subjects] were part of the second season per-protocol analysis population. Outcome was culture-confirmed influenza like illness.

The overall efficacy in the first year against influenza virus subtypes antigenically matched to those in the vaccine was 85.4% (95%CI 74.3–92.2). Against individual subtypes the efficacies were as follows: 91.8% (95%CI 80.8–97.1) against A/H1N1 and 72.6% (95%CI 38.6–88.9) against B. A/H3N2 was only detected in one placebo subject. The vaccine also provided similar protection against all influenza strains regardless of match with an overall efficacy of 85.9% (95%CI 76.3–92.0). Efficacy restricted to Belgian cases (501 subjects) was significant estimated at 93.3% (95%CI 78.5–98.7%) for any strain, in season with good match.



In year 2 of the study, efficacy against strains matched to those in the vaccine was 88.7% (95%CI 82.0–93.2). Efficacy of FLUENZ in year 2 against each of the individual vaccine strains was found to be 90.0% (95%CI 56.3–98.9), 90.3% (95%CI 82.9–94.9) and 81.7% (95%CI 53.7–93.9) for the A/H1N1, A/H3N2 and B subtypes, respectively. Vaccine efficacy was found to be 85.8% (95%CI 78.6–90.9) against all strains (regardless of match). Vaccination with FLUENZ in both years provided efficacy against acute otitis media associated with a nasal culture positive for influenza virus.

Placebo controlled RCT, D153-P504

This was a randomized, double-blind, placebo-controlled, two year crossover designed to determine safety and efficacy of a refrigerated formulation of FLUENZ (R-FLUENZ) in children 6 months and < 36 months of age. The study was done in South Africa, Brazil and Argentina, over the periods April 2001–November 2001 and March 2002–November 2002. In the 1st year 3200 subjects were randomized to receive a primary series of either 1 or 2 doses of FLUENZ vaccine, or 2 doses of either excipient or saline placebo. The following year, 2202 subjects continued the study and received 1 dose of vaccine or saline placebo. Due to incorrect implementation of treatment allocations in the 2nd year, approximately half of the subjects randomized to FLUENZ received saline placebo, and approximately half of the subjects randomized to placebo received FLUENZ, making the overall year 2 per-protocol population 1364 subjects (61.9%). Outcome was culture-confirmed influenza like illness.

In season 1, of the 3200 subjects randomized, 2821 subjects were included in the per protocol efficacy population. In season 2, of the 2202 subjects participating, 1364 were included in the per protocol efficacy population.

Two doses of FLUENZ given during the first year demonstrated a 72.0 (95%CI 61.9–79.8%) and 73.5% (95%CI 63.6–81.0) efficacy against any strain and against any antigenically similar strain, respectively, while 1 dose of FLUENZ demonstrated a 56.3% (95%CI 43.1–66.7%) and 57.7% (95%CI 44.7–67.9) efficacy, respectively. Relative efficacy of 2 doses vs. 1 dose was 36.0 (95%CI 8.5–55.6%) and 37.3% (95%CI 9.5–56.9), respectively, but this could not be reproduced in the second year, i.e. 0.5% and 24.1% (95%CI -104.2–75.7), respectively. In year 2, for subjects receiving either 1 or 2 doses of FLUENZ in the first year, absolute efficacy against antigenically similar strains was 65.2% (95%CI 31.2–82.8) and 73.6% (95%CI 33.3–91.2) respectively, and efficacy against any strains was 46.4% (95%CI 21.2–63.5%) and 46.6% (95%CI 14.9–67.2%) respectively. Efficacy of 1 dose, in the 2nd year, of FLUENZ in subjects who received placebo in year 1 was 59.4% (95%CI 32.3–76.4%) and 60.3% (95%CI 10.9–83.8) against any strain and against any antigenically similar strain respectively, more or less equal to the estimate for 1 FLUENZ dose in year 1 (i.e. 56.3%, 95%CI 43.1–66.7%, and 57.7%, 95%CI 44.7–67.9) respectively for any strain and for any antigenically similar strain. Second season efficacy in subjects who received 2 doses of FLUENZ in year 1 and placebo in year 2 was 35.3% (95%CI -0.3–58.7%) and 57.0% (95%CI 6.1–81.7) respectively for any strain and for any antigenically similar strain.

Placebo controlled RCT, D153-P522

This was a, randomized, double-blind, placebo controlled, multi-centre trial in children aged 11 months to 24 months. The study was conducted in Asia (Singapore, Hong Kong, Malaysia, Thailand, Korea, Philippines, Bangladesh), Europe (Finland, Poland, Lithuania, Belgium, Germany) and Mexico (32 sites) over the period October 2002 - May 2003.



The two dose regime of FLUENZ was efficacious (78.4%, 95%CI 50.9–91.3) against influenza illness caused by strains antigenically matched to those contained in the vaccine. Efficacy for individual vaccine strains was greatest against the B strain, 81.7% (95%CI 38.2–95.8). The point estimate of efficacy against the A/H3 strain was 68.5%, but the CI included zero (95%CI -9.0–91.9). Although the point estimate for efficacy against the A/H1 strain viruses was 100.0% (95%CI -168.0–100.0), there were too few cases to make an accurate assessment of efficacy against this strain (only 2 cases, both in the placebo group). Efficacy against all strains regardless of match was 63.8% (95%CI 36.2–79.8).

Discussion based on the EPAR

At the current state of technology, influenza research is extremely difficult. Even in a best-case scenario using gold standard trial methodology (randomised, double-blind controlled trials) two external factors are very important for the potential success of the tested vaccine:

- The immunogenic match of the strain chosen by the WHO experts
- The magnitude of the epidemic: in some seasons the caseload is small, such that the number of influenza cases in either arm of the trial is too small to draw conclusions from the trial

The data summarized in section 3.1.2 of the report (Influenza vaccine efficacy in children) are illustrative for this. When the vaccine and circulating strains match well and the caseload is large, the tested vaccine can be shown to be efficacious. The clinical efficacy of a two dose primary series has been repeatedly shown better than placebo:

- against matched strains ranging from 62% to 85%,
- against all strains regardless of antigenic match ranging from 49% to 93%,
- against specific matched subtypes of influenza virus varied by studies.

Compared to TIV, the LAIV seems to be more efficacious in children, based on the large double blind trial MI-CP111: administration of the FLUENZ vaccine resulted in a 44.5% (95%CI 22.4–60.6) higher reduction in influenza illness compared to TIV caused by virus strains antigenically matched to those used in the vaccine blend. The incidence of illness due to all possible strains showed a 55% larger reduction (95%CI 45.4–62.9).

Along these lines, some published studies⁶⁻⁹ also suggested higher efficacy for TIV compared to LAIV. These elements are consistent with the a priori biological concern that pre-existing immunisation could alter the efficacy of a LAIV vaccine. Indeed, in contrast to trivalent inactivated vaccine, LAIV vaccines induce an immune response through viral replication. Therefore, pre-existing immunity may negatively affect the response to LAIV through the activity of existing neutralising antibodies on the vaccine's virus replication itself.

In light of this concern and even though in children LAIV could offer better protection against flu as compared to TIV, the fact that in children the sustainability of the vaccine efficacy could only be judged over two seasonal periods in studies versus placebo (AV006, D153-P501, D153-P502, D153-P504), was further discussed in the EPAR.

More specifically, no evidence was available on frequency and years of exposure needed in order to establish baseline immunity which, even if unspecific to surface antigens, will scavenge live attenuated influenza vaccine viruses before a specific immune response to seasonal HA and NA could effectively be mounted. The data available did not indicate that this question might be as relevant for a paediatric and adolescent population as it might become for an adult and elderly population.

In the paediatric population, FLUENZ consistently performed better than placebo and than TIV and the degree of variability observed between studies and geographical area was considered as acceptable and related to the variability of influenza viral circulation (intensity, strength, strains). The efficacy of FLUENZ in children is thus considered established.

1.1.2. Published data on LAIV & TIV in children

Table 3 and Table 4 list the primary research and review articles, respectively, which our updated search identified for further scrutiny, along with the reasons for their exclusion (if applicable) from our discussion. The tables show that only one original research article of interest related to childhood vaccination was identified, along with a number of review articles.

In the following sections we discuss first some of the recent review articles on influenza vaccine efficacy, and end with a discussion of the new original research article.

**Table 3 – Original research articles on influenza vaccine trials in children identified through search update and selected for full text screening**

First author	Title	Year	Interpretation / reason for exclusion of further consideration, if applicable
Ambrose¹⁰	An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2-17 years	2011	Integrated analysis of the published data of LAIV trials, no meta analysis, no new data
Cowling¹¹	The effectiveness of seasonal influenza vaccine in preventing pandemic and seasonal influenza infection: a randomized controlled trial	2011	Not relevant: data relate only to pandemic influenza
Esposito¹²	Pandemic influenza A/H1N1 vaccine administered sequentially or simultaneously with seasonal influenza vaccine to HIV-infected children and adolescents	2011	Not relevant: data relate only to pandemic influenza
Halasa¹³	Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer	2011	Experimental, only immunogenicity
Kang¹⁴	Safety and Immunogenicity of a New Trivalent Inactivated Split-virus Influenza Vaccine in Healthy Korean Children: A Randomized, Double-blinded, Active-controlled, Phase III Study	2011	Only immunogenicity, no clinical efficacy
Skowronski¹⁵	Influenza B/Victoria Antigen Induces Strong Recall of B/Yamagata But Lower B/Victoria Response in Children Primed With Two Doses of B/Yamagata	2011	Only immunogenicity, no clinical efficacy
Vesikari¹⁶	Oil-in-water emulsion adjuvant with influenza vaccine in young children	2012	Of potential interest, see discussion in text



Table 4 – Review articles identified through search update and selected for full text screening

First author	Title	Year	Focus	Interpretation / reason for exclusion of further consideration, if applicable
Brenner¹⁷	Efficacy and safety of influenza vaccines	2011	A/P	No new data, narrative review
Carter¹⁸	Live Attenuated Influenza Vaccine (FluMist (R); Fluenz (TM)) A Review of its Use in the Prevention of Seasonal Influenza in Children and Adults	2011	A/P	Data from EPAR are repeated and presented in a more positive light. Although the Monto et al trial is cited with very low efficacy for LAIV. No fundamental criticism is given on the results. The authors conclude that this vaccine is very effective for adults.
Cheuk¹⁹	Vaccines for prophylaxis of viral infections in patients with hematological malignancies	2011	A/P	High risk of bias for most of the included RCTs Most of the trials also focused on laboratory outcomes of immunological response to vaccines All included RCTs recruited small numbers of participants
Esposito²⁰	Different influenza vaccine formulations and adjuvants for childhood influenza vaccination	2011	P	No new data or interpretations
Heikkinen²¹	Effectiveness and safety of influenza vaccination in children: European perspective	2011	P	Selected, see in text
Ioannidis²²	Publication Delay of Randomized Trials on 2009 Influenza A (H1N1) Vaccination	2011	A/P	No data on influenza vaccination
Manzoli²³	Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines	2011	A/P	This article gives data on the pandemic H1N1 vaccination, and not in later seasonal setting
Michiels²⁴	A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups	2011	A/P	Selected, see in text
Osterholm²⁵	Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis	2012	A/P	Selected, see in text
Puig-Barbera²⁶	MF59 (TM)-adjuvanted seasonal influenza vaccine in young children	2011	P	No new data, narrative review
Tsai²⁷	MF59 (R) Adjuvanted Seasonal and Pandemic Influenza Vaccines	2011	P	Repetition of the data of Vesikari ¹⁶

A: Adults focus; P: Pediatrics focus.

**Heikkinen & Heinonen, 2011²¹**

Heikkinen & Heinonen²¹ performed a non-systematic review that focused on influenza effectiveness studies in children ≤ 5 years of age during seasonal influenza outbreaks, involving both LAIV and TIV. Diagnoses were confirmed by virology (tests not specified), and only data from fully vaccinated children were taken into account.

The authors identified ten original reports of the effectiveness of TIV that fulfilled the predefined selection criteria, but only one study²⁸ was a randomised, placebo-controlled trial. It ran over two consecutive respiratory seasons among children 6–24 months of age. During the first season the attack rate in the placebo group was 16% and thus the influenza activity was regarded as normal. A significant efficacy of 66% was reported, shown with point estimates for efficacy in children aged 6–12 months, 13–18 months, and 19–24 months at 63%, 66%, and 69%, respectively. These estimates can be considered high for TIV in children. A decrease of the incidence of influenza-associated acute otitis media by 62% in the vaccinated group was noted. In the second season, however an exceptionally low influenza activity in the area (attack rate in the placebo group, 3%) was noted and no vaccine efficacy against influenza could be observed. The other studies are not considered because they are not randomised controlled double blind clinical trials.

Six randomized clinical trials, including a total of approximately 14 000 children aged 6–71 months, have been reported and evaluate LAIV versus placebo. All these data have been discussed in this report in section 3.1 based on EPAR. The publications reporting most of these data were also reviewed by Rhorer et al.²⁹ Rhorer performed meta-analyses of the six placebo-controlled RCTs described under the EPAR studies, involving around 14,000 healthy children. Meta-analyses were performed using a fixed effect model, regardless of heterogeneity across studies. Pooled VE for two LAIV doses was estimated at 72% ($p < 0.001$, 95%CI not provided) against any strain of culture-confirmed influenza and at 77% (95%CI 72–80%) for subtypes antigenically similar to vaccine strains, but heterogeneity across studies ($p < 0.001$ for Cochran Q test) was found. When data were restricted to children < 3 years of age, pooled VE was estimated at 69% for any strains (95%CI not provided) and 74% (95%CI 69–78%) for vaccine similar strains, with some indication of heterogeneity ($p = 0.078$). A meta-analysis of subsets of data on one dose of LAIV in previously unvaccinated children (not all by protocol) from three studies yielded an estimated pooled efficacy of 59% ($p < 0.001$) for any strains and 60% (95%CI 51–68%) for vaccine similar strains (heterogeneity test not provided). These meta-analyses confirm that LAIV is highly efficacious against culture-confirmed influenza in children, and did not show differences in efficacy by age or circulating subtype.

From virologically confirmed studies performed during different seasons, Heikkinen & Heinonen²¹ conclude that the effectiveness of TIV varies from year to year, largely depending on the match between the vaccine and the circulating strains of influenza viruses and suggest that this match is one of the key drivers of the effectiveness of the vaccine. In addition they conclude that in seasons with a good antigenic match, TIVs are effective in children younger than 2 years of age, but that LAIV provides greater effectiveness in children (albeit not indicated in children below 2 years of age). However, they consider recent data to indicate - contrary to popular belief - that in seasons with good antigenic match, TIV is efficacious against virologically confirmed influenza even in the youngest children. The poor predictability of the antigenic evolution of influenza viruses provides a huge challenge for the annual selection of vaccine strains, and it is obvious that influenza vaccines that could provide broader than just strain-specific immunity are needed.



These conclusions on both vaccines can be criticised as being too positive: the data suggest that substantial improvements remain possible through adjuvantation of the vaccines, whereas these conclusions did not account for this further potential improvement.

The first author declared a conflict of interest for Novartis, AstraZeneca/MedImmune, GlaxoSmithKline, and Abbott/Solvay.

Osterholm, et al, 2012²⁵

Osterholm et al²⁵ searched between Jan 1, 1967, and Feb 15, 2011 in Medline for randomised controlled trials assessing a relative reduction in influenza risk of all circulating influenza viruses during individual seasons after vaccination (efficacy) and observational studies meeting inclusion criteria (effectiveness). A further inclusion criterion was reporting on laboratory-confirmed influenza, which was defined as RT-PCR confirmed or culture-confirmed influenza. Studies that used serology endpoints to diagnose influenza were excluded, because of biased case detection in vaccinated individuals. Efficacy and effectiveness were regarded as statistically significant if the 95%CI for efficacy or effectiveness did not include 0.

When data were available for statistical analysis (e.g., at least three studies that assessed comparable age groups), the pooled random-effects were reported for both LAIV and TIV.

5707 articles were screened and 31 eligible studies (17 randomised controlled trials and 14 observational studies) were identified.

Overall, only one trial assessing TIV effectiveness in children was eligible.²⁸ In this trial, healthy of children 6-24 months of age were randomly allocated to receive either TIV or placebo, over two seasons with good matches between circulating and vaccine strains. Swabbing also involved patients with AOM. In the first year, vaccine efficacy was 66% and in the second year it was -7%. Key elements of this study are given in Table 5. No trial on TIV met inclusion criteria for children aged 2–17 years.

In children aged 6 months to 7 years, there were six LAIV trials covering eight influenza seasons. In all eight seasons, the vaccine provided sufficient protection against infection, with a random-effect pooled vaccine efficacy of 83% (95%CI 69–91%). No such trials in children aged 8–17 years met the inclusion criteria.

These data were also discussed in the section based on the EPAR above.

Osterholm et al²⁵ conclude that based on a track record of substantial safety and moderate efficacy in many seasons, the current influenza vaccines (TIV and LAIV) will continue to have a role in reducing influenza morbidity until more effective interventions are available. Given the current public health burden caused by seasonal influenza, an urgent need for a new generation of more effective and cross-protective vaccines remains.

Michiels et al, 2012²⁴

Michiels et al²⁴ aimed to assess the evidence of efficacy (against laboratory-proven influenza only), effectiveness (as defined in some Cochrane reviews as efficacy against clinically defined influenza-like illness) and potential risks of the use of TIV vaccines in several target groups: adults (16–65 years), healthy children (younger than 16 years), elderly (65 years or older), pregnant women, healthcare workers and individuals of all ages with chronic medical conditions. A search covering the period Jan 2006-March 2011 was done in the Cochrane Central Register of Controlled Trials and Pubmed using the string 'influenza AND vaccine'. Only studies on seasonal influenza were considered. Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) with clinical endpoints (efficacy and/or effectiveness versus placebo or no intervention) that were not yet included in a previous Cochrane review, were withheld for review. Cohort studies, case-control studies and observational studies not included in Cochrane reviews were not discussed.

For children, a published Cochrane review³⁰ was consulted, in which the quality of the original studies was generally considered moderate. In children older than 6 years the vaccine was found to be 69% efficacious against proven influenza, but for younger age groups results were non-significant.

**Table 5 – RCTs in healthy children included in the Cochrane systematic review of Jefferson et al³⁰ (adapted from Michiels et al²⁴)**

Age (years)	Outcome	Nr of studies	Nr of participants	Incidence of outcome	Efficacy-effectiveness % (95%CI)	Grade
<2	influenza	1	786	10%	NS	B
<6	influenza	2	132	37.2%	NS	B
≥6	influenza	3	710	35.4%	69 (55–78)	B
<2	ILI	0	NA	NA	NA	NA
<6	ILI	3	476	31.4%	61 (31–79)	B
≥6	ILI	4	18 912	29.7%	28 (22–34)	A

ILI: Influenza Like Illness; Influenza: proven (lab confirmed) influenza; NS: Non-significant; NA: Not applicable; A: reliable evidence; B: moderate evidence.

According to Michiels, no efficacy of TIV was seen in the single RCT performed in children under two years of age during two consecutive years when the vaccine was a good match of the circulating influenza strains. This study is described in section 3.1.2.3 (TIV studies in children) from Osterholm, who has another conclusion than Michiels. This is likely because the findings from the two seasons were pooled in the Cochrane review (taken by Michiels) and the pooled efficacy estimate over the two seasons was not significant; however, a significant efficacy was shown in the first season while no efficacy was shown in the second season showing a low influenza intensity. For children younger than 2 years, Michiels found no evidence for or against TIV efficacy against ILI. Even the cohort studies included in this systematic review, which have slightly higher point estimates of efficacy and effectiveness, were unable to show a significant effect of TIV in children younger than two years. With respect to school absenteeism, otitis media and pneumonia, no benefit of TIV was demonstrated.

Updating from the Cochrane database reviews, Michiels et al²⁴ discussed three other publications on TIV efficacy in children.³¹⁻³³ These additional studies do not substantially alter the above results for children. The Jansen trial³³ was set up to measure the effects of TIV vaccination with or without heptavalent pneumococcal conjugate vaccination on respiratory tract infections (RTIs) in children aged 18 to 72 months with a previous history of physician-diagnosed RTI over three influenza seasons (2003-06). As this is a randomised, double blind, placebo controlled trial, vaccine efficacy could also be measured as a secondary parameter. However, the confidence intervals were relatively wide because only 117 of the 330 febrile RTI episodes were tested for influenza virus by PCR. Compared to placebo, the occurrence of PCR-confirmed influenza was reduced by 52% (95%CI 7–75%) in the TIV/PCV7 group and by 51% (95%CI 3–75%) in the TIV/placebo group.

The other two additional publications identified by Michiels et al²⁴ are not discussed here because Marchisio et al³² did not use laboratory confirmed outcome, and Ochiai et al³¹ study was not randomised nor blinded.

**Vesikari et al¹⁶**

Vesikari et al¹⁶ described an interesting RCT sponsored by Novartis in 4707 healthy children 6-71 months of age who had not previously been vaccinated against influenza with a MF 59 adjuvanted TIV (ATIV) vaccine. The children were randomly assigned to three study groups, each of which received the assigned vaccines in two doses, 28 days apart, during two consecutive influenza seasons. Two of the groups were given age-appropriate doses of TIV either with or without the MF59 adjuvant, and the third group was given control (non-influenza) vaccines to assess their absolute and relative efficacy against influenza-like illness, as confirmed by means of polymerase-chain-reaction (PCR) assay. The authors concluded that influenza vaccine with the MF59 adjuvant is efficacious against PCR-confirmed influenza in infants and young children with efficacy rates for ATIV 79% (95%CI 55–90%) at 6-35 months of age and 92% (95%CI 77–97%) at 36-71 months of age, as compared with 40% (95%CI -6–66%) and 45% (95%CI 6–68%), respectively, for TIV.

However the European Medicine Agency (EMA) has critically reviewed this study prior to its publication and published the following assessment about this study: “Based on the review of the data and the company’s response

to the CHMP list of questions, at the time of the withdrawal, the CHMP had several major concerns. The CHMP was particularly concerned by shortcomings in good clinical practice (GCP) that came to light following an inspection of the sites of the main study. The shortcomings included incorrect data in the dossier submitted to the Agency, which greatly impacted the reliability of the study results. There were also concerns about deficiencies in the laboratory tests used to confirm whether patients had influenza or not. Other main concerns were related to inadequate data from the company, including the data provided on children aged between six to nine years, children with health conditions and on revaccination. Therefore, at the time of the withdrawal, the CHMP’s conclusion was that the vaccine could not have been approved since the company had not addressed the Committee’s main concerns.”

Since EMA, the main regulatory European body on medicine use performed a GCP inspection and identified several critical shortcomings in this RCT, it decided not to take these data into account. It seems the robustness of the data cannot be guaranteed (despite publication of this study in a major medical journal).

1.2. Influenza vaccine efficacy in healthy adults

Table 6 – Original primary studies identified through search update and selected for full text screening

Author	Title	Year	Focus	Interpretation / reason for exclusion, if applicable
Barrett ³⁴	Efficacy, safety, and immunogenicity of a Vero-cell culture-derived trivalent influenza vaccine: a multicentre, double-blind, randomised, placebo-controlled trial	2011	A	Included
Berthoud ³⁵	Potent CD8(+) T-Cell Immunogenicity in Humans of a Novel Heterosubtypic Influenza A Vaccine, MVA-NP+M1	2011	A	Immunogenicity, no clinical efficacy data
Block ³⁶	A randomized, double-blind non-inferiority study of quadrivalent live attenuated influenza vaccine in adults	2011	A	Immunogenicity, no clinical efficacy data
Chadha ³⁷	Effect of 25-Hydroxyvitamin D Status on Serological Response to Influenza Vaccine in Prostate Cancer Patients	2011	A	Not relevant



Chan³⁸	Efficacy of dual vaccination of pandemic H1N1 2009 influenza and seasonal influenza on institutionalized elderly: A one-year prospective cohort study	2011	A	Interesting RCT showing a reduction of mortality when H1N1 vaccine was combined with seasonal versus seasonal or no vaccine. Not relevant for the research focus of the current report
Chen³⁹	Antibody and Th1-type cell-mediated immune responses in elderly and young adults immunized with the standard or a high dose influenza vaccine	2011	A	Immunogenicity, no clinical efficacy data
Coleman⁴⁰	Respiratory illnesses in Canadian health care workers: a pilot study of influenza vaccine and oseltamivir prophylaxis during the 2007/2008 influenza season	2011	A	Not relevant: comparison of oseltamivir versus fluviral in 4:1 setting
Cooper⁴¹	Vitamin D supplementation does not increase immunogenicity of seasonal influenza vaccine in HIV-infected adults	2011	A	Immunogenicity, no clinical efficacy data
Cooper⁴²	Influenza vaccine oculorespiratory syndrome incidence is reduced in HIV	2011	A	Not relevant
Cooper⁴³	Immunogenicity is not improved by increased antigen dose or booster dosing of seasonal influenza vaccine in a randomized trial of HIV infected adults	2011	A	Immunogenicity, no clinical efficacy data
den Elzen⁴⁴	Cytomegalovirus infection and responsiveness to influenza vaccination in elderly residents of long-term care facilities	2011	A	Not relevant
Desheva⁴⁵	Detection of anti-neuraminidase antibody in preclinical and clinical studies of live influenza vaccine	2011	A	Not relevant
Sacadura-Leite⁴⁶	Antibody response to the influenza vaccine in healthcare workers	2011	A	Immunogenicity, no clinical efficacy data
Steinhoff⁴⁷	Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial	2011	A/P	Immunogenicity, no clinical efficacy data.
Wu⁴⁸	Optimal vaccination strategies for 2009 pandemic H1N1 and seasonal influenza vaccines in humans	2011	A	Not relevant: about sequence of pandemic and seasonal vaccine

**Table 7 – Randomised controlled trials of TIV in adults meeting the inclusion criteria by Osterholm et al**

First Author (year)	Participants (trial period)	Trial size*	Vaccine efficacy (95%CI)	Reported antigenic match	
Ohmit (2006) ⁷	Healthy (18–46y) (2004–05)	728	75% (42–90)	Type A: drifted H3N2	Type B: mixed lineage
Ohmit (2008) ⁴⁹	Healthy (18–48y) (2005–06)	1205	16% (-171–70)	Type A: drifted H3N2	Type B: lineage mismatch^
Beran (2009) ⁵⁰	Healthy (18–64y) (2005–06)	6203	22% (-49–59)	Type A: similar H3N2 and H1N1	Type B: lineage mismatch
Beran (2009) ⁵¹	Healthy (18–64y) (2006–07)	7652	62% (46–73)	Type A: similar H3N2	Type B: lineage mismatch
Monto (2009) ⁸	Healthy (18–49y) (2007–08)	1139	68% (46–81)	Type A: drifted H3N2	Type B: lineage mismatch
Jackson (2010) ⁵²	Healthy (18–49y) (2005–06)	3514	50% (14–71)	Type A: similar H3N2	Type B: lineage mismatch
Jackson (2010) ⁵²	Healthy (18–49y) (2006–07)	4144	50% (-3–75)	Type A: similar H3N2	Type B: mixed lineage
Frey (2010) ⁵³	Healthy (18–49y) (2007–08)	7576	63%**	Type A: mixed strains	Type B: lineage mismatch
Madhi (2011) ⁵⁴	HIV+ (18–55y) (2008–09)	506	76% (9–96)	Type A: drifted H1N1	Type B: not reported

* Number of participants randomly allocated to receive TIV or placebo.

** One-sided 97.5% lower limit of 47%.

^ One isolate.



2. SELECTION OF QUALITY OF LIFE STUDIES FOR REVIEW

2.1. Search strategy for quality of life studies

Table 8 – Search strategy and results for HTA database (CRD)

Date	2/8/2011		
Database	HTA (CRD)		
Date covered	No restriction		
Search strategy	#	Searches	Results
	1	" Influenza, Human " / in HTA	48
	2	" Influenza Vaccines " / in HTA	16
	3	1 or 2	52
	4	"Costs and Cost Analysis" / in HTA	11330
	5	3 and 4	9
Note	Re-run for the search period 2011 to 29/10/2012. Search results: 1 refs. #3 AND ("Quality-Adjusted Life Years" / OR "Health Status Indicators" /) returned 0 hits.		

Table 9 – Search strategy and results for NHS EED (CRD)

Date	2/8/2011		
Database	NHS EED (CRD)		
Date covered	No restriction		
Search strategy	#	Searches	Results
	1	" Influenza, Human " / in NHS EED	102
	2	" Influenza Vaccines " / in NHS EED	85
	3	1 or 2	125
	4	MeSH DESCRIPTOR Quality-Adjusted Life Years EXPLODE ALL TREES	1862
	5	3 and 4	29
Note	Re-run for the search period 2011 to 29/10/2012. Search results: 8 refs.		

Table 10 – Search strategy and results for Medline (OVID)

Date	2/8/2011		
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)		
Date covered	1950 to Present		
Search strategy	#	Searches	Results
	1	Influenza, Human /	27574
	2	Influenza Vaccines /	12767
	3	1 or 2	33104
	4	"Quality of Life" /	92696
	5	"Value of Life" /	5170
	6	"Quality-Adjusted Life Years" /	5114
	7	qol\$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	12949
	8	qaly\$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	3352
	9	"Health Status Indicators" /	16792
	10	4 or 5 or 6 or 7 or 8 or 9	116378
	11	3 and 10	112
	12	Cost-Benefit Analysis /	51568
	13	quality adjusted life year\$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	6729
	14	6 or 8 or 13	7099
	15	3 and 12 and 14	58
	16	11 or 15	119
Note	Re-run for the search period 2011 to 29/10/2012. Search results: 29 refs.		

**Table 11 – Search strategy and results for Embase (OVID)**

Date	4/08/2011		
Database	Embase (OVID)		
Date covered	No restrictions		
Search strategy	#	Searches	Results
	1	'influenza virus'/exp	37605
	2	'influenza vaccine'/exp	20477
	3	#1 OR #2	51369
	4	'quality of life'/exp	181420
	5	'quality adjusted life year'/exp	7539
	6	qaly*	4731
	7	#4 OR #5 OR #6	182202
	8	#3 AND #7	317
	9	'cost utility analysis'/exp	3545
	10	#3 AND #9	25
	11	#8 OR #10	325
Note	Re-run for the search period 2011 to 29/10/2012. Search results: 98 refs.		

Table 12 – Search strategy and results for PsycINFO (OVID)

Date	4/08/2011		
Database	PsycINFO		
Date covered	No restriction		
Search strategy	#	Searches	Results
	1	"influenza"/	594
	2	"quality of life"/	19737
	3	qaly.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	335
	4	qol.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	4157
	5	quality adjusted life year\$.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	483
	6	2 or 3 or 4 or 5	20438
	7	1 and 6	2

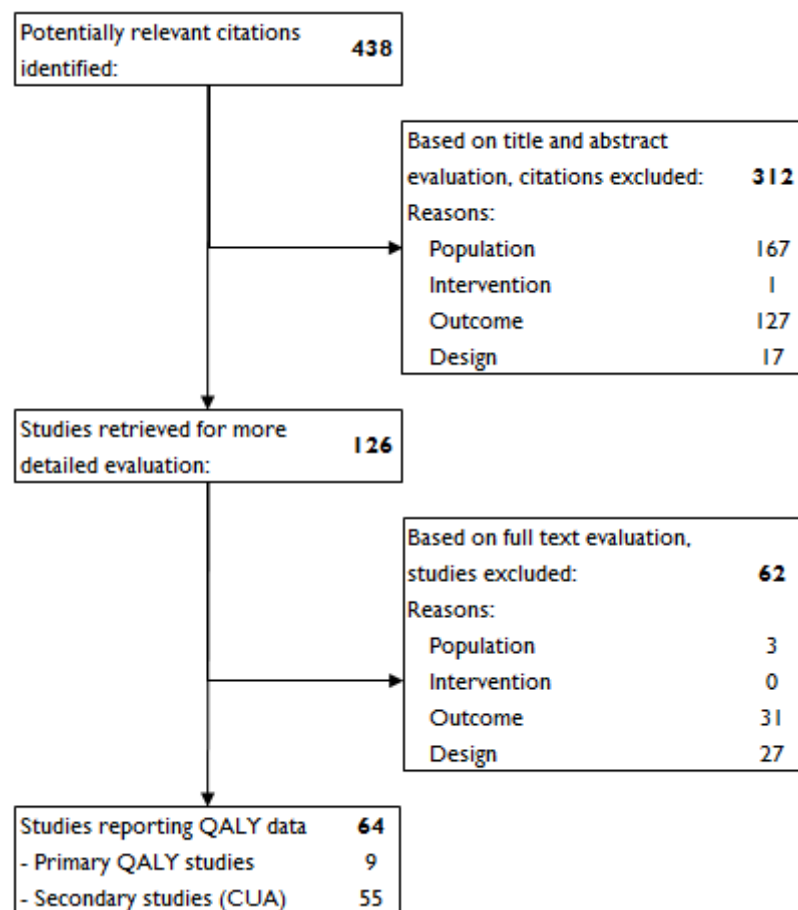
Note	Re-run for the search period 2011 to 29/10/2012. Search results: 0 refs.
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2.2. Categorisation and selection of quality of life studies

Table 13 – Search results for quality of life studies

Databases	Time window for references identification		
	Up to 08/2011	08/2011 up to current (11/2012)	Total
HTA (CRD)	9	1	10
NHS EED (CRD)	29	8	37
Medline (OVID)	119	29	148
Embase (OVID)	325	98	423
PsycINFO (OVID)	2	0	2
Total references identified	484	136	620

The searches on the databases returned 620 citations. After exclusion of 182 duplicates, **438 unique citations** were left. Three-hundred and twelve (312) references were discarded based on title and abstract, leaving 126 references for full-text evaluation. Another 62 references were excluded at this stage, mostly because of the unmet design and outcome criteria. Of the 64 remaining references reporting QoL weights on the burden of ILI/influenza, 55 were cost-utility analyses (CUA) in which QoL values were not directly estimated but selected from the literature (secondary studies). There were 9 primary studies reporting original QoL weights on the burden of influenza/ILI.⁵⁵⁻⁶³ Two articles reported the results of the same QoL weights primary study and were thus analysed together.^{55, 63}

**Figure 1 – Flowchart of the literature selection process**



3. COST DATA

3.1. List of comorbidities combined with a diagnosis of influenza

Table 14 – Comorbidities, their ICD9 codes and description

Comorbidity	ICD9	Description
Asthma	493	Asthma
	V17.5	Family history of certain chronic disabling diseases: Asthma
Cardiovascular Disease	989.1	Strychnine and salts
	402.01	Hypertensive heart disease; Malignant; With heart failure
	402.11	Hypertensive heart disease; Benign; With heart failure
	402.91	Hypertensive heart disease; Unspecified; With heart failure
	404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
	404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
	404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
	428	Heart failure
	413	Angina pectoris
	412	Old myocardial infarction
	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	414	Other forms of chronic ischemic heart disease
	420	Acute pericarditis



	422	Acute myocarditis
Chronic obstructive pulmonary disorder	490	Bronchitis, not specified as acute or chronic
	491	Chronic bronchitis
	492	Emphysema
	496	Chronic airway obstruction, not elsewhere classified
Diabetes	250	Diabetes mellitus
	249	Secondary diabetes mellitus
	V18.0	Family history of certain other specific conditions: Diabetes mellitus
	V77.1	V77 Special screening for endocrine, nutritional, metabolic, and immunity disorders; V77.1 Diabetes mellitus
	253.5	Diabetes insipidus
	588.1	Nephrogenic diabetes insipidus
Hypertension - (402 and 404 chapters in Cardiovascular	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
	997.91	Complications affecting other specified body systems, not elsewhere classified; 997.91 Hypertension
	459.3	Chronic venous hypertension (idiopathic)
Pneumococcal pneumonia	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
Pneumonia	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
	480	Viral pneumonia
	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
	482	Other bacterial pneumonia
	483	Pneumonia due to other specified organism
	484	Pneumonia in infectious diseases classified elsewhere
	485	Bronchopneumonia, organism unspecified
	486	Pneumonia, organism unspecified
Secondary respiratory infection	480	Viral pneumonia
	482	Other bacterial pneumonia
	483	Pneumonia due to other specified organism



	484	Pneumonia in infectious diseases classified elsewhere
	485	Bronchopneumonia, organism unspecified
	486	Pneumonia, organism unspecified
	460	Acute nasopharyngitis [common cold]
	462	Acute pharyngitis
	466	Acute bronchitis and bronchiolitis
	390	Rheumatic fever without mention of heart involvement
	391	Rheumatic fever with heart involvement
	392	Rheumatic chorea
	041	Bacterial infection in conditions classified elsewhere and of unspecified site
	465.9	Acute upper respiratory infections of unspecified sites
	034.0	Streptococcal sore throat
	038.0	Streptococcal septicemia
	320.2	Streptococcal meningitis
	482.31	Pneumonia due to Streptococcus group A
Stroke	430	Subarachnoid hemorrhage
	431	Intracerebral hemorrhage
	432	Other and unspecified intracranial hemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease
	342	Hemiplegia and hemiparesis
HIV	042	Human immunodeficiency virus [HIV] disease



3.2. List of pregnancy complications

ICD9CM	Date_start	Date_end	Label_NI
633	19850101	29991231	Ectopische zwangerschap
6330	19850101	20041231	Abdominale zwangerschap
63300	20050101	29991231	Abdominale zwangerschap,zonder intrauteriene zwangerschap
63301	20050101	29991231	Abdominale zwangerschap, met intrauterien zwangerschap
6331	19850101	20041231	Tubaire zwangerschap
63310	20050101	29991231	Tubaire zwangerschap, zonder intrauteriene zwangerschap
63311	20050101	29991231	Tubaire zwangerschap, met intrauteriene zwangerschap
6332	19850101	20041231	Ovarium zwangerschap
63320	20050101	29991231	Ovariele zwangerschap, zonder intrauteriene zwangerschap
63321	20050101	29991231	Ovariele zwangerschap, met intrauteriene zwangerschap
6338	19850101	20041231	Overige ectopische zwangerschappen
63380	20050101	29991231	Andere ectopische zwangerschappen, zonder intrauteriene zwangerschap
63381	20050101	29991231	Andere ectopische zwangerschappen, met intrauteriene zwangerschap
6339	19850101	20041231	Niet gespecificeerde ectopische zwangerschap
63390	20050101	29991231	Niet gespecificeerde ectopische zwangerschap, zonder intrauteriene zwangerschap
63391	20050101	29991231	Niet gespecificeerde ectopische zwangerschap, met intrauteriene zwangerschap
639	19850101	29991231	Complicaties na abortus en ectopische of mola zwangerschap
6398	19850101	29991231	Overige gespecificeerde complicaties na abortus of ectopische en mola zwangerschap
6399	19850101	29991231	Niet gespecificeerde complicatie na abortus of ectopische en mola zwangerschap
640	19850101	29991231	Bloeding vroeg in de zwangerschap
6400	19850101	29991231	Bloeding vroeg in de zwangerschap dreigende abortus
64000	19850101	29991231	Dreigende abortus, niet gespecificeerde behandelingsperiode
64003	19850101	29991231	Dreigende abortus, ante partum
6408	19850101	29991231	Overige gespecificeerde bloeding vroeg in de zwangerschap
64080	19850101	29991231	Overige gespecificeerde bloeding vroeg in de zwangerschap, niet gespecificeerde behandelingsperiode
64083	19850101	29991231	Overige gespecificeerde bloeding vroeg in de zwangerschap, complicatieante partum
6409	19850101	29991231	Niet gespecificeerde bloeding vroeg in de zwangerschap
64090	19850101	29991231	Niet gespecificeerde bloeding vroeg in de zwangerschap, niet gespecificeerde behandelingsperiode



64093	19850101	29991231	Niet gespecificeerde bloeding vroeg in de zwangerschap, complicatie ante partum
6410	19850101	29991231	Placenta praevia zonder bloeding
64100	19850101	29991231	Placenta praevia zonder bloeding, niet gespecificeerde behandelingsperiode
64103	19850101	29991231	Placenta praevia zonder bloeding, complicatie ante partum
6411	19850101	29991231	Bloeding door placenta praevia
64110	19850101	29991231	Bloeding door placenta praevia, niet gespecificeerde behandelingsperiode
64113	19850101	29991231	Bloeding door placenta praevia, ante partum
6412	19850101	29991231	Premature loslating van de placenta
64120	19850101	29991231	Premature loslating van de placenta, niet gespecificeerde behandelingsperiode
64123	19850101	29991231	Premature loslating van de placenta, ante partum
6413	19850101	29991231	Bloeding ante partum verband houdend met stollingsstoornissen
64130	19850101	29991231	Bloeding ante partum verband houdend met stollingsstoornissen, nietgespecificeerde behandelingperiode
64133	19850101	29991231	Bloeding ante partum verband houdend met stollingsstoornissen
6418	19850101	29991231	Overige gespecificeerde bloedingen ante partum
64180	19850101	29991231	Overige gespecificeerde bloedingen ante partum, niet gespecificeerde behandelingsperiode
64183	19850101	29991231	Overige gespecificeerde bloedingen ante partum
6419	19850101	29991231	Niet gespecificeerde bloeding ante partum
64190	19850101	29991231	Niet gespecificeerde bloeding ante partum, niet gespecificeerde behandelingsperiode
64193	19850101	29991231	Niet gespecificeerde bloeding ante partum
64203	19850101	29991231	Benigne essentiële hypertensie, complicatie ante partum
64213	19850101	29991231	Hypertensie, secundair aan nierziekte, complicatie ante partum
64223	19850101	29991231	Overige vormen van reeds bestaande hypertensie, complicatie ante partum
6423	19850101	29991231	Voorbijgaande hypertensie van de zwangerschap
64230	19850101	29991231	Voorbijgaande hypertensie van de zwangerschap, niet gespecificeerde behandelingsperiode
64233	19850101	29991231	Voorbijgaande hypertensie van de zwangerschap, complicatie ante partum
6424	19850101	29991231	Lichte of niet gespecificeerde preeclampsie
64240	19850101	29991231	Lichte of niet gespecificeerde preeclampsie, niet gespecificeerde behandelingsperiode
64243	19850101	29991231	Lichte of niet gespecificeerde preeclampsie, complicatie ante partum
6425	19850101	29991231	Ernstige preeclampsie
64250	19850101	29991231	Ernstige preeclampsie, niet gespecificeerde behandelingsperiode



64253	19850101	29991231	Ernstige preeclampsie, complicatie ante partum
6426	19850101	29991231	Eclampsie
64260	19850101	29991231	Eclampsie, niet gespecificeerde behandelingsperiode
64263	19850101	29991231	Eclampsie, complicatie ante partum
6427	19850101	29991231	Preeclampsie of eclampsie bij reeds bestaande hypertensie
64270	19850101	29991231	Preeclampsie of eclampsie bij reeds bestaande hypertensie, niet gespecificeerde behandelingsperiode
64273	19850101	29991231	Preeclampsie of eclampsie bij reeds bestaande hypertensie, complicatie ante partum
64293	19850101	29991231	Niet gespecificeerde hypertensie, complicatie ante partum
643	19850101	29991231	Overvloedig braken in de zwangerschap
6430	19850101	29991231	Lichte hyperemesis gravidarum
64300	19850101	29991231	Lichte hyperemesis gravidarum, zonder specificatie met betrekking tot de behandelingsperiode
64303	19850101	29991231	Lichte hyperemesis gravidarum, ante partum
6431	19850101	29991231	Hyperemesis gravidarum met stofwisselingsstoornis
64310	19850101	29991231	Hyperemesis gravidarum met stofwisselingsstoornis, niet gespec. Behandelingsperiode
64313	19850101	29991231	Hyperemesis gravidarum met stofwisselingsstoornis, complicatie ante partum
6432	19850101	29991231	Laat braken in de zwangerschap
64320	19850101	29991231	Braken in de late zwangerschap, niet gespecificeerde behandelingsperiode
64323	19850101	29991231	Braken in de late zwangerschap, complicatie ante partum
6438	19850101	29991231	Overige vormen van braken als complicatie van de zwangerschap
64380	19850101	29991231	Overige vormen van braken als complicatie van de zwangerschap, niet gespecificeerde behandelingsperiode
64383	19850101	29991231	Overige vormen van braken als complicatie van de zwangerschap, ante partum
6439	19850101	29991231	Niet gespecificeerd braken in de zwangerschap
64390	19850101	29991231	Niet gespecificeerd braken tijdens de zwangerschap, niet gespec. Behandelingsperiode
64393	19850101	29991231	Niet gespecificeerd braken tijdens de zwangerschap, complicatie ante partum
644	19850101	29991231	Vroege of dreigende ween
6440	19850101	29991231	Dreigende premature partus
64400	19850101	29991231	Dreigende premature partus, niet gespecificeerde behandelingsperiode,
64403	19850101	29991231	Dreigende premature partus, ante partum
6441	19850101	29991231	Overige dreigende partus
64410	19850101	29991231	Overige dreigende partus, zonder specificatie met betrekking tot de behandelingsperiode



64413	19850101	29991231	Overige dreigende partus, ante partum
645	19850101	20011231	Verlengde zwangerschap
645	20020101	29991231	Late zwangerschap
6450	19850101	20011231	Verlengde zwangerschap
64500	19850101	20011231	Verlengde zwangerschap, niet gespecificeerde behandelingsperiode
64503	19850101	20011231	Verlengde zwangerschap, complicatie ante partum
6451	20020101	29991231	Overdragen zwangerschap
64510	20020101	29991231	Overdragen zwangerschap, niet gespecificeerde behandelingsperiode
64513	20020101	29991231	Overdragen zwangerschap, complicatie of conditie ante partum
6452	20020101	29991231	Verlengde zwangerschap
64520	20020101	29991231	Verlengde zwangerschap, niet gespecificeerde behandelingsperiode
64523	20020101	29991231	Verlengde zwangerschap, complicatie of conditie ante partum
646	19850101	29991231	Overige complicaties van de zwangerschap, niet elders geclassificeerd
6460	19850101	29991231	Foetus papyraceus
64600	19850101	29991231	Foetus papyraceus, niet gespecificeerde behandelingsperiode
64603	19850101	29991231	Foetus papyraceus, complicatie ante partum
6461	19850101	29991231	Oedeem of excessieve gewichtstoename in de zwangerschap, zonder vermelding van hypertensie
64610	19850101	29991231	Oedeem of excessieve gewichtstoename tijdens de zwangerschap, zonder vermelding van hypertensie, niet gespecificeerde behandelingsperiode
64613	19850101	29991231	Oedeem of excessieve gewichtstoename in de zwangerschap, zonder vermelding van hypertensie, complicatie ante partum
6462	19850101	29991231	Niet gespecificeerde nierziekte in de zwangerschap, zonder vermelding van hypertensie
64620	19850101	19961231	Niet gespecificeerde nierziekte tijdens de zwangerschap zonder vermelding van hypertensie, niet gespecificeerde behandelingsperiode
64620	19970101	29991231	Niet gespecificeerde nierziekte tijdens de zwangerschap zonder vermelding van hypertensie, niet gespecificeerde behandelingsperiode
64623	19970101	29991231	Niet gespecificeerde nierziekte in de zwangerschap, zonder vermelding van hypertensie, complicatie ante partum
6463	19850101	29991231	Habituele abortus patient
64630	19850101	29991231	Habituele abortus patient, niet gespecificeerde behandelingsperiode
64633	19850101	29991231	Habituele abortus patient, ante partum
6464	19850101	29991231	Perifere neuritis in de zwangerschap
64640	19850101	29991231	Perifere neuritis tijdens de zwangerschap, niet gespecificeerde behandelingsperiode
64643	19850101	29991231	Perifere neuritis in de zwangerschap, complicatie ante partum
6465	19850101	29991231	Asymptomatische bacteriurie in de zwangerschap



64650	19850101	29991231	Asymptomatische bacteriurie tijdens de zwangerschap, niet gespec. Behandelperiode
64653	19850101	29991231	Asymptomatische bacteriurie in de zwangerschap, complicatie ante partum
6466	19850101	29991231	Infectie van de tractus urogenitalis in de zwangerschap
64660	19850101	29991231	Infectie van de tractus urogenitalis tijdens de zwangerschap, niet gespecificeerde behandelingsperiode
64663	19850101	29991231	Infectie van de tractus urogenitalis in de zwangerschap, complicatie ante partum
6467	19850101	29991231	Leveraandoeningen in de zwangerschap
64670	19850101	29991231	Leveraandoeningen tijdens de zwangerschap, niet gespecificeerde behandelingsperiode
64673	19850101	29991231	Leveraandoeningen in de zwangerschap, complicatie ante partum
6468	19850101	29991231	Overige gespecificeerde complicaties van de zwangerschap
64680	19850101	29991231	Overige gespecificeerde complicaties van de zwangerschap, niet gespecificeerde behandelingsperiode
64683	19850101	29991231	Overige gespecificeerde complicaties van de zwangerschap, ante partum
6469	19850101	29991231	Niet gespecificeerde complicatie van de zwangerschap
64690	19850101	29991231	Niet gespecificeerde complicatie van de zwangerschap, niet gespec. Behandelperiode
64693	19850101	29991231	Niet gespecificeerde complicatie van de zwangerschap, ante partum
64700	19850101	29991231	Syfilis, niet gespecificeerde behandelingsperiode
64703	19850101	29991231	Syfilis, complicatie ante partum
64710	19850101	29991231	Gonorrhoe, niet gespecificeerde behandelingsperiode
64713	19850101	29991231	Gonorrhoe, complicatie ante partum
64720	19850101	29991231	Overige geslachtsziekten, niet gespecificeerde behandelingsperiode
64723	19850101	29991231	Overige geslachtsziekten, complicatie ante partum
64730	19850101	29991231	Tuberculose, niet gespecificeerde behandelingsperiode
64733	19850101	29991231	Tuberculose, complicatie ante partum
64740	19850101	29991231	Malaria, niet gespecificeerde behandelingsperiode
64743	19850101	29991231	Malaria, complicatie ante partum
64750	19850101	29991231	Rubella, niet gespecificeerde behandelingsperiode
64753	19850101	29991231	Rubella, complicatie ante partum
64760	19850101	29991231	Overige virusziekten, niet gespecificeerde behandelingsperiode
64763	19850101	29991231	Overige virusziekten, complicatie ante partum
64780	19850101	29991231	Overige gespecificeerde infectieuze en parasitaire ziekten, niet gespecificeerde behandelingsperiode
64783	19850101	29991231	Overige gespecificeerde infectieuze en parasitaire ziekten, complicatie ante partum



64790	19850101	29991231	Niet gespecificeerde infectie of besmetting, niet gespecificeerde behandelingsperiode
64793	19850101	29991231	Niet gespecificeerde infectie of besmetting, complicatie ante partum
6480	19850101	29991231	Diabetes mellitus
64800	19850101	29991231	Diabetes mellitus, niet gespecificeerde behandelingsperiode
64803	19850101	29991231	Diabetes mellitus, complicatie ante partum
64810	19850101	29991231	Stoornis van de schildklierfunctie, niet gespecificeerde behandelingsperiode
64813	19850101	29991231	Stoornis van de schildklierfunctie, complicatie ante partum
64820	19850101	29991231	Anemie, niet gespecificeerde behandelingsperiode
64823	19850101	29991231	Anemie, complicatie ante partum
64830	19850101	29991231	Verslaving aan drugs, niet gespecificeerde behandelingsperiode
64833	19850101	29991231	Verslaving aan drugs, complicatie ante partum
64840	19850101	29991231	Psychische aandoeningen, niet gespecificeerde behandelingsperiode
64843	19850101	29991231	Psychische aandoeningen, complicatie ante partum
64850	19850101	29991231	Aangeboren cardiovasculaire afwijkingen, niet gespecificeerde behandelingsperiode
64853	19850101	29991231	Aangeboren cardiovasculaire afwijkingen, complicatie ante partum
64860	19850101	29991231	Overige cardiovasculaire ziekten, niet gespecificeerde behandelingsperiode
64863	19850101	29991231	Overige cardiovasculaire ziekten, complicatie ante partum
64870	19850101	29991231	Bot- en gewrichtsaandoeningen van rug, bekken en onderste extremiteiten, niet gespecificeerde behandelingsperiode
64873	19850101	29991231	Bot- en gewrichtsaandoening van rug, bekken en onderste extremiteiten, complicatie ante partum
6488	19850101	29991231	Abnormale glucose tolerantie
64880	19850101	29991231	Abnormale glucose tolerantie, niet gespecificeerde behandelingsperiode
64883	19850101	29991231	Abnormale glucose tolerantie, complicatie ante partum
64890	19850101	29991231	Overige thans bestaande aandoeningen, elders classificeerbaar, niet gespecificeerde behandelingsperiode
64893	19850101	29991231	Overige thans bestaande aandoeningen, elders classificeerbaar, complicatie ante partum
6510	19850101	29991231	Tweeling zwangerschap
65100	19850101	29991231	Tweeling zwangerschap, niet gespecificeerde behandelingsperiode
65103	19850101	29991231	Tweeling zwangerschap, complicatie ante partum
6511	19850101	29991231	Drieling zwangerschap
65110	19850101	29991231	Drieling zwangerschap, niet gespecificeerde behandelingsperiode
6512	19850101	29991231	Vierling zwangerschap



6513	19850101	29991231	Tweelingzwangerschap met afsterven van een van beide foetussen
6514	19850101	29991231	Drielingzwangerschap met afsterven van een of twee foetussen
6515	19850101	29991231	Vierlingzwangerschap met afsterven van een gedeelte van de foetussen
6516	19850101	29991231	Andere meerlingzwangerschap met afsterven van een gedeelte van de foetussen
671	19850101	29991231	Veneuze complicaties in zwangerschap en kraambed
V22	19850101	29991231	Normale zwangerschap
V220	19850101	29991231	Controle van een normale eerste zwangerschap
V221	19850101	29991231	Controle van een andere normale zwangerschap
V222	19850101	29991231	Zwangerschap als bijkomstige bevinding
V23	19850101	29991231	Controle van een zwangerschap met verhoogd risico -high risk-
V230	19850101	29991231	Controle van een zwangerschap met onvruchtbaarheid in de anamnese
V231	19850101	29991231	Controle van een zwangerschap met trofoblast aandoening in de anamnese
V232	19850101	29991231	Controle van een zwangerschap met abortus in de anamnese
V234	19850101	20041231	Controle van een zwangerschap met anderszins slechte verloskundige anamnese
V2341	20050101	29991231	Zwangerschap met geschiedenis van preterm arbeid
V2349	20050101	29991231	Zwangerschap met andere gespecificeerde slechte verloskundige anamnese
V235	19850101	29991231	Controle van een zwangerschap met anderszins slechte voortplantingsanamnese
V238	19850101	20011231	Controle van overige gespecificeerde vormen van 'high risk' zwangerschap
V238	20020101	29991231	Controle van overige gespecificeerde vormen van 'high risk' zwangerschap
V2389	20020101	29991231	Overige "high risk"-zwangerschap
V239	19850101	29991231	Controle van een niet gespecificeerde 'high risk' zwangerschap
V616	19850101	29991231	Onwettigheid of ongehuwde zwangerschap
V617	19850101	29991231	Andere ongewenste zwangerschap
V724	19850101	20041231	Zwangerschapsonderzoek of -test waarbij de zwangerschap niet wordt bevestigd
V7240	20050101	29991231	Zwangerschapsonderzoek of -test, niet bevestigd
V7241	20050101	29991231	Zwangerschapsonderzoek of -test, negatief resultaat



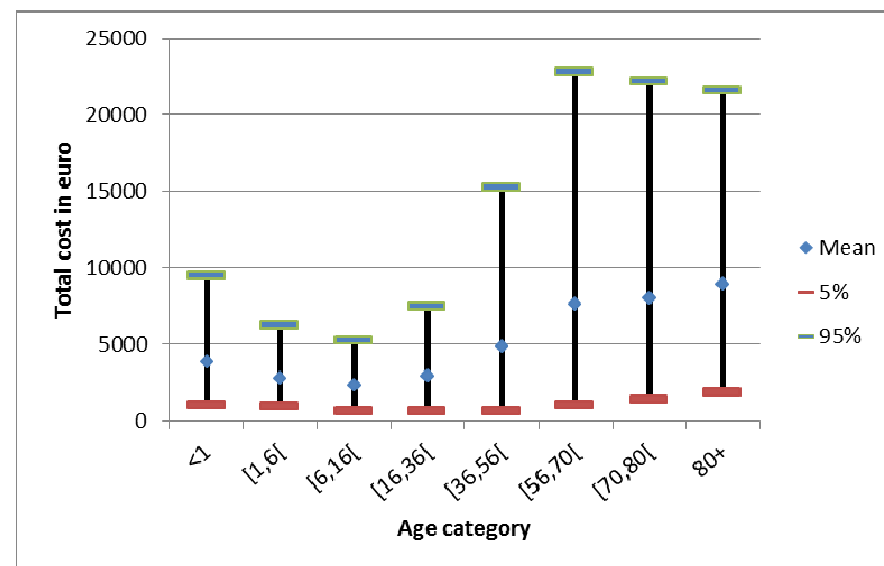
3.3. In-hospital costs for hospitalized influenza patients

3.3.1. Aggregated data on in-hospital cost for hospitalised influenza patients

Patients with a secondary (but no primary) diagnosis of influenza

In patients with only a secondary diagnosis of influenza, the trend in increasing costs with age saturates at a relatively young age. That is, the costs incurred by adults over 55 years of age are independent of age, if influenza is indicated to be a secondary diagnosis only (see Figure 2). These patients incur substantially higher mean (€5015) and median (€2766) costs than those with a primary diagnosis of influenza.

Figure 2 – Age-specific hospitalization costs for patients with a secondary (and no primary) diagnosis of influenza, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



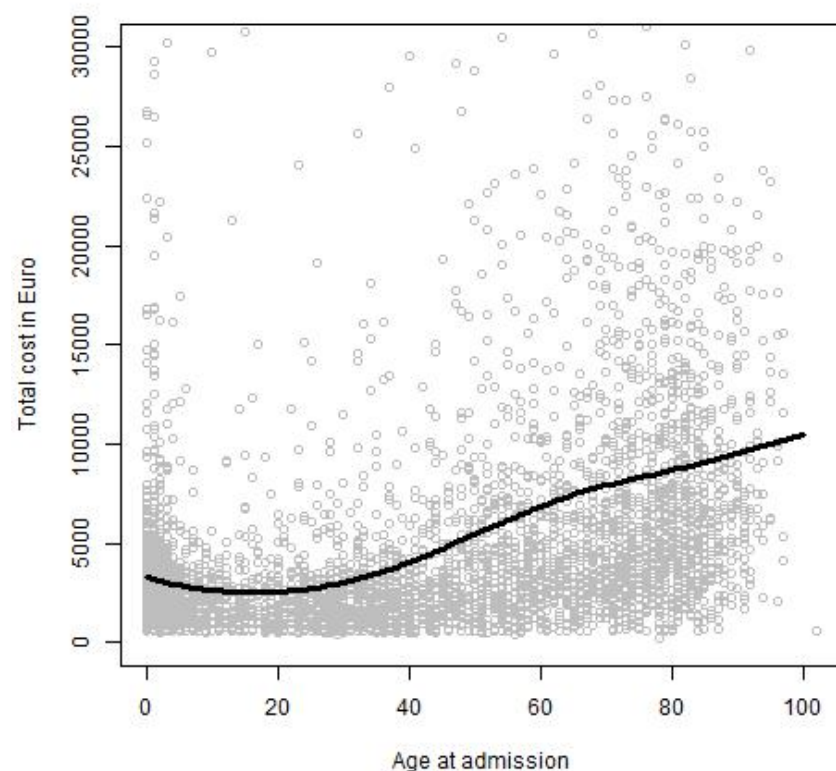
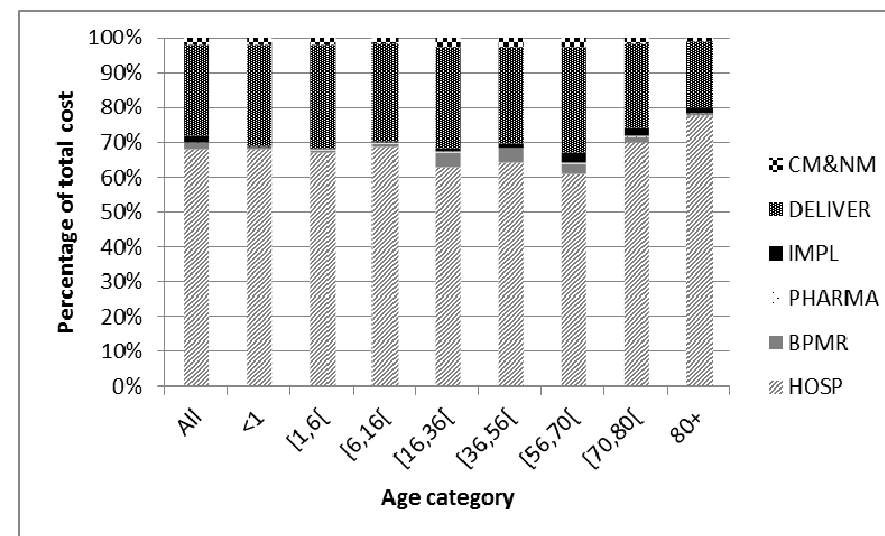


Figure 3 below reveals that for a relatively larger part of these patients, costs for blood plasma, mother's milk, radio-isotopes (BPMR) as well as implantations (IMPL) emerge as more important contributors to the overall costs.

Figure 3 – Age-specific hospitalization cost distribution per cost category for patients with a secondary (and no primary) diagnosis of influenza





Patients with a primary or secondary diagnosis of influenza

Figure 4 – Age-specific hospitalization costs for patients with a primary or secondary diagnosis of influenza, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

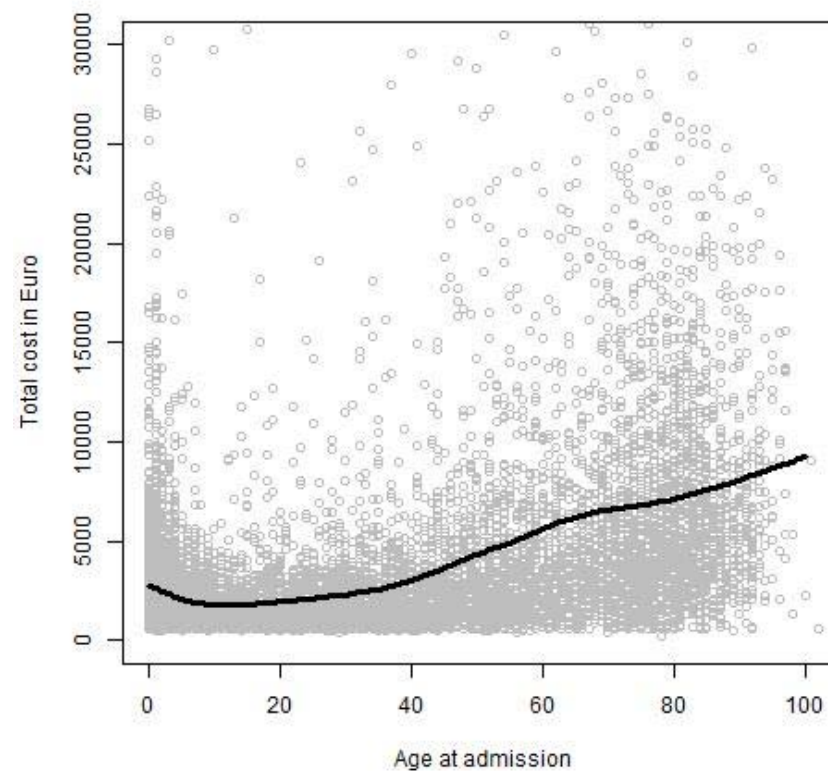
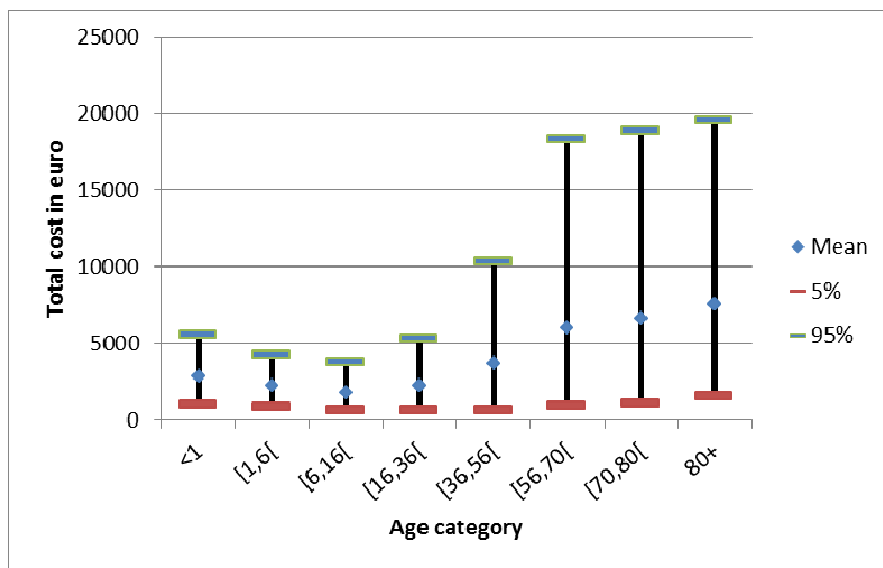
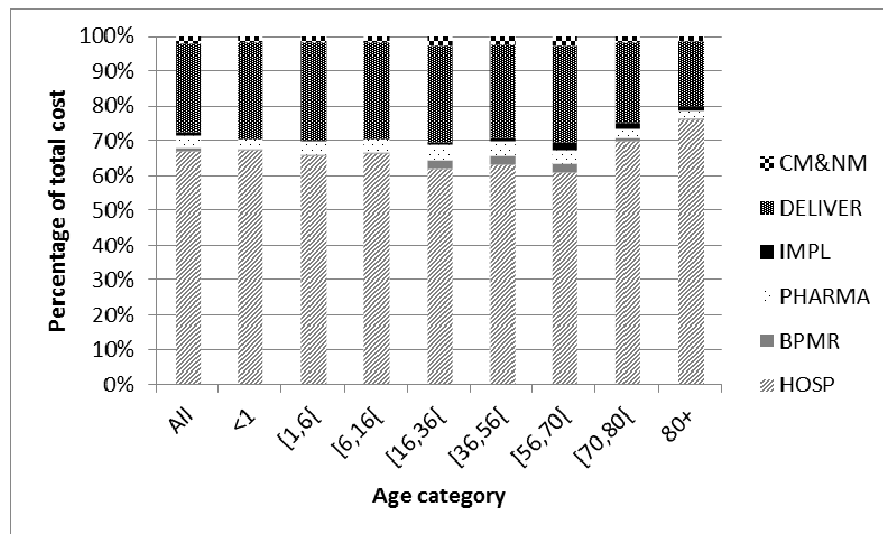




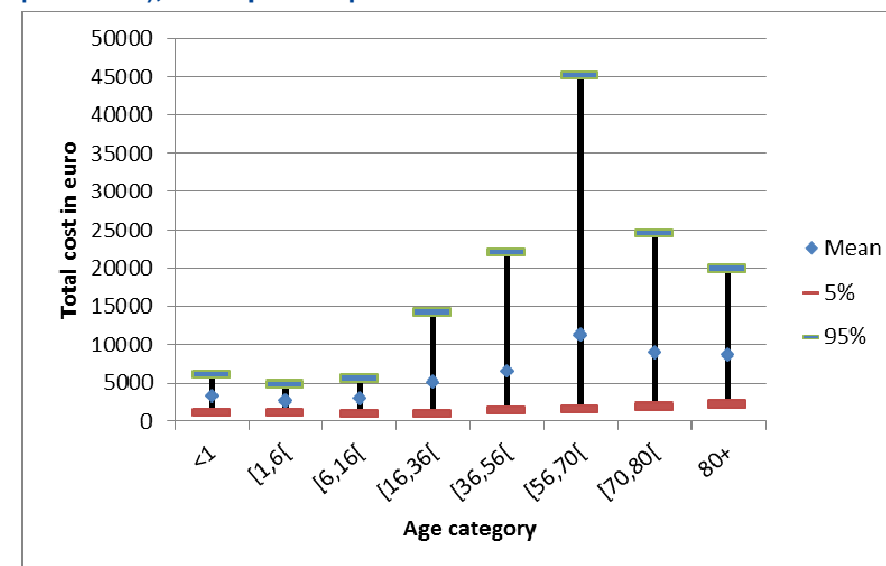
Figure 5 – Age-specific hospitalization cost distribution per cost category for patients with a primary or diagnosis of influenza



Patients with a combined diagnosis (primary or secondary) of influenza and pneumonia

If we investigate more closely patients admitted with diagnoses of both influenza and pneumonia, there is a trend towards substantially higher costs in the age group 56-70 years of age (with a peak around age 65 years, see Figure 6). The mean and median costs for these patients are €4153 and €2594, respectively.

Figure 6 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and pneumonia, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



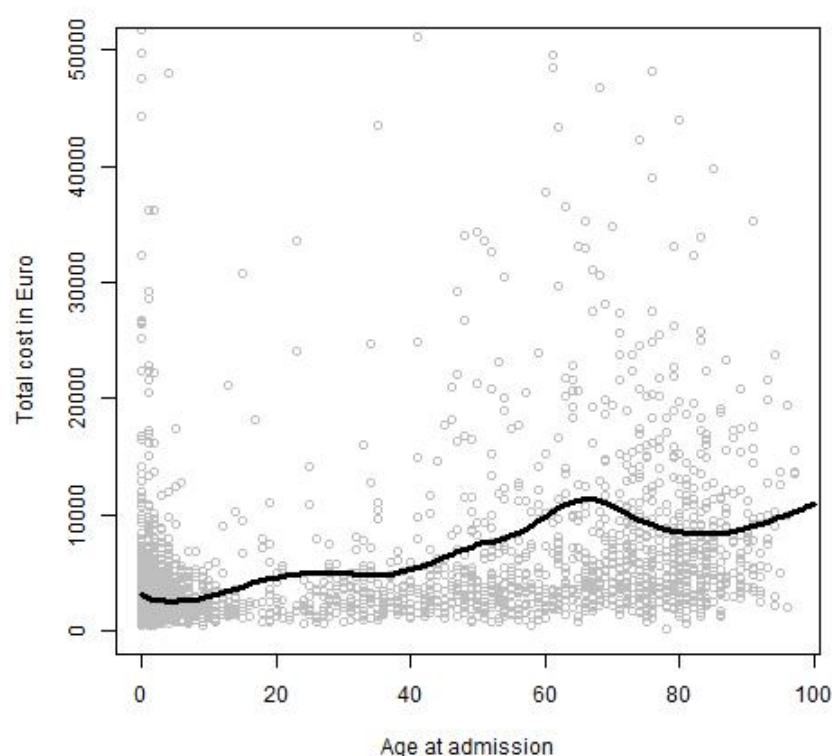
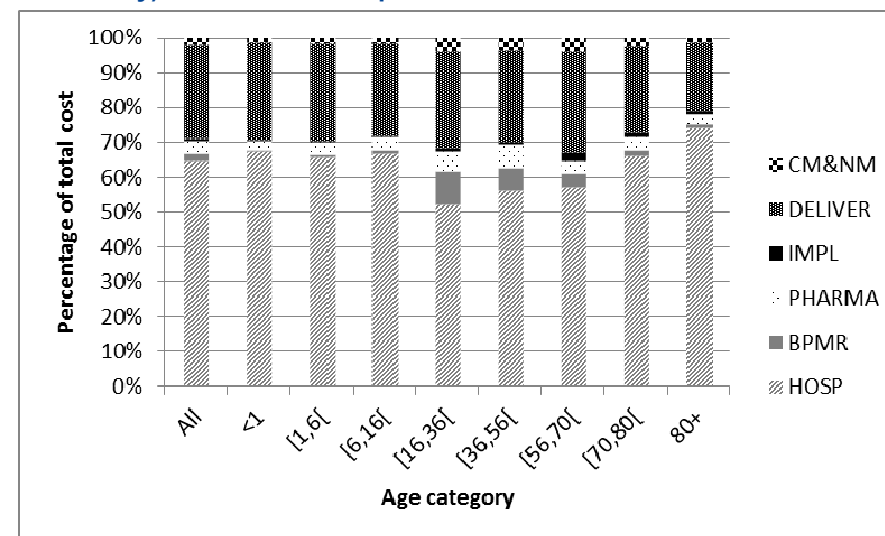


Figure 7 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and pneumonia



Patients with a combined diagnosis (primary or secondary) of influenza and pneumococcal pneumonia

It is of interest to investigate the impact of co-infection with *Streptococcus Pneumonia*. In this group we show costs incurred for patients admitted with a combined diagnosis (primary or secondary) of influenza and pneumococcal pneumonia (Figure 7).

The number of observations in this group (n=79), versus the previous one (n=5086) clearly indicates that interpretation of these results is problematic for some age groups (see appendix for details). The mean and median costs in this group are substantially higher than in the previous group combining influenza with any pneumonia (€7025 and €3550, respectively), but the sheer size of the previous group absorbs the impact of these higher costing pneumococcal pneumonia cases.



Figure 8 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and pneumococcal pneumonia, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

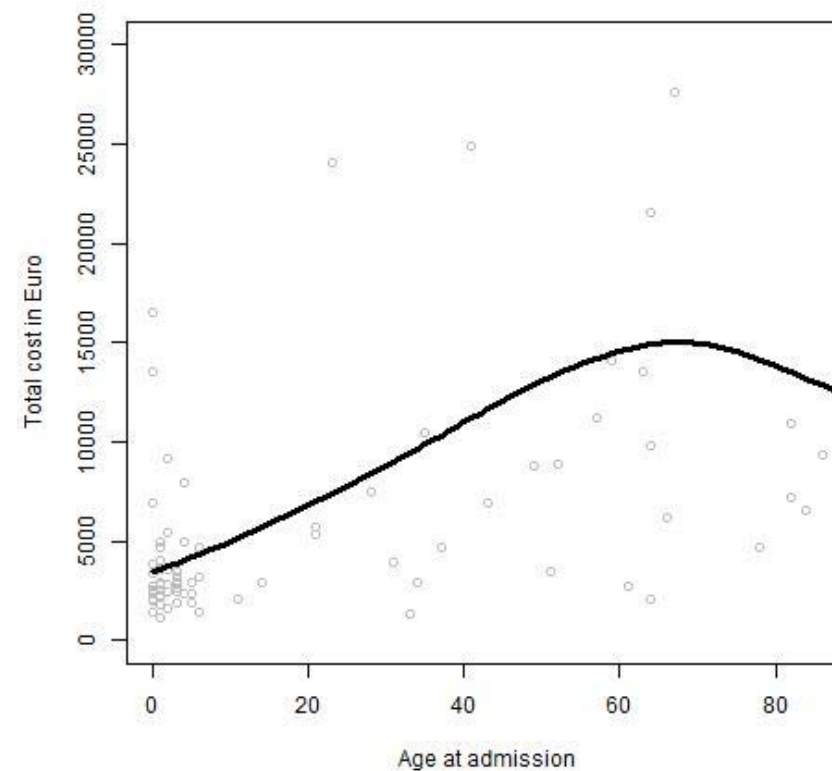
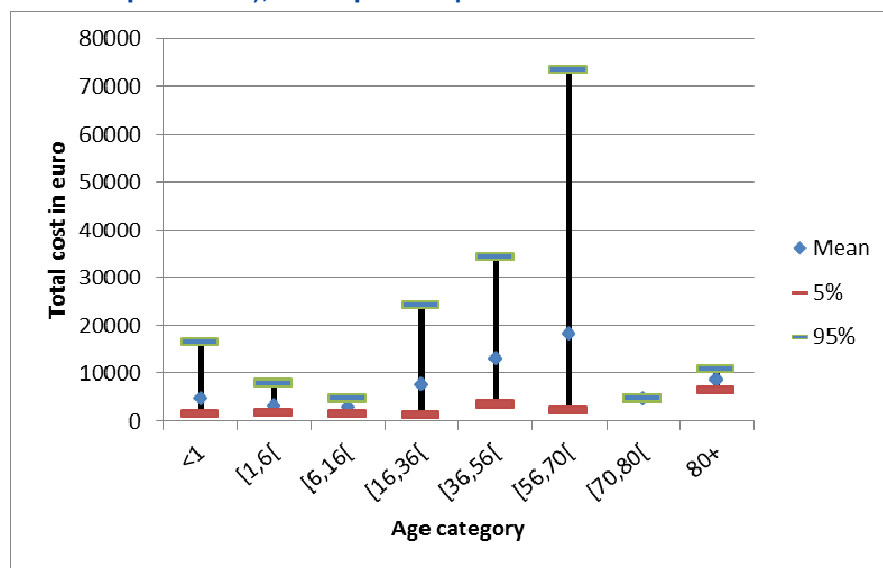
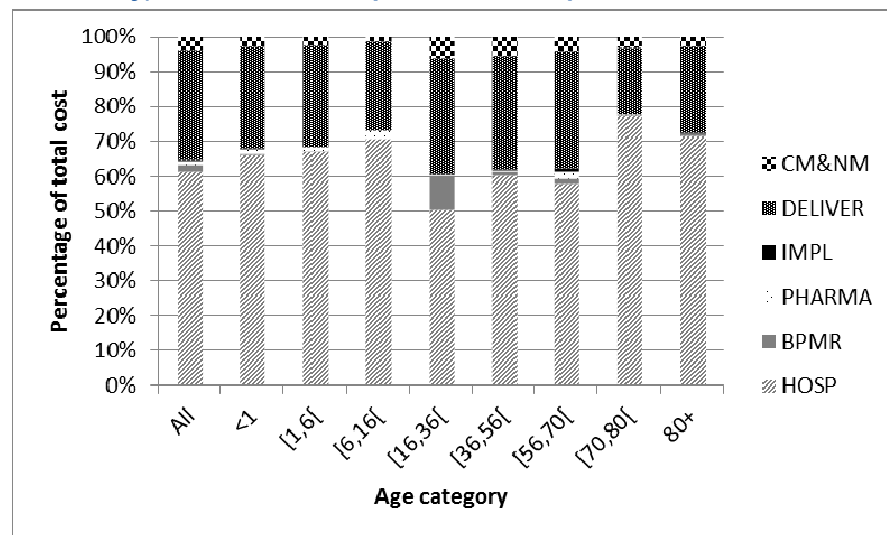




Figure 9 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and pneumococcal pneumonia

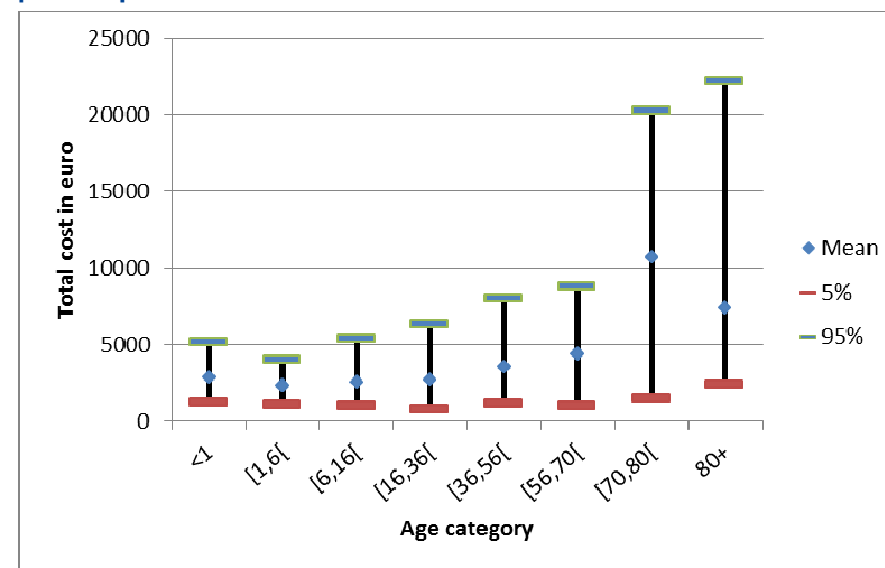


Patients with a combined diagnosis (primary or secondary) of influenza and asthma

The group of hospitalisations with a combination of diagnoses for influenza and asthma in our datasets counts 642 admissions, relatively evenly distributed over the various age groups. The mean and median costs are €3629 and €2504, respectively.

The age-specific profiles exhibit a steep rise in costs between age 60 and 80, followed by a rapid decline in those between 80 and 100 years of age (influenced by a scarce number of data points in older age groups).

Figure 10 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and asthma, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



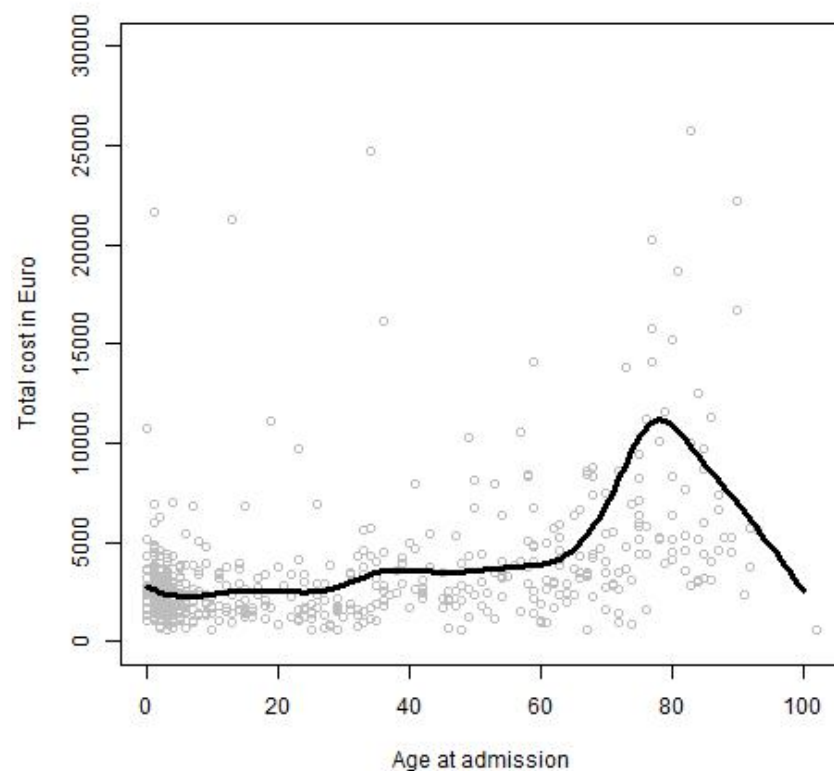
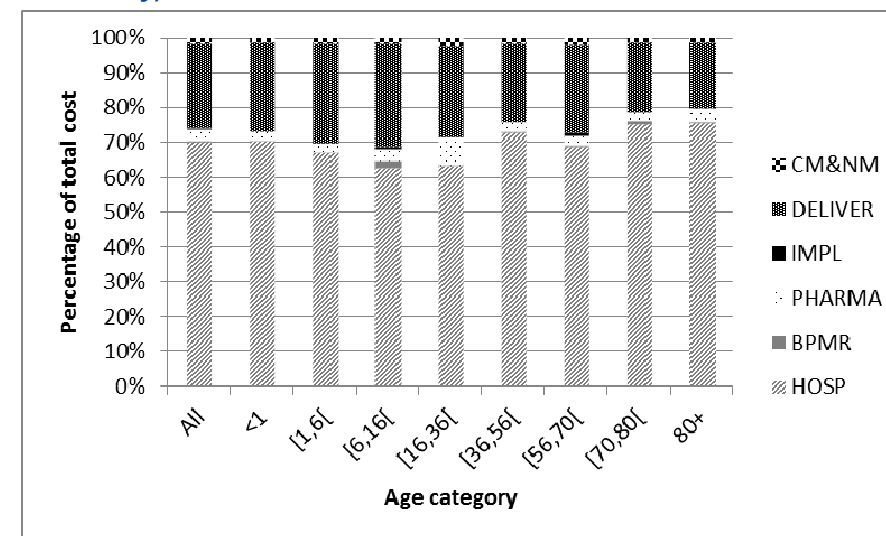


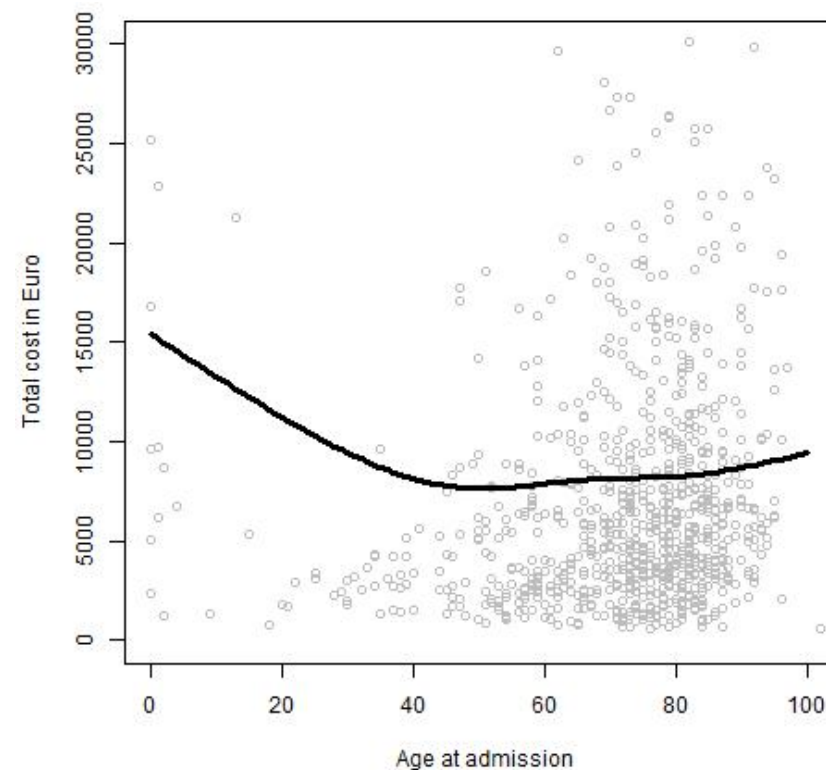
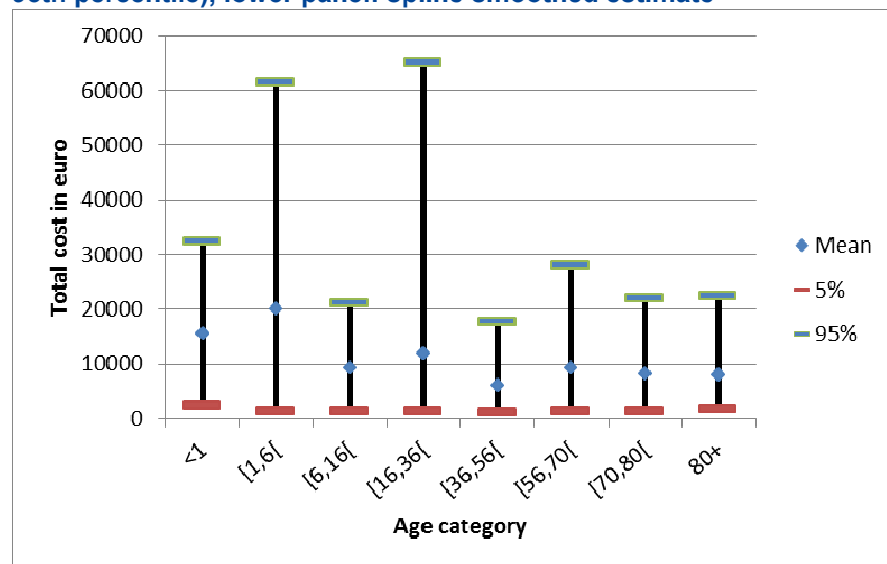
Figure 11 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and asthma





Patients with a combined diagnosis (primary or secondary) of influenza and cardiovascular disease

Figure 12 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and cardiovascular disease, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

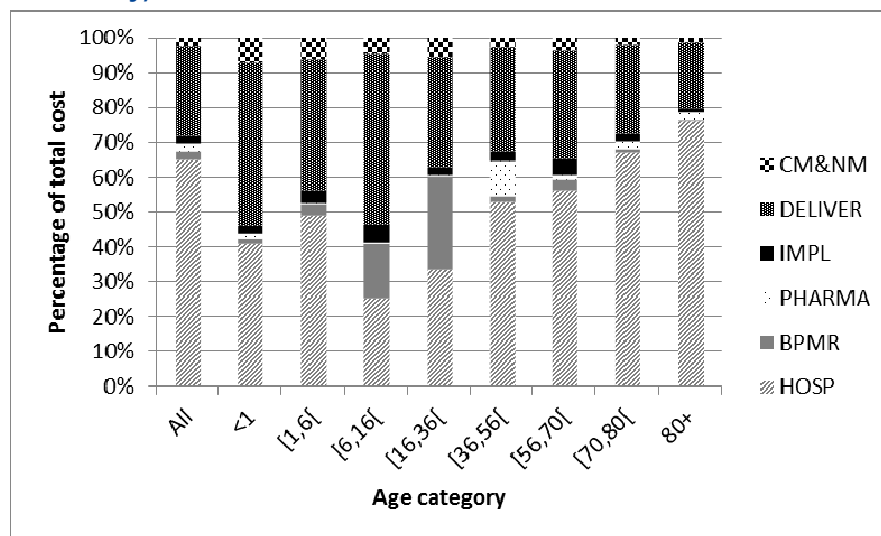


With 879 records, the group of patients admitted and classified as being diagnosed with both influenza and cardiovascular disease is slightly larger than the asthma group (see above). It comes at no surprise, however, that these records are much more concentrated in adult age groups. The mean and median costs for this category are €8368 and €5378, respectively.

Medical deliveries, pharmaceutical products and implantations have a larger relative weight in the costs, compared to the previous groups.



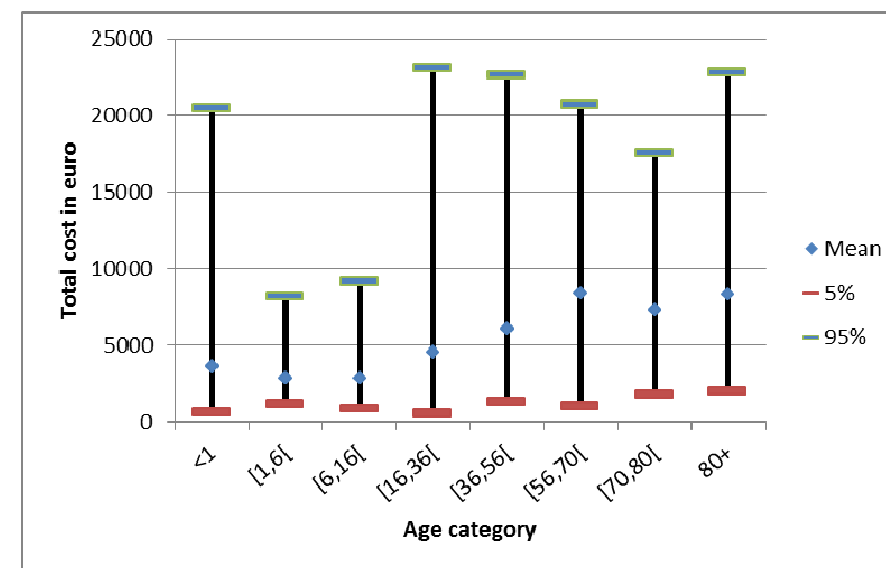
Figure 13 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and cardiovascular disease



Patients with a combined diagnosis (primary or secondary) of influenza and Chronic Obstructive Pulmonary Disease (COPD)

A group similar to the previous one in size (n=879) and in mean (€8368) and median (€5378) costs is the group categorised with Chronic Obstructive Pulmonary Disease (COPD) in one of the diagnostic fields alongside influenza in another diagnostic field.

Figure 14 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and Chronic Obstructive Pulmonary Disease (COPD), upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



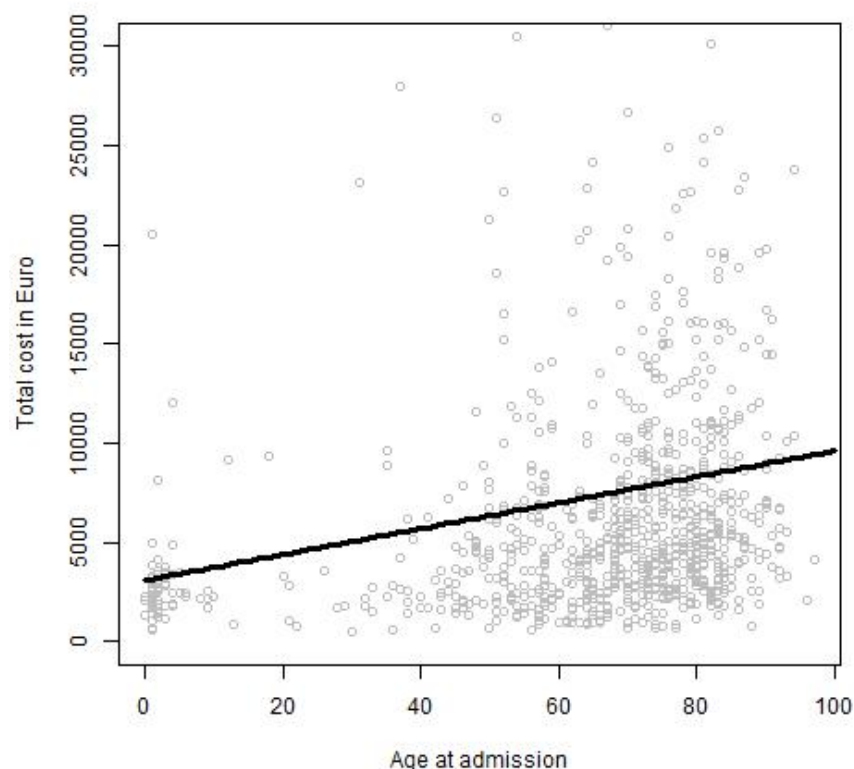
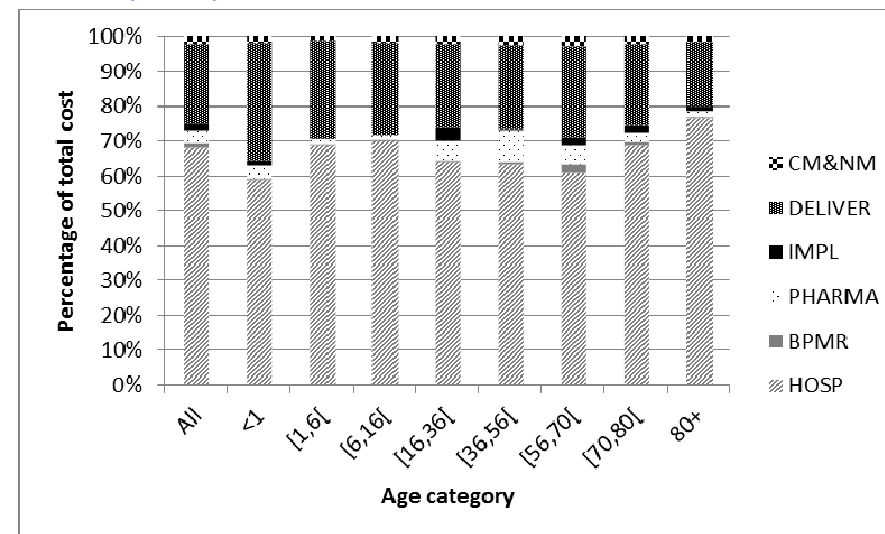


Figure 15 – Age-specific hospitalization cost distribution per cost category (cf. Table) for patients with a combined diagnosis (primary or secondary) of influenza and Chronic Obstructive Pulmonary Disease (COPD)



Patients with a combined diagnosis (primary or secondary) of influenza and diabetes

Another group, which may be considered for influenza vaccination are diabetes patients.

These admissions are again similar in number (n= 742) with the preceding groups, but very few admissions occurring in the younger age groups (see spline plot below and appendix table). The mean and median costs for these admissions are €6528 and €4237, respectively.



Figure 16 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and diabetes, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

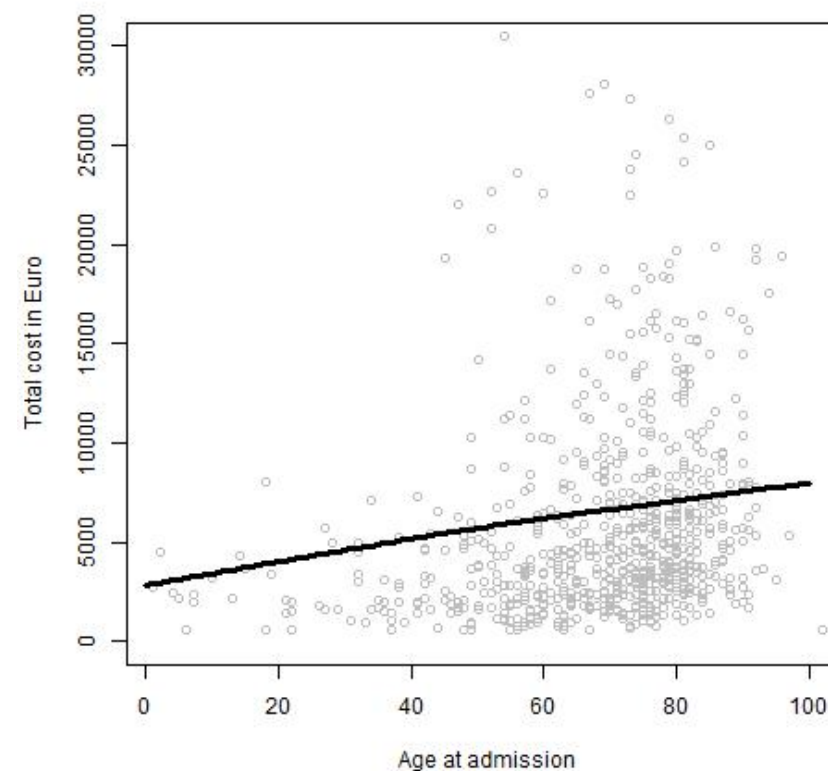
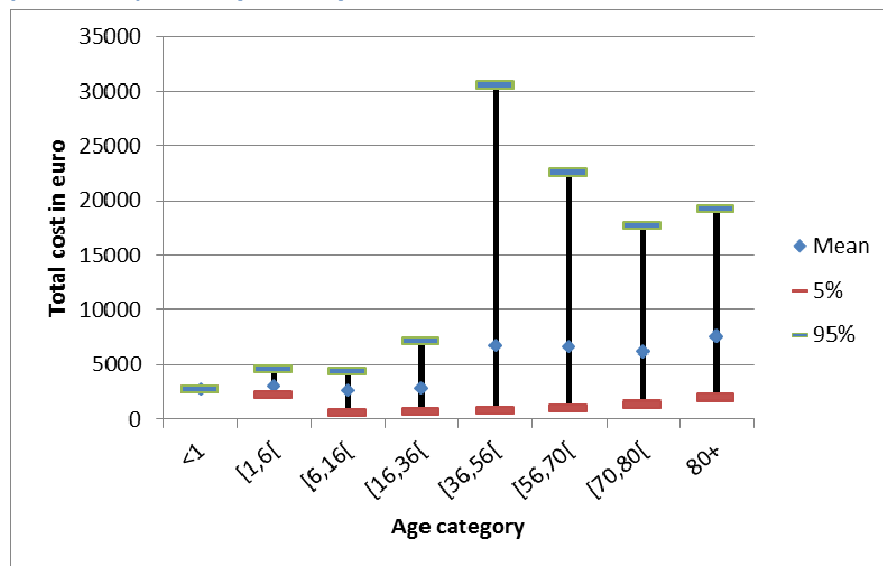
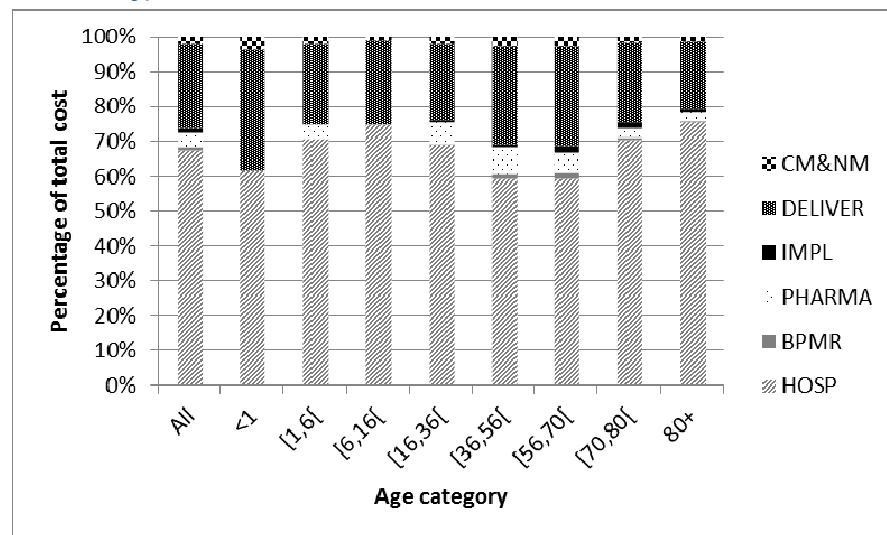




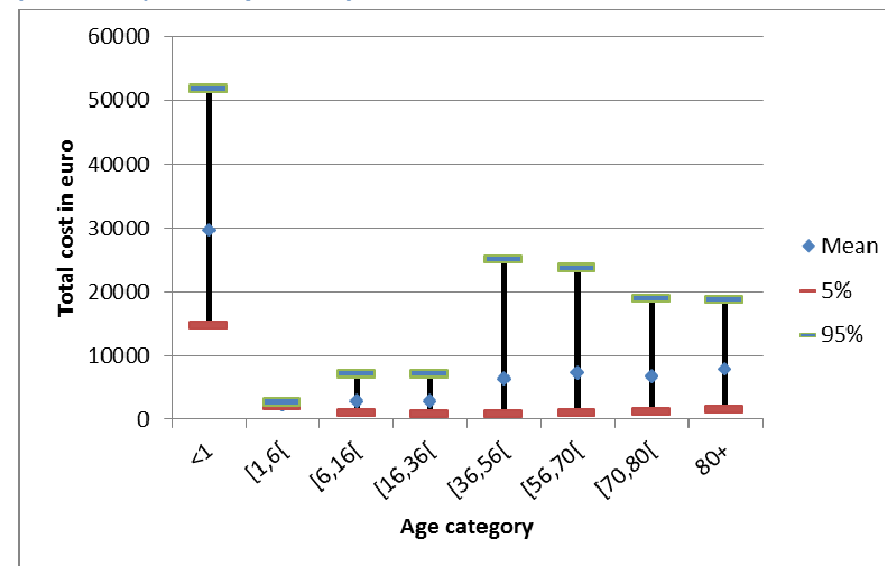
Figure 17 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and diabetes



Patients with a combined diagnosis (primary or secondary) of influenza and hypertension

For hypertension, there is a similar concentration of adult admissions (overall n=1378). The mean and median costs are €7042 and €4213, respectively.

Figure 18 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and hypertension, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



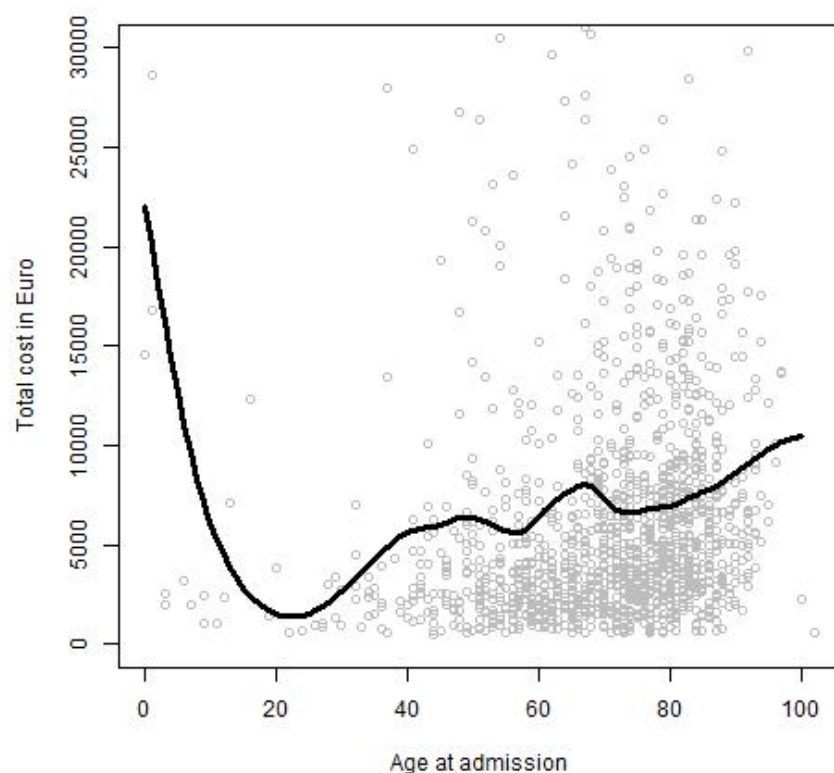
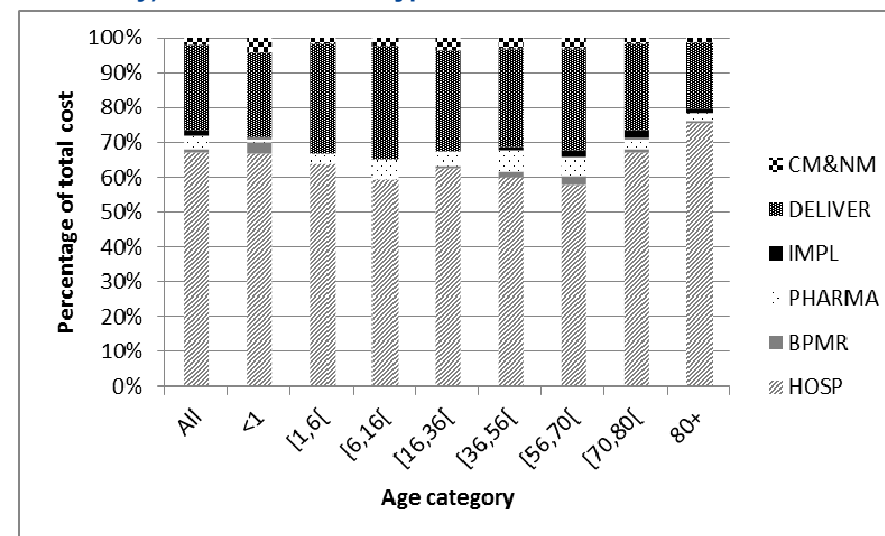


Figure 19 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and hypertension



Patients with a combined diagnosis (primary or secondary) of influenza and stroke

The group of admissions including a diagnosis of stroke is smaller than the preceding ones (n=419), but tends to be more costly with a mean and median of €8749 and €6388, respectively.



Figure 20 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and stroke, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

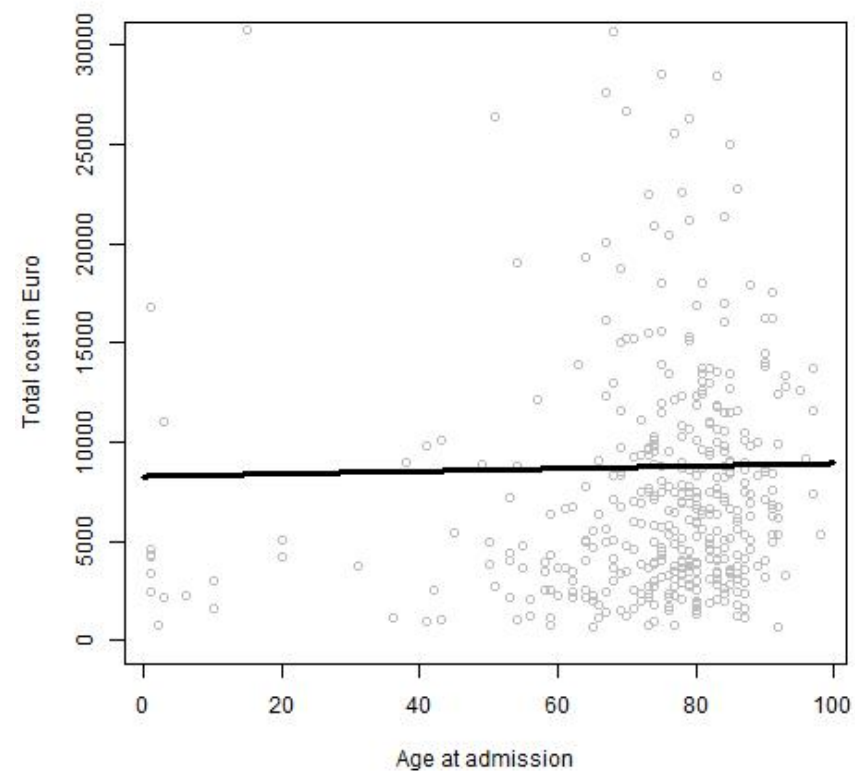
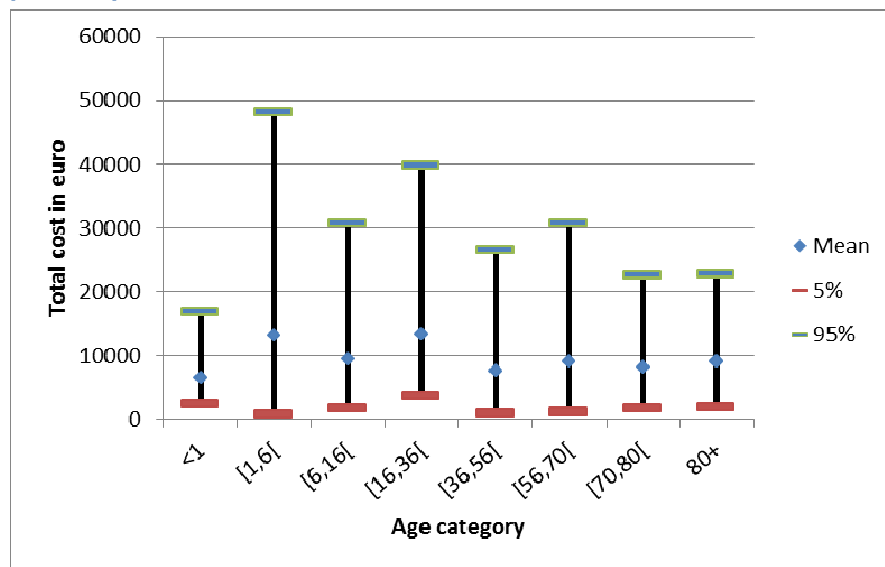
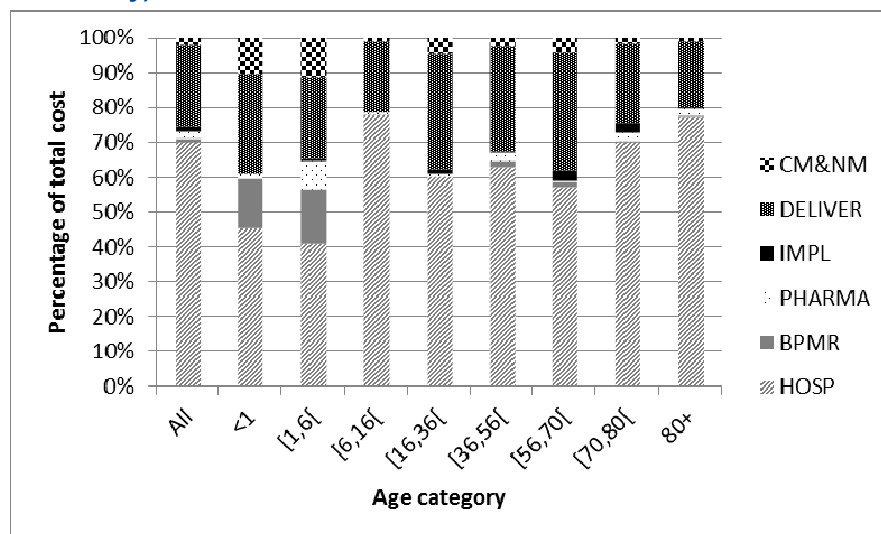




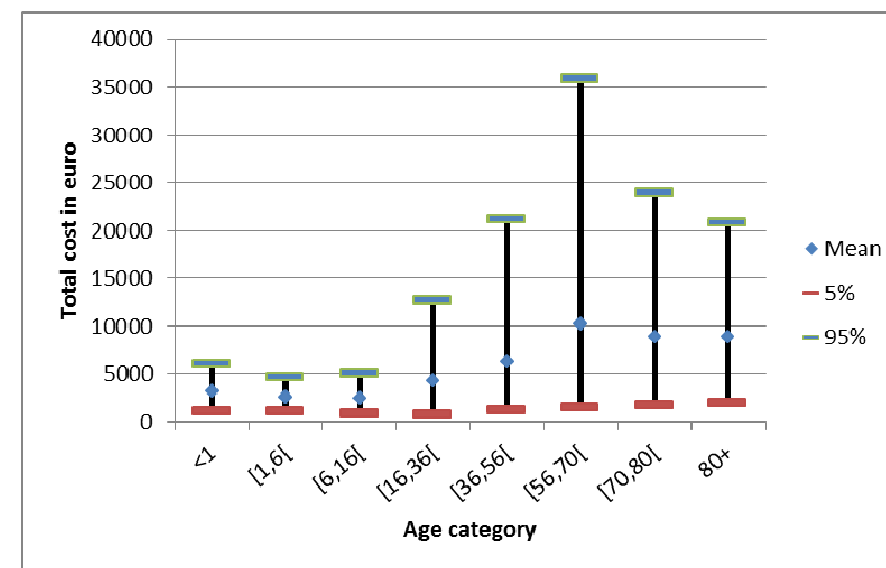
Figure 21 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and stroke



Patients with a combined diagnosis (primary or secondary) of influenza and secondary respiratory tract infections

The diagnosis of secondary respiratory tract infections (SRTI) is commonly associated with a diagnosis of influenza. We collected information on 6458 such admissions, with a mean and median cost of €4289 and €2577, respectively.

Figure 22 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and secondary respiratory tract infections, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



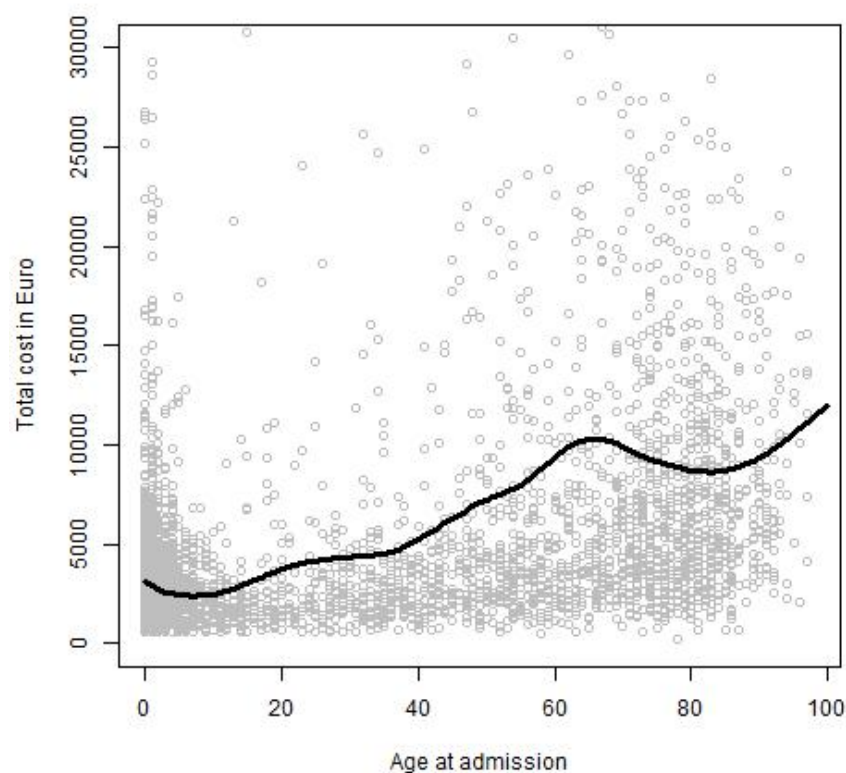
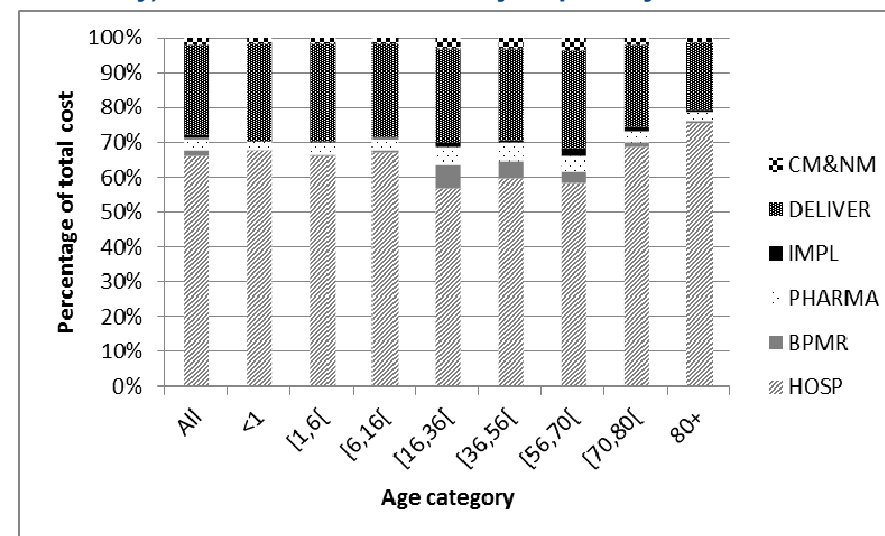


Figure 23 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and secondary respiratory tract infections



Patients with a combined diagnosis (primary or secondary) of influenza and Human Immunodeficiency Virus (HIV)

In our dataset, there are only 29 admissions combining diagnostics of Human Immunodeficiency Virus (HIV) with influenza. None of these occurred below the age of 6 years. The mean and median costs of these admissions were €5501 and €2855, respectively.



Figure 24 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and Human Immunodeficiency Virus (HIV), upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

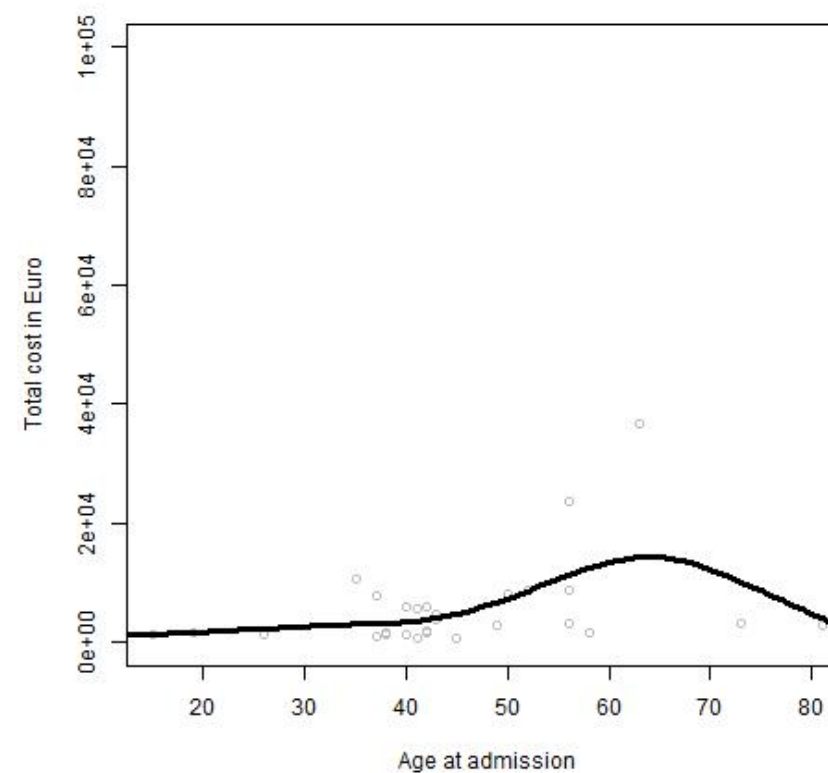
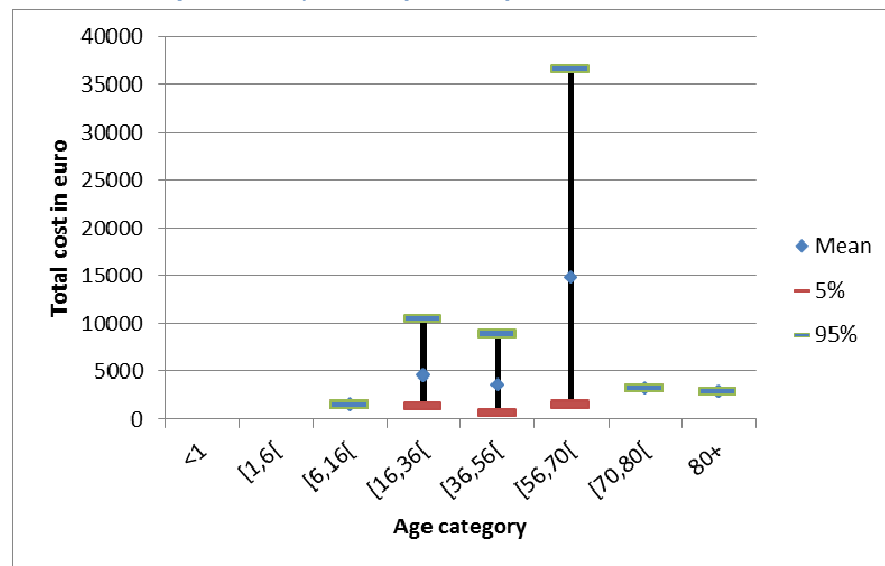
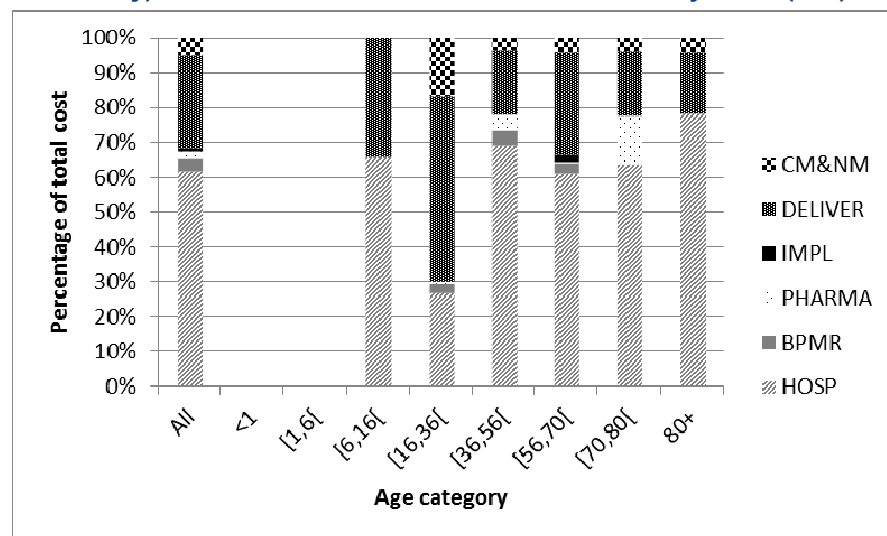




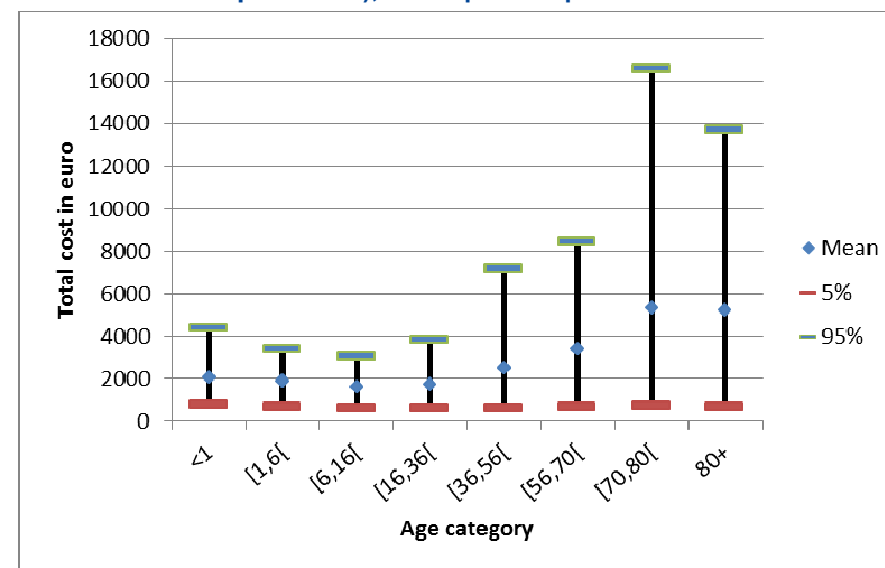
Figure 25 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and Human Immunodeficiency Virus (HIV)



Patients with a combined diagnosis (primary or secondary) of influenza without any of the comorbidities above

It is of interest to verify the impact of excluding all the above comorbidities (in addition to the hospital departments we excluded at the onset). This leaves us with a dataset of 6449 admissions, at a mean and median cost of €2150 and €1581, respectively. That is, the costs are substantially lower than for the preceding groups, but to a much lesser extent lower than all admissions with a primary diagnosis of influenza (€2599 and €1922, respectively).

Figure 26 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza and without any of the preceding comorbidities, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



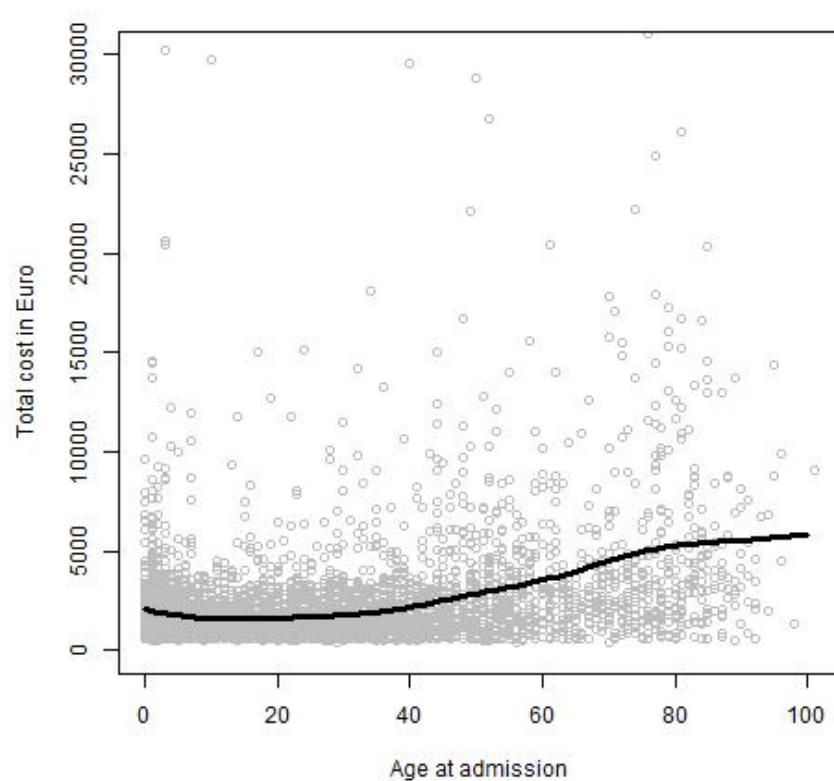
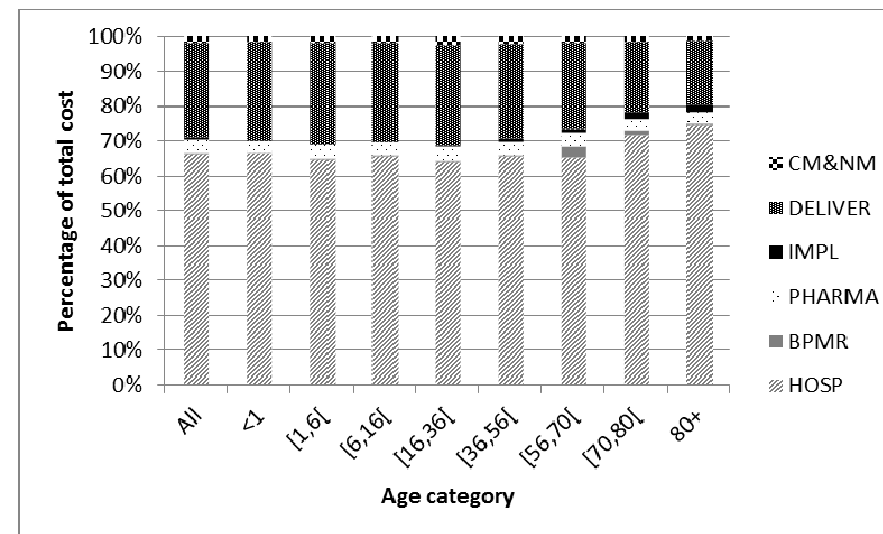


Figure 27 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and without any of the preceding comorbidities





Patients with a combined diagnosis (primary or secondary) of influenza with any of comorbidities

Figure 28 – Age-specific hospitalization costs for patients with a combined diagnosis (primary or secondary) of influenza with any of following comorbidities: asthma, cardiovascular, COPD, diabetes, HIV, hypertension, stroke; upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

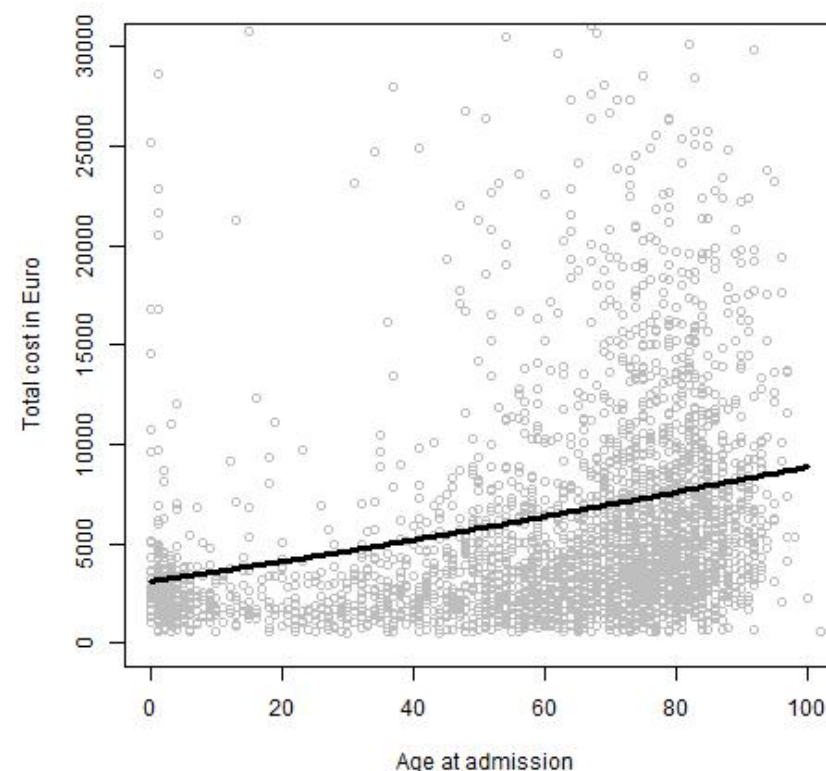
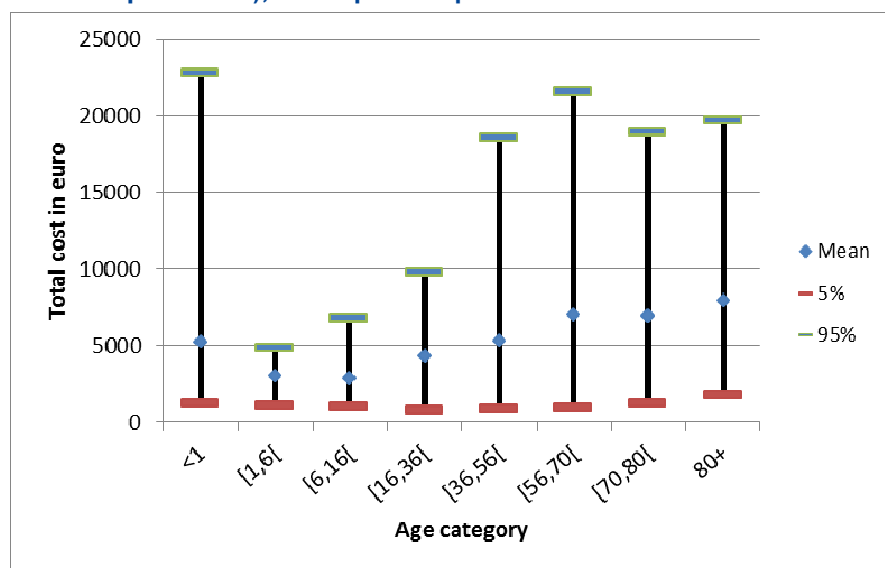
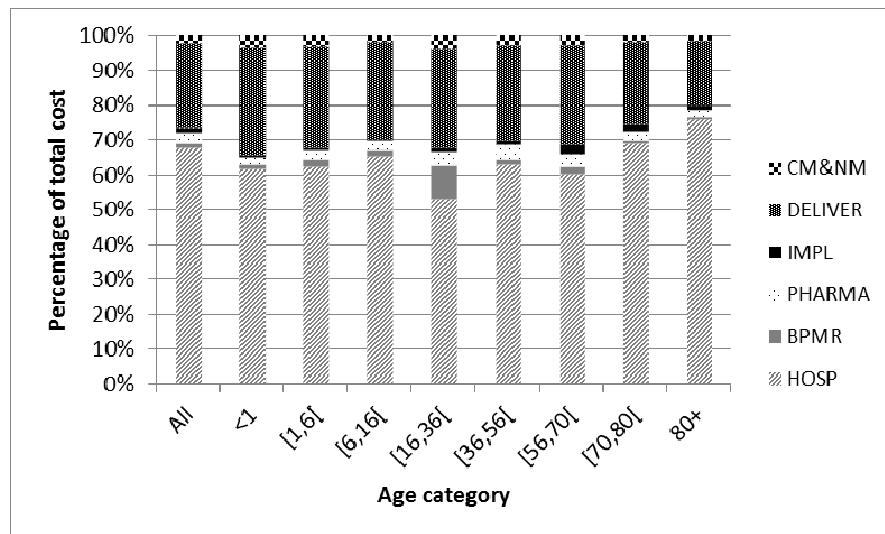




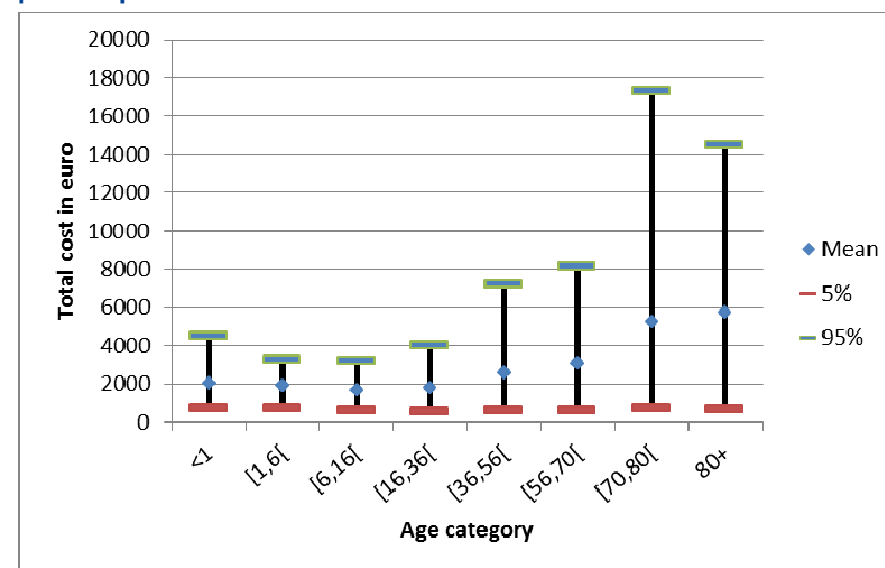
Figure 29 – Age-specific hospitalization cost distribution per cost category for patients with a combined diagnosis (primary or secondary) of influenza and with any of following comorbidities: asthma, cardiovascular, COPD, diabetes, HIV, hypertension, stroke



Combined diagnosis (primary or secondary) without comorbidities of influenza for female patients

The figures below refer to females without comorbidities.

Figure 30 – Age-specific hospitalization costs for female patients with a diagnosis (primary or secondary) of influenza (no comorbidities), upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



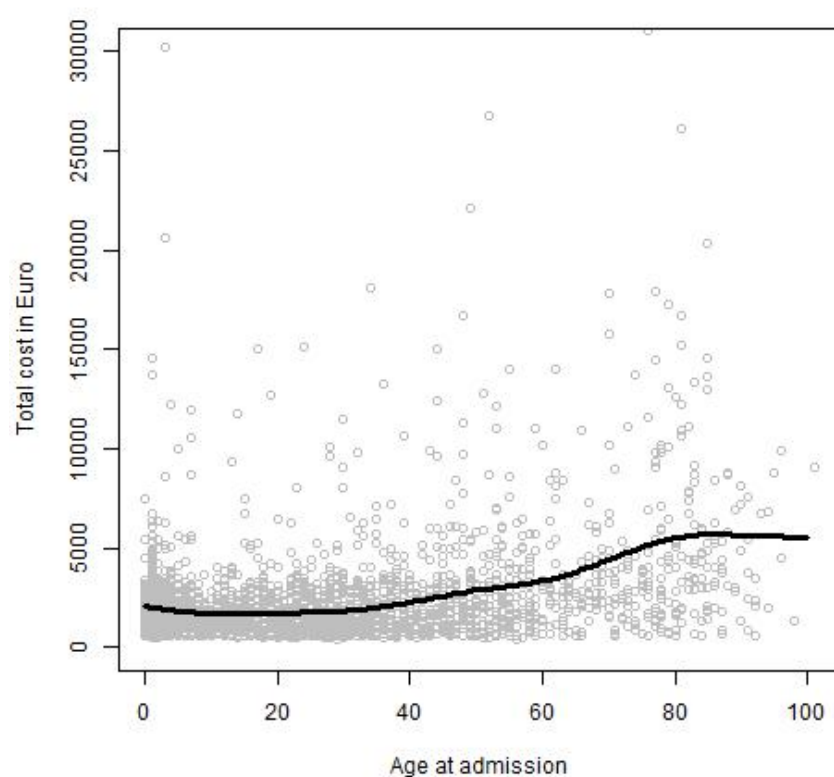
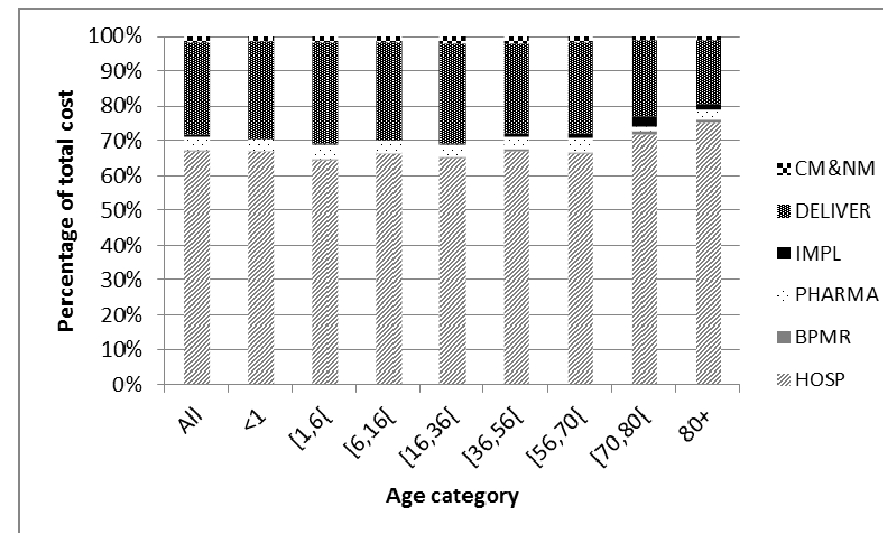


Figure 31 – Age-specific hospitalization cost distribution per cost category for female patients



Patients with a primary diagnosis of influenza and with pregnancy complications

These costs refer to admissions for complications of pregnancy combined with a primary diagnosis of influenza. A list of pregnancy complications can be found in the appendix above.



Figure 32 – Age-specific hospitalization costs for patients with primary diagnosis influenza and pregnancy complications, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate

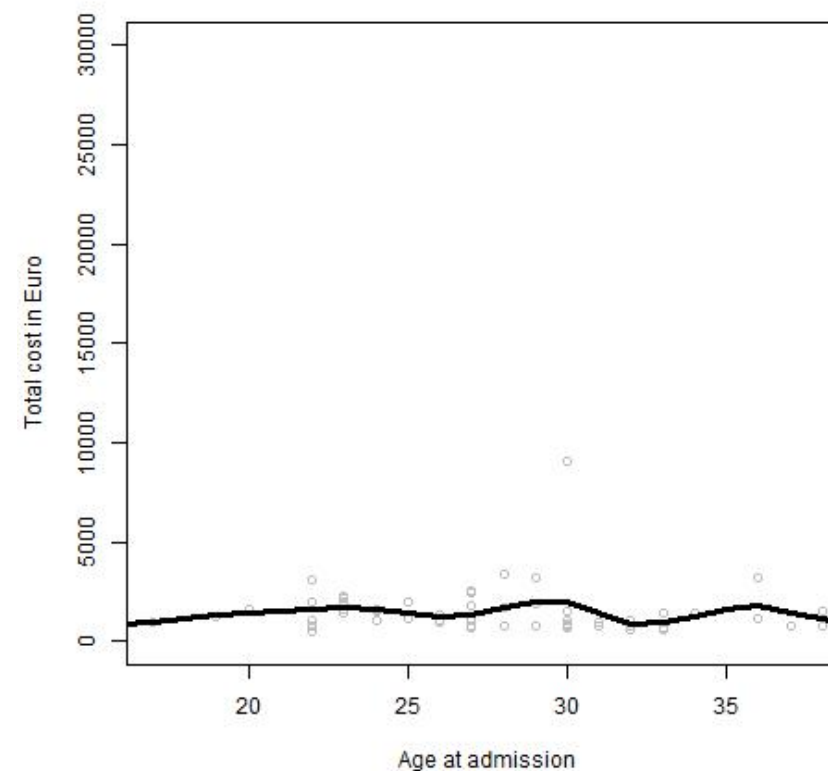
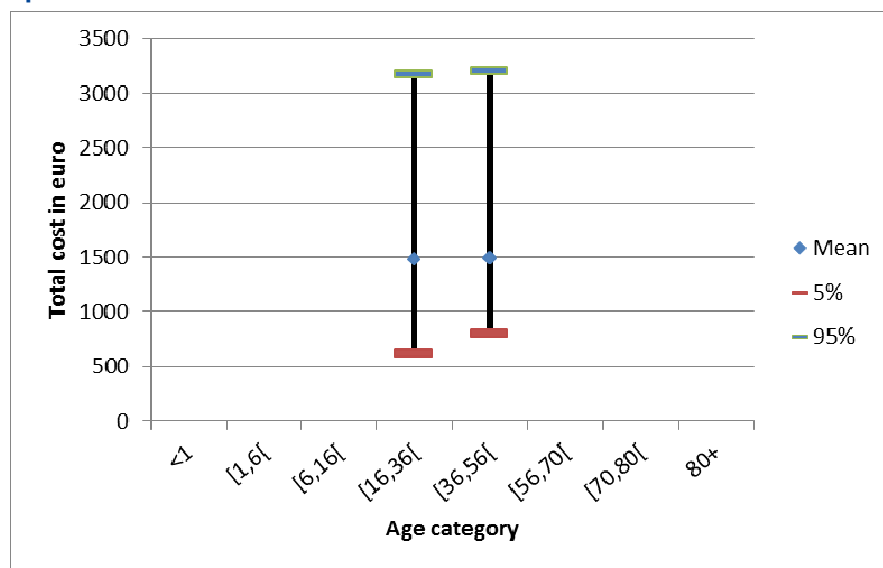
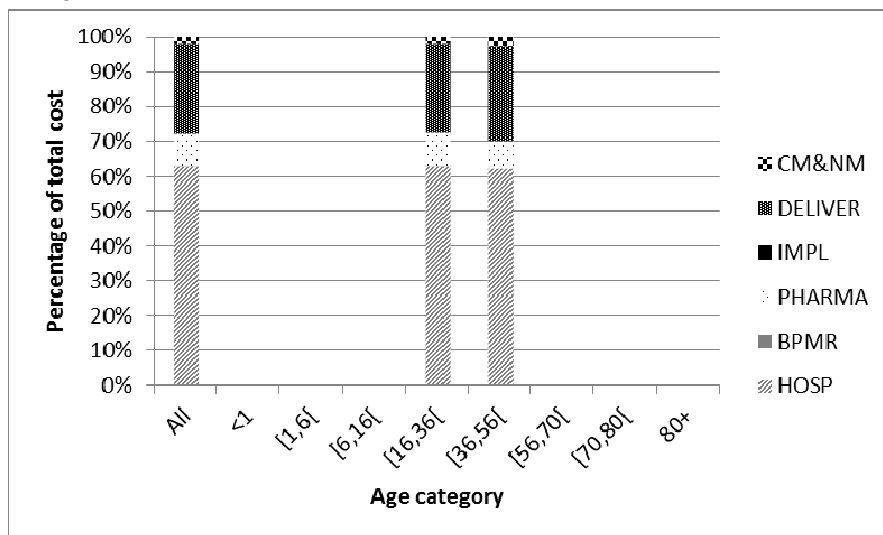


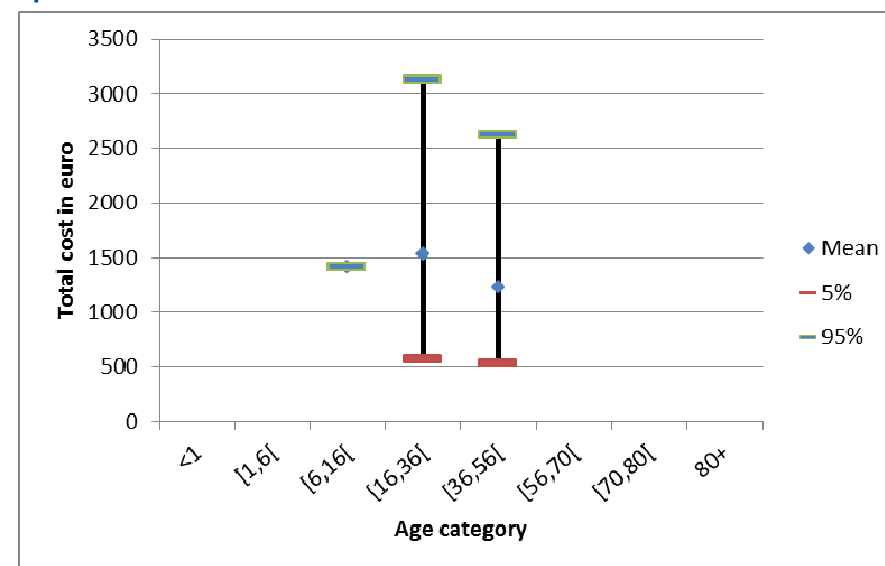


Figure 33 – Age-specific hospitalization cost distribution per cost category for patients with primary diagnosis influenza and pregnancy complications



Patients with a secondary diagnosis of influenza and with pregnancy complications

Figure 34 – Age-specific hospitalization costs for patients with secondary diagnosis influenza and pregnancy complications, upper panel: age groups (mean and 5th and 95th percentile), lower panel: spline smoothed estimate



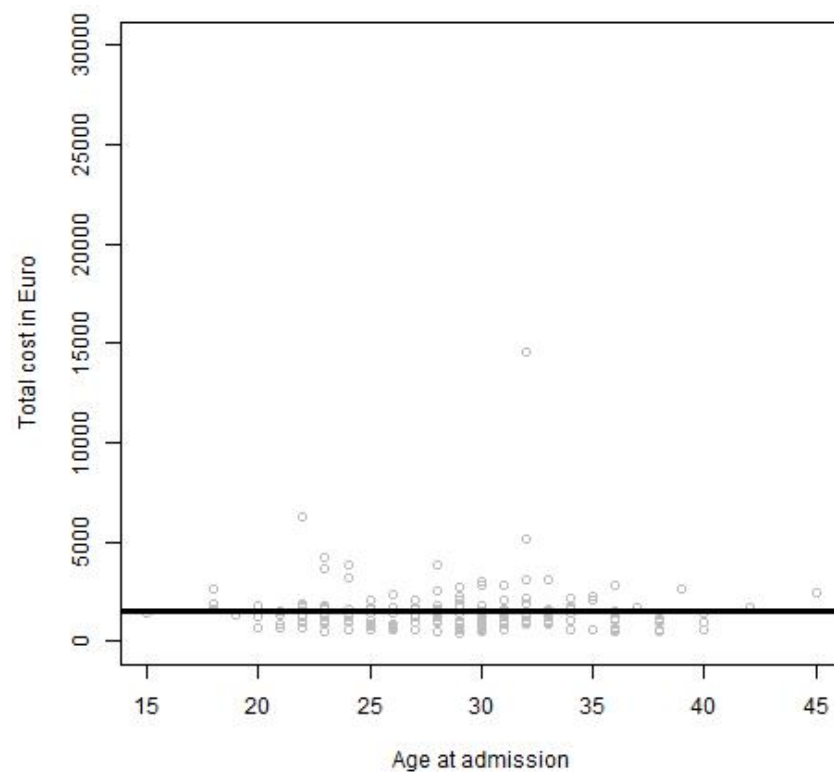
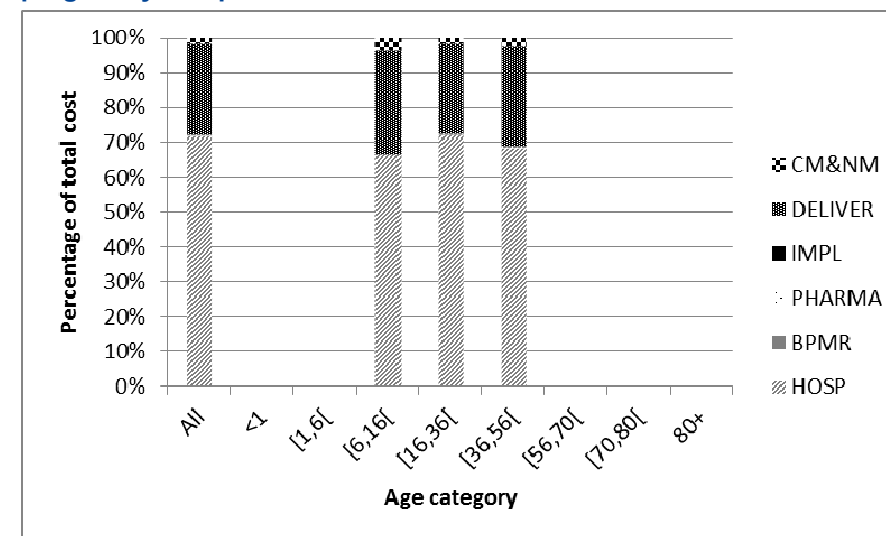


Figure 35 – Age-specific hospitalization cost distribution per cost category for patients with secondary diagnosis influenza and pregnancy complications





3.3.2. Disaggregated data on in-hospital cost for hospitalised influenza patients

Table 15 – Hospitalisation costs: Primary diagnosis of influenza

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	9705	5	4	1	1	2	6	14	183
	HOSP	9705	1703	1273	311	327	670	1965	4358	58254
	BPMR	9705	8	0	0	0	0	0	0	9111
	PHARMA	9705	173	119	1	4	29	181	375	51468
	IMPL	9705	4	0	0	0	0	0	0	5933
	DELIVER	9705	655	535	6	252	390	735	1326	19347
	CM&NM	9705	44	29	0	2	16	49	114	6612
	TOTAL	9705	2599	1922	362	704	1322	2875	6305	118646
<=1	Hospitalization days	1821	5	4	1	2	3	6	11	86
	HOSP	1821	1684	1340	311	623	982	2010	3502	26773
	BPMR	1821	2	0	0	0	0	0	0	286
	PHARMA	1821	106	88	1	3	27	166	224	1808
	IMPL	1821	1	0	0	0	0	0	0	694
	DELIVER	1821	687	599	192	311	456	774	1155	9846
	CM&NM	1821	34	24	0	0	14	38	73	1255
	TOTAL	1821	2523	2157	528	951	1535	2979	4841	36214
[2,6[	Hospitalization days	3250	4	4	1	1	3	5	8	47
	HOSP	3250	1376	1245	311	335	934	1675	2680	15748
	BPMR	3250	4	0	0	0	0	0	0	9111
	PHARMA	3250	109	91	1	4	29	167	216	8423
	IMPL	3250	0	0	0	0	0	0	0	285
	DELIVER	3250	589	539	6	297	421	695	976	11164
	CM&NM	3250	31	24	0	2	14	37	67	6612
	TOTAL	3250	2119	1872	503	834	1413	2566	3837	48047
[6,16[	Hospitalization days	1235	3	3	1	1	2	4	7	31
	HOSP	1235	1075	982	311	318	637	1310	2292	10151
	BPMR	1235	0	0	0	0	0	0	0	100



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	PHARMA	1235	86	48	1	1	13	157	217	1020
	IMPL	1235	0	0	0	0	0	0	0	176
	DELIVER	1235	458	410	155	231	315	548	812	2212
	CM&NM	1235	28	23	0	1	14	35	65	335
	TOTAL	1235	1656	1434	526	595	997	2005	3312	11936
[16,36[	Hospitalization days	1094	3	3	1	1	1	4	8	57
	HOSP	1094	1095	934	311	311	335	1332	2680	17745
	BPMR	1094	3	0	0	0	0	0	0	501
	PHARMA	1094	164	113	1	4	22	178	371	7567
	IMPL	1094	1	0	0	0	0	0	0	366
	DELIVER	1094	480	387	108	209	284	554	973	9633
	CM&NM	1094	47	35	0	2	21	57	118	1328
	TOTAL	1094	1802	1351	504	598	877	2105	4041	33529
[36,56[	Hospitalization days	822	5	4	1	1	2	6	13	75
	HOSP	822	1626	1273	311	311	655	1965	4047	23792
	BPMR	822	15	0	0	0	0	0	77	2483
	PHARMA	822	286	148	1	5	48	218	602	40500
	IMPL	822	5	0	0	0	0	0	0	1977
	DELIVER	822	671	515	160	236	363	758	1336	19347
	CM&NM	822	65	45	0	5	28	74	152	2209
	TOTAL	822	2678	1924	521	663	1178	3084	6188	76785
[56,70[	Hospitalization days	471	8	5	1	1	3	9	20	157
	HOSP	471	2521	1675	311	327	1005	2802	6226	48876
	BPMR	471	42	0	0	0	0	0	188	3643
	PHARMA	471	507	189	1	9	92	291	1543	51468
	IMPL	471	8	0	0	0	0	0	2	1507
	DELIVER	471	957	634	154	252	427	1001	2255	16926
	CM&NM	471	96	52	0	5	31	85	236	3160
	TOTAL	471	4145	2612	506	759	1661	4306	10348	118646



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[70,80[	Hospitalization days	501	11	7	1	1	4	13	29	183
	HOSP	501	3433	2345	311	335	1310	4138	9169	58254
	BPMR	501	29	0	0	0	0	0	180	3809
	PHARMA	501	389	193	1	13	104	322	1342	11410
	IMPL	501	20	0	0	0	0	0	2	3492
	DELIVER	501	1035	760	6	309	510	1159	2374	16606
	CM&NM	501	82	54	0	9	33	91	191	1945
	TOTAL	501	5001	3451	362	919	2107	5920	13669	64942
80+	Hospitalization days	511	13	10	1	3	6	16	32	101
	HOSP	511	4352	3351	311	934	2010	5292	10585	33170
	BPMR	511	28	0	0	0	0	0	200	995
	PHARMA	511	352	211	1	19	139	331	1176	5387
	IMPL	511	38	0	0	0	0	0	2	5933
	DELIVER	511	1128	891	136	369	615	1331	2484	11204
	CM&NM	511	80	59	0	11	35	95	197	1229
	TOTAL	511	5991	4592	529	1386	3020	7368	14839	38277



Table 16 – Hospitalisation costs: Secondary (but not primary) diagnosis influenza

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	5140	11	6	1	1	3	11	36	358
	HOSP	5140	3415	1910	193	335	1005	3686	11461	119189
	BPMR	5140	96	0	0	0	0	0	200	54989
	PHARMA	5140	7	4	1	1	2	7	22	222
	IMPL	5140	83	0	0	0	0	0	224	18224
	DELIVER	5140	1296	732	17	278	488	1213	3816	90439
	CM&NM	5140	103	42	0	3	21	81	276	10700
	TOTAL	5140	5015	2766	223	774	1615	5191	16119	230551
<=1	Hospitalization days	660	8	6	1	2	4	8	19	168
	HOSP	660	2610	1868	311	623	1245	2680	5973	55932
	BPMR	660	23	0	0	0	0	0	39	4592
	PHARMA	660	5	4	1	1	2	5	11	104
	IMPL	660	7	0	0	0	0	0	0	1420
	DELIVER	660	1104	696	200	324	501	932	2489	35691
	CM&NM	660	78	26	0	0	14	50	181	3126
	TOTAL	660	3839	2617	584	984	1701	3753	9451	95822
[2,6[	Hospitalization days	936	6	4	1	2	3	6	13	103
	HOSP	936	1833	1340	311	623	955	2010	4356	34511
	BPMR	936	16	0	0	0	0	0	40	2812
	PHARMA	936	4	2	1	1	2	4	8	64
	IMPL	936	16	0	0	0	0	0	0	4426
	DELIVER	936	799	594	178	317	457	773	1504	21908
	CM&NM	936	55	27	0	2	16	44	121	4068
	TOTAL	936	2734	2021	504	917	1412	2920	6213	61477
[6,16[	Hospitalization days	370	5	3	1	1	2	6	11	79
	HOSP	370	1582	1005	311	327	655	1868	3686	26469
	BPMR	370	23	0	0	0	0	0	20	4200
	PHARMA	370	3	2	1	1	1	4	7	49
	IMPL	370	7	0	0	0	0	0	0	1477



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	370	639	484	145	249	353	675	1248	11156
	CM&NM	370	39	29	0	4	16	43	100	1092
	TOTAL	370	2303	1684	485	620	1065	2566	5231	30780
	Hospitalization days	713	6	4	1	1	2	6	15	97
	HOSP	713	1823	1273	311	318	655	1965	4981	30197
	BPMR	713	124	0	0	0	0	0	40	54989
	PHARMA	713	3	2	1	1	1	4	9	60
	IMPL	713	36	0	0	0	0	0	3	8692
	DELIVER	713	832	529	68	214	336	865	1877	33542
	CM&NM	713	78	34	0	2	19	65	162	8628
[36,56[	TOTAL	713	2909	1815	397	586	1084	2886	7510	128432
	Hospitalization days	718	10	6	1	1	3	11	33	155
	HOSP	718	3117	1868	311	327	955	3424	10273	48253
	BPMR	718	185	0	0	0	0	0	201	47150
	PHARMA	718	6	4	1	1	2	7	20	96
	IMPL	718	61	0	0	0	0	0	330	3011
	DELIVER	718	1335	750	170	255	482	1255	3854	36520
	CM&NM	718	126	53	0	2	25	103	377	4209
	TOTAL	718	4846	2734	508	624	1598	5052	15249	94274
[56,70[	Hospitalization days	562	14	9	1	2	5	16	45	291
	HOSP	562	4617	2802	311	623	1592	4981	14742	97501
	BPMR	562	247	0	0	0	0	38	800	20184
	PHARMA	562	9	6	1	1	3	10	28	180
	IMPL	562	228	0	0	0	0	0	1490	18224
	DELIVER	562	2261	1032	48	354	664	1813	7421	90439
	CM&NM	562	214	65	0	9	33	129	691	10700
	TOTAL	562	7599	4048	383	970	2442	7538	22837	230551
[70,80[	Hospitalization days	600	18	12	1	2	7	22	49	358
	HOSP	600	5646	3736	193	670	2224	6934	15475	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	600	105	0	0	0	0	39	401	9661
	PHARMA	600	11	7	1	1	4	13	30	222
	IMPL	600	206	0	0	0	0	0	1464	11892
	DELIVER	600	1916	1172	17	393	802	2103	5685	29805
	CM&NM	600	146	72	0	10	40	124	499	4161
	TOTAL	600	8049	5336	223	1400	3226	9844	22192	152210
80+	Hospitalization days	581	22	16	1	3	10	28	58	175
	HOSP	581	6904	5093	311	1005	3015	8717	17765	55515
	BPMR	581	53	0	0	0	0	39	300	2887
	PHARMA	581	14	10	1	2	6	17	36	109
	IMPL	581	146	0	0	0	0	0	544	6790
	DELIVER	581	1681	1300	171	475	820	1967	4315	16786
	CM&NM	581	100	75	0	17	48	116	245	1440
	TOTAL	581	8913	6752	546	1833	4134	11359	21557	60855

**Table 17 – Hospitalisation costs: Primary or secondary diagnosis influenza**

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	14845	7	4	1	1	3	7	22	358
	HOSP	14845	2296	1340	193	327	934	2345	7036	119189
	BPMR	14845	39	0	0	0	0	0	75	54989
	PHARMA	14845	116	29	1	1	5	155	273	51468
	IMPL	14845	32	0	0	0	0	0	0	18224
	DELIVER	14845	877	588	6	258	414	851	2136	90439
	CM&NM	14845	65	32	0	2	18	58	159	10700
	TOTAL	14845	3435	2159	223	713	1397	3398	10075	230551
<=1	Hospitalization days	2481	6	5	1	2	3	7	12	168
	HOSP	2481	1930	1557	311	623	982	2228	4021	55932
	BPMR	2481	7	0	0	0	0	0	0	4592
	PHARMA	2481	79	39	1	1	5	152	209	1808
	IMPL	2481	3	0	0	0	0	0	0	1420
	DELIVER	2481	798	622	192	313	467	809	1335	35691
	CM&NM	2481	45	24	0	0	14	41	84	3126
	TOTAL	2481	2873	2254	528	960	1567	3124	5524	95822
[2,6[	Hospitalization days	4186	5	4	1	1	3	5	9	103
	HOSP	4186	1478	1273	311	335	934	1675	3015	34511
	BPMR	4186	7	0	0	0	0	0	0	9111
	PHARMA	4186	85	48	1	1	6	155	206	8423
	IMPL	4186	4	0	0	0	0	0	0	4426
	DELIVER	4186	636	551	6	301	428	711	1052	21908
	CM&NM	4186	37	25	0	2	15	38	72	6612
	TOTAL	4186	2257	1906	503	848	1413	2627	4240	61477
[6,16[	Hospitalization days	1605	4	3	1	1	2	4	8	79
	HOSP	1605	1192	982	311	318	655	1340	2680	26469
	BPMR	1605	6	0	0	0	0	0	0	4200
	PHARMA	1605	67	22	1	1	3	132	205	1020
	IMPL	1605	2	0	0	0	0	0	0	1477



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	1605	500	425	145	233	324	578	937	11156
	CM&NM	1605	30	24	0	2	15	38	69	1092
	TOTAL	1605	1805	1482	485	600	1012	2140	3799	30780
	Hospitalization days	1807	4	3	1	1	2	5	11	97
	HOSP	1807	1382	955	311	311	623	1637	3602	30197
	BPMR	1807	51	0	0	0	0	0	0	54989
	PHARMA	1807	101	15	1	1	2	149	250	7567
	IMPL	1807	15	0	0	0	0	0	0	8692
	DELIVER	1807	619	435	68	211	302	646	1325	33542
	CM&NM	1807	59	35	0	2	20	60	128	8628
	TOTAL	1807	2239	1514	397	595	962	2448	5298	128432
[36,56[	Hospitalization days	1540	7	4	1	1	2	8	23	155
	HOSP	1540	2321	1340	311	318	670	2547	7182	48253
	BPMR	1540	94	0	0	0	0	0	100	47150
	PHARMA	1540	155	15	1	1	3	157	367	40500
	IMPL	1540	31	0	0	0	0	0	73	3011
	DELIVER	1540	980	603	160	242	404	971	2454	36520
	CM&NM	1540	93	48	0	4	27	84	230	4209
	TOTAL	1540	3689	2269	508	649	1321	3820	10301	94274
	Hospitalization days	1033	11	7	1	1	4	12	33	291
	HOSP	1033	3661	2179	311	335	1273	3929	10585	97501
[56,70[	BPMR	1033	153	0	0	0	0	0	400	20184
	PHARMA	1033	236	14	1	1	4	175	546	51468
	IMPL	1033	128	0	0	0	0	0	467	18224
	DELIVER	1033	1666	837	48	283	531	1395	5343	90439
	CM&NM	1033	161	58	0	6	32	104	417	10700
	TOTAL	1033	6024	3285	383	882	2026	6103	18363	230551
[70,80[	Hospitalization days	1101	14	9	1	2	5	17	40	358
	HOSP	1101	4639	3015	193	623	1675	5412	12452	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	1101	71	0	0	0	0	0	244	9661
	PHARMA	1101	183	19	1	2	6	179	713	11410
	IMPL	1101	121	0	0	0	0	0	416	11892
	DELIVER	1101	1515	960	6	328	629	1618	4446	29805
	CM&NM	1101	117	63	0	10	35	110	333	4161
	TOTAL	1101	6662	4346	223	1105	2625	7593	18915	152210
80+	Hospitalization days	1092	18	13	1	3	8	22	51	175
	HOSP	1092	5710	4093	311	934	2490	7020	15877	55515
	BPMR	1092	41	0	0	0	0	0	204	2887
	PHARMA	1092	172	26	1	3	9	201	624	5387
	IMPL	1092	95	0	0	0	0	0	214	6790
	DELIVER	1092	1422	1078	136	405	695	1651	3752	16786
	CM&NM	1092	91	66	0	13	42	109	223	1440
	TOTAL	1092	7545	5598	529	1515	3441	9401	19569	60855



Table 18 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and pneumonia

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	5086	8	5	1	2	4	8	25	291
	HOSP	5086	2681	1675	193	637	1245	2680	8186	97501
	BPMR	5086	79	0	0	0	0	0	99	54989
	PHARMA	5086	159	64	1	2	11	171	346	40500
	IMPL	5086	29	0	0	0	0	0	0	18224
	DELIVER	5086	1101	682	6	353	517	934	2781	90439
	CM&NM	5086	90	32	0	3	17	59	246	10700
	TOTAL	5086	4153	2594	223	1099	1829	3788	11767	230551
<=1	Hospitalization days	1488	7	5	1	2	4	7	14	168
	HOSP	1488	2203	1675	311	637	1245	2345	4450	55932
	BPMR	1488	7	0	0	0	0	0	0	4305
	PHARMA	1488	91	58	1	2	9	161	228	1808
	IMPL	1488	4	0	0	0	0	0	0	1420
	DELIVER	1488	903	685	207	360	534	873	1459	35691
	CM&NM	1488	49	24	0	2	14	41	92	2880
	TOTAL	1488	3268	2602	572	1099	1873	3392	5981	95822
[2,6[	Hospitalization days	2135	5	4	1	2	3	6	11	103
	HOSP	2135	1671	1340	311	637	982	1965	3424	34511
	BPMR	2135	9	0	0	0	0	0	0	9111
	PHARMA	2135	101	71	1	2	18	167	228	5138
	IMPL	2135	3	0	0	0	0	0	0	2559
	DELIVER	2135	707	614	6	351	474	771	1184	21908
	CM&NM	2135	42	26	0	2	15	42	79	6612
	TOTAL	2135	2544	2205	545	1062	1636	2899	4752	61477
[6,16[	Hospitalization days	222	6	5	1	2	3	7	12	73
	HOSP	222	1900	1557	311	623	1005	2179	3736	24991
	BPMR	222	33	0	0	0	0	0	0	4200
	PHARMA	222	101	69	1	1	6	163	273	850
	IMPL	222	11	0	0	0	0	0	0	1477

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	DELIVER	222	755	593	214	308	431	777	1437	11156
	CM&NM	222	46	31	0	2	16	49	120	1092
	TOTAL	222	2856	2272	533	959	1697	3033	5569	30780
[16,36[	Hospitalization days	176	8	6	1	2	3	9	26	97
	HOSP	176	2687	1772	311	623	982	2802	8094	30197
	BPMR	176	487	0	0	0	0	0	301	54989
	PHARMA	176	290	131	1	1	7	236	990	7567
	IMPL	176	45	0	0	0	0	0	61	2923
	DELIVER	176	1430	634	211	277	461	1151	5136	33542
	CM&NM	176	190	59	0	12	33	104	527	8628
	TOTAL	176	5151	2698	667	924	1657	4482	14177	128432
[36,56[	Hospitalization days	276	11	7	1	2	5	12	42	87
	HOSP	276	3634	2345	311	655	1557	3820	13688	27695
	BPMR	276	427	0	0	0	0	39	770	47150
	PHARMA	276	439	96	1	2	7	247	1169	40500
	IMPL	276	25	0	0	0	0	0	125	1011
	DELIVER	276	1724	866	241	383	592	1356	5766	36520
	CM&NM	276	212	71	0	17	41	139	930	4041
	TOTAL	276	6485	3576	777	1303	2376	5754	22053	94274
[56,70[	Hospitalization days	240	20	11	1	3	6	22	64	291
	HOSP	240	6421	3502	318	944	1988	7003	20381	97501
	BPMR	240	408	0	0	0	0	59	1663	16777
	PHARMA	240	425	41	1	2	9	236	1846	23021
	IMPL	240	262	0	0	0	0	0	1360	18224
	DELIVER	240	3288	1173	154	398	774	2507	13707	90439
	CM&NM	240	400	90	0	23	57	248	1951	10700
	TOTAL	240	11241	5143	506	1501	3192	10841	45092	230551
[70,80[	Hospitalization days	282	18	13	1	3	8	23	49	138
	HOSP	282	5844	4198	193	982	2538	7371	15598	43777



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	282	156	0	0	0	0	41	673	9661
	PHARMA	282	335	28	1	3	9	264	1519	11410
	IMPL	282	130	0	0	0	0	0	611	11892
	DELIVER	282	2168	1246	17	469	847	2220	7367	20016
	CM&NM	282	222	99	0	18	54	180	707	4161
	TOTAL	282	8879	6066	223	1791	3711	10555	24562	60540
80+	Hospitalization days	267	21	16	1	4	9	26	55	138
	HOSP	267	6378	5026	327	1340	3015	8186	16083	43777
	BPMR	267	75	0	0	0	0	59	402	2887
	PHARMA	267	253	34	1	4	11	240	1032	5387
	IMPL	267	66	0	0	0	0	0	186	5683
	DELIVER	267	1688	1205	281	464	785	1858	4315	16786
	CM&NM	267	129	81	0	19	48	147	375	1440
	TOTAL	267	8607	6772	644	2148	4026	10720	19928	55000


Table 19 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and pneumococcal pneumonia

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	79	13	8	2	3	5	16	44	112
	HOSP	79	4303	2490	623	982	1592	5239	14325	35653
	BPMR	79	129	0	0	0	0	0	523	5643
	PHARMA	79	80	7	1	2	4	28	233	3235
	IMPL	79	32	0	0	0	0	0	172	1490
	DELIVER	79	2181	899	367	450	692	1719	7878	29270
	CM&NM	79	272	70	6	14	33	218	1799	4218
	TOTAL	79	7025	3550	1141	1457	2465	7510	24876	73488
<=1	Hospitalization days	16	10	7	3	3	5	10	34	34
	HOSP	16	3079	2099	982	982	1574	3183	10823	10823
	BPMR	16	10	0	0	0	0	0	116	116
	PHARMA	16	68	8	2	2	4	72	580	580
	IMPL	16	12	0	0	0	0	0	187	187
	DELIVER	16	1362	870	450	450	674	1035	4876	4876
	CM&NM	16	126	43	14	14	25	66	900	900
	TOTAL	16	4673	3082	1457	1457	2357	4333	16523	16523
[2,6[	Hospitalization days	28	7	6	2	3	5	8	14	18
	HOSP	28	2190	1889	623	1005	1557	2490	4691	5894
	BPMR	28	4	0	0	0	0	0	0	100
	PHARMA	28	43	4	1	2	3	40	233	243
	IMPL	28	0	0	0	0	0	0	0	0
	DELIVER	28	958	740	450	491	638	949	2196	4085
	CM&NM	28	73	56	9	14	25	83	253	314
	TOTAL	28	3281	2856	1141	1624	2313	3543	7943	9155
[6,16[	Hospitalization days	5	6	6	3	3	4	7	11	11
	HOSP	5	2007	2010	934	934	1310	2179	3602	3602
	BPMR	5	0	0	0	0	0	0	0	0
	PHARMA	5	68	7	2	2	4	147	180	180
	IMPL	5	0	0	0	0	0	0	0	0

[illegible]



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	1	0	0	0	0	0	0	0	0
	PHARMA	1	7	7	7	7	7	7	7	7
	IMPL	1	0	0	0	0	0	0	0	0
	DELIVER	1	892	892	892	892	892	892	892	892
	CM&NM	1	144	144	144	144	144	144	144	144
	TOTAL	1	4661	4661	4661	4661	4661	4661	4661	4661
80+	Hospitalization days	4	19	19	15	15	16	22	23	23
	HOSP	4	6066	6084	4775	4775	5034	7099	7322	7322
	BPMR	4	60	0	0	0	0	120	240	240
	PHARMA	4	12	12	9	9	10	14	14	14
	IMPL	4	30	0	0	0	0	60	121	121
	DELIVER	4	2071	1696	1572	1572	1591	2551	3322	3322
	CM&NM	4	243	153	97	97	101	385	568	568
	TOTAL	4	8508	8285	6518	6518	6872	10144	10944	10944



Table 20 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and asthma

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	642	8	5	1	2	3	8	19	358
	HOSP	642	2535	1675	311	623	1005	2620	6048	119189
	BPMR	642	20	0	0	0	0	0	41	4200
	PHARMA	642	119	20	1	1	4	160	325	7567
	IMPL	642	9	0	0	0	0	0	0	2535
	DELIVER	642	876	648	108	323	489	894	1729	29805
	CM&NM	642	58	35	0	3	20	62	160	1393
	TOTAL	642	3629	2504	536	1025	1653	3719	8586	152210
<=1	Hospitalization days	71	6	6	2	2	4	8	12	25
	HOSP	71	1990	1868	623	655	1245	2547	3766	7958
	BPMR	71	2	0	0	0	0	0	0	41
	PHARMA	71	73	30	1	2	4	151	206	254
	IMPL	71	0	0	0	0	0	0	0	0
	DELIVER	71	716	644	323	370	495	861	1300	2525
	CM&NM	71	39	32	0	8	20	50	79	249
	TOTAL	71	2830	2624	1040	1242	1812	3466	5142	10780
[2,6[	Hospitalization days	213	5	4	1	2	3	6	9	46
	HOSP	213	1559	1310	311	637	982	1965	2802	15063
	BPMR	213	1	0	0	0	0	0	0	41
	PHARMA	213	66	25	1	1	3	111	216	342
	IMPL	213	0	0	0	0	0	0	0	22
	DELIVER	213	662	606	214	350	474	760	1110	5073
	CM&NM	213	36	25	0	3	16	38	64	1393
	TOTAL	213	2334	2082	559	1053	1514	2869	4004	21675
[6,16[	Hospitalization days	78	5	4	1	2	3	6	12	16
	HOSP	78	1576	1310	311	623	934	1965	3736	5093
	BPMR	78	55	0	0	0	0	0	0	4200
	PHARMA	78	82	16	1	1	3	156	273	1020
	IMPL	78	19	0	0	0	0	0	0	1477



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	78	736	567	243	297	396	703	1248	11156
	CM&NM	78	46	29	0	2	17	44	77	1092
	TOTAL	78	2525	1889	566	994	1448	2871	5387	21232
	Hospitalization days	80	5	4	1	1	2	7	14	34
	HOSP	80	1705	1245	311	311	670	2179	4487	10823
	BPMR	80	5	0	0	0	0	0	19	200
	PHARMA	80	214	15	1	1	2	167	397	7567
	IMPL	80	5	0	0	0	0	0	0	351
	DELIVER	80	697	558	108	238	408	757	1775	5465
	CM&NM	80	64	40	0	0	23	70	182	814
[36,56[	TOTAL	80	2702	1732	545	751	1315	3259	6330	24760
	Hospitalization days	60	8	6	1	2	5	9	23	42
	HOSP	60	2599	1910	318	646	1592	2940	7005	13370
	BPMR	60	8	0	0	0	0	0	49	77
	PHARMA	60	103	7	1	1	4	183	413	817
	IMPL	60	0	0	0	0	0	0	0	0
	DELIVER	60	798	691	193	373	532	996	1422	2437
	CM&NM	60	57	48	0	0	27	70	145	226
	TOTAL	60	3575	2809	536	1144	2203	4119	8019	16130
[56,70[	Hospitalization days	58	9	8	1	2	6	12	20	39
	HOSP	58	3015	2418	311	623	1868	3736	6226	12141
	BPMR	58	14	0	0	0	0	0	80	400
	PHARMA	58	125	8	1	1	4	176	502	1551
	IMPL	58	46	0	0	0	0	0	60	2535
	DELIVER	58	1099	860	248	312	643	1314	2263	5343
	CM&NM	58	86	70	0	0	35	103	279	387
	TOTAL	58	4398	3811	578	975	2498	5695	8815	14106
[70,80[	Hospitalization days	43	25	11	1	2	6	21	53	358
	HOSP	43	8081	3686	335	623	1965	6876	16871	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	43	118	0	0	0	0	0	200	2822
	PHARMA	43	221	21	2	4	7	251	827	2543
	IMPL	43	25	0	0	0	0	0	125	611
	DELIVER	43	2130	1028	264	369	662	1564	4050	29805
	CM&NM	43	146	75	6	22	43	139	544	1307
	TOTAL	43	10741	5263	845	1447	3118	8606	20288	152210
80+	Hospitalization days	39	17	12	1	6	10	19	61	74
	HOSP	39	5553	3736	335	1868	3113	6048	18990	23037
	BPMR	39	30	0	0	0	0	0	200	342
	PHARMA	39	269	50	1	4	7	218	1614	4283
	IMPL	39	3	0	0	0	0	0	2	108
	DELIVER	39	1391	1123	224	396	736	1518	3979	4433
	CM&NM	39	97	75	0	0	32	116	332	540
	TOTAL	39	7357	5280	594	2392	4052	8735	22202	25753


Table 21 – Hospitalisation costs: Combined diagnosis (primary or secondary) of influenza and cardiovascular disease

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	742	14	9	1	2	5	17	42	155
	HOSP	742	4405	2865	311	623	1637	5292	13324	48269
	BPMR	742	64	0	0	0	0	0	244	6099
	PHARMA	742	267	18	1	2	6	173	538	51468
	IMPL	742	88	0	0	0	0	0	275	6325
	DELIVER	742	1556	920	6	325	559	1564	4580	36520
	CM&NM	742	132	70	0	13	41	123	387	4208
	TOTAL	742	6528	4237	536	1050	2434	7479	18800	118646
<=1	Hospitalization days	1	5	5	5	5	5	5	5	5
	HOSP	1	1675	1675	1675	1675	1675	1675	1675	1675
	BPMR	1	0	0	0	0	0	0	0	0
	PHARMA	1	3	3	3	3	3	3	3	3
	IMPL	1	0	0	0	0	0	0	0	0
	DELIVER	1	951	951	951	951	951	951	951	951
	CM&NM	1	88	88	88	88	88	88	88	88
	TOTAL	1	2728	2728	2728	2728	2728	2728	2728	2728
[2,6[	Hospitalization days	3	7	5	4	4	4	11	11	11
	HOSP	3	2156	1557	1310	1310	1310	3602	3602	3602
	BPMR	3	0	0	0	0	0	0	0	0
	PHARMA	3	123	100	7	7	7	261	261	261
	IMPL	3	0	0	0	0	0	0	0	0
	DELIVER	3	691	746	578	578	578	748	748	748
	CM&NM	3	65	68	23	23	23	105	105	105
	TOTAL	3	3047	2485	2181	2181	2181	4473	4473	4473
[6,16[	Hospitalization days	7	6	5	1	1	4	8	11	11
	HOSP	7	1936	1675	327	327	1340	2680	3424	3424
	BPMR	7	0	0	0	0	0	0	0	0
	PHARMA	7	4	3	1	1	2	5	7	7
	IMPL	7	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	7	618	613	224	224	546	775	922	922
	CM&NM	7	30	24	8	8	11	52	53	53
	TOTAL	7	2597	2392	571	571	1931	3669	4271	4271
	Hospitalization days	23	6	4	1	1	3	9	15	16
	HOSP	23	1957	1369	318	335	955	2802	4670	4981
	BPMR	23	2	0	0	0	0	0	0	39
	PHARMA	23	185	4	1	1	2	98	1174	1820
	IMPL	23	19	0	0	0	0	0	0	433
	DELIVER	23	612	430	215	229	310	888	1291	1650
	CM&NM	23	54	40	0	6	28	72	137	181
[36,56[	TOTAL	23	2840	1995	548	590	1523	4464	7108	8021
	Hospitalization days	98	12	6	1	1	4	11	50	155
	HOSP	98	3924	1889	311	335	1245	3686	15916	48253
	BPMR	98	92	0	0	0	0	39	400	4634
	PHARMA	98	529	13	1	1	4	160	386	40500
	IMPL	98	38	0	0	0	0	0	275	1381
	DELIVER	98	1853	762	187	242	431	1447	7550	36520
	CM&NM	98	184	70	0	12	36	159	930	3119
	TOTAL	98	6639	2918	536	698	1695	5354	30500	76785
[56,70[	Hospitalization days	187	12	7	1	1	4	14	43	141
	HOSP	187	3906	2345	311	335	1310	4584	14080	48269
	BPMR	187	115	0	0	0	0	0	546	6099
	PHARMA	187	371	12	1	1	5	155	363	51468
	IMPL	187	138	0	0	0	0	0	597	5128
	DELIVER	187	1867	849	201	302	514	1699	8410	19003
	CM&NM	187	174	67	0	9	40	120	824	4208
	TOTAL	187	6591	3526	580	941	2153	7152	22561	118646
[70,80[	Hospitalization days	233	13	10	1	2	6	17	37	72
	HOSP	233	4336	3113	311	655	1965	5292	11727	24124



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	233	39	0	0	0	0	0	200	1499
	PHARMA	233	171	23	1	3	7	193	546	3316
	IMPL	233	99	0	0	0	0	0	264	4522
	DELIVER	233	1398	959	6	370	594	1564	4333	10939
	CM&NM	233	111	72	0	14	43	113	358	2007
	TOTAL	233	6169	4454	658	1335	2852	7371	17714	38486
80+	Hospitalization days	190	18	14	1	3	8	22	48	105
	HOSP	190	5667	4584	335	1005	2490	7003	15598	33424
	BPMR	190	41	0	0	0	0	0	239	1420
	PHARMA	190	169	23	1	4	9	190	682	3309
	IMPL	190	63	0	0	0	0	0	10	6325
	DELIVER	190	1456	1130	224	454	720	1689	3877	15278
	CM&NM	190	105	76	4	19	48	127	313	722
	TOTAL	190	7516	5870	594	1904	3607	9055	19211	39794



Table 22 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and diabetes

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	742	14	9	1	2	5	17	42	155
	HOSP	742	4405	2865	311	623	1637	5292	13324	48269
	BPMR	742	64	0	0	0	0	0	244	6099
	PHARMA	742	267	18	1	2	6	173	538	51468
	IMPL	742	88	0	0	0	0	0	275	6325
	DELIVER	742	1556	920	6	325	559	1564	4580	36520
	CM&NM	742	132	70	0	13	41	123	387	4208
	TOTAL	742	6528	4237	536	1050	2434	7479	18800	118646
<=1	Hospitalization days	1	5	5	5	5	5	5	5	5
	HOSP	1	1675	1675	1675	1675	1675	1675	1675	1675
	BPMR	1	0	0	0	0	0	0	0	0
	PHARMA	1	3	3	3	3	3	3	3	3
	IMPL	1	0	0	0	0	0	0	0	0
	DELIVER	1	951	951	951	951	951	951	951	951
	CM&NM	1	88	88	88	88	88	88	88	88
	TOTAL	1	2728	2728	2728	2728	2728	2728	2728	2728
[2,6[	Hospitalization days	3	7	5	4	4	4	11	11	11
	HOSP	3	2156	1557	1310	1310	1310	3602	3602	3602
	BPMR	3	0	0	0	0	0	0	0	0
	PHARMA	3	123	100	7	7	7	261	261	261
	IMPL	3	0	0	0	0	0	0	0	0
	DELIVER	3	691	746	578	578	578	748	748	748
	CM&NM	3	65	68	23	23	23	105	105	105
	TOTAL	3	3047	2485	2181	2181	2181	4473	4473	4473
[6,16[	Hospitalization days	7	6	5	1	1	4	8	11	11
	HOSP	7	1936	1675	327	327	1340	2680	3424	3424
	BPMR	7	0	0	0	0	0	0	0	0
	PHARMA	7	4	3	1	1	2	5	7	7
	IMPL	7	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	7	618	613	224	224	546	775	922	922
	CM&NM	7	30	24	8	8	11	52	53	53
	TOTAL	7	2597	2392	571	571	1931	3669	4271	4271
	Hospitalization days	23	6	4	1	1	3	9	15	16
	HOSP	23	1957	1369	318	335	955	2802	4670	4981
	BPMR	23	2	0	0	0	0	0	0	39
	PHARMA	23	185	4	1	1	2	98	1174	1820
	IMPL	23	19	0	0	0	0	0	0	433
	DELIVER	23	612	430	215	229	310	888	1291	1650
	CM&NM	23	54	40	0	6	28	72	137	181
[36,56[	TOTAL	23	2840	1995	548	590	1523	4464	7108	8021
	Hospitalization days	98	12	6	1	1	4	11	50	155
	HOSP	98	3924	1889	311	335	1245	3686	15916	48253
	BPMR	98	92	0	0	0	0	39	400	4634
	PHARMA	98	529	13	1	1	4	160	386	40500
	IMPL	98	38	0	0	0	0	0	275	1381
	DELIVER	98	1853	762	187	242	431	1447	7550	36520
	CM&NM	98	184	70	0	12	36	159	930	3119
	TOTAL	98	6639	2918	536	698	1695	5354	30500	76785
[56,70[	Hospitalization days	187	12	7	1	1	4	14	43	141
	HOSP	187	3906	2345	311	335	1310	4584	14080	48269
	BPMR	187	115	0	0	0	0	0	546	6099
	PHARMA	187	371	12	1	1	5	155	363	51468
	IMPL	187	138	0	0	0	0	0	597	5128
	DELIVER	187	1867	849	201	302	514	1699	8410	19003
	CM&NM	187	174	67	0	9	40	120	824	4208
	TOTAL	187	6591	3526	580	941	2153	7152	22561	118646
[70,80[	Hospitalization days	233	13	10	1	2	6	17	37	72
	HOSP	233	4336	3113	311	655	1965	5292	11727	24124



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	233	39	0	0	0	0	0	200	1499
	PHARMA	233	171	23	1	3	7	193	546	3316
	IMPL	233	99	0	0	0	0	0	264	4522
	DELIVER	233	1398	959	6	370	594	1564	4333	10939
	CM&NM	233	111	72	0	14	43	113	358	2007
	TOTAL	233	6169	4454	658	1335	2852	7371	17714	38486
80+	Hospitalization days	190	18	14	1	3	8	22	48	105
	HOSP	190	5667	4584	335	1005	2490	7003	15598	33424
	BPMR	190	41	0	0	0	0	0	239	1420
	PHARMA	190	169	23	1	4	9	190	682	3309
	IMPL	190	63	0	0	0	0	0	10	6325
	DELIVER	190	1456	1130	224	454	720	1689	3877	15278
	CM&NM	190	105	76	4	19	48	127	313	722
	TOTAL	190	7516	5870	594	1904	3607	9055	19211	39794


Table 23 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and COPD

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	879	17	11	1	2	6	20	50	358
	HOSP	879	5434	3602	311	655	1965	6538	15877	119189
	BPMR	879	187	0	0	0	0	41	299	54989
	PHARMA	879	208	15	1	2	6	173	674	40500
	IMPL	879	186	0	0	0	0	0	1381	18224
	DELIVER	879	2130	1181	187	381	750	1969	6941	90439
	CM&NM	879	201	79	0	15	44	139	571	10700
	TOTAL	879	8368	5378	566	1250	3027	9312	23750	230551
<=1	Hospitalization days	8	20	19	3	3	7	31	42	42
	HOSP	8	6326	6101	982	982	2179	9848	13370	13370
	BPMR	8	216	160	0	0	6	296	806	806
	PHARMA	8	237	15	2	2	7	21	1808	1808
	IMPL	8	318	17	0	0	0	543	1420	1420
	DELIVER	8	7184	6443	756	756	2639	9920	18713	18713
	CM&NM	8	1116	593	45	45	361	2047	2880	2880
	TOTAL	8	15509	13262	2388	2388	7363	24013	32410	32410
[2,6[	Hospitalization days	6	30	13	1	1	11	37	103	103
	HOSP	6	9868	4314	327	327	3424	12318	34511	34511
	BPMR	6	574	86	0	0	0	462	2812	2812
	PHARMA	6	77	43	7	7	7	159	200	200
	IMPL	6	782	56	0	0	0	2024	2559	2559
	DELIVER	6	7520	3180	692	692	1428	14728	21908	21908
	CM&NM	6	1198	566	9	9	89	1889	4068	4068
	TOTAL	6	20107	7724	1195	1195	6213	36310	61477	61477
[6,16[	Hospitalization days	3	7	9	3	3	3	10	10	10
	HOSP	3	2355	2947	934	934	934	3183	3183	3183
	BPMR	3	1461	184	0	0	0	4200	4200	4200
	PHARMA	3	5	6	2	2	2	6	6	6
	IMPL	3	492	0	0	0	0	1477	1477	1477



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	3	4537	2093	361	361	361	11156	11156	11156
	CM&NM	3	409	112	23	23	23	1092	1092	1092
	TOTAL	3	9306	5356	1330	1330	1330	21232	21232	21232
	Hospitalization days	21	13	5	1	2	4	7	70	97
	HOSP	21	3971	1637	335	637	1245	2292	22206	30197
	BPMR	21	3200	0	0	0	0	0	12118	54989
	PHARMA	21	42	4	1	2	2	43	173	288
	IMPL	21	267	0	0	0	0	0	2383	2923
	DELIVER	21	3711	850	218	284	634	1477	24301	33542
	TOTAL	21	657	84	12	30	56	122	3328	8628
[36,56[	Hospitalization days	76	10	6	1	2	4	12	27	80
	HOSP	76	3183	1937	318	623	1245	3929	8595	26804
	BPMR	76	100	0	0	0	0	53	100	5817
	PHARMA	76	605	8	1	1	2	125	373	40500
	IMPL	76	155	0	0	0	0	0	1381	3011
	DELIVER	76	1789	982	302	352	659	1713	7906	19347
	CM&NM	76	166	69	9	19	39	121	377	2827
	TOTAL	76	6017	3440	866	1099	2029	5561	17731	76785
[56,70[	Hospitalization days	169	16	9	1	2	5	16	47	291
	HOSP	169	5186	2802	318	623	1637	5239	14742	97501
	BPMR	169	287	0	0	0	0	54	825	13066
	PHARMA	169	99	10	1	1	4	94	468	1689
	IMPL	169	457	0	0	0	0	0	3297	18224
	DELIVER	169	2858	1238	187	428	721	2264	7172	90439
	CM&NM	169	312	76	0	15	42	161	873	10700
	TOTAL	169	9227	4567	774	1197	2567	8592	28115	230551
[70,80[	Hospitalization days	275	17	12	1	2	7	20	45	358
	HOSP	275	5449	3686	311	637	2179	6538	14325	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	275	74	0	0	0	0	41	224	2810
	PHARMA	275	215	17	1	2	6	193	1182	3410
	IMPL	275	146	0	0	0	0	0	1369	6790
	DELIVER	275	2068	1201	193	344	788	2072	7710	29805
	CM&NM	275	169	83	0	9	42	148	650	3942
	TOTAL	275	8141	5390	566	1179	3245	9312	21916	152210
80+	Hospitalization days	321	19	14	1	3	8	23	55	101
	HOSP	321	6104	4358	311	955	2680	7322	17682	32294
	BPMR	321	35	0	0	0	0	39	201	500
	PHARMA	321	179	20	1	2	9	203	659	4895
	IMPL	321	62	0	0	0	0	0	122	5933
	DELIVER	321	1529	1184	224	397	761	1816	3811	11204
	CM&NM	321	104	78	0	20	47	125	250	1229
	TOTAL	321	8028	6147	594	1659	3793	10046	22366	36776



Table 24 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and hypertension

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	1378	15	9	1	2	5	17	44	358
	HOSP	1378	4708	2865	311	623	1637	5604	14125	119189
	BPMR	1378	87	0	0	0	0	0	264	16777
	PHARMA	1378	249	19	1	2	6	179	654	51468
	IMPL	1378	128	0	0	0	0	0	396	18224
	DELIVER	1378	1707	984	176	332	605	1649	4934	90439
	CM&NM	1378	145	67	0	11	37	116	412	10700
	TOTAL	1378	7042	4213	513	982	2468	7776	19570	230551
<=1	Hospitalization days	5	61	55	9	9	23	86	134	134
	HOSP	5	19764	17122	3015	3015	7296	26773	44613	44613
	BPMR	5	1014	141	39	39	117	181	4592	4592
	PHARMA	5	273	83	6	6	34	585	660	660
	IMPL	5	74	0	0	0	0	4	368	368
	DELIVER	5	7198	6569	5889	5889	5955	8173	9404	9404
	CM&NM	5	1216	603	411	411	521	1418	3126	3126
	TOTAL	5	29623	28650	14582	14582	16828	36214	51838	51838
[2,6[	Hospitalization days	2	5	5	4	4	4	5	5	5
	HOSP	2	1448	1448	1340	1340	1340	1557	1557	1557
	BPMR	2	0	0	0	0	0	0	0	0
	PHARMA	2	59	59	2	2	2	116	116	116
	IMPL	2	0	0	0	0	0	0	0	0
	DELIVER	2	715	715	585	585	585	846	846	846
	CM&NM	2	35	35	30	30	30	40	40	40
	TOTAL	2	2267	2267	1976	1976	1976	2558	2558	2558
[6,16[	Hospitalization days	7	5	4	2	2	2	5	14	14
	HOSP	7	1608	1340	623	623	637	1675	4691	4691
	BPMR	7	0	0	0	0	0	0	0	0
	PHARMA	7	157	39	1	1	1	259	544	544
	IMPL	7	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	7	880	752	336	336	397	1185	1738	1738
	CM&NM	7	67	74	16	16	31	102	120	120
	TOTAL	7	2723	2343	999	999	1062	3168	7058	7058
	Hospitalization days	25	5	5	1	1	2	6	12	24
	HOSP	25	1682	1592	318	318	655	1965	3736	8041
	BPMR	25	12	0	0	0	0	0	0	301
	PHARMA	25	107	15	1	1	2	162	289	754
	IMPL	25	0	0	0	0	0	0	0	0
	DELIVER	25	783	540	215	299	437	676	2912	3830
	CM&NM	25	90	57	6	12	28	97	412	440
[36,56[	TOTAL	25	2686	2386	548	690	1083	3038	6969	12322
	Hospitalization days	164	12	6	1	1	3	12	48	108
	HOSP	164	3798	1886	311	327	994	3929	14961	35365
	BPMR	164	122	0	0	0	0	0	638	4986
	PHARMA	164	375	15	1	1	5	156	367	40500
	IMPL	164	70	0	0	0	0	0	333	2635
	DELIVER	164	1774	856	176	272	515	1435	7878	26620
	CM&NM	164	198	72	0	15	37	138	698	4209
	TOTAL	164	6360	3018	513	759	1766	5980	24876	76785
[56,70[	Hospitalization days	325	13	7	1	2	4	13	44	291
	HOSP	325	4199	2228	311	623	1310	4356	14325	97501
	BPMR	325	159	0	0	0	0	0	500	16777
	PHARMA	325	383	11	1	1	4	147	554	51468
	IMPL	325	161	0	0	0	0	0	447	18224
	DELIVER	325	2104	876	187	333	558	1596	6968	90439
	CM&NM	325	216	64	0	10	34	128	691	10700
	TOTAL	325	7244	3331	538	948	2121	6420	23598	230551
[70,80[	Hospitalization days	432	14	9	1	2	5	17	35	358
	HOSP	432	4402	2860	311	623	1675	5292	11207	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	432	62	0	0	0	0	0	244	3164
	PHARMA	432	197	19	1	2	6	190	765	8434
	IMPL	432	152	0	0	0	0	0	500	11892
	DELIVER	432	1621	1005	215	322	626	1639	4810	29805
	CM&NM	432	115	63	0	9	35	106	414	2108
	TOTAL	432	6564	4174	553	1026	2639	7558	18880	152210
80+	Hospitalization days	418	18	14	1	3	8	22	54	105
	HOSP	418	5846	4670	311	982	2490	7036	15877	33424
	BPMR	418	40	0	0	0	0	0	200	2887
	PHARMA	418	159	26	1	3	9	201	606	3309
	IMPL	418	110	0	0	0	0	0	379	6131
	DELIVER	418	1471	1148	214	413	725	1706	3824	16786
	CM&NM	418	92	69	0	14	44	109	213	1440
	TOTAL	418	7731	6210	594	1558	3532	9424	18703	43933


Table 25 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and stroke

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	419	19	14	1	3	8	23	56	175
	HOSP	419	6123	4457	311	934	2490	7371	17765	55515
	BPMR	419	87	0	0	0	0	20	244	9111
	PHARMA	419	172	16	1	2	8	143	901	5387
	IMPL	419	131	0	0	0	0	0	273	6790
	DELIVER	419	2039	1292	217	414	815	2114	6662	37863
	CM&NM	419	178	72	0	8	43	127	501	8180
	TOTAL	419	8749	6388	662	1469	3495	10312	26712	97676
<=1	Hospitalization days	5	9	10	4	4	9	11	12	12
	HOSP	5	2926	3113	1340	1340	3015	3424	3736	3736
	BPMR	5	918	0	0	0	0	0	4592	4592
	PHARMA	5	95	7	6	6	7	143	314	314
	IMPL	5	0	0	0	0	0	0	0	0
	DELIVER	5	1859	853	723	723	838	926	5955	5955
	CM&NM	5	648	41	0	0	19	57	3126	3126
	TOTAL	5	6481	4320	2444	2444	4210	4604	16828	16828
[2,6[	Hospitalization days	5	16	8	1	1	5	20	47	47
	HOSP	5	5343	2490	335	335	1592	6549	15748	15748
	BPMR	5	2029	0	0	0	0	1033	9111	9111
	PHARMA	5	1056	48	1	1	12	79	5138	5138
	IMPL	5	70	0	0	0	0	0	351	351
	DELIVER	5	3041	732	414	414	482	2410	11164	11164
	CM&NM	5	1459	44	17	17	21	602	6612	6612
	TOTAL	5	13067	3356	775	775	2152	11004	48047	48047
[6,16[	Hospitalization days	4	22	5	3	3	4	40	73	73
	HOSP	4	7331	1675	982	982	1161	13500	24991	24991
	BPMR	4	0	0	0	0	0	0	0	0
	PHARMA	4	67	24	2	2	3	132	218	218
	IMPL	4	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	4	1903	847	369	369	585	3220	5546	5546
	CM&NM	4	100	87	45	45	54	145	179	179
	TOTAL	4	9413	2614	1645	1645	1956	16871	30780	30780
	Hospitalization days	4	24	10	8	8	8	40	69	69
	HOSP	4	7979	3153	2490	2490	2555	13402	23119	23119
	BPMR	4	0	0	0	0	0	0	0	0
	PHARMA	4	95	72	7	7	25	165	229	229
	IMPL	4	158	0	0	0	0	315	631	631
	DELIVER	4	4358	1402	918	918	1121	7596	13712	13712
	CM&NM	4	595	56	28	28	41	1149	2240	2240
[36,56[	TOTAL	4	13217	4661	3702	3702	3970	22463	39842	39842
	Hospitalization days	23	15	11	1	2	4	21	47	67
	HOSP	23	4792	3502	335	637	1245	6538	14961	21328
	BPMR	23	142	0	0	0	0	0	200	2853
	PHARMA	23	169	11	1	1	4	42	570	2770
	IMPL	23	21	0	0	0	0	0	112	273
	DELIVER	23	2286	1277	238	302	800	2749	8215	11281
	CM&NM	23	191	73	34	39	66	124	565	1499
	TOTAL	23	7621	4783	934	1003	2532	8930	26383	33628
[56,70[	Hospitalization days	66	16	11	1	2	5	16	50	129
	HOSP	66	5136	3387	318	670	1637	5239	17117	43222
	BPMR	66	142	0	0	0	0	39	944	2269
	PHARMA	66	36	10	1	2	6	27	183	292
	IMPL	66	251	0	0	0	0	0	2594	6293
	DELIVER	66	3059	1259	217	297	595	2502	11991	37863
	CM&NM	66	353	73	0	13	43	141	1414	8180
	TOTAL	66	9006	4793	662	1180	2444	9060	30656	97676
[70,80[	Hospitalization days	129	18	14	1	3	8	23	51	71
	HOSP	129	5678	4358	311	982	2490	7160	17459	22601



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	129	30	0	0	0	0	19	155	662
	PHARMA	129	200	16	1	3	8	177	1143	3410
	IMPL	129	207	0	0	0	0	0	1143	6790
	DELIVER	129	1851	1280	268	478	909	1955	7050	10939
	CM&NM	129	126	74	0	7	39	123	454	1532
	TOTAL	129	8110	6415	752	1734	3495	9713	22557	38486
80+	Hospitalization days	183	22	17	1	4	10	27	54	175
	HOSP	183	7002	5292	318	1245	3183	8376	16811	55515
	BPMR	183	28	0	0	0	0	38	149	500
	PHARMA	183	184	20	1	4	10	179	932	5387
	IMPL	183	56	0	0	0	0	0	117	5683
	DELIVER	183	1701	1307	299	487	870	2013	4260	15278
	CM&NM	183	94	72	0	7	45	122	227	568
	TOTAL	183	9079	7131	676	1905	4146	11441	22799	60855



Table 26 – Hospitalisation costs: Combined diagnosis (primary or secondary) influenza and SRI

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	6458	9	5	1	2	4	9	28	358
	HOSP	6458	2829	1675	193	623	1245	2802	8913	119189
	BPMR	6458	70	0	0	0	0	0	100	54989
	PHARMA	6458	152	45	1	2	7	164	333	51468
	IMPL	6458	32	0	0	0	0	0	2	18224
	DELIVER	6458	1104	677	6	333	508	953	2853	90439
	CM&NM	6458	88	34	0	3	18	63	231	10700
	TOTAL	6458	4289	2577	223	1043	1796	3926	12841	230551
<=1	Hospitalization days	1720	7	5	1	2	4	7	14	168
	HOSP	1720	2164	1675	311	637	1245	2345	4446	55932
	BPMR	1720	7	0	0	0	0	0	0	4305
	PHARMA	1720	83	43	1	2	6	155	220	1808
	IMPL	1720	4	0	0	0	0	0	0	1420
	DELIVER	1720	886	676	207	347	520	862	1458	35691
	CM&NM	1720	49	24	0	0	14	42	93	2880
	TOTAL	1720	3204	2547	572	1055	1842	3367	5979	95822
[2,6[	Hospitalization days	2443	5	4	1	2	3	6	10	103
	HOSP	2443	1664	1340	311	623	982	1965	3423	34511
	BPMR	2443	9	0	0	0	0	0	0	9111
	PHARMA	2443	94	62	1	2	9	163	221	5138
	IMPL	2443	3	0	0	0	0	0	0	2559
	DELIVER	2443	701	606	6	341	471	761	1157	21908
	CM&NM	2443	42	26	0	2	16	42	79	6612
	TOTAL	2443	2524	2186	536	1044	1597	2874	4727	61477
[6,16[	Hospitalization days	378	5	4	1	1	3	6	11	73
	HOSP	378	1622	1310	311	335	955	1910	3602	24991
	BPMR	378	20	0	0	0	0	0	0	4200
	PHARMA	378	80	32	1	1	4	137	256	1020
	IMPL	378	6	0	0	0	0	0	0	1477



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	378	650	544	160	265	385	702	1245	11156
	CM&NM	378	41	31	0	3	17	46	104	1092
	TOTAL	378	2430	2015	533	809	1392	2735	5079	30780
	Hospitalization days	304	8	5	1	1	3	8	22	97
	HOSP	304	2485	1557	311	327	955	2547	7371	30197
	BPMR	304	285	0	0	0	0	0	100	54989
	PHARMA	304	231	43	1	1	4	190	748	7567
	IMPL	304	56	0	0	0	0	0	3	8692
	DELIVER	304	1156	593	202	255	413	988	2635	33542
	CM&NM	304	137	50	0	10	29	87	257	8628
[36,56[	TOTAL	304	4369	2319	547	757	1488	3831	12725	128432
	Hospitalization days	396	12	7	1	2	4	12	42	155
	HOSP	396	3723	2179	311	637	1340	3711	13753	48253
	BPMR	396	319	0	0	0	0	0	603	47150
	PHARMA	396	340	38	1	2	6	207	817	40500
	IMPL	396	27	0	0	0	0	0	199	1011
	DELIVER	396	1632	798	187	341	550	1273	5274	36520
	CM&NM	396	189	69	0	14	39	133	808	4209
	TOTAL	396	6251	3321	623	1176	2201	5383	21245	94274
[56,70[	Hospitalization days	353	18	10	1	3	6	20	56	291
	HOSP	353	5965	3351	318	934	1965	6226	18010	97501
	BPMR	353	345	0	0	0	0	41	1655	16777
	PHARMA	353	464	29	1	3	7	206	1537	51468
	IMPL	353	221	0	0	0	0	0	899	18224
	DELIVER	353	2900	1141	154	373	709	2177	12271	90439
	CM&NM	353	336	85	0	19	51	187	1710	10700
	TOTAL	353	10262	5035	506	1430	2947	9827	35888	230551
[70,80[	Hospitalization days	427	19	13	1	3	8	23	51	358
	HOSP	427	6120	4138	193	982	2490	7296	16871	119189



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	427	119	0	0	0	0	40	479	9661
	PHARMA	427	277	22	1	4	8	224	1182	11410
	IMPL	427	119	0	0	0	0	0	462	11892
	DELIVER	427	2058	1175	17	426	821	2044	7050	29805
	CM&NM	427	191	89	0	18	51	163	674	4161
	TOTAL	427	8907	5881	223	1734	3572	10239	23858	152210
80+	Hospitalization days	437	21	16	1	4	10	28	55	138
	HOSP	437	6689	5361	327	1245	3113	8717	16871	43777
	BPMR	437	60	0	0	0	0	40	301	2887
	PHARMA	437	205	22	1	4	10	203	901	5387
	IMPL	437	81	0	0	0	0	0	352	6790
	DELIVER	437	1704	1238	281	496	809	1967	4315	16786
	CM&NM	437	117	81	0	13	49	133	313	1440
	TOTAL	437	8872	7166	644	1984	4327	11387	20805	55000

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	29	10	6	1	1	3	12	49	58
	HOSP	29	3395	1910	327	335	982	3929	15544	19433
	BPMR	29	190	0	0	0	0	0	1457	2738
	PHARMA	29	118	14	1	1	4	147	616	817
	IMPL	29	51	0	0	0	0	0	0	1470
	DELIVER	29	1465	546	191	199	387	1062	6478	13456
	CM&NM	29	266	113	0	0	36	250	1350	2183
	TOTAL	29	5507	2855	551	689	1431	6118	23598	36606
<=1	Hospitalization days	0								
	HOSP	0								
	BPMR	0								
	PHARMA	0								
	IMPL	0								
	DELIVER	0								
	CM&NM	0								
	TOTAL	0								
[2,6[	Hospitalization days	0								
	HOSP	0								
	BPMR	0								
	PHARMA	0								
	IMPL	0								
	DELIVER	0								
	CM&NM	0								
	TOTAL	0								
[6,16[	Hospitalization days	1	3	3	3	3	3	3	3	3
	HOSP	1	934	934	934	934	934	934	934	934
	BPMR	1	0	0	0	0	0	0	0	0
	PHARMA	1	2	2	2	2	2	2	2	2
	IMPL	1	0	0	0	0	0	0	0	0

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	1	486	486	486	486	486	486	486	486
	CM&NM	1	0	0	0	0	0	0	0	0
	TOTAL	1	1429	1429	1429	1429	1429	1429	1429	1429
	Hospitalization days	3	4	4	3	3	3	4	4	4
	HOSP	3	1195	1310	934	934	934	1340	1340	1340
	BPMR	3	133	0	0	0	0	400	400	400
	PHARMA	3	19	17	2	2	2	38	38	38
	IMPL	3	0	0	0	0	0	0	0	0
[36,56[	DELIVER	3	2377	345	307	307	307	6478	6478	6478
	CM&NM	3	747	36	23	23	23	2183	2183	2183
	TOTAL	3	4509	1704	1325	1325	1325	10499	10499	10499
	Hospitalization days	18	8	5	1	1	3	12	22	22
	HOSP	18	2483	1592	327	327	934	3929	7204	7204
	BPMR	18	159	0	0	0	0	0	2738	2738
	PHARMA	18	157	33	1	1	4	227	817	817
	IMPL	18	0	0	0	0	0	0	0	0
[56,70[	DELIVER	18	666	530	191	191	307	1051	1381	1381
	CM&NM	18	125	79	0	0	32	250	298	298
	TOTAL	18	3606	2348	551	551	1303	5936	8914	8914
	Hospitalization days	5	27	20	3	3	7	49	58	58
	HOSP	5	9001	6701	982	982	2345	15544	19433	19433
	BPMR	5	451	0	0	0	0	800	1457	1457
	PHARMA	5	17	12	2	2	4	30	36	36
	IMPL	5	294	0	0	0	0	0	1470	1470
[70,80[	DELIVER	5	4357	1947	387	387	731	5267	13456	13456
	CM&NM	5	597	221	115	115	125	1173	1350	1350
	TOTAL	5	14764	8897	1512	1512	3208	23598	36606	36606
	Hospitalization days	1	6	6	6	6	6	6	6	6
	HOSP	1	2010	2010	2010	2010	2010	2010	2010	2010
	BPMR	1	10	10	10	10	10	10	10	10
	PHARMA	1	10	10	10	10	10	10	10	10
	IMPL	1	10	10	10	10	10	10	10	10

[illegible]



Table 28 – Hospitalisation costs: Influenza (primary or secondary) without any of the comorbidities above

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	6449	4	3	1	1	2	5	11	183
	HOSP	6449	1422	982	311	318	637	1592	3686	58254
	BPMR	6449	10	0	0	0	0	0	0	20184
	PHARMA	6449	81	22	1	1	3	147	220	8423
	IMPL	6449	14	0	0	0	0	0	0	5933
	DELIVER	6449	575	461	6	230	340	645	1195	14829
	CM&NM	6449	38	27	0	1	16	45	100	1745
	TOTAL	6449	2150	1581	362	618	1049	2367	5231	64942
<=1	Hospitalization days	742	4	3	1	1	2	5	10	84
	HOSP	742	1376	1005	311	335	670	1637	3275	28145
	BPMR	742	2	0	0	0	0	0	0	452
	PHARMA	742	70	31	1	1	4	147	190	1233
	IMPL	742	0	0	0	0	0	0	0	181
	DELIVER	742	583	503	192	279	388	651	1014	9963
	CM&NM	742	31	24	0	0	15	38	71	1498
	TOTAL	742	2072	1687	528	758	1198	2367	4366	40178
[2,6[	Hospitalization days	1667	4	3	1	1	2	4	7	62
	HOSP	1667	1198	1005	311	327	670	1340	2345	20302
	BPMR	1667	3	0	0	0	0	0	0	2195
	PHARMA	1667	75	30	1	1	4	147	190	8423
	IMPL	1667	5	0	0	0	0	0	0	4426
	DELIVER	1667	540	477	6	264	375	616	873	14829
	CM&NM	1667	29	22	0	0	14	34	59	1745
	TOTAL	1667	1859	1590	503	686	1180	2174	3369	32364
[6,16[	Hospitalization days	1160	3	3	1	1	2	4	7	79
	HOSP	1160	1035	934	311	318	623	1273	2204	26469
	BPMR	1160	1	0	0	0	0	0	0	416
	PHARMA	1160	62	19	1	1	3	133	193	758
	IMPL	1160	0	0	0	0	0	0	0	285



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	1160	445	397	145	229	302	526	782	3265
	CM&NM	1160	27	22	0	2	14	34	60	335
	TOTAL	1160	1579	1371	485	587	972	1839	3062	29773
	Hospitalization days	1379	3	3	1	1	1	4	8	44
	HOSP	1379	1109	934	311	311	335	1340	2680	13698
	BPMR	1379	3	0	0	0	0	0	0	687
	PHARMA	1379	74	14	1	1	2	143	216	2895
	IMPL	1379	6	0	0	0	0	0	0	5191
	DELIVER	1379	493	393	68	206	285	582	1066	4892
	CM&NM	1379	42	32	0	1	19	54	107	650
	TOTAL	1379	1738	1346	397	582	881	2158	3818	18110
[36,56[	Hospitalization days	865	5	3	1	1	2	6	13	75
	HOSP	865	1633	1005	311	311	623	1910	4356	23971
	BPMR	865	10	0	0	0	0	0	51	1097
	PHARMA	865	88	14	1	1	3	142	251	6065
	IMPL	865	27	0	0	0	0	0	2	2257
	DELIVER	865	671	501	160	220	349	763	1772	12874
	CM&NM	865	52	38	0	1	22	66	143	683
	TOTAL	865	2493	1750	508	610	1047	2892	7154	29618
	Hospitalization days	267	7	5	1	1	3	9	19	59
	HOSP	267	2192	1637	311	318	934	2802	6222	20198
[56,70[	BPMR	267	99	0	0	0	0	0	200	20184
	PHARMA	267	145	14	1	1	4	179	401	5661
	IMPL	267	26	0	0	0	0	0	46	2559
	DELIVER	267	831	662	48	234	429	994	1926	6538
	CM&NM	267	60	40	0	0	25	72	180	1035
	TOTAL	267	3364	2563	383	639	1467	4042	8406	46748
[70,80[	Hospitalization days	200	12	7	1	1	4	13	34	183
	HOSP	200	3832	2345	311	318	1245	4079	10815	58254



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	200	70	0	0	0	0	0	300	3809
	PHARMA	200	150	27	1	1	7	169	385	7759
	IMPL	200	119	0	0	0	0	0	755	3492
	DELIVER	200	1084	714	35	276	432	1160	3579	11694
	CM&NM	200	66	47	0	8	26	74	150	893
	TOTAL	200	5332	3241	362	725	1783	6054	16565	64942
80+	Hospitalization days	169	12	8	1	1	4	15	34	130
	HOSP	169	3875	2680	311	311	1340	4691	10585	43557
	BPMR	169	30	0	0	0	0	0	201	779
	PHARMA	169	171	63	1	2	9	224	543	3572
	IMPL	169	101	0	0	0	0	0	16	5933
	DELIVER	169	965	744	136	270	533	1178	2201	5369
	CM&NM	169	60	48	0	11	31	78	146	228
	TOTAL	169	5212	3659	529	689	2066	6170	13704	48422


Table 29 – Hospitalisation costs: Influenza (primary or secondary) without comorbidities for female patients

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	3209	5	3	1	1	2	5	12	130
	HOSP	3209	1509	1005	311	318	655	1637	4021	43557
	BPMR	3209	8	0	0	0	0	0	38	2243
	PHARMA	3209	79	18	1	1	3	141	224	8423
	IMPL	3209	16	0	0	0	0	0	0	5191
	DELIVER	3209	595	469	48	228	341	668	1275	14829
	CM&NM	3209	38	27	0	2	16	45	100	1745
	TOTAL	3209	2255	1638	383	624	1065	2470	5630	48422
<=1	Hospitalization days	312	4	3	1	1	2	5	10	37
	HOSP	312	1374	1005	311	327	670	1637	3351	11519
	BPMR	312	1	0	0	0	0	0	0	187
	PHARMA	312	69	31	1	1	4	146	191	375
	IMPL	312	1	0	0	0	0	0	0	181
	DELIVER	312	573	514	192	278	376	670	971	3364
	CM&NM	312	29	24	0	0	15	37	70	165
	TOTAL	312	2055	1719	528	731	1187	2411	4503	14527
[2,6[	Hospitalization days	757	4	3	1	1	2	4	7	62
	HOSP	757	1222	1005	311	335	670	1340	2345	20302
	BPMR	757	5	0	0	0	0	0	0	2195
	PHARMA	757	78	28	1	1	3	143	190	8423
	IMPL	757	6	0	0	0	0	0	0	4426
	DELIVER	757	556	490	178	284	391	614	865	14829
	CM&NM	757	31	22	0	1	14	33	59	1745
	TOTAL	757	1907	1651	503	751	1246	2141	3288	32364
[6,16[	Hospitalization days	521	3	3	1	1	2	4	7	31
	HOSP	521	1089	955	311	318	637	1310	2292	10151
	BPMR	521	1	0	0	0	0	0	0	100
	PHARMA	521	59	17	1	1	3	114	191	758
	IMPL	521	1	0	0	0	0	0	0	285



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[16,36[	DELIVER	521	458	403	181	232	318	531	846	3265
	CM&NM	521	28	22	0	2	13	34	66	335
	TOTAL	521	1645	1398	526	600	996	1888	3205	11936
	Hospitalization days	801	4	3	1	1	1	5	8	44
	HOSP	801	1170	934	311	311	335	1557	2680	13698
	BPMR	801	5	0	0	0	0	0	0	687
	PHARMA	801	63	7	1	1	2	118	214	1859
	IMPL	801	8	0	0	0	0	0	0	5191
	DELIVER	801	512	387	68	203	284	619	1142	4892
	CM&NM	801	40	29	0	2	18	50	100	650
[36,56[	TOTAL	801	1807	1386	397	582	890	2257	3989	18110
	Hospitalization days	441	5	4	1	1	2	7	15	75
	HOSP	441	1740	1245	311	311	623	2179	4670	23792
	BPMR	441	12	0	0	0	0	0	80	828
	PHARMA	441	94	15	1	1	3	140	255	6065
	IMPL	441	21	0	0	0	0	0	2	2257
	DELIVER	441	666	499	160	216	347	773	1785	4615
	CM&NM	441	53	36	0	1	18	64	149	683
	TOTAL	441	2597	1773	508	615	1047	3113	7212	26737
[56,70[	Hospitalization days	151	6	5	1	1	3	9	16	29
	HOSP	151	2035	1637	311	311	934	2802	5239	9496
	BPMR	151	15	0	0	0	0	0	81	201
	PHARMA	151	126	14	1	1	4	175	413	2378
	IMPL	151	34	0	0	0	0	0	17	2559
	DELIVER	151	803	664	48	228	418	994	1749	6538
	CM&NM	151	51	37	0	0	22	64	144	412
	TOTAL	151	3075	2553	383	592	1487	3900	8125	14031
[70,80[	Hospitalization days	112	12	7	1	1	4	12	34	86
	HOSP	112	3741	2345	311	327	1245	3820	10823	28815



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
	BPMR	112	56	0	0	0	0	0	300	2243
	PHARMA	112	78	20	1	1	6	147	239	745
	IMPL	112	144	0	0	0	0	0	1510	2561
	DELIVER	112	1137	719	203	274	417	1115	3707	11694
	CM&NM	112	59	46	0	6	22	68	126	522
	TOTAL	112	5226	3308	568	758	1869	5667	17308	33976
80+	Hospitalization days	114	13	10	1	1	5	16	34	130
	HOSP	114	4299	3064	311	311	1557	5361	10585	43557
	BPMR	114	28	0	0	0	0	0	201	448
	PHARMA	114	184	62	1	3	10	228	543	3572
	IMPL	114	97	0	0	0	0	0	447	4843
	DELIVER	114	1030	794	171	276	552	1257	2431	5369
	CM&NM	114	60	49	0	11	32	84	139	228
	TOTAL	114	5711	4246	546	689	2305	7203	14519	48422



Table 30 – Hospitalisation costs: Primary influenza and pregnancy complication

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	60	3	2	1	1	1	4	7	16
	HOSP	60	926	670	311	311	335	1125	2345	5093
	BPMR	60	3	0	0	0	0	0	0	205
	PHARMA	60	135	132	1	1	28	169	246	1722
	IMPL	60	0	0	0	0	0	0	0	0
	DELIVER	60	377	337	108	191	251	413	670	1597
	CM&NM	60	30	21	0	0	10	34	61	427
	TOTAL	60	1481	1088	521	619	765	1710	3190	9095
[6,16[	Hospitalization days	0								
	HOSP	0								
	BPMR	0								
	PHARMA	0								
	IMPL	0								
	DELIVER	0								
	CM&NM	0								
	TOTAL	0								
[16,36[	Hospitalization days	55	3	2	1	1	1	4	7	16
	HOSP	55	927	670	311	311	335	1245	2345	5093
	BPMR	55	4	0	0	0	0	0	0	205
	PHARMA	55	137	127	1	1	26	170	247	1722
	IMPL	55	0	0	0	0	0	0	0	0
	DELIVER	55	375	336	108	179	250	405	747	1597
	CM&NM	55	29	19	0	0	9	33	62	427
	TOTAL	55	1480	1058	521	614	747	1761	3173	9095
[36,56[	Hospitalization days	5	3	2	1	1	1	3	7	7
	HOSP	5	919	670	311	311	335	934	2345	2345
	BPMR	5	0	0	0	0	0	0	0	0
	PHARMA	5	117	140	7	7	67	169	205	205
	IMPL	5	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[56,70[	DELIVER	5	398	419	266	266	272	441	593	593
	CM&NM	5	40	34	22	22	32	55	58	58
	TOTAL	5	1484	1118	801	801	805	1490	3208	3208
	Hospitalization days	0								
	HOSP	0								
	BPMR	0								
	PHARMA	0								
	IMPL	0								
	DELIVER	0								
	CM&NM	0								
	TOTAL	0								

**Table 31 – Hospitalisation costs: Secondary influenza and pregnancy complication**

Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
All	Hospitalization days	190	3	3	1	1	2	4	7	37
	HOSP	190	1072	934	311	311	623	1310	2345	12116
	BPMR	190	1	0	0	0	0	0	0	200
	PHARMA	190	2	2	1	1	1	2	4	23
	IMPL	190	0	0	0	0	0	0	0	0
	DELIVER	190	389	326	68	187	261	450	740	2369
	CM&NM	190	25	23	0	2	11	35	64	103
	TOTAL	190	1498	1295	397	549	894	1723	3112	14602
[6,16[	Hospitalization days	1	3	3	3	3	3	3	3	3
	HOSP	1	934	934	934	934	934	934	934	934
	BPMR	1	0	0	0	0	0	0	0	0
	PHARMA	1	2	2	2	2	2	2	2	2
	IMPL	1	0	0	0	0	0	0	0	0
	DELIVER	1	422	422	422	422	422	422	422	422
	CM&NM	1	47	47	47	47	47	47	47	47
	TOTAL	1	1416	1416	1416	1416	1416	1416	1416	1416
[16,36[	Hospitalization days	168	3	3	1	1	2	4	8	37
	HOSP	168	1102	955	311	318	630	1310	2490	12116
	BPMR	168	1	0	0	0	0	0	0	200
	PHARMA	168	2	2	1	1	1	2	5	23
	IMPL	168	0	0	0	0	0	0	0	0
	DELIVER	168	393	326	68	191	261	458	740	2369
	CM&NM	168	25	23	0	2	11	33	63	103
	TOTAL	168	1532	1320	397	576	898	1738	3126	14602
[36,56[	Hospitalization days	21	3	2	1	1	1	3	6	6
	HOSP	21	838	670	311	311	335	1005	1868	2010
	BPMR	21	0	0	0	0	0	0	0	0
	PHARMA	21	2	1	1	1	1	2	4	4
	IMPL	21	0	0	0	0	0	0	0	0



Age category	Cost group	N	mean	median	min	p5	p25	p75	p95	max
[56,70[	DELIVER	21	354	345	170	178	252	405	663	742
	CM&NM	21	28	23	0	2	10	42	69	79
	TOTAL	21	1230	1077	508	530	619	1466	2627	2807
	Hospitalization days	0								
	HOSP	0								
	BPMR	0								
	PHARMA	0								
	IMPL	0								
	DELIVER	0								
	CM&NM	0								
	TOTAL	0								

