Supplementary online resource 2 linked to:

Title: Cost-utility of quadrivalent versus trivalent influenza vaccine in Germany, using an individual-based dynamic transmission model

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Online resource 2: Data inputs

In order to adapt a previous static model to the German context for this study, the required data were obtained from a targeted literature review and official government or statistics websites (e.g., for demographic and epidemiologic data). The search included English and German language papers and most recent and best quality studies were selected and used as a source for the model inputs shown in the tables below.

The input data used in the model were derived from published economic evaluations, national databases and government reports. Where no data for Germany were available, the published literature was used. The following sections report the probabilities, costs and outcomes used in the model. All cost data were expressed in 2014 price levels.

1. Probabilities

Probability of seeking medical advice (Table 1), receiving effective antiviral treatment (Table 2), having complications (Table 3, Table 4, Table 5, Table 6), being hospitalised (Table 7) and death due to influenza during hospitalisation (Table 8, Table 9) are provided below. In addition to these tables, the probability of visiting a general practitioner (GP) in case of seeking medical advice was estimated at 97%, The latter was reflected in the probabilistic sensitivity analysis (PSA) as:

1- Beta distribution (alpha = 8.35, beta = 261.76).

The 'At risk' population includes people at risk of complications due to influence influenza including people with one or more chronic conditions, people working in the health care or public order section (adults only), as well as people living in residential care (elderly only) [1].

2. Calculation of costs

2.1. Vaccinated individuals

Vaccinated individuals from the 4Flu-model were assigned vaccination costs, which included from the healthcare payer perspective:

- TIV or QIV vaccine price: A weighted mean price of O.24 was calculated from all TIV vaccines listed in the official price list (Lauer-Taxe, for December 2014), weighted by market share. The prices are published prices, not individually-negotiated (published or secret) prices, which can be much lower. The price for one dose QIV (calculated from a pack of 10) was set at O.24 was cal

- Vaccine administration costs are listed in Table 10.

From the societal perspective, vaccination costs included costs in the payer perspective as well as transportation costs for vaccine administration equalling 0.07 per vaccinated person for all age-groups and both vaccines [3,4].

2.2. Clinical influenza cases

Clinical symptomatic influenza cases resulting from 4Flu were assigned costs of managing influenza; based on the probability of an event (see Figure 4) multiplied by its associated cost. These costs from the payer perspective included:

- Reimbursable costs of visits for medical advice by a GP or at an accident and emergency (A/E) department (Table 11)
- Reimbursable antiviral and antibiotic costs (Table 11)
- Reimbursable inpatient (Table 12) and outpatient (Table 13) costs
- Costs borne by the child sickness benefit (Table 14), for parental absenteeism to care for a sick child (≤ 12 years of age). We conservatively assumed that only mothers would stay home and considered their age- and sex-specific net earnings corrected for the age- and sex-specific labour force participation and unemployment rates.

From the societal perspective, costs of managing influenza, in addition to payer perspective costs, included:

- Non-reimbursable antiviral and antibiotic costs (Table 15)
- Over-the-counter (OTC) medication (Table 15)
- Non-reimbursable hospitalisation (Table 16) and outpatient costs (estimated at € from 18 years of age)
- Transportation costs related to administration of antivirals, medical advice visits and outpatient treatment visits were estimated at ⊕.07 for all age-groups and all risk groups. Transportation costs related to hospitalisation were estimated at €1.47 for all age-groups and all risk groups [5].
- Absenteeism costs related to uncomplicated influenza and complications (Table 17). These indirect costs were calculated on the basis of the working days lost and the average net product per day which was estimated with the labour costs corrected for the respective labour force participation and unemployment rates. For uncomplicated or outpatient influenza cases, the loss of 2.6 working days was assumed [6]. For inpatient influenza cases, a loss of 8.8 working days for sick adults (4 days hospitalization + 4.8 days at home) and of 4.8 days for sick children (no work loss of parents during hospitalization, 4.8 days at home) was applied [6].

2.3. Influenza deaths

The loss of productivity due to influenza deaths was estimated using the present value of the future net product (Table 18). The future net product was estimated considering labour costs, labour force participation and unemployment rates as well as survival probabilities, by age and sex respectively. When using the human capital approach, the remaining life time was taken into account while in the friction cost method only the German friction time of 82 days was applied [7].

3. Calculation of health outcomes

3.1. Vaccinated individuals

No disutility due to vaccination was attributed.

3.2. Clinical influenza cases

Average utility decrements during an influenza episode were multiplied by duration of influenza symptoms to obtain the disutility associated with clinical influenza cases. Utility decrements were applied to these events:

- Uncomplicated influenza (Table 19)
- Hospitalisation for complicated influenza (Table 20)
- Outpatient treatment for complicated influenza (Table 20)

3.3. Influenza deaths

Finally, influenza deaths were assigned (QA)LYs lost due to premature mortality. These were calculated based on the age-specific life expectancy which in turn was calculated from the population all-cause mortality data (Table 9), assuming that all-cause mortality rates in the at-risk population were ten times the all-cause mortality rates in healthy individuals, and using the method described by the London Health Observatory[8]. These life expectancies were discounted and multiplied by age-dependent baseline utilities (Table 21) to obtain the qualityadjusted life expectancies.

Tables for probabilities

Age group (years)	0–4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+			
Healthy	20.23%	28.58%	28.58%	37.48%	16.39%	16.39%	16.39%	16.39%	16.39%			
At risk	37.48%	37.48%	37.48%	37.48%	37.48%	37.48%	37.48%	37.48%	37.48%			

 Table 1: Age-specific probabilities of seeking medical advice [9,10]

 Table 2: Age-specific probabilities of effective antiviral treatment in patients seeking medical advice
 [11,12]

Age group (years)	0–4	5–17	18–49	50–64	65–69	70–74	75–79	80–84	85+
Healthy	14.72%	14.72%	14.72%	14.72%	14.72%	14.72%	14.72%	14.72%	14.72%
At risk	19.63%	19.63%	19.63%	19.63%	19.63%	19.63%	19.63%	19.63%	19.63%

Table 3: Age-specific probability of influenza complication [13]

Age group (years)	0–4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
Healthy	14.05%	14.05%	7.61%	7.95%	10.34%	10.34%	10.34%	10.34%	10.34%
At risk	18.29%	18.29%	12.32%	12.59%	13.76%	13.76%	13.76%	13.76%	13.76%

Note: The relative risk of complication with antiviral treatment was assumed to be 100% of the relative risk without antiviral treatment

Table 4: Age-specific probability that an influenza complication is a respiratory complication [10]

Age group (years)	0–4	5–17	18–49	50-64	65–69	70–74	75–79	80–84	85+
Healthy	70.08%	70.08%	86.52%	86.52%	86.50%	86.50%	86.50%	86.50%	86.50%
At risk	76.51%	76.51%	89.41%	89.41%	82.60%	82.60%	82.60%	82.60%	82.60%

Note: All other complications (i.e. 100% – probability of respiratory complication) were defined as non-respiratory complications in the model

Table 5: Age-specific probability of a respiratory complication [10,13]

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Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+				
Probability of bronchitis complication													
Healthy	6.65%	6.65%	18.75%	18.75%	33.29%	33.29%	33.29%	33.29%	33.29%				
At risk	4.03%	4.03%	19.05%	19.05%	33.91%	33.91%	33.91%	33.91%	33.91%				
Probability of pneum	ionia comp	lication											
Healthy	1.71%	1.71%	4.20%	4.20%	12.93%	12.93%	12.93%	12.93%	12.93%				
At risk	1.73%	1.73%	3.19%	3.19%	12.85%	12.85%	12.85%	12.85%	12.85%				
Probability of upper	respiratory	y tract infe	ction comp	lication*									
Healthy	91.64%	91.64%	77.04%	77.04%	53.78%	53.78%	53.78%	53.78%	53.78%				
At risk	94.24%	94.24%	77.75%	77.75%	53.25%	53.25%	53.25%	53.25%	53.25%				

Note: *100% – Prob. of bronchitis complication – Prob. of pneumonia complication

Tuble of fige specific probability of non respiratory complications [10,15]											
Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+		
Probability of cardia	c complica	tion									
Healthy	0.00%	0.00%	1.48%	1.48%	7.03%	7.03%	7.03%	7.03%	7.03%		
At risk	0.00%	0.00%	12.61%	12.61%	37.11%	37.11%	37.11%	37.11%	37.11%		
Probability of renal of	complicatio	n									
Healthy	0.28%	0.28%	0.91%	0.91%	3.91%	3.91%	3.91%	3.91%	3.91%		
At risk	0.00%	0.00%	2.17%	2.17%	7.55%	7.55%	7.55%	7.55%	7.55%		
Probability of centra	l nervous s	ystem com	plication								
Healthy	2.34%	2.34%	10.82%	10.82%	16.41%	16.41%	16.41%	16.41%	16.41%		
At risk	0.00%	0.00%	6.52%	6.52%	14.47%	14.47%	14.47%	14.47%	14.47%		
Probability of otitis n	nedia										
Healthy	94.34%	94.34%	62.41%	62.41%	16.41%	16.41%	16.41%	16.41%	16.41%		
At risk	95.63%	95.63%	47.83%	47.83%	6.92%	6.92%	6.92%	6.92%	6.92%		
Probability of gastro	intestinal b	leeding*									
Healthy	3.03%	3.03%	24.37%	24.37%	56.25%	56.25%	56.25%	56.25%	56.25%		
At risk	4.38%	4.38%	30.87%	30.87%	33.96%	33.96%	33.96%	33.96%	33.96%		

 Table 6: Age-specific probability of non-respiratory complications [10,13]

Note: *100% – Prob. of cardiac complication – Prob. of renal complication – Prob. of central nervous system complication – Prob. of otitis media

Table 7: Age-specific probability of hospitalisation for influenza complications [14–16]

Age group (years)	0–4	5–17	18–49	50–64	65–69	70–74	75–79	80-84	85+
Healthy	12.10%	5.69%	5.26%	5.03%	42.55%	42.55%	42.55%	42.55%	42.55%
At risk	9.29%	4.37%	3.25%	3.18%	71.22%	71.22%	71.22%	71.22%	71.22%

Note: All non-hospitalised influenza complications (i.e. 100% – probability to be hospitalised for influenza complication) were defined as influenza complications treated in outpatient setting

Table 8: Age-specific probability of influenza death after hospitalisation for influenza [13–16]

Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
Healthy	0.26%	0.26%	0.45%	0.45%	10.00%	10.00%	10.00%	10.00%	10.00%
At risk	0.26%	0.26%	0.45%	0.45%	10.00%	10.00%	10.00%	10.00%	10.00%

Age	Rate								
0	0.003296370								
1	0.000284966	21	0.000316722	41	0.001080550	61	0.008341450	81	0.058237607
2	0.000142112	22	0.000308864	42	0.001184856	62	0.009043873	82	0.068709668
3	0.000123367	23	0.000346517	43	0.001358565	63	0.009830805	83	0.074899099
4	0.000089397	24	0.000343137	44	0.001477879	64	0.010535550	84	0.085724070
5	0.000107144	25	0.000370003	45	0.001657630	65	0.011212327	85	0.154872608
6	0.000081217	26	0.000384326	46	0.001902491	66	0.012524456	86	0.154872608
7	0.000082736	27	0.000346048	47	0.002049634	67	0.012233383	87	0.154872608
8	0.000081080	28	0.000406893	48	0.002309535	68	0.017936268	88	0.154872608
9	0.000090836	29	0.000427836	49	0.002582015	69	0.016285869	89	0.154872608
10	0.000061419	30	0.000477093	50	0.002777541	70	0.016857255	90	0.154872608
11	0.000058931	31	0.000465166	51	0.003326866	71	0.020983410	91	0.154872608
12	0.000084326	32	0.000506520	52	0.003616012	72	0.020297756	92	0.154872608
13	0.000087114	33	0.000531660	53	0.004108419	73	0.022415784	93	0.154872608
14	0.000107360	34	0.000592365	54	0.004441420	74	0.023526565	94	0.154872608
15	0.000150049	35	0.000648692	55	0.004993454	75	0.026083813	95	0.154872608
16	0.000198558	36	0.000637252	56	0.005374986	76	0.030365074	96	0.154872608
17	0.000220727	37	0.000692573	57	0.005869635	77	0.033897024	97	0.154872608
18	0.000316466	38	0.000806242	58	0.006590000	78	0.038962730	98	0.154872608
19	0.000338737	39	0.000927081	59	0.007032840	79	0.039942431	99	0.154872608
20	0.000330642	40	0.001009784	60	0.007763990	80	0.050489664	100	0.154872608

 Table 9: All-cause mortality rates for the entire population [17]

Tables for costs

Age group (years)	0–4	5–17	18–49	50–64	65–69	70–74	75–79	80-84	85+
Vaccine administration	€7.41	€7.41	€7.41	€7.41	€7.41	€7.41	€7.41	€7.41	€7.41
cost									
GP visit	€22.48	€14.08	€ 10.66	€11.37	€ 0.00				
Total cost for vaccine	€29.89	€21.49	€18.08	€18.79	€7.41	€7.41	€7.41	€7.41	€7.41
administration									

 Table 10: Vaccine administration costs [18]

GP: general practitioner

Table 11: Costs of GP, A/E visits, antivirals and antibiotics [11,18–20]

Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
GP visits	€36.41	€27.69	€25.81	€27.82	€28.75	€28.75	€32.87	€34.12	€34.12
A&E visits	€39.81	€31.10	€28.33	€30.44	€ 1.80	€ 1.80	€35.92	€37.17	€37.17
Antivirals	€25.59	€35.44	€27.72	€27.72	€27.72	€27.72	€27.72	€27.72	€27.72
Antibiotics	€5.36	€5.36	€4.49	€ 4.49	€ 4.49	€4.49	€ 4.49	€4.49	€4.49

A&E: accident and emergency; GP: general practitioner

Note: antibiotics cost is average cost of antibiotics and proportion of influenza patients receiving antibiotics

Table 12: Mean hospitalisation cost,	, calculated from	ı German	DRGs for	different	types of	complications
[21–23]						

Age group	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
(years)									
Bronchitis	€2,770.75	€2,770.75	€2,770.75	€2,770.75	€2,770.75	€2,770.75	€2,770.75	€2,770.75	€2,770.75
Pneumonia	€3,918.05	€3,918.05	€3,918.05	€3,918.05	€3,918.05	€3,918.05	€3,918.05	€3,918.05	€3,918.05
URTI	€2,101.56	€2,101.56	€2,101.56	€2,101.56	€2,101.56	€2,101.56	€2,101.56	€2,101.56	€2,101.56
Cardiac	€3,130.84	€3,130.84	€3,130.84	€3,130.84	€3,130.84	€3,130.84	€3,130.84	€3,130.84	€3,130.84
Renal	€4,258.17	€4,258.17	€4,258.17	€4,258.17	€4,258.17	€4,258.17	€4,258.17	€4,258.17	€4,258.17
CNS	€2,678.94	€2,678.94	€2,678.94	€2,678.94	€2,678.94	€2,678.94	€2,678.94	€2,678.94	€2,678.94
ОМ	€1,344.74	€1,344.74	€1,344.74	€1,344.74	€1,344.74	€1,344.74	€1,344.74	€1,344.74	€1,344.74
GI	€1,689.91	€1,689.91	€1,689.91	€1,689.91	€1,689.91	€1,689.91	€1,689.91	€1,689.91	€1,689.91
bleeding									

CNS: central nervous system; DRG: diagnosis-related group; GI: gastrointestinal; OM: otitis media; URTI, upper respiratory tract infection

Age group (years)	0–4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
Bronchitis	€60.42	€60.42	€55.42	€55.42	€55.42	€55.42	€55.42	€55.42	€55.42
Pneumonia	€107.00	€107.00	€102.00	€102.00	€102.00	€102.00	€102.00	€102.00	€102.00
URTI	€67.97	€67.97	€62.97	€62.97	€62.97	€62.97	€62.97	€62.97	€62.97
Cardiac, renal, CNS	€372.58	€372.58	€367.58	€367.58	€367.58	€367.58	€367.58	€367.58	€367.58
& GI bleeding									
Otitis media	€62.24	€62.24	€59.20	€59.20	€59.20	€59.20	€59.20	€59.20	€59.20

 Table 13: Outpatient treatment cost for complications [5,24,25]

CNS: central nervous system; GI: gastrointestinal; URTI, upper respiratory tract infection

Note: Duration of outpatient complication treatment assumed to be same as LOS in hospital (Table 12)

Table 14: Child sickness benefit [26–28]

Age group (years)	0–4	5–17	18–49	50–64	65–69	70–74	75–79	80–84	85+
Cost	€62.75	€44.91	€ 0.00						

Table 15: Non-reimbursable antiviral and antibiotic costs, OTC medication [20,29]

Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
Antivirals	€0.0	€0.0	€5.00	€5.00	€5.00	€5.00	€5.00	€5.00	€ 5.00
Antibiotics	€0.0	€0.0	€ 0.88						
OTC medication	€5.74	€5.74	€5.74	€5.74	€5.74	€5.74	€5.74	€5.74	€ 5.74

OTC: Over-the-counter

Table 16: Non-reimbursable hospitalisation costs [21,22,30]

Age group (years)	0–4	5–17	18–49	50–64	65–69	70–74	75–79	80–84	85+
Bronchitis	€0	€0	€67.05	€67.05	€67.05	€67.05	€67.05	€67.05	€67.05
Pneumonia	€0	€0	€ 91.56						
URTI	€0	€0	€60.11	€60.11	€60.11	€60.11	€60.11	€60.11	€60.11
Cardiac complications	€0	€0	€71.03	€71.03	€71.03	€71.03	€71.03	€71.03	€71.03
Renal complications	€0	€0	€101.43	€101.43	€101.43	€101.43	€101.43	€101.43	€101.43
CNS	€0	€0	€64.39	€64.39	€64.39	€64.39	€64.39	€64.39	€64.39
Otitis media	€0	€0	€33.29	€33.29	€33.29	€33.29	€33.29	€33.29	€33.29
GI bleeding	€0	€0	€42.37	€42.37	€42.37	€42.37	€42.37	€42.37	€42.37

CNS: central nervous system; GI: gastrointestinal; URTI, upper respiratory tract infection

Table 17: Absenteeism costs [31,32]

Age group (years)	0–4	5–17	18–64	65+
Uncomplicated influenza	€524.69	€542.53	€587.44	€0.00
/ Outpatient treatment				
Hospitalisation	€524.69	€542.53	€1,655.52	€0.00

 Table 18: Age-specific productivity loss costs due to premature mortality (Human Capital Approach, 3% discount rate) [17,32,33]

Age group	Value (€)						
(years)		(years)		(years)		(years)	
0-4	€535,147	20-24	€907,466	40-44	€696,860	60-61	€102,705
5-9	€620,742	25-29	€928,037	45-49	€557,925	65-69	€24,812
10-14	€719,951	30-34	€889,482	50-54	€400,730	70+	€0
15-19	€826,833	35-39	€809,018	55-59	€237,494		

Tables for outcomes

Age group (years)	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
Disutility influenza	-0.32	-0.32	-0.32	-0.32			-0.32		
Influenza duration (no	6.6	6.6	7.7	7.7	10.0 days				
antiviral treatment)	days	days	days	days					
Influenza duration	5.6	5.6	6.7	6.7			9.0 days		
(antiviral treatment)	days	days	days	days					

Table 19: Influenza disutility and duration of influenza in case of uncomplicated influenza [14–16,34–36]

Table 20: Influenza disutility and duration of influenza in case of complicated influenza [14–16,22,36,37]

Complication	Bronchitis	Pneumonia	URTI	Cardiac	Renal	CNS	ОМ	GI
name								bleeding
Disutility influenza				-0.38				
hospitalisation								
Disutility influenza	-0.251	-0.251	-0.127	-0.13	-0.176	-0.262	-0.015	-0.118
outpatient								
treatment*								
Influenza duration	6.7	9.2	6.0	7.1	10.1	6.4	3.3	4.2
(days)*								

* No difference in values is observed between age-groups.

CNS: central nervous system; GI: gastrointestinal; OM: otitis media; URTI, upper respiratory tract infection

Table 21: Baseline utilities[37]

Age group	0-4	5–17	18–49	50-64	65–69	70–74	75–79	80-84	85+
(years)									
Healthy	0.96	0.96	0.95	0.93	0.93	0.92	0.90	0.88	0.82
At risk	0.94	0.94	0.91	0.82	0.80	0.78	0.75	0.70	0.65

Table 22: PSA distributions and type of input parameters

Parameter	PSA distribution	PSA type of input parameters
Probabilities		
Probability to seek for medical advice	Beta	Uninf SE
Probability of GP visit	Beta	Alpha, Beta
Probability to receive effective NI in patients seeking MA	Beta	Uninf SE
Probability of influenza complication	Beta	Alpha, Beta
Probability of a respiratory-related complication	Beta	Alpha, Beta
Probability that a respiratory complication is bronchitis, pneumonia or URTI	Beta	Alpha, Beta
Probability that a non-respiratory complication is cardiac, renal, CNS, OM, GI	Beta	Alpha, Beta
Probability of hospitalisation for influenza complications	Beta	Uninf SE
Probability of influenza death after hospitalisation for influenza	Beta	Uninf SE

Reimbursable medical costs		
Cost of antibiotics	Gamma	Uninf SE
Cost of hospitalisation with complication	Gamma	SE
Cost of outpatient treatment for complication	Gamma	SE or uninf SE
Reimbursable non-medical costs		
Child sickness benefit ("Kinderkrankengeld")	Normal (0-17y)	Lower and upper limit CI = -/+ 5% mean
Non-reimbursable costs (for societal perspective)		
Non-reimbursed OTC medication	Gamma	Uninf SE
Non-reimbursed costs related to hospitalisation	Gamma (>17y)	SE
Transportation costs	Gamma	Uninf SE
Indirect costs (for societal perspective)		
Absenteeism with uncomplicated influenza	Normal (0-64y)	Lower and upper limit CI = -/+ 5% mean
Absenteeism because of hospitalisation	Normal (0-64y)	Lower and upper limit CI = -/+ 5% mean
Absenteeism because of outpatient treatment	Normal (0-64y)	Lower and upper limit CI = -/+ 5% mean
Outcomes		
Baseline utilities	Beta	SE
Disutility with influenza	Beta	Estimated SE
Influenza duration (with and without antiviral treatment)	Lognormal	Ln(mean) and SE(ln mean)
Disutility influenza in case of hospitalisation	Beta	Estimated SE
Influenza duration of hospitalisation	Gamma	SE
Disutility influenza in case of outpatient treatment	Gamma Lognormal	Uninf SE
Influenza duration of outpatient treatment	Gamma	SE

CI: confidence interval; CNS: central nervous system; GI: gastrointestinal; GP: general practitioner; MA: medical advice; NI: neuraminidase inhibitors; OM: otitis media; OTC: over-the-counter; PSA: probabilistic sensitivity analysis; SE: standard error; Unif: uniformed; URTI: upper respiratory tract infection; y: years

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