Evaluating costs and health consequences of sick leave strategies against pandemic and seasonal influenza in Norway using a dynamic model

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SUPPLEMENTARY FILE 1: MATERIALS AND METHODS

SURVEY ON INFLUENZA-RELATED SICK LEAVE AMONG NORWEGIAN EMPLOYEES

A questionnaire consisting of 14 questions was issued either electronically via Questback©, or on paper via personal distribution to a convenience sample of Norwegian employees in the Oslo area between November 2013 and January 2014. The convenience sample was selected based on network recruitment, and consisted mainly of public sector employees. All data gathered on paper were folded and placed in an envelope, and were later entered into Questback©, and the original responses were destroyed. The data were stored in Questback© and analyzed in Excel 2013. Once analyses were completed the original data and any imported copies were deleted. The first 6 questions were concerning age, gender, inclusive work life status of employer, household size, the number of children below 12 years living in the household, and presence of influenza-like symptoms in the previous season (defined as August 2012 to April 2013). Questions 7-9 were only asked to the respondents who indicated having children below the age of 12 living in the household. The questions addressed: whether these children had experienced influenza-like symptoms in the previous winter, whether the children were sick simultaneously with the respondent, and if yes, the number of days of sickness overlap. The last 4 questions were asked to respondents who indicated having experienced influenza-like symptoms in the previous season. The respondents were asked to indicate the number of days of symptoms, the number of days spent at home from work during the symptomatic period (and which symptomatic days were spent at home), whether the days spent at home were GP-certified or self-certified, at what day of symptoms a physician was contacted, and on which days (if any) children below the age of 12 were sick simultaneously with the respondent.

A total of 490 employees completed the questionnaire. 72% of the respondents were females, and the remaining 28% were males. The age of the respondents ranged from 20 -70 years, with a mean age of 46. Most (96%) of the employees had employers with an inclusive work life agreement (IW-agreement). There were no apparent differences between employees with and without IW–employers but the proportion of non-IW respondents was too small to meaningfully compare the two.

Among the 490 respondents, 224 reported having experienced symptoms of influenza last season. The number of days of symptoms varied from 1-20 days with a mean and median of approximately 6.5 and 5, respectively (Figure SMM1). Among the respondents that reported ILI symptoms, 161 respondents were absent from work, 58 respondents did not take time off work, the remaining 5 were missing. The duration of sick leave varied from 1-13 days, with a mean and median of 2.4 and 2 days, respectively.

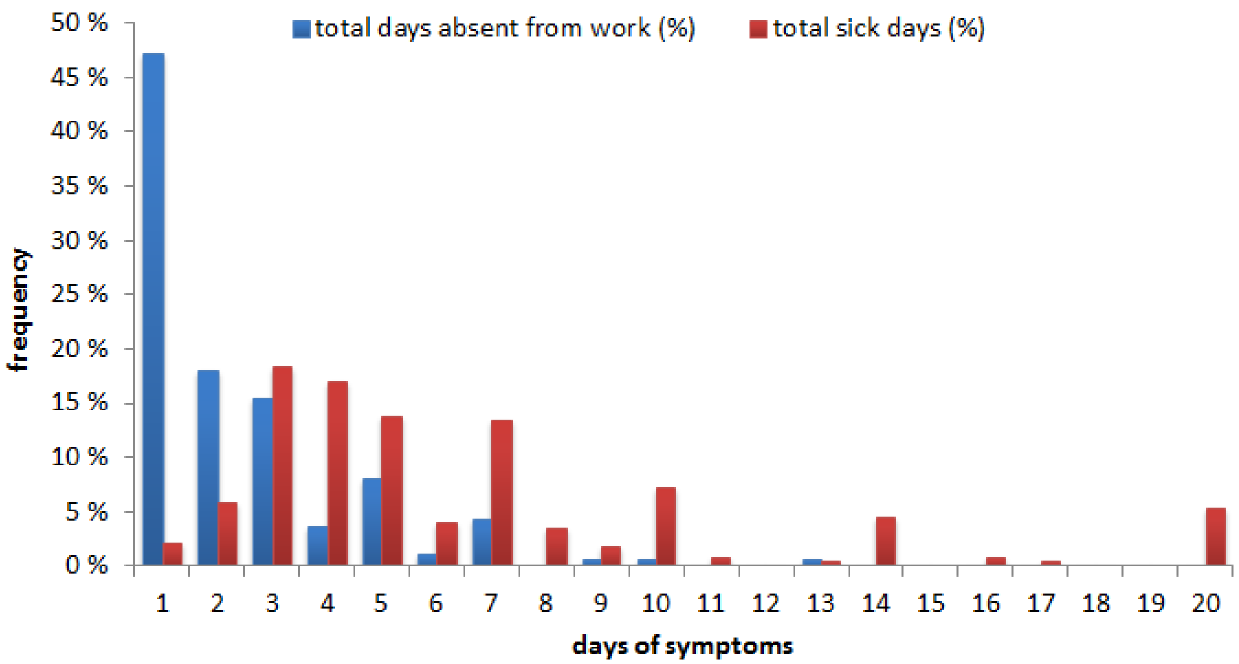

Figure SMM1: Frequency distributions showing the duration of symptoms (N=224) and the distribution of days absent from work (N=161) among respondents with ILI-symptoms.

Of the respondents that had influenza-like illness 20% reported visiting a GP for their symptoms, and 58% of these went on to take sick leave, while 42% continued to work. In total 14% of sick leaves were GP-certified, the remaining were self-certified.

Sick leave was initiated within 1-8 days after symptom onset. The shortest duration between sickness onset and sick leave was less than 1 day, and the longest duration was 7-8 days (Figure SMM2). We did not collect any information about which factors affected the likelihood of staying at home. We suspect that in addition to having mild symptoms at onset, possible explanatory factors for delayed onset of sick leave may be social pressure or deadlines at work. In our paper we truncated the final category into 4 days or later (simulated as 4 days maximum) such that 24% took sick leave on the first day following symptom onset, 43% on the second day, 19% on the third day, and the remaining 14% on the 4th day or later.

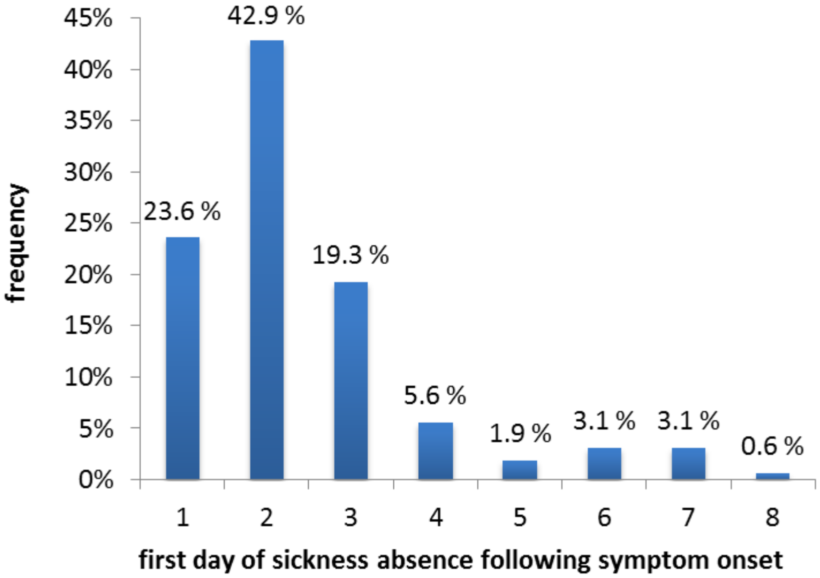

Figure SMM2: Frequency distribution showing the timing of sick leave onset counted in days from the time when symptom appeared (N=161)

The sick leave periods mainly occurred over consecutive days, with the exception of 5 respondents who reported intermittent sick leave histories. For the latter only the first sick leave period was counted. A total of 15 respondents reported being absent on one or more days without experiencing symptoms on these days; these sick leaves did not seem to be linked with sick children in the household.

Among the respondents, 155 said they had children <12 years in the household, 101/155 of the children had been ill in the past winter. The number of children was significantly correlated ($p>0.01$) with ILI symptoms in parents. The frequency of ILI symptoms in respondents was 16% higher when the household had one or more children <12 years. There was also a strong correlation ($p>0.01$) between experiencing ILI symptoms and having sick children. Although the correlation works from parent to child, and from child to parent, the latter is perhaps more correct as the sample of parents is non-random. If a child<12 in the household was ill, 74% of parents experienced ILI symptoms, otherwise 23% of parents experienced symptoms.

The survey was an attempt at providing a rough estimate of sick leave practice during influenza among the working population in Norway. Our sample is not representative of the Norwegian working population, and was largely made up of people working within health professions. Some respondents indicated that they had been on sick leave on days without symptoms (N = 6), this may be a result of measurement error or could reflect that the sick leave period was used in its full length as these sick leave periods were 7 days or longer. Since we were asking about past health states and sick leave behavior, recall bias may have been a problem. In the responses replies involving round numbers (10 days, 20 days) were relatively more common. This may have been a result of recall bias.

Survey on influenza-related sickness absence among Norwegian employees [August 2012 - April 2013]

Please enter or circle your response

1. Age:	
2. Gender:	F M

3. Do you have an employer with an agreement about inclusive worklife (IW-agreement)?	Yes No
4. How many people were living in your household last winter? (including yourself)	Yes No
5. How many children under the age of 12 years were living in your household last winter?	Yes No
6. Did you have flu-like symptoms last winter? Typical symptoms of flu are: fever / cough / sore throat / headache / fatigue / muscle pain / stuffy nose)	Yes No

(Questions 7-8 are only relevant if you had children under 12 years living in your household last winter)

7. Were any of the children (under 12 years living in the household) ill with flu-like symptoms in the previous winter?	Yes No
8. Were any children ill at the same time as you?	Yes No

(Questions 9 to 13 are only relevant if you experienced influenza-like symptoms last winter)

Please indicate the following by ticking the relevant day(s)	Symptom start Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	
9. On which days did you experience influenza-like symptoms? (for how long were you ill?)																					More than 14 days
10. On which days did you stay home from work?																					No days
11. Which absence days were GP-certified?																					No days
12. On which day did you visit a GP?																					I did not visit a GP
13. On which days were children less than 12 years living in your household experiencing symptoms as well?																					Not relevant

THE INFLUENZA MODEL

An age-stratified compartmental SEIR (*Susceptible-Exposed-Infected-Recovered*) model was developed to simulate the spread of influenza. Due to lack of local data, the social mixing patterns were adapted from published synthetic contact matrices, which were based on the simulation of an agent-based virtual population parameterized with detailed Norwegian census and social demographic data[1]. Mixing between age groups (Figure SMM3) were defined using four setting-specific contact matrices, accounting for contacts within households $\left(\mathbf{M}^{H}\right)$, contacts within schools $\left(\mathbf{M}^{S}\right)$, contacts within workplaces $\left(\mathbf{M}^{W}\right)$ and contacts in the general population $\left(\mathbf{M}^{GP}\right)$. Each matrix provides the relative frequency of contacts between different age classes. The overall contact matrix $\left(\mathbf{M}^{tot}\right)$ was obtained as a linear combination $\mathbf{M}_{ij}^{TOT} = \sum_{K} \alpha_K \mathbf{M}_{ij}^{K}$, where α_K accounts for the proportion of transmission occurring in the various settings, $K \in \{H, S, W, GP\}$. The weights, α_K ,were chosen at 0.3 for households, 0.18 for schools, 0.19 for workplaces and 0.33 for transmission occurring in the general community in accordance with empirical observations and previously published studies on influenza-like diseases[1-5]. Further details on the calculation of the mixing matrices are provided elsewhere[1].

The population was divided into 100 one-year age groups according to the size and age-distribution of the Norwegian population at 1 January 2013[6]. Newly infected individuals pass through an incubation phase which was modelled using 8 compartments (E_1.E_2...E_8). The mean incubation period was fixed at 1.9 days[7] including the E_1-E_8 compartments, and the average latency period was assumed at 1.425 days covering the first six compartments. The mean duration of the infectious phase was assumed at 7.475 days, consisting of E_7-E_8 compartments and 14 infectious compartments, all assumed to last for 0.5 days. The infectious compartments were further split into three groups: people with asymptomatic infection $(Asym_1 ... Asym_{14})$, people with symptomatic infection $(Sym_1 ... Sym_{14})$ and people with symptomatic infection at home $(Symh_1 ... Symh_2)$. The timing and the rates of flow between the two latter categories were modelled according to the type of intervention studied, as detailed in the main text. The variation of infectivity as a function of the duration of time since infection (the infectivity profile) was adapted from a study on household transmission[5], which is in alignment with data from the 2009 H1N1 pandemic where most transmission was found to occur early after and to peak around the time of symptom onset[7] (Figure SMM4).

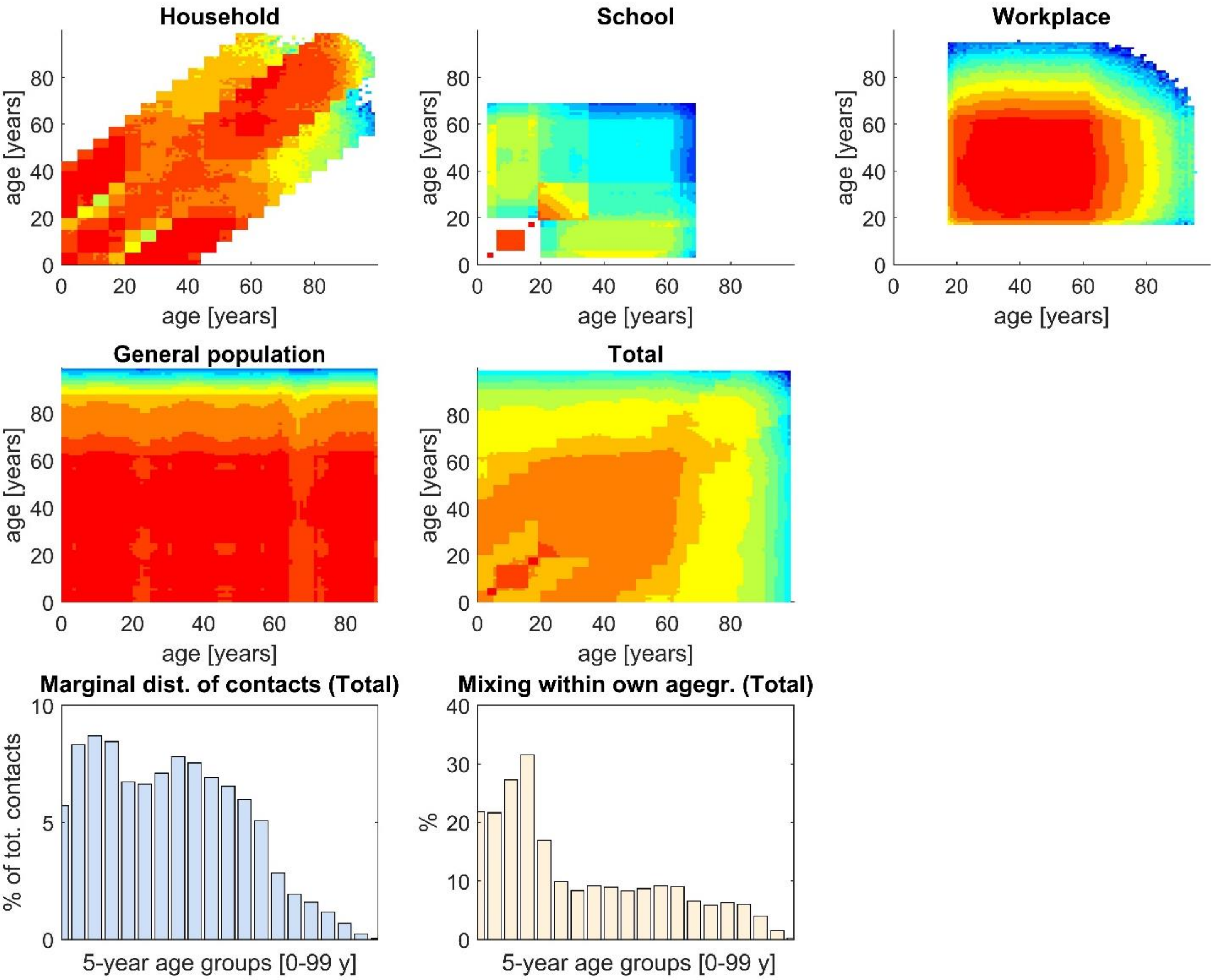

Figure SMM3: ***Mixing patterns by age assumed in the model:*** *Mixing matrices of the relative frequency of contacts among age classes in households, schools, workplace and the general population (top rows). The total mixing matrix was obtained as a weighted sum of the setting-specific matrices. The matrices are represented using a logarithmic scale (blue: low intensity; red: high intensity). The bottom row shows the marginal distribution of contacts (left) and the proportion of contacts with people of the same age (right) in the total matrix, aggregated into five-yearly age groups.*

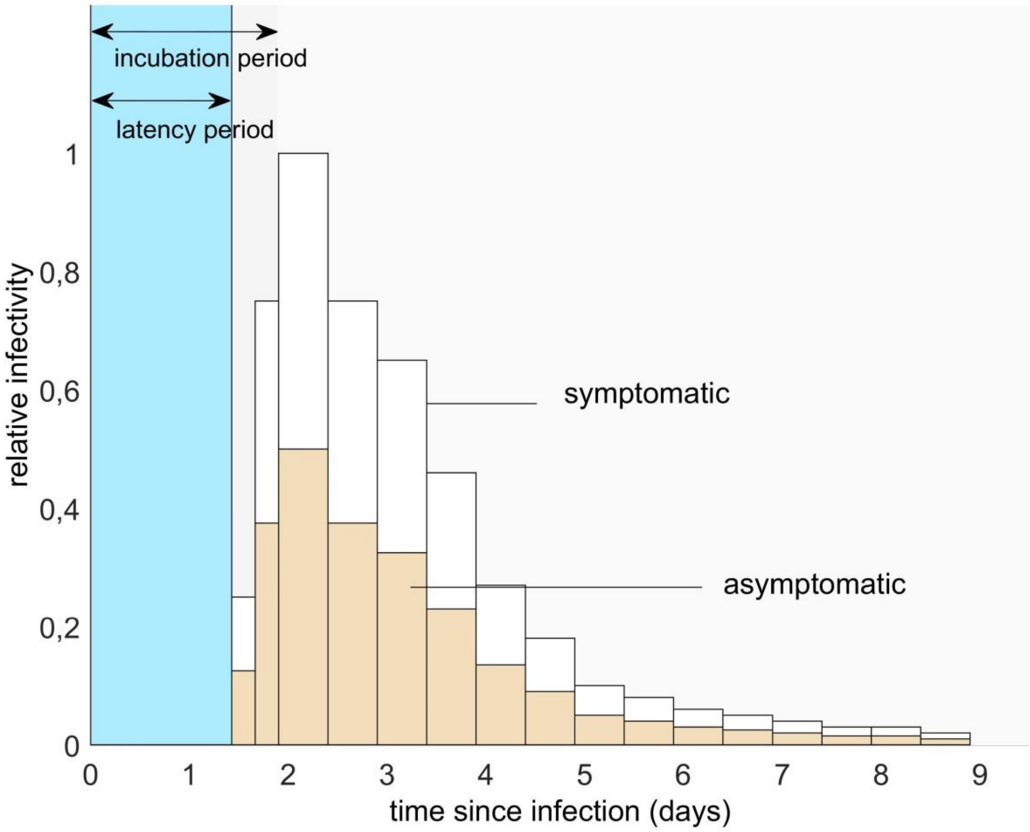

Figure SMM4: Schematic representation of the infectivity profile assumed in the model for individuals with symptomatic and asymptomatic influenza infection. The latency period is 1.5 days, the incubation period is 1.9 days, and infectivity peaks around 2 days after infection.

Recent analyses suggest that approximately 3 in 4 cases of seasonal and pandemic influenza are asymptomatic[8] and we assumed the baseline probability for symptomatic infection to be 0.35 for children <16 years and 0.25 for adults. However, in other scenarios we assumed that 50% of adults and 65% of children < 16 years develop symptoms in accordance with Longini et al.[9]. We assumed higher susceptibility and infectivity in children < 16 years of 1.05 and 1.30, respectively, compared to that of adults based on results from a Norwegian study using data from the 2009-H1N1 pandemic[10].

We modelled pandemic influenza by assuming a fully susceptible population at the simulation outset and using basic reproductive numbers: R_0=1.4, 1.6, or 1.8. For seasonal influenza we assumed that 0. 075, 0.20, and 0.40 of children < 16 years, adults 16-69 years, and elderly 70+ years were fully immune at the simulation outset based on personal communication with experts at the Norwegian Institute of Public Health. In these simulations we considered effective reproductive numbers: R_eff=1.2, 1.3, and 1.4.

Sensitivity analyses

In the main scenarios we modelled sick leave by eliminating mixing at the workplace (0%) and in the general population (0%). There is lack of knowledge about how people behave during influenza sickness absence[11] , which impacts both their transmission potential and whom they will infect. We therefore performed sensitivity analyses by assuming that people during influenza sick leave would increase their likelihood of transmission in the household and in the general population. This was implemented in the model by adjusting the household mixing matrix (+10%) and the general population mixing matrix (-90%) compared to the mixing assumed in non-infected people at the same age.

COST-EFFECTIVENESS

We developed a probabilistic health economic model to capture the health consequences, healthcare costs, productivity losses from work absences, and campaign cost for each intervention. The age-specific incidence of clinical events was based on results from the dynamic model. The probabilities of clinical events leading to a healthcare encounter (general practitioner (GP) visit or hospitalization) or death were taken from the Norwegian Pandemic Preparedness Plan[12]. The plan includes distinct morbidity estimates for moderate, severe, and very severe pandemics. The morbidity during seasonal influenza was assumed similar to a moderate pandemic (Table SMM1).

Table SMM1: Parameters of the economic model. Mean values and distributions used for the cost-effectiveness analysis.

Parameter	Mean value	Distribution	Source
Probability of dying			
Seasonal /moderate pandemic	0.15%	$Tri(0.0015 \pm 0.0009)$	*
Severe pandemic	0.22%	$Tri(0.0022 \pm 0.00132)$	
Very severe pandemic	0.70%	$Tri(0.0070 \pm 0.0042)$	
Probability of hospitalization			
Seasonal / moderate	0.75%	$Beta(7.49, 992)$	**
Severe pandemic	2.00%	$Beta(19.98, 979)$	
Very severe pandemic	3.50%	$Beta(34.97, 964)$	
Probability of intensive care in hospital			
Seasonal / Moderate Pandemic	10.00%	$Beta(99, 899)$	**
Severe pandemic	17.00%	$Beta(169, 829)$	
Very severe pandemic	25.00%	$Beta(250, 749)$	
Probability of visiting a GP			
Seasonal / moderate Pandemic	15.00%	$Beta(150, 849)$	**
Severe pandemic	20.00%	$Beta(200, 799)$	
Very severe pandemic	25.00%	$Beta(250, 749)$	
Probability of working from home when ill	8.00%	$Beta(929, 10825)$	**[13]
Daily productivity loss adults	Age-specific (5-year)	Log Normal, mean (provided in ref. 6), 20% variation about mean	***[6]
Daily productivity loss caretakers	$ 337	$ln(337, 4543)$	***[6]
Productivity lost before and after (per absence)	5.00%	$ln(0.95, 0.0361)$	***[14]
Productivity when working from home/work	65.00%	$ln(0.65, 0.017)$	***[15-17]
Cost of a GP consultation	$ 68	$N(68, 185)$	#[18 19]
Cost of medications			
0-14 years (+5% severe+10% very severe)	$ 10.6	$N(10.6, 4.48)$	#[20 21]
15-64 years (+5% severe+10% very severe)	$ 10.4	$N(10.4, 4.32)$	#[20 21]
65+ years (+5% severe+10% very severe)	$ 14.0	$N(14.0, 7.90)$	#[20 21]
Cost of hospitalization			
Non-intensive care	$ 9 503	$Gamma(0.126, 75401)$	##[22]
Intensive care	$ 20 435	$Gamma(4.3, 4768)$	##[22]
National cost of campaign			
Cost of increasing adherence			
to 80%	$ 2 040 378	$N(2040378, 408076^2)$	
to 90%	$ 3 490 120	$N(3490120, 698024^2)$	
Cost of earlier onset of sick leave			#[23]
2 days of delay	$ 1 238 321	$N(1238321, 247664^2)$	
1.5 days of delay	$ 1 762 679	$N(1762679, 352535^2)$	
1 day of delay	$ 2 418 124	$N(2418124, 483625^2)$	
0.5 days of delay	$ 3 237 432	$N(3237432, 647486^2)$	
QALY losses (per case)			
QALY loss un-hospitalized cases	0.0078	$ln(0.0078, 0.000024)$	***[24 25]
QALY loss hospitalized cases	0.0170	$ln(0.017, 0.000012)$	
QALY loss influenza mortality	Age-specific (1-year)	Normal, 20% variation about the mean	PC

* Triangular distribution; Tri(a ± b) has mean a and standard deviation $b/\sqrt{6}$

** Beta distribution; Beta(a,b) has mean a/(a+b) and standard deviation $\sqrt{\frac{ab}{(a+b)^2(a+b+1)}}$

*** Log-normal distribution, parameters are mean and variance of this distribution, standard deviation is 20% of mean

Normal distribution, parameters are mean and variance of this distribution, standard deviation is 20% of mean

Gamma distribution; Gamma(a,b) has mean ab and standard deviation $b\sqrt{a}$

$PC\ mean = 0.94 - 0.002 \times age$. Personal communication with Kim Rand-Hendriksen (2014).

HEALTHCARE COSTS

We compared the number of GP visits, hospitalizations, and deaths as well as the health-related quality of life, under each sick leave intervention, with the baseline intervention (Table SMM1). The cost of an influenza-related hospitalization was estimated using data from the Norwegian Patient Registry, on patients admitted with ICD-10 diagnoses J10-J11 (influenza) and J12-J18 (pneumonia) and discharged with influenza-associated diagnoses. We estimated the average hospitalization cost per patient by identifying the DRG codes most commonly related to influenza and pneumonia. For intensive care patients we used the DRG for diseases in respiratory organs requiring ventilation support as an estimate for the cost per hospitalized case. Costs were computed using the DRG unit price, trim points and cost weights (for 2013).[22] The cost of a GP consultation was assumed at $68.[18 19]

MEDICATION COSTS

The types of medication and proportion of users was based on findings in Meier et al.[21], while use of throat drops and tissues was assumed. The cost of antibiotics was assumed equal to the cost of Fenoksymetylpenicillin[20] deducted VAT. Costs of over-the-counter drugs were based on the average cost at three pharmacies and four grocery stores in Oslo.

CAMPAIGN COSTS

Each intervention was assumed to involve a campaign to communicate recommendations. We assumed the cost of the baseline intervention (65% compliance, maximum of 4 days from symptom onset to sick leave) to be similar to the campaign cost associated with the 2009 H1N1 Pandemic in Norway ($USD 1.7 million), equally divided into costs associated with adherence and sick leave onset delay. The campaign costs were assumed to increase by a factor of 1.5 per 10% increase in the adherence, and by a factor of 1.25 per half day reduction in the maximum delay time to work absence. The costs were converted to 2012 monetary equivalents by adjusting for inflation.

HEALTH EFFECTS

Health related quality measures based on the EuroQol-5D[26] were used to compute QALYs (Quality Adjusted Life Years) associated with mortality and morbidity. QALYs associated with mortality were based on the expected value of remaining life years using age-dependent life-expectancies[27] with a yearly discount rate of 4%. The age distribution of deaths was based on those specified in a Norwegian study of seasonal influenza mortality[28].

INDIRECT COSTS

In the baseline intervention (65% compliance, 4 days of maximum delay from symptoms onset to sick leave) we assumed that symptomatic workers would stay at home for an average of 3 workdays for seasonal influenza and 5.21 workdays for pandemic influenza, corresponding to 3.5 and 6.5 calendar days respectively. The average number of workdays lost was higher for interventions that reduced the delay from symptom onset to sick leave, following the implementation of interventions in the dynamic model.

Productivity losses were valued using a human capital approach. Labor costs were based on full-time equivalent wages and the value of labor not returned to the worker. For sick adults, 5-year age-specific wage rates for ages 16-74[6] were used, and for caretakers the average population wage was used. In Norway, all employees have a right to at least 3 days of self-certified leave with full salary, while self-employed workers (8%) may take out insurance and their income loss during work absenteeism will depend on their insurance policy.[29] About 60% of employees have an inclusive-work life (IW) employer with more flexible sick leave arrangements and a right to 8 days of self-certified leave. Once the self-certified sick leave period ends, additional sick leave days require a GP certificate. The first 16 days are covered by the employer, and additional days by the state.[30-32] For each sick leave event, we included a productivity loss equal to 5% of the labor cost to account for productivity losses before and after the sick leave period[14]. We assumed that 8% of adults on sick leave worked from home, guided by the proportion working from home from a 2009 survey.[13] Sick persons working from home, and workers going to work despite feeling ill were assumed to work at 65% of full capacity[15-17] In Norway, parental leave is 1 year and parents have the right to care benefits during child sickness when the child <12 years.[33] Therefore all ill children between 1 and 12 years of age were assumed to require parental care. We assumed that 15% of parents were homemakers[34] with no associated productivity loss. Overlap between parental and child sickness absences, which was found to be 37.5% in our sick leave survey, was also adjusted for.

SENSITIVITY ANALYSES

For each epidemiological scenario (seasonal influenza R_eff = 1.2-1.4 with moderate morbidity; pandemic influenza R_0= 1.4-1.8 with moderate, severe, or very severe morbidity) we performed a probabilistic sensitivity analysis using Monte Carlo sampling (10 000 draws) of the parameters listed in Table SMM1.

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