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The burden of 2009 pandemic influenza A(H1N1) in the Netherlands

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ABSTRACT

Background: The disease burden of the 2009 influenza pandemic has been debated but reliable estimates are lacking. To guide future policy and control, these estimates are necessary. This study uses burden of disease measurements to assess the contribution of the pandemic influenza A(H1N1) virus to the overall burden of disease in the Netherlands.

Methods: The burden of disease caused by 2009 pandemic influenza was estimated by calculating Disability Adjusted Life Years (DALY), a composite measure that combines incidence, sequelae and mortality associated with a disease, taking duration and severity into account. Available influenza surveillance data sources (primary care sentinel surveillance, notification data on hospitalizations and deaths and death registries) were used. Besides a baseline scenario, five alternative scenarios were used to assess effects of changing values of input parameters.

Results: The baseline scenario showed a loss of 5800 DALY for the Netherlands (35 DALY per 100 000 population). This corresponds to 0.13% of the estimated annual disease burden in the Netherlands and is comparable to the estimated disease burden of seasonal influenza, despite a different age distribution in incidence and mortality of the pandemic compared to seasonal influenza.

Conclusions: This disease burden estimate confirmed that, although there was a higher mortality observed among young people, the 2009 pandemic was overall a mild influenza epidemic. The disease burden of this pandemic was comparable to the burden of seasonal influenza in the Netherlands.

INTRODUCTION

In April 2009, a novel influenza virus subtype emerged in Mexico.¹ After identification of the first cases in Mexico and the USA, an increase in cases all over the world was observed, which led to the declaration of a new pandemic on 11 June 2009 by the World Health Organization (WHO).² In the Netherlands, the first case was diagnosed on 30 April 2009.³ A national mandatory notification system was set up for surveillance of all suspected cases with a 2009 pandemic influenza A(H1N1) virus infection and to collect data for research purposes.³ Case-finding of suspected individuals was carried out by Municipal Health Services and samples of all suspected cases were sent to the laboratory of the National Institute for Public Health and the Environment. In a later stage the outbreak assistance laboratory network in the Netherlands was also involved in the detection of influenza A(H1N1) virus.^{3,4} On the 15th of August, the notification criteria of this system were modified and from then on only cases who were admitted to hospital or who died with a laboratory confirmed infection were notifiable.⁵ The regular influenza surveillance system based on consultations for influenza-like illness (ILI) in general practice and laboratory confirmation of a subset of these patients provided additional monitoring data for less severe cases.⁶

The introduction of the pandemic virus led to numerous investigations to obtain initial insight into essential parameters, like the case fatality rate, reproduction number, risk groups, transmission rates and other measures of impact.^{7,8} It is also important to make an estimation of the overall burden of disease (BOD) due to pandemic influenza. In some media, it has been suggested that the pandemic alert was exaggerated and that the WHO may have overreacted.⁹ On the other hand, others warn that the proclaimed mild character of the pandemic might be too early a judgement, and suggest that hidden mortality needs to be explored,¹⁰ or that a more severe clinical presentation is observed among younger age groups compared to seasonal influenza.⁷ For a balanced judgement of the disease burden of the pandemic, it is essential not to focus exclusively on isolated parameters or perceptions, but to obtain a comprehensive measurement of the BOD, and put this in the context of the overall disease burden and the burden of seasonal influenza.

The intensified and extended influenza surveillance resulted in the availability of more specific data from different sources compared to a seasonal influenza outbreak.¹¹ This provided the possibility to assess the effect of the pandemic and associated complications not only on incidence and mortality, but also to aggregate these data in a composite health measure.¹² This measure, the Disability Adjusted Life Year (DALY), combines incidence, sequelae and mortality associated with a disease. It also takes duration and severity into account. The Dutch Public Health Status and Forecast (DPHSF) studies¹³ estimated that overall 4.49 million DALY were lost in 2003 in the Netherlands (27 656 DALY per 100 000 population). Of this burden, 2.9% could be attributed to communicable diseases and 0.15% to influenza in particular (6817 DALY or 42 DALY per 100 000 population).¹³ In a European pilot study on the disease burden of different infectious diseases, seasonal influenza (mean incidence 2003–2005) was estimated at 7462 DALY (46 DALY per 100 000 population), although methodology was not very detailed.¹⁴

Although the 2009 pandemic has been stated as being a 'mild epidemic',¹⁵ it is evident that this pandemic also caused a loss of life years. The purpose of this study was to investigate the BOD caused by 2009 pandemic influenza A(H1N1) in the Netherlands using available data sources designed for rapid feedback. Additionally, the calculated burden was compared to BOD estimates for seasonal influenza and the overall BOD in the Netherlands.

METHODS

Data sources

Available data sources in the Netherlands included the primary care sentinel surveillance network for ILI provided by the Netherlands Institute for Health Services Research (NIVEL), covering ~0.8% of the Dutch population,⁶ and the temporarily national mandatory notification system,^{3,5} which included hospitalizations and deaths due to pandemic influenza. Data were collected between 30 April and 31 December 2009 (Weeks 18–53). Mortality from previous influenza seasons was derived from the death registry of Statistics Netherlands.¹⁶

DALY methodology

A DALY is a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability. One DALY represents one lost year of 'healthy' life (WHO definition).¹⁷ The DALY methodology used in this study has been described in the Global Burden of Disease project and is calculated by the number of years of life lost due to mortality (YLL) plus the number of years lived with a disability, weighted with a factor between 0 (representing full health) and 1 (representing death) for the severity of the disability (YLD).¹⁸

The YLL of the pandemic in the Netherlands was calculated by summation of the number of fatal cases (d) in 5-year age groups (j) multiplied by the remaining expected life span (e) at age of death for the age group (j):

$$YLL = \sum_j d_j \times e_j$$

YLD was calculated by multiplying the duration of illness (t) by the severity weight (w), accumulated over all cases (n) for each health outcome (i):

$$YLD = \sum_i n_i \times t_i \times w_i$$

To estimate the burden of pandemic influenza by applying the DALY methodology, the Dutch life expectancy in 2008 was used, rather than life expectancy from a standard life table, since we only used data collected in the Netherlands. Additionally, discounting and age-weighting have not been applied, as validity of both modifications is debatable.¹⁹⁻²¹

Scenario 1 (baseline scenario)

The baseline scenario gives the best estimate for health outcomes of the recent pandemic. Besides acute illness, four different complications and their long-term sequelae were included: pneumonia,¹⁴ otitis media,¹⁴ acute respiratory distress syndrome (ARDS)²²⁻²⁴ and sepsis²²⁻²⁵ (see outcome tree in [figure 1](#)). Long-term outcomes of pneumonia in Western countries can be neglected.²⁶

[FIGURE 1]

The incidence of acute illness and pneumonia was estimated from the number of general practitioner (GP) visits and telephone calls (includes only telephone calls which meet the influenza case definition, see footnote 'b' in [table 1](#)) registered by the NIVEL sentinel surveillance network. This number was corrected for the assumption that 30% of individuals with ILI visited or telephoned their GP and the probability that ILI was due to pandemic influenza. A 20% GP visit estimate was found by an internet-based monitoring system,²⁷ but as children and elderly visit the GP most often due to ILI and are underrepresented in this system, and telephone calls are not included, the 20% estimate is likely to be an underestimate for GP consultation of the total population. Furthermore, a recent US study reported an increase of ~10% in the proportion of persons with ILI symptoms who report seeking medical care during the (early) pandemic compared to seasonal estimates.²⁸ Therefore, we used a 30% estimate, as has also been used previously in some Dutch BOD studies.^{13,29} The number of patients diagnosed with sepsis, ARDS and the number of deaths reported to the national mandatory notification system before 1 January 2010 were also included ([table 1](#)).

[TABLE 1]

Scenario analysis

Besides the baseline scenario, five alternative scenarios were calculated to obtain some insight into consequences of using alternative morbidity estimates, life expectancies, or severity weights (see [table 1](#) for more details on data sources and input parameters for all scenarios).

Scenario 2

In the second scenario, the European BOD pilot study conducted by van Lier et al.¹⁴ was adapted to the pandemic situation by putting the pandemic influenza incidence and number of deaths into this model. This model used only pneumonia, otitis media and deafness due to otitis media as complications of influenza. For YLD, pilot scenario 2 of the study conducted by van Lier et al.¹⁴ was used, while YLL was derived from pilot scenario 1, because pilot scenario 2 did not include a YLL calculation.

Scenario 3

As the number of pneumonia cases might have been underestimated, we set the pneumonia incidence twice as high in scenario three than in the baseline scenario.

Scenario 4

In this scenario, we assumed that pandemic influenza had an impact on quality of life that was half of that due to seasonal influenza: a severity weight of 0.005 instead of 0.01 per year was used. This enabled us to estimate the BOD of a similarly transmitted, but less severe outcome of disease for pandemic influenza.

Scenario 5

The assumption about the number of people with ILI symptoms that also visit or telephone their GP is highly dominant for the estimate of the incidence of acute illness, and it is unknown in the pandemic situation. Therefore, in scenario five, we used the 20% estimate of people with ILI symptoms visiting their GP from the internet-based monitoring system for seasonal influenza,²² which results in an increased number of acute illness cases.

Scenario 6

In the Netherlands, 90% of patients who died due to a pandemic virus infection had an underlying medical condition.⁵ This means that most of the deceased patients had a shorter life expectancy at time of infection than the general Dutch population. For 96% of the deceased patients, information on the underlying medical condition was available, and life expectancy was adjusted to this medical condition (see [table 1](#) for the corrected medical conditions).

Furthermore, the age distribution of disease outcomes during the pandemic is different than during seasonal influenza.^{2,30} Therefore, the relative average age distribution of seasonal influenza related mortality from 2000 to 2008 was applied to the observed pandemic influenza related mortality in 2009. This additional calculation assesses what the BOD estimate would have been with a mortality age distribution similar to that of seasonal influenza.

RESULTS

In [figure 2](#), the BOD of the influenza pandemic calculated for the six different scenarios is presented. The influenza incidence in the baseline scenario was 267 589 cases in the Netherlands (178 per 10 000 population). The pneumonia incidence was 2 per 10 000 population, which implies a total of 3289 people in the Netherlands, and the otitis media incidence was 1 per 10 000 or 1739 people. Of all notified hospitalizations, 62 people were hospitalized with ARDS and 26 people with sepsis. A total of 55 deaths were reported to the national mandatory notification system by 1 January 2010. For more details on numbers of cases, see [table 1](#). The BOD estimate in the baseline scenario was 5800 DALY (35 per 100 000 population).

[FIGURE 2]

The previously developed model¹⁴ used in scenario 2 resulted in 4827 DALY. In scenario 3, a doubled pneumonia incidence resulted in 6578 pneumonia cases in the Netherlands. From scenario 4, it can be seen that halving the acute illness severity weight resulted in the smallest YLD estimate of the scenarios investigated, 1338 DALY ([figure 2](#)). Changing the percentage of ILI patients that visit or telephone their GP

(scenario 5) resulted in the highest estimate. The final scenario included a change in YLL, in contrast to scenarios 3, 4 and 5. This scenario showed a decrease of 748 DALY compared to baseline scenario 1.

The additional calculation with the mortality age distribution of seasonal influenza showed a more than four times decrease in YLL compared to scenario 1 (510 vs. 2216 DALY), due to the higher mortality among people <65 years of age during the pandemic compared to seasonal influenza.

DISCUSSION

We found a pandemic influenza burden which was comparable to the estimated burden of seasonal influenza. At present there are no studies published from other affected countries that have used the DALY methodology for pandemic influenza and we can therefore only make comparisons with the overall BOD or with the burden due to seasonal influenza.

The DPHSF studies estimated the Dutch influenza burden in 2003 as equivalent to 6817 DALY.¹³

However, this estimate was much more crude as it assumed a very high influenza incidence (545 386 cases, or 336 per 10 000 population). The influenza incidence was likely to be an overestimate as the authors assumed all ILI to be due to an influenza virus infection. Additionally, the four complications used in the present study (pneumonia, otitis media, ARDS and sepsis) were not included in this 2003 influenza BOD estimate, whereas the recorded number of influenza deaths was higher in 2003 than in 2009 (166 vs. 55). In scenario 2, we adapted the BOD estimate of van Lier et al.¹⁴ Compared to our baseline scenario, the difference found was caused by a higher pneumonia incidence and a lower number of deaths during the 2009 wave. Overall, we found the best estimate of the BOD of the pandemic (0.13% of the total burden, baseline scenario) to be comparable to the estimated burden of seasonal influenza (0.15% of the total disease burden in 2003) in the Netherlands.

Of all scenarios investigated, the lowest influenza burden estimate was obtained from scenario 4 (halving the acute illness severity weight). On the other hand, doubling the severity weight for acute illness would have led to the highest estimate [8476 DALY (data not shown)]. It should be noted, however, that there are at present no data in the literature to suggest that pandemic influenza indeed had a larger or smaller influence upon disease burden than seasonal influenza. Furthermore, the percentage of people with ILI symptoms that visit or telephone their GP was investigated by applying two different values, 20% in scenario 5 and 30% in all other scenarios. The 20% estimate was derived from an internet-based monitoring system,²² but because children and elderly visit the GP most often due to ILI and are underrepresented in this system, and telephone calls are not included, the 20% estimate is likely to be an underestimate for GP consultation of the total population. Therefore we used this estimate only as an alternative scenario. The 30% estimate has been used previously in some Dutch studies.¹³⁻²⁹ The GP consultation rate is an arbitrary estimate, but the result of this estimate on the BOD estimate is shown by scenario 5 and makes it possible to estimate the consequences of other consultation rates on the BOD. Scenario 6 showed a decrease in YLL due to correction in life expectancy for people with underlying illness. The additional calculation of the BOD with a seasonal influenza mortality age distribution demonstrated a larger decline in YLL. This means that with a seasonal influenza mortality age distribution the BOD would have been much lower. To illustrate this point, from 2000 to 2008, ~90% of the people with influenza as cause of death were aged ≥ 65 years.¹⁶ In 2009, this was only the case for 13% of the deaths.

The incidence of acute illness calculated in the baseline scenario (267 589 cases in the Netherlands) results in a symptomatic attack rate of 1.6% of the Dutch population. Although this is low compared to the high attack rates expected at the start of the 2009 pandemic and previous pandemics,⁷ the incidence found is comparable to seasonal influenza, which has been estimated at 1–2% in the last 10 years in the Netherlands.⁵⁰ Additionally, the attack rates were possibly lower than expected due to cross-protective immunity in older age groups.⁷ The number of symptomatic cases, and therefore the BOD, may also have been reduced by the national vaccination campaign, albeit only started around the peak of the epidemic, and greater compliance with hygienic advice. Approximately 30% of the Dutch population was vaccinated from October 2009 up to mid December, starting in October with medical risk groups, health-care workers and pregnant women (trimester two or three), followed from mid November onwards by children aged 6 months

to 4-years old, and caretakers of babies <6 months. Further, data were collected up to 31 December 2009, when the 2009 pandemic management response in the Netherlands was downscaled as all epidemic indicators returned below the epidemic baseline. The end of the influenza epidemic in the Netherlands was declared on 24 December 2009.⁵¹ As some transmission of the virus was still present, the total BOD of the 2009 pandemic will be slightly higher if the complete tail in 2010 is also included. Finally, some other factors which also contribute to the burden of the pandemic were different from seasonal influenza, like public anxieties in the community and costs. These were not included in our BOD estimate.

There were some limitations in data availability and quality. Concerning data availability, there was no reporting of the actual incidence of otitis media and chronic sequelae of complications. The values required were obtained from the literature, but consequently, it is not sure whether they might need some modification for the Netherlands and/or the pandemic.

Regarding data quality, the amount of underreporting of morbidity and mortality is unknown, although surveillance of pandemic influenza cases and deaths was intensive. From 2000 to 2008, the number of deaths due to influenza reported on death registries ranged between 42 and 369 annually.¹⁶ During the pandemic, 55 deaths were reported to the notification system before 1 January 2010. It is unknown whether this is a true observation, or whether there was some underreporting despite increased diagnostics and higher alertness among medical practitioners during the 2009 pandemic wave. In previous studies it has also been noted that the number of deaths caused by pandemic influenza might be considerably below the number associated with seasonal influenza.⁵² One thing to note about the number of deaths observed in 2009 compared to that in previous seasons is the fact that the 2009 deaths included only confirmed cases, which might underestimate the actual number of deaths. Furthermore, two different data sources were used (notifications compared to death registries) which both are probably biased. A limitation in attributing mortality to seasonal influenza is that this can be overestimated or underestimated due to limited laboratory confirmation or not reporting influenza as the cause of death when there is another underlying cause of death. For total seasonal influenza mortality, estimations based upon time series regression models that attribute total mortality to ILI data also exist. Such models, however, seem not very suitable for estimating influenza attributed mortality in young children, due to the low baseline numbers in this age category. Since mortality in young children was relatively high during the 2009 pandemic, comparison of seasonal and pandemic influenza mortality based on such estimations seems complicated.

A second issue regarding data quality is that it is unknown whether all complications have been registered exhaustively, since it can be hard to distinguish between different conditions, and Municipal Health Services and medical practitioners were under significant workload pressures. This would have led to an underestimation of the actual BOD, but is unlikely to have led to major differences.

In conclusion, our rapid BOD estimate confirms that, although there was a higher mortality observed among young people, the 2009 pandemic was overall a mild epidemic. The disease burden of this pandemic was comparable to the burden of recent seasonal influenza outbreaks. This stresses the necessity to link virological and clinical case-reports with a comprehensive epidemiological assessment of an infectious disease outbreak, to be able to prioritise scarce resources, to enable appropriate communication with the general public, and to inform policy makers of the actual BOD in relation to other pressing needs. The strength of the DALY methodology is that it combines incidence and mortality data weighted for severity and duration. Moreover, the advantage of the presented BOD approach is that it uses all available population data and allows comparison between different health problems, between different years and between countries, and can also form the basis for cost estimates of the pandemic.

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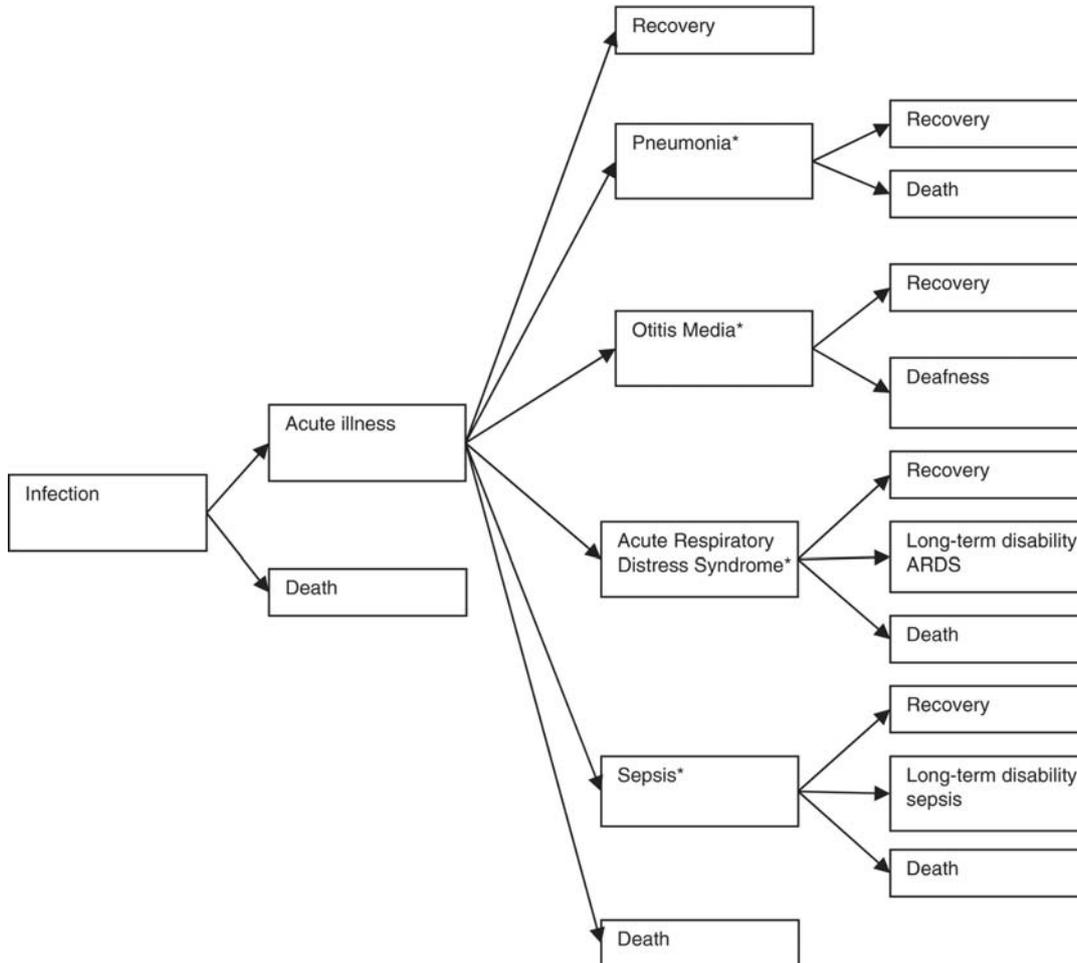
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TABLES AND FIGURES

FIGURE 1



ARDS: acute respiratory distress syndrome

*Complications include pneumonia, otitis media, acute respiratory distress syndrome, and sepsis

TABLE 1

Data sources and input parameters

	Scenario 1 (baseline)	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Difference compared to baseline scenario	N/A	Incidence of acute illness and no. of deaths are added to the pilot model of van Lier et al. ¹⁴ (original data 2003–2005) (YLD from pilot scenario 2 and YLL from pilot scenario 1)	Incidence of pneumonia is two times higher	Lower severity weight for acute illness: 0.005 ^a	Health care seeking behaviour: only 20% of people with ILI symptoms visit or telephone their GP	Life-expectancy of deceased patients is corrected for underlying medical conditions
Incidence (n) Acute illness	267 589 (178 per 10 000) GP visits and telephone consultations (includes only telephone calls which meet the influenza case definition ^b) related to ILI between Week 18 and 53 (2009) in the Netherlands, assessed by the sentinel surveillance network provided by NIVEL, ⁶ corrected for influenza patients who do visit or call their GP [30%, based on (i) A 20% visit rate according to an internet-based monitoring system of five influenza seasons in the Netherlands, ²⁷ which is an underestimation of GP attendance for the total population because children and elderly are under-represented and telephone calls are	Baseline	Baseline	Baseline	401 383 (244 per 10 000)	Baseline

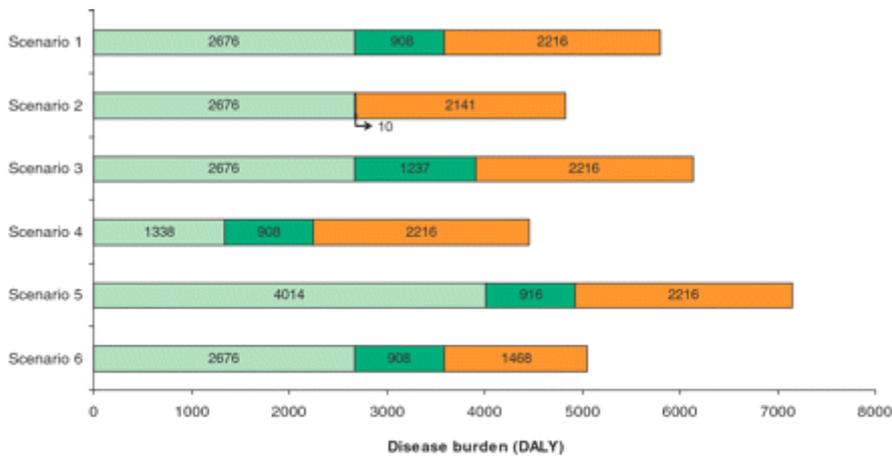
	Scenario 1 (baseline)	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
	not included, (ii) A recent US study which reported a 10% increase in the proportion of persons with ILI symptoms who report seeking medical care during the (early) pandemic compared to seasonal estimates ²⁸ and (iii) Previous Dutch BOD studies ^{13,29}] and the percentage of ILI which can be related to the pandemic virus (27.5% based on laboratory confirmation of specimens collected by the sentinel surveillance network ³¹)					
Complications Pneumonia	3289 (2.00 per 10 000) Pneumonia incidence in the Netherlands, assessed by the sentinel surveillance network provided by NIVEL, corrected for pneumonia which is not related to a 2009 pandemic influenza A(H1N1) virus infection ^d	1739 (0.36% of influenza cases ³²)	6578 (4.00 per 10 000)	Baseline	Baseline	Baseline
Otitis media	1739 (1.06 per 10 000) 0.65% of influenza cases ³²	Baseline	Baseline	Baseline	Baseline	Baseline
Deafness	0.10 (0.00 per 10 000) 0.006% of otitis media cases ³³	Baseline	Baseline	Baseline	Baseline	Baseline
ARDS	62 (0.04 per 10 000) Hospitalizations reported to the Dutch mandatory notification	N/A	Baseline	Baseline	Baseline	Baseline

	Scenario 1 (baseline)	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
	system for hospitalizations and deaths due to 2009 pandemic influenza A(H1N1) virus infection ^{3,5} between 30 April and 31 December 2009					
LT disability	29 (0.02 per 10 000) 56% of patients surviving ARDS ³³	N/A	Baseline	Baseline	Baseline	Baseline
Sepsis	26 (0.02 per 10 000) Hospitalizations reported to the Dutch mandatory notification system for hospitalizations and deaths due to 2009 pandemic influenza A(H1N1) virus infection ^{3,5} between 30 April and 31 December 2009	N/A	Baseline	Baseline	Baseline	Baseline
LT disability	19 (0.01 per 10 000) 82% of patients surviving sepsis ²⁵	N/A	Baseline	Baseline	Baseline	Baseline
Severity weight (w)						
Acute illness	0.01 ^{a,34}	Baseline	Baseline	0.005 ^a	Baseline	Baseline
Complications ^c						
Pneumonia	0.10 ^{a,34}	0.278 ³³	Baseline	Baseline	Baseline	Baseline
Otitis media	0.007 ^{a,35}	0.023 ³³	Baseline	Baseline	Baseline	Baseline
Deafness	0.23 ³⁴	0.168 ³³	Baseline	Baseline	Baseline	Baseline
ARDS	0.53 ^{e,34}	N/A	Baseline	Baseline	Baseline	Baseline
LT disability	0.18 ³⁶	N/A	Baseline	Baseline	Baseline	Baseline
Sepsis	0.93 ²⁹	N/A	Baseline	Baseline	Baseline	Baseline
LT disability	0.28 ²⁵	N/A	Baseline	Baseline	Baseline	Baseline
Duration (years) (t)						
Acute illness	1 ^{a,34}	Baseline	Baseline	Baseline	Baseline	Baseline
Complications ^c						

	Scenario 1 (baseline)	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Pneumonia	1 ^{a,34}	0.02 ²⁶	Baseline	Baseline	Baseline	Baseline
Otitis media	1 ^{a,35}	0.08 ²⁶	Baseline	Baseline	Baseline	Baseline
Deafness	RLE	Baseline	Baseline	Baseline	Baseline	Baseline
ARDS	0.09 ³⁷	N/A	Baseline	Baseline	Baseline	Baseline
LT disability	RLE	N/A	Baseline	Baseline	Baseline	Baseline
Sepsis	0.02 ³⁸	N/A	Baseline	Baseline	Baseline	Baseline
LT disability	RLE	N/A	Baseline	Baseline	Baseline	Baseline
Mortality						
Number of deaths (d)	55 Fatal cases reported to the Dutch mandatory notification system for hospitalizations and deaths due to 2009 pandemic influenza A(H1N1) virus infection between 30 April and 31 December 2009	Baseline	Baseline	Baseline	Baseline	Baseline
Life expectancy (e)	Dutch (2008) Calculation based on total mortality and average population of the Netherlands in 2008	European (2004)	Baseline	Baseline	Baseline	Dutch (2008) corrected for underlying medical conditions ^f

FIGURE 2

Disease burden of the 2009 influenza A(H1N1) pandemic in the Netherlands, calculated for six different scenarios



Scenario 1: Baseline
 Scenario 2: Other pilot model¹⁴
 Scenario 3: Higher pneumonia incidence
 Scenario 4: Lower severity weight acute illness
 Scenario 5: Other health care seeking behaviour
 Scenario 6: Correction for underlying medical conditions

■ YLD acute illness (number of years lived with a disability)
■ YLD complications (number of years lived with a disability)
■ YLL (number of years of life lost due to mortality)