



## **Economic Evaluation of Health Services Costs During Pandemic Influenza A (H1N1) Pdm09 Infection in Pregnant and Non-Pregnant Women in Spain**

**\*María MORALES-SUÁREZ-VARELA<sup>1,2,3</sup>, Agustín LLOPIS-GONZÁLEZ<sup>1,2,3</sup>, Fernando GONZÁLEZ-CANDELA<sup>2,4</sup>, Jenaro ASTRAY<sup>5</sup>, Jordi ALONSO<sup>2,6,7</sup>, Olatz GARIN<sup>2,6,7</sup>, Ady CASTRO<sup>8</sup>, Juan Carlos GALAN<sup>2,9</sup>, Nuria SOLDEVILA<sup>2,10</sup>, Jesús CASTILLA<sup>2,11</sup>, Pere GODOY<sup>2,12</sup>, Miguel DELGADO-RODRÍGUEZ<sup>2,13</sup>, Vicente MARTIN<sup>2,14</sup>, Jose María MAYORAL<sup>15</sup>, Tomas PUMAROLA<sup>16</sup>, José María QUINTANA<sup>2,17</sup>, Sonia TAMAMES<sup>18</sup>, Nuria RUBIO-LÓPEZ<sup>1,2,3</sup>, Angela DOMINGUEZ<sup>2,19</sup>**

1. *Unit of Public Health, Hygiene and Environmental Health, Department of Preventive Medicine and Public Health, Food Science, Toxicology and Legal Medicine, University of Valencia, 46010 Valencia, Spain*
2. *CIBER Epidemiología y Salud Pública (CIBERESP), Spain*
3. *Center for Public Health Research (CSISP-FISABIO), Valencia, Spain*
4. *Research Unit "Genomics and Health" CSISP-University of Valencia, Spain*
5. *Surveillance Branch, Community of Madrid, Spain*
6. *University Pompeu Fabra, Barcelona, Spain*
7. *Institute for Research IMIM-Hospital del Mar, Spain*
8. *CIBER Respiratory Diseases, Spain*
9. *Ramón y Cajal University Hospital, Madrid, Spain*
10. *University of Girona, Spain*
11. *Public Health Institute of Navarra, Spain*
12. *Dept. of Health, Generalitat of Catalonia, Spain*
13. *University of Jaen, Spain*
14. *University of León, Spain*
15. *Security Service of Andalusia, Spain*
16. *Red Española de Investigación en Patología Infecciosa (REIPI), Spain*
17. *Basque Foundation for Health Innovation and Research, Spain*
18. *Dept. of Public Health, Development and Innovation, Junta de Castilla y León, Spain*
19. *Dept. of Public Health, University of Barcelona, Spain*

**\*Corresponding Author:** Email: Maria.M.Morales@uv.es

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## Abstract

**Background:** The healthcare and socio-economic burden resulting from influenza A (H1N1) pdm09 in Spain was considerable. Our aim was to estimate and compare the management (resource utilization) and economic healthcare impact in an at-risk group of unvaccinated pregnant women with an unvaccinated group of non-pregnant woman of childbearing age (15-44 yr old).

**Methods:** We addressed this question with a longitudinal, observational, multicentre study. Inputs were the requirements in managing both groups of women. Outcome measures were healthcare costs. Direct healthcare (including medical utilisation, prescriptions of antivirals, medication, diagnostic tests, and hospitalisation) costs and indirect (productivity loss) costs were considered. Unit of cost was attributed to the frequency of health service resources utilisation. The mean cost per patient was calculated in this group of women.

**Results:** We found that the influenza clinical pattern was worse in non-pregnant women as they had a high medical risk of 20.4% versus 6.1% of pregnant women. Non-pregnant required more antipyretics and antibiotics, and needed more health service resource utilisation (338 medical visits in non-pregnant women *vs.* 42 in pregnant women). The total cost of non-pregnant women was higher (€4,689.4/non-pregnant and €2,945.07/pregnant).

**Conclusions:** Cost per (H1N1) pdm09 was lower for pregnant women, probably due to more preventive measures adopted for their protection in Spain. The highest costs were incurred by hospitalisations/day and work absenteeism for non-pregnant than for pregnant women. These data will allow better future pandemic influenza planning.

**Keywords:** Pandemic influenza A (H1N1), Costs, Health services, Pregnant women, Spain

## Introduction

Annually, influenza viruses are associated with a substantial disease burden worldwide. Since its emergence in April 2009, an outbreak of influenza A (H1N1) pdm09 began in Mexico and spread rapidly across many countries, including Spain. A pandemic was declared by WHO on 11 June 2009. Since then, our knowledge about influenza A (H1N1) in pregnancy has increased enormously. Much more attention has been paid to pregnancy issues because it is known that pregnant women (PW) are more susceptible to developing serious influenza complications (1-4), besides suffering adverse effects during pregnancy; e.g. spontaneous miscarriage and preterm delivery (5-7). The influenza A (H1N1) pdm09 virus extraordinarily increased both the hospital admission rate among PW and the number of maternal mortalities in the USA, Australia, New Zealand, South Africa, Brazil, Greece, Peru, Chile, France and Turkey during the pandemic (5, 9, 11-20). Given the high incidence rates, the medical costs incurred during the 2009 pandemic were considerable everywhere (23, 24). Pregnant women are more susceptible to complications from influenza, which often results in admission to hospital. For all these reasons, PW were considered an at-risk group. Studies of the consequences for pregnancy and the fetus, both

for the influenza and its treatment, are also important in the context of public health (8, 9).

The Spanish Ministry of Health (10) recommended giving priority to immunising people at increased risk of influenza complications in influenza A (H1N1)pdm09, such as PW in any trimester of pregnancy (10). Although prioritisation was important, these recommendations were based on the medical literature, and their potential cost-effectiveness was largely unknown.

Therefore, up-to-date information on the cost of a non-vaccinated risk group, such as pregnant women, and non-pregnant women (NPW), will improve the prioritisation and acceptability of influenza vaccination uptake, inform policy-makers in Spain, and could be useful for making similar decisions in other countries.

In order to prevent pandemic influenza A (H1N1)pdm09 from spreading, the Spanish government applied not only its regular health policies, such as quarantine, isolation and hygiene campaigns, but also a special protocol in at-risk groups such as PW (e.g., offering vaccination) (21, 22). Nonetheless, there were no data available on the related cost of the virus infection to allow a comparison between non-vaccinated PW and NPW of childbearing age to be made.

Knowing the health cost incurred by women of childbearing age will allow us to: 1) learn what spending has resulted from influenza A (H1N1) pdm09 in Spain in these important groups of women; 2) improve health management strategies (prioritisation of vaccines, control programs, etc.) in future epidemics; 3) know its relevance for future health policy and practice decisions.

Thus, our aim was to estimate and compare direct healthcare costs (medical visits, medication, diagnosis tests, and hospitalisation) and indirect healthcare costs (work absenteeism) that resulted from pandemic influenza A (H1N1) pdm09 in PW with those resulting in non-vaccinated NPW of childbearing age.

## **Methods**

### ***Study population and design***

This work was a pharmaco-epidemiological study of health costs that formed part of a multicentre matched case-control study of influenza A (H1N1) pdm09 infection carried out in 28 hospitals in seven Spanish Autonomous Communities (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre and the Valencian Community). A protocol was followed whose objective was to determine the impact of influenza A (H1N1) pdm09 on the Spanish population between 1 November 2009 and 28 February 2010 during the pandemic wave (16). The healthcare cost (€) for unvaccinated women of childbearing age with influenza A (H1N1) pdm09 was evaluated.

For the base case analysis, it was assumed that of those who developed clinical symptoms of (H1N1) pdm09, some would choose no treatment, while others would seek treatment from general practitioners (GPs). Those who received treatment could be prescribed medication for symptomatic relief, antibiotics or antivirals for complementation, or could be admitted to hospital.

Associated outcomes (consequences) and costs were summed for each group, these being: PW and NPW; the cost of each intervention (e.g. cost of treatment); the cost of each consequence (e.g. cost of hospitalisations). They all constituted healthcare costs. Inputs were the requirements in

managing both groups of women. Outcome measures were healthcare costs.

### ***Sample selection***

In all, 3,790 influenza A (H1N1) pdm09-infected subjects were surveyed. Of these, 1,165 were women of childbearing age (between 15-44 years old). They had visited the participating hospitals during the study period. Their influenza A (H1N1) pdm09 virus infection was confirmed by a Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) in a microbiology laboratory. The inclusion criteria considered for this study were having been microbiologically confirmed to be infected by the virus and being hospitalised for more than 24 h. Of the 219 women who met the inclusion criteria, 170 were NPW and 49 were PW. None had been vaccinated against seasonal or pandemic influenza viruses during the 2009-2010 seasons.

The economic burden resulting from pandemic influenza A (H1N1) pdm09 was estimated by an incidence approach. The associated direct healthcare costs and indirect costs deriving from absenteeism from work were calculated from a healthcare provider's perspective. Since consequences of influenza generally occur during a short period of time, the time horizon was set at 4 months. Due to this short period, discount rates were not needed. Therefore, we considered the healthcare costs per hospitalised patient as the reported Surveillance System number of severe influenza cases coordinated by the Centre for Health Alerts and Emergencies of the Spanish Ministry of Health and Social Policy (inpatients) (5,16).

### ***Data collection***

Information was collected at two time points: baseline (Primary Care General Practitioner (GP) or hospital) and follow-up (hospitalisation time). The variables measured at the baseline referred to the 7 days (medical visit index (outpatients)) before hospital admission (inpatients) and the duration of this hospitalisation. As this study started after the pandemic had begun, this information was collected retrospectively: the median time from the medical visit index or hospital admission to the time that information was collected was 125

days (IQR 89-166). The following variables were obtained from telephone interviews or during the personal face-to-face interviews conducted with patients diagnosed and hospitalised with the influenza A (H1N1) pdm09 virus: age; if they were pregnant or not; if so, trimester of pregnancy; city/town of residence; level of education; marital status; days of absenteeism from work. Other variables were also obtained from medical records for hospital databases: number of medical visits; pharmacological treatment (doses were not available); diagnostic tests; Health Scale SF-36; length of stay of inpatients in a hospitalisation unit. We also used medical risk, which was evaluated by each patient's GP in relation with patient co-morbidity. The same variables were recorded for PW and NPW, except for weeks of gestation, obtained for only PW.

#### *Estimating unit costs*

While information on the management of patients and pharmacological treatment was collected, the specific drug and dose were not available. So we assumed utilisation rates in accordance with recommendations from Clinical Practice Guidelines (17,18). The Spanish National Health System does not have information on unit costs. Hence alternative sources were considered for the monetary evaluation of healthcare resources utilisation (24). The unit costs of the considered healthcare resources included the retail price of the drugs published in a Spanish Vademecum (25). We adjusted treatment to a minimum dose (1/day), and we evaluated complete treatment for Oseltamivir (5-day treatment). The actual costs of the diagnostic tests were calculated using the price list offered by the Hospital Clinic of Barcelona and the mass media publications of the pandemic vaccine price (26). The cost per day of hospitalisation was obtained from one of the participating hospitals (Hospital del Mar of Barcelona) during the same study period (24). This hospital has a clinical-cost evaluation system that establishes hospital expenses according to the hospitalisation unit (27). Costs per day in an intensive care unit (ICU) and on a general ward were calculated separately by dividing total expenses by the total number of hospitalisa-

tion days in each unit. We used the cost estimated by all the regions participating in this study (26, 28, 29). For the cost per day derived from absenteeism from work, we evaluated only 1 day of absenteeism using the national estimation (27).

#### *Statistical analysis*

An economic descriptive analysis was done to characterise the study population (women of childbearing age: PW *vs.* NPW). The number and percentage of patients who partook in healthcare resources utilisation and absenteeism from work were informed. Mean utilisation frequencies and standard deviations (SD) were calculated. Patients' absenteeism from work was estimated from those who were working when the disease started.

The direct costs associated with healthcare resources utilisation and the indirect costs associated with patients' absenteeism from work (loss of income) were estimated by multiplying the frequency of utilisation by each unit cost. The mean cost due to the utilisation of each resource type was calculated for all the patients. Costs per patient are presented in € (2009) in accordance with unit costs, along with the frequency of social and healthcare resources utilisation.

All the data were included and analyses were performed with the SPSS software, v.19 (SPSS Inc., Chicago, IL, USA). Chi-square tests were performed to compare differences between PW and NPW. The normally distributed continuous variables were compared between PW and NPW by *t*-tests, and *P* values of <0.05 were considered statistically significant.

#### *Ethical statement*

The information collected in the present study has been treated confidentially according to legislation currently in force. The project was presented to the Ethics and Research Committee (CEIC, in Spanish) of the Mar Parc de Salut Consortium of Barcelona (Spain) as the CIBERESP-linked centre, and to the CEICs of all the other participating hospitals. The project was approved by them all. The study followed the ethical standards of the Declaration of Helsinki. All the participants were invited to sign an informed written consent after

explaining the aim and concerns of the study to them. Data sheets were coded to ensure anonymity and confidentiality of patients' data.

## Result

### Patients' characteristics

Table 1 describes the characteristics of the non-vaccinated PW and NPW of childbearing age (15-44 yr old) infected with the influenza A (H1N1) pdm09 virus in Spain (2009-2010). A similar mean age was obtained for both groups: 33.2 (SD=9.3) years for NPW and 30.8 (SD=6.4) for PW. When considering marital status, married women pre-

dominated with 75.5% and 49.5%, respectively. A higher proportion of PW had completed secondary or higher education *vs.* NPW (91.8% *vs.* 63.6%, respectively). A significant difference in medical risk was also observed despite the moderate risk of becoming infected by the (H1N1) pdm09 virus category being more frequent in both PW and NPW. PW were mostly in their third trimester of pregnancy (75.5%). We can see that NPW showed a high medical risk (20.4%) *vs.* PW 6.1% ( $P < 0.001$ ). The Health Scale SF-36 value was similar in both groups ( $P = 0.480$ ).

**Table 1:** Characteristics of PW and NPW infected with pandemic influenza A (H1N1) pdm09 virus in Spain (2009-2010)

Variable	NPW <sup>a</sup> (n= 170) N (%)	PW <sup>a</sup> (n=49) N (%)	P <sup>b</sup>
<b>Age, mean (SD)</b>	33.2 (9.3)	30.8 (6.4)	0.110
<b>Age group (years)</b>			0.001
<20	20 (11.8)	14 (28.6)	
20-29	70 (41.2)	3 (6.1)	
30-34	19 (11.2)	19 (38.8)	
>34	61 (35.9)	13 (26.5)	
<b>Trimester of pregnancy</b>			
First (week 1-12)		4 (8.2)	
Second (weeks 13-25)		8 (16.3)	
Third (weeks 26-40)		37 (75.5)	
<b>Autonomous Community</b>			
Andalusia	24 (20.5)	17 (34.7)	
Castile and León	9 (7.7)	3 (7.2)	0.070
Catalonia	36 (30.8)	9 (18.4)	
Basque Country	15 (12.8)	2 (4.1)	
Madrid	20 (17.1)	15 (30.6)	
Valencian Community	6 (5.1)	2 (4.1)	
Navarre	7 (6.0)	1 (2.0)	
<b>Level of education</b>			
None /primary studies	59 (36.4)	4 (8.2)	<0.001
Secondary/higher education	103 (63.6)	45 (91.8)	
<b>Marital status</b>			
Single	53 (50.5)	11 (24.4)	
Married	52 (49.5)	34 (75.6)	0.009
<b>Medical risk</b>			
Low	26 (26.5)		
Moderate	52 (53.1)	46 (93.9)	0.001
High	20 (20.4)	3 (6.1)	
<b>Health Scale (SF-36), mean (SD)</b>			
Previous diagnosis	69.3 (26.5)	72.7 (29.4)	0.401
Influenza	53.3 (30.6)	57.9 (31.6)	0.480

<sup>a</sup> Percentages refer to the actual number of responses/data for each group/ <sup>b</sup>Chi-square test./ANOVA/SD, standard deviation; N, number

**Healthcare economic burden**

Table 2 describes the healthcare costs related to women's requirements (according to patient management) for pandemic influenza A (H1N1) pdm09 who were not vaccinated and attended the hospital. The most widely used previous treatment was antibiotics and antipyretics in NPW, while only eight of the 49 PW cases studied (16%) used antibiotics. The cost of medical visits was higher, especially for NPW. Of the medication required by hospitalised patients, Oseltamivir and ibupro-

fen-acetaminophen stood out in both PW and NPW. The most commonly used diagnostic tests done were X-rays in NPW and PCR in the controls. Notwithstanding, differences were found in days of absenteeism from work depending on the Spanish Autonomous Community to which the patient belonged. Table 3 summarises the direct, indirect and total costs per patient. Each case in the NPW group generated a higher individual total cost (€4,689.4) than the PW group (€2,945.07). The most important difference was due to higher direct costs.

**Table 2:** Healthcare costs for women infected with the pandemic A (H1N1) 2009 influenza virus in Spain (2009-2010)

Variable	Unit Cost	NPW (n=170)				PW (n=49)			
		N	u/at	(u/at)/N	Cost/p(€)	N	u/at	(u/at)/N	Cost/p(€)
<b>Previous Treatment*</b>									
Antibiotic	1.61	83	83	0.48	0.77	8	19	2.37	3.82
Oral glucocorticoids	0.62	31	31	0.18	0.11				
Inhaled glucocorticoids	0.05	71	71	0.41	2.05				
AntiH2		10	10	0.06	5.40				
Antipyretics	0.35	94	94	0.55	0.19				
<b>Medical visits</b>									
Total number of visits			338				42		
Primary care GP's	37.5	116	166	1.43	53.62	15	23	1.53	57.37
Home medical care	58.5	17	17	1.0	58.50	2	2	1.0	58.50
Occupational care	100	3	5	1.67	167.00	1	1	1.0	100.00
Outpatients office	167.3	12	14	1.17	163.33	3	3	1.0	139.60
Primary care ED	87.7	44	52	1.18	103.48	5	7	1.4	122.78
Hospital ED	139.6	71	84	1.18	164.72	6	6	1	139.6
Cost per day of hospitalisation	505.2	281	2122	7.55	3814.26	45	198	4.4	2222.8
<b>Medication*</b>									
Oseltamivir (day of treatment for adult)**	6.514	110	550	5	32.57	32	160	5	3.26
Antibiotics (day of treatment)	1.61	95		0.55	0.88	16			0.52
Oral glucocorticoids (day of treatment)	0.62	44		0.25	0.15	2			0.02
Ibuprophen-acetaminophen (day of treatment)	0.35	96		0.56	0.19	33			0.23
<b>Diagnosis Tests</b>									
Radiography (front and side views)	21.3	170	272	1.6	34.8	21		0.42	9.12
Computed Tomography without contrast	120.2	13		0.07	9.19	0			
Laboratory (RT-PCR)	9.6	170	203	1.19	11.46	38		0.77	7.44
<b>Cost per work absenteeism (day)#†</b>									
Andalusia	129.2	27			20.52	7			18.46
Catalonia	134	57			44.92	3			8.20
Castille and Leon	129.4	9			6.85	2			5.28
Madrid	137.6	9			7.28	2			5.61
Navarre	127.7	7			5.25	7			18.24
Basque Country	127.9	19			14.29	1			2.61
Valencian Community	133.1	7			5.48	2			5.43
n.c.		9				0			

\*Minimum dose (1 day of treatment). / \*\*5 days depending on dosage (Vademecum). /# Only 1working day.

† We only have data on 135 NPW and 24 PW.

**Table 3:** Direct healthcare and indirect costs per patient (in euros)

	<b>NPW (n=170)</b>	<b>PW (n=49)</b>
<b>Direct Healthcare Cost (€)</b>		
Medical visits	710.65	617.85
Medication	4.45	4.03
Diagnostic tests	55.45	16.56
Hospitalisation (days)	3814.26	2222.8
<b>Indirect Cost (€)</b>		
Work absenteeism	104.59	63.83
<b>Total Cost (€)</b>	<b>4689.4</b>	<b>2945.07</b>

## Discussion

The results of this study suggest that during the 2009-2010 influenza pandemic, the management of NPW was more complicated than of PW, and the healthcare cost increased in NPW compared to PW. This result indicates the recommendation of extending the preventive protocol with vaccination to all women of childbearing age, and not only PW.

Based on the primary data of non-vaccinated PW and NPW patients with a confirmed influenza A (H1N1) pdm09 diagnosis, we estimated the pattern of healthcare resources utilisation and absenteeism from work of patients. The derived cost per patient and the economic impact on healthcare services were described. From an economic point of view, and on an individual basis, NPW patients incurred more costs (€4,689.4 per patient) than PW patients (€2,945.07 per patient). From the healthcare provider's perspective, 81.34% of the national economic burden resulted from hospitalisations of NPW patients and 75.48% of PW patients. In our pandemic outbreak analysis, cost of hospitalisation had the strongest impact. From these results, the benefits of vaccination and other protection strategies could be beneficial for both PW and NPW.

Assuming that healthcare costs are an indirect indicator of patient complications, this study reveals that Spanish PW were not at a higher risk of severe complications from influenza A (H1N1)pdm09 infection in 2009-2010 than NPW, which is not consistent with earlier reports on PW in other countries [6, 7, 26, 27]. As stated

above, the Spanish Ministry of Health offered vaccination to the whole population, particularly to risk groups, which included PW. (10) Perhaps this is the reason why fewer PW were attended to if compared with other countries. Furthermore, our expected sample size became smaller.

The healthcare utilisation description is essential for making an economic evaluation of health technologies and for estimating the burden of influenza A (H1N1) pdm09 in women of childbearing age. Every year, approximately 10-20% of the world population is infected by an influenza virus, which results in a significant number of outpatients and hospital visits, as well as a substantial economic burden for the healthcare system and society. This study into PW and NPW in Spain has helped highlight influenza A (H1N1) pdm09, and recommends that all women of childbearing age should be considered in preventive programmes, such as promoting vaccination in not only PW.

These cost estimates were obtained from all women of childbearing age, of whom some were hospitalised for influenza A (H1N1) pdm09.

The risk of serious complications was not high in patients with influenza A (H1N1) pdm09 if compared with recent seasonal strains (30). Nevertheless, we found that NPW were at higher medical risk than PW. Thus longer hospitalisations might be attributed to differences in medical practice during a pandemic outbreak when clinical evolution is uncertain. In our study, the mean hospitalisation stay required for NPW lasted over 7.55 days, while it was 4.4 days for PW, which meant a higher healthcare cost for NPW. Our study offers

a detailed description of healthcare resources utilisation for women of childbearing age, including medical assistance (such as home medical visits or occupational care visits), which are also relevant for organising health services.

In this study, antibiotics were prescribed to 32.65% of PW and to 55.88% of NPW. Since influenza is a viral infection, antibiotic prescriptions were probably inappropriate for most cases. Nevertheless, existing evidence does not clearly demonstrate that antiviral drugs mitigate influenza complications (31).

The results of this study show the effectiveness of health care in both medical and patient treatment terms (PW and NPW) because all the patients recovered from influenza A (H1N1) pdm09. Length of absenteeism from work during the pandemic in Spain also exceeded that reported in other European countries (39). This is not an exclusive feature of pandemic influenza A (H1N1) pdm09 because it has also been observed in other pathologies (33).

The costs of pandemic influenza A (H1N1) pdm09 were clearly lower than the direct medical costs associated with other pathologies in Spain, such as metabolic syndrome (€1,900 million) and knee and hip osteoarthritis costs (€4,075 million) (34, 35).

## Limitations

This study is not without its limitations. Firstly, the study population was a subsample of patients recruited for a case-control study. To correctly interpret the results, it is necessary to remember that the cases with this influenza had consulted their GP. Therefore, a significant association is expected to be found in the variables that influenced the frequency of medical consultations in cases with influenza, which should produce no potential bias on the eligibility criteria and source population. Therefore, external validity might be compromised. However, patients were temporally representative of the pandemic surge in Spain (2), and the prevalence of comorbidities among our hospitalisations was similar to that previously reported (5, 6). Although the follow-up response

was not 100%, the demographic characteristics of lost patients and those who continued in the study were not statistically different. Secondly, none of the recruited PW and NPW patients died during the influenza infection. Consequently, our cost estimates underestimate the actual impact of the pandemic, especially for treatments required because we did not have complete information on the doses employed. Therefore, we used a 1-day minimum dose, except for Oseltamivir, whose minimum dose was 5 days. Nevertheless, most of the patients who died during the pandemic were either old or had previous severe chronic conditions, which barely affected our estimation of indirect costs (5, 36). Thirdly, we were able to analyse only the flu cases who had been in contact with health services and laboratory-confirmed cases. This might have prevented us from overestimating costs due to influenza over diagnosis. However, it may have led us to underestimate the productivity costs among specific populations (housekeepers, non-contracted individuals, for instance) (37). Fourthly, despite there being evidence for possible differences in average costs according to social class (7), it was not possible to make comparisons by stratifying by this variable because many values were missing. Finally, the limitations related with the sources of the data used in our study deserve further comment. Some of the information was collected directly from patients (patients or proxies) during interviews. In other cases, it was collected several months after having had influenza, which implies a high risk of recall bias. However, it probably lowered given the mass media repercussion that the 2009 influenza pandemic had (38). We had to consider alternative sources of information for unit costs because the Spanish National Health System has no accepted common information source (36). While the sources of unit costs for hospitals and days of absenteeism from work were reliable, many ambulatory unit costs were probably overestimated as they had been obtained from the list of health services provision prices from third parties.



Finally, the power of the study may be insufficient to generalise (external validity) our results and further studies would be worthwhile.

## Conclusion

The health cost for the number of persons affected by influenza A (H1N1) pdm09 was considerable compared with non-vaccinated individuals. It is not clear as to whether and how the incidence of influenza A (H1N1) pdm09 will change in the future. Such changes will likely affect the healthcare cost in both PW and NPW.

## Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors

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**The members of the CIBERESP Cases and Controls in Pandemic Influenza Working Group are:** Andalusia: E. Azor, J. Carrillo, R. Moyano, J.A. Navarro, M. Vázquez, F. Zafra (Red de Médicos Centinela, Andalusia), M.A. Bueno, M.L. Gómez, M. Mariscal, B. Martínez, J.P. Quesada, M. Sillero (Complejo Hospitalario de Jaén), M. Carnero, J. Fernández-Crehuet, J. del Diego Salas (Hospital Virgen de la Victoria), M. Delgado Rodríguez (CIBERESP, Universidad de Jaén), V. Fuentes (Hospital Costa del Sol), V. Gallardo, E. Pérez (Servicio de Epidemiología, Junta de Andalucía), R. López (Hospital Infanta Elena, Huelva), J.R. Maldonado (Hospital de Torrecárdenas), J.M. Mayoral (Servicio de Vigi-

lancia de Andalucía), Á. Morillo (Hospital Virgen del Rocío), J.M. Navarro, M. Pérez (Laboratorio de Referencia de Gripe), S. Oña (Hospital Carlos Haya), M.J. Pérez (Hospital Virgen de Valme), M.C. Ubago (Hospital Virgen de las Nieves), M. Zarzuela (Hospital Puerta del Mar). Valencian Community: J. Blanquer (Hospital Clínico Universitario, Valencia), F. González Candelas (CIBERESP, CSISP-Universitat de Valencia), M. Morales (CIBERESP, CSISP-Universitat de Valencia, Hospital Doctor Peset). Castile and Leon: D. Carriedo, F. Díez, I. Fernández, S. Fernández, M.P. Sanz (Complejo Asistencial Universitario de León), J.J. Castrodeza, A. Pérez, S. Tamames (Dirección General de Salud Pública, Desarrollo e Innovación, Junta de Castilla y León), V. Martín (CIBERESP, Universidad de León), A. Molina (Instituto de Biomedicina, Universidad de León), J. Ortiz de Saracho (Hospital del Bierzo), R. Ortiz de Lejarazu (Centro Nacional de Gripe, Valladolid), A. Pueyo, J.L. Viejo (Complejo Asistencial, Burgos), P. Redondo (Servicio Territorial de Sanidad y Bienestar Social, León). Catalonia: A. Agustí, A. Torres, A. Trilla, A. Vilella (Hospital Clínic de Barcelona), J. Alonso (CIBERESP, Universitat Pompeu Fabra, IMIM-Instituto Recerca Hospital del Mar), F. Barbé (Hospital Arnau de Vilanova), M. Baricot, N. Soldevila (CIBERESP), L. Blanch, G. Navarro (Hospital de Sabadell), X. Bonfill, J. López-Contreras, V. Pomar, M.T. Puig (Hospital de Sant Pau), E. Borràs, A. Martínez, Núria Torner (Dirección General de Salud Pública, Generalitat de Catalunya), C. Bravo, F. Moraga (Hospital Vall d'Hebrón), F. Calafell, O. Garín (Universitat Pompeu Fabra), J. Caylà, C. Tortajada (Agencia de Salud Pública de Barcelona), Á. Domínguez (CIBERESP, Universitat de Barcelona), I. Garcia, J. Ruiz (Hospital Germans Trias i Pujol), J.J. Garcia (Hospital Sant Joan de Deu), (Universitat Pompeu Fabra), J. Gea, J.P. Horcajada (Hospital del Mar), P. Godoy (CIBERESP, Departament de Salut Generalitat de Catalunya), N. Hayes (Hospital Clínic-CRESIB), T. Pumarola (REIPI, Universitat de Barcelona), A. Rosell (Hospital de Bellvitge), M. Sáez (CIBERESP, Universitat de Girona). Madrid: Carlos Álvarez, M. Enríquez, F. Pozo (Hospital 12 de

Octubre), J. Astray (Subdirección de Vigilancia, Comunidad de Madrid), F. Baquero, R. Cantón, J. C. Galán (CIBERESP, Hospital Ramón y Cajal), A. Robustillo, M.A. Valdeón (Hospital Universitario Ramón y Cajal), E. Córdoba, F. Domínguez, J. García, R. Génova, E. Gil, S. Jiménez, M.A. Lopaz, J. López, F. Martín, M.L. Martínez, M. Ordobás, E. Rodríguez, S. Sánchez, C. Valdés (Area de Epidemiología de la Comunidad de Madrid), J.R. Paño, M. Romero (Hospital Universitario La Paz), J. Navarra: J. Castilla (CIBERESP, Instituto de Salud Pública de Navarra), P. Fanlo, F. Gil, V. Martínez Artola, M. Ruiz (Complejo Hospitalario de Navarra), J. Gamboa, F. Pérez-Afonso M. Sota, M.E. Ursua, M.T. Virto (Red de Médicos Centinela, Navarra), A. Martínez, L. Martínez (Instituto de Salud Pública, Navarra). Basque Country: U. Aguirre, A. Caspelastegui, P.P. España, S. García (Hospital Galdakao), J. Alustizac (Hospital Mendaró), J.M. Antoñana, I. Astigarraga, J.I. Pijoan, I. Pocheville, M. Santiago, J.I. Villate (Hospital de Cruces), J. Arístegui, A. Escobar, M.I. Garrote (Hospital Basurto), A. Bilbao, C. Garaizar (Fundación Vasca de Innovación e Investigación Sanitarias), G. Cilla, J. Korta, E. Pérez Trallero, C. Sarasqueta (Hospital Donostia), F. Esteban, J.L. Lobo, C. Salado, E. Tato (Hospital Txagorritxu), J.M. Quintana (CIBERESP, Fundación Vasca de Innovación e Investigación Sanitarias).

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