Impact factor 5.49

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 18 | Weekly issue 26 | 27 June 2013

Editorials

Rapid communications

Research articles

News

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Note from the editors: The 2012 impact factors

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Citation style for this article:
Eurosurveillance editorial team. Note from the editors: The 2012 impact factors . Euro Surveill. 2013;18(26):pii=20515. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20515

Article submitted on 27 June 2013 / published on 27 June 2013

Public health experts, epidemiologists and other scientists are used to handle numbers. They use numeric data to compare and evaluate trends, and often put forward recommendations and act based on their analyses. Publishers and editors do the same for their journals. The best known metric to compare scientific journals is the journal impact factor. It is computed based on a formula developed by Eugene Garfield and used by Thomson Reuters [1], who have recently released their 2012 Journal Citation Reports and journal impact factors [2].

Due to its known limitations, a number of renowned editors and publishers of scholarly journals suggested in *The San Francisco Declaration on Research Assessment* (DORA) in late 2012, that the much debated impact factor should not be marketed without putting it into context with other metrics [3]. Nonetheless, it is still used widely to appraise journals.

The first ever impact factor for *Eurosurveillance* for the year 2011 was high: 6.15. Many assumed that this was mainly a result of the unique role of *Eurosurveillance* in 2009 with regard to the rapid publishing of peer-reviewed papers on the influenza A(H1N1)2009 pandemic. However, our second impact factor of 5.49 is still considerable. We also retain the sixth position among the 69 journals in the category Infectious Diseases and with that remain in the first quartile [2]. Our second impact factor confirms that we are well established among the journals in our field. The 2012 figures for the increasingly popular Scopus-based SCImago Journal Rank (SJR) are not yet available for comparison, but in 2011 we held place 60 amongst 1,563 journals in the field of Medicine (miscellaneous) [4].

Of course we would like to use this occasion to thank our readers and contributors once again for their engagement and confidence in our journal and to provide additional information to allow our audience to see our impact factor in a broader context. In particular we want to highlight the top 10 *Eurosurveillance* articles from 2010 and 2011 receiving the highest number of citations in 2012 according to Scopus (Table) [5]. The listed articles demonstrate that a variety of subjects has contributed to the 2012 impact factor.

There were other indicators of the impact and increasing reputation of *Eurosurveillance* in the past year, such as the a number of submissions to our journal on influenza A(H7N9) from China and other countries outside Europe, as well as a considerable increase in submissions overall.

In particular, we note a new trend in the speed with which articles on the emergence of the influenza A(H7N9) virus and on the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) were published in a number of scientific journals, including such prestigious journals as the British Medical Journal (BMJ), the Lancet and the New England Journal of Medicine (NEJM), while during the 2009 influenza pandemic, *Eurosurveillance* was still quite unique in communicating findings within days through our 'Rapid Communications'. We feel encouraged by the thought that our journal might have led the way to faster sharing of information in times of emerging pathogens or outbreaks with an impact on public health.

As in previous years, our articles featured regularly in traditional and social media. Our Twitter account has now more than 2,000 followers, many of whom are very active on social media. In 2012, ProMED, the Internet-based platform dedicated to rapid global dissemination of information on outbreaks of infectious diseases and acute exposures to toxins that affect human health, posted more than 50 *Eurosurveillance* articles [6].

Our editorial policy and way of working is attractive to other journals. In the past two years, we were approached on several occasions by editors in the process of establishing regional journals outside Europe with a similar scope to ours, who were following the *Eurosurveillance* model. This is a satisfying acknowledgement of our work. We are happy to collaborate and share our experiences, to further the communication, in a local/regional context, of public health events that may not be not be in the scope own journal as they may lie outside our focus on events of European relevance.

These positive signs encourage us to remain true to our editorial policy in which we strive to be of practical use for our readers and to have an impact, sometimes immediate, on public health action.

Table

10 most cited *Eurosurveillance* articles in 2012 published in 2010 and 2011

Article	Number of citations
Köck R, Becker K, Cookson B, van Gemert-Pijnen JE, Harbarth S, Kluytmans J, Mielke M, Peters G, Skov RL, Struelens MJ, Tacconelli E, Navarro Torné A, Witte W, Friedrich AW. Methicillin-resistant Staphylococcus aureus (MRSA): burden of disease and control challenges in Europe. Euro Surveill. 2010;15(41):pii=19688. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19688	42 times
La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P, Lenglet A, Jourdain F, Leparc-Goffart I, Charlet F, Ollier L, Mantey K, Mollet T, Fournier JP, Torrents R, Leitmeyer K, Hilairet P, Zeller H, Van Bortel W, Dejour-Salamanca D, Grandadam M, Gastellu-Etchegorry M. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010;15(39):pii=19676. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19676	37 times
Grundmann H, Livermore DM, Giske CG, Canton R, Rossolini GM, Campos J, Vatopoulos A, Gniadkowski M, Toth A, Pfeifer Y, Jarlier V, Carmeli Y, the CNSE Working Group. Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts. Euro Surveill. 2010;15(46):pii=19711. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19711	36 times
Scheutz F, Møller Nielsen E, Frimodt-Møller J, Boisen N, Morabito S, Tozzoli R, Nataro JP, Caprioli A. Characteristics of the enteroaggregative Shiga toxin/verotoxin-producing Escherichia coli O104:H4 strain causing the outbreak of haemolytic uraemic syndrome in Germany, May to June 2011. Euro Surveill. 2011;16(24):pii=19889. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19889	35 times
Ready PD. Leishmaniasis emergence in Europe. Euro Surveill. 2010;15(10):pii=19505. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19505	31 times
Ikonen N, Strengell M, Kinnunen L, Österlund P, Pirhonen J, Broman M, Davidkin I, Ziegler T, Julkunen I. High frequency of cross-reacting antibodies against 2009 pandemic influenza A(H1N1) virus among the elderly in Finland. Euro Surveill. 2010;15(5):pii=19478. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19478	29 times
Unemo M, Golparian D, Syversen G, Vestrheim DF, Moi H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. Euro Surveill. 2010;15(47):pii=19721. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19721	28 times
Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. Euro Surveill. 2011;16(14):pii=19833. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19833	27 times
Hardelid P, Fleming DM, McMenamin J, Andrews N, Robertson C, SebastianPillai P, Ellis J, Carman W, Wreghitt T, Watson JM, Pebody RG. Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010. Euro Surveill. 2011;16(2):pii=19763. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19763	24 times
Kilander A, Rykkvin R, Dudman SG, Hungnes O. Observed association between the HA1 mutation D222G in the 2009 pandemic influenza A(H1N1) virus and severe clinical outcome, Norway 2009-2010. Euro Surveill. 2010;15(9):pii=19498. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19498	23 times

Source: [5].

References

1. Garfield E. The history and meaning of the journal impact factor. JAMA. 2006;295(1):90-3.
2. Thomson Reuters. Journal Citation Reports. Journal summary list. New York, NY: Thomson Reuters. [Accessed 26 Jun 2013]. Available from: http://admin-apps.webofknowledge.com/JCR/JCR
3. San Francisco Declaration on Research Assessment (DORA): San Francisco, California [accessed 27 June 2013] Avaliable from: http://am.ascb.org/dora/
4. SCImago. SJR – journal rank. [Accessed 26 Jun 2013]. Available from: http://www.scimagojr.com/journalrank.php?category=2701&area=0&year=2011&country=&order=sjr&min=0&min_type=cd&page=1
5. Scopus. Philadelphia: Elsevier. [Accessed 27 Jun 2013]. Available from: http://www.scopus.com/home.url
6. ProMED-mail. Brookline, MA: International Society For Infectious Diseases. [Accessed 26 Jun 2013]Available from: http://www.promedmail.org/?p=2400:1200:424240

Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013

J Ai[1], Y Huang[2,3], K Xu[1], D Ren[3,4], X Qi[1], H Ji[1], A Ge[1], Q Dai[1], J Li[1], C Bao[1], F Tang[1], G Shi[3], T Shen[3], Y Zhu (jszyf@jscdc.cn)[1], M Zhou[1], H Wang[1]

1. Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu, China
2. Tongling Center for Disease Control and Prevention, Tongling, Anhui, China
3. Chinese Field Epidemiology Training Program, Chinese Center for Disease Control and Prevention, Beijing, China
4. Tongren Center for Disease Control and Prevention, Tongren, Guizhou, China

Citation style for this article:
Ai J, Huang Y, Xu K, Ren D, Qi X, Ji H, Ge A, Dai Q, Li J, Bao C, Tang F, Shi G, Shen T, Zhu Y, Zhou M, Wang H. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. Euro Surveill. 2013;18(26):pii=20510. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20510

Article submitted on 01 June 2013 / published on 27 June 2013

We describe a case-control study performed in Jiangsu, China, to evaluate risk factors for human infection with novel avian influenza A(H7N9) virus. Twenty-five cases and 93 controls matched by age, sex, and location were included in the study. Direct contact with poultry or birds in the two weeks before illness onset, chronic medical conditions (hypertension excluded), and environment-related exposures were significantly associated with A(H7N9) infection.

Since it was discovered in February 2013, the emerging outbreak of human infections with a novel avian influenza A(H7N9) virus in China, has raised serious concerns for public health throughout the world [1]. According to reports by China National Health and Family Planning Commission, a total of 130 confirmed cases of human infection including 37 deaths (28%) were reported in mainland China as of 27 May 2013. Few descriptive studies have been reported on risk factors associated with avian influenza A(H7N9) virus infection [1,2]. We conducted a matched case-control study to identify potential risk factors for human influenza A(H7N9) cases in Jiangsu Province, one of the areas where the novel reassortant influenza A(H7N9) virus emerged earliest.

Selection of cases and controls

All confirmed human cases of avian influenza A(H7N9) virus infection in Jiangsu Province were included in this study. Cases were defined according to *The diagnosis and treatment programs of human infections with H7N9 virus* issued by the National Health and Family Planning Commission of the People's Republic of China [3]. As of 27 May 2013, 27 confirmed cases of human infection with influenza A(H7N9) were reported in Jiangsu; of these, eight cases were fatal.

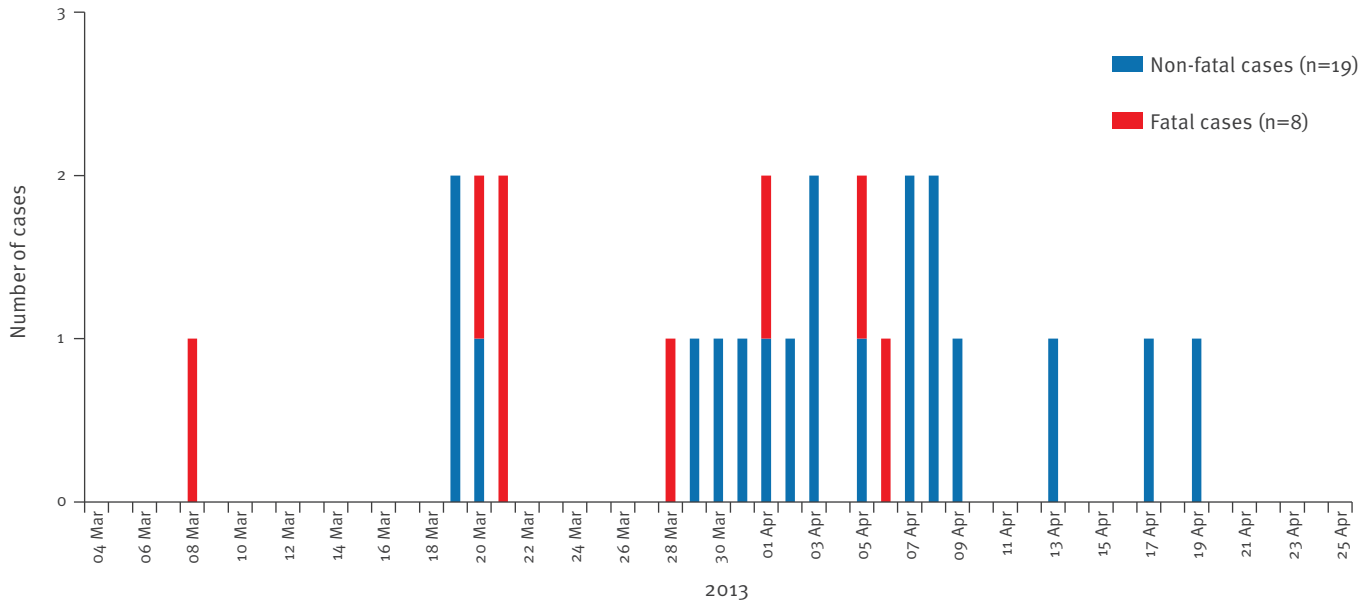
We matched four neighbours as controls for each patient. The selection criteria included: testing negative for influenza A(H7N9) virus, same sex, no more than five-year age difference, and no respiratory tract symptom like cough or sore throat, or other symptoms like fever (≥38°C) within two weeks of illness onset of the matched case. Cases were classified according to the area in which they lived: rural or urban. For cases from rural areas in the Province, controls were recruited from each patient's village according to the principle of proximity. The nearest neighbours were recruited first; if there were no eligible controls, additional controls were recruited among more distant neighbours. For cases living in urban areas, the apartment building where the patient lived was selected first. The persons in the same unit of the building were recruited first; if there were no eligible controls, the neighbours of the nearest unit were recruited next, and additional controls were recruited from the closest apartment building if needed. Investigators recruited the potential controls by visiting their homes. After the recruitment, all the eligible controls were asked to visit the local clinics for interview and blood sample collection. From each control 5 ml venous blood was collected to exclude unapparent and/or past influenza A(H7N9) virus infection. The study was approved by the Ethics Committee of the Jiangsu Provincial Center for Disease Control and Prevention (Jiangsu CDC). Before the investigation, we obtained the informed consent of all the participants in the interview.

Data collection

We performed an epidemiological survey for all participants including demographic characteristics, health status, daily habits, and other potential risk behaviour, such as not washing hands frequently (i.e. before meals and after using toilet), smoking, etc. Interview questions were also related to the activities and environment-related exposures for both cases and controls within two weeks before the illness onset of the case. Environment-related exposure was defined as possible

Figure

Confirmed human cases of influenza A(H7N9) virus infection, Jiangsu Province, China, 2013 (n=27)



exposure due to the environment, including visiting live poultry market, bird market, buying freshly slaughtered poultry or birds in live poultry market, and chickens or pigeons raised in the neighbourhood. Direct contact included direct contact with live poultry or birds in the wet market (i.e. through culling and slaughtering), direct contact at home (i.e. through cleaning, processing or cutting), and occupational exposure. For fatal cases of influenza A(H7N9) infection, or for the patients too ill to participate in the interview, a family member (usually the spouse) responded to the questions for the purpose of this study. The interview was carried out by trained staff of the Jiangsu CDC and trainees of the Chinese Field Epidemiology Training Program.

Laboratory investigation

Serum samples from controls were tested by haemagglutination inhibition assay with turkey red blood cells against avian influenza A(H7N9) virus strain (A/Jiangsu/XWQ/2013), with two confirmed patients' series serum as positive reference. All tests were performed in Jiangsu CDC.

Statistical analyses

Data were analysed using Stata/SE 9.0 for Windows (Stata Corp LP, College Station, TX, USA). Each study factor was compared between cases and controls using exact conditional logistic regression. Further multivariate conditional logistic regression was performed including all variables with $P \leq 0.10$ in univariate analyses and backward method was applied to exclude the variables with $P > 0.10$.

Case-control study results

A total of 25 confirmed human influenza A(H7N9) cases were included in the study. Two cases were excluded: one was possibly infected by human-to-human transmission (data not shown), and for the second one data were insufficient. All 25 cases included were positive in real-time PCR for influenza A virus subtype H7N9, and 16 cases were positive in virus isolation.

The epidemiological survey was conducted from 25 April to 12 May 2013. Ninety-three controls were enrolled in this study: 22 cases had four controls matched for each, and the remaining three cases only had one, two, and two controls matched, respectively, due to unavailability of eligible controls according to the control selection criteria. All enrolled controls were seronegative for avian influenza A(H7N9) virus antibodies. Data for 13 patients (including the eight fatal cases and the five severe cases) were obtained from family members, while data for the remaining cases and all controls were provided by themselves.

The demographic characteristics of cases and controls are showed in Table 1. The age of the patients varied between 21 and 85 years with a median of 56 years. Twelve patients were older than 60 years and 19 were male. Twenty-two cases lived in the urban area. The characteristics of cases and controls were similar in terms of education level, family size, and family income per capita. Two patients worked in a wet poultry market (slaughtering and selling poultry) and one patient and one control worked in poultry transportation. Fifteen patients and 39 controls had chronic medical diseases,

Table 1

Baseline characteristics of participants in a case-control study of avian influenza A(H7N9) in Jiangsu Province, China, 2013

Characteristics	Cases (n=25) n (%)	Controls (n=93) n (%)	*P*[a]
Age, median (range), years	56 (21-85)	57 (24-88)	
<60	13 (52)	49 (53)	
≥60	12 (48)	44 (47)	
Male	19 (76)	69 (74)	
Location			
Urban area	22 (88)	81 (87)	
Rural area	3 (12)	12 (13)	
Interviewed by proxy[b]	13 (52)	0 (0)	NA[c]
Education level			0.485
Primary school or below	2 (8)	18 (17)	
Junior middle school	13 (52)	30 (32)	
Senior middle school	4 (16)	32 (34)	
College or higher	6 (24)	13 (14)	
Family size, median (range), persons	2 (1-5)	3 (1-7)	0.085
Family income per capita			0.726
<2,000 RMB (cca.250 EUR)	7 (28)	23 (25)	
2,000-5,000 RMB (cca. 250-625 EUR)	14 (56)	53 (57)	
>5,000 RMB (cca. 625 EUR)	4 (16)	17 (18)	
Working in wet poultry market	2 (8)	0 (0)	NA[c]
Working in poultry transporting	1 (4)	1 (1)	NA[c]
Chronic medical conditions	15 (60)	39 (42)	0.052
Hypertension	10 (40)	31 (33)	
Diabetes	4 (16)	7 (8)	
Chronic bronchitis	3 (12)	3 (3)	
Cancer	3 (12)	0 (0)	
Rheumatic arthritis	2 (8)	1 (1)	
Coronary disease	1 (4)	5 (5)	
Other	0 (0)	6 (6)	

NA: not available.

[a] Comparison of frequencies between cases and controls was analysed by exact conditional logistic regression; matched factors (age, sex, and location) were excluded from analyses.

[b] For the fatal cases or for those too ill to respond to the survey, a family member (usually the spouse) responded to the survey.

[c] Information not available because of small sample size or because data distribution was not suitable for conditional logistic regression model.

including hypertension, diabetes, cancer, chronic bronchitis, rheumatic arthritis, and coronary disease (Table 1).

In the univariate analysis, the following exposures were associated with a high risk of infection with influenza A(H7N9): direct contact with poultry or birds within two weeks before illness onset (direct contact with poultry or birds in live poultry market, direct contact through preparing and cooking poultry or birds at home); environment-related exposures (visiting the market where live poultry was commercialised, buying freshly slaughtered poultry or birds in live poultry market). Frequent hand washing was associated with a reduced risk of getting infected with influenza A(H7N9) virus and this habit was reported more often by controls (89%) than by cases. Body Mass Index (BMI) (≥25), having ever smoked, and travel history were not significantly different between cases and controls (Table 2).

Although a higher proportion of chronic medical diseases was noticed in cases than in controls, the difference was not statistically significant ($P>0.05$).

Table 2

Univariate matched-pair analysis of risk factors for human infection with avian influenza A(H7N9) virus in Jiangsu Province, China, 2013

Characteristics	Cases (n=25) n (%)	Controls (n=93) n (%)	OR (95% CI)	*P*[a]
Chronic medical conditions	15 (60)	39 (42)	3.2 (1.0-10.0)	0.052
Hypertension	10 (40)	31 (33)	1.7 (0.6-5.4)	0.334
Chronic medical conditions (hypertension excluded)	12 (48)	19 (20)	5.1 (1.5-16.9)	0.008
Body Mass Index (BMI) (≥25)	5 (20)	32 (34)	0.4 (0.1-1.3)	0.147
Having ever smoked	12 (48)	51 (55)	0.6 (0.2-1.9)	0.425
Frequent hand washing	17 (68)	83 (89)	0.1 (0.02-0.6)	0.008
Direct contact with poultry or birds[b]	10 (40)	6 (6)	13.7 (2.9-64.8)	0.001
Direct contact with poultry or birds in live poultry market[c]	7 (28)	1 (1)	23.3 (2.8-192.0)	0.003
Prepared and cooked poultry or birds at home	7 (28)	4 (4)	8.1 (2.1-31.7)	0.003
Occupational contact with poultry[d]	3 (12)	1 (1)	NA[e]	
Environment-related exposures[f]	20 (80)	45 (48)	6.9 (1.9-25.2)	0.003
Visited the market where live poultry was commercialised	15 (60)	35 (38)	3.1 (1.1-8.3)	0.027
Frequency of visits to the market, mean (±SD), days	9.3 ± 5.6	6.4 ± 5.0		
Never	10 (40)	58 (62)	Reference	
1-5 times	5 (20)	17 (18)	1.5 (0.4-5.5)	0.547
6-10 times	1 (4)	9 (10)	0.8 (0.1-7.4)	0.822
>10 times	9 (36)	9 (10)	8.8(2.2-35.1)	0.002
Bought freshly slaughtered poultry or birds in live poultry market	13 (52)	18 (19)	7.3 (2.3-23.8)	0.001
Raise poultry or birds	1 (4)	4 (4)	0.7 (0.1-6.7)	0.752
Travel history[g]	3 (12)	8 (9)	1.2 (0.2-7.2)	0.850
Exposed to persons with fever and respiratory symptoms	0 (0)	1 (1)	NA[e]	

CI: confidence interval; NA: not available; OR: odds ratio; SD: standard deviation.

[a] Comparison of frequencies between patients and controls were analysed by exact conditional logistic regression.
[b] Birds include pigeons and quails.
[c] Live poultry market includes poultry stall, retail or wholesale market selling live poultry and birds.
[d] Workplace exposure to live poultry (e.g. poultry stall, retail or wholesale market, live poultry transporting).
[e] Information not available because of small sample size or because data distribution was not suitable for conditional logistic regression model.
[f] Includes visiting live poultry market, bird market, buying freshly slaughtered poultry or birds in live poultry market and chickens or pigeons raised in neighbourhood.
[g] Travel outside home place for more than 24 hours during the two weeks prior to the patient's illness onset.

Hypertension was high in both groups, the proportion was 40% among cases and 33% among controls (P>0.05). By excluding hypertension, 48% of cases had chronic medical diseases compared to 20% of controls, resulting an OR of 5.1 (95% CI 1.5-16.9; P =0.008).

In the multivariate conditional logistic regression model, three variables represented significant risk factors for human influenza A(H7N9) virus infection: direct contact with poultry or birds, chronic medical conditions (hypertension excluded) and environment-related exposures (Table 3).

Discussion

In this study, we identified in the multivariate analysis three risk factors for human influenza A(H7N9) cases in Jiangsu, China, including direct contact with poultry or birds, environment-related exposures, and chronic medical conditions (hypertension excluded). Direct contact with poultry or birds was the most significant risk factor, which is consistent with previous studies on human cases of avian influenza A(H5N1) and A(H7N9) virus infection [2,4-8]. The mixing of multiple

Table 3

Results of multivariate analysis of risk factors for human infection with avian influenza A(H7N9) virus infection in Jiangsu Province, China, 2013

Exposure and characteristics	Odds ratio (95% confidence interval)	*P*[a]
Chronic medical conditions (hypertension excluded)	6.0 (1.3-27.3)	0.021
Direct contact with poultry	9.1 (1.6-50.9)	0.012
Environment-related exposures	4.2 (0.9-19.6)	0.064

Variables with *P* <0.10 were included in univariate matched analyses for the initial model.

[a] Multivariate analysis using conditional logistic regression, final model with three variables entered.

species of live poultry and birds in live poultry markets in China creates a dynamic micro-environment that favours interspecies transmission [9]. In wet poultry markets, the secretions, faeces and organs of poultry were splashed out, which made the surroundings easily contaminated and visitors more likely be exposed to infected poultry. Surveillance of live poultry markets in epidemic regions indicated that the poultry cages were positive for avian influenza A(H7N9) virus [10]. The univariate analysis showed that for persons who went to live poultry markets more frequently (>10 times within two weeks of illness onset) the risk of exposure to influenza A(H7N9) virus was significantly higher and this could be due to the frequency of exposures. In addition, inhalation of aerosolised material contaminated with influenza A(H7N9) viruses may be a possible transmission route; however, our study did not investigate this potential transmission vehicle.

Different from influenza A(H5N1) virus infection, our findings show that having an underlying medical condition/co-morbidities (hypertension excluded) was significantly associated with influenza A(H7N9) virus infection. Age increases the risk for chronic diseases, which has been well-matched between cases and controls in this study. Therefore, a high proportion of elderly patients with severe influenza A(H7N9) virus infection may be due to decreased immune function caused by underlying chronic diseases [9].

Although influenza A(H7N9) virus is highly pathogenic in humans, poultry infected with it do not develop any obvious or visible diseases. It is thus difficult to separate the infected poultry or birds from the un-infected ones. People, especially those with underlying diseases, such as chronic bronchitis, diabetes, cancers, rheumatic arthritis, and immunodeficiency disease, could avoid the risk by reducing exposure to possibly contaminated environment. Persons exposed to poultry are advised to undertake appropriate protection and to develop correct hand washing habits.

Our study has several potential limitations. First, the number of cases was small, limiting the power of the study to demonstrate significant associations. Second, for some cases, family members responded to the interview and it is possible that they were less likely to be aware of specific exposures and activities, and this may result in bias to the data. Third, recall bias may be included as well since participants in the study were asked about activities that had occurred one month before the survey. Fourth, as residence was one of matching factors for cases and controls in this study, this could lead to some underestimation of the risk as the neighbourhood may share some living environmental exposures with cases.

In conclusion, ongoing education of the public is needed for behavioural changes in order to decrease the exposure risk to influenza A(H7N9) virus. Additionally, effective control strategies should be implemented; the most drastic measure would be closing the live poultry markets but if this is not possible, other measures such as segregating bird species, improving biosecurity, and having centralised poultry slaughtering locations, regular disinfection, and a periodical rest day, should be considered [11,12]. In addition, wearing protective masks or respirators by workers and visitors to wet poultry markets could be discussed.

Acknowledgements

We thank the Centers for Disease Control and Prevention of Nanjing, Suzhou, Wuxi, Zhenjiang, Changzhou, Yancheng, Yangzhou, Suqian cities in Jiangsu Province for coordinating our field investigations and collecting data. This work was supported by the Jiangsu Province Health Development Project with Science and Education (ZX201109 and RC2011085) and Chinese Field Epidemiology Training Program.

Conflict of interest

None declared.

Authors' contributions

Jing Ai, Yong Huang, Ke Xu, Dafei Ren contributed equally to this study. Yefei Zhu, Guoqing Shi, Tao Shen, Minghao Zhou, Hua Wang designed the study. Jing Ai, Yong Huang, Ke Xu, Dafei Ren, Hong Ji, and Qigang Dai collected, analysed and interpreted data. Xian Qi detected the specimens. Jing Ai, Yong Huang, Ke Xu, Jingxin Li, and Yefei Zhu drafted the article. All authors reviewed and revised the first and final drafts of this manuscript.

References

1. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W, et al. Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus. N Engl J Med. 2013;368(20):1888-97. http://dx.doi.org/10.1056/NEJMoa1304459. PMid:23577628.
2. Chen Y, Liang W, Yang S, Wu N, Gao H, Sheng J, et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. Lancet. 2013;381(9881):1916-25. http://dx.doi.org/10.1016/S0140-6736(13)60903-4
3. China National Health and Family Planning Commission. Diagnostic and treatment protocol for human infections with avian influenza A (H7N9) (2nd edition, 2013). Beijing: China National Health and Family Planning Commission. 11 Apr 2013. Available from: http://www.moh.gov.cn/yjb/bmdt/201304/9e989ebaodod4500ba5dbb89c3bd7829.shtml
4. Mounts AW, Kwong H, Izurieta HS, Ho Y-y, Au T-k, Lee M, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis. 1999;180(2):505-8. http://dx.doi.org/10.1086/314903. PMid:10395870.
5. Dinh PN, Long HT, Tien NTK, Hien NT, Mai LTQ, Phong LH, et al. Risk factors for human infection with avian influenza A H5N1, Vietnam, 2004. Emerg Infect Dis. 2006;12(12):1841-7. http://dx.doi.org/10.3201/eid1212.060829. PMid:17326934. PMCid:3291373.
6. Areechokchai D, Jiraphongsa C, Laosiritaworn Y, Hanshaoworakul W, O'Reilly M. Investigation of avian influenza (H5N1) outbreak in humans—Thailand, 2004. MMWR Morb Mortal Wkly Rep. 2006;55(Suppl 1):3-6. PMid:16645574.
7. Zhou L, Liao Q, Dong L, Huai Y, Bai T, Xiang N, et al. Risk factors for human illness with avian influenza A (H5N1) virus infection in China. J Infect Dis. 2009;199(12):1726-34. http://dx.doi.org/10.1086/599206. PMid:19416076. PMCid:2759027.
8. Li Q, Zhou L, Zhou M, Chen Z, Li F, Wu H, et al. Preliminary Report: Epidemiology of the Avian Influenza A (H7N9) Outbreak in China. N Engl J Med. 2013 Apr 24. [Epub ahead of print]. http://dx.doi.org/10.1056/NEJMoa1304617
9. Guan Y, Farooqui A, Zhu H, Dong W, Wang J, Kelvin DJ. H7N9 Incident, immune status, the elderly and a warning of an influenza pandemic. J Infect Dev Ctries. 2013;7(4):302-7. http://dx.doi.org/10.3855/jidc.3675. PMid:23592638.
10. Bao CJ, Cui LB, Zhou MH, Hong L, Gao GF, Wang H. Live-Animal Markets and Influenza A (H7N9) Virus Infection. N Engl J Med. 2013;368(24):2337-9. http://dx.doi.org/10.1056/NEJMc1306100. PMid:23697471.
11. Kung N, Guan Y, Perkins N, Bissett L, Ellis T, Sims L, et al. The impact of a monthly rest day on avian influenza virus isolation rates in retail live poultry markets in Hong Kong. Avian Dis. 2003;47(3 Suppl):1037-41. http://dx.doi.org/10.1637/0005-2086-47.s3.1037. PMid:14575106.
12. Ellis TM, Barry Bousfield R, Bissett LA, Dyrting KC, Luk GS, Tsim S, et al. Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002. Avian Pathol. 2004;33(5):492-505. http://dx.doi.org/10.1080/03079450400003601. PMid:15545029.

Hospital-based cluster randomised controlled trial to assess effects of a multi-faceted programme on influenza vaccine coverage among hospital healthcare workers and nosocomial influenza in the Netherlands, 2009 to 2011

J Riphagen-Dalhuisen (j.riphagen@umcg.nl)[1,2], J G Burgerhof[2], G Frijstein[3], A D van der Geest-Blankert[4], M B Danhof-Pont[5], H J de Jager[6], A A Bos[7], E E Smeets[8], M J de Vries[9], P M Gallee[10], E Hak[1,2]

1. Department of PharmacoEpidemiology & PharmacoEconomics, University Center of Pharmacy, University of Groningen, Groningen, the Netherlands
2. Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands
3. Department of Occupational Health and Environment, Academic Medical Center, Amsterdam, the Netherlands
4. Department of Occupational Health and Environment, University Medical Center St. Radboud Nijmegen, Nijmegen, the Netherlands
5. Department of Occupational Health and Environment, Leiden University Medical Center, Leiden, the Netherlands
6. Department of Occupational Health and Environment, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands
7. Department of Occupational Health and Environment, University Medical Center Utrecht, Utrecht, the Netherlands
8. Department of Medical Microbiology, Maastricht University Medical Center, Maastricht, the Netherlands
9. Department of Occupational Health and Environment, University Medical Center Groningen, Groningen, the Netherlands
10. Department of Occupational Health and Environment, Free University Medical Center, Amsterdam, the Netherlands

Citation style for this article:
Riphagen-Dalhuisen J, Burgerhof JG, Frijstein G, van der Geest-Blankert AD, Danhof-Pont MB, de Jager HJ, Bos AA, Smeets EE, de Vries MJ, Gallee PM, Hak E. Hospital-based cluster randomised controlled trial to assess effects of a multi-faceted programme on influenza vaccine coverage among hospital healthcare workers and nosocomial influenza in the Netherlands, 2009 to 2011. Euro Surveill. 2013;18(26):pii=20512. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20512

Article submitted on 26 July 2012 / published on 27 June 2013

Nosocomial influenza is a large burden in hospitals. Despite recommendations from the World Health Organization to vaccinate healthcare workers against influenza, vaccine uptake remains low in most European countries. We performed a pragmatic cluster randomised controlled trial in order to assess the effects of implementing a multi-faceted influenza immunisation programme on vaccine coverage in hospital healthcare workers (HCWs) and on in-patient morbidity. We included hospital HCWs of three intervention and three control University Medical Centers (UMCs), and 3,367 patients. An implementation programme was offered to the intervention UMCs to assess the effects on both vaccine uptake among hospital staff and patient morbidity. In 2009/10, the coverage of seasonal, the first and second dose of pandemic influenza vaccine as well as seasonal vaccine in 2010/11 was higher in intervention UMCs than control UMCs (all $p<0.05$). At the internal medicine departments of the intervention group with higher vaccine coverage compared to the control group, nosocomial influenza and/or pneumonia was recorded in 3.9% and 9.7% of patients of intervention and control UMCs, respectively ($p=0.015$). Though potential bias could not be completely ruled out, an increase in vaccine coverage was associated with decreased patient in-hospital morbidity from influenza and/or pneumonia.

Introduction

The value of vaccinating healthcare workers (HCWs) against influenza has been subject of debate over decades. In the United States (US), despite respective immunisation recommendations since 1981, vaccine coverage among HCWs was only 63.5% in 2010-/11 [1]. In the United Kingdom (UK), the Netherlands and other European countries, coverage is even lower [2,3]. Several arguments support influenza vaccination of HCWs. First, each year, influenza causes substantial morbidity and mortality among vulnerable patients in hospitals and nursing homes [4-6]. Since contacts between patients, visitors and HCWs are frequent in such settings, and HCWs who are infected with mild symptoms often continue to work [7], epidemics can easily develop and can be large [8]. Second, prophylaxis with neuraminidase inhibitors can be effective, but viral resistance may develop rendering these drugs less effective during influenza infections and such a strategy has not been routinely implemented in healthcare settings. Third, immunisation with the inactivated influenza vaccine has been shown in a large meta-analysis of randomised controlled trials among healthy adults representative of the HCWs population to be 59% effective in preventing laboratory-confirmed influenza infection [9]. Fourth, a mathematical model for a 30-bed hospital predicted that seven HCWs need to be vaccinated to prevent one influenza infection in a patient [10]. Finally, despite some methodological constraints, a meta-analysis of four large randomised controlled trials in long-term care institutions showed significant reductions in patients presenting influenza-like illness and patient mortality in settings with high

vaccine coverage among HCWs versus control settings with low coverage [11].

In the Netherlands, a high influenza vaccine uptake is reached among those belonging to risk groups for influenza. Each year, in October/November, general practitioners immunise patients aged 60 years or older and patients with risk-elevating diseases with stable high vaccination uptake rates above 71% across most parts of the Netherlands [12]. However, if younger than 60 years and admitted for the first time with a high-risk diagnosis, patients are mostly not immunised since they did not belong to a risk group before. Also they are infrequently vaccinated in the hospital since there is no vaccination programme for hospitalised patients in the Netherlands.

In contrast, in both the Netherlands and most other European countries, vaccine uptake among HCWs remains low and influenza vaccination programmes have been voluntary. To be effective in reaching high vaccine coverage against influenza, a large variety of behavioural and organisational factors has to be targeted [13] and a setting- and culture- specific quantitative need assessment is essential to focus the programme on the most influential factors [14].

We applied the Intervention Mapping (IM) method [15] to structure the development of an influenza vaccination programme targeted at hospital staff. We here report the results of an evaluation of this programme. In the study, University Medical Centers (UMCs) from the Netherlands participated during the 2009/10 and 2010/11 influenza seasons. We primarily set out to determine the effects of the programme on vaccine coverage among HCWs using a pragmatic cluster randomised controlled trial. As clinical assessments from hospital settings are lacking, we also set out to determine the effects on patient outcomes during the studied influenza seasons.

Methods

Design, setting and participants

We aimed to assess the clustered effects of a multifaceted influenza vaccination programme on influenza vaccine coverage in HCWs as well as the effect on influenza morbidity in hospitalised patients in UMCs in the Netherlands. In our trial, a cluster is the unit of randomisation defined as one UMC. In this study, we consider HCWs to be all employees working in the hospital. The study period included the influenza seasons 2009/10 and 2010/11.

To reach the objectives we conducted a pragmatic cluster randomised trial because the developed influenza vaccine implementation programme was best applied at hospital level rather than at individual level. All eight UMCs (Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Groningen; University Medical Center, Utrecht; University Medical Center, Maastricht; Free University Medical Center, Amsterdam; University Medical Center, Nijmegen; Leiden University Medical Center, Leiden) were invited to participate in the trial. After permission from the Dutch Federation of UMCs, the board of directors of six of the eight UMCs agreed to randomisation at cluster level. The board of directors of the two remaining UMCs refused to be randomised because their institutions had already undertaken considerable efforts to raise influenza vaccine coverage among staff, but they agreed to act as external controls. Unfortunately, the two UMCs did not give permission to collect patient data.

At baseline, policies for the randomised UMCs were either to offer influenza vaccination to selected healthcare workers or not to vaccinate at all, and the highest vaccine coverage in any UMC was estimated at just below 27%. The baseline vaccine coverage in the external UMCs was somewhat higher reaching levels as high as estimated at 37%, and there was more experience with immunistion campaigns.

UMCs are tertiary referral centers each taking care of special hospitalised patient populations in the eight geographical regions of the Netherlands where they are placed. Acute care is delivered for a large number of patients who are admitted for a wide variety of indications.

In May 2009, prior to the upcoming 2009/10 influenza season, six UMCs were randomly allocated by computer (using the procedure Random in SPSS version 18.0) into two clusters, either the intervention or the control group, by a researcher blinded to the identity of the UMCs. Since the UMCs were about similar in size, number of HCWs and annual number of hospitalisations, we did not match before randomisation. Since we conducted a pragmatic study, the outcome of randomisation was neither blinded for the research group nor for the lead contacts of the UMCs. Although most HCWs were aware that they were targeted for vaccination, they did not know to which arm their UMC was randomly allocated. The study period covered the period from the first influenza vaccination campaign in September/October 2009 to the end of the influenza season 2010/11. The protocol of the trial was waived by the medical ethical committee of the University Medical Center Groningen for ethical approval according to the Dutch Law of Research with Humans (No. 2009.267). The study was conducted in accordance with the Dutch Law for the Protection of Personal Data (Wet Bescherming Persoonsgegevens) and the Declaration of Helsinki [16].

Intervention

In November and December 2008, prior to the trial start in 2009, we conducted a survey to assess which behavioural and organisational factors were associated with vaccine uptake among hospital staff of the UMCs [17]. An 11-item prediction model with nine behavioural and

two demographic predictors could be developed that was highly accurate in discriminating vaccinated from non-vaccinated staff in approximately 95% of the study population. Subsequently, we used the Intervention Mapping (IM) method to thoroughly plan, develop and evaluate a programme that was directed at HCWs in order to influence their behaviour towards immunisation [15,18]. This IM method is a theoretical framework to systematically develop health education interventions and can be used as part of the dynamic process of planning intervention strategies in health education. It contains six consecutive steps: (i) a needs assessment, (ii) creating a matrix of proximal programme objectives, (iii) selecting theory-based intervention methods and practical strategies, (iv) programme planning, (v) adopting and implementing the programme, and (vi) monitoring and programme evaluation.

Various educational tools were developed following the proximal objectives based on the needs assessment (Box). Prior to the immunisation campaign in September 2009 and 2010, the programme educational tools were offered to the lead contact persons from the departments of occupational health of each UMC in the intervention and external group. These departments, in close collaboration with the communication units, are responsible for the influenza vaccination campaign. Information on the methods was provided to them by communication experts within the research group and they were encouraged to communicate the methods at various levels including the board of directors, heads of departments and staff members. The intervention and external group were allowed to make their own choices and decisions regarding the implementation of programme elements. An evaluation of the process showed that intervention and external UMCs targeted most of the behavioural determinants and choose to implement a variety of the developed methods, whereas the control UMCs targeted less determinants [18], Figure. However, actual exposure of HCWs to these methods was variable and in 2009 largely affected by the pandemic preparedness plans. Lead contacts from the control group did not receive the developed methods and were encouraged to follow their usual influenza vaccination policy. We did not seek to influence vaccine coverage among patients.

Outcomes

The primary outcome measure of this trial was the influenza vaccine uptake among all HCWs at UMC level. Vaccine uptake was expressed as percentage calculated through dividing the number of all vaccinated HCWs by the total number of HCWs multiplied by 100. For financial administrative reasons all immunisations are accurately recorded at the hospital level, hence this information was regarded most valid.

Secondary outcome measures were absenteeism rates among HCWs during December of each study year as this is normally the month in which influenza circulates at epidemic levels [19]. The cumulative absenteeism

Box

Behavioural determinants associated with vaccine uptake and developed health education methods to increase influenza vaccine uptake, the Netherlands, 2009

Behavioural determinants	Developed health education methods
Awareness of personal risk for influenza infection	• Provision of information on influenza, transmission and risks through an information stand at the UMC restaurants, a website, a folder and plenary meetings • Polls and a quiz on the intranet • Video testimonials with role models
Awareness of risk of infecting patients	• Provision of information on influenza and the risk of transmission to patients through an information stand at the UMC restaurants, a website, a folder and plenary meetings • Polls and a quiz on the intranet • Video testimonials with role models
Belief that vaccination reduces the risk of infecting patients	• Provision of information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings • Polls and a quiz on the intranet • Video testimonials with role models
Usefulness of vaccination despite the constant flow of visitors	• Provision of information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings • Polls and a quiz on the intranet • Video testimonials with role models
Knowledge on the contents of the Health Council's Advice	• Provide and explain contents of the advice on the intranet or website • Explain and discuss in a plenary meeting
Vaccination of HCWs to ensure continuity of care	• Explain and discuss ethical aspects (plenary meeting, website) • Video testimonials with role models • Involve board of directors (e.g. first vaccination, be present at vaccination, column) • Distribute pins to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
Vaccination of HCWs because of their duty to do no harm	• Explain and discuss ethical aspects (plenary meeting, website) • Video testimonials with role models • Involve board of directors (e.g. first vaccination, be present at vaccination, column) • Distribute pins to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
Belief that people around me think it is important for me to get vaccinated	• Personal invitation letter with information folder and a link to the website at the home address
Willingness to get vaccinated if the vaccine was available at a convenient time	• Poster with practical information on location and time • Personal invitation at home address with location and time • Extended vaccination hours which take changing shifts into account

HCW: healthcare worker; UMC: University Medical Center.

Table 1

Baseline characteristics of University Medical Centers, randomised controlled trial in the Netherlands, 2009 (n=8)

	Intervention UMCs (n=3)	Control UMCs (n=3)	External UMCs (n=2)
Mean number of HCWs' full time equivalents	8,065	5,765	6,584
Mean number of clinical admissions	34,395	28,841	25,999
Mean HCW/patient ratio	0.23	0.20	0.25
Mean percentage of HCWs older than 40 years[a]	37.8 (SD 48.6)	42.6 (SD 49.6)	42.1 (SD 49.6)
Mean percentage of female HCWs[a]	86.7 (SD 34.0)	75.6 (SD 43.0)	88.9 (SD 31.6)

HCW: healthcare worker; SD: standard deviation; UMC: University Medical Center.

[a] Data derived from web-based questionnaire in 2009.

rates for the month December were provided by each department of occupational health of all UMCs after the influenza seasons. Vaccine uptake and absenteeism among HCWs were both analysed at cluster level.

As further secondary outcome, patient outcome data from two selected high risk departments i.e. paediatrics and internal medicine, were collected retrospectively for all patients hospitalised three days or more, to ensure nosocomial exposure during both study seasons. In the 2009/10 influenza season, a lower number of patients could be included after vaccination of HCWs, since the campaign had begun late in the epidemic, whereas we could observe a high number of patients during the complete season of 2010/11. The outcomes collected were laboratory-confirmed influenza and/or pneumonia, length of hospital stay in days, admittance to intensive care and duration. They were compiled by scrutinising computerised discharge letters from the patients' medical files and information from the microbiology laboratories by two reviewers. Influenza was defined as laboratory-confirmed influenza A (all subtypes) or influenza B during hospital stay. Pneumonia was defined as any pneumonia which was clinically diagnosed during hospital stay. Since vaccination coverage was different between departments, patient data were analysed at department level. Since pneumonia is a common complication following influenza, influenza remains often undiagnosed and the combined outcome is regarded most accurate and specific. In accordance with previous studies among seniors we combined this outcome [11].

We were able to obtain patient outcome data on a large number of patients in two departments during the influenza seasons.

Sample size

We aimed to include all HCWs from the eight UMCs prior to conducting the study. Sample size calculations for cluster randomised studies were applied. Based on the high vaccine uptake among patients (around 70%) we expected that we could raise the vaccine coverage of staff in the intervention group from 37%, the highest vaccination rate in all UMCs as estimated by questionnaire [17] to at least 70% and that the control group would remain at 37% coverage. We assumed that all eight UMCs would participate. A minimum of 32 participants per UMC (128 per cluster) were needed to provide more than 80% power if the intra-class correlation (ICC) was estimated at 10% and significance level was set at 5%. Given the much higher numbers of HCWs per UMC, smaller effects could be detected with adequate power.

Statistical methods

Data were analysed using SPSS for Windows, version 18.0 and SAS statistical package 9.1. All outcomes were analysed at cluster level. In addition, patient outcomes were analysed at departmental level. For the primary outcome influenza vaccine coverage and absenteeism rates, we calculated risk differences (RD) and relative risks (RR) with their corresponding 95% confidence intervals (95% CI) and the levels of statistical significance in the different clusters for both influenza seasons combined. This was done by a specifically designed bootstrap program in R statistical software [20] to account for clustering. To account for dependencies of individual observations within hospitals and possible heterogeneity between hospitals we addressed our research questions within the generalised linear mixed model framework. To estimate RR, the binomial distribution was used employing the logarithmic function as link between the mean of the response and the linear part of the model using SAS statistical package. RD were obtained using the identity link function and the normal distribution. We calculated RR and corresponding 95% CI as well as levels of statistical significance for the patient outcomes pooled over both years after adjustments for small baseline differences

Table 2

Baseline characteristics of patients in eight University Medical Centers by intervention/control and department, randomised controlled trial in the Netherlands, 2009–2011 (n=3,367)

	Intervention UMCs n=1,387	Intervention UMCs Department of Internal Medicine n=769/1,804	Intervention UMCs Department of Paediatrics n=618/1,563	Control UMCs n=1,980	Control UMCs Department of Internal Medicine n=1,035/1,804	Control UMCs Department of Paediatrics n=945/1,563
Baseline characteristics						
Mean age (years)	35.3 (range 0-101, SD 31.0)	59.8 (range 18-101, SD 18.8)	4.7 (range 0-19, SD 5.5)	34.1 (range 0-104, SD 30.4)	60.0 (range 17-104, SD 18.3)	5.8 (range 0-23, SD 5.6)
Male (%)	54.2 752/1,387	51.2 394/769	57.9 358/618	51.1 1,012/1,980	50.6 524/1,035	51.6 488/945

SD: standard deviation; UMC: University Medical Center.
None of the outcomes were statistically significant.

of sex (see results). We chose to pool the data to obtain a more precise estimate of the effect because both seasons were dominated by influenza A(H1N1)pdm09 and vaccines matched the circulating strain in both seasons. Adjusted differences in duration of hospitalisation and intensive care admission between clusters were compared after transformation of extreme values to a clinically relevant maximum (30 days for hospital and seven days for intensive care stay). Results were similar as for the non-transformed values.

Results

Baseline characteristics

At the beginning of the measurements in 2009, the baseline characteristics at the level of the whole UMC were determined per group (Table 1). On average, the intervention UMCs were somewhat larger than control and external UMCs with more staff full time equivalents and a higher number of clinical admissions each year. However, the mean HCW/patient ratio was comparable for all three groups. The age and sex distribution of staff as estimated from a web-based survey in 2009 was similar as well (response rate 30.1%) (data not presented). The pooled baseline characteristics of patients from the selected departments of the intervention and control groups showed similar mean age and percentage of men in the intervention and control group (Table 2). The percentage of patients from the internal medicine department and study year 2010/11 was also similar between both groups.

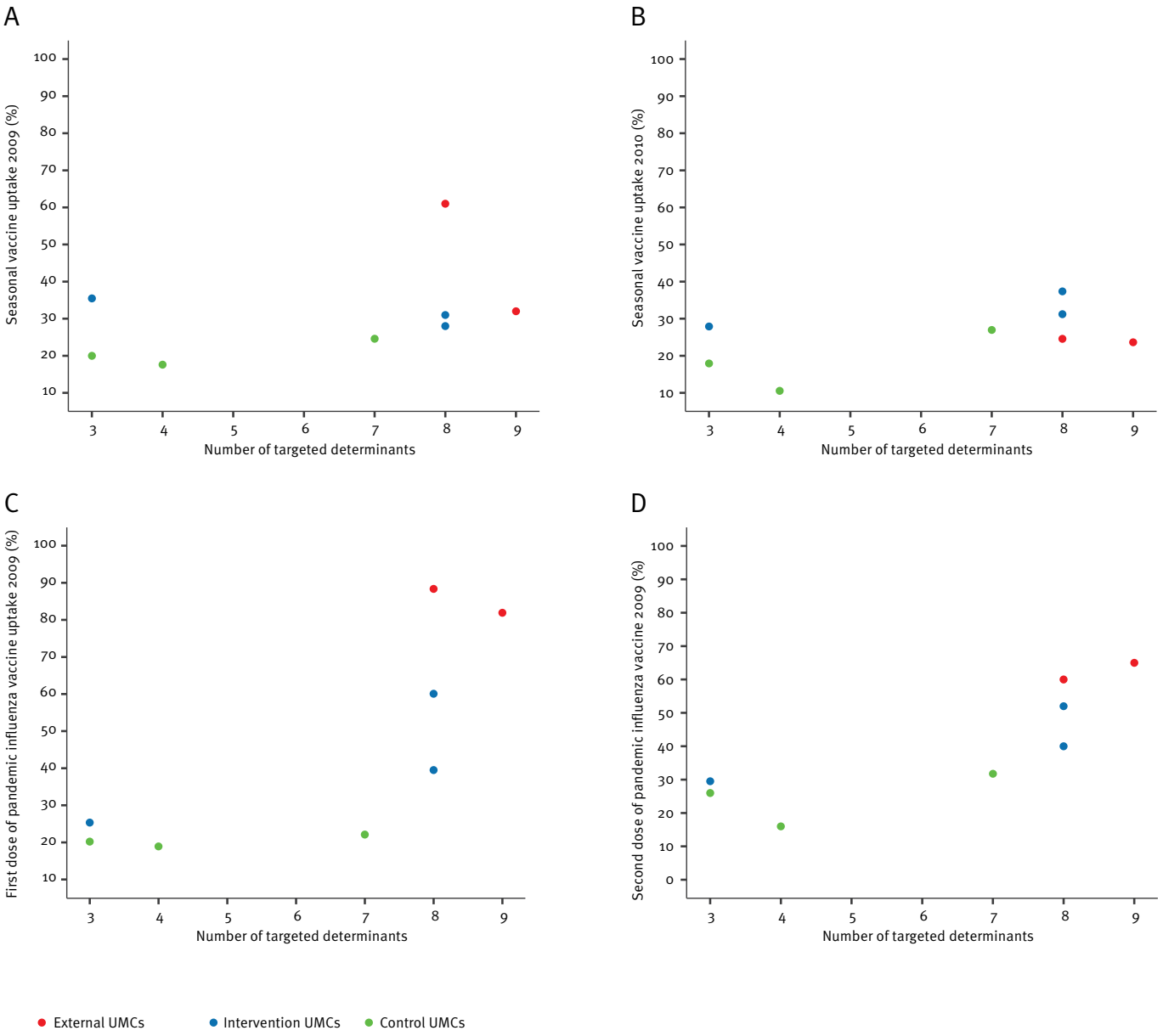
Influenza vaccine uptake

In both study seasons, influenza vaccine coverage among HCWs was significantly higher in the intervention group compared with the control group (Table 2). In 2009 three influenza vaccination rounds were offered because of the emergence of the influenza A(H1N1)pdm09 pandemic virus. In all three groups coverage was highest for the first dose of the pandemic vaccine. In the intervention group the absolute difference in vaccine coverage compared with the control group, for the first dose of the pandemic vaccine was 23.7% (95% CI 4.3% to 47.8%, $p<0.05$). For the second pandemic vaccine dose, coverage was lower in all groups than for the first one, but still 21.4% higher in the intervention than in the control group (95% CI: 3.6% to 40.3%; $p<0.05$). The external UMCs, which were already more active in their vaccination campaign prior to the study than the randomised UMCs, reached even higher influenza vaccine uptake rates compared to the control UMCs in all vaccination rounds with an outstanding 44.0% absolute higher uptake of the first pandemic vaccine dose from 38.0% to 82.0% (95% CI: 30.0% to 53.7%; $p<0.05$). In 2010/11, when the pandemic threat was no longer an issue, coverage of the seasonal influenza vaccine was much lower than the pandemic vaccine coverage in the year before for each group. The absolute RD was the intervention and external group, respectively, compared with the control group (both p-levels <0.05).

To obtain more insights into exposure to different programme methods and the vaccine uptake, we related the number of targeted determinants to vaccine uptake (Figure). There was a clear trend towards increased vaccine coverage if more methods were applied. There was a significant correlation between the number of applied methods and vaccine coverage for both pandemic vaccines (first pandemic vaccine dose Spearman r=0.79,

Figure

Number of targeted behavioural determinants in the influenza vaccination programme and vaccine uptake in healthcare workers in University Medical Centers by vaccine, randomised controlled trial in the Netherlands, 2009–2011



UMC: University Medical Center.

P=0.021; second pandemic vaccine dose Spearman r=0.90, P=0.003). Correlation estimates were not significant for the seasonal vaccines (2009/10: Spearman r=0.41, P=0.317; 2010/11: Spearman r=0.27, P=0.51).

Absenteeism

Work absenteeism rates among HCWs were recorded for December 2009 and December 2010 (Table 3). For both seasons, absenteeism rates were 0.7% to 1.2% higher (absolute RD) on average in both the intervention and external cluster compared with the control group (all $p<0.05$ except for comparison between external and control UMCs in 2010 where $p>0.05$).

Patient outcomes

Self-reported vaccine coverage in 2009/10 and 2010/11 influenza seasons among HCWs differed between the two studied departments. In 2009/10 coverage of a pandemic vaccine in the internal medicine and pediatric departments of intervention UMCs was 100% and 50%, and 92% and 81% in control UMCs, respectively. In 2010/11, corresponding vaccine coverage were 57% and 50%, and 51% and 44%, respectively. Over the two

Table 3

Influenza vaccine uptake rates and work absenteeism rates for the month of December among healthcare workers in eight University Medical Centers, randomised controlled trial in the Netherlands, 2009–2011

	Intervention UMCs	Control UMCs	External UMCs	RD Intervention vs Control	(95% Confidence interval)	RD External vs Control	(95% Confidence interval)
Year 2009							
Seasonal influenza vaccine uptake	32.3% (9,022/27,900)	20.4% (4,572/22,451)	48.7% (8,231/16,893)	11.9%[a]	(7.5 – 15.5)	28.3%[a]	(8.6 – 42.3)
Pandemic influenza vaccine uptake (first dose)	61.7% (17,212/27,900)	38.0% (8,541/22,451)	82.0% (13,852/16,893)	23.7%[a]	(4.3 – 47.8)	44.0%[a]	(30.0 – 53.7)
Pandemic influenza vaccine uptake (second dose)	45.8% (12,772/27,900)	24.4% (5,480/22,451)	56.7% (9,582/16,893)	21.4%[a]	(3.6 – 40.3)	32.3%[a]	(23.4 – 40.5)
Work absenteeism (December 2009)	4.6% (1,297/27,900)	3.4% (579/17,229)	4.1% (701/16,893)	1.2%[a]	(0.9 – 1.7)	0.7%[a]	(0.2 – 1.3)
Year 2010							
Seasonal influenza vaccine uptake	28.6% (8,176/28,621)	17.8% (4,345/24,459)	27.2% (4,555/16,717)	10.8%[a]	(2.0 – 19.9)	9.4%[a]	(1.0 – 17.2)
Work absenteeism (December 2010)	4.6% (1,318/28,621)	3.9% (745/19,267)[b]	4.6% (765/16,717)	0.7%[a]	(0.1 – 1.3)	0.7%	(-0.2 to 1.4)

RD: risk difference; UMC: University Medical Center.

[a] These results are statistically significant.

[b] For this variable no data could be obtained from one control UMC.

study years, the probability of being tested for the presence of influenza virus during the influenza epidemics was nearly twice as high in the intervention cluster compared with the control group, though not statistically significant (Table 4). Despite higher diagnostic testing rates, a diagnosis of influenza and/or pneumonia during hospitalisation was made in half as many cases in the internal medicine department of intervention UMCs compared with the control UMCs (RR=0.5; 95% CI: 0.3-0.9; p=0.015). Nosocomial pneumonia was reduced by a relative reduction of 76% (p=0.028). Other characteristics did not significantly differ between groups and no statistically significant differences were observed in the paediatric departments.

Discussion

In a 2008 publication, Nicoll et al. stated that there is strong evidence for immunising HCWs against influenza that take care of the elderly and the chronically ill in long-term care facilities. However, they did not find strong data on whether or not to vaccinate HCWs in other healthcare settings, such as hospitals [21].

Our study is the first hospital-based trial that showed that adopting a multi-faceted influenza vaccination programme was associated with improved vaccine coverage among HCWs. We also observed a lower risk for nosocomial influenza and/or pneumonia in hospitalised patients at the internal medicine departments during two consecutive influenza seasons, but we did not observe this effect in the studied paediatric departments.

It is surprising that only a small self-reported higher vaccine uptake in the departments of internal medicine led to our observation of a 50% reduction of the RR in patient outcomes. There may be several explanations for this finding. Actual vaccine coverage differences might have been higher than our self-reported estimates given that we observed an absolute higher difference of 23.7% (from 38.0% to 61.7%) and 11.9% (from 20.4% to 32.3%) respectively at group level in both seasons. Other explanations might be that not only vaccine uptake was higher in the intervention UMCs but that the programme led to more hygienic measures such as earlier diagnosis of influenza and isolation or better compliance with hand hygiene. This agrees with the fact that the number of influenza tests was twice higher in the intervention clusters than in the control clusters. Alternatively, baseline risks of patient outcomes might by chance have been different between the departments. For example, we did not have pre-intervention patient outcome prevalences of nosocomial influenza for both clusters. Potential of confounding bias cannot be completely ruled out, but is unlikely given similar age and sex distributions between the two groups.

Table 4

Pooled analysis of patient outcomes by department for intervention and control of eight University Medical Centers, randomised controlled trial in the Netherlands, 2009-2011 (n=3,367)

	Intervention UMCs Department of Internal Medicine n=769/1,804	Intervention UMCs Department of Paediatrics n=618/1,563	Control UMCs Department of Internal Medicine n=1,035/1,804	Control UMCs Department of Paediatrics n=945/1,563	RR (95% Confidence interval) p value Department of Internal Medicine	RR (95% Confidence interval) p value Department of Paediatrics
Outcomes						
Tested for influenza during hospitalisation	17.6% 121/688[a]	10.4% 46/441[a]	7.2% 75/1,035	7.6% 72/945	2.1 (0.5 – 8.4) p=0.29	2.0 (0.7 – 6.1) p=0.22
Influenza and/or pneumonia during hospitalisation	3.9% 30/769	3.6% 22/618	9.7% 100/1,035	1.9% 18/945	0.47 (0.3 – 0.9) p=0.015	2.1 (0.7 – 6.7) p=0.19
Pneumonia during hospitalisation	1.4% 11/769	1.3% 8/618	8.5% 88/1,035	1.1% 10/945	0.24 (0.1 – 0.9) p= 0.03	1.5 (0.3 – 7.3) p=0.65
Use of intensive care during hospitalisation	5.5% 42/769	8.3% 51/618	7.4% 77/1,035	8.5% 80/945	0.7 (0.4 – 1.3) p=0.29	0.6 (0.1 – 3.5) p=0.56
Mean duration of hospitalisation (in days, risk difference is given)[b]	10.2 (SD 8.1)	8.7 (SD 7.6)	10.7 (SD 8.4)	8.1 (SD 7.1)	0.96 (-11.82 to 13.73) p=0.85	0.60 (-3.32 to 4.52) p=0.69
Mean duration of intensive care use (in days, risk difference is given)[c]	3.5 (SD 2.3) n=42	3.2 (SD 2.0) n=51	4.4 (SD 2.5) n=77	4.3 (SD 2.3) n=80	-0.91 (-1.83 to 0.009) p=0.12	-1.14 (-1.92 to -0.36) p=0.06

RR: relative risk; SD: standard deviation; UMC: University Medical Center.

[a] For this variable no data could be obtained from one intervention UMC.
[b] Until 30 days.
[c] Until 7 days.

Further, vaccine uptake was measured at the level of the UMCs and could not be obtained from all individual departments because of the centralisation of the immunisation in most UMCs. Of note, at baseline prior to the trial start, vaccine coverage might have been higher in departments of intervention UMCs than in control UMCs. Self-reported data from HCWs showed, however, that the seasonal influenza vaccine coverage in 2008/09 was 44% and 14% among HCWs of the internal medicine and paediatric departments in intervention UMCs and 54% and 58% in control UMCs, respectively, hence baseline differences cannot explain the improved coverage. The uptake at UMC level most probably accurately reflects the coverage in most but not all departments as observed for the departments of paediatrics and internal medicine. The self-reported coverage was almost twice higher than the overall UMC level data because of the high-risk residents of these departments and longer tradition of taking hygienic preventive measures against infectious diseases in internal medicine and paediatric departments, as compared with most other departments.

The lead contacts and researchers were not blinded for the allocated strategy; hence this may have caused information bias. However, since the numbers of administered vaccines is a marker of quality of care in the UMCs and administration has financial consequences, it is highly unlikely that such bias has occurred.

A major strength of the study includes the randomised design which resulted in largely comparable HCWs and patient populations over the study years. Also, the presence of a control group accounted for natural fluctuation in vaccine coverage as well as external factors at a national level, and the presence of an external group confirming the positive correlation between a targeted campaign and influenza vaccine uptake among HCWs was a major strength. Moreover, the size of the trial HCWs population and patient population was more than adequate to obtain highly precise

estimates of the main effects. Finally, in day-to-day practice swabbing is not routinely done and can therefore not have affected differentially the intervention and control UMCs.

The work absenteeism rate was 1.2 HCWs per 100 HCWs higher in the whole month of December 2009 in the intervention than in control clusters. Since testing for influenza appeared to be more frequent in intervention than control UMCs, if anything, it is likely a marker of stricter working rules applied during influenza seasons in the intervention compared with control UMCs. Obviously, routine swabbing of all patients suspected of influenza would have been the ideal study outcome. Because the pandemic threat was over in 2010 [22], the absolute risk difference for the trial population was down to 0.7 per 100 HCWs during the latter study season. One participating UMC from the control group could not reliably obtain absenteeism data at their UMC level. However, department specific data that could be obtained showed similar rates as within similar departments of the other control UMCs.

The participating hospitals were tertiary centers and the observed effects may not necessarily be applicable to all types of hospitals. In a survey among administrators of all hospitals in the Netherlands in 2010 with a response rate of over 53%, we observed that the average vaccine coverage of staff reported by the administrators was comparable with the coverage in control UMCs (17.7% versus 17.8% in our study) [23]. Interestingly, in that survey we observed a clear association between economic spending on the immunisation programme in these hospitals and vaccine coverage, with higher programme spending (›1,250 Euro versus ≤1,250 euro) leading to 9% improved coverage (24% versus 15%; 95% CI for the difference: 0.7% to 17%). We also observed in our trial that the higher the number of determinants targeted, the higher vaccine uptake in both study seasons (Figure). Although evidence is scarce, the introduction of a thoroughly developed programme likely leads to improved coverage in any type of hospital.

In 2009, the influenza A(H1N1)pdm09 pandemic also affected the Netherlands, starting in early October and ending in December 2009. Following the advice from the World Health Organization and the Dutch Health Council, the Ministry of Health decided that risk patient groups should be prioritised for pandemic vaccination against this new influenza variant. HCWs were considered both as an important potential transmitter of influenza to risk patients and essential in the care of patients during a pandemic and were considered a target group for pandemic vaccination. As in most other countries, the pandemic was associated with enormous media attention and fear in the community. Therefore, in summer of 2009, all UMCs installed their pandemic response team and prepared for a worst case scenario [24]. The installed preventive measures were very costly, reaching hundred thousands of Euros per UMC, and led to pressure on both management and HCWs. It was therefore unexpected to see that despite general circumstances, both the intervention and external cluster reached higher vaccine coverage than the controls.

After the pandemic was declared over and it appeared to be much less severe than had initially been feared [24], we hypothesized that many HCWs were displeased about the pressure on them and the measures taken. In 2010/11, therefore, seasonal vaccine coverage was half the coverage of the first dose of pandemic vaccine, and despite higher coverage in the intervention than the control cluster, it remained below a staggering low of 30%.

In conclusion, our results suggest that a multi-faceted influenza vaccination programme for hospital HCWs is effective in raising vaccine uptake among HCWs. Although bias cannot be completely ruled out, an increase in vaccine coverage was associated with a decrease in influenza and/or pneumonia among patients during hospitalisation. Given the current evidence for annual risks of influenza complications in hospital and benefits of vaccination, and the low voluntary coverage, mandatory programmes should be seriously considered.

Acknowledgements

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw), grant number 125030012. The funding organisation had neither a role in conduct and analysis of the data-analysis nor in the report of the study.

Conflict of interest

None declared.

Authors' contributions

JRD conducted the study, collected and analysed the data and drafted the manuscript. JB re-analysed the data and commented on the final version of the manuscript. GF, AGB, MDP, HJ, AB, ES, MV and PG contributed to the design of the study, were lead contacts during the study and critically reviewed the manuscript. EH obtained funding, supervised the conduct and report of the study and critically commented on the manuscript. JRD and EH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of a manuscript.

Trial registration number

NCT01481467 (www.clinicaltrials.gov)

References

1. Centers for Disease Control and Prevention (CDC). Influenza vaccination coverage among health-care personnel - United States, 2010-11 influenza season. MMWR Morb Mortal Wkly Rep. 2011;60(32):1073-7. PMid:21849963.
2. Kroneman M, Paget WJ, van Essen GA. Influenza vaccination in Europe: An inventory of strategies to reach target populations and optimise vaccination uptake. Euro Surveill. 2003;8(6):pii=418. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=418. PMid:12878803.
3. Mereckiene J, Cotter S, Nicoll A, Lévy-Bruhl D, Ferro A, Tridente G, et al. National Seasonal Influenza Vaccination Survey in Europe, 2008. Euro Surveill. 2008;13(43):pii=19017. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19017
4. Lee N, Choi KW, Chan PK, Hui DS, Lui GC, Wong BC, et al. Outcomes of adults hospitalised with severe influenza. Thorax. 2010;65(6):510-5. http://dx.doi.org/10.1136/thx.2009.130799. PMid:20522848.
5. Hak E, Hoes AW, Verheij TJ. Influenza vaccinations: Who needs them and when? Drugs. 2002;62(17):2413-20. http://dx.doi.org/10.2165/00003495-200262170-00001. PMid:12421099.
6. Everts RJ, Hanger HC, Jennings LC, Hawkins A, Sainsbury R. Outbreaks of influenza A among elderly hospital inpatients. N Z Med J. 1996;109(1026):272-4. PMid:8769048.
7. Weingarten S, Riedinger M, Bolton LB, Miles P, Ault M. Barriers to influenza vaccine acceptance. A survey of physicians and nurses. Am J Infect Control. 1989;17(4):202-7. http://dx.doi.org/10.1016/0196-6553(89)90129-6
8. van den Dool C, Bonten MJ, Hak E, Wallinga J. Modeling the effects of influenza vaccination of health care workers in hospital departments. Vaccine. 2009;27(44):6261-7. http://dx.doi.org/10.1016/j.vaccine.2009.07.104. PMid:19686690.
9. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: A systematic review and meta-analysis. Lancet Infect Dis. 2012;12(1):36-44. http://dx.doi.org/10.1016/S1473-3099(11)70295-X
10. van den Dool C, Bonten MJ, Hak E, Heijne JC, Wallinga J. The effects of influenza vaccination of health care workers in nursing homes: Insights from a mathematical model. PLoS Med. 2008;5(10):e200. http://dx.doi.org/10.1371/journal.pmed.0050200. PMid:18959470. PMCid:2573905.
11. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev. 2010;(2):CD005187. PMid:20166073.
12. Tacken M, Mulder J, van den Hoogen H, Tiersma W, Donkers J, Verheij R, et al. Monitoring Nationaal Programma Grieppreventie 2008. [Monitoring the National Program for Influenza Prevention 2008]. Netherlands Information Network of General Practice (LINH). 2009; Dutch. Available from: http://www.nivel.nl/sites/default/files/bestanden/grieprap2008%20met%20erratum_.pdf
13. Riphagen-Dalhuisen J, Gefenaite G, Hak E. Predictors of seasonal influenza vaccination among healthcare workers in hospitals: A descriptive meta-analysis. Occup Environ Med. 2012;69(4):230-5. http://dx.doi.org/10.1136/oemed-2011-100134 PMid:22172951.
14. Looijmans-van den Akker I, Hulscher ME, Verheij TJ, Riphagen-Dalhuisen J, van Delden JJ, Hak E. How to develop a program to increase influenza vaccine uptake among workers in health care settings? Implement Sci. 2011;6:47. http://dx.doi.org/10.1186/1748-5908-6-47. PMid:21595877. PMCid:3115899.
15. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence -based health education programs. Health Educ Behav. 1998;25(5):545-63. http://dx.doi.org/10.1177/109019819802500502. PMid:9768376.
16. World Medical Association (WMA). WMA Declaration of Helsinki: Ehtical Principles for Medical Research Involving Human Subjects. Seoul: WMA; Oct 2008; Available from: www.wma.net/en/30publications/10policies/b3/
17. Hopman CE, Riphagen-Dalhuisen J, Looijmans-van den Akker I, Frijstein G, Van der Geest-Blankert AD, Danhof-Pont MB, et al. Determination of factors required to increase uptake of influenza vaccination among hospital-based healthcare workers. J Hosp Infect. 2011;77(4):327-31. http://dx.doi.org/10.1016/j.jhin.2010.10.009. PMid:21316803.
18. Riphagen-Dalhuisen J, Frijstein G, van der Geest-Blankert N, Danhof-Pont M, de Jager H, Bos N, et al. Planning and process evaluation of a multi-faceted influenza vaccination implementation strategy for health care workers in acute health care settings. BMC Infect Dis. 2013;13:235 http://dx.doi.org/10.1186/1471-2334-13-235. PMid:23701921. PMCid:3680164.
19. Netherlands institute for health services research (NIVEL). Wekelijkse griepcijfers Nederland. [Weekly influenza report, the Netherlands]. Utrecht: NIVEL. 19 Jun 2013. Dutch. Available from: http://www.nivel.nl/dossier/wekelijkse-griepcijfers-nederland
20. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2010.
21. Nicoll A, Ciancio BC, Tsolova S, Blank PR, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill. 2008;13(43):pii=19018. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19018
22. Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M, et al. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ. 2011;343:d3908 http://dx.doi.org/10.1136/bmj.d3908. PMid:21750072. PMCid:3134565.
23. Riphagen-Dalhuisen J, Kuiphuis JC, Procé AR, Luytjes W, Postma MJ, Hak E. Contributing factors to influenza vaccine uptake in general hospitals: an explorative management questionnaire study from the Netherlands. BMC Public Health. 2012;12:1101. http://dx.doi.org/10.1186/1471-2458-12-1101. PMid:23259743. PMCid:3545720.
24. van der Sande MA, Jacobi A, Meijer A, Wallinga J, van der Hoek W, van der Lubben M. The 2009 influenza A (H1N1) pandemic. Management and vaccination strategies in The Netherlands. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2013;56(1):67-75. http://dx.doi.org/10.1007/s00103-012-1582-4. PMid:23275958.

Reminder: Call for Abstracts for the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) closes on Friday 5 July 2013

Eurosurveillance editorial team (eurosurveillance@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Citation style for this article:
Eurosurveillance editorial team. Reminder: Call for Abstracts for the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) closes on Friday 5 July 2013 . Euro Surveill. 2013;18(26):pii=20511. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20511

Article submitted on 27 June 2013 / published on 27 June 2013

The 2013 European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) conference is being held in Stockholm, Sweden on 5-7 November 2013. The conference welcomes abstracts in all areas related to infectious disease prevention and control, including epidemiology, public health microbiology, surveillance, and the application of tools and methods to support infectious disease outbreaks or interventions. Submitting an abstract to ESCAIDE gives an opportunity to present work to public health professionals from the European Union and around the globe, and share experiences and knowledge that can help the prevention of communicable disease. The deadline for submitting an abstract expires 5 July 2013.

Abstracts can be submitted via the dedicated 'call for abstracts' portal on the ESCAIDE website. The ESCAIDE website also contains information on the conference programme, registration and other 2013 ESCAIDE activities. You can also sign up to receive regular updates on the conference.