VACUNACIÓ ANTIGRIPAL I MORTALITAT HIVERNAL A LA POBLACIÓ MAJOR DE 65 ANYS DE L'ÀREA DE TARRAGONA

Cinta de Diego Cabanes

Dipòsit Legal: T.195-2013

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VACUNACIÓ ANTIGRIPAL I MORTALITAT HIVERNAL A LA POBLACIÓ MAJOR DE 65 ANYS DE L'ÀREA DE TARRAGONA.

TESI DOCTORAL

Dirigida pel Dr. Ángel Vila Córcoles i Dr. Carles Llor

Departament de Medicina i Cirurgia

UNIVERSITAT ROVIRA I VIRGILI

TARRAGONA
OCTUBRE 2012

UNIVERSITAT ROVIRA I VIRGILI
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Als meus pares, per estar sempre al meu costat

Al Quim, per fer el camí junts

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AGRAÏMENTS

A Ángel Vila pel seu suport, ser el guia del projecte, sense ell res hagués sigut possible.

Als directors de tesi, Dr. Ángel Vila i Dr. Carles Llor per la seva ajuda en el disseny i redacció.

A la Direcció del Servei d'Atenció Primària de Tarragona - Valls de l'Institut Català de la Salut, a la Direcció del CAP Torreforta per facilitar la investigació en Atenció Primària.

Als companys del CAP Torreforta per la seva ajuda.

A Teresa Rodríguez per la realització de les anàlisis estadístiques.

A la Nohemí Macaya i a la Jennifer González per la seva ajuda tècnica.

Al personal de Sistemes de Informació del Servei d'Atenció Primària de Tarragona - Valls per l'elaboració de bases de dades.

A tot el personal que treballa a les 8 Àrees Bàsiques de Salut incloses a l'estudi.

Als meus amics pel seu suport.

A tots els pacients inclosos a l'estudi.

A la Fundació Jordi Gol per la seva ajuda econòmica.

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LLISTAT D'ABREVIATURES

AAFP: l'American Academy of Family Physicians.

ABS: Àrea Bàsica de Salut.

ACIP: Advisory Committee on Immunization Practices.

CDC: Centres for Disease Control and Prevention.

DM: Diabetis Mellitus.

MPOC: Malaltia pulmonar obstructiva crònica.

HCAP: Historia clínica d'Atenció Primària.

HR: Hazard Ratio.

IC: Interval de confiança.

ICD-9: Classificació internacional de malalties en la seva 9ª revisió.

NNV: Nombre necessari de vacunacions.

OR: Odds ratio.

PAPPS: Programa de Actividades Preventivas y de Promoción de la Salud.

PHCC: Primary health care center.

RA: Risc atribuïble.

SEMFyC: Sociedad Española de Medicina Familiar y Comunitaria.

SIDA: Síndrome d'immunodeficiència adquirida.

VAG: Vacuna antigripal.

WHO: World Health Organization.

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I - INTRODUCCIÓ

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El virus de la grip és un virus d'ARN de la família dels Orthomyxoviridae. Una de les característiques més típiques de la coberta del virus és la presència d'espícules que es projecten radialment i que conformen 2 tipus morfològics diferents: les HA (hemaglutinina) de forma de bastó i les NA (neuroaminidases). Tots dos antígens de superfície estan agregats a la coberta lipídica, per curtes seqüències d'aminoàcids hidrofòbics. En la part interna d'aquesta coberta, derivada de la membrana plasmàtica de la cèl·lula hoste, es troba la proteïna M (matriu o membrana) que dóna forma i estabilitat a l'embolcall (Cox 1999).

La grip és una infecció vírica aguda que es transmet fàcilment d'una persona a una altra. Els virus de la grip circulen per tot el món i poden afectar a qualsevol persona de qualsevol edat. La grip causa epidèmies anuals que en les regions templades arriben al seu màxim durant l'hivern. La grip és un problema greu de salut pública que pot ser causa de malaltia greu i mort en poblacions d'alt risc. Les epidèmies poden exercir gran pressió assistencial i tenir importants repercussions econòmiques degut a la reducció de la productivitat laboral. La vacunació és la forma més eficaç de prevenir la infecció (WHO 2002).

La grip estacional és una infecció vírica aguda causada per un virus gripal. Hi ha tres tipus de grip estacional: A, B i C. Els virus gripals de tipus A es classifiquen en subtipus en funció de les diferents combinacions de dues proteïnes de la superfície del virus (H i N). Els casos de grip C són molt menys freqüents que els de grip A o B, i és per això que les vacunes antigripals estacionals només inclouen virus dels tipus A i B (WHO 2002).

La grip és una causa important de morbi-mortalitat a tot el món. La infecció del virus de la grip té una incidència alta en persones joves i en nens, més que en gent gran, però la mortalitat i morbiditat associades a la infecció pel virus de la grip augmenta amb l'edat, especialment en individus amb patologia concomitant (WHO 2002).

Les epidèmies de grip es repeteixen anualment, durant la tardor i l'hivern a les regions templades. La malaltia és causa d'hospitalització i mort, sobretot en nens petits, ancians i malalts crònics. Aquestes epidèmies anuals causen uns 3 a 5 milions de casos de malaltia greu i unes 250.000 a 500.000 morts anuals. En els països industrialitzats la majoria de les morts associades a la grip corresponen a majors de 65 anys. (WHO 2002).

La vacunació antigripal (VAG) està considerada una mesura preventiva molt efectiva i la vacunació en gent gran i persones amb risc de complicacions de la infecció pel virus de la grip és una estratègia clau en la política sanitària per a la prevenció de morbi-mortalitat en molts països (WHO 2002; CDC 2004; Van Essen 2003).

Molts estudis observacionals han demostrat l'efectivitat de la VAG en la prevenció d'hospitalització i mortalitat en individus d'alt risc, les metanàlisis conclouen que la VAG disminueix el risc de mortalitat hivernal en gent gran en un 50% aproximadament (Gross 1995; Vu 2002). Alguns estudis de cohorts suggereixen que l'efectivitat vacunal en la prevenció de mortalitat per totes les causes en la gent gran pot haver estat sobreestimada en estudis previs i en les metanàlisis (Simonsen 2005; Mantagni 2004). Una revisió Cochrane de l'any 2006, va concloure que tot i que la VAG apareix clarament associada a una disminució del risc de mortalitat en estudis hospitalaris, no apareix com una mesura estadísticament significativa en gent gran que viu a la comunitat (Rivetti 2006).

L'efectivitat de la VAG en la prevenció de la morbilitat i mortalitat relacionades amb la grip han estat extensament estudiades durant les estacions gripals amb alta incidència, persones institucionalitzades i individus d'alt risc. Però pocs estudis a mig i llarg temps s'han realitzat per a l'avaluació del benefici clínic de la vacunació anual en la població anciana en general, i poc se sap de l'efectivitat dels programes de

vacunació anuals en gent gran sense factors de risc que viuen a la comunitat.

El virus de la grip està relacionat amb un increment de la morbi-mortalitat sobretot en gent amb malaltia pulmonar obstructiva crònica (MPOC) (Lupatkin 2005), i la vacunació anual es considera una mesura preventiva cost - efectiva (Nichol 2003; Sprenger 1993), encara que els estudis que s'han vingut realitzant són observacionals i pocs estudis clínics controlats i randomitzats en població amb MPOC s'han realitzat fins el moment. La infecció pel virus de la grip ocasiona un excés de morbiditat i de mortalitat en pacients MPOC, però l'efecte de la VAG en la prevenció de mortalitat en aquest grup de pacients no està clar (Poole 2006). S'han realitzat estudis en pacients ancians i en pacients d'alt risc, alguns dels quals tenien patologies pulmonars cròniques (Nichol 2003; Voordouw 2004), però hi ha pocs estudis específics en pacients amb MPOC (Wongsurakiat 2004; Gorse 2004).

Un altre subgrup de risc per la infecció gripal son els pacients cardiòpates. Durant les èpoques de grip, s'ha demostrat un augment de mortalitat per patologia cardiovascular i morts coronàries confirmades per autòpsia relacionades amb la infecció pel virus de la grip (Madjid 2007). Dades obtingudes d'estudis clínics i experimentals, suggereixen que mecanismes autoimmunes són els responsables de l'aterosclerosi coronària accelerada en la infecció pel virus de la grip. Tant la immunitat humoral com cel·lular podrien participar en la formació i progressió de les lesions arterioscleròtiques degudes a la infecció gripal (Gurevich 2005; Madjid 2005). Fins a la data, tot i que alguns estudis han mostrat resultats que relacionen un excés específic de mortalitat cardíaca deguda a la infecció pel virus de la grip (Madjid 2007; Wang 2007), l'efecte de la VAG en la prevenció de mortalitat entre pacients amb patologia cardíaca crònica no és ben conegut, ja que pocs estudis s'han centrat en aquest grup de població (Gurfinkel 2004; Heffelfinger 2006) i les seves conclusions no sempre van a favor de la VAG (Heffelfinger 2006).

Els diabètics son també, encara que en menor mesura, un subgrup de pacients de risc per la grip (especialment per la possibilitat de presentar complicacions i descompensacions derivades de la infecció) (Heymann 2004; CDC 2004; WHO 2002).

La immunització antigripal és important en la medicina preventiva de malalties cròniques com la diabetis on l'equip d'atenció primària té un paper protagonista. D'acord amb l'Advisory Committee on Immunization Practices (ACIP), l'American Academy of Family Physicians (AAFP), el Ministerio de Sanidad y Consumo i les recomanacions del Programa de Actividades Preventivas y de Promoción de la Salud (PAPPS) de la Sociedad Española de Medicina de Familia y Comunitaria (SEMFyC), la vacunació anual d'individus d'alt risc abans de l'època gripal, és la mesura més efectiva per a reduir l'impacte de la grip. En relació amb la diabetis mellitus, l'objectiu a l'atenció primària hauria de ser la immunització de totes aquelles persones diabètiques, sobretot si tenen factors de risc com a malaltia renal o cardíaca, o aquelles que han sigut hospitalitzades recentment (Smith 2004).

Tot i que l'efectivitat de la vacuna antigripal a la prevenció de la mortalitat ha sigut extensament estudiada en pacients institucionalitzats i hospitalitzats en èpoques d'alta activitat gripal, hi ha pocs estudis sobre el benefici de la vacunació a mitjà i llarg termini en pacients no institucionalitzats (Colquhoun 1997; Wang 2007; Ortqvist 2007; Nichol 2007; Voordouw 2003; Nichol 1998; Nordin 2001; Looijmans-Van den Akker 2006; Mangtani 2004), i poc se sap de l'efectivitat dels programes de vacunació anuals de les persones grans amb patologia de risc (Simonsen 2007).

II - JUSTIFICACIÓ

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Amb la finalitat d'estudiar l'impacte potencial de la discutida vacuna antipneumocòccica polisacàrida en la població major de 65 anys, al nostre àmbit es va iniciar l'any 2002 un estudi prospectiu de cohorts, anomenat estudi EVAN-65 (Vila - Córcoles 2006), que incloïa el seguiment durant 40 mesos consecutius de tota la població major de 65 anys adscrita al Servei d'Atenció Primària de l'Institut Català de la Salut a Tarragona - Vallls. Aquest estudi, finançat pel Fondo de Investigación Sanitaria (FIS) de l'Instituto de Salud Carlos III, va constituir una excel·lent oportunitat per a avaluar de forma concomitant l'impacte de la vacunació antigripal en aquesta població, donat que en el protocol de l'estudi original figurava el registre de la vacunació antigripal al llarg dels 4 anys d'estudi. Aquest estudi inclou 11.240 persones majors de 65 anys, assignades a 8 àrees bàsiques de salut (ABS) de Tarragona-Valls que van ser seguides des del 01/01/2002 fins al 30/04/2005 (Vila - Córcoles 2006).

En la present tesi, donat que la magnitud de la possible efectivitat de la vacunació antigripal en la gent gran (amb o sense factors de risc) és també discutida en els últims temps, es va considerar pertinent i justificat analitzar la possible relació entre la recepció de la vacuna antigripal convencional i la mortalitat (hivernal i al llarg de tot el període) en la mateixa cohort.

A més, considerant la possible diferent efectivitat de la vacunació en distints subgrups de risc, es va considerar també pertinent estudiar l'impacte de la vacunació sobre la mortalitat en els subgrups de pacients amb MPOC (1.298 persones), cardiopatia crònica (1.340 persones) i/o Diabetis Mellitus (2.650 persones).

III - OBJECTIUS

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Objectius específics:

1. Avaluar la relació entre la recepció de la vacuna antigripal inactivada convencional i la mortalitat hivernal en la població general major de 65 anys.

2. Avaluar els efectes de la vacunació antigripal anual sobre la mortalitat hivernal en gent gran amb MPOC.

3. Avaluar els efectes de la vacunació antigripal anual sobre la mortalitat hivernal en gent gran amb cardiopatia crònica

4. Avaluar l'impacte de la vacunació antigripal anual sobre la mortalitat hivernal en diabètics majors de 65 anys.

IV - METODOLOGIA

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Disseny de l'estudi, emplaçament i criteris d'inclusió - exclusió.

Estudi de cohorts, de tipus prospectiu i multicèntric. Es van incloure a totes les persones de 65 anys o més (n=11.240), no institucionalitzades, assignades a 8 de les 12 àrees bàsiques de salut (ABS) del Servei d'Atenció Primària de la regió de Tarragona - Valls, pertanyents a l'Institut Català de la Salut. Es van triar com a participants 8 de les 12 ABS, tenint en compte l'existència d'història clínica informatitzada des de 1999 o abans. Les 4 restants ABS van quedar fora de l'estudi al no complir aquest requisit.

La cohort va incloure un total d'11.240 pacients majors de 65 anys a la data d'inici del seguiment (1 de gener de 2002).

Els membres de la cohort foren seguits des del començament de l'estudi fins el cessament per trasllat, mort o final de l'estudi (30 d'abril de 2005) i va ser realitzat conforme als principis generals per estudis observacionals. L'estudi fou aprovat pel comitè ètic de l'Institut Català de la Salut.

Totes les ABS participants tenien històries clíniques informatitzades amb registres específics per a immunitzacions, analítiques clíniques, medicació i diagnòstics codificats segons la classificació internacional de malalties en la seva 9ª revisió (ICD-9). Els registres electrònics de cada membre de la cohort van ser usats per a conèixer l'estat vacunal i per a identificar la presència de comorbiditats.

El període gripal fou definit com el període durant el qual són generalment diagnosticats els quadres influenza - like a l'àrea d'estudi, considerant-ne des de l'1 de gener fins el 30 d'abril per a cada any.

L'estat vacunal front la grip es va considerar com una condició dicotòmica (vacunat - no vacunat) variable en el temps durant el període d'estudi. Per exemple 2002-2005, en l'anàlisi de tot el període d'estudi, una

mateixa persona podia estar no vacunada l'any 2002, vacunada l'any 2003 i no vacunada l'any 2004, d'acord amb la recepció o no de la vacuna antigripal la tardor prèvia.

Mesura de l'efecte.

La variable utilitzada per a mesurar l'impacte de la vacunació fou la mort per totes les causes. Inicialment es van reclutar les morts a la base de dades demogràfiques de la institució (actualitzat mensualment amb dades administratives sobre morts, pacients traslladats o nous pacients assignats). Posteriorment, es va completar i validar la data exacta de la mort amb una revisió dels registres civils municipals. Finalment, les morts foren classificades com a ocorregudes dins el període gripal (gener - abril) o fora del període gripal (maig - desembre).

Covariables.

Es van considerar edat, sexe, malaltia pulmonar crònica (incloent asma, emfisema o bronquitis crònica), malaltia cardíaca crònica, hipertensió, obesitat, tabaquisme, immunodeficiència (càncer d'òrgan sòlid o neoplàsia hematològica), nefropatia crònica greu (síndrome nefròtica, insuficiència renal, diàlisi o trasplantament renal), malaltia hepàtica greu (cirrosi), anesplènia funcional o anatòmica, SIDA, teràpia oral corticoide de llarga duració (20mg/dia de prednisona) o altra medicació immunosupressiva. La presència de condicions de comorbiditat va ser determinada per revisió de codis diagnòstics a la història clínica electrònica per a cada membre de la cohort.

Proves estadístiques.

Les taxes de mortalitat varen ser calculades com a persones/any i persones/setmana (al numerador, el nombre de morts, i al denominador, el total de persones - temps). El risc atribuïble (RA) va ser la diferència entre les taxes de mortalitat entre els no vacunats i els vacunats (RA=incidència en exposats - incidència en no exposats). El nombre necessari de

vacunacions (NNV) anuals antigripals per a evitar una mort fou calculada per períodes gripals (gener - abril=17,1 setmanes) i es va calcular com a l'invers del RA (NNV=1/RA).

En l'anàlisi bivariant, per a comparar variables categòriques entre grups es va utilitzar el test de Khi quadrat i per a les variables contínues el test de la T de Student o l'anàlisi de la variança.

Per analitzar la relació entre la recepció de la vacuna antigripal i ocorrença de mort per qualsevol causa es va realitzar una anàlisi multivariant mitjançant Regressió de Cox per variables que canvien en el temps ("time - varying covariates"). L'estat vacunal front la grip va ser considerat una variable que podia variar en el temps al llarg de l'estudi, mentre que la resta de covariables van ser fixades a la data de l'inici de l'estudi. Tots els models de Cox es varen iniciar incloent totes aquelles variables amb un nivell de significació $p<0.20$ en l'anàlisi bivariant així com aquelles altres variables jutjades epidemiològicament importants. Com a mesura de la relació es van calcular "hazard ratios" (HR) ajustats per vacunats en relació a no vacunats. Tots els resultats s'expressen amb el seu interval de confiança (IC) del 95%. El programa estadístic utilitzat va ser el SPSS versió 15.1. Es van realitzar anàlisis separadament per període gripal (gener–abril) i 4 anàlisis suplementàries per anys i període gripal. L'estat vacunal va ser una covariable canviant en el temps en l'estudi estratificat per períodes gripals i una condició fixa dicotòmica (vacunat / no - vacunat) a l'anàlisi per anys. A més de l'anàlisi en la població total, es van realitzar 3 subgrups (MPOC, Cardiòpates i Diabetis Mellitus) que es van analitzar separadament.

V - RESULTATS

V – RESULTATS

Publicacions generades:

1. Ángel Vila - Córcoles, Teresa Rodríguez, Cinta de Diego, Olga Ochoa, Amparo Valdivieso, Elisabet Salsench, Xabier Ansa, Waleska Badía, Neus Saún, EPIVAC Study Group. Effect of influenza vaccine status on winter mortality in Spanish community - dwelling elderly people during 2002–2005 influenza periods. Vaccine. 2007 Sep 17;25(37-38):6699-707. Epub 2007 Jul 27. Índex d'impacte: 3.337. Quartil i àrea: 1er.

2. A. Vila - Córcoles, O. Ochoa, C. de Diego, A. Valdivieso, I. Herreros, F. Bobé, M. Alvarez, M. Juárez, I. Guinea, X. Ansa, N. Saún. Effects of annual influenza vaccination on winter mortality in elderly people with chronic pulmonary disease. Int J Clin Pract. 2008 Jan;62(1):10-7. Epub 2007 Jun 15. Índex d'impacte: 1.594. Quartil i àrea: 3r.

3. Cinta de Diego, Angel Vila - Córcoles, Olga Ochoa, Teresa Rodriguez -Blanco, Elisabeth Salsench, Imma Hospital, Ferran Bejarano, M. del Puy Muniain, Mercé Fortin, Montserrat Canals, and EPIVAC Study Group. Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease. European Heart Journal. 2009 Jan;30(2):209-16. Epub 2008 Nov 8. Índex d'impacte: 7.924. Quartil i àrea: 1er.

4. C. de Diego, Á. Vila - Córcoles, O.Ochoa - Gondar, A.Valdivieso, V.Arija y T.Rodríguez - Blanco. Vacunación antigripal y mortalidad invernal en pacientes diabéticos mayores de 65 años. Semergen. 2010;36(1):3–9. Índex d'impacte: 0.026. Quartil i àrea: 3er.

ARTICLES PUBLICATS

PUBLICACIONS GENERADES

ARTICLE 1

Efecte de la vacuna antigripal sobre la mortalitat hivernal en persones grans espanyoles que viuen a la comunitat durant els períodes gripals 2002-2005. Ángel Vila - Córcoles, Teresa Rodríguez, Cinta de Diego, Olga Ochoa, Amparo Valdivieso, Elisabet Salsench, Xabier Ansa, Waleska Badía, Neus Saún, EPIVAC Study Group. Effect of influenza vaccine status on winter mortality in Spanish community - dwelling elderly people during 2002 - 2005 influenza periods. Vaccine 2007 Sep 17; 25(37-38):6699-707.

Resum

Aquest estudi va avaluar la relació entre la recepció de la vacuna antigripal inactivada convencional i la mortalitat hivernal en un estudi de cohorts prospectiu que va incloure a 11.240 persones grans residents a la comunitat i varen ser seguits entre gener de 2002 fins abril de 2005. L'estat vacunal antigripal anual era una condició variable en el temps i el resultat primari va ser la mort per qualsevol causa durant el període d'estudi. Es van utilitzar models multivariables proporcionals de Cox ajustat per edat, sexe i comorbiditat per avaluar l'eficàcia de la vacuna. La vacunació antigripal es va associar amb una reducció significativa del 23% en el risc de mortalitat hivernal durant els períodes gripals totals. El risc atribuïble de mortalitat en les persones no vacunades va ser de 24 morts per cada 100.000 persones - setmana en períodes gripals, la fracció de prevenció per a la població general va ser del 14%, i es va prevenir una mort per cada 239 vacunacions anuals (variant de 144 a l'hivern 2005 fins 1.748 a l'hivern 2002).

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 6699–6707
Vaccine
www.elsevier.com/locate/vaccine

Effect of influenza vaccine status on winter mortality in Spanish community-dwelling elderly people during 2002–2005 influenza periods

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Received 22 November 2006; received in revised form 10 May 2007; accepted 10 July 2007
Available online 27 July 2007

Abstract

This study assessed the relationship between the reception of conventional inactivated influenza vaccine and winter mortality in a prospective cohort that included 11,240 Spanish community-dwelling elderly individuals followed from January 2002 to April 2005. Annual influenza vaccine status was a time-varying condition and primary outcome was all-cause death during study period. Multivariable Cox proportional-hazard models adjusted by age, sex and co-morbidity were used to evaluate vaccine effectiveness. Influenza vaccination was associated with a significant reduction of 23% in winter mortality risk during overall influenza periods. The attributable mortality risk in non-vaccinated people was 24 deaths per 100,000 persons-week within influenza periods, the prevented fraction for the population was 14%, and one death was prevented for every 239 annual vaccinations (ranging from 144 in Winter 2005 to 1748 in Winter 2002).

Keywords: Influenza vaccination; Effectiveness; Mortality; Elderly; Influenza

1. Introduction

Immunisation against influenza is generally considered a very effective preventive means and vaccination of elderly people and other persons at risk for complications from influenza is a key public health strategy for preventing associated morbidity and mortality in many countries [1–3].

Many observational studies have demonstrated the effectiveness of influenza vaccination to prevent hospitalisation and death in high-risk individuals, and meta-analyses concluded that influenza vaccination reduces winter mortality risk by approximately 50% in elderly people [4,5]. However, some recent historical cohort studies have suggested that vaccine effectiveness in preventing all-cause mortality in the general elderly population could have been overestimated in previous studies and meta-analyses [6,7].

The effectiveness of influenza vaccination in preventing vaccine-related morbidity and mortality had been extensively studied in severe influenza seasons, institutionalised patients and high-risk individuals. However, few large studies have systematically evaluated the clinical benefit of annual vaccination in the general elderly population over the medium or long term [6–10], and little is known about the effectiveness of the annual vaccination programmes in generally healthy elderly people living in the community.

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doi:10.1016/j.vaccine.2007.07.015

This study assessed the relationship between the reception of conventional inactivated influenza vaccine and winter mortality in Spanish community-dwelling elderly individuals from January 2002 to April 2005.

2. Methods

2.1. Design, setting and study population

We conducted a prospective cohort study including 11,240 community-dwelling individuals 65 years or older assigned to eight Primary Health Care Centers (PHCC) in Tarragona (Catalonia, Spain). Cohort members were followed from when the study started (January 1, 2002) until enrolment from the PHCC ceased, the occurrence of death or until the end of the study (April 30, 2005).

In the Spanish Health Care System, as in the study area, all persons are assigned to a PHCC, and their General Practitioner files relevant medical details on patients during primary care visits. Every year a specific influenza vaccination campaign is carried out from October 15 to November 30, and a free conventional inactivated influenza vaccine are offered in PHCCs for all elderly subjects and some adults or children with predefined high-risk conditions.

When the study started, the Health District of Tarragona had 12 PHCCs with an overall assigned population of 134,232 inhabitants. The selection of the eight participating PHCCs was not randomised and they were chosen taking into account the existence of electronic clinical registries working since 1998 or before. The other four PHCCs in the Health District were not included because they had computerised clinical records more recently. The present study included all community-dwelling persons aged 65 years or older when the study started, who were assigned to 8 of the 12 PHCCs and who had at least 1 year of recorded database history prior to the start of the study. Thus, the eligible population included 11,240 persons 65 years or older on January 1, 2002

The study was conducted in accordance with the general principles for observational studies set out by the Catalan Health Institute.

2.2. Sources of data

All participating PHCCs have an institutional computerised clinical record system which contains registries of immunisations, laboratory tests, medication prescription, diagnoses associated with outpatient visits and chronic diseases coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9). The electronic records of each cohort member were used to identify whether the individual had received or not the influenza vaccine in each influenza vaccination campaign, and it was also used to identify the presence of co-morbidity and other medical conditions.

2.3. Outcome measure and definitions

Influenza seasons were considered on the basis of surveillance data obtained from the Communicable Disease Report National System. In Spain, a country with 40 million people, the influenza epidemic activity was low in the 2001–2002 season (708,457 cases reported of influenza-like illness) [11], in the 2002–2003 season (682,219 cases) [12], in the 2003–2004 season (353,722 cases) [13], and it was high in the 2004–2005 season (1,217,574 cases) [14]. Influenza seasons within this study were characterized by the mixed circulation of the A and B influenza viruses, the beginning of the epidemic wave in December, higher incidences between January and February, and the disappearance of the epidemic wave during March–April. There was a good match between vaccine and circulating virus strains each year [11–14].

In the study area, according to data provided by the Communicable Disease Unit of Tarragona, the absolute number of influenza-like illness reported from the eight participating PHCCs between January 2002 and December 2005 was 5797 cases, of which 4268 (75.5%) were reported within weeks 1–18. Appendix A shows the weekly distribution of influenza-like cases reported in the study area during 2002–2005. According to this data, the influenza period was considered from January 1 to April 30, whereas July–August (weeks 26–34) was considered as a reference non-influenza control period throughout the study.

Primary outcome was all-cause death. Deaths were initially identified in the Institutional Demographic Database (which is monthly updated with administrative data about deaths occurred, patients moved or new patients assigned to a PHCC. Afterwards, a review of the reference Civil Registry Offices of the eight PHCCs were used to identify those deaths occurred in cohort patients who had not been registered in the Institutional database and they were also used to validate the exact date of death in all cases. According to this date, deaths have been classified as occurring within January–April (influenza period), July–August (control period) or the overall study period (January–December). Finally, a review of clinical records was used to identify specific cause of deaths.

2.4. Exposure to influenza vaccination

For each year, information on the influenza vaccination status before the outcome seasons was retrieved by a computerised search on the clinical records of all cohort members. Influenza vaccine status was considered as a dichotomic (vaccinated or unvaccinated) time-varying condition throughout the study period (for example, in the analysis covering overall study period, the same person was considered unvaccinated in 2002, vaccinated in 2003 and unvaccinated in 2004 according to the reception or not of the influenza vaccine in each respective prior Autumn). Those persons who had received a dose of influenza vaccine were considered as vaccinated from 14 days after the reception of the vaccine until the beginning

of the next influenza vaccination campaign. Thus, persons were newly re-classified as vaccinated or unvaccinated for the next influenza period according to the reception or not of a new dose of the influenza vaccine.

2.5. Covariates

Covariates were age, sex and the presence of some medical conditions related with an increasing risk of all-cause mortality: chronic lung disease (including asthma, emphysema or chronic bronchitis), chronic heart disease (including heart failure and coronary artery disease), diabetes mellitus, hypertension, obesity, current smoking, and immunocompromised status. Immunocompromise was a composite variable defined by the presence of any one of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), chronic severe liver disease (cirrhosis), anatomical or functional asplenia, AIDS, and long-term corticosteroid therapy (20 mg/day of prednisone) or another immunosuppressive medication. The presence of co-morbid conditions was determined by a review of the diagnosis codes in the electronic clinical record of each cohort member.

2.6. Statistical analysis

Incidence rates (IR) of death were calculated as persons-year and persons-week, considering that in the denominator the total persons-time for the study period was simply the sum of the persons-time contributed to each individual. Attributable risk (AR) was the difference between IR among vaccinated and unvaccinated subjects (AR = IR exposed − IR non-exposed). Numbers needed to be vaccinated (NNV) to save one death were estimated for influenza periods (January–April = 17.1 weeks) and were calculated as the inverse of the AR (NNV = 1/AR) [15]. The prevented fraction of risk among vaccinated was calculated as [1 − (IR vaccinated/IR non-vaccinated)]. The prevented fraction for the population was calculated as prevented fraction among exposed multiplied by person-time of exposed and divided by total person-time [16].

The association between influenza vaccine exposure and mortality risk was evaluated by multivariable Cox proportional-hazards models. Influenza vaccine status was considered a time-varying variable whereas the other covariates were defined at study entry.

The relationship between influenza vaccination and all-cause mortality risk was evaluated in an analysis that included overall study period (January 2002–April 2005) and four supplementary analyses within each influenza season. The variables that have been considered in all the inicials models are: age, sex, chronic heart disease, chronic lung disease, diabetes, hypertension, obesity, smoking and immunocompetence. The method to select a subset of covariates to include in the final proportional-hazards regression model is the purposeful selection [17]. Exploratory analysis (method of fractional polynomials) confirmed the appropriateness of modelling continuous variable, age, as linear. The proportional-hazard assumptions were assessed, adding the covariate by time interactions to the model and plotting the scaled and smoothed Schöenfeld residuals obtained from the main effects model where possible. The authors checked for confounders, interactions and multicolinearity among the independent variables. In addition all the models have been compared through the partial likelihood ratio test and the Akaike's information criterion (AIC).

All results were expressed with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. The analyses were performed using Stata/SE Version 9.1 (Stata Corp.).

3. Results

The 11,240 cohort members (mean age: 74.6-years-old at baseline, S.D. 7.5; 4892 male and 6348 female) were observed for a total of 34,490 persons-year throughout the study period. In total 717,392 persons-week were observed within January–April periods (435,214 persons-week vaccinated and 282,178 persons-week non-vaccinated against influenza in the respective prior Autumn).

At baseline 8351 (74.4%) of the population had some form of co-morbidity, mostly hypertension (53.3%), diabetes mellitus (23.6%), chronic heart disease (11.9%) or chronic lung disease (11.5%). The baseline characteristics of cohort members according to their reception of influenza vaccine in Autumn 2001 are shown in Table 1.

An amount of 6051 (53.8%) of baseline subjects had received the influenza vaccine in Autumn 2001 before the study started. Of the remaining 5189 subjects not vaccinated at baseline, 2771 subjects did not receive any influenza vaccine during the study period and 2418 (46.6%) subjects received at least one dose of the influenza vaccine during the next three influenza vaccination campaigns. If we consider those cohort members who were eligible in each influenza period, the annual vaccination coverage reached 58.9% in 2003, 64.3% in 2004 and 63.2% in 2005.

During the 40-month follow-up, an amount of 1497 deaths for any cause were observed. Cause specific mortality was not available in 586 (39%) of 1497 cohort members who died during the study period. Among those 911 people who had registered specific cause of death in their clinical record, causes of death were: cardiovascular disorders in 29%, cancer in 25%, respiratory diseases in 9%, neurologic disorders in 8%, infectious diseases in 7%, digestive diseases in 4%, metabolic disorders in 3%, traumas and accidents in 3%, other causes in 4% and badly defined causes in 8%.

Overall all-cause mortality rate (per 1000 persons-year) was 43.4 (95% CI: 41.3–45.6). Mortality rates were strongly associated with age (18.7 in people 65–74 years, 54.6 in people 75–84 years, 164.4 in people more than 85 years) and gender (48.8 in male versus 39.3 in female). The mortality

Table 1
Baseline characteristics of the study population according to their influenza vaccine status at starting of the study (January 1, 2002)

Characteristic	Number of persons (%)		*P*-value[a]
	Unvaccinated before entry ($N = 5189$)	Vaccinated before entry ($N = 6051$)	
Age group[b]			
65–74 years	3236 (62.4)	2969 (49.1)	0.000
75–84 years	1460 (28.1)	2399 (39.6)	
≥85 years	493 (9.5)	683 (11.3)	
Sex			
Male	2210 (42.6)	2682 (44.3)	0.065
Female	2979 (57.4)	3369 (55.7)	
Medical conditions			
Chronic heart disease	480 (9.3)	860 (14.2)	0.000
Diabetes mellitus	1064 (20.5)	1586 (26.2)	0.000
Chronic lung disease	462 (8.9)	836 (13.8)	0.000
Hypertension	2422 (46.7)	3567 (58.9)	0.000
Obesity	789 (15.2)	1186 (19.6)	0.000
Smokers	472 (9.1)	458 (7.6)	0.003
Chronic liver disease	104 (2)	111 (1.8)	0.512
Chronic nephropathy	143 (2.8)	267 (4.4)	0.000
Active neoplasia	112 (2.2)	192 (3.2)	0.001
Immunosupressive medication	221 (4.3)	472 (7.8)	0.000
Immunocompromised status[c]	518 (10)	928 (15.3)	0.000

[a] *P*-values were calculated with Chi-square test.
[b] The median ages of the unvaccinated and vaccinated subjects were 73.4 and 75.6, respectively.
[c] Immunocompromised status included the presence of any of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), chronic severe liver disease (cirrhosis), anatomical or functional asplenia, AIDS or immunodeficiency, and long-term corticosteroid therapy (20 mg/day of prednisone) or another immunosuppressive medication.

was highest for individuals with neoplasia (92.7), chronic nephropathy (81.8) and those with chronic lung disease (70.7).

In the total population, we observed 670 deaths from any cause during the months of January–April and 827 deaths in May–December. This means a mortality rate of 93.4 per 100,000 persons-week within the influenza periods (95% CI: 86.7–100.4) and 77.9 per 100,000 persons-week within non-influenza periods (95% CI: 71.3–81.7).

According to influenza vaccine status throughout the overall study period, 675 and 822 deaths were observed among vaccinated and unvaccinated subjects, respectively. This meant that all-cause mortality rates during the overall study period were 76.4 per 100,000 persons-week (95% CI: 71.4–81.7) in vaccinated subjects and 94.1 (95% CI: 87.3–101.5) in non-vaccinated subjects (Table 2).

Within influenza periods, all-cause mortality rates were 83.7 per 100,000 persons-week (95% CI: 75.4–92.5) in vaccinated subjects and 108.1 (95% CI: 96.9–120.6) in non-vaccinated subjects. Considering overall influenza periods, attributable risk was 24.4 deaths per 100,000 persons-week, and the number needed to vaccinate to save one death during an influenza period was 239 annual vaccinations (95% CI: 176–366).

Unadjusted analysis showed that influenza vaccination was associated with a statistically significant reduction of mortality risk within the overall influenza periods (hazard ratio [HR]: 0.77; 95% CI: 0.65–0.89) whereas it was not significant during the July–August control period (HR: 0.85; 95% CI: 0.64–1.13). Considering the total influenza periods, the prevented fraction of winter mortality risk among the vaccinated was 23% and the prevented fraction for the population was 13.9%.

In the multivariable analysis, the adjusted mortality risk reduction was 37% within overall influenza periods (HR: 0.63; 95% CI: 0.54–0.74) whereas it was not significant during the reference summer period (HR: 0.76; 95% CI: 0.54–1.07). A significant interaction between influenza vaccine and sex with age was observed when overall study period was observed (see footnotes in Table 2) and, consequently, the effect of vaccination on mortality varied in function of age. As it can be seen in Table 3, the adjusted vaccine's effectiveness was highest in people 65-years-old (48%) and decreased with increasing age.

During study period, the mean incidence rates of influenza-like illness reported within January–April among the overall population in the eight participating PHCCs were 63.4 cases per 100,000 persons-week in 2002, 14.0 in 2003, 13.6 in 2004 and 84.3 in 2005. During the July–August control period, the mean incidence rates were 0.9 cases per 100,000 persons-week in 2002, 0.8 in 2003, 1.1 in 2004 and 0.8 in 2005 (see Appendix A).

When each influenza period was considered separately, the unadjusted protective effect of influenza vaccination against all-cause mortality varied between 6% in the 2002 influenza period (HR: 0.94; 95% CI: 0.68–1.30) and 28% in the 2005 influenza period (HR: 0.72; 95% CI: 0.52–0.90). The numbers needed of influenza vaccinations to save one winter death

Table 2
Incidence and risk of all-cause mortality among elderly people within influenza epidemic period, reference summer period, and the overall study period according to the reception of influenza vaccine in prior Autumn

Parameter	Study period		
	Within influenza periods (January–April)	Within reference non-influenza periods (July–August)	Overall study period (from January 1, 2002 to April 30, 2005)
Time followed (person-year)			
Overall	13.796	5.261	34.490
Unvaccinated	5.426	2.186	13.795
Vaccinated	8.369	3.075	20.694
Number of deaths			
Unvaccinated	306	87	675
Vaccinated	364	104	822
Unadjusted all-cause mortality rate per 100,000 person-week			
Unvaccinated (95% CI)[a]	108.1 (96.9–120.6)	76.5 (61.6–93.9)	94.1 (87.3–101.5)
Vaccinated (95% CI)	83.7 (75.4–92.5)	65.1 (53.3–78.5)	74.5 (71.3–81.8)
Unadjusted hazard ratio (95% CI)	0.77 (0.65–0.89)	0.85 (0.64–1.13)	0.81 (0.72–0.91)
P-value	0.000	0.261	0.000
Age-adjusted hazard ratio (95% CI)	0.67 (0.58–0.78)	0.78 (0.59–1.03)	0.70 (0.63–0.78)
P-value	0.000	0.078	0.000
Age and sex-adjusted hazard ratio (95% CI)	0.66 (0.56–0.76)	0.77 (0.58–1.03)	0.68 (0.62–0.76)
P-value	0.000	0.076	0.000
Multivariable-adjusted hazard ratio (95% CI)	0.63[b] (0.54–0.74)	0.76[c] (0.54–1.07)	0.61[d] (0.48–0.73)
P-value	0.000	0.113	0.000

The hazard ratios are for subjects vaccinated against influenza in prior Autumn as compared with unvaccinated subjects.
[a] CI denotes confidence interval.
[b] Adjusted for age, sex, chronic lung disease, chronic heart disease, diabetes, hypertension, immunocompromise and the interaction immunocompromise × age.
[c] Adjusted for age, sex, chronic heart disease and immunocompromise.
[d] At the mean age (74.6 years) and adjusted for sex, diabetes, chronic heart disease, chronic lung disease, hypertension, obesity, immunocompetence and the interactions age × sex, age × chronic heart disease, age × immunocompetence, chronic lung disease × diabetes, and age × influenza vaccine.

Table 3
Multivariable-adjusted risk of all-cause mortality in elderly people (according to age and gender) in relation to influenza vaccine status

Age	Multivariable-adjusted risk of death from all-causes	
	Risk for overall population according to age and influenza vaccine status[a]	Risk for women as compared with men according to age[b]
People 65-years-old		
Multivariable hazard ratio (95% CI)[c]	0.52 (0.31–0.74)	0.60 (0.38–0.82)
People 70-years-old		
Multivariable hazard ratio (95% CI)	0.57 (0.40–0.73)	0.65 (0.48–0.82)
People 75-years-old		
Multivariable hazard ratio (95% CI)	0.61 (0.49–0.73)	0.70 (0.57–0.83)
People 80-years-old		
Multivariable hazard ratio (95% CI)	0.66 (0.55–0.76)	0.76 (0.65–0.87)
People 85-years-old		
Multivariable hazard ratio (95% CI)	0.71 (0.59–0.83)	0.82 (0.70–0.94)
People 90-years-old		
Multivariable hazard ratio (95% CI)	0.77 (0.61–0.92)	0.88 (0.72–1.05)
People 95-years-old		
Multivariable hazard ratio (95% CI)	0.83 (0.62–1.03)	0.96 (0.74–1.17)

[a] The hazard ratios are for vaccinated subjects as compared with unvaccinated, and were adjusted for sex, diabetes, chronic heart disease, chronic lung disease, hypertension, obesity, immunocompetence and the interactions age × sex, age × chronic heart disease, age × immunocompetence, chronic lung disease × diabetes, and age × influenza vaccine.
[b] The hazard ratios are for women as compared with men, and were adjusted for diabetes, chronic heart disease, chronic lung disease, hypertension, obesity, immunnocompetence, influenza vaccine status, and the interactions age × sex, age × chronic heart disease, age × immunocompetence, diabetes × chronic lung disease, and age × influenza vaccine.
[c] CI denotes confidence interval.

Table 4
Incidence and risk of all-cause mortality among elderly people within the different influenza periods between 2002 and 2005 according to annual influenza vaccine status

	Influenza period (January–April)			
	2002	2003	2004	2005
Number of eligible subjects	11240	10751	10254	9883
Unvaccinated	5189	4415	3657	3636
Vaccinated	6051	6336	6597	6247
Influenza vaccine coverage (%)	53.8	58.9	64.3	63.2
Number of deaths				
Unvaccinated	69	76	68	93
Vaccinated	77	86	85	116
Unadjusted all-cause mortality rate per 100,000 person-week				
Unvaccinated (95% CI)[a]	76.7 (66.7–87.7)	99.3 (87.1–112.7)	107.3 (93.5–122.5)	147.6 (131.3–164.8)
Vaccinated (95% CI)	73.4 (64.4–83.3)	78.3 (69.2–88.3)	70.5 (65.6–83.8)	107.1 (96.5–118.7)
NNV to save one death within the influenza period[b] (95% CI)	1748 (212–∝)[c]	278 (123–∝)[d]	159 (93–1553)	144 (77–1107)
Unadjusted hazard ratio (95% CI)	0.94 (0.68–1.30)	0.79 (0.57–1.06)	0.68 (0.49–0.93)	0.72 (0.52–0.90)
P-value	0.734	0.124	0.019	0.005
Age-adjusted hazard ratio (95% CI)	0.78 (0.56–1.08)	0.71 (0.52–0.97)	0.61 (0.44–0.84)	0.62 (0.48–0.81)
P-value	0.141	0.035	0.003	0.000
Age and sex-adjusted				
Hazard ratio (95% CI)	0.77 (0.55–1.06)	0.68 (0.50–0.93)	0.60 (0.43–0.82)	0.60 (0.45–0.78)
P-value	0.109	0.016	0.002	0.000
Multivariable-adjusted				
Hazard ratio (95% CI)	0.80[e] (0.58–1.12)	0.66[f] (0.48–0.90)	0.54[g] (0.39–0.75)	0.57[h] (0.43–0.76)
P-value	0.192	0.010	0.000	0.000

The hazard ratios are for subjects vaccinated against influenza in prior Autumn as compared with unvaccinated subjects.
[a] CI denotes confidence interval.
[b] NNV is the number needed to vaccinate to prevent one death within an influenza period (January–April = 17.1 weeks) and is estimated as 1/([mortality rate difference/100,000] × 17.1).
[c] The 95% CI of NNV includes NNB 212 to ∝ to NNH 217. NNB is the number needed to be treated in order to benefit one person and NNH is the number needed to be treated in order to harm one person.
[d] The 95% CI of NNV includes NNB 123 to ∝ to NNH 848.
[e] Adjusted for age, sex, chronic lung disease and hypertension.
[f] Adjusted for age, sex, chronic lung disease, chronic heart disease, diabetes and hypertension.
[g] Adjusted for age, sex, chronic lung disease, chronic heart disease, hypertension, current smoking and immunocompromise.
[h] Adjusted for age, sex, chronic lung disease, chronic heart disease, diabetes, hypertension and immunocompromise.

were 1748 in the 2002 influenza period, 278 in the 2003 influenza period, 159 in the 2004 influenza period and 144 in the 2005 influenza period. The prevented fraction for the population was 3.2% in 2002, 12.4% in 2003, 20.6% in 2004 and 17.7% in 2005. The adjusted vaccine's effectiveness in preventing winter mortality varied from a non-statistically significant 20% in the 2002 influenza period (HR: 0.80; 95% CI: 0.58–1.12) to a clearly significant 43% in the 2005 influenza period (HR: 0.57; 95% CI: 0.43–0.76). The values of different results evaluating the relationship between the reception of influenza vaccine and all-cause mortality in each of the four analysed influenza periods are shown in Table 4.

4. Discussion

The efficacy of influenza vaccination and the estimated impact of annual influenza epidemics on morbid-mortality have been the basis for implementing influenza vaccination programmes for elderly and high-risk individuals [1–3]. However, the effectiveness of vaccination has been reported to decrease in older age-groups and high-risk persons, and the magnitude of clinical effectiveness of annual vaccination campaigns is unclear. Nowadays, in this field, the gold standard of a large randomised controlled trial would be unethical and non-experimental studies evaluating influenza vaccination effectiveness must be applied [18,19].

In this long prospective cohort study we have evaluated the relationship between annual influenza vaccination and all-cause mortality in older adults living in the community. Although it is not randomised, the large size of our study population together with the adjustment for important covariates in the multivariable analysis, provides an adequate basis for assessing the effects of the influenza vaccination on winter mortality in the general elderly population throughout a time-period with different severity of influenza seasons.

In this study, annual influenza vaccine coverages varied from 54 to 64%, which is consistent with previously reported uptakes among Spanish elderly people in recent years [20,21]. Overall mortality rate (43 deaths per 1000 persons-year) is also in agreement with all-cause mortality rates reported for adults over 65 years in developed countries [22].

In the present study, influenza vaccination was associated with a significant reduction of 23% (95% CI: 11–35) in the unadjusted risk of all-cause mortality within overall influenza periods, whereas in the multivariable analysis this risk reduction reached 37% (95% CI: 26–46). These results fit with those recently reported by Voordouw et al. in a large cohort study from 1996 to 2002 among 26,071 community-dwelling elderly in the Netherlands, who found that the annual influenza vaccination was associated with an all-cause mortality risk reduction of approximately 24% during the overall study period and 28% during the influenza epidemic periods [10].

The effectiveness of the influenza vaccine in preventing all-cause mortality in healthy elderly people is controversial, and nowadays there is disagreement about the magnitude of protective effects from the vaccination [7,8]. There is a paucity of randomised trials [23], and cohort studies have reported higher level of vaccine effectiveness than case-controlled studies [4,5]. Gross et al. estimated that influenza vaccine effectiveness against all-cause mortality varied from 27 to 30% in case-control studies to 56–76% in cohort studies [4]. In a meta-analysis among elderly people living in the community, Vu et al. estimated the vaccine's effectiveness in preventing all-cause mortality by 45–56% [5]. In the present authors' opinion, it is possible that the magnitude of the protective effect of the influenza vaccine against mortality in the general elderly population could have been overestimated considering that many studies focussed on high-risk subjects in epidemic periods with a high incidence of influenza, and few studies have been carried out over a long period of time including low or moderate severity of influenza seasons.

Mangtani et al., in a historical cohort of individuals 65 years or older in England and Wales, did not find a clear protective effect of influenza vaccination against death due to all causes between 1989 and 1999 [7]. Simonsen et al. analysed influenza vaccine coverages and the estimates of influenza-related mortality and all-cause deaths for 33 influenza seasons from 1968 to 2001 in USA elderly population [6]. They report that fewer than 10% of all winter deaths were attributable to influenza in any season, and they could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group, concluding that more observational studies substantially overestimated vaccination benefits [6].

In this study, the absolute risk reduction observed in winter mortality in vaccinated people was 24.4 deaths per 100,000 persons-week within overall influenza periods, the prevented fraction among vaccinated was 23% and the prevented fraction for the population was 14%. We estimated that one death was prevented for every 239 annual vaccinations (ranging from 1748 in the 2002 influenza period to 144 in the 2005 influenza period, considering that annual vaccine coverages varied from 54 to 64% throughout the 2002–2005 influenza periods. Our estimate of 239 persons that need to be vaccinated to prevent one winter death fits with data reported by Hak et al. in Minnesota during 1990–1996 influenza periods (NNV = 174) [9], and Voordouw et al. in the Netherlands (NNV = 302) [10].

Our study has several strengths. Vaccination was evaluated by survival analysis methods to estimate vaccine effectiveness adjusted for age and major co-morbidities. The study population was large enough to evaluate the relationship between the reception of annual influenza vaccine and winter mortality throughout a 4 years series including different severity of influenza seasons. In addition, the study population (a community-based cohort) was largely representative for the target population for influenza vaccination.

On the other hand, it has some intrinsic limitations and to interpret our findings, some characteristics of the study need to be addressed. In this study, influenza vaccination was considered as a simple dichotomic variable ("vaccinated" or "unvaccinated") in each year, but other categories of influenza vaccine status (as "first vaccination", "revaccination", "vaccination interruption" or "vaccination restart") which can influence vaccine effects were not evaluated [10].

The main limitation of observational designs is a possible selection bias. In Spain all individuals are assigned to a PHCC and a free influenza vaccine is offered each Autumn for all individuals over 65 years (with or without high-risk conditions), but the possibility of selection bias cannot be excluded considering that the exposure rates and distribution of prevalence of some important risk factors across the exposure groups substantially differ in vaccinated and non-vaccinated subjects. However, considering that data on several important prognostic variables were identified and adjusted in the multivariable analysis, it is unlikely that these confounders explain vaccine effectiveness. Our observation that the presence of high-risk conditions and vaccination were predictors for mortality concurs with previous findings.

Information bias may have occurred if some co-morbidity or vaccination was not recorded, but such misclassification would likely be random because exposure was recorded before occurrence of death. If considering the possible confounding by indication due to a "healthy vaccine" effect, in the present study healthier subjects were not more likely to have received the vaccination. Vaccinated subjects were older and had more co-morbidity than non-vaccinated subjects, so unadjusted analyses underestimated vaccine effectiveness. The significant differences between groups were controlled in the multivariable analysis [17]. However, the adjusted winter mortality risk reduction of 37% within overall influenza periods is relatively high, considering the fact that all-cause mortality was chosen as an outcome measure, and the fact that there was only mild epidemic activity in two

of four analysed influenza seasons. Thus, as observational study, the possible influence of residual confounding on the estimates of vaccine effectiveness cannot be completely excluded [24].

In this study, the cause specific of death was not available in considerable number of cohort members who died during study period and furthermore, in some patients the cause of death was not specific enough to classify as influenza-related mortality or not. Thus, we have chosen all-cause mortality as main outcome measure. In favour of choosing all-cause death as the outcome to assess the effect of influenza vaccination on mortality is the difficulty to classify a death as influenza-related mortality and, consequently, the possibility of misclassification bias when cause specific mortality is considered. In general, when the event of interest is the death, all-cause mortality is considered a more robust event than cause specific mortality [25]. Considering this and the difficulties of serological confirmed diagnosis of influenza infections, all-cause death has been considered an acceptable outcome to evaluate influenza vaccine effectiveness in many observational studies and meta-analyses [4,5].

Important aspects that determine vaccine effectiveness are the intensity of viruses circulating during the study periods and the similarity between vaccine strains and circulating strains [18]. During the study period, influenza activity in northern hemisphere countries was mild to moderate in most countries, and was associated with a mixed circulation of virus A and virus B [26–29]. In this period, vaccine strains and the predominant circulating strain (mainly A[H_3N_2]) generally were well matched [26–29].

In the study area, there was not a general surveillance system to diagnose laboratory-confirmed influenza illness and, consequently, the true incidence of flu among the study population was unknown. We provide data on influenza-like illness reported weekly during 2002–2005 from the eight participating PHCCs and, although this data does not discriminate for other agents causing flu-like illnesses, it can be used as an indirect measure of epidemic activity in the study area. Since vaccine "effectiveness", in contrast to vaccine "efficacy", is a function of the incidence of influenza attack rate in the year of the study, we have found that the highest efficiency of vaccination occurred within the influenza period 2005 (NNV = 144), which was the period with the highest attack rate of influenza-like illness and the highest all-cause mortality rate observed among the study population during the four influenza periods.

In our study population, the adjusted protective effect of influenza vaccination decreases with increasing age. Differences in the protective effect of vaccination in relation to age and gender seems to reflect age and gender-related differences in causes of death, but probably it also reflects age-related decreasing immunogenicity of vaccination as several studies have shown [30]. However, although vaccine effectiveness decreases with increasing age, it should not be forgotten that influenza vaccination could have a greater level of vaccine efficiency in very elderly people. The greatest burden of mortality falls upon this population group and they can obtain an important benefit from the vaccination, even considering low vaccine effectiveness in very elderly subjects.

The aggregate financial and administrative cost of providing annual influenza vaccination to all individuals at risk is substantial. Our findings provide important information for cost-effectiveness analysis and public policy for influenza vaccination in the general elderly population, considering that vaccine efficiency is dependent on the uncertainties around vaccine effectiveness estimates [31–33].

5. Conclusions

In summary, the present study shows that the reception of annual conventional inactivated influenza vaccine was associated with a significant low risk of all-cause winter mortality among Spanish community-dwelling elderly individuals throughout a consecutive year series that included four influenza seasons from January 2002 to April 2005.

This data confirms the benefit of the influenza vaccination, even considering mild or moderate severity of influenza seasons, and it supports an annual vaccination strategy for all the community-dwelling elderly.

Acknowledgments

This study was supported by a Grant from the "Fondo de Investigación Sanitaria" of the Spanish Ministry of Health (Expedient PI-02117) and the "Fundació Jordi Gol i Gurina".

The authors would like to thank to all family physicians and nurses of Primary Care Centers in Tarragona-Valls for their collaboration in this study. The authors would like to thank to Sofía Minguell and Enric Rovira, who provided data on Communicable Diseases Report National System in the study area. The authors also thank Timothy Bowring, Marc Vila and Dolors Rovira for their help in the production of this paper.

Contributors: A. Vila-Córcoles, C. de Diego, O. Ochoa, E. Salsench, X. Ansa, W. Badía and N. Saún designed the study, assessed outcomes, and wrote and edited the paper. A. Vila-Córcoles coordinated the study. C. De Diego and O. Ochoa obtained the data. T. Rodríguez and A. Valdivieso did statistical analysis. *Conflict of interest:* None declared.

Appendix A

Absolute number of cases of influenza-like illness weekly reported from the eight participating PHCC ($N = 134{,}232$ all-age inhabitants) to the Communicable Disease Report National System during the study period (data provided by Communicable Disease Unit, Servei Territorial de Tarragona, Department de Sanitat de la Generalitat de Catalunya)

Number of weeks	Year			
	2002	2003	2004	2005
Week 1 (January 1)	30	7	28	305
2	85	15	32	418
3	191	20	33	339
4	191	30	34	217
5	231	38	17	203
6	217	14	21	117
7	166	29	13	62
8	142	4	10	147
9	106	39	19	65
10	64	52	43	57
11	31	8	21	44
12	13	27	24	22
13	21	38	12	21
14	18	27	10	6
15	14	20	5	1
16	10	7	3	5
17	5	9	0	6
Week 18 (April 30)	1	2	4	2
Overall weeks 1–18	1536	386	329	2037
Overall weeks 26–34 (July–August)	11	10	13	10
Overall weeks 1–52 (January–December)	2049	869	707	2162

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ARTICLE 2

Efectes de la vacunació antigripal anual sobre la mortalitat hivernal en gent gran amb malaltia pulmonar crònica. A. Vila - Córcoles, O. Ochoa, C. de Diego, A. Valdivieso, I. Herreros, F. Bobe´, M. Alvarez, M. Juárez, I. Guinea, X. Ansa, N. Saún. Effects of annual influenza vaccination on winter mortality in elderly people with chronic pulmonary disease. Int J Clin Pract. 2008 Jan;63(1):10-7

Resum

Introducció: Encara que hi ha un acord general per a la recomanació de la vacuna antigripal a les persones amb malaltia pulmonar obstructiva crònica (MPOC), la magnitud de l'efectivitat clínica i el benefici de la vacunació anual antigripal és objecte de controvèrsia. Aquest estudi va avaluar els efectes de la vacunació antigripal anual sobre la mortalitat hivernal en gent gran amb MPOC. Material i mètodes: cohort prospectiva que va incloure 1.298 persones residents a la comunitat majors de 65 anys amb diagnòstic de MPOC els quals foren seguits des de l'1 de gener 2002 fins el 30 abril 2005. La mesura principal de l'efecte va ser mort per qualsevol causa durant els períodes gripals (gener - abril). La regressió de Cox amb càlcul de hazard ratios (HR) ajustats per edat, sexe i comorbiditat es va utilitzar per avaluar l'efectivitat de la vacunació. Resultats: La vacunació antigripal es va associar amb una reducció estadísticament no significativa del 16% en la mortalitat hivernal entre els pacients amb MPOC vacunats [HR: 0,84, interval de confiança (IC) al 95%: 0.60-1.17]. L'anàlisi multivariant va mostrar, encara que no va assolir significació estadística, que hi havia una tendència cap a una reducció de la mortalitat en el grup dels vacunats considerant els períodes totals de la grip 2002-2005 (HR ajustat: 0,76; IC 95%: 0,52-1,06; p = 0,098). Estimem que, en la població total de MPOC, es va prevenir una mort per cada 187 vacunacions anuals (IC 95%: 62 a ¥). Conclusions: les dades suggereixen un benefici de la vacunació contra la grip i donen suport a les campanyes vacunals anuals en pacients ancians amb MPOC.

doi: 10.1111/j.1742-1241.2007.01414.x

ORIGINAL PAPER

International Journal of Clinical Practice

Effects of annual influenza vaccination on winter mortality in elderly people with chronic pulmonary disease

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Disclosures
The authors stated that they had no interests which might be perceived as posing a conflict or bias.

SUMMARY

Background: Although there is a general agreement for the recommendation of the influenza vaccine to persons with chronic obstructive pulmonary disease (COPD), the magnitude of clinical effectiveness and benefit from the annual vaccination is controversial. We assessed the effects of annual influenza vaccination on winter mortality in older adults with COPD. **Methods:** This prospective cohort study included 1298 Spanish community-dwelling individuals aged 65 years or older with a diagnosis of COPD followed from 1 January 2002 to 30 April 2005. The primary outcome was all-cause death during influenza periods (January–April). Multivariable Cox proportional hazard models adjusted by age, sex and comorbidity were used to evaluate vaccine effectiveness. **Results:** Influenza vaccination was associated with a non-statistically significant 16% reduction in winter mortality among vaccinated COPD patients [unadjusted hazard ratio (HR): 0.84; 95% confidence interval (CI): 0.60–1.17]. Multivariable analysis showed that there was an insignificant trend towards a reduced mortality in the vaccinated group considering overall influenza periods 2002–2005 (adjusted HR: 0.76; 95% CI: 0.52–1.06; $p = 0.098$). We estimated that, in the total COPD population, one death was prevented for every 187 annual vaccinations (95% CI: 62 to ∞). **Conclusions:** Our data suggest benefit from the influenza vaccination and support an annual vaccination strategy for elderly COPD patients.

What's known
Annual influenza vaccination is generally considered a cost-effective preventative health intervention for elderly and COPD patients, but estimates of vaccine effectiveness are based largely on evidence from observational studies with very few randomised controlled trials focused on COPD patients.

What's new
Our findings provide important information for cost-effectiveness analysis and public policy for influenza vaccination, considering that vaccine efficiency is very dependent on the uncertainties around vaccine effectiveness estimates.

Introduction

Influenza viruses are a major determinant of morbidity and mortality caused by respiratory disease. The incidence of flu is higher in children and younger adults than in older individuals, but influenza-associated morbidity and mortality increase with age, especially for individuals with underlying medical conditions such as chronic obstructive pulmonary disease (COPD) (1).

Nowadays, immunisation against influenza is generally considered a very effective preventive measure. Vaccination of elderly people and persons at risk of complications from influenza is a key public health strategy for preventing associated morbidity and mortality in many countries (2–4).

Several clinical trials have demonstrated the efficacy of influenza vaccines in reducing influenza or influenza-like illness, and many observational studies have reported protective effects of vaccination against hospitalisation and death in high-risk people (5–7). Two meta-analyses concluded that the influenza vaccination reduces mortality risk by approximately 50% in elderly people (5,6), but a recent Cochrane review has concluded that, although vaccination appears clearly associated with reductions in mortality risk in hospital-based studies, influenza vaccines did not appear to be significantly effective in elderly individuals living in the community (7).

Annual influenza vaccination is generally considered a cost-effective preventative health intervention for elderly and COPD patients (1,8,9), but estimates of vaccine effectiveness are based largely on evidence from observational studies with very few randomised controlled trials focused on COPD patients (10).

Influenza infection causes excess morbidity and mortality in COPD patients, but the effect of vaccination in preventing mortality in these patients is not

clear (10). Although many studies about the influenza vaccine were conducted among elderly and high-risk individuals, some of whom had chronic lung disease (11,12), few studies were specifically performed in COPD patients (13,14). In the latest Cochrane review it appears, from the limited number of studies performed, that inactivated influenza vaccines reduce exacerbations and influenza-related infections in COPD patients, but the studies are too small to have detected any effect on mortality (10).

In the present cohort study, we assessed the relationship between the annual influenza vaccine status and all-cause winter mortality among 1298 community dwelling elderly people with COPD who were followed from January 2002 to April 2005.

Patients and methods

Design, setting and study population

Prospective cohort study that included all community-dwelling elderly assigned to eight urban Primary Health Care Centres (PHCC) in Tarragona (Catalonia, Spain) who had a diagnosis of COPD registered in their clinical record when study started (1 January 2002).

In the Spanish healthcare system, all persons are assigned to their own PHCC, and their general practitioner files comorbidity, medical conditions, immunisations, prescriptions and other relevant medical details on patients from primary care visits. Every year a specific vaccination campaign is carried out (October–November), and a free conventional inactivate influenza vaccine is offered in PHCCs for all elderly subjects and adults or children with predefined high-risk conditions.

Study population were all community-dwelling subjects who were 65 years or older at the start of the study, who had at least 1 year of recorded database history prior to the study starting to determine health status and vaccination status. Institutionalised persons and those without assignation to a general practitioner were excluded. The eligible population thus included an amount of 1298 COPD patients aged 65 years or more.

All 1298 cohort members were followed up from the start of the study until enrolment from the PHCC ceased, the occurrence of death or until the end of the study (30 April 2005). The study was conducted in accordance with the general principles for observational studies set out by the Catalan Health Institute.

Data sources

All participating PHCCs have an institutional database with registries of immunisations, laboratory tests, medication prescription and diagnoses associated with hospitalisations, outpatient visits and chronic diseases coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9). This institutional database (working since 1998) and the computerised clinical records of each PHCCs were used to identify cohort members (ICD-9: 491–496) and it was also used to identify whether the individual had received influenza vaccination for every year of the survey and the presence of underlying medical conditions.

Outcome measure

The primary outcome was all-cause mortality. Deaths by any cause were initially identified in the cohort by institutional demographic database. The systematic review of computerised clinical records and reference Civil Registry Offices were used to validate the exact date of death and to identify those deaths which were not registered in the institutional database.

The period of influenza was considered as the period during which influenza viruses can be usually isolated from patients in the study area (from January to April for every year of the study) (15–18).

Influenza vaccine status was a time-varying condition. Considering that influenza vaccination periods were from 1 October to 30 November for each year of the survey, persons were considered to be vaccinated against influenza since 14 days after reception of influenza vaccine until May in the next year.

Covariates

Covariates were age, sex, number of outpatient visits in 24 months before study start, presence of comorbidity (diabetes mellitus, chronic cardiopathy, hypertension, obesity), current smoking and immunological situation. Immunocompromise was a composite variable defined by the presence of any one of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), chronic severe liver disease (cirrhosis), anatomical or functional asplenia, AIDS, and long-term corticosteroid therapy (20 mg/day of prednisone) or another immunosuppressive medication.

Statistical analysis

Incidence rates of all-cause mortality were calculated as persons-year and persons-week, considering that in the denominator the total persons-time for the study period was simply the sum of the persons-time contributed to each individual. Attributable risk (AR) was the difference between mortality rates among unvaccinated and vaccinated subjects. Numbers needed of annual influenza vaccinations to save one death were

calculated as 1/AR within the total time of each influenza season (1 January to 30 April).

The association between influenza vaccine exposure and mortality risk was evaluated by multivariable Cox proportional hazards models. Influenza vaccine status was considered a time-varying condition for each year of survey, whereas the other covariates were defined at study entry. Cox models were developed to estimate the hazard ratios (HRs) adjusting for age, sex, and comorbidity. To fully adjust for the strong influence of age on death, in this analysis we used age as continuous years, while the other covariates were considered as categorical variables. The relationship between influenza vaccine status with mortality risk was evaluated in an analysis that included overall study period, and four specific analyses modelling separately each influenza season.

Multivariable Cox models began with all variables significant in the univariate analysis at the 25th percentile level (19). All results were expressed with 95% confidence intervals (CIs). The analyses were performed using Stata/SE version 9.1. Statistical significance was set at $p < 0.05$.

Results

Considering the total study period, the 1298 cohort members were observed for an amount of 3890 persons-year (202,280 persons-week). The mean age when the study started was 75.4 years (SD: 6.9) and 74% were men. Of the 1298 cohort members, 275 (21.2%) died during the 40-month study period and 11 (0.8%) were lost patients during follow-up. At baseline, 1068 (82.3%) patients had some other form of comorbidity, mostly hypertension (51.8%), diabetes mellitus (25.2%) or chronic heart disease (19.9%). Table 1 shows the characteristics of the study population when the study started (1 January 2002) according to the reception or non-reception of influenza vaccine in autumn 2001. As can be seen in the Table, at the beginning of the study, vaccinated subjects were slightly older than unvaccinated subjects (mean age: 76.1 vs. 74.1; $p < 0.001$), and they had a higher frequency of attendance and comorbidity than unvaccinated subjects.

If we consider those cohort members who were eligible in each influenza vaccination campaign, the annual vaccination coverage reached 64.4% in autumn 2001, 67.8% in autumn 2002, 74.3% in autumn 2003 and 73.7% in autumn 2004. In total, 79,203 persons-week were observed within overall influenza periods 2002–2005, of which 55,301 persons-week (69.8%) were vaccinated and 23,902 persons-week were non-vaccinated against influenza in the respective previous autumn.

Table 1 Baseline characteristics of the study population according to their influenza vaccine status when the study started (1 January 2002)

	Number of persons (%)		
	Unvaccinated in autumn 2001 ($n = 462$)	Vaccinated in autumn 2001 ($n = 836$)	p-value*
Age group†			
65–74 years	263 (53.9)	378 (45.2)	0.000
75–84 years	152 (32.9)	357 (42.7)	
≥85 years	47 (10.2)	101 (12.1)	
Sex			
Male	344 (74.5)	616 (73.7)	0.761
Female	118 (25.5)	220 (26.3)	
Number of outpatient visits during previous 2 years			
0–14 visits	141 (30.5)	59 (7.1)	0.000
15–29 visits	153 (33.1)	249 (29.8)	
30 or more visits	168 (36.4)	528 (63.2)	
Medical conditions			
Chronic heart disease	76 (16.5)	183 (21.9)	0.019
Diabetes mellitus	98 (21.2)	229 (27.4)	0.014
Hypertension	222 (48.1)	450 (53.8)	0.046
Obesity	78 (16.9)	188 (22.5)	0.017
Smokers	109 (23.6)	141 (16.9)	0.003
Chronic liver disease	20 (4.3)	22 (2.6)	0.098
Chronic nephropathy	24 (5.2)	46 (5.5)	0.814
Active neoplasia	16 (3.5)	29 (3.5)	0.996
Corticosteroid therapy	61 (13.2)	202 (24.2)	0.000

*p-values were calculated with the χ^2 test. †The mean age of the unvaccinated and vaccinated subjects were 74.1 years old (SD: 6.8) and 76.3 years old (SD: 6.9) respectively ($p < 0.001$).

Overall mortality rate was 70.7 deaths per 1000 persons-year (95% CI: 62.8–79.2). Mortality varied significantly through the months of the year. We observed 135 deaths from any cause in January–April and 140 deaths in May–December. This means that all-cause mortality rate (per 100,000 persons-week) was 135.9 (95% CI: 120–153) through the overall study period, whereas mortality rates were 170.3 (95% CI: 143–202) within the influenza time period (January–April) and 113.7 (95% CI: 96–134) within the non-influenza period (May–December).

Within influenza periods, 89 deaths were observed among persons who had received influenza vaccine in the prior autumn and 46 deaths among persons who did not receive the vaccine in the previous autumn. This meant an all-cause mortality rate (per 100,000 persons-week) of 160.9 (95% CI: 129–198) in vaccinated and 192.5 (95% CI: 141–256) in non-vaccinated subjects. Table 2 shows vaccine coverages,

Table 2 Incidence and risk of all-cause winter mortality among COPD elderly patients during influenza periods 2002–2005 according to influenza vaccine status*

	Influenza period (1 January to 30 April)				
Parameter	**2002**	**2003**	**2004**	**2005**	**Overall flu periods 2002–2005**
Number of eligible subjects	1298	1233	1149	1050	79203†
Unvaccinated in prior autumn	462	397	295	276	23902†
Vaccinated in prior autumn	836	836	854	774	55301†
Influenza vaccine coverage (%)	(64.4)	(67.8)	(74.3)	(73.7)	(69.8)†
Number of deaths (%)					
Unvaccinated	13 (2.8)	12 (3.0)	10 (3.4)	11 (4.0)	46 (13.2)
Vaccinated	13 (1.8)	22 (2.6)	27 (3.2)	27 (3.5)	89 (11.1)
Unadjusted all-cause mortality rate per 100,000 persons-week (95% CI)					
Unvaccinated	164.6 (119–222)	177.1 (126–241)	198.9 (136–278)	234.6 (165–322)	192.5 (141–256)
Vaccinated	90.4 (65–123)	153.8 (120–194)	185.4 (149–228)	204.8 (165–251)	160.9 (129–198)
Unadjusted all-cause mortality rate per 1000 persons-winter period (95% CI)					
Unvaccinated	28.2 (20.4–38.1)	30.4 (21.6–41.3)	34.2 (23.3–47.6)	40.3 (28.3–55.2)	32.9 (24.2–43.9)
Vaccinated	15.4 (11.1–21.1)	26.5 (20.6–33.3)	31.8 (25.5–39.1)	35.1 (28.3–43.0)	27.6 (22.1–33.9)
Attributable risk per 1000 persons and winter period (95% CI)	12.8 (−4.9 to 30.6)	3.9 (−25.4 to 33.2)	2.4 (−21.7 to 26.5)	5.2 (−21.8 to 32.2)	5.3 (−5.5 to 16.1)
Number need of vaccination to save one death in winter period (95% CI)	78 (34 to ∞)	254 (42 to ∞)	415 (38 to ∞)	194 (32 to ∞)	187 (62 to ∞)
Unadjusted hazard ratio	0.55	0.86	0.94	0.87	0.84
95% CI	0.25–1.18	0.50–2.26	0.54–2.38	0.43–1.75	0.60–1.17
p value	0.126	0.864	0.729	0.689	0.305
Age-adjusted hazard ratio	0.47	0.82	0.96	0.81	0.80
95% CI	0.22–1.02	0.45–2.01	0.51–2.13	0.40–1.63	0.56–1.15
p-value	0.058	0.889	0.866	0.551	0.237
Multivariable-adjusted hazard ratio	0.48	0.79	0.95	0.87	0.76
95% CI	0.22–1.04	0.37–1.60	0.48–2.03	0.43–1.77	0.52–1.06
p-value	0.064	0.551	0.899	0.699	0.098

*The hazard ratios are for vaccinated subjects when compared with non-vaccinated and were adjusted, where appropriate, for age, sex, number of outpatient visits in the previous 2 years, chronic cardiopathy, diabetes mellitus, smoking, hypertension, obesity and immunocompetence. †In the total influenza periods 2002–2005, eligible population, vaccinated and non-vaccinated people was considered as persons-week followed within January–April of the overall study period.

number of deaths and the results of the effectiveness of vaccination against all-cause mortality within overall influenza periods 2002–2005 and according to each influenza season.

Unadjusted vaccine effectiveness against all-cause mortality within overall influenza time periods was 16% (unadjusted HR: 0.84; 95% CI: 0.60–1.17). During overall influenza periods, the AR was 5.4 deaths per 1000 persons-winter period). In the total COPD patients, within overall influenza period one death was prevented for every 187 annual vaccinations, although this number did not reach statistical significance (95% CI: 62 to ∞).

Multivariable analysis showed that annual vaccination was associated with an almost significant 24% lower risk of all-cause mortality considering overall influenza periods 2002–2005 (adjusted HR: 0.76; 95% CI: 0.52–1.06; $p = 0.098$).

When we consider the effects of vaccination on winter mortality in each of the four analysed influenza seasons, the protective effect of annual influenza vaccination against winter mortality ranged from a nearly significant protective effect of 52% in the 2001–2002 influenza season (adjusted HR: 0.48; 95% CI: 0.22–1.04; $p = 0.064$) to a non-significant effect of 5% in 2003–2004 influenza season (adjusted HR: 0.95; 95% CI: 0.48–2.03; $p = 0.899$). Although the upper limit of the CI did not reach statistical significance, we estimated that the numbers needed of annual vaccinations to save one death within each influenza periods were 78 in the 2001–2002 influenza season, 254 in the 2002–2003 influenza season, 415 in the 2003–2004 influenza season, and 194 in the 2004–2005 influenza season. The values of different results evaluating influenza vaccination effects on all-cause mortality within the

Table 3 Risk of all-cause winter mortality among COPD elderly patients during influenza periods 2002–2005 according to the presence of certain diseases and risk factors*

	Influenza period (1 January to 30 April)				
Parameter	**2002**	**2003**	**2004**	**2005**	**Overall flu periods 2002–2005**
Chronic heart disease ($n = 259$)					
Number of deaths	5	12	12	9	38
Multivariable hazard ratio	0.87 (0.32–2.34)	2.09 (1.01–4.30)	1.52 (0.75–3.10)	1.36 (0.63–2.92)	1.49 (1.02–2.20)
p-value	0.788	0.045	0.247	0.429	0.041
Diabetes mellitus ($n = 327$)					
Number of deaths	4	9	11	7	31
Multivariable hazard ratio	0.69 (0.23–2.02)	1.12 (0.52–2.43)	1.25 (0.60–2.59)	0.71 (0.31–1.64)	0.95 (0.63–1.43)
p-value	0.494	0.774	0.542	0.424	0.822
Hypertension ($n = 672$)					
Number of deaths	13	17	18	14	62
Multivariable hazard ratio	1.19 (0.54–2.61)	0.99 (0.50–2.01)	0.88 (0.45–1.73)	0.55 (0.27–1.10)	0.84 (0.60–1.20)
p-value	0.667	0.987	0.707	0.086	0.347
Obesity ($n = 266$)					
Number of deaths	3	4	7	4	18
Multivariable hazard ratio	0.73 (0.21–2.53)	0.62 (0.21–1.84)	1.07 (0.45–2.56)	0.61 (0.21–1.80)	0.76 (0.45–1.28)
p-value	0.623	0.393	0.873	0.373	0.300
Smokers ($n = 250$)					
Number of deaths	3	5	3	8	19
Multivariable hazard ratio	0.66 (0.16–1.92)	0.77 (0.29–2.04)	0.44 (0.13–1.49)	1.20 (0.53–2.73)	0.74 (0.45–1.22)
p-value	0.360	0.595	0.186	0.662	0.246
Immunocompromise ($n = 360$)					
Number of deaths	6	8	18	12	44
Multivariable hazard ratio	0.83 (0.33–2.10)	0.76 (0.33–1.65)	2.31 (1.20–4.48)	1.30 (0.65–2.60)	1.24 (0.87–1.80)
p-value	0.503	0.462	0.012	0.454	0.232

Values within parenthesis are 95% CI. *The multivariable-adjusted hazard ratios of winter mortality are for persons who had the disease or risk factor when compared with those without the disease or risk factor, and were adjusted for age (continuous), sex, number of outpatient visits in the previous 2 years, chronic cardiopathy, diabetes mellitus, smoking, hypertension, obesity and immunocompetence.

four analysed influenza seasons through study periods are shown in Table 2.

Table 3 shows the absolute number of winter deaths and the multivariable-adjusted risks of all-cause winter mortality among COPD elderly patients during influenza periods 2002–2005 according to the presence of comorbidities. Considering the overall study period, only the presence of chronic heart disease was associated with a significant increasing risk of winter death in cohort members (HR: 1.49; 95% CI: 1.02–2.20), if we consider separately each influenza period, a statistically significant increasing risk in winter mortality only reached statistical significance for patients with chronic heart disease in 2003 and immunocompromised patients in 2004.

Discussion

The efficacy of influenza vaccination and the estimated impact of annual influenza epidemics on morbid mortality have been the basis for implementing influenza vaccination programmes for elderly and high-risk individuals (1–4). However, the effectiveness of vaccination has been reported to decrease in older age groups and high-risk persons (20,21), and the magnitude of the clinical effectiveness of annual vaccination campaigns is controversial (22,23).

In a large prospective cohort study we evaluated the effectiveness of the annual influenza vaccination against winter mortality in older adults with COPD. Although not randomised, the large size of our study population together with the adjustment for important covariates in the multivariable analysis provides an adequate basis for assessing the effects of the influenza vaccine status on mortality in the elderly COPD population throughout a time period with different severity of influenza seasons.

In this study, annual influenza vaccine coverages varied from 64% to 74%, which is consistent with previous studies in Spain and other developed countries, which reported that approximately 30% of elderly subjects (including those with COPD)

are not annually immunised against influenza (1,11,12,24,25).

In the present study, influenza vaccination was associated with a non-significant reduction of 16% in the unadjusted risk of all-cause winter mortality in elderly COPD patients, whereas the multivariable analysis showed a near-significant effectiveness of 24% in preventing the risk of winter mortality throughout the overall study period among those COPD patients who had received influenza vaccine in the prior autumn. Our result fits with those of Voordouw et al. – in a retrospective cohort study focused on general elderly people in the Netherlands – who found that the annual influenza vaccination was associated with an all-cause mortality risk reduction of approximately 24% during the overall study period and 28% during the epidemic periods (12).

The effectiveness of influenza vaccine in preventing all-cause mortality is controversial, and nowadays there is disagreement about the magnitude of protection provided by the vaccination (5,6,7,22,23). There is a paucity of randomised trials (especially in COPD patients), and cohort studies have reported a higher level of vaccine effectiveness than case-controlled studies (5–7). In a classical meta-analysis, Gross et al. estimated that the effectiveness of influenza vaccine against all-cause mortality varied from 27–30% in case–control studies to 56–76% in cohort studies (5). In a meta-analysis focused on community-dwelling elderly people, Vu et al. estimated the effectiveness of the vaccine against all-cause mortality to be 45–56% (6). Recently, Sorensen et al. analysed influenza vaccine coverages and the estimates of influenza-related mortality and all-cause deaths for 33 influenza seasons from 1968 to 2001 in elderly people in the USA. They reported that fewer than 10% of all winter deaths were attributable to influenza in any season, and they could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group, concluding that more studies substantially overestimated the benefit of vaccination (23).

In the present study, the difference between all-cause mortality in unvaccinated and vaccinated subjects within the total influenza periods was 31.5 deaths per 100,000 persons-week (AR: 5.4 deaths per 1000 persons-winter period), and the prevented fraction of winter mortality among the elderly COPD population was approximately 5%. We estimated that in the total population one winter death was prevented for every 187 annual influenza vaccinations (ranging from 78 vaccinations in 2001–2002 influenza season to 415 in the 2003–2004 influenza season), but these estimates were not statistically significant as the values of the upper limits in the CIs reached infinity (Table 2).

In a recent Cochrane review of COPD patients, Poole et al. found that inactivated influenza vaccines reduced significantly the number of exacerbations and influenza-related respiratory infections in COPD patients, but they also concluded that the number of studies focused on COPD patients is too small to have detected any effect on mortality (10).

Important aspects that determine the effectiveness of the vaccine are the intensity of viruses circulating during the study periods and the similarity between vaccine strains and circulating strains (25). During our study period (2002–2005), influenza activity in most of the countries of the northern hemisphere was mild to moderate, and was associated with a mixed circulation of virus A and virus B. In this period, vaccine strains and the predominant circulating strain (mainly A[H3N2]) generally were well matched (26–29).

In Spain, a country with 40 million people, the influenza epidemic activity was low in the 2001–2002 season (708,457 cases reported of influenza-like illness) (15), 2002–2003 season (682,219 cases) (16), 2003–2004 season (353,722 cases) (17), but was moderate in the 2004–2005 season (1,217,574 cases) (18). In Spain the flu season usually starts at the end of December and runs until March–April. All influenza seasons within this study were characterised by the mixed circulation of the A and B influenza viruses, the beginning of the epidemic wave at the end of December, higher incidences between January and February, and the disappearance of the epidemic wave during March–April (15–18). During the study period, the maximum incidence of influenza-like illness in Spain ranged between 14 cases per 10,000 persons-week (2002–2003 season) and 54 cases per 10,000 persons-week (2004–2005 season), and were observed during weeks 4 and 2 respectively (15–18).

Our study has several strengths. Vaccination was evaluated by survival analysis methods to estimate the effectiveness of the vaccine adjusted for age and comorbidity. The study was population based, and the study population was large enough for evaluating the relationship between annual influenza vaccine status and winter mortality throughout the overall study period, but the sample size was too small to assess the effectiveness of the vaccine separately for each influenza season.

As an observational study that included all community-dwelling elderly who had any ICD-9 diagnosis of COPD, we were not able to determine the severity of airflow obstruction because a high

number of cohort members had not a recent spirometry do not appear in their clinical record, and this was an important limitation in this study. Information bias may have occurred if some comorbidity or vaccination was not recorded, but such misclassification would probably be random because exposure was recorded before the occurrence of death.

If considering the possible confounding by indication due to a 'healthy vaccine' effect, in this study no healthier subjects have received vaccination with more probability. Vaccinated subjects were older and had more comorbidity than non-vaccinated subjects (Table 1), so unadjusted analyses underestimated the effectiveness of the vaccine. The significant differences between groups were controlled adjusting for the appropriate variables in the final multivariable analysis and treating the confounding through purposeful selection method (19). However, as with all observational studies, the possible influence of residual confounding on the estimates of vaccine effectiveness cannot be completely excluded.

In summary, the present study shows that the annual influenza vaccination was associated with an almost significant reduction of 24% in the adjusted risk of all-cause winter mortality among older adults with COPD during four consecutive influenza seasons. Our data suggest benefit from the annual influenza vaccination in elderly COPD patients, even considering the mild or moderate severity of influenza seasons. However, conclusions may not be definitive as the results were not clearly significant. Further studies are needed to estimate accurately the magnitude of the potential benefits from influenza vaccination in these patients.

In our opinion annual vaccination should be recommended as a larger cohort of the vaccinated subjects in the general population might provide a significant reduction in mortality. This could not be demonstrated in this study because of the smaller number of subjects studied. It must be kept in mind that approximately one-third of elderly COPD patients remain annually unvaccinated, and the increase in vaccination uptakes has to be a major goal in the care of COPD patients (30).

Acknowledgements

This study was supported by a grant from the Health Research Fund (FIS) of the Spanish Ministry of Health and Consumer Affairs (Madrid, FIS PI-021117).

The authors thank the Fundació Jordi Gol (Barcelona) and all family doctors and nurses of Primary Care Centers in Tarragona-Valls for their collaboration in this study. The authors also thank Timothy Bowring, Joan Fort, Marc Vila and Dolors Rovira for help in the preparation of this manuscript.

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Paper received January 2007, accepted April 2007

ARTICLE 3

Efectes de la vacunació antigripal anual sobre la mortalitat hivernal a la gent gran amb cardiopatia crònica. Cinta de Diego, Ángel Vila - Córcoles, Olga Ochoa, Teresa Rodriguez - Blanco, Elisabeth Salsench, Imma Hospital, Ferran Bejarano, M. del Puy Muniain, Mercé Fortin, Montserrat Canals, and EPIVAC Study Group. Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease. Eur Heart J. 2009 Jan;30(2):209-16.

Resum

Introducció: Encara que existeix un acord general per a la recomanació de la vacuna antigripal en gent gran i d'alt risc, la magnitud de l'efectivitat clínica i el benefici de la vacunació anual és objecte de controvèrsia. En aquest estudi, hem avaluat els efectes de la vacunació antigripal anual sobre la mortalitat hivernal en els adults grans amb cardiopatia crònica. Mètodes: Estudi de cohort que va incloure a 1.340 persones residents a la comunitat de 65 anys o més que tenien cardiopatia crònica (insuficiència cardíaca congestiva o malaltia coronària), seguits des de gener 2002 a abril de 2005. L'estat anual de vacunació antigripal era una condició variable en el temps i la mesura de l'efecte va ser la mort per qualsevol causa durant el període d'estudi. Es van utilitzar models multivariables de Cox ajustats per edat, sexe i comorbiditat per avaluar l'eficàcia vacunal. Resultats: Vacunar-se contra la grip es va associar amb una reducció significativa del 37% en el risc ajustat de mortalitat hivernal durant tot el període 2002-2005. La reducció atribuïble del risc de mortalitat en persones vacunades va ser de 8,2 morts per cada 1.000 persones - hivern. Estimem que una mort va ser previnguda per cada 122 vacunacions anuals (variant entre 49 a l'hivern de 2005 i 455 l'hivern de 2003). Conclusió: Els nostres resultats suggereixen un benefici de la vacunació contra la grip i recolzen una estratègia de vacunació anual per a les persones grans amb malalties cardíaques.

European Heart Journal (2009) **30**, 209–216
doi:10.1093/eurheartj/ehn498

CLINICAL RESEARCH
Prevention and epidemiology

Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease

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Received 4 December 2007; revised 13 October 2008; accepted 16 October 2008; online publish-ahead-of-print 8 November 2008

Aims Although there is general agreement for the recommendation of the influenza vaccine to elderly and high-risk adults, the magnitude of clinical effectiveness and benefit from the annual vaccination is controversial. In this study, we have assessed the effects of annual influenza vaccination on winter mortality in older adults with chronic heart disease.

Methods and results Cohort study that included 1340 Spanish community-dwelling individuals 65 years or older who had chronic heart disease (congestive heart failure or coronary artery disease) followed from January 2002 to April 2005. Annual influenza vaccine status was a time-varying condition and primary outcome was all-cause death during the study period. Multivariable Cox proportional-hazard models adjusted by age, sex, and comorbidity were used to evaluate vaccine effectiveness. Influenza vaccination was associated with a significant reduction of 37% in the adjusted risk of winter mortality during the overall period 2002–2005. The attributable mortality risk reduction in vaccinated people was 8.2 deaths per 1000 person-winters. We estimated that one death was prevented for every 122 annual vaccinations (ranging between 49 in Winter 2005 and 455 in Winter 2003).

Conclusion Our results suggest a benefit from the influenza vaccination and support an annual vaccination strategy for elderly people with cardiac diseases.

Keywords Influenza vaccine • Effectiveness • Elderly • Heart disease • Mortality

Introduction

Influenza viruses are a major determinant of morbidity and mortality mainly caused by respiratory disease. The incidence of flu is higher in children and younger adults than in older individuals, but influenza-associated morbidity and mortality increase with age, especially for individuals with underlying medical conditions such as chronic heart diseases.[1–3]

During influenza epidemics, it has been reported that this viral infection was associated with increased death rates from cardiovascular diseases and a rise in autopsy-confirmed coronary deaths.[4] Clinical and experimental data suggest that autoimmune mechanisms are responsible for accelerated coronary atherosclerosis in influenza infection. Both cellular and humoral autoimmune modes could participate in the onset or progression of atherosclerotic lesions due to influenza infection.[5,6]

To date, although some studies have reported that influenza infection causes excess specific cardiac mortality,[4,7] the effect of the influenza vaccination in preventing mortality among patients with chronic heart diseases is not well known. This is because few studies have specifically focused on these patients[8–10] and their conclusions were not always in favour of vaccination.[10]

On the other hand, although the effectiveness of the influenza vaccination in preventing mortality has been extensively studied among hospitalized or institutionalized patients during severe influenza seasons, few large studies have systematically evaluated the

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clinical benefit of vaccination in community-dwelling individuals over the medium or long term,[11–15] and little is known about the effectiveness of the annual vaccination programmes in high-risk elderly people living in the community.

To assess influenza vaccine effectiveness in preventing mortality, we conducted a cohort study of 11 240 Spanish community-dwelling elderly individuals followed between 2002 and 2005. The analysis on vaccine effectiveness covering the general elderly and chronic obstructive pulmonary disease patients has been published.[15,16] In the present study, we assessed the relationship between the annual influenza vaccine status and all-cause winter mortality among a group of 1340 individuals with chronic heart disease.

Methods

Design, setting, and study population

We conducted a cohort study that included all community-dwelling individuals 65 years or older assigned to eight Primary Health Care Centres (PHCCs) in the region of Tarragona (Catalonia, Spain) who had a diagnosis of chronic heart disease (including heart failure or coronary artery disease) registered in their clinical record at the start of the study.

When the study started, the Health District of Tarragona had 12 PHCCs with an overall assigned population of 134 232 all-age inhabitants. The selection of the eight participating PHCCs was not randomized and they were chosen taking into account the existence of electronic clinical registries working since 1998 or before. The other four PHCCs in the Health District were not included because they had only computerized the clinical records more recently.

The 1340 cohort members were followed from the beginning of the study (1 January 2002) until enrolment from the PHCC ceased, the occurrence of death, or until the end of the study (30 April 2005). The study was approved by the Ethical Committee of the Catalonian Health Institute and conducted in accordance with the general principles for observational studies.

Sources of data

All participating PHCCs have an institutional computerized clinical record system which contains registries of immunizations, laboratory tests, medication prescription, diagnoses associated with outpatient visits, and chronic diseases coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9). The electronic records of each cohort member were used to identify whether the individual had received or not the influenza vaccine in each influenza vaccination campaign, and it was also used to identify the presence of chronic heart disease (heart failure: ICD-9 codes 428, 428.0 and 428.1; coronary artery disease: ICD-9 codes 410–414), co-morbidities, and other medical conditions.

Outcome measure and definitions

The influenza period was defined as the period during which influenza-like illnesses were frequently reported in the study area, from 1 January to 30 April for each year of the study.[15]

Primary outcome was all-cause death. Deaths were initially identified in the Institutional Demographic Database (which is updated monthly with administrative data about deaths, patients who have moved or new patients assigned to a PHCC). Afterwards, a review of the reference Civil Registry Offices of the eight PHCCs was used to identify those deaths that had occurred in cohort patients who had not been registered in the Institutional Database. This review was also used to validate the exact date of death in all cases. Finally, deaths were classified as occurring within the influenza period (January–April) or within a reference control summer period (June–September).

Exposure to influenza vaccination

For each year, information on the influenza vaccination status of the subjects was determined by a review of the PHCCs' clinical records, which contain specially designated fields for annual influenza vaccinations. We assumed that information in clinical records was complete, so a subject was considered as non-vaccinated when data on vaccination was missing or vaccination was not recorded (in other words, a patient was considered as non-vaccinated when the specific field for annual vaccination was empty).

Influenza vaccine status was considered as a dichotomous (vaccinated or non-vaccinated) time-varying condition throughout the study period (i.e. in the analysis covering the overall study period, the same person could be considered non-vaccinated in 2002, vaccinated in 2003, and non-vaccinated in 2004 according to the reception or not of the influenza vaccine in the prior autumn).

Covariates

Covariates included dichotomous variables for sex, chronic lung disease (including asthma, emphysema, or chronic bronchitis), diabetes mellitus, hypertension, obesity, current smoking, and immunocompromised status. Age and the number of outpatient visits in the previous 2 years were considered as continuous covariates. Immunocompromise was a composite variable defined by the presence of any one of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis, or transplantation), chronic severe liver disease (cirrhosis), anatomical or functional asplenia, AIDS, and long-term corticosteroid therapy (20 mg/day of prednisone) or another immunosuppressive medication. The presence of co-morbid conditions was determined by a review of the diagnosis codes in the electronic clinical record of each cohort member.

Statistical analysis

Incidence rates (IR) of death were calculated as person-years and person-weeks. For the numerator we used number of deaths. The denominator was the total number of person-years/person-weeks of observation for each study period considered. So, for each individual we determine the amount of observation time contributed to that period and to add up those contributions for all cohort members. Attributable risk (AR) was the difference between IR among vaccinated and non-vaccinated subjects (AR=IR exposed − IR non-exposed). Numbers needed to be vaccinated (NNV) to save one death were estimated for influenza periods (January–April = 17.1 weeks) and were calculated as the inverse of the AR (NNV=1/AR).[16]

The differences between groups were evaluated by means of the χ^2 test for categorical variables and Student's *t*-test for continuous variables.

Multivariate Cox proportional-hazards models were used to evaluate the association between receiving influenza vaccine and the time to death during the study period. We performed stratified analysis by influenza period (defined from January to April) and a reference non-influenza period (from June to September) of the overall study period and four supplementary analyses of the influenza season of each year. Influenza vaccine status was a time-varying covariate in the stratified analysis by influenza period and a dichotomous fixed condition

(vaccinated/non-vaccinated in the previous autumn) in the analysis of each year.

The variables that have been considered in all the initial models are: age, sex, number of outpatient visits in the previous 2 years, chronic lung disease, diabetes, hypertension, obesity, smoking, and immunocompetence. The method to select a subset of covariates to include in the final proportional-hazards regression model is the purposeful selection.[17] Age and sex have been judged epidemiologically relevant variables, being included in all the final models. The authors checked for confounders (change-in-estimate $\geq$ 20%), interactions, and multicolinearity among the independent variables. In addition, all the models have been compared by the partial likelihood ratio test and the Akaike's information criterion (AIC). The proportional-hazard assumptions were assessed, adding the covariate by time interactions to the model and plotting the scaled and smoothed Schöenfeld residuals obtained from the main effects model. All results were expressed with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$ (two-tailed). The analyses were performed using Stata/SE version 9.1 (Stata Corp.).

Results

During the total study period, the 1340 cohort members were observed for an amount of 4027 person-years (209 968 person-weeks). The mean age when the study started was 76.2 years (SD: 7.1) and 47.4% were men. At baseline, 1068 (82.3%) of patients had some other form of co-morbidity, mostly hypertension (64.5%), diabetes mellitus (32.3%), or chronic lung disease (19.3%). *Table 1* shows the characteristics of the Study Population when the study started (1 January 2002) according to the reception or non-reception of the influenza vaccine in the Autumn 2001. As it can be seen in *Table 1*, at the beginning of the study, vaccinated subjects were slightly older than non-vaccinated subjects (mean age: 76.7 vs. 75.5; $P = 0.004$), and they had more frequency of attendance and co-morbidity than non-vaccinated subjects.

Of the 1340 cohort members, 277 (20.7%) died during the total 40 months follow-up, and 16 (1.2%) moved during the study

Table 1 Characteristics of the study population according to their influenza vaccine status at starting of the study (1 January 2002)

	No. of persons (%)		*P*-value[a]
	Non-vaccinated ($n = 480$)	Vaccinated ($n = 860$)	
Age group			
65–74 years	237 (49.4%)	350 (40.7%)	0.002
75–84 years	171 (35.6%)	392 (45.6%)	
≥85 years	72 (15%)	118 (13.7%)	
Age (years, mean/SD)	75.5 (7.6)	76.7 (6.7)	0.004
Sex			
Male	222 (46.3%)	413 (48%)	0.533
Female	258 (53.8%)	447 (52%)	
Number of outpatient visits during previous 2 years			
0–14 visits	128 (26.7%)	58 (6.7%)	0.000
15–29 visits	156 (32.5%)	229 (26.6%)	
30 or more visits	196 (40.8%)	573 (66.6%)	
Number of outpatient visits during previous 2 years (continuous) (years, mean/SD)	41.8 (26.1)	29.7 (26.1)	<0.001
Medical conditions			
Chronic heart disease	480 (100%)	860 (100%)	–
Diabetes mellitus	157 (32.7%)	276 (32.1%)	0.817
Chronic lung disease	76 (15.8%)	183 (21.3%)	0.015
Hypertension	291 (60.6%)	574 (66.7%)	0.025
Obesity	85 (17.7%)	206 (24%)	0.008
Smokers	39 (8.1%)	56 (6.5%)	0.270
Chronic liver disease	5 (1.0%)	10 (1.2%)	0.840
Chronic nephropathy	31 (6.5%)	72 (8.4%)	0.207
Active neoplasia	7 (1.5%)	32 (3.7%)	0.018
Immunosupresive medication	30 (6.3%)	96 (11.2%)	0.003
Immunocompromised status[b]	69 (14.4%)	183 (21.3%)	0.002

[a]*P*-values were calculated with χ^2 test or *t*-test.
[b]Immunocompromise was a composite variable defined by the presence of any one of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis, or transplantation), chronic severe liver disease (cirrhosis), anatomical or functional asplenia, AIDS, and long-term corticosteroid therapy (20 mg/day of prednisone), or another immunosuppressive medication.

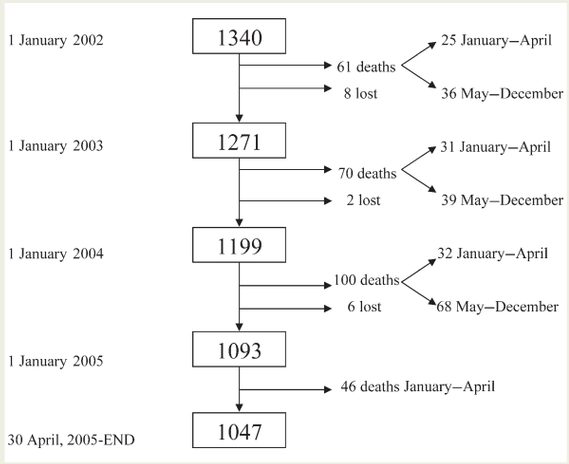

Figure 1 A survival flow chart of cohort members during the 40 month study period.

period. *Figure 1* shows the survival of cohort members throughout the 40 months study period.

If we consider those cohort members who remained in the closed cohort at the beginning of each year (excluding patients who died or moved during the prior year), the annual vaccination coverage reached 64.2% in the winter 2002, 69.3% in 2003, 73.5% in 2004, and 72.3% in 2005. In total 83 196 person-weeks were observed within the overall January–April periods 2002–2005, of which 57 980 person-weeks (69.7%) were vaccinated and 25 216 person-weeks were non-vaccinated against influenza in the respective previous autumn.

The mean incidence rate of all-cause death throughout the total 40 months study period was 68.8 deaths per 1000 person-years (132 per 100 000 person-weeks). Mortality varied significantly throughout the months of the year. We observed 134 deaths within the influenza periods of January–April and 75 deaths during the reference summer periods (June–September).

Among the total 134 deaths occurring within January–April, cause-specific death was registered in the primary care clinical record in only 82 cases (61.2%). Among these 82 patients, the specific cause of death was a cardiovascular disorder in 28 cases (34.1%), a cancer in 24 cases (29.3%), a respiratory cause in seven cases (8.5%), an infectious cause in six cases (7.3%), and other causes in 17 cases (20.7%).

Considering the overall influenza periods 2002–2005, 85 deaths were observed among persons who had received the influenza vaccine in the prior autumn and 49 deaths among persons who had not received the vaccine in the previous autumn. This meant an all-cause mortality rate (per 100 000 person-weeks) of 146.6 (95% CI: 117–181) in vaccinated subjects and 194.3 (95% CI: 144–257) in non-vaccinated subjects. *Table 2* shows the absolute number of deaths, mortality rates, and different results of the influenza vaccine's effectiveness in reducing mortality risk within the influenza periods (January–April) and within the reference non-influenza periods (June–September).

Unadjusted analysis showed that influenza vaccination was associated with a marginally significant decreasing rate of mortality within the overall influenza periods [hazard ratio (HR): 0.75; 95% CI: 0.52–1.06; $P = 0.101$], whereas it was not significant during the June–September control period (HR: 1.15; 95% CI: 0.68–1.90; $P = 0.630$).

Considering the sum of influenza periods 2002–2005, attributable risk among non-vaccinated subjects was 47.7 deaths per 100 000 person-weeks, so the number needed to vaccinate to save one death during one influenza period was 122 annual vaccinations (95% CI: 53 to infinite).

Multivariable analyses showed that annual vaccination was associated with a statistically significant reduction in the risk of all-cause mortality of 37% throughout the overall influenza periods 2002–2005 (adjusted HR: 0.63; 95% CI: 0.44–0.91; $P = 0.013$), whereas it was not significant during the reference summer period (adjusted HR: 0.94; 95% CI: 0.56–1.58; $P = 0.814$).

When we consider vaccine impact on winter mortality in each of the four analysed influenza seasons, the unadjusted protective effect of vaccination ranged from −8 to 40% (*Table 3*). Although the upper limit of the confidence interval did not reach statistical significance, we estimated that the numbers needed of annual vaccinations to save one death within each influenza period were 99 in the 2001–2002 influenza season, 455 in the 2002–2003 influenza season, 162 in the 2003–2004 influenza season, and 49 in the 2004–2005 influenza season.

Multivariable analysis showed that the adjusted effectiveness of vaccination against winter mortality varied between 20% in the 2002–2003 influenza season (adjusted HR: 0.80; 95% CI: 0.36–1.76; $P = 0.572$) to 54% in the 2001–2002 influenza season (adjusted HR: 0.46; 95% CI: 0.21–1.03; $P = 0.059$) (*Table 3*).

In supplementary analyses by sex, table not shown, vaccine effectiveness did not reach statistical significance in men. Vaccination effectiveness within the overall influenza period 2002–2005 was found in women (HR: 0.49; 95% CI: 0.30–0.78; $P = 0.003$). In stratified analyses by year, no statistically significant effect was observed in men, whereas a marginally significant effect was found in women in Winter 2002 (HR: 0.32; 95% CI: 0.10–1.04; $P = 0.059$) and 2005 (HR: 0.49; 95% CI: 0.23–1.02; $P = 0.058$).

Discussion

Nowadays, there is a general agreement for the recommendation of the influenza vaccine to elderly and high-risk adults.[2,3] However, the magnitude of clinical effectiveness and benefit from the annual vaccination campaigns is controversial.[14,18]

In this study, we have assessed the effects of the annual influenza vaccination on winter mortality in older adults with chronic heart disease (basically congestive heart failure and/or coronary artery disease). Although it was not randomized, the relatively large size of the study population together with the adjustment for important covariates in the multivariable analysis, provides an adequate basis for assessing the effects of the influenza vaccine status on winter mortality throughout a time-period with different severity of influenza seasons.

Table 2 Incidence and risk of all-cause mortality among elderly people with chronic cardiopathy within the influenza epidemic period and reference summer period, according to the reception of the influenza vaccine in the prior autumn[a]

Parameter	Study period	
	Within influenza periods (January–April)	Within non-influenza control periods (June–September)
Number of deaths		
Non-vaccinated	49	21
Vaccinated	85	54
Time followed (person-weeks)		
Non-vaccinated	25 216	16 619
Vaccinated	57 980	36 627
Unadjusted incidence rate per 100 000 person-weeks		
Non-vaccinated (95% CI)[b]	194.3 (144–257)	126.4 (78–193)
Vaccinated (95% CI)	146.6 (117–181)	147.4 (111–192)
Unadjusted hazard ratio for all subjects (95% CI)	0.75 (0.52–1.06)	1.15 (0.68–1.90)
P-value	0.101	0.630
Age-adjusted hazard ratio for all subjects (95% CI)	0.71 (0.50–1.01)	1.09 (0.65–1.83)
P-value	0.058	0.731
Age and sex-adjusted hazard ratio for all subjects (95% CI)	0.69 (0.48–0.98)	1.06 (0.63–1.78)
P-value	0.039	0.820
Multivariable-adjusted		
Hazard ratio (non-interact) (95% CI)	0.63 (0.44–0.91)[c]	0.94 (0.56–1.58)[d]
P-value	0.013	0.814

Cox regression analyses adjusted for age, sex, number of outpatient visits in the previous 2 years, chronic lung disease, diabetes, hypertension, obesity, smoking, and immunocompetence showed point estimates and confidence intervals that hardly varied compared with the reported multivariable hazard ratios (data available on request).
[a]The hazard ratios are for vaccinated subjects as compared with non-vaccinated subjects.
[b]CI denotes confidence interval.
[c]Adjusted for sex ($P = 0.089$), age ($P < 0.001$), chronic lung disease ($P = 0.032$), and number of outpatient visits ($P = 0.009$).
[d]Adjusted for age ($P < 0.001$), number of outpatient visits ($P < 0.001$), sex ($P = 0.116$), and immunocompromise ($P = 0.120$, confounder).

In the present study, annual influenza vaccine coverages varied from 64 to 74%, which is consistent with data reported for elderly people with chronic heart diseases in Spain and other developed countries, which have reported that approximately 30% of these subjects are not annually immunized against influenza.[2,19,20]

In this study, the influenza vaccination was associated with a nearly significant reduction of 25% in the unadjusted rate of all-cause winter mortality in vaccinated subjects, whereas the multivariable analysis showed a significant effectiveness of 37% (9–56%) in decreasing the risk of winter mortality throughout the overall study period among those patients who had received influenza vaccine in the prior autumn. Our result fits with those recently reported by Voordouw *et al.*[13] in a retrospective cohort study focussed on people over 65 in the Netherlands, who found that the annual influenza vaccination was associated with an all-cause mortality risk reduction of approximately 24% during the overall study period and 28% during the epidemic periods.

Although a benefit of the influenza vaccination to prevent hospitalization and death has been largely reported, the effectiveness of the vaccine is not well understood for major cause-specific mortality, except pneumonia. Recently, Wang *et al.*[7] have analysed 10 months mortality data of 102 692 individuals aged 65 years or older in Southern Taiwan, reporting that the influenza vaccination was significantly associated with a 44% lower risk of all-cause mortality and they have also reported a significant 22% reduction in the risk of death from heart diseases among vaccinated subjects.

In our study, cause specific mortality was not available in 39% of cohort members who died during the study period and furthermore, in some patients the cause of death was not specific enough to classify as influenza-related mortality or not. Thus, we have chosen all cause mortality as the main outcome measure, taking into consideration a possible misclassification bias and a lack of statistical power from an analysis of specific mortality. Given the difficulty for laboratory confirmed diagnosis of influenza infections, all-cause death has been considered an acceptable outcome to evaluate influenza vaccine effectiveness in many observational studies and meta-analyses.[21,22] In favour of choosing all-cause mortality as the outcome to assess the effect of influenza vaccination on mortality is the difficulty to classify a death as influenza-related mortality and, consequently, the possibility of misclassification bias when cause-specific mortality is considered. In general, when the event of interest is death, all-cause mortality is considered a more robust event than cause specific mortality. Nevertheless, we emphasize that, given that specific mortality was not evaluated, a residual confounding in the estimates of vaccine effectiveness cannot be completely excluded.

Table 3 **Incidence and risk of all-cause mortality among the study population during influenza periods 2002–2005 according to Influenza Vaccine Status[a]**

Parameter	2002	2003	2004	2005
Number of eligible subjects	1340	1271	1199	1093
Non-vaccinated	480	390	318	303
Vaccinated	860	881	881	790
Influenza vaccine coverage	64.2	69.3	73.5	72.3
Number of deaths and percentage (%)				
Non-vaccinated	12 (2.5)	10 (2.5)	10 (3.1)	17 (5.6)
Vaccinated	13 (1.5)	21 (2.4)	22 (2.5)	29 (3.7)
Unadjusted all-cause mortality rate per 100 000 person-weeks				
Non-vaccinated (95% CI)[b]	147.7 (76–258)	151.5 (58–245)	183.6 (88–337)	336.8 (196–538)
Vaccinated (95% CI)	88.9 (47–152)	138.6 (86–212)	147.5 (93–223)	218.2 (146–313)
Number of vaccinations needed to save one death during January–April period[c] (95% CI)	99 (38 to ∞)[d]	455 (46 to ∞)	162 (36 to ∞)	49 (20 to ∞)
Unadjusted hazard ratio (95% CI)	0.60 (0.27–1.31)	1.08 (0.50–2.35)	0.78 (0.37–1.65)	0.62 (0.34–1.13)
P-value	0.197	0.845	0.518	0.119
Age-adjusted hazard ratio (95% CI)	0.56 (0.26–1.24)	1.05 (0.49–2.29)	0.76 (0.36–1.60)	0.58 (0.32–1.06)
P-value	0.153	0.894	0.466	0.076
Age and sex-adjusted hazard ratio (95% CI)	0.55 (0.25–1.22)	0.94 (0.43–2.06)	0.72 (0.34–1.53)	0.59 (0.32–1.08)
P-value	0.141	0.885	0.390	0.085
Multivariable-adjusted hazard ratio (95% CI)	0.46 (0.21–1.03)[e]	0.80 (0.36–1.76)[f]	0.59 (0.27–1.28)[g]	0.59 (0.32–1.08)[h]
P-value	0.059	0.572	0.182	0.085

Cox regression analyses adjusted for age, sex, number of outpatient visits in the previous 2 years, chronic lung disease, diabetes, hypertension, obesity, smoking, and immunocompetence showed point estimates and confidence intervals that hardly varied compared with the reported multivariable hazard ratios (data available on request).

[a]The hazard ratios are for vaccinated subjects as compared with non-vaccinated subjects.

[b]CI denotes confidence interval.

[c]NNV is the number needed to vaccinate to save one death within an influenza period (January–April=17.1 weeks) and is estimated as 1/([mortality rate difference/100 000] × 17.1).

[d]The symbol ∞ indicates that the upper limit of confidence interval tends to infinite.

[e]Adjusted for age ($P < 0.001$), number of outpatient visits ($P = 0.004$), and sex ($P = 0.187$).

[f]Adjusted for age ($P < 0.001$), number of outpatient visits ($P = 0.022$), chronic lung disease ($P = 0.071$), and sex ($P = 0.056$, confounder).

[g]Adjusted for age ($P < 0.001$), chronic lung disease ($P = 0.018$), sex ($P = 0.247$), and diabetes ($P = 0.061$, confounder).

[h]Adjusted for age ($P < 0.001$) and sex ($P = 0.637$).

The effectiveness of the influenza vaccine to decrease all-cause mortality is controversial, and nowadays there is disagreement about the magnitude of the protective effects from the vaccination. In a classical meta-analysis, Gross *et al.*[21] estimated that influenza vaccine effectiveness against all-cause mortality varied from 27 to 30% in case–control studies to 56–76% in cohort studies. In a meta-analysis focused on elderly people living in the community, Vu *et al.*[22] estimated vaccine effectiveness against all-cause mortality as 45–56%. Simonsen *et al.*[18] have analysed influenza vaccine coverages and the estimates of influenza-related mortality and all-cause deaths for 33 influenza seasons from 1968 to 2001 in the USA elderly population. They reported that there was no correlation between increasing vaccination coverage after 1980 with declining mortality rates in any age group and concluded that many studies substantially overestimated the benefits of vaccination.[18]

In the present study, the difference between all-cause mortality in non-vaccinated and vaccinated subjects (attributable risk) was 47.7 deaths per 100 000 person-weeks during the overall January–April period, and we estimated that in the total population one winter death was prevented for every 122 annual influenza vaccinations, although this estimation does not exclude the possibility of a greater number since the value of the upper limits in the confidence interval reached infinite.

Important aspects that determine vaccine effectiveness are the intensity of viruses circulating during the study periods and the similarity between vaccine strains and circulating strains.[23] During our study period (2002–2005), influenza activity in northern hemisphere countries was mild-to-moderate in most countries, and was associated with a mixed circulation of Virus A and Virus B. In this period, vaccine strains and the predominant circulating strain (mainly A[H3N2]) generally were well matched.[24–27] In the study area, during the study period, the mean incidence rates of influenza-like illness reported between January and April among the overall population in the eight participating PHCCs were 63.4 cases per 100 000 person-weeks in 2002, 14.0 in 2003, 13.6 in 2004, and 84.3 in 2005.[15] Our findings are epidemiologically plausible considering that, as it can be expected, in the present study the greatest level of vaccine effectiveness was observed in the winters with the highest influenza epidemic activity (2002 and 2005) where unadjusted vaccine effectiveness was 40 and 38% (with NNVs ranging from 49 to 99), whereas the lowest vaccine effectiveness occurred in those winters with lower epidemic activity (2003 and 2004) where unadjusted vaccine effectiveness reached only −8 and 22% (with NNVs ranging between 162 and 455).

Our study has several strengths. Vaccination was evaluated by survival analysis methods to estimate vaccine effectiveness adjusted for age and co-morbidity. The study was population-based and study population was large enough to evaluate the relationship between annual influenza vaccine status and winter mortality throughout the overall study period. On the other hand, the sample size was small in assessing vaccine effectiveness separately for each influenza season. The study also has some intrinsic limitations and to interpret our findings, some characteristics of the study need to be addressed. In this study, influenza vaccination was considered as a simple dichotomous variable ('vaccinated' or 'non-vaccinated') in each year, but other categories of influenza vaccine status (such as 'first vaccination', 'revaccination', 'vaccination interruption', or 'vaccination restart') which can influence vaccine effects were not evaluated.[13]

The main limitation of observational designs is a possible selection bias. In our study, vaccinated subjects were older and had more co-morbidity than non-vaccinated subjects (*Table 1*). Moreover those patients who had a higher number of underlying conditions had more visits than those patients who did have not, and this meant a higher probability of vaccination. However, in Spain all individuals are assigned to a PHCC and a free influenza vaccine is offered each autumn for all individuals over 65 years. We account for differences between vaccinated and non-vaccinated subjects in the analysis, by adjusting for these variables in the multivariable Cox proportional hazard model. However, as with all observational studies, the possible influence of residual confounding due to unknown confounding factors on the estimates of vaccine effectiveness cannot be completely excluded (Szklo M., Nieto J., 2000). Information bias may have occurred if some co-morbidity or vaccination was not recorded, but such misclassification would likely be random because vaccination and covariates were recorded before occurrence of death.

The efficacy of influenza vaccination and the estimated impact of annual influenza epidemics on morbid-mortality have been the basis for implementing influenza vaccination programmes for elderly and high-risk individuals.[2,3,21,22] However, the effectiveness of vaccination has been reported to decrease in older age-groups and high-risk persons, and the magnitude of clinical effectiveness of annual vaccination campaigns is unclear. Nowadays, in this field, the gold standard of a large randomized controlled trial would be unethical and non-experimental studies evaluating influenza vaccination effectiveness must be applied.[23,28] Our results show that the reception of the annual conventional inactivated influenza vaccine was associated with a significant low risk of all-cause winter mortality among community-dwelling elderly patients with chronic heart disease followed throughout a consecutive 4 year series that included four influenza seasons.

Our data confirms the benefit of the influenza vaccination, even considering mild-or-moderate severity of influenza seasons, and it supports an annual vaccination strategy for these patients. It must not be forgotten that approximately one-third of elderly patients with chronic heart diseases remain annually non-vaccinated, and the increase in vaccination uptakes should be a major goal in the care of these patients.

Acknowledgements

The authors thank V. Arija for her help in the statistical analysis. The authors also thank Joan Fort and Timothy Bowring for their help in the production of this paper. The authors would like to thank all the family physicians and nurses of the Primary Care Centres in Tarragona-Valls who collaborated in this study.

Conflict of interest: none declared.

Appendix: Author contributions

C.D., A.V.-C., O.O., E.S., I.H., and F.B. designed the study, assessed outcomes, and wrote and edited the paper. A.V.-C. co-ordinated the

study; C.D., O.O., M.M., M.F., and M.C. obtained the data; T.R.-B. did statistical analysis.

Funding

This study was supported by Grants from the Health Research Fund (FIS) of the Spanish Ministry of Health and Consumer Affairs (Madrid, FIS PI-021117) and the Jordi Gol Foundation, Barcelona.

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ARTICLE 4

Vacunació antigripal i mortalitat hivernal en pacients diabètics majors de 65 anys. C. de Diego, Á. Vila - Córcoles, O.Ochoa - Gondar, A.Valdivieso, V.Arija y T.Rodríguez - Blanco. Vacunación antigripal y mortalidad invernal en pacientes diabéticos mayores de 65 años. Semergen.2010;36(1):3–9.

Resum

Objectiu: Analitzar l'impacte de la vacunació antigripal anual sobre la mortalitat hivernal en una cohort de diabètics majors de 65 anys seguits durant 4 anys. Material i mètodes: Cohort de 2.650 individus majors de 65 anys amb diabetis mellitus, no institucionalitzats, seguits des de gener de 2002 fins l'abril de 2005, pertanyents a 8 àrees bàsiques de salut. L'estat vacunal antigripal es va considerar com una condició canviant en el temps i la variable principal fou la mort per totes les causes en els períodes gener-abril del quadrienni d'estudi. Resultats: Globalment, durant els períodes gener-abril de 2002-2005, la mortalitat hivernal (per 100.000 persones/setmana) fou de 97,0 per a vacunats i de 110,5 per a no vacunats, amb un risc atribuïble de 13,5 morts hivernals per 100.000 persones/setmana (IC 95%:11,4-38,4). La recepció de la vacuna antigripal es va associar amb una reducció no significativa del 12% en el risc de mortalitat hivernal per qualsevol causa (risc relatiu: 0,88; IC 95%:0,67–1,19). Conclusió: Les nostres dades apunten cap a un petit benefici de la vacunació antigripal per a disminuir la mortalitat hivernal en pacients diabètics majors de 65 anys, encara que la possibilitat d'un efecte nul no pot ser exclosa totalment.

Semergen. 2010;36(1):3–9

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ORIGINAL

Vacunación antigripal y mortalidad invernal en pacientes diabéticos mayores de 65 años

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Recibido el 2 de marzo de 2009; aceptado el 29 de julio de 2009
Disponible en Internet el 15 de enero de 2010

PALABRAS CLAVE
Vacuna antigripal;
Ancianos;
Diabetes mellitus;
Mortalidad

Resumen
Introducción: Analizar el impacto de la vacunación antigripal anual sobre la mortalidad invernal en una cohorte de diabéticos mayores de 65 años seguidos durante 4 años.
Material y métodos: Cohorte de 2.650 individuos mayores de 65 años con diabetes mellitus, no institucionalizados, seguidos desde enero de 2002 hasta abril de 2005, pertenecientes a 8 áreas básicas de salud. El estado vacunal antigripal se consideró como una condición cambiante en el tiempo y la variable principal fue la muerte por todas las causas en los períodos enero-abril del cuatrienio de estudio.
Resultados: Globalmente, durante los períodos enero–abril de 2002–2005, la mortalidad invernal (por 100.000 personas/semana) fue de 97,0 para vacunados y de 110,5 para no vacunados, con un riesgo atribuible de 13,5 muertes invernales por 100.000 personas/semana (IC 95%: −11,4 a 38,4). La recepción de la vacuna antigripal se asoció con una reducción no significativa del 12% en el riesgo de mortalidad invernal por cualquier causa (riesgo relativo: 0,88; IC 95%: 0,67–1,19).
Conclusión: Nuestros datos apuntan hacia un pequeño beneficio de la vacunación antigripal para disminuir la mortalidad invernal en pacientes diabéticos mayores de 65 años, aunque la posibilidad de un efecto nulo no puede ser excluida totalmente.

KEYWORDS
Influenza vaccine;
Elderly;
Diabetes mellitus;
Mortality

Influenza vaccination and winter mortality in diabetic patients over 65 years

Summary
Introduction: To analyze the effectiveness of annual influenza vaccination on winter mortality in a cohort of diabetic patients over 65 years followed-up for 4 years.

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1138-3593/$ - see front matter
doi:10.1016/j.semerg.2009.07.001

Methods: Cohort of 2650 non-institutionalized, individuals older than 65 years with Diabetes Mellitus, followed-up from January 2002 until April 2005, from 8 primary health care centers. The vaccination status was considered as a condition changing over time and the endpoint was death from all causes in the period from January to April of the 4-year study period.
Results: Overall, during the January to April periods including the years 2002–2005, the winter mortality (per 100,000 person-week) was 97.0 for vaccinated and 110.5 for non-vaccinated subjects, with an attributable risk of 13.5 deaths per 100,000 person-weeks in winter (95% CI: −11.4 to 38.4). The reception of the influenza vaccine was associated with a non-significant reduction of 12% in the risk of mortality from all causes during winter in the 2002–2005 overall period (relative risk 0.88; 95% CI: 0.67–1.19).
Conclusion: Our data suggest a small benefit of influenza vaccination to reduce winter mortality in diabetic patients over 65 years, although the possibility of no effect cannot be excluded completely.

Introducción

El virus de la gripe es uno de los mayores causantes de morbimortalidad, sobre todo por enfermedades respiratorias. La incidencia de gripe es mayor en niños y adultos jóvenes, pero la morbilidad asociada y la mortalidad aumentan con la edad, especialmente en individuos con enfermedades crónicas de base como la diabetes mellitus[1–3].

El impacto de las epidemias anuales de gripe sobre la morbimortalidad en personas mayores y la efectividad de la vacuna antigripal han sido la base de la implementación de programas de vacunación en personas mayores a nivel mundial[4].

La inmunización antigripal es importante en la medicina preventiva de enfermedades crónicas como la diabetes, en la cual el equipo de atención primaria tiene un papel protagonista. De acuerdo con el Advisory Committee on Immunization Practices (ACIP), el American Academy of Family Physicians (AAFP), el Ministerio de Sanidad y Consumo y las recomendaciones del Programa de Actividades Preventivas y de Promoción de la Salud (PAPPS) de la Sociedad Española de Medicina de Familia y Comunitaria (SEMFyC), la vacunación anual de individuos de alto riesgo antes de la época gripal es la medida más efectiva para reducir el impacto de la gripe. En relación con la diabetes mellitus, el objetivo en la atención primaria debería ser la inmunización de todas aquellas personas diabéticas, sobre todo si tienen factores de riesgo como enfermedad renal o cardíaca, o aquellas que han sido hospitalizadas recientemente[5].

Aunque la efectividad de la vacuna antigripal en la prevención de la mortalidad ha sido extensamente estudiada en pacientes institucionalizados y hospitalizados en épocas de alta actividad gripal, hay pocos estudios sobre el beneficio clínico de la vacunación a medio o largo plazo en pacientes no institucionalizados[6–14], y poco se sabe sobre la efectividad de los programas de vacunación anual de personas mayores con patología de riesgo[15].

Con objeto de estudiar el impacto potencial vacunal en la prevención de mortalidad en nuestro medio se realizó un estudio de cohortes que incluyó 11.240 personas no institucionalizadas mayores de 65 años y que fueron seguidas entre los años 2002–2005. Los análisis de la efectividad de la vacuna antigripal en personas mayores con enfermedad pulmonar obstructiva crónica y con cardiopatía han sido publicados previamente[16–18]. En el presente estudio nos planteamos analizar la relación entre la vacunación antigripal anual y la mortalidad invernal en el subgrupo de 2.650 diabéticos seguidos durante el cuatrienio de estudio.

Material y métodos

Diseño del estudio, emplazamiento y criterios de inclusión/exclusión

Estudio de cohortes multicéntrico. Se incluyó a todos los diabéticos de 65 años o más (n=2.650), no institucionalizados, asignados a las 12 áreas básicas de salud (ABS) del Servicio de Atención Primaria de la región de Tarragona-Valls, pertenecientes al Institut Català de Salut. Se eligió como participantes a 8 de las 12 ABS, teniendo en cuenta la existencia de historia clínica informatizada desde 1999 o antes. Las 4 restantes ABS quedaron fuera del estudio al no cumplir este requisito.

La cohorte incluyó un total de 2.650 pacientes que constaban registrados como diabéticos y fueron seguidos desde el comienzo del estudio (1 de enero de 2002) hasta el cese por traslado, muerte o final del estudio (30 de abril de 2005). El estudio fue aprobado por el comité ético del Institut Català de la Salut.

Todas las ABS participantes tenían historias clínicas informatizadas, con registro de inmunizaciones, análisis clínicos, medicación y diagnósticos codificados según la clasificación internacional de enfermedades en su 9.ª revisión (ICD-9). El registro electrónico de cada miembro de la cohorte fue usado para conocer el estado vacunal y para identificar la presencia de diabetes mellitus y comorbilidades.

Estado vacunal

El período gripal fue definido como el período durante el cual son generalmente diagnosticados los cuadros *influenza-like* en el área de estudio, considerándose entre el 1 de enero hasta el 30 de abril para cada año.

El estado vacunal se consideró como una condición dicotómica (vacunado-no vacunado) variable en el tiempo durante el período de estudio. Por ejemplo, en el análisis de todo el período de estudio, una misma persona podía estar no vacunada en el año 2002, vacunada en el año 2003 y no vacunada en el año 2004, de acuerdo con la recepción o no de la vacuna antigripal el otoño previo.

Medida del efecto

La variable principal fue la muerte por todas las causas. Inicialmente se reclutaron las muertes en la base de datos demográficos de la institución (actualizado mensualmente con datos administrativos sobre muertes, pacientes trasladados o nuevos pacientes asignados). Posteriormente, se completó y validó la fecha exacta de muerte con una revisión de los registros civiles municipales. Finalmente, las muertes fueron clasificadas como ocurridas dentro del período gripal (enero–abril) o fuera del período gripal (mayo–diciembre).

Covariables

Se incluyeron edad, sexo, enfermedad pulmonar crónica (incluyendo asma, enfisema o bronquitis crónica), enfermedad cardíaca crónica, hipertensión, obesidad, tabaquismo, inmunodeficiencia (cáncer de órgano sólido o neoplasia hematológica), nefropatía crónica grave (síndrome nefrótico, insuficiencia renal, diálisis o trasplante renal), enfermedad hepática grave (cirrosis), asplenia funcional o anatómica, sida, terapia oral corticoidea de larga duración (20 mg/día de prednisona) u otra medicación inmunosupresiva. La presencia de condiciones de comorbilidad fue determinada por revisión de códigos diagnósticos en la historia clínica electrónica para cada miembro de la cohorte.

Pruebas estadísticas

Las tasas de mortalidad fueron calculadas como personas/año y personas/semana (en el numerador, el número de muertes, y en el denominador, el total de personas-tiempo). El riesgo atribuible (RA) fue la diferencia entre las tasas de mortalidad entre los no vacunados y los vacunados (RA=incidencia en expuestos-incidencia en no expuestos). El número necesario de vacunaciones anuales antigripales para evitar una muerte fue calculado por períodos gripales (enero–abril=17,1 semanas) y fue calculado como el inverso del RA (número necesario de vacunaciones=1/RA). Para comparar variables categóricas entre grupos se utilizó el test de Ji cuadrado, y para las variables continuas el test de la t de Student. Todos los resultados se expresan con su intervalo de confianza (IC) del 95%.

Se hicieron análisis separadamente por período gripal (enero–abril) y 4 análisis suplementarios por años y período gripal. El estado vacunal fue una covariable cambiante en el tiempo en el estudio estratificado por períodos gripales y una condición fija dicotómica (vacunado/no-vacunado) en el análisis por años.

Resultados

Considerando los 40 meses del período de estudio, los 2.650 miembros de la cohorte fueron observados por un total de 8.167 personas/año (426.143 personas/semana). La edad media al inicio del estudio era de 74,4 años (desviación estándar: 6,7), siendo un 58,8% mujeres. Fallecieron 384 (14,5%) durante el período de estudio (167 durante enero-abril y 217 durante mayo–diciembre) y 38 (1,4%) fueron pérdidas.

Un total de 2.180 (82,3%) de los sujetos tenían, además de la diabetes, alguna otra comorbilidad, principalmente hipertensión arterial (66,6%), cardiopatía (16,3%) o enfermedad pulmonar crónica (12,3%). La tabla 1 muestra las características basales de la cohorte de estudio al inicio del periodo de seguimiento.

Si consideramos los sujetos elegibles en cada campaña vacunal, la cobertura alcanzó un 59,8% en el otoño de 2001, un 65,8% en el otoño de 2002, un 70,8% en el otoño de 2003 y un 71,3% en el otoño de 2004. En total, 168.512 personas/semana fueron observadas dentro de los períodos enero-abril, de los cuales 112.416 personas/semana (66,8%) correspondían a personas vacunadas y 56.096 personas/semana no habían recibido la vacuna antigripal en el otoño previo.

A lo largo del período de estudio, la tasa de mortalidad por cualquier causa fue de 47,5 muertes por 1.000 personas/año (IC 95%: 43,0–52,3). La mortalidad varió significativamente durante los meses del año, observándose 167 muertes durante enero–abril y 217 muertes durante mayo-diciembre, lo cual significó una tasa de mortalidad (por 100.000 personas/semana) de 90,2 (IC 95%: 81,5–99,3) durante el período total de estudio; 99,1 (IC 95%: 84,8–114,9) en el período enero–abril, y 84,2 (IC 95%: 73,6–95,8) dentro del período mayo-diciembre.

Durante la suma de los cuatro períodos enero–abril 2002–2005, se observaron 106 muertes entre las personas que habían recibido la vacuna antigripal en el otoño previo y 61 muertes entre las personas que no la habían recibido; esto significó una tasa de mortalidad invernal (por 100.000 personas/semana) de 97,0 (IC 95%: 80,1–116,4) en vacunados y de 110,5 (IC 95%: 85,3–140,5) en no vacunados. Estos valores supusieron un RA para no vacunados de 13,5 muertes invernales por 100.000 personas/semana (IC 95%: −11,4 a 38,4) a lo largo del período total de estudio. El RA a lo largo del estudio fue de 2,3 muertes por 1.000 personas/invierno (IC 95%: −1,9 a 6,6).

El análisis global del cuatrienio estudiado (2002–2005) mostró que la recepción de una dosis de vacuna antigripal en el otoño previo no se asociaba a una reducción significativa en el riesgo de mortalidad invernal por cualquier causa (RR: 0,88; IC 95%: 0,67–1,19).

Cuando analizamos separadamente la relación entre la recepción de la vacuna antigripal en cada otoño y el riesgo de muerte por cualquier causa en el siguiente invierno, tampoco observamos un efecto protector estadísticamente significativo, con unos RR para vacunados que oscilaron entre un 0,67 (IC 95%: 0,29–1,48) en el período gripal 2001-2002, un 0,77 (IC 95%: 0,43–1,39) en el período 2002–2003, un 0,79 (IC 95%: 0,41–1,56) en el período 2003–2004 y un 0,97 (IC 95%: 0,48–1,82) en el período 2004–2005.

La tabla 2 muestra las coberturas vacunales, el número de muertes y los diferentes resultados evaluando la relación

Tabla 1 Características de la población de estudio al comienzo del período de seguimiento (1 enero de 2002)

	Hombres (n=1.093) Número de personas (%)	Mujeres (n=1.557)	p[a]
Grupo de edad[b]			
65–74 años	658 (60,2)	830 (53,3)	0,001
75–84 años	374 (34,2)	565 (36,3)	
≥85 años	61 (5,6)	162 (10,4)	
Recepción vacuna antigripal en el año previo (otoño de 2001)			
Vacunados	670 (61,3)	916 (58,8)	0,202
No vacunados	423 (38,7)	641 (41,2)	
Número de visitas ambulatorias en los 2 años previos			
0–14 visitas	211 (19,3)	191 (12,3)	0,001
15–29 visitas	374 (34,2)	510 (32,8)	
30 o más visitas	508 (46,5)	856 (55,0)	
Comorbilidad asociada			
Diabetes mellitus	1.093 (100)	1.557 (100)	–
Cardiopatía	160 (14,6)	273 (17,5)	0,047
EPOC	212 (19,4)	115 (7,4)	0,001
HTA	611 (55,9)	1.154 (74,1)	0,001
Obesidad	209 (19,1)	469 (30,1)	0,001
Tabaquismo	190 (17,4)	20 (1,3)	0,001
Hepatopatía	37 (3,4)	31 (2,0)	0,025
Nefropatía	56 (5,1)	63 (4,0)	0,187
Neoplasia activa	37 (3,4)	32 (2,1)	0,034
Medicación inmunosupresiva	73 (6,7)	83 (5,3)	0,147

DE: desviación estándar; EPOC: enfermedad pulmonar obstructiva crónica; HTA: hipertensión arterial.
[a]Los valores de p fueron calculados con el test de Ji cuadrado.
[b]La edad media de hombres y mujeres fue de 73,65 años (DE: 6,2) y 74,8 años (DE: 7,0), respectivamente; $p<0,001$.

entre la recepción de la vacuna antigripal en el otoño previo y la mortalidad invernal por todas las causas durante cada una de las estaciones gripales 2002–2005.

Discusión

Aunque existe consenso para la recomendación de la vacuna antigripal en personas mayores y adultos de alto riesgo[2,3], la magnitud de la efectividad clínica y el beneficio de las campañas vacunales anuales son controvertidos[14,15,19].

Nuestro estudio apunta un posible efecto beneficioso de la vacunación en la reducción de mortalidad invernal en los pacientes diabéticos mayores de 65 años, puesto que, globalmente y para cada una de las cuatro estaciones gripales analizadas, los pacientes vacunados presentaron menores tasas de mortalidad invernal por cualquier causa que los no vacunados. Sin embargo, nuestros hallazgos deben ser interpretados con cautela puesto que, considerando el relativamente bajo número de eventos, nuestros resultados no alcanzaron significación estadística en ninguno de los períodos analizados.

Nuestros resultados son inferiores a los reportados por Voordouw et al en un estudio de cohortes retrospectivo en mayores de 65 años en Holanda, que demostraron que la vacunación anual estaba asociada a una reducción del riesgo de mortalidad de aproximadamente el 24% durante el período total de estudio y de un 28% durante los períodos epidémicos[10].

En el presente estudio, las coberturas vacunales anuales variaron entre el 59,8 y el 71,3%, datos que concuerdan con otros reportados en gente mayor con diabetes mellitus en España y otros países desarrollados, donde aproximadamente un 30% de estos pacientes diabéticos no se vacuna anualmente contra la gripe[1,2,20–22].

En el presente estudio se analizaron 4 épocas gripales, con variabilidad interanual sustancial de virus circulantes y con buena correlación antigénica entre las cepas circulantes y vacunales[23]. Durante nuestro período de estudio (2002–2005), la actividad gripal en los países del hemisferio norte fue moderada-débil en la mayoría de los países, y se asoció con una circulación mixta de virus A y B. En este período, las cepas vacunales y las circulantes predominantes (principalmente A [H3N2]) fueron coincidentes[24–27].

Aunque el beneficio de la vacunación antigripal para prevenir hospitalización y muerte ha sido largamente estudiado, la efectividad de la vacunación antigripal no es bien conocida en la mayoría de las causas específicas de muerte, excepto para la neumonía. En el año 2007, Wang et al analizaron datos de mortalidad durante 10 meses de 102.689 pacientes de 65 años o más en el sur de Taiwán, describiendo que la vacuna antigripal se asoció con un 44% de menor riesgo de mortalidad por todas las causas y una reducción significativa de un 55% en el riesgo de muerte por diabetes ente los sujetos vacunados[7].

Recientes estudios sugieren que existe una clara asociación entre la gripe, las infecciones respiratorias y el desencadena-

Tabla 2 Incidencia y riesgo de mortalidad por cualquier causa entre la población a estudio durante los períodos gripales 2002–2005 según la recepción o no de la vacuna antigripal

Año parámetro	2002	2003	2004	2005
Número de sujetos elegibles	2.650	2.558	2.422	2.286
No vacunados	1.064	876	707	657
Vacunados	1.586	1.682	1.715	1.629
Cobertura vacunal	59,8%	65,8%	70,8%	71,3%
N.º defunciones enero–abril	24	47	38	58
N.º defunciones mayo–diciembre	62	81	74	–
N.º pérdidas período total	6	8	24	–
Seguimiento vacunados	27.088	28.601	29.182	27.545
(112.416 personas/semana enero–abril)	18.127	14.855	12.007	11.107
Seguimiento no vacunados (56.096 personas/semana enero–abril)	45.215	43.456	41.189	38.652
Total 168.512				
N.º defunciones enero–abril				
No vacunados	12 (1,1%)	19 (2,2%)	13 (1,8%)	17 (2,6%)
Vacunados	12 (0,8%)	28 (1,7%)	25 (1,5%)	41 (2,5%)
Tasa de mortalidad por 100.000 personas/semana				
No vacunados	66,2	127,9	108,27	153,06
IC 95%	(34,4–114,9)	(77,4–198,7)	(57,9–184,1)	(87,5–245,1)
Vacunados	44,3	97,9	85,67	148,85
IC 95%	(22,9–77,2)	(65,3–140,9)	(55,6–126,0)	(105,7–202,3)
Tasa de mortalidad por todas las causas por 1.000 personas-período invernal				
No vacunados	11,3	21,7	18,4	25,9
IC 95%	(5,9–19,7)	(13,3–34,1)	(9,9–31,5)	(15,1–42,1)
Vacunados	7,6	16,7	14,6	25,2
IC 95%	(3,9–13,2)	(11,2–24,2)	(9,5–21,6)	(18,2–34,8)
Riesgo atribuible por 1.000 personas y período invernal	3,7	5,0	3,8	0,7
IC 95%	−3,9 a 11,4	−6,4 a 16,5	−7,6 a 15,2	−18,3 a 19,7
Riesgo relativo[a]	0,67	0,77	0,79	0,97
IC 95%	0,29–1,48	0,43–1,39	0,41–1,56	0,48–1,82
p	0,320	0,389	0,510	0,732

IC: intervalo de confianza.
[a]Riesgo relativo en vacunados respecto no vacunados.

miento de eventos cardiovasculares agudos (infartos agudos de miocardio, muerte súbita, accidentes vasculares cerebrales), y, por tanto, la vacuna antigripal reduciría no sólo la muerte específica por gripe o neumonía, sino que de forma indirecta reduciría la muerte por eventos cardiovasculares[27].

En el presente estudio, como medida del efecto hemos elegido mortalidad por todas las causas para minimizar un posible sesgo de clasificación y falta de poder estadístico en el análisis de mortalidad específica. En general, cuando el evento de interés es la muerte, la mortalidad por todas las causas se considera como un evento más robusto que la causa específica de muerte[28]. Considerando, además, las dificultades de la confirmación serológica de las infecciones por el virus de la gripe, la mortalidad por todas las causas es considerada como un parámetro aceptable para evaluar la efectividad de la vacuna antigripal en varios estudios observacionales[29,30].

Debido a las dificultades que comporta un diagnóstico serológico y atendiendo a los problemas éticos derivados de un diseño randomizado, la efectividad de la vacuna a nivel poblacional ha sido evaluada generalmente mediante estudios observacionales que utilizaban índices poco específicos y/o indirectos de efectividad (incidencia de cuadros *influenza-like*, hospitalizaciones y muerte por enfermedad respiratoria o por cualquier causa). La efectividad descrita hasta ahora de la vacuna antigripal para reducir la mortalidad por todas las causas se ha situado entre un 45–56% en estudios de cohortes y un 17–30% en estudios de casos y controles[29,30]. La efectividad de la vacuna antigripal para prevenir la mortalidad por todas las causas es controvertida. Simonsen et al analizaron las coberturas vacunales y estimaron la mortalidad relacionada con la gripe y las muertes por cualquier causa en 33 períodos gripales desde 1968 a 2001 en población anciana de EE. UU., sin encontrar correlación entre el aumento de cobertura vacunal después de 1980 con las descendentes tasas de mortalidad en cualquier grupo de edad, y concluyeron que muchos estudios sobrestimaban sustancialmente los beneficios de la vacuna[19].

En nuestro estudio, la diferencia entre la mortalidad por todas las causas en no vacunados y vacunados fue de 13,5 muertes por 100.000 personas/semana durante el período enero-abril total. Esto implicaría un RA de 2,3 muertes por 1.000 personas/invierno y, por tanto, un número aproximado de 431 vacunaciones anuales necesarias para prevenir una muerte, aunque debe resaltarse que el IC del RA no excluyó la posibilidad de un efecto negativo de la vacunación.

Algunas cuestiones metodológicas deben ser comentadas para una mejor valoración de los resultados. El estado vacunal se consideró como una variable dicotómica (''vacunado'' o ''no vacunado'') para cada año, pero otras categorías tales como ''primera vacunación'', ''revacunación'', ''vacunación interrumpida'' o ''restablecimiento de la vacunación'', que pueden influir en los efectos de la vacuna antigripal, no se consideraron[4,13]. En nuestro estudio, la situación vacunal y la presencia de comorbilidad fueron consideradas sobre la base de la información registrada. Somos conscientes de que puede haber existido un cierto sesgo de clasificación al considerar como no vacunadas a algunas personas que en realidad podrían haber estado vacunadas pero en las que este hecho no constase registrado en nuestras fuentes de datos (por falta de reinformación de la vacunación o por vacunación fuera del ABS). Un problema similar, motivado por las mismas razones, puede haberse producido en la consideración de los antecedentes de factores de riesgo y/o patologías crónicas de la población estudiada. Por último, y tratándose de un estudio no randomizado, un posible problema puede radicar en la falta de comparabilidad inicial de los grupos. Este hecho puede haber supuesto cierta infraestimación de la efectividad vacunal, puesto que los vacunados eran algo más viejos y tenían más comorbilidad que los no vacunados.

La eficacia de la vacunación antigripal y la estimación del impacto de ésta sobre la morbimortalidad han sido las bases para la implementación de los programas de vacunación en gente mayor y en individuos de riesgo[2,3,23,30]. Nuestros datos sugieren un beneficio de la vacunación antigripal en pacientes diabéticos, incluso en épocas gripales moderadas y de baja severidad. Para confirmar esta tendencia es necesaria la realización de estudios que controlen mejor las variables principales, los criterios de selección y amplíen el tiempo de seguimiento para estimar la verdadera efectividad de la vacuna antigripal en pacientes diabéticos en nuestro medio, con el fin de desarrollar e implementar nuevas estrategias vacunales. No olvidemos que el gold estándar sería conseguir un 100% de vacunaciones entre los pacientes diabéticos.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Financiación

Este estudio está becado con una de la Fundación Jordi Gol i Gurina, Barcelona.

Agradecimientos

Los autores agradecen a los médicos de familia y enfermeras de los centros de Atención Primaria de Tarragona-Valls su colaboración en este estudio.

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VI – DISCUSSIÓ

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L'eficàcia de la vacuna i l'impacte estimat de les epidèmies gripals anuals sobre la morbi - mortalitat ha estat la base per a la implementació dels programes de vacunació antigripals en la gent gran i en individus d'alt risc (WHO 2002; Van Essen 2003).

No obstant això, sembla ser que l'efectivitat de la vacunació disminueix en gent gran i persones d'alt risc, i la magnitud de l'efectivitat clínica de les campanyes anuals de vacunació no està clara. Avui dia, en aquest camp, el gold standard d'un gran assaig controlat aleatori seria poc ètic i s'haurien de realitzar estudis no experimentals que avaluessin l'eficàcia de vacunació contra la grip (Fukuda 2004; Hak 2003).

En el present estudi de cohorts prospectiu a llarg temps s'han avaluat la relació entre la vacunació antigripal anual i la mortalitat per qualsevol causa en la gent gran al llarg d'un quadrienni consecutiu. Encara que no és un estudi randomitzat, la grandària de la nostra població d'estudi juntament amb l'ajust d'importants covariables en l'anàlisi multivariable, proporciona una base adequada per a avaluar els efectes de la vacunació contra la grip en la mortalitat hivernal en la població anciana general al llarg d'un període de temps amb temporades de grip amb diferent grau de severitat.

Aspectes metodològics

El present estudi té diverses fortaleses. La vacunació es va avaluar mitjançant els mètodes d'anàlisi de supervivència per estimar l'efectivitat de la vacuna ajustada per edat i les comorbiditats importants. La població d'estudi va ser prou gran com per avaluar la relació entre la recepció de la vacuna antigripal anual i la mortalitat hivernal durant quatre anys seguits, incloent la severitat de diferents temporades amb diferent intensitat de grip. A més, la població d'estudi (una cohort de base comunitària) va ser molt representativa de la població diana per a la vacunació contra la grip.

D'altra banda, l'estudi té algunes limitacions intrínseques i per a la interpretació dels resultats s'han de comentar algunes de les característiques de l'estudi. En aquest estudi, la vacunació antigripal va ser considerada com una variable dicotòmica simple ("vacunat" o "no vacunat") en cada any, però les altres categories de l'estat vacunal antigripal (com "primovacunació", "revacunació", "interrupció de la vacunació" o "re-iniciació de la vacunació") que podrien influir en els efectes vacunals, no es van avaluar (Voordouw 2004).

La principal limitació dels dissenys observacionals és el possible biaix de selecció. En la nostra àrea, tots els individus són assignats a una ABS i la vacuna antigripal s'ofereix gratuïtament cada tardor a totes les persones majors de 65 anys (amb o sense condicions d'alt risc), però la possibilitat de biaix de selecció no es pot excloure tenint en compte que els índexs d'exposició i distribució de la prevalença d'alguns factors de risc importants entre els grups d'exposició difereixen substancialment en els subjectes vacunats i no vacunats. Malgrat això, tenint en compte que les dades sobre algunes variables pronòstigues importants van ser identificades i ajustades en l'anàlisi multivariable, és poc probable que aquests factors de confusió expliquin l'eficàcia de la vacuna. La nostra observació que la presència de condicions d'alt risc i la vacunació van ser predictors de mortalitat concorda amb els resultats anteriorment publicats.

Pot haver hagut un biaix d'informació si alguna comorbiditat o la vacunació no van ser registrades, però aquesta possible classificació errònia seria probablement aleatòria ja que l'exposició es va registrar abans de l'aparició de la mort. Si considerem la possibilitat de confusió d'indicació per un possible biaix per "healthy vaccine effect", en aquest estudi els subjectes més sans eren menys propensos a haver rebut la vacuna. Els subjectes vacunats eren més vells i tenien més co-morbiditat que els no vacunats, així que les anàlisis no ajustades podien subestimar l'efectivitat vacunal. Les diferències significatives entre els grups van ser controlades en l'anàlisi multivariable (Hosmer 1999). No obstant això, la

reducció del risc de mortalitat hivernal ajustada va ser del 37% en els períodes gripals totals, que és relativament alta, tenint en compte el fet que la mortalitat per totes les causes va ser triada com una mesura de resultat, i el fet que només hi va haver activitat epidèmica lleu en dues de les quatre temporades de grip analitzades. Per tant, com a tots els estudis observacionals, la possible influència de factors de confusió residuals en les estimacions de l'efectivitat de la vacuna no es pot excloure del tot (Szklo 2000).

En aquest estudi, la causa específica de mort no es va poder saber en un considerable nombre de membres de la cohort que van morir durant el període d'estudi i, a més, en alguns pacients la causa de la mort no era prou específica com per classificar-la com a mortalitat relacionada amb la grip o no. Per tant, hem optat per triar qualsevol causa de mort com a principal mesura de resultat. A favor de la tria de mortalitat per totes les causes com a mesura d'avaluació de l'efecte de la vacunació antigripal sobre la mortalitat, es pot argumentar la dificultat que hi ha per classificar una mort com a relacionada amb la grip i, en conseqüència, la possibilitat de biaix de classificació errònia quan s'ha considerat la causa específica de mortalitat. En general, quan l'esdeveniment d'interès és la mort, la mortalitat per qualsevol causa es considera més sòlida com a "variable de càlcul" que la mortalitat per causes específiques (Clark 2003). Tenint en compte això i les dificultats del diagnòstic serològic per a confirmar la infecció per grip, la mortalitat per totes les causes ha estat considerada com un resultat acceptable per a avaluar l'efectivitat de la vacuna antigripal en molts estudis observacionals i metanàlisis (Gross 1995; Vu 2002).

Aspectes importants que determinen l'efectivitat de la vacuna són la intensitat dels virus circulants durant els períodes d'estudi i la similitud entre les soques de la vacuna i les soques circulants (Fukuda 2004). Durant el període d'estudi, l'activitat de la grip en els països de l'hemisferi nord va ser lleu o moderada en la majoria dels països, i es va associar amb una circulació mixta de virus A i B (WHO 2002; WHO 2003; WHO 2004;

WHO 2005). En aquest període, les soques de la vacuna i la soca circulant predominant (sobretot A [H3N2]) en general van ser concordants (WHO 2002; WHO 2003; WHO 2004; WHO 2005).

A l'àrea de l'estudi, no hi havia un sistema general de vigilància per al diagnòstic de confirmació de la grip per laboratori i, en conseqüència, la veritable incidència de la grip entre la població de l'estudi era desconeguda. Es van obtenir dades sobre casos d'influenza - like recollits setmanalment durant el període 2002-2005 a partir de les 8 ABSs participants i, encara que aquestes dades no discriminen altres agents que causen malalties similars a la grip, poden ser utilitzades com una mesura indirecta de l'activitat de l'epidèmia en l'àrea d'estudi (annexa 1). Atès que l'efectivitat vacunal, a diferència de la eficàcia vacunal, està en funció de la incidència de la taxa d'atac de grip en l'any de l'estudi, hem trobat que la major eficiència de la vacunació va ocórrer dins del període de la grip de 2005 (NNV=144), que va ser el període amb la major taxa d'atac de casos d'influenza - like i la taxa de mortalitat per totes les causes més alta observada entre la població estudiada durant els quatre períodes de grip.

1.- Estimació de l'efectivitat vacunal a la població general major de 65 anys.

En aquest estudi, les cobertures anuals de vacunació contra la grip variaven entre un 54% a un 64%, la qual cosa és consistent amb les cobertures recollides anteriorment entre els ancians espanyols en els últims anys (Jiménez - García 2005; Sarriá - Santamera 2003). La taxa global de mortalitat (43 morts per 1.000 persones - any) també concorda amb les taxes de mortalitat per totes les causes registrades en adults majors de 65 anys en els països desenvolupats (Murray 1997).

En aquest estudi, la vacunació contra la grip es va associar amb una reducció estadísticament significativa del 23% (IC 95%: 11 a 35) en el risc ajustat de mortalitat per qualsevol causa dins dels períodes gripals en general, mentre que en l'anàlisi multivariable la reducció del risc va aconseguir un 37% (IC 95%: 26 a 46). Aquests resultats concorden amb

els reportats per Voordouw et al qui, en un estudi de cohorts des de 1996 fins 2002 en una mostra de 26.071 persones d'edat avançada no institucionalitzades que vivien en els Països Baixos, van trobar que la vacunació anual antigripal es va associar amb una reducció del risc de mortalitat per totes les causes d'aproximadament un 24 % durant el període d'estudi general i un 28% durant els períodes d'epidèmia gripal (Voordouw 2004).

L'efectivitat de la vacuna antigripal en la prevenció de la mortalitat en persones grans sanes és polèmica, i en l'actualitat hi ha un desacord sobre la magnitud de l'efecte protector de la vacunació (Mantagni 2004; Nordin 2001). Existeix una escassetat d'assaigs aleatoris (Govaert 1994), i estudis de cohorts han demostrat un major nivell d'efectivitat de la vacuna que els estudis de casos i controls. Gross et al estimaren que l'eficàcia de la vacuna contra la grip per a prevenir la mortalitat per totes les causes varia de 27-30% en estudis casos - control i en 56-76% en els estudis de cohorts (Gross 1995). En una metanàlisi entre les persones grans que viuen a la comunitat, Vu et al estimaren l'efectivitat de la vacuna en la prevenció de la mortalitat per totes les causes en un 45-56% (Vu 2002). Segons la nostra opinió, és possible que la magnitud de l'efecte protector de la vacuna contra la grip en la mortalitat de la població anciana en general podria haver estat sobreestimada, tenint en compte que molts estudis es van centrar en subjectes d'alt risc en els períodes d'epidèmia amb una alta incidència de grip, i pocs estudis s'han realitzat al llarg d'un període de temps incloent temporades gripals amb baixa intensitat de circulació del virus.

Mangtani et al, en una cohort històrica de persones majors de 65 anys a Anglaterra i Gal·les, no va trobar un clar efecte protector de la vacunació antigripal en la mortalitat per totes les causes entre 1989 i 1999 (Mangtani 2004). Simonsen et al analitzaren les cobertures vacunals antigripals i les estimacions de mortalitat relacionades amb la grip i la mortalitat per totes les causes de 33 temporades gripals des de 1968 fins

2001 a la població dels EUA. Demostraren que menys del 10% de totes les morts hivernals eren atribuïbles a la grip durant tot l'any, i no van poder correlacionar l'augment de cobertura de vacunació antigripal a partir de 1980 amb el descens de les taxes de mortalitat en qualsevol grup d'edat, concloent que els estudis observacionals sobreestimaven considerablement els beneficis de la vacunació (Simonsen 2005).

En aquest estudi, la reducció del risc absolut observat en la mortalitat hivernal en els vacunats va ser de 24,4 morts per cada 100.000 persones - setmana en els períodes de grip en general, la fracció de prevenció entre els vacunats va ser del 23% i la fracció de prevenció per a la població general va ser del 14%. Estimem que una mort va ser previnguda per cada 239 vacunacions anuals (variant des de 1.748 en el període gripal de l'any 2002 a 144 en el període gripal del 2005), tenint en compte que les cobertures vacunals anuals antigripals variaven de 54% a 64% durant tot el període 2002-2005. Es va estimar que es necessiten vacunar 239 persones per a prevenir una mort hivernal, i això concorda amb les dades obtingudes per Hak i altres a Minnesota durant els períodes gripals de 1990-1996 (NNV = 174) (Hak 2004) i Voordouw et al en els Països Baixos (NNV = 302) (Voordouw 2004).

En la nostra població d'estudi, l'efecte ajustat de protecció de la vacunació antigripal disminueix amb l'edat. L'efecte protector de la vacunació en relació amb l'edat i el gènere sembla reflectir diferències en les causes de la mort, però probablement també reflecteix que amb l'edat disminueix la immunogenicitat de la vacuna tal com diversos estudis han demostrat anteriorment (Bernstein 1999). No obstant això, tot i que l'efectivitat de la vacuna disminueix amb l'edat, no cal oblidar que la vacunació contra la grip podria tenir un major nivell d'eficiència en persones d'edat molt avançada. La major càrrega de mortalitat recau en aquest grup de població i es pot obtenir un important benefici de la vacunació, fins i tot tenint en compte l'efectivitat baixa de la vacuna en els subjectes d'edat molt avançada.

El cost total financer i administratiu de la vacunació anual de totes les persones en situació de risc és considerable. Els nostres resultats proporcionen informació important per a l'anàlisi de cost - efectivitat i les polítiques públiques per a la vacunació antigripal en la població anciana en general, tenint en compte que l'eficiència de la vacuna depèn de la incertesa al voltant de les estimacions de l'efectivitat de la vacuna (Postma 2000; Nichol 2003; Maciosek 2006).

2.- Estimació de l'efectivitat vacunal en les persones amb malaltia pulmonar crònica.

Considerant els pacients amb MPOC, les cobertures anuals de vacuna antigripal varien d'un 64% a 74%, la qual cosa és consistent amb estudis anteriors a Espanya i altres països desenvolupats, que van referir que aproximadament el 30% dels subjectes d'edat avançada (incloent les persones amb MPOC) no estan immunitzats contra la grip anualment (Lupatkin 2005; Nichol 1998; Woorduw 2004; Jiménez - García 2005; Fukuda 2004).

En el present estudi, la vacunació contra la grip es va associar amb una reducció no significativa del 16% en el risc ajustat de mortalitat hivernal per qualsevol causa en pacients ancians amb MPOC, mentre que l'anàlisi multivariant va mostrar una efectivitat gairebé significativa del 24% en la prevenció del risc de mortalitat hivernal durant el període total d'estudi entre els pacients amb MPOC que havien rebut la vacuna antigripal la tardor anterior. La diferència entre la mortalitat per qualsevol causa en pacients no vacunats i vacunats dins dels períodes gripals totals va ser de 31,5 morts per cada 100.000 persones - setmana, RA: 5,4 morts per cada 1.000 persones - període hivernal, i la fracció de prevenció de la mortalitat hivernal entre la població de MPOC més gran va ser d'aproximadament 5%. Es va estimar que en la població total es va prevenir una mort hivernal per cada 187 vacunacions anuals antigripals (variant de 78 vacunacions en la temporada de grip 2001-2002 a 415 a la temporada gripal 2003-2004), però aquestes estimacions no van ser

estadísticament significatives ja que els valors dels límits superiors dels intervals de confiança van arribar a infinit.

En una revisió Cochrane centrada en pacients amb MPOC, Poole et al van trobar que les vacunes inactivades de grip van reduir significativament el nombre d'exacerbacions i infeccions respiratòries relacionades amb la grip, però també van arribar a la conclusió que el nombre d'estudis centrats en pacients amb MPOC era massa petit i que no s'havia pogut detectar cap efecte sobre la mortalitat (Poole 2006).

Com a estudi de base comunitària que va incloure a totes les persones majors de 65 anys amb diagnòstic codificat de MPOC segons codis ICD-9, no es va poder determinar la severitat de l'obstrucció al flux aeri a causa de l'alt nombre de membres de la cohort on no hi havia una espirometria recent registrada en la seva història clínica, i aquesta va ser una limitació important en l'estudi.

Com a principal conclusió, aquest estudi mostra que la vacunació anual contra la grip es va associar amb una reducció gairebé significativa en el risc ajustat de mortalitat hivernal per qualsevol causa en els adults grans amb MPOC durant períodes consecutius gripals. Les nostres dades suggereixen un benefici de la vacunació anual contra la grip en pacients ancians amb MPOC, fins i tot tenint en compte la intensitat lleu o moderada de les temporades de grip. No obstant això, les conclusions no poden ser definitives en aquest grup de pacients, ja que aquests resultats no van ser clarament significatius i es necessiten més estudis per estimar la magnitud de beneficis potencials de la vacunació contra la grip. La vacunació anual seria recomanable ja que la vacunació d'un grup més gran dels subjectes de la població podria proporcionar una reducció significativa de la mortalitat que no es va poder demostrar en aquest estudi, a causa del menor nombre de subjectes estudiats. Cal no oblidar que aproximadament un terç dels pacients ancians amb MPOC romanen sense vacunar cada any, i l'augment dels índexs de vacunació ha de ser una fita important en la cura dels pacients amb MPOC (Nichol 2003).

3.- Estimació de l'efectivitat vacunal en les persones amb cardiopatia crònica

Aquest subanàlisi va incloure 1.340 membres de la cohort general que presentaven alguna malaltia cardíaca crònica (bàsicament, la insuficiència cardíaca congestiva i/o cardiopatia isquèmica). Encara que no es tracta d'un estudi randomitzat, la mida relativament gran de la població de l'estudi juntament amb l'ajust de les covariables importants en l'anàlisi multivariable, proporciona una base adequada per a avaluar els efectes de la situació vacunal contra la grip sobre la mortalitat hivernal en aquest pacients.

Les cobertures anuals vacunals antigripals varien d'un 64% a 74%, la qual cosa és consistent amb les dades obtingudes en persones d'edat avançada amb malalties cròniques del cor a Espanya i altres països desenvolupats, que han observat que un 30% d'aquests pacients no estan immunitzats contra la grip anualment (CDC 2004; Jiménez - García 2006; Sarrià - Santamera 2003).

En aquest estudi, d'acord amb les dades obtingudes, la vacunació contra la grip es va associar amb una reducció significativa de gairebé 25% en la taxa ajustada de mortalitat per qualsevol causa a l'hivern en els subjectes vacunats, mentre que l'anàlisi multivariant va mostrar una eficàcia del 37% (IC 95%: 9-56) per disminuir el risc de mortalitat hivernal en tot el període d'estudi en general entre els pacients que havien rebut la vacuna contra la grip a la tardor anterior. Malgrat que s'ha publicat un benefici de la vacunació contra la grip per prevenir l'hospitalització i mort, l'efectivitat de la vacuna no és ben entesa per a les principals causes específiques de mortalitat, a excepció de la pneumònia. Wang et al han analitzat durant 10 mesos les dades de mortalitat de 102.692 persones majors de 65 anys o més al sud de Taiwan, observant que la vacunació contra la grip es va associar significativament amb un risc 44% menor de mortalitat per qualsevol causa i una reducció significativa del 22% en el risc de mort per malalties cardíaques entre els subjectes vacunats (Wang 2007). La diferència entre la mortalitat per qualsevol causa en pacients no

vacunats i vacunats (RA) era del 47,7 morts per cada 100.000 persones - setmanes durant el període total de gener a abril, i es va estimar que en la població total pacients cardiòpates es prevén una mort hivernal per cada 122 vacunes anuals contra la grip, encara que aquesta estimació no exclou la possibilitat d'un major nombre ja que el valor dels límits superiors en l'interval de confiança va arribar a infinit.

Aquest resultats confirmen el benefici de la vacunació contra la grip en pacients amb cardiopatia crònica, fins i tot tenint en compte l'activitat lleu o moderada de les temporades de grip, i és compatible amb una estratègia de vacunació anual per a aquests pacients.

4.- Estimació de l'efectivitat vacunal en els pacients amb Diabetis Mellitus.

Aquest subanàlisi va incloure 2.650 membres de la cohort general que presentaven diabetis mellitus. Encara que l'estudi no va ser aleatoritzat, la relativa grandària de la mostra de la cohort de l'estudi, el model de regressió logística utilitzat ("time-hazard regression modelling"), juntament amb l'ajust de covariables rellevants i l'ajustament addicional per la propensió d'haver rebut la vacuna ("propensity score"), proporciona una base adequada per avaluar els efectes de la vacuna contra la grip sobre la mortalitat hivernal en aquestes persones.

En aquest estudi, la vacunació antigripal es va associar amb una reducció estadísticament significativa del 33% en el risc de mortalitat hivernal per qualsevol causa durant tot el quadrienni d'estudi entre els pacients diabètics, coincidint amb el resultat observat a l'avaluar l'efectivitat vacunal entre la població general major de 65 anys del mateix àmbit (Vila - Córcoles 2007).

Les cobertures anuals entre els pacients diabètics de la vacuna antigripal van oscil·lar entre 59,8% i 71,3%, la qual cosa és consistent amb altres dades publicades a Espanya en persones grans amb diabetis i altres països desenvolupats, on anualment aproximadament el 60-70% d'aquests persones són immunitzades contra la grip (Heymann 2004; CDC 2004; Vu

2002; Gross 1995). Malgrat la cobertura de vacunació va augmentar durant el període d'estudi, el risc de mort també va augmentar, arribant al valor màxim l'any 2005. Aquest resultat és difícil d'interpretar a causa del fet que la cohort es va anar envellint. No obstant això, es va observar que la taxa de supervivència acumulada va ser major en els vacunats que en els subjectes no vacunats en els períodes d'hivern dels quatre anys analitzats. La diferència entre la mortalitat per qualsevol causa en els no vacunats i vacunats va ser de 13,5 morts per cada 100.000 persones - setmana tenint en compte els períodes de grip total entre 2002 i 2005, i es va estimar que en la població total es prevén una mort hivernal per cada 435 vacunacions anuals, encara que aquesta estimació no exclou la possibilitat d'un major nombre ja que el valor dels límits superiors en l'interval de confiança van arribar a infinit.

En la comparació dels efectes de la vacuna a l'hivern amb el període d'estiu, quan el virus de la grip no és circulant, es va trobar una estimació puntual de l'efecte ajustat molt similar de la vacuna antigripal en la mortalitat hivernal per totes les causes (OR: 0,67, p = 0,03) en comparació amb l'estiu (OR: 0,70, p = 0,26), de manera que, malgrat la significació estadística, la proximitat d'aquestes dues estimacions (hivern i estiu) fa necessària una interpretació cautelosa dels resultats. De fet, la possibilitat d'una confusió residual en l'anàlisi no pot ser totalment exclosa.

Les dades del present estudi mostren un benefici de la vacunació anual contra la grip, fins i tot tenint en compte una lleu o moderada gravetat de les èpoques gripals, i és compatible amb una estratègia de vacunació anual per als diabètics d'edat avançada. Les guies clíniques actuals recomanen vacunar totes les persones d'edat avançada (amb o sense diabetis). Segons el present estudi, els efectes de la vacunació dels diabètics d'edat avançada en la mortalitat hivernal és similar als efectes de la vacunació en la població general d'edat avançada (Vila - Córcoles 2007; Vila - Córcoles 2008; de Diego 2009).

VII - CONCLUSIONS

VII – CONCLUSIONS

1.- Vacunació antigripal en la població general major de 65 anys (Vaccine 2007)

- La present tesi doctoral mostra que la recepció anual de la vacuna convencional antigripal inactivada es va associar amb una significativa reducció del risc de mortalitat hivernal per totes les causes de 23% (IC 95%: 11 a 35) entre la gent gran resident a Tarragona - Valls durant una sèrie d'anys consecutius que va incloure quatre temporades de grip entre gener de 2002 i abril de 2005.

- El risc atribuïble de mortalitat en no vacunats va ser de 24 morts per cada 100.000 persones - setmana en períodes gripals.

- Es va estimar que es podia haver previngut una mort per cada 239 vacunacions anuals (variant des de 144 a l'hivern del 2005 fins 1.748 a l'hivern del 2002).

- Aquestes dades confirmen el benefici de la vacunació antigripal, tot i considerar períodes gripals lleus i moderats, i és compatible amb una estratègia de vacunació anual a tots els ancians que viuen a la comunitat.

2.- Vacunació antigripal en la població major de 65 anys amb malaltia pulmonar obstructiva crònica (International Journal of Clinical Practice 2008)

- Si considerem els pacients amb malaltia pulmonar crònica, la vacuna antigripal es va associar amb una reducció estadísticament no significativa del 16% en la mortalitat hivernal entre els pacients vacunats.

3.- Vacunació antigripal en la població major de 65 anys amb cardiopatia crònica (European Heart Journal 2009)

- En els pacients amb antecedent de cardiopatia crònica, la vacunació antigripal es va associar amb una reducció significativa del 37% en el risc ajustat de mortalitat hivernal durant tot el període 2002-2005.

- La reducció del risc atribuïble de mortalitat a les persones vacunades va ser de 8.2 morts per 1.000 persones - hivern.

- En pacients amb cardiopatia crònica, es va estimar que es va prevenir una mort per cada 122 vacunacions anuals (variant entre 49 a l'hivern del 2005 i 455 a l'hivern del 2003).

4.- Vacunació antigripal en la població major de 65 anys amb diabetis mellitus (SEMERGEN 2010)

- La vacunació antigripal es va associar amb una reducció del 33% (IC 95%: 4-53) en el risc ajustat de mortalitat per qualsevol causa durant el conjunt dels períodes gripals 2002-2005.

- El risc atribuïble de la vacunació en la reducció de la mortalitat va ser de 13,5 per 100.000 persones - setmana en períodes gripals.

- Es va estimar que en pacients diabètics, una mort podria ser previnguda per cada 435 vacunacions anuals.

VIII - BIBLIOGRAFIA

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IX - ANNEXOS

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Aquestes són les xifres en nombre absolut de casos de malaltia influenza - like que es van detectar setmanalment a les 8 ABS participants (n=134.232 habitants de totes les edats) i es van comunicar al Sistema Nacional durant el període d'estudi (dades proporcionades per la Unitat de Malalties Declarables, Servei Territorial de Tarragona, Departament de Sanitat de la Generalitat de Catalunya).

Nombre de setmanes	Any			
	2002	2003	2004	2005
Setmana 1 (Gener 1)	30	7	28	305
2	85	15	32	418
3	191	20	33	339
4	191	30	34	217
5	231	38	17	203
6	217	14	21	117
7	166	29	13	62
8	142	4	10	147
9	106	39	19	65
10	64	52	43	57
11	31	8	21	44
12	13	27	24	22
13	21	38	12	21
14	18	27	10	6
15	14	20	5	1
16	10	7	3	5
17	5	9	0	6
Setmana 18 (Abril 30)	1	2	4	2
Total setmanes 1-18	1536	386	329	2037
Total setmanes 26–34 (Juliol-Agost)	11	10	13	10
Total setmanes 1–52 (Gener-Desembre)	2049	869	707	2162

UNIVERSITAT ROVIRA I VIRGILI
VACUNACIÓ ANTIGRIPAL I MORTALITAT HIVERNAL A LA POBLACIÓ MAJOR DE 65 ANYS DE L'ÀREA DE TARRAGONA
Cinta de Diego Cabanes
Dipòsit Legal: T.195-2013