The effect of influenza vaccination among general practitioners: a controlled trial [NCT00221676].

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Introduction

Two important aspects emerge when considering influenza vaccination of general practitioners (GPs) as advocated by many guidelines[1, 2]. Firstly a flu vaccine must give personal protection to the GP. To a certain extent this item is covered by efficacy studies among healthy adults[3]. Secondly the vaccine might be useful to prevent transmission of influenza between GPs and their patients. In long-term care hospitals a possible benefit of influenza vaccination of the healthcare workers was noticed in reducing mortality among the elderly[4, 5]. Because of a low basic immunity against influenza in healthy adults or healthcare workers working in long-term care facilities the results of these studies are not fully transmissible to general practice.

GPs, having frequent close contact with several influenza cases, build up a high basic immunity and probably only suffer from minor symptoms[6, 7]. The question remains if the vaccine is adding substantial benefit to this naturally acquired immunity. In addition doubts arise in the literature if an inactivated vaccine, which elicits especially humoral immune response, can give substantial protection against sub-clinical influenza infections and virus replication in the upper airways with consequent infectiousness[8, 9]. Until now no efficacy studies of influenza vaccination among GPs were published. High time to look closer into these issues. So, we aimed to assess the effect of an inactivated influenza vaccine in GPs on clinical respiratory tract infections (RTIs) and more particularly against influenza cases with influenza positive nose and throat swabs (diagnosed by reverse transcriptase polymerase chain reaction RT-PCR), besides serologically defined influenza cases and taking important co-variates into account.

Methods

A controlled trial during two consecutive winter periods (2002-2003 and 2003-2004) was performed, comparing vaccinated and unvaccinated GPs recruited in Flanders on voluntarily basis in July and August 2002 and 2003. Participants of the first year were asked to re-enter the study during the second winter period. Subjects were enrolled after giving their written informed consent. The study was approved by the medical Ethics Committee of the University Clinic of Antwerp. Participating GPs had to fill in a questionnaire relating to general characteristics and previous influenza vaccinations. On account of ethical reasons they were free to choose
whether or not to receive an influenza vaccination during the study period. Those who wanted to be vaccinated were instructed to have the 0.5ml vaccine administered into the deltoid muscle, at the end of October of each study year. GlaxoSmithKline n.v. provided Alfarix®, a commercially available non-adjuvanted trivalent inactivated split-influenza vaccine, for this study to each participating GP personally. In 2002 – 2003 and 2003 - 2004 the vaccine contained the same strains: 15µ hemaglutinin from A/New Caledonia/20/99 (H1N1), A/Moscow/10/99 (= A/Panama/2007/99) (H3N2) and B/Hong Kong/330/2001.

Blood specimens for antibody studies were taken immediately prior to and three to five weeks after vaccination. Unvaccinated GPs only had to give one blood specimen in November before the influenza epidemic, assuming this would give the same antibody titres as one month earlier (= post-immunisation). Three weeks after the influenza epidemic both groups had to give another blood specimen (= post-epidemic). The blood samples were collected by local medical laboratories for serum extraction and preservation (-20°C). After the last blood sample was taken the serum tubes were transported to Viroclinics in Rotterdam.

Viroclinics executed a hemagglutination-inhibition (HAI) test using standard methods to measure the influenza antibody titre against the circulating influenza strains. In 2002-2003 antibody titres were determined against A/H1N1 (IVR-116), A/H3N2 (ResVir-17) and B/Shangdong/7/97. In 2003-2004 only one strain was circulating and in consequence only the titre against A/H3N2 (Fujian-like) was measured. Each test was performed twice and the average titre was considered as outcome. Laboratory personnel were blinded to the identity and study group of the serum samples. We considered a 4-fold or greater titre rise detected in paired samples collected at any time between post-immunisation and post-epidemic periods as indicative of an immune reaction against an influenza virus infection.

During 60 consecutive days (weekends and holidays included) GPs were asked to complete their diaries. Instruction to start daily registration was given as soon as the Scientific Institute of Public Health (IPH - www.iph.fgov.be/flu) in Brussels detected the first influenza viruses in nose and throat swabs collected by sentinel physicians in Belgium during two successive weeks (Figure 1). In the 2002-2003 winter period the registration started on February the 13th 2003 (7th week), in the 2003-2004 winter period we had to start much earlier on November the 22nd (2003) (47th week).

GPs were asked to register the number of contacts with patients in general and with those diagnosed as influenza cases (patients, family and other contacts) in particular. They also had to mention the number of influenza patients they had already examined for any other reason during the week prior to the consult where influenza was diagnosed. An influenza case was defined as any person for whom the GP established a clinical diagnosis of
influenza based on the following symptoms and signs: sudden onset, high fever (above 38°C), cough and myalgia.

When the GP was suffering from the slightest symptom of RTI he had to mention this in his diary. He had to register his body temperature (measured orally) and he had to evaluate his own signs and symptoms by indicating the severity and his diagnosis, the medication and sick leave taken.

After the registration period the diaries were collected by post (2002-2003) or personally (2003-2004). GPs had to brush their nose with two cotton swabs and their throat with one cotton swab the first to the fourth day of each RTI period they suffered from during the registration period. The used swabs were immersed in a transport medium (Earle’s minimal essential medium (EMEM) with addition of antibiotics and antimycotic products) and preserved by the local medical laboratory where the samples were collected by a courier of the Scientific Institute of Public Health (IPH). After the influenza epidemic the transport media were analysed with a nested RT-PCR test first to distinguish between A or B strains, afterwards to subtype the A strains in H3 or H1. Uncertain results were retested. Laboratory personnel were blinded to the identity and study group of the swabs. Difference in proportions were assessed by Pearson $\chi^2$ tests and odds ratios (95%CI), continuous variables were analysed by Student T-tests after converting serum titres to the natural logarithm using SPSS version 12.0. Influence of several variables on the outcome was evaluated using correlated data analysis GEE (Generalized Estimating Equations, GENMOD in SAS statistics version 8.02) following the Hierarchical Backward Elimination Approach of Kleinbaum DG[10]

Results

122 GPs, of whom 77 were vaccinated against influenza in October 2002, were included in the first part of the study. 140 GPs, 100 vaccinated in October 2003, participated in the second part. 72 GPs participated in both winters. Missing and eliminated data (diaries and serology) are shown in figure2.

In 2003 we had to consider 47 (46 vac) second serum samples as missing because these were taken during the flu epidemic which in 2003 started as early as the 22nd of November. In 2002 and 2003 13 and 11 ill GPs respectively didn’t take nose and throat swabs as indicated.

Table 1 shows that there is no difference in most characteristics between the vaccinated and unvaccinated group. There were fewer patient contacts in the unvaccinated group (p = 0.05 and 0.01 respectively). As expected the
vaccinated group was also highly vaccinated against influenza in previous years: more than 80% versus less than 20% in the unvaccinated group. In consequence in the first serum sample higher geometric mean serum antibody titres (GMT) and a higher seroprotection level, were measured in the vaccinated group.

In 2002 and 2003 more than half of the GPs suffered at least once from a RTI (mild infections included). For influenza vaccination of GPs no efficacy could be seen to prevent RTIs in general in 2002 nor in 2003 (Table 2). In 2002 only about 5% GPs had positive swabs, both in the vaccinated and unvaccinated group. However in 2003 12% vaccinated GPs had positive swabs compared with 23% unvaccinated GPs. The efficacy (= 100(1 – RR)) of vaccination in preventing virus replication in nose and throat and thus preventing nose and throat swabs to become positive seems to increase (21% and 52% in 2002 and 2003 respectively), but without reaching significance even when we look at both years together. In the two years together we noticed a significant effect on a four fold titre rise alone (75% (95%CI 33% – 90%)) and in combination with positive swabs (58% (95%CI 17% - 78%)). In these comparisons possible confounders were not taken into account.

The average highest body temperature was 37.4 °C in the influenza infections (positive swabs) and statistically significantly higher than in the other RTIs (p = 0.005). The influenza infections lasted in general 2 days longer (p= 0.03). Twenty percent of GPs with positive swabs did take sick leave, compared to 12% GPs suffering from other RTIs (p = 0.3).

To know which factors besides vaccination influence the dichotomous outcomes defined as RTIs in general, RTIs with influenza positive nose and throat swabs, and RTIs with positive nose and throat swabs and/or a four fold titre rise and to control for confounding variables, we performed a multivariate regression analysis for correlated data using Generalized Estimating Equations (GEE) (Table 3). For the 3 outcomes vaccine*age was the only significant and important interaction term.

This interaction term gives different effect sizes for different age groups. As you can see in Table 3 an influenza vaccination of a young GP (30 years old) is effective independent of the definition of the outcome. At this age the efficacy to prevent positive nose and throat swabs with a vaccine is as high as 90%. However in the age group of 50 year olds no effect of influenza vaccination showed (OR>1), except for the prevention of flu cases defined as positive swabs and/or 4-fold titre rise. For the prevention of RTIs in general the OR is statistically significant under 32 years of age (OR 0.41 (0.16 – 1.03)) [and is 1 at 43 years] (Figure 3). For the prevention of proven influenza subjects (positive swabs) the OR is statistically significant under 36 years of age (OR 0.22 (0.04 – 1.06)) [and becomes 1 at 48 years] (Figure 4) and if we consider positive swabs and /or a 4 fold titre rise, the OR is significant under 33 years (OR 0.17 (0.03 – 1.00)) [and reaches 1 at 53 years] (Figure 5). Besides
vaccination no other variable had an important effect on RTIs in general. On the contrary the prevention of positive swabs and/or 4-fold titre rise was dependable on the basic immunity against influenza presented in this model by the natural logarithm of A/H3N2 influenza antibody titre of the first serum sample. In addition the presence of family members with the flu was highly predictable for retrieving positive nose and throat swabs and/or 4-fold titre rise. If we take a closer look at the diary data we see that in 20 out of 25 PCR proven influenza cases a family member was also affected. In 13 cases the family member was ill prior to and in 3 cases together with the GP.

**Discussion**

Multivariate analysis revealed that an influenza vaccination prevents respiratory tract infections in general and proven influenza during the flu epidemic only among young general practitioners. Independent from vaccination a low basic antibody titre against influenza and the presence of flu cases in the family are highly predictive for an episode of influenza with positive swabs and/or fourfold titre rise.

During the registration period half of the GPs were suffering from some kind of a RTI. There was no difference between the two years. The 50% seems rather high but could be explained by the fact that also slight symptoms were registered and reflects the occurrence of mild infections through which the natural immunity is constantly updated. The incidence of influenza cases (RT-PCR positive) shows a marked difference between the two years, going from 5% to 23% in the unvaccinated group. In the first study period (2002-2003) there was a high basic immunity against influenza A as the cumulative result of the previous 2 years in which the circulating influenza virus A strains didn’t change much[11]. The IPH recorded a peak incidence of influenza like illnesses in the community of 5% in week 9 in the first study year and of 10% in week 50 in the following influenza season (2003-2004) [12]. During this year a slightly different influenza A virus was circulating. Although this new A/Fujian like A/H3N2 virus was different from the A strains contained in the vaccine, the vaccine could elicit a good immune response[13, 14]. An epidemiologic study performed among GPs during the Asian flu epidemic of 1957 concluded that doctors in many parts of Britain were exposed to a risk of influenza at least double that of the general population in their practices[15].

A RT-PCR test is more sensitive than a virus culture[4, 16], it also detects death virus particles and is not quantitative. Therefore no conclusions can be drawn from the infectiousness of each GP with positive nose and throat swabs, but it is clear that transmission is not possible when the upper airways are free from virus particles. Comparing the number of patients diagnosed with flu seen one week before for another reason 14 days before
and after the GP became ill, we could not see a significant difference between the GPs with infectious influenza and the other GPs with RTIs. Perhaps ill GPs are aware of their infectiousness and take precautions to avoid transmission to patients.

As mentioned before no efficacy studies of influenza vaccination among GPs were ever published, so we can only compare our results with trials performed among other healthcare professionals working in hospitals. A Cochrane review about vaccines for preventing influenza in healthy adults contained results of trials with healthcare workers as participants[3]. None of these studies could demonstrate a significant efficacy of influenza vaccination on influenza cases (clinically defined and sometimes serologically confirmed) and none of them presented results, evaluating the ability of this vaccination to interrupt the spread of the disease (see additional file 1: Existing literature concerning our study results.)

The most striking result in our study is the diminishing effect of an influenza vaccine with age. Monto et al. demonstrated that the incidence of influenza declines with age and is higher before 30 years[17, 18]. This age group has starting families with young children[17]. This fact can explain the high efficiency of influenza vaccination among hospital personnel found by Wilde et al., which reached 88% (95%CI 47% - 97%) in preventing a 4-fold titre rise against A/H3N2[19]. The mean age of the study group was about 30 years.

Pachucki et al. demonstrated that medical students were the first to introduce influenza in hospital boards[20]. An important recommendation emerges from these findings: young GPs are the first to be vaccinated against influenza. Also medical students and post-graduates could benefit from this measure.

Can influenza vaccination be stopped at a certain age? The answer is yes for those already working for more than twenty years fulltime in practice and having yearly enough contact with flu patients. During these twenty years contacts with different types of virus strains (wild and/or vaccine types) will give a variety in immunity to withstand an influenza infection without the additional help of a vaccination. Besides GPs, this could also apply to paediatricians and nurses working in child day-care centres. Other healthcare workers like for instance surgeons who do not have enough contact with flu cases each year, will need the help of an influenza vaccination during their entire career. It is the wrong decision not to vaccinate themselves because of lesser patient contacts with the underlying idea that the chance to become infected will be less[21]. These considerations are only applicable in the inter-pandemic period. In the situation where a new virus emerges like an adapted avian flu virus and when an appropriate vaccine is available, all health care workers would be a priority group for vaccination without exception.
The level of anti-haemagglutinin antibody titres before vaccination is another independent protective variable already known of for some time[22]. It is the cumulative effect of previous vaccinations and natural infections and was relatively high in our GP population[14]. The age factor was not reflected by the level of the antibody titres before the flu epidemic in our study. Besides serological immunity other unmeasured immune factors like cellular[23] and local mucosal immunity may play an important role[24].

Another underestimated factor is the infectiousness of family members with the flu. Independent of age or vaccination status, sick family members especially children, are very contagious. This has already been known for several years[18, 25], but the consequences were minimized. The study among GPs during the Asian flu epidemic of 1957 already noticed that 9 of 19 GPs with a typical influenza attack had a family member with the flu. The authors concluded that GPs were liable to be infected with the flu at home, even after escaping infection for several weeks during repeated daily contact with influenza among their patients[15].

We think here might be a place for neuraminidase-inhibitors: each healthcare worker who has to deal with a family member, who suffers most probably from influenza, could take neuraminidase-inhibitors preventively[26]. Treating the GP only when he is suffering from the flu will not work, because the signs and symptoms will be mostly light and non-specific, hence the diagnosis of influenza will be difficult. Better than this medication, which already introduced resistant virus strains by its use[27], prevention must be offered by a better designed vaccine.

Inactivated vaccines are not very useful in preventing cross-infection and shedding of viruses from nose and throat[8, 9], they are only known to diminish the severity of the flu symptoms and prevent complications, especially when compared with intra-nasally administered influenza vaccines (inactivated whole virus [24] or with adjuvants [28] or live cold-adapted[8]) who elicit a better local immune response (mucosal IgA) in nose, throat and airways. Unfortunately these new vaccines are not yet commercially available in Europe.

Further research is urgently required; especially we must assess the efficacy of new vaccines among healthcare workers with focus on prevention of influenza virus development in nose and throat, even when only family members become infected by the flu.

Some limitations of this study are to be considered. Unfortunately the influenza epidemic started very early in the second study year (22nd of November, 2003). Therefore we had to consider 47 serum samples taken after vaccination (T2) during this epidemic as missing. Titres measured in these samples were significantly higher than those taken before the 22nd of November. But general characteristics between GPs with missing serum
samples and those used in the analysis were not different except in the case of allergy. Fewer GPs with missing serology were suffering from allergy, but because allergy didn’t show any influence on the incidence of RTIs or influenza this has no consequence on the results. The only problem which arises is an underestimation of influenza cases defined as a 4-fold titre rise after the epidemic. But this definition of a case of influenza remains questionable especially in a study group with high antibody titres before the flu epidemic. Because the unvaccinated group started with a lower antibody titre a higher amount of 4-fold titre rise cases could be expected in this group. Other authors [7, 19, 29, 30] already mentioned this disproportion and the lack of clinical accordance and relevance.

In this article we didn’t focus on the immunogenetic properties of the vaccine[14], because the efficacy of the vaccine on clinical outcomes after an epidemic challenge is far more interesting to build further policies on. Despite the fact that the GPs in our study were not chosen at random, we believe the results are representative. In fact the participants did not differ in age with national averages. In 2003 slightly more women than average were participating in our study, but this is accounted for in the multivariate analysis.

Possibly the free choice for vaccination could give selection bias. Indeed the most important difference between vaccinated and unvaccinated GPs is the number of influenza vaccinations in previous years and their effect on the basic immunity. But by allowing for basic influenza antibody titre we accounted for this in the multivariate analysis.

**Conclusion**

During the interpandemic period, the role of an inactivated influenza vaccine to prevent infectious influenza is limited in general practitioners. The higher natural immunity acquired during several years of practice, by older colleagues makes the vaccine effect less clear. Only in younger GPs the efficacy of flu vaccination can be shown against proven influenza infections. Especially this group should be the first to be vaccinated. Family members with the flu, rather than the daily burden of flu patients, make every GP, vaccinated or not, very vulnerable to infectious influenza. Every GP should be aware of this infection road to take adequate precautions.

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The sponsors of the study played no role in study design, data collection, data analysis, data interpretation, nor writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests

The author(s) declare that they have no competing interests

Author contributions

BM participated in the coordination and the design of the study, in the data collection and management, in the statistical analysis, in the writing and editing of the manuscript.

HP participated in the coordination and the design of the study, in the data collection and management, in the editing of the manuscript.

SC participated in the design of the study, in the statistical analysis, in the writing and editing of the manuscript.

FY participated in the design of the study, in the data collection, in the laboratory analysis and in the editing of the manuscript.

TS and SS participated in the data collection and management and in the editing of the manuscript.

JD participated in the design of the study, in the supervision and in the editing of the manuscript.

PVR participated in the coordination and the design of the study, in the funds raising, in the data collection, in the statistical analysis, in the supervision and editing of the manuscript.

All authors read and approved the final manuscript.

References

Figure 1: The incidence of influenza-like illnesses (ILI) and acute respiratory infections (ARI) recorded by sentinel physicians in Belgium.

Figure 2: Flow of GPs’ diaries and serology data

Figure 3: The effect of flu vaccination on RTIs in general for different ages: odds ratios and 95% confidence intervals

Figure 4: The effect of flu vaccination on RTIs with influenza positive nose and throat swabs for different ages: odds ratios and 95% confidence intervals

Figure 5: The effect of flu vaccination on RTIs with influenza positive nose and throat swabs and/or 4-fold titre rise for different ages: odds ratios and 95% confidence intervals

Tables legends

Table 1: General characteristics of participating GPs: figures are numbers (percentage) unless stated otherwise.

Table 2: Efficacy and effectiveness of influenza vaccination according to different outcomes: crude results

Table 3: Effect of influenza vaccination on respiratory tract infections in general, with influenza positive swabs and/or four fold titre rise: odds ratios and 95% confidence intervals

Additional file

File name: GVS existing literature.doc
Title: Existing literature concerning our study results
Description: To situate our study results in the existing literature
Figure 1: The incidence of influenza-like illnesses (ILI) and acute respiratory infections (ARI) recorded by sentinel physicians in Belgium.
Figure 2: Flow of GPs’ diaries and serology data

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Age (years)

Figure 4
Figure 5: The effect of flu vaccination on RTIs with influenza positive nose and throat swabs and/or 4-fold titre rise for different ages: odds ratios and 95% confidence intervals

Age (years)
Additional files provided with this submission:

Additional file 4: GVS situering.doc: 38Kb
http://www.biomedcentral.com/imedia/9783908829238394/sup4.DOC

Additional file 3: GVS artikel Tabel 3 R.doc: 78Kb
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Additional file 2: GVS artikel Table 2 R.doc: 51Kb
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Additional file 1: GVS artikel Table 1R.doc: 85Kb
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