



Influenza

INFORMATION AND NEWS ON INFLUENZA

SPECIAL SECTION

INTRODUCTION

For the first time, the *Influenza* bulletin sees the addition of a special section focusing on general practice. An influenza symposium will be held at the Conference of the European Society of General Practice/Family Medicine – WONCA (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians), Region Europe. This conference will take place from 1–4 June this year in Amsterdam, The Netherlands. The event will offer general practitioners (GPs) from all over the world the opportunity to improve their clinical performance, communication skills and practice management and to update their knowledge of the main topics relevant to daily practice.

WONCA Europe 2004's ambition is to pay special attention to the most important aspects of quality improvement in general practice. Within priority clinical areas attention will be focused on diagnostic features and comorbidity, ethics, gender, prevention, emergency care, therapy and interdisciplinary collaboration. In addition, the conference will focus on leadership and team building, quality systems, work stress, time-management and information, and communication technology to improve practice management. Posters will be discussed in small, group sessions moderated by international key opinion leaders from the relevant fields. On 2 June, a symposium will be held on influenza vaccination in asthmatic children. This section of the *Influenza* bulletin

presents the introduction to the symposium, along with short interviews with the seven speakers. It is hoped that after the symposium, delegates will be able to make an evidence-based decision on whether to change or continue their current practice.

In December 2003, Europe was confronted with an epidemic of the Fujian type influenza virus. The composition of the recommended vaccine for at risk groups did not cover this virus subtype. GPs were confronted with a growing number of influenza cases and recognised that further spread needed to be prevented. On short notice the Dutch College of General Practitioners was asked to inform their members of the best available policy. Louwrens Boomsma will present this advice.

Reliable uptake rates are essential for discussions on pandemic planning. Madelon Kroneman presents data from the ESWI/European Influenza Surveillance Scheme (EISS) project on vaccine uptake rates in Europe, performed by The Netherlands Institute for Health Services research (NIVEL). Madelon concludes that carrying out a population survey in each country could solve the lack of insight into uptake rates among at risk groups in Europe. In the longer term, a uniform monitoring system could be developed, preferably in cooperation with ESWI and EISS. However, such a system would have to deal with differences in healthcare system characteristics.

In the future, the *Influenza* bulletin will have special sections for different audiences, connected with special occasions such as congresses. We hope that this first special section for GPs/family physicians will attract their attention and encourage them to continue the battle against influenza.

G.A. van Essen

Section Editor

Julius Center for Health Sciences and Primary Care
University Medical Center
Utrecht, The Netherlands

CONTENTS

- PAGE 1** – Introduction
Which antiviral drug should be used in the treatment of influenza?
- PAGE 2** – WONCA symposium, Amsterdam RAI, 2 June, 11.00am: influenza vaccination in asthmatic children. Where do we stand?
- PAGE 3** – What do we know about influenza vaccine uptake in Europe?
- PAGE 4** – How to inform the Dutch general practitioners during the outbreak of the Fujian epidemic around Christmas 2003?

WHICH ANTIVIRAL DRUG SHOULD BE USED IN THE TREATMENT OF INFLUENZA?

Antiviral drugs are effective for the treatment of influenza and are especially advised during epidemics with drifted types of influenza virus and in pandemics. However, it is unclear which antiviral drug should be the drug of choice. Dr Hak and colleagues from the Dutch University Medical Center, Utrecht, The Netherlands, conducted a study based on the InforMatrix method

(www.informatrix.nl) to quantify the pharmacotherapeutical properties of amantadine, oseltamivir and zanamivir. An essential step is the evaluation of the different properties of the drugs by experts in the influenza treatment field. The study group is interested in possible between-country variations in the ratings of the importance of drug properties. Experts from countries

such as the USA, UK, Scandinavia, New Zealand and Australia, are therefore kindly requested to participate in this international comparison. For more information please e-mail Dr Hak (e.hak@med.uu.nl).

E. Hak

Dutch University Medical Center
Utrecht, The Netherlands

WONCA SYMPOSIUM, AMSTERDAM RAI, 2 JUNE, 11.00AM:

INFLUENZA VACCINATION IN ASTHMATIC CHILDREN. WHERE DO WE STAND?

In many countries influenza vaccination is recommended for asthmatic children. Most children are vaccinated in general practice. However, the reason for targeting asthmatic children has been debated time and again and is reflected in disappointing vaccination rates.

This symposium will bring together a variety of viewpoints and is of interest to all general practitioners (GPs) with or without doubts on the subject of influenza vaccination in children with asthma. An international group of experts has been asked to present and discuss their evidence for the efficacy benefits and adverse effects of influenza vaccination. Data will be presented from various angles, thus providing a comprehensive overview of the current state of affairs. The symposium includes:

Part 1

- Current vaccination guidelines throughout the Western world (G.A. van Essen).
- Vaccine coverage in asthmatic children in the United States (P. Kramarz).
- Evidence for efficacy from a primary healthcare database in The Netherlands (E. Hak).
- Should we vaccinate all children to protect those with asthma? (D. Fleming).

Part 2

- Choice of endpoints in efficacy studies of influenza vaccination (A. Monto).
- Results from a recently finished randomised placebo-controlled trial (H. Bueving).
- An update of the Cochrane systematic review of the literature (C. Cates).

There will be ample time for discussion and after the symposium, delegates should be able to make an evidence-based decision on whether to change or continue their current practice. For this *Influenza* bulletin, we have asked all the speakers to give a brief outline of their presentation.

J.C. van der Wouden
Chair, Department of General Practice,
Rotterdam, The Netherlands

Current vaccination guidelines throughout the Western world

G.A. van Essen

Q: What was the reason for choosing this topic?

A: I have been interested in the vaccination rate for influenza in different countries. Is the difference because of differences in official recommendations or is it differences in the implementation? In 1995 and subsequently in 2002, ESWI gathered information on influenza vaccination guidelines and vaccine use in 29 European countries. ESWI developed an accurate and timely system of reporting directly from the manufacturers.

Q: What will be the main ingredients of your presentation?

A: In 2000, most of these countries had national recommendations to vaccinate elderly people and those with high-risk conditions. Levels of vaccine use, however, varied widely and several rapidly developing countries had higher levels than those seen in many developed countries. The age criterion is changing: some countries advise vaccination for all above 50 years of age. Although there is evidence of the effectiveness of vaccination in the very young, no country has recommendations for that age group.

Q: What do you wish to accomplish?

A: Since the recommendations do not differ between European countries, the difference in vaccination rate must be the implementation. By comparing implementation strategies, ESWI will help individual countries to identify interventions that will improve the vaccination rate. With increasing vaccine use, all countries will be better prepared for the next pandemic.

Vaccine coverage in asthmatic children in the USA

P. Kramarz

When I worked at the Centers for Diseases Control and Prevention (CDC) in Atlanta, Georgia, I was involved in a number of studies focusing on influenza vaccination in children with asthma. One of these studies looked at compliance with influenza vaccination recommendations among asthmatic children. We used data from three Health Maintenance Organizations on the West Coast of the USA, with electronic records for almost 38,000 asthmatic children aged 1–6 years. Overall, we found that only 9% of these children were vaccinated against influenza. As we also had some demographic

characteristics, we were able to look at differences between subgroups of children. We also examined influenza vaccination efficacy and safety in children with asthma; however, we were not able to look into the reasons for non-compliance with current guidelines. I am looking forward to meeting my Dutch colleagues who tested methods to enhance vaccination rates.

Evidence for efficacy from a primary healthcare database in The Netherlands

E. Hak

Q: Can you tell us something about the background and design of your study?

A: Because of the uncertainty regarding prevention effectiveness of influenza vaccination across age groups and associated direct medical costs, we set up the Prevention of Infection, Surveillance and Management (PRISMA) study at the Julius Center. To ensure adequate power and applicability of the study results, we estimated vaccine effectiveness and costs in a case-control study set in a primary care population using medical databases.

Q: And what did you find?

A: The study revealed that the vaccine was effective in reducing severe complications during epidemics, and neither age nor presence of comorbidity modified the effectiveness substantially. However, some differences in cost-effectiveness were observed. The results might further convince health providers of the benefits of influenza vaccination for all recommended people.

Should we vaccinate all children to protect those with asthma?

D. Fleming

Rational vaccination policies, whether for all children or just for those with asthma, must be based on the likelihood that asthma attacks will increase because of influenza infection. This presentation is concerned with the impact of influenza on asthma attacks presenting to GPs.

Choice of endpoints in efficacy studies of influenza vaccination

A. Monto

In studies on the burden of influenza and the efficacy of interventions, a major challenge is the choice of outcomes that should be used. Ideally, the endpoint would be

laboratory-confirmed influenza; that needs to be the case in the basic efficacy studies of vaccines and antivirals. However, once efficacy is defined under controlled conditions, it is often necessary to carry out larger studies. For example, it may be necessary to evaluate the effectiveness of vaccination in preventing hospitalisation. Of necessity, these will involve less precise endpoints. This was the case in the large-scale studies we conducted that resulted in influenza vaccine becoming a covered benefit in older individuals in the USA. The endpoint used was prevention of 'pneumonia and influenza' hospitalisation without laboratory confirmation, but in a defined influenza season. Defining total burden and impact of influenza is even more difficult.

Results from a recently finished randomised placebo-controlled trial

H. Bueving

For many years GPs, including myself, have been concerned about the lack of hard data supporting the recommendation to vaccinate asthmatic children. In 1995, one of our colleagues, Philip Rothbarth, wrote a paper entitled 'The sense and nonsense of influenza vaccination in asthma and COPD'. This paper triggered us to design a study that would provide medicine-based evidence. We were very pleased when ZonMW provided

funding for our placebo-controlled trial. It was quite a job to recruit enough GPs, and after that children with asthma. Thanks to a marvellous team of dedicated research nurses we managed to include and follow nearly 700 children. I will present the results at the symposium and look forward to discussing them with these experts.

An update of the Cochrane systematic review of the literature

C. Cates

Q: You are an active member of the Cochrane Collaboration. Can you tell us something about this?

A: The Cochrane Collaboration is an international organisation, made up of Review Groups responsible for different clinical areas. I have belonged to the Airways Review Group for the past 6 years, and we collect data from controlled clinical trials from all over the world that address the treatment of asthma and chronic obstructive pulmonary disease (COPD). We have prepared, and maintain, more than 150 reviews in our topic area on the Cochrane Library to help healthcare professionals and users in making informed decisions about some of the treatments available to them.

Q: Why did you do this systematic review of studies on influenza vaccination in asthmatics?

A: I became aware that the guidance on influenza vaccination and asthma was originally based on extrapolation of benefits found in older people with COPD. I wanted to find out what evidence there was from controlled trials in adults and children with asthma. Does influenza vaccination prevent asthma attacks in the influenza season, and does the vaccination make asthmatics worse just after it has been administered?

Q: When you finished the first version of your review in 1998, were you surprised by the results?

A: I was surprised that little work had been done to look at the risks of influenza vaccination in people with asthma, and even less on checking for benefits.

Q: Did the results of your review change your policy regarding vaccination of children with asthma in your practice?

A: Although UK guidelines suggested that all children with asthma should be vaccinated, we have taken a rather more pragmatic view. What do we mean by 'a child with asthma'? One who wheezed as a baby and takes no treatment now? We tend to target those children with more severe asthma (for example those who have required oral steroids or hospital admission) for influenza vaccination, as the evidence base is currently weak.

WHAT DO WE KNOW ABOUT INFLUENZA VACCINE UPTAKE IN EUROPE?

In Europe, influenza vaccination of the elderly and other high-risk populations is seen as an important practice, it is both life- and cost-saving. All European countries have influenza vaccination recommendations for high-risk groups. Despite these recommendations there is considerable variation in influenza vaccine uptake rates between European countries. This observation motivated ESWI to initiate a study. The study was performed by the Netherlands Institute for Health Services Research (NIVEL) in cooperation with the European Influenza Surveillance Scheme (EISS). The first part of the study was an inventory of the availability of uptake figures among European countries, while the second part studied the feasibility of a population survey to determine uptake rates.

The first part of the study started in 2001, with a survey among national influenza experts in 26 Western and Eastern European countries. It revealed that only 14 countries were able to provide uptake rates for the elderly. The uptake rates in these 14 countries

varied from 15% in Romania, to 81% in The Netherlands. In Western Europe, Finland had the lowest vaccination rate (25%). For other at risk groups, even fewer countries could provide data. For instance, for the pulmonary diseases group, only three countries were able to report uptake rates, again the lowest was Romania (10%) and the highest was The Netherlands (75%). Some countries could not differentiate between specific diseases, but were able to provide data on the total high-risk group due to disease. In France, the uptake rate was 44% for this total high-risk group and in Germany about 50% (for people aged ≥ 18 years).

The first part of the study confirmed that knowledge of uptake rates is limited. To improve knowledge, methods need to be developed for the collection of uptake rates. Information about vaccination rates can be gathered from general practitioners (GPs) who register patients who have had a vaccination. In most countries, the GP is the main person to administer vaccines. In some countries public health organisations also

take care of this task. Besides keeping track of the number of vaccinations, computing uptake rates requires population data about disease prevalence. In countries where the population is enlisted to a personal GP, this can be realised. In most European countries this is not the case. Here, population denominators, essential for computing uptake rates, should be established using other methods. A second possibility for collecting vaccination information is a population survey, asking a sample of the population whether they have had a vaccination and whether they belong to a high-risk group.

To confirm whether a population survey is a reliable method of data collection, the second part of our study was carried out. In The Netherlands, patients are enlisted in a general practice, and a monitoring system for influenza uptake based on the GP-information system, already exists. Therefore, the results of the survey could be compared with reliable uptake rate information. A questionnaire was sent out to households in The Netherlands and the

response rate was 73%. Questions concerned vaccine uptake, pre-existing diseases and reasons to have (or not have) a vaccination. This resulted in influenza and influenza vaccination data for 4,037 people during the 2001–2002 influenza season. The uptake rates and size of different risk groups from the population survey were comparable with the results of the monitoring system. The size of the population sample (4,037 people) was sufficient in the four largest risk groups (the elderly, cardiovascular diseases, pulmonary diseases and diabetes mellitus) to be able to provide reliable uptake rates.

Results of the population survey indicated that the elderly were more likely to be vaccinated than people who are deemed high risk due to pre-existing diseases. The lowest uptake rates were among people with pulmonary disease, renal failure or compromised immunity. Children (<18 years) were mainly vaccinated due to pulmonary disease. Two reasons were most frequently reported for refusing influenza vaccination. Firstly, people believed they did not qualify, especially high-risk groups <65 years old.

Secondly, people believed they already had enough resistance to influenza. Among the elderly and people with pulmonary disease, one in 10 thought that influenza would not seriously affect them. The elderly, in particular, refrain from vaccinations because of bad experiences in the past, such as getting influenza despite vaccination and feeling bad after a vaccination. Cost and distance as other reasons for not being vaccinated were not factored into the study, because they are not applicable in The Netherlands. Vaccination in The Netherlands, including GP consultation, is free of charge for those at risk. In less densely populated countries, distance to the GP's office may play a significant role, especially for the elderly.

Comparable data for uptake rates enable countries to learn from each other's strategies and improve vaccination rates. Reliable uptake rates are essential for the discussion of pandemic planning. With survey data, uptake rates can be collected in an efficient and relatively cheap way. An advantage is that other questions, for instance on reasons to comply with influenza vaccination,

can be added. The lack of insight into uptake rates among at risk groups in Europe could be solved in the short term by carrying out such a survey. However, monitoring real uptake rates will provide more reliable data. In the longer term, a uniform monitoring system could be developed, preferably in cooperation with ESWI and EISS. Such a system would have to deal effectively with differences in healthcare system characteristics.

M. Kroneman

NIVEL, Utrecht, The Netherlands

G.A. van Essen

Julius Center for Health Sciences and Primary Care University Medical Center, Utrecht, The Netherlands

References

1. Kroneman M, Paget WJ, van Essen GA. Influenza vaccination in Europe: an inventory of strategies to reach target populations and optimise vaccination uptake. *Euro Surveill* 2003; 8: 130–138.
2. Kroneman MW, van Essen GA, Tacken MAJB, Paget WJ, Verheij R. Does a population survey provide reliable influenza vaccine uptake rates among high-risk groups? A case study of The Netherlands. *Vaccine* 2004. In press.

HOW TO INFORM THE DUTCH GENERAL PRACTITIONERS DURING THE OUTBREAK OF THE FUJIAN EPIDEMIC AROUND CHRISTMAS 2003?

In December 2003 the Dutch healthcare system was confronted with an epidemic of the Fujian type influenza virus. The composition of the recommended vaccine for people at risk was the same as the vaccine used in the 2002–2003 season. During 2003 some scientists warned of the spread of a new H3N2 virus-type that was not fully covered by the existing H3N2 vaccine [1]. Unfortunately the production of a modified vaccine could not be scheduled. As the recommended vaccine did not fully match with the prevailing Fujian virus, an epidemic occurred peaking around Christmas. Dutch general practitioners were confronted with a growing number of influenza cases and recognised that further spread needed to be prevented. Members of the Dutch College of General Practitioners were asked for advice about the best available policy.

The Dutch College of General Practitioners had published a review in December 2002 on the neuraminidase inhibitors (NI) zanamivir and oseltamivir, which corresponded fully with a systematic review of this subject, published in 2003 [2]. This review concluded that NI therapy in healthy people, including children, reduced the period of illness from approximately 7 to 6 days. In addition, there was a 3% reduction in antibiotic use. If NI therapy was started

within 48 hours of disease onset in high-risk patients, the period of illness was reduced by 1–2 days. Data on hospital admissions or death were not available. NI therapy can also be used prophylactically; it reduced the number of influenza cases in the general population from 4.8–1.2%, in families from 7.4–0.8%, and in nursing homes and elderly people's residences from 4.4–0.4%.

A second review of trials with 3,564 patients revealed that in people with a high risk of developing influenza complications, oseltamivir reduced the use of antibiotics for lower respiratory tract infections from 18.5–12.2% ($p=0.02$), and hospital admissions from 1.7–0.7% ($p=0.02$). These significant findings were only for virologically confirmed influenza cases. In clinically suspected, but not confirmed, influenza cases the reduction in antibiotic use and hospital admissions were not significant [3]. Approximately 60% of clinically suspected influenza cases are virologically confirmed.

On the basis of the available evidence, the Dutch College of General Practitioners could not advise NI therapy for patients with influenza. As a prophylactic treatment, NI therapy can be useful if influenza is confirmed in nursing homes or elderly people's residences. The effectiveness of oseltamivir

may be even greater if the number of influenza cases is more than the stated 4.4%. A statement on NI use was published on the website of the Dutch College of General Practitioners and was then easily accessible for all the college's members. E-mail statements during epidemics will give an opportunity for rapid action when a situation calls for it [4].

L.J. Boomsma, T.J. Wiersma

Dutch College of General Practitioners, Utrecht, The Netherlands

References

1. de Jong JC, Rimmelzwaan GF, Bartelds AI, Wilbrink B, Fouchier RA, Osterhaus ADME. [The 2002/2003 influenza season in The Netherlands and the vaccine composition for the 2003/2004 season]. *Ned Tijdschr Geneesk* 2003; 147: 1971–1975. (Article in Dutch).
2. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; 326: 1235–1240.
3. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003; 163: 1667–1672.
4. http://nhg.artsennet.nl/content/articles/1032/AMGATE_6059_104_TICH_R127659868430694/ (in Dutch).