

Short communication

Is there a role for influenza vaccination in cystic fibrosis?

Dennis Wat^{a,*}, Colin Gelder^b, Sam Hibbitts^c, Ian Bowler^d,
Marcus Pierrepont^e, Rachel Evans^f, Iolo Doull^a

^a Department of Cystic Fibrosis, University Hospital of Wales, Cardiff, UK

^b Llandough Hospital, Penarth, UK

^c University of Wales College of Medicine, Cardiff, UK

^d Royal Gwent Hospital, Newport, UK

^e Neville Hall Hospital, Abergavenney, UK

^f Singleton Hospital, Swansea, UK

Received 7 March 2007; received in revised form 22 April 2007; accepted 7 May 2007

Available online 5 July 2007

Abstract

Background: Influenza vaccination is generally recommended to patients with Cystic Fibrosis (CF). Previous studies have shown that influenza infections cause worsening lung functions, disease progression and increase propensity of bacterial infections in CF. However, the clinical evidence in the effectiveness of influenza vaccination in CF is lacking.

Aims: This study retrospectively reviewed the influenza vaccination status in the patients with CF and compared the influenza infection rates between the vaccinated and non-vaccinated groups. Finally the factors associated with non-adherence with vaccination were determined.

Methods: Nasal swabs were obtained from 63 patients with CF between the age of 6 months to 18 years routinely and during respiratory exacerbations between October 2003 to April 2004. Influenza A and Influenza B were detected using Nucleic Acid Sequence Based Amplification (NASBA). The influenza vaccination status of these patients was retrospectively reviewed.

Results: 41 patients (65%) were vaccinated against influenza. For the 22 patients (35%) who were not vaccinated, 7 of them were scared of needles leading to non-adherence. Influenza virus was detected on 5 occasions; 3 were Influenza A (60%) and 2 were Influenza B (40%). 1 virus in the vaccinated group and 4 in the non-vaccinated were detected during the study period (p -value=0.046).

Conclusions: Although the current available evidence to support routine influenza vaccination is limited in CF, this study has shown that such practice may yet play a role in preventing its subsequent acquisition.

Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society.

Keywords: Influenza vaccination; Cystic fibrosis; NASBA

1. Background

Cystic Fibrosis (CF) is a common autosomal recessive inherited disease with progressive obstructive lung disease being the main cause of death in 95% of the patients [1]. Bacteria play an important role in producing airway damage and altering pulmonary function, with *Pseudomonas aeruginosa* being the major pathogen [2]. However, there is evidence in the literature that exacerbations in CF are associated with

non-bacterial pathogens including respiratory viruses which have been implicated in contributing to pulmonary exacerbations. Influenza viruses [3 4 5] in particular have been shown to cause disease progression in CF by contributing to worsening in lung function, increasing hospitalisation rates [4] and predisposing to bacterial infections [3].

There are two types of influenza viruses; A and B, which are distinguished by the antigenicity of the ribonucleoprotein core and the internal non-glycosylated matrix protein layer. Influenza A viruses are further subdivided into subtypes on the basis of their surface glycoproteins, haemagglutinin and neuraminidase proteins. One of the most remarkable and unique features of influenza viruses is the ability to exhibit

* Corresponding author. Department of Cystic Fibrosis, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, United Kingdom. Tel.: +44 29 20747747.

E-mail address: denniswat118@hotmail.com (D. Wat).

antigenic drift or antigenic shift allowing them to escape the host defence mechanisms, heralding epidemic and pandemic outbreaks, respectively.

Influenza immunisation is generally advised to all patients with CF. However, there is no existing study that shows the benefits of influenza vaccination given to patients with CF [6]. The lack of clinical evidence to support its use in CF prompted this retrospective review with the following generated objectives:

1. To look at the incidence of influenza acquisition between the vaccinated and non-vaccinated patients during the influenza season.
2. To evaluate the rates of respiratory exacerbations in the vaccinated and non-vaccinated groups.
3. To study the differences in symptom complaints between the two groups.
4. To investigate the reasons for non-adherence to vaccination.

2. Method

Patients in this review were between the ages of 6 months to 18 years from four CF centres namely University Hospital of Wales in Cardiff, UK, Royal Gwent Hospital in Newport, UK, Neville Hall Hospital in Abergavenny, UK, and Singleton Hospital in Swansea, UK. They were part of a prospective study looking at the prevalence of respiratory viruses in CF. Informed consent was obtained from all participants. This study received ethical approval from each of the institution's ethics committee. The immunisation status of the patients and reasons for non-adherence were retrospectively obtained from the patients or their parents at the end of the study.

The influenza season was determined by the European Influenza Surveillance Scheme to be between October 2003 and April 2004. Patients who were vaccinated before this period and the ones who were not vaccinated were included in this review.

Nasal swabs were obtained from the patients whenever they developed symptoms suggestive of respiratory exacerbations and whenever they attended for routine assessment between 1st October 2003 to 30th April 2004 (7 month duration). Each nasal swab was obtained by inserting a sterile cotton wool swab into one of the nostrils to a depth of 2 to 3 cm. The swab was then subjected into 500 µl of guanidium thiocyanate lysis buffer. It was transported with ice packs to the laboratory and then stored at -80°C until undergoing nucleic acid extraction at a later date.

Influenza A and B nucleic acid materials were extracted from the nasal swabs using silica slurry as described by Boom et al. [8]. Extracted materials were amplified at 'real-time' using Nucleic Acid Sequence Based Amplification (NASBA) in conjunction with molecular beacons [9]. Analysis of results was undertaken using the NucliSens® Easy Q Analyser (BioMérieux Ltd) isothermally at 41°C

for 120 minutes. The sensitivities of the 'real-time' assays were found to be within the range of 0.1–0.0150% tissue culture infective dose (TCID₅₀) virus input and 100–1 copies of synthetic RNA. The cut-off threshold for a positive result was defined as 20% above the negative control wild-type signal [9].

In this study, each patient (and parents) had been provided with a symptom diary card which comprised of upper and lower respiratory symptoms that included runny nose, blocked nose, sore throat, hoarse voice, fever/shivering, cough (daytime and night-time), wheeze (daytime and night-time), shortness of breath and school absenteeism. Patients and parents had been asked to score their symptoms using the diary card regularly. The symptom score ranged from 0 (no symptoms) to 3 (severe symptoms) for each criteria. Each patient above the age of 5 years was also provided with a mini-Wright Peak Flow Meter and was asked to record the best of three readings every morning and evening.

The definition of a 'respiratory exacerbation' was when: 1) the symptom score totalled to 4 or more, or 2) if peak expiratory flow fell by more than 50 l/min from the child's usual best value, or 3) if the parent subjectively felt that the child was developing a cold [7]. Under these circumstances, the parents or patients were encouraged to contact the investigators to have a nasal swab taken. Throughout the study period, both the parents and patients received telephone and written reminders to contact the investigators in the event of a respiratory exacerbation.

During the season 2003/2004, a trivalent influenza vaccine was used, the composition of which included: an A/Moscow/10/99(H3N2)-like strain, an A/New Caledonia/20/99 (H1N1)-like strain and a B/Hong Kong/330/2001-like strain. The majority of circulating strains isolated in 2003/04 showed a partial match with the corresponding influenza vaccine component. The influenza A Fujian/411/2002 (H3N2)-like subtype that predominated in the UK was not included in the vaccine, but a degree of cross protection was offered by the influenza A (H3N2) strain that was included in the vaccine.

Fisher's exact test was used in analysing the influenza identification rates, the respiratory exacerbation rates and the differences in symptomology between the vaccinated and non-vaccinated groups using the software package GraphPad InStat version 3.0 for windows (GraphPad software, San Diego, CA).

Table 1
Reasons used to define respiratory exacerbations

Reasons used to define respiratory exacerbations	Vaccinated group	Non-vaccinated group	<i>p</i> -value
Symptom score totalled >4	26 (87%)	7 (47%)	0.001
Peak flow fell >50 l/min from usual best	3 (10%)	5 (33%)	0.09
Subjective feeling of coming down with a cold	1 (3%)	3 (20%)	0.1

3. Results

Sixty-three patients were included in this review with the average age at 9.9 (SD±5) years. Twenty-five (40%) of them were females. Forty-one patients (65%) were vaccinated with a mean age of 11.5 (SD±4) years. Within this group, fifteen (37%) patients were female. In contrast, twenty-two (35%) patients were not vaccinated with a mean age of 7.0 (SD±5) and ten (45%) were females.

Forty-one nasal swabs were obtained from forty-five reported episodes of respiratory exacerbations. There were also twenty-nine routine samples submitted, giving a total of seventy samples being analysed by NASBA. Five influenza viruses (7%) were identified from these samples and they all belonged to the exacerbation group with no viruses identified from the routine group. Three of the viruses were influenza A (60%) and two were influenza B (40%). Four influenza viruses (80%) were identified in the non-vaccinated group compared to one (20%) in the vaccinated group (p -value=0.046), giving a relative risk of 0.13.

Thirty of the forty-five episodes (73%) of respiratory exacerbations were reported by the vaccinated group with fifteen (68%) from the non-vaccinated group (p -value=0.772). In the 10 months prior to this review, the respiratory exacerbation rates between the vaccinated and non-vaccinated groups were similar, 2.9 per patient per year in the vaccinated group versus 3.3 per patient per year in the non-vaccinated group.

Table 1 summarises the reasons used for defining respiratory exacerbations in the vaccinated and non-vaccinated groups. There were significantly more patients in the vaccinated group using the summated symptom score to define exacerbations, twenty-six of the thirty episodes (87%) of exacerbations in the vaccinated group in comparison to seven of the fifteen episodes (47%) in the non-vaccinated group (p =0.001). The mean symptom score during respiratory exacerbations in the vaccinated group was 5 compared to that of the non-vaccinated group at 8. However, where there was a positive influenza virus identified, the mean symptom scores of the two groups were identical at 8. There were a

slightly higher proportion of patients using peak expiratory flow reduction to define an exacerbation in the non-vaccinated group.

Table 2 summarises the symptoms recorded in the diary card between the vaccinated and non-vaccinated groups during respiratory exacerbations. There was a higher proportion of patients in the non-vaccinated group complaining of upper respiratory tract symptoms such as runny nose (54% versus 100%, p =0.03) and sore throat (19% versus 71%, p =0.016) during exacerbations. The frequencies in lower respiratory tract complaints were otherwise similar between the two groups.

For the 22 patients who were not vaccinated, 5 (23%) of them forgot, 7 (32%) were scared of needles, 1 (4%) was worried about side effects, 6 (27%) were too unwell to be vaccinated and 3 (14%) did not feel influenza vaccination was effective.

4. Discussion

This review suggests that influenza vaccination offers protection against influenza acquisition in patients with CF, with significantly more non-vaccinated patients having a positive nasal swab for influenza (p =0.046). Although influenza vaccination does not appear to have any impact on respiratory exacerbation rates, it does have a role in preventing live infections. However, the results have to be handled with care because of the small study sample.

Thus far the clinical evidence to support the use of influenza vaccination in patients with CF is limited. A recent Cochrane review [6] of 4 randomised trials comparing any influenza vaccine with a placebo or with another type of influenza vaccine in CF did not show any clinical benefits in vaccination. It therefore concluded that the available evidence did not support national recommendations of vaccinating these patients, although many CF units recommend their patients of receiving annual influenza vaccination.

The clinical evidence to support the routine use of influenza vaccination in other chronic respiratory diseases such as asthma is similarly lacking. A Cochrane review in influenza vaccination in asthma showed that there was no immediate increase in asthma exacerbation rate in the 2 weeks following vaccination [10]. However, a randomised placebo-controlled trial did not show a significant reduction in number, severity or duration of asthma exacerbations caused by virally proven influenza infection despite vaccination. In addition, there was no difference in respiratory symptoms between vaccination group and placebo group [11].

In contrast, influenza vaccination in patients with chronic obstructive pulmonary disease (COPD) led to a significant reduction in the total number of exacerbations compared to those who received placebo (p =0.006). There was also no increase in early exacerbations following vaccination [12].

In this study, respiratory exacerbation rates in the preceding 10 months before the study between the vaccinated and non-vaccinated groups were similar, indicating that these

Table 2
Frequencies of upper and lower respiratory tract symptoms reported by vaccinated and non-vaccinated groups

Symptoms reported	Vaccinated group (n=22)	Non-vaccinated group (n=7)	p -value
Runny nose	14 (54%)	7 (100%)	0.03
Blocked nose	13 (50%)	4 (57%)	1
Sore throat	5 (19%)	5 (71%)	0.016
Hoarse voice	2 (8%)	1 (14%)	0.52
Fever/shivery	10 (38%)	4 (57%)	0.42
Cough during the day	14 (54%)	5 (71%)	0.67
Cough at night	8 (31%)	4 (57%)	0.38
Wheeze during the day	7 (27%)	4 (57%)	0.18
Wheeze at night	2 (8%)	1 (14%)	0.52
School absenteeism	4 (15%)	2 (29%)	0.58

were unlikely to be the reasons influencing the decision on immunisation. The decision may be down to a combination of patient/parent education, social background, awareness of vaccination and accessibility of vaccination. There were significantly more patients in the vaccinated group using increased symptoms to define respiratory exacerbations; this may be that they had a higher perception and awareness of increased respiratory symptoms. Although the non-vaccinated group had a higher mean symptom score during exacerbations compared to the vaccinated group, this difference was no longer present during positive influenza infection episodes.

The non-vaccinated group had significantly more upper respiratory tract symptoms such as runny nose and sore throat during respiratory exacerbations compared to the vaccinated group, but there was no difference in terms of lower respiratory complaints. In view of this, intranasal vaccination maybe an effective and attractive option as this will offer local protection in the upper airways and can help arrest infection at an early phase before symptom complications arise.

Regarding the reasons for not being vaccinated, needle phobia was cited as the commonest reason for non-adherence. This was a somewhat surprising observation as many of these patients were used to the vigorous blood test investigations and intravenous antibiotics as part of their treatment regime. Maybe the intramuscular route of administration posed a less attractive option, especially as some of these patients had low muscle mass and were less likely to tolerate pain at the site of injection.

Previous studies have demonstrated the detrimental effects of influenza on CF. A retrospective study conducted by Pribble et al. [4] showed that infection with influenza A virus led to a higher proportion of CF patients with a 20% decrease in forced expiratory volume per second and forced expiratory flow in first 25% of vital capacity than patients with other non-bacterial infection and the group without non-bacterial infection (p -value < 0.05 for all comparisons). Conway and colleagues [3] also reported similar findings.

Immunisation against influenza A virus has been shown to provoke an adequate antibody response in patients with CF [13]. Rapid diagnostic tests may have a role in infection control; the use of anti-virals, such as neuraminidase inhibitors, requires prompt detection of influenza though their role in CF is not yet defined. NASBA as used in this review offers greater sensitivity and specificity than traditional laboratory methods such as direct immunofluorescence (IF) and cell culture [14]. It also has several advantages over PCR in that it is a continuous isothermic process that does not require a thermocycler. It also allows targeted RNA to be amplified exponentially at each step of the reaction and hence more efficient than PCR methods that are restricted to binary increases per cycle. Finally, the closed-tube format of NASBA assay greatly reduces the risk of contamination and thus of false-positive results.

In conclusion, despite the lack of randomised placebo controlled trial addressing the effectiveness of influenza vaccination in CF, this review demonstrated the protective effect of influenza vaccination in patients with CF. Therefore annual influenza vaccination should be routinely offered to these patients as part of their management.

Acknowledgements

We would like to thank the patients and their parents for the participation in this review. We would also like to thank Dr Pauline Pang for proof reading this article.

This project was funded by the Welsh Office of Research and Development.

References

- [1] Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med* 2005;352(19):1992–2001.
- [2] Murray TS, Egan M, Kazmierczak BI. *Pseudomonas aeruginosa* chronic colonization in cystic fibrosis patients. *Curr Opin Pediatr* 2007;19(1):83–8.
- [3] Conway SP, Simmonds EJ, Littlewood JM. Acute severe deterioration in cystic fibrosis associated with influenza A virus infection. *Thorax* 1992;47(2):112–4.
- [4] Pribble CG, Black PG, Bosso JA, Turner RB. Clinical manifestations of exacerbations of cystic fibrosis associated with nonbacterial infections. *J Pediatr* 1990;117(2 Pt 1):200–4.
- [5] Garcia DF, Hiatt PW, Jewell A, Schoonover SL, Cron SG, Riggs M, et al. Human metapneumovirus and respiratory syncytial virus infections in older children with cystic fibrosis. *Pediatr Pulmonol* 2007;42(1):66–74.
- [6] Tan A, Bhalla P, Smyth R. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database Syst Rev* 2000;2 [CD001753].
- [7] Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310(6989):1225–9.
- [8] Boom R, Sol CJ, Salimans MM, Jansen CL, Wertheim-van Dillen PM, van der Noordaa J. Rapid and simple method for purification of nucleic acids. *J Clin Microbiol* 1990;28(3):495–503.
- [9] Moore C, Hibbitts S, Owen N, Corden SA, Harrison G, Fox J, et al. Development and evaluation of a real-time nucleic acid sequence based amplification assay for rapid detection of influenza A. *J Med Virol* 2004;74(4):619–28.
- [10] Cates CJ, Jefferson TO, Bara AI, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2004;2 [CD000364].
- [11] Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med* 2004;169(4):488–93.
- [12] Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;1 [CD002733].
- [13] Ong EL, Bilton D, Abbott J, Webb AK, McCartney RA, Caul EO. Influenza vaccination in adults with cystic fibrosis. *BMJ* 1991;303(6802):557.
- [14] Harnden A, Brueggemann A, Shepperd S, White J, Hayward AC, Zambon M, et al. Near patient testing for influenza in children in primary care: comparison with laboratory test. *BMJ* 2003;326(7387):480.