ACKNOWLEDGEMENTS

We thank the Fluid research grant of Christian Medical College, Vellore for providing financial assistance for this study.

REFERENCES

1. Jesudason MV, Shanthakumari R, John TJ. *Burkholderia pseudomallei*—an emerging pathogen in India. *Ind J Med Res* 1997; **105**: 1–2.
2. Jesudason MV, Anandaraj WS, Malathi B. An indirect ELISA for the diagnosis of melioidosis. *Ind J Med Res* 2001; **114**: 51–53.
3. Jesudason MV, Anbarasu A, John TJ. Septicaemic melioidosis in a tertiary care hospital in south India. *Ind J Med Res* 2003; **117**: 119–121.
4. Tiangpitayakorn C, Songsivilai S, Piyasangthong N, Dharakul T. Speed of detection of *Burkholderia pseudomallei* in blood cultures and its correlation with the clinical outcome. *Am J Trop Med Hyg* 1997; **57**: 96–99.
5. Haase A, Brennan M, Barrett S *et al*. Evaluation of PCR for diagnosis of melioidosis. *J Clin Microbiol* 1998; **36**: 1039–1041.
6. Sirisinha S, Anuntagool N, Dharakul T *et al*. Recent developments in laboratory diagnosis of melioidosis. *Acta Trop* 2000; **74**: 235–245.
7. Jesudason MV, Thangavelu CP, Lalitha MK. Rapid screening of fecal samples for *Vibrio cholerae* by a coagglutination technique. *J Clin Microbiol* 1984; **19**: 712–713.
8. George OV, Jesudason MV, John TJ. Co-agglutination for the rapid detection of *V. cholerae* 0139. *Ind J Med Res* 1995; **13**: 185–186.
9. Rockhill RC, Rumans LW, Lesmana M, Dennis DT. Detection of *Salmonella typhi* D, and Vi antigens, by slide coagglutination, in urine from patients with typhoid fever. *J Clin Microbiol* 1980; **11**: 213–216.
10. John TJ, Sivadasan K, Kurien B. Evaluation of passive bacterial agglutination for the diagnosis of typhoid fever. *J Clin Microbiol* 1984; **20**: 751–753.
11. Shetty NP, Srinivasa H, Bhat P. Coagglutination and counter immunoelectrophoresis in the rapid diagnosis of typhoid fever. *Am J Clin Pathol* 1985; **84**: 80–84.
12. Sarvamangala Devi JN, Shivananda PG. Coagglutination for diagnosis of enteric fever. *Ind J Pathol Microbiol* 1985; **28**: 349–353.
13. Samosornsuk N, Lulitanond A, Saenla N, Anuntagool N, Wongratanacheewin S, Sirisinha S. Short report: evaluation of a monoclonal antibody-based latex agglutination test for rapid diagnosis of septicemic melioidosis. *Am J Trop Med Hyg* 1999; **61**: 735–737.
14. Anuntagool N, Naigowit P, Petkanchanapong V, Aramsri P, Panichakul T, Sirisinha S. Monoclonal antibody-based rapid identification of *Burkholderia pseudomallei* in blood culture fluid from patients with community-acquired septicaemia. *J Med Microbiol* 2000; **49**: 1075–1078.
15. Ewing WH. The genus *Salmonella*. In: Ewing WH, ed. *Edwards and Ewings identification of Enterobacteriaceae*, 4th edn. New York: Elsevier, 1986; 239–245.
16. Smith MD, Wuthiekanun V, Walsh AL, Pitt TL. Latex agglutination test for identification of *Pseudomonas pseudomallei*. *J Clin Pathol* 1993; **4**: 374–375.
17. Smith MD, Wuthiekanun V, Walsh AL *et al*. Latex agglutination for rapid detection of *Pseudomonas pseudomallei* antigen in urine of patients with melioidosis. *J Clin Pathol* 1995; **48**: 74–76.
18. Pongsunk S, Thirawattanasuk N, Piyasangthong N, Ekpo P. Rapid identification of *Burkholderia pseudomallei* in blood cultures by a monoclonal antibody assay. *J Clin Microbiol* 1999; **37**: 3662–3667.
19. Dharakul T, Songsivilai S, Smithikarn S, Thepthai C, Leelaporn A. Rapid identification of *Burkholderia pseudomallei* in blood cultures by latex agglutination using lipopolysaccharide-specific monoclonal antibody. *Am J Trop Med Hyg* 1999; **61**: 658–662.
20. Steinmetz I, Reganzerowski A, Brenneke B, Haussler S, Simpson A, White NJ. Rapid identification of *Burkholderia pseudomallei* by latex agglutination based on an exopolysaccharide-specific monoclonal antibody. *J Clin Microbiol* 1999; **37**: 225–228.

RESEARCH NOTE

Clinical and socio-economic impact of influenza and respiratory syncytial virus infection on healthy children and their households

S. Esposito[1], R. Gasparini[2], S. Bosis[1], P. Marchisio[1], C. Tagliabue[1], S. Tosi[1], C. Bianchi[3], P. Crovari[2] and N. Principi[1]

[1]Institute of Pediatrics, Fondazione IRCCS 'Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena', University of Milan, Milan, [2]Department of Health Sciences, University of Genoa, Genoa and [3]Wyeth Lederle Vaccines, Rome, Italy

ABSTRACT

This prospective study compared the clinical and socio-economic impact of laboratory-confirmed influenza and respiratory syncytial virus (RSV) infection on healthy children and their families. Among 1520 otherwise healthy children aged < 15 years attending the Emergency Department for acute conditions other than trauma, influenza

Corresponding author and reprint requests: N. Principi, Institute of Pediatrics, Fondazione IRCCS 'Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena', University of Milan, Via Commenda 9, 20122 Milano, Italy
E-mail: Nicola.Principi@unimi.it

© 2005 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **11**, 925–936

viruses and RSV were found in 234 (15.4%) and 116 (7.6%; $p < 0.0001$) patients, respectively. The fact that influenza has a similar global clinical impact on the community to that of RSV infection, but represents a greater socio-economic burden, may contribute to broadening the acceptance of influenza vaccination.

Keywords Children, epidemiology, influenza, respiratory syncytial virus, socio-economic impact, virus infections

Original Submission: 25 February 2005; **Revised Submission:** 21 April 2005; **Accepted:** 8 June 2005

Clin Microbiol Infect 2005; 11: 933–936
10.1111/j.1469-0691.2005.01270.x

In the northern hemisphere, influenza viruses and respiratory syncytial virus (RSV) cause epidemics between November and April, and are the main aetiological agents of acute respiratory diseases in infants and children during this period [1,2]. Although the infections caused by these pathogens can have similar clinical pictures, involving all sections of the respiratory tract, RSV is usually considered to be much more important than influenza viruses, as it is the main cause of bronchiolitis, which is one of the main reasons for hospitalisation of children in the first years of life, and has a major impact on public health resources [2,3]. However, recent data suggest that paediatric influenza can play a much more important clinical role than previously thought, with important socio-economic consequences for the patients' families [4–12]. The present prospective study was designed to analyse the clinical and socio-economic impact of laboratory-confirmed cases of influenza and RSV infection on healthy children and their families.

Between 1 November 2002 and 31 March 2003, subjects aged <15 years were enrolled who attended the Emergency Department at the Pediatric Institute of the University of Milan (Italy) twice-weekly (Wednesday and Sunday) because of an acute condition other than trauma. Other exclusion criteria were concomitant chronic diseases leading to an increased risk of the complications of influenza or RSV infection [2,7]. The protocol was approved by the Institutional Review Board of the University of Milan, and the written informed consent of a parent or legal guardian was acquired.

Upon enrolment, each patient's demographic characteristics and medical history were recorded using a standardised written questionnaire. After a complete physical examination, the children were divided into different disease groups using well-established criteria [13]. Virocult (Medical Wire and Equipment, Corsham, UK) nasopharyngeal swabs were collected for the detection of influenza viruses and RSV RNA by RT-PCR as described previously [14–17].

The medical history of the children studied was re-evaluated 5–7 days after enrolment, and until the resolution of their illness, by means of interviews and clinical examinations by trained investigators using a standard questionnaire. During these evaluations, information was also obtained concerning acute illnesses and related morbidity among household contacts. The data were analysed using SAS for Windows v. 12 (SAS Institute, Cary, NC, USA). Parametric data were compared using analysis of variance (ANOVA); abnormally distributed or non-parametric data were analysed using the Kruskal–Wallis test. Categorical data were analysed using contingency analysis and chi-squared or Fisher's tests.

The study involved 1520 otherwise healthy children (815 males; mean age 3.41 ± 3.06 years). Influenza viruses were demonstrated in 234 patients (15.4%), including 228 with influenza A virus (97.5%; 148 H3N2, 64.9%; 80 H1N1, 35.1%) and six (2.5%) with influenza B virus, while RSV was detected in 116 patients (7.6%; $p < 0.0001$ vs. influenza-positive cases). Influenza-positive cases were observed significantly more frequently among children aged >2 years (66.7% vs. 35.3%; $p < 0.0001$), whereas RSV was detected significantly more frequently among patients aged <2 years (64.7% vs. 33.3%; $p < 0.0001$). Table 1 shows the clinical presentations by aetiological diagnosis. At enrolment, most diagnoses involved the respiratory system. The differences in clinical presentation between the influenza- and RSV-positive children were similar regardless of age.

Upon admission, diagnostic tests were used more frequently in RSV-positive than in influenza-positive children, although the difference was statistically significant only in the case of microbiological tests (9.5% vs. 2.1%; p 0.004). The frequency of antibiotic prescriptions was similar

© 2005 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **11**, 925–936

Table 1. Clinical presentation of the patients according to aetiological diagnosis

Clinical presentation	Influenza-positive cases (n = 234)	RSV-positive cases (n = 116)
Presence of fever[a] (%)	212 (90.6)[c]	77 (66.4)
High-grade fever[b] (%)	179 (76.5)[c]	60 (51.7)
Respiratory tract infection (%)	190 (81.2)[d]	108 (93.1)
Upper respiratory tract infection (%)	144 (61.5)[d]	47 (40.5)
Common cold (%)	33 (14.1)	12 (10.3)
Pharyngitis (%)	75 (32.1)[d]	19 (16.4)
Acute otitis media (%)	33 (14.1)	14 (12.1)
Croup (%)	3 (1.3)	2 (1.7)
Lower respiratory tract infection (%)	46 (19.7)[c]	61 (52.6)
Acute bronchitis (%)	27 (11.5)	15 (12.9)
Wheezing (%)	10 (4.3)*	25 (21.6)
Pneumonia (%)	9 (3.9)*	21 (18.1)
Gastrointestinal tract infection (%)	8 (3.4)	7 (6.0)
Fever without source (%)	27 (11.6)[d]	1 (0.9)
Febrile seizures (%)	9 (3.8)[d]	0

RSV, respiratory syncytial virus.
[a]Defined as an axillary temperature ≥ 37.6°C or a rectal temperature ≥ 38°C.
[b]Defined as an axillary temperature ≥ 39°C or a rectal temperature ≥ 39.5°C.
[c]$p < 0.0001$ and [d]$p < 0.05$ vs. RSV-positive cases; no other statistically significant differences.

Table 2. Socio-economic impact of influenza and RSV infection on the household contacts of the study children

Characteristics	Household contacts of influenza-positive children (n = 651)	Household contacts of RSV-positive children (n = 311)
Disease similar to that of the infected child (%)	119/651 (18.3)[a]	25/311 (8.0)
Mothers, n (%)	49/234 (20.9)[b]	13/116 (11.2)
Fathers, n (%)	24/234 (10.3)	6/116 (5.2)
Siblings, n (%)	46/183 (25.1)[b]	6/79 (7.6)
Additional medical visits (%)	88/651 (13.5)[a]	16/311 (5.1)
Mothers, n (%)	27/234 (11.5)[b]	5/116 (4.3)
Fathers, n (%)	15/234 (6.4)	3/116 (2.6)
Siblings, n (%)	46/183 (25.1)[b]	8/79 (10.1)
Anti-pyretic prescriptions (%)	107/651 (16.4)[a]	15/311 (4.8)
Mothers, n (%)	43/234 (18.4)[b]	7/116 (6.0)
Fathers, n (%)	20/234 (8.6)[b]	2/116 (1.7)
Siblings, n (%)	44/183 (24.0)[b]	6/79 (7.6)
Antibiotic prescriptions (%)	35/651 (5.4)	11/311 (3.5)
Mothers, n (%)	9/234 (3.9)	4/116 (3.4)
Fathers, n (%)	7/234 (3.0)	2/116 (1.7)
Siblings, n (%)	19/183 (10.4)	4/79 (5.1)
Hospitalisation (%)	2/651 (0.3)	0/311 (0)
Mothers, n (%)	0/234 (0)	0/116 (0)
Fathers, n (%)	0/234 (0)	0/116 (0)
Siblings, n (%)	2/183 (1.1)	0/79 (0)
Missed working days by mothers, median (range)	4 (1–9)[b]	2 (2–5)
Missed working days by fathers, median (range)	3 (2–8)[b]	1 (1–4)
Missed school days, median (range)	6 (2–15)[b]	3 (2–5)

RSV, respiratory syncytial virus.
[a]$p < 0.0001$ and [b]$p < 0.05$ vs. RSV-positive cases; no other statistically significant differences.

for both groups, whereas anti-pyretics were used significantly more frequently with influenza-positive patients (82.5% vs. 50.0%; $p < 0.0001$), and bronchodilators and steroids were administered significantly more often to RSV-positive children (29.3% vs. 6.4%, $p < 0.0001$, and 28.4% vs. 11.5%, $p < 0.0001$, respectively). Hospitalisation was required for a significantly larger proportion of RSV-positive children (17.2% vs. 5.6%; p 0.0007), whereas school absence was significantly more prevalent among influenza-positive patients (median, 12 vs. 5 days; p 0.003). The between-group differences in diagnostic procedures and therapeutic approaches remained similar regardless of the patients' ages, whereas the frequency of hospitalisation was significantly higher only for the RSV-positive patients aged <2 years (22.7% vs. 6.4%; $p < 0.05$).

Table 2 shows that the household contacts of the influenza-positive children had significantly more diseases resembling that of the infected child than those of the RSV-positive children, and required significantly more medical visits, received more anti-pyretics, and missed significantly more working or school days. These differences were more evident among mothers and siblings, and remained similar regardless of the patients' ages.

To the best of our knowledge, this is the first prospective study, starting from laboratory-confirmed diagnoses, to compare simultaneously the clinical and socio-economic impact of influenza and RSV infections in otherwise healthy children on themselves and their households. The clinical data confirmed that RSV affects younger children more frequently, involves mainly the lower respiratory tract, and (especially in the first 2 years of life) often leads to hospitalisation, even in the absence of any known risk-factor [3–6,18,19]. However, the importance of influenza viruses cannot be considered marginal, since the present results (which extend those of previous studies) [4,20] indicate that a substantial number of children of all ages, without any risk-factor, attend the Emergency Department with influenza during epidemic periods, that >5% of influenza-positive children of any age attending the Emergency Department may have a severe illness requiring hospitalisation, and that most children spread the infection among the members of their household. In terms of socio-economic impact, the greater relevance of influenza in healthy children for household contacts is demonstrated by the higher incidence of similar disease in the parents and siblings of influenza-positive cases, a larger number of whom required medical visits and anti-pyretics, and missed work or school days. These findings indicate that influ-

© 2005 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **11**, 925–936

enza in healthy children has a considerable impact on their families, and thereby justifies extending the recommendation to vaccinate healthy children [7].

In conclusion, the present study showed that the global clinical impact of influenza on the community may be similar to that of RSV infection, and that it represents a greater socio-economic burden. These data may help to modify the mistaken attitude of some physicians and parents towards influenza and its prevention, and may contribute to broadening the acceptance of influenza vaccination.

ACKNOWLEDGEMENTS

This study was supported in part by a grant from Wyeth-Lederle Vaccines, Italy.

This study was presented in part at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, 2003).

REFERENCES

1. Esposito S, Marchisio P, Morelli P, Crovari P, Principi N. Effect of a rapid influenza diagnosis. *Arch Dis Child* 2003; **88**: 525–526.
2. Lanari M, Giovannini M, Giuffré L *et al.* Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. *Pediatr Pulmonol* 2002; **33**: 458–465.
3. Weisman LE. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. *Pediatr Infect Dis J* 2003; **22**: S33–S39.
4. Principi N, Esposito S, Marchisio P, Gasparini R, Crovari P. Socioeconomic impact of influenza in healthy children and their families. *Pediatr Infect Dis J* 2003; **22**: S207–S210.
5. Izurieta HS, Thompson WW, Kramarz P *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; **342**: 232–239.
6. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; **342**: 225–231.
7. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2004; **53**: 1–40.
8. Principi N, Esposito S. Prevention or control of influenza in the pediatric population. *Emerg Infect Dis* 2004; **10**: 574–580.
9. Principi N, Esposito S. Are we ready for universal influenza vaccination in paediatrics? *Lancet Infect Dis* 2004; **4**: 75–83.
10. Meury S, Zeller S, Heininger U. Comparison of clinical characteristics of influenza and respiratory syncytial virus infection in hospitalised children and adolescents. *Eur J Pediatr* 2004; **163**: 359–363.
11. Coiras MT, Pérez-Brena P, Garcìa ML, Casas I. Simultaneous detection of influenza A, B, and C viruses, respiratory syncytial virus, and adenoviruses in clinical samples by multiplex reverse transcription nested-PCR assay. *J Med Virol* 2003; **69**: 132–144.
12. Sugaya N, Mitamura K, Nirasawa M, Takahashi K. The impact of winter epidemics of influenza and respiratory syncytial virus on paediatric admissions to an urban general hospital. *J Med Virol* 2000; **60**: 102–106.
13. Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases*, 4th edn. Philadelphia, PA: Saunders, 1998.
14. Principi N, Esposito S, Gasparini R, Marchisio P, Crovari P, for the Flu-Flu Study Group. Burden of influenza in healthy children and their households. *Arch Dis Child* 2004; **89**: 1002–1007.
15. Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001; **358**: 1410–1416.
16. Atmar RL, Baxter BD. Typing and subtyping clinical isolates of influenza virus using reverse transcription–polymerase chain reaction. *Clin Diagn Virol* 1996; **7**: 77–84.
17. Stockton J, Ellis JS, Saville M, Clewley JP, Zambon MC. Multiplex PCR for typing and subtyping influenza and respiratory syncytial viruses. *J Clin Microbiol* 1998; **36**: 2990–2995.
18. Rietveld E, de Jonge HCC, Polder JJ *et al.* Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. *Pediatr Infect Dis J* 2004; **23**: 523–529.
19. Constantopoulos AG, Kafetzis DA, Syrogiannopoulos GA *et al.* Burden of respiratory syncytial viral infections on paediatric hospitals: a two-year prospective epidemiological study. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 102–107.
20. Heikkinen T, Silvennoinen H, Peltola V *et al.* Burden of influenza in children in the community. *J Infect Dis* 2004; **190**: 1369–1373.

© 2005 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **11**, 925–936

Copyright of Clinical Microbiology & Infection is the property of Blackwell Publishing Limited. The copyright in an individual article may be maintained by the author in certain cases. Content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.