EDITORIAL

Respiratory syncytial virus: a sleeping giant?

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The study by JANSEN *et al.* [1] in the present issue of the *European Respiratory Journal* focuses on the impact of influenza and respiratory syncytial virus (RSV) on mortality and hospital admissions. As in many other similar publications, it emphasises the significance of RSV (and influenza) in all age groups and not just children, in whom the impact is already well recognised [1]. In common with other similar studies, the evidence presented is derived by linking independent data on virus circulation (mainly from specimens sampled in children) with data on healthcare utilisation. As such, it falls short of direct linkage between cause and effect, although this has been demonstrated in experimental studies, which have included wild-type virus in addition to low temperature attenuated strains. In one of these studies, MCKAY *et al.* [2] administered wild-type virus to 20 human volunteers, and nine of them developed upper respiratory tract symptoms.

In community-based observational cohort studies between 1977 and 1981, MONTO and SULLIVAN [3] demonstrated average RSV isolation rates of 56 per 100 person-yrs in children aged 0–4 yrs, seven in those aged 5–19 yrs and somewhat less in older people. RSV demonstrated a clearer seasonality than other viruses studied. ZAMBON *et al.* [4] identified RSV in nose/throat virology specimens from community-based persons of all ages with influenza-like illness. Several studies have shown high rates of laboratory-confirmed infection in older people and especially in persons with chronic respiratory disease [5, 6]. Basing their findings on serological studies, DOWELL *et al.* [5] considered RSV to be one of the four most common pathogens identified in cases of lower respiratory tract infection in hospitalised adults, but went on to comment that none of the 57 cases of RSV infection included in the study were diagnosed during their period of hospitalisation. In an excellent recent review of RSV infection in adults, FALSEY [7] described RSV as a predictable cause of yearly epidemics of respiratory illness in temperate climates and drew attention to the clustering of cases in the staff and patients of a nursing home, which pointed to nosocomial spread. The impact of RSV infection in nursing homes has been recognised in several publications [8–10].

In data obtained in the Weekly Returns Service of the Royal College of General Practitioners (Birmingham, UK) [11], ELLIOT *et al.* [12] have shown that the clinical incidence of acute

bronchitis in the elderly peaks ~3 weeks later than that in children, unlike the incidence of influenza-like illness, which peaks in all age groups at the same time. Acute bronchitis diagnosed in children in the community coincides with the period of RSV reports to the Health Protection Agency mainly from hospitalised children; however, no comparable data are available from a sufficient number of adults. This finding influences the interpretation of clinical incidence data of both influenza and acute bronchitis. Since RSV precedes the appearance of influenza in most winters, the impact of RSV is sometimes lost in that attributable to influenza and tends to inflate the latter [13].

Notwithstanding the increasing evidence of the pathogenicity of RSV, why is it that the impact of this virus is so widely under-recognised? Why is it that the World Health Organization gives such a high priority to influenza but considers RSV an illness of little importance?

PERCEPTIONS OF ILLNESS

Common acute respiratory illnesses are minor in their impact in the majority of persons who become infected. “It is only a cold” or “It is a virus infection” reflect attitudes, even among the medical profession, that are only dislodged after repeated publications of research work demonstrating sufficient persons with serious manifestations of apparently “minor infections” which, together, constitute a large public health problem. A small study of RSV infections in hospital employees showed an average absence from work of 6 days [14]; a later study reported an average of 9.5 days in 211 healthy working adults [15]. In comparison, sickness absence due to influenza has been estimated at ~3 days per case [16]. It would appear, therefore, that RSV-related disease has a greater economic impact than influenza in relation to days lost from work; perhaps data on economic impact speak louder than data on disease incidence.

Perceptions of illness reinforce decision behaviour. As a result, paediatricians caring for babies with acute respiratory infections routinely look for RSV, whereas at the opposite end of the age spectrum, doctors caring for the elderly are more likely to investigate for influenza. Is the evidence now not sufficient enough that, in cases of acute infection prompting investigation, both these pathogens should be sought as routine and not simply one or the other? Perhaps an emphasis on influenza surveillance should be replaced by a much broader surveillance of acute respiratory infections? That is not to argue for routine diagnostic investigation, which can never be justified on economic grounds, but for structured respiratory disease surveillance in dedicated networks.

Perceptions of illness often steer us along particular pathways. The impetus for case definition in disease surveillance has laid

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such a strong emphasis on elevated temperature as an important criterion for diagnosing influenza that the absence of a raised temperature reduces the likelihood of virological investigation. RSV infection in adults and the elderly is not particularly associated with a raised temperature and afebrile persons are less likely to be investigated in surveillance networks concentrating specifically on the diagnosis of influenza.

The similarity of timing of the clinical presentation of persons with respiratory disease, whether symptomatically more focussed on upper or lower respiratory tracts, demonstrates that most common respiratory pathogens have the potential to cause widely diverse upper and lower symptoms, making it very difficult to discriminate between them. Both influenza and RSV infections are associated with increased numbers of persons presenting to general practitioners with a variety of respiratory syndromes, including acute bronchitis, common cold and otitis media [13]. Nevertheless, there are some pointers towards the diagnosis of RSV infection, such as wheeze, which has been commonly reported as more prominent in RSV than in influenza [5, 6]. Studies of exacerbation of chronic bronchitis often concentrate on the appropriateness of antibiotic use but comparatively few have seriously looked at possible virological causes and, in particular, RSV, for which antibiotics are probably irrelevant.

CASE PRESENTATION

In observational studies in the community, RSV is commonly identified as an important pathogen. However, routine studies of persons presenting to doctors do not do so to the same extent. Part of this reason lies in late presentation of most older persons when suffering from acute respiratory illnesses. Ross *et al.* [17] observed that whilst 80% of children aged 0–4 yrs presented within 48 h of symptom onset of influenza-like illness, only 19% of persons aged >65 yrs did. Older persons frequently present because their cough is not getting better, and well past the critical initial period of maximum viral replication during which the respiratory epithelial lining is damaged. Virus shedding of influenza reduces sharply after the third day of illness [18] but much less is known about the natural history of virus shedding in RSV infection [19].

DIAGNOSIS

If RSV is to achieve a higher profile, more confirmed clinical cases need to be recognised, and, ideally, be confirmed from routine clinical practice in the community and in hospitals. However, there are many issues surrounding accurate diagnosis. Firstly, the preferred swab specimen, a specimen for viral culture, is not a realistic option in most community circumstances because the virus is highly labile and does not survive routine transport methods. The best specimen site has not been established, although there seems to be a consensus around the use of a nose/throat swab obtained from “vigorous swabbing”. Nasal washes may be better but are much less acceptable. Sensitivity has been much improved by the use of RT-PCR tests, although these are expensive and labour intensive and are not widely used [7]. There is a tradition of investigating patients with acute exacerbations of bronchitis predominantly for bacteria, but specimens obtained for sputum culture could be used for PCR investigation [7]. There are a number of near patient tests currently available for

RSV with sufficient sensitivity and specificity to encourage their routine use (especially if coupled with investigation of influenza) in selected situations [20, 21]. For example, when contemplating admission of a patient with acute respiratory infection, a positive RSV and negative influenza result would favour admission if respiratory symptoms are severe, whereas a negative RSV and a positive influenza result may, in some circumstances, prompt appropriate antiviral treatment and avoid admission [22].

TREATMENT AND PREVENTION

There are no specific treatments for respiratory syncytial virus infection, and prevention using monoclonal antibodies is only indicated for premature infants [23, 24]. However, the absence of treatment is perhaps the main reason why respiratory syncytial virus is not actively sought when persons present with acute respiratory infection. Many attempts have been made to establish a safe respiratory syncytial virus vaccine but these seem perpetually like the mirage over the horizon. A chicken and egg situation exists. Further developments on both prevention and treatment will follow a clearer and unequivocal understanding of the impact of respiratory syncytial virus infection; however, routine budgets are unlikely to fund the investigation of an organism for which there is no treatment. Continuing research is needed to quantify the contribution of respiratory syncytial virus to respiratory infection and to clarify its role as a major factor in the aetiology of asthma [25]. Routine virological studies in influenza surveillance networks carry this work forward, but the methodologies and case sampling procedures have been developed around influenza, and may not be ideal for the detection of respiratory syncytial virus [4, 26, 27]. Even if respiratory syncytial virus is not universally accepted as a priority illness, the uncertainty surrounding the impact of respiratory syncytial virus is a serious problem that calls for prompt resolution. Priorities for research include: improved information on virus shedding in naturally occurring respiratory infections in persons of all ages; further studies of disease impact in terms of sickness absence and time to recovery; and the investigation of the relative impact of differing virus subtypes and of simultaneous infection with more than one respiratory virus [4, 26, 28].

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