# Common respiratory infections diagnosed in general practice

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## Abstract

Acute respiratory infections are one of the most common causes for presentation to a general practitioner. The range of symptoms associated with each infection can be wide ranging in both presentation and severity, depending on age of the patient, underlying co-morbidities and other confounding factors. In this chapter we describe the most common respiratory infections ranging from relatively mild infections such as the common cold, through to more serious presentations including pneumonia. Data are presented from a general practitioner morbidity surveillance system based in England and Wales. Each acute respiratory syndrome is described in respect of seasonality, secular trends and microbiological aetiology providing an insight into the complex nature of these acute respiratory episodes. The more serious endpoints of acute respiratory infections are hospitalisation and death. Many acute respiratory infections are mild in nature and generally self-limiting and therefore do not commonly require further medical interventions. However, despite major advances in the prevention and treatment of acute respiratory infections in recent years, hospitalisation and deaths continue to exert pressures on national health resources and provide an economic burden in countries across the world on an annual basis.

## Introduction

Acute respiratory infections present one of the most common reasons for consulting a general practitioner (GP) in England and Wales [1]. Approximately 30% of the general population consulted at least once because of a respiratory illness during the 1991/92 GP-based National Morbidity Survey: by 2001, the proportion had fallen to 25% and by 2007 to 21% [2]. Eighty five per cent of all episodes of illness classified to the International Classification of Diseases (ICD) chapter on respiratory disorders are due to acute respiratory infections. The Royal College of General Practitioners (RCGP) Weekly Returns Service (WRS), a sentinel

GP surveillance network located across England and Wales has monitored the incidence of acute respiratory infections since 1966 [3]. In 1991 approximately 18% of all consultations were attributable to the respiratory chapter of the ICD9; the vast majority of these were acute respiratory infections [4]. In recent years this proportion has decreased due to reducing numbers of respiratory infections diagnosed, and increasing numbers of total consultations [5, 6]. There are large age-related differences in the illness episode and consultation rates with children reporting much higher rates of upper respiratory tract infection (URTI) and older persons higher rates of lower respiratory tract infection (LRTI). In pre-school children (aged less than 5 years), the incidence of respiratory infections is higher in males than females; in school children and the elderly there is no gender difference; in most adult years reported incidence is higher in females, partly because of gender bias in consultation but also partly because of a greater potential of spread from children.

In this chapter, we address the most commonly diagnosed URTI and LRTI, starting with the organisms that are responsible for the presenting symptoms. We then address the presenting clinical syndromes and diagnoses; these are ordered in degree of severity, starting with mild episodes encountered in general practice, finishing with severe episodes that result in hospital admission and/or death. We relate these to long-term and secular trends, the microbiological aetiology of the diagnoses, and possible prevention strategies in the primary care setting.

## The viruses

In this chapter, the majority of the clinical syndromes described are primarily of a viral cause. In this section, a short introduction to the viruses responsible is provided with an emphasis on the clinical aspects of infection. A more detailed summary including the taxonomy, structure, replication, transmission and immunology of each virus is provided in the chapter by Olaf Weber.

### Influenza virus

The influenza viruses are grouped into three distinctive classes: A, B and C. Influenza B and C are found almost exclusively in humans with sporadic isolations in seals and pigs [7, 8] and cause relatively mild seasonal outbreaks of disease [9]. The natural reservoir of influenza A is in aquatic birds [10]. There are further subgroups of influenza A [10, 11]. The ability of influenza A viruses to undergo major genetic reassortments (antigenic shift) makes them ideal candidates for causing major outbreaks of disease on a global scale. Over the last century, three influenza pandemics have

led to the introduction of novel variants into the human population: H1N1 (1918/19); H2N2 (1957/58); and H3N2 (1968/69) [12]. Currently, two influenza A subtypes H3N2 and H1N1 (reintroduced in 1977/78) circulate in the human population. Despite recent scares involving highly pathogenic avian influenza viruses, e.g. H5N1, H7N7 causing severe disease and high mortality rates in humans, efficient human-to-human transmission has yet to be confirmed and therefore these isolated incidents have not developed into potential pandemic strains.

In the Northern Hemisphere, during each winter, influenza A and B strains cause annual outbreaks of respiratory illness in the community. Continual evolution of these viruses allows them to evade of the immune response, thus enabling new epidemics of disease to occur from year to year.

### Respiratory syncytial virus

There is an increasing awareness that human respiratory syncytial virus (RSV) is a major cause of serious lower respiratory illness. It has been shown that RSV can cause significant respiratory disease across all age groups [13]; however, the effect of RSV has been most frequently recorded in young children [14–16]. Despite the association with severe disease in the elderly, the exact role that RSV plays is not clearly understood partly due to the difficulty in recognising the clinical symptoms presented by RSV and influenza A infections in the elderly [17].

Similar to the influenza viruses, RSV is classified into subgroups (RSV A and B) and is also subject to annual evolution [18]. Despite the serious burden of RSV in respect of morbidity and mortality, there are currently no licensed vaccines, although there are candidate vaccines that are undergoing early safety and immunogenicity studies [19]. There were major setbacks during early RSV vaccine trials in the late 1960s: children administered formalin-inactivated RSV vaccines suffered severe LRTI following subsequent exposure to wild-type RSV leading to hospitalisation rates of up to 80% and the deaths of two patients [20].

### Human parainfluenza virus

There are four distinct human parainfluenza virus (HPIV) serotypes that have been identified (types 1–4) and are important causes of URTI and LRTI, especially in children [21, 22]. Circulation in summer is unusual for a respiratory virus: HPIV type 3 activity typically peaks during May–June. HPIV type 1 has circulation from September to December (i.e. earlier than common winter respiratory viruses) and HPIV 2 has typical winter circulation peaking December/January [23].

## Human coronavirus

Human coronaviruses (HCoV) can be divided into two distinct groups, those that cause respiratory infections and those causing gastrointestinal disease. Respiratory HCoV were originally isolated from the respiratory tract of an adult with a common cold. Until recently, respiratory HCoV were thought to cause relatively minor upper respiratory tract illnesses. However, the emergence of Severe Acute Respiratory Syndrome (SARS) in 2002, which was subsequently shown to be caused by a new variant of a HCoV, changed opinion on the relative importance of these viruses on public health [24–26].

## Rhinovirus

Rhinovirus (RV) is known to cause common cold symptoms and due to the large number of serotypes can cause repeated infections throughout an individual's life. In children, RV infections are commonly associated with recurrent wheeze, or exacerbations of asthma [27, 28]. The role of RV in the development of more severe disease in adults is not clear, but there is growing evidence of a link between RV infections and lower respiratory tract disease, especially in the elderly [29–31].

## Human metapneumovirus

Human metapneumovirus (HMPV) is a relatively newly detected respiratory pathogen discovered in a group of young children in the Netherlands presenting with respiratory tract infections [32]. The virus is classified in the same *Pneumovirus* subfamily as human RSV. Hospital-based studies have demonstrated that HMPV is a common respiratory pathogen often implicated in respiratory admissions of young children [15, 33]. Community-based studies have shown that HMPV is the cause of acute respiratory tract infections across many age groups [34]. Although infection in adults is common and often asymptomatic, infections can cause serious illness and lead to hospitalisation [35, 36].

## Human bocavirus

Human bocavirus (HBoV) is a parvovirus recently identified in Sweden, and now independently identified in children presenting with acute LRTI in several other countries [37]. The prevalence of viral detection in LRTI ranges from 3.1% to 10.3% with a relatively high rate of co-infection with other viruses [37–40].

## Microbiological aetiology

The underlying microbiological aetiology of URTI and LRTI is complex due to the potential number of pathogens involved. The majority of acute uncomplicated respiratory infections are caused by viral pathogens, with further secondary complications induced by bacterial colonisation of damaged cells lining the respiratory tract. Each viral pathogen has a distinct seasonality, although some are more predictable in their nature (Fig. 1). Influenza viruses are not consistent in their circulation; however, one can generalise their circulation as peaking during winter months, mainly between November and February. It has been noted that the more severe epidemics (for example in 1989/90) have started earlier in the winter, and peaked well before the Christmas/New Year period. Influenza B virus circulation is distinct from influenza A as these viruses commonly circulate later in the winter. Typically, influenza B circulation follows that of influenza A, and viruses can be isolated from cases during February and into March.

RSV is much more predictable in its circulation. Laboratory reports peak during weeks 50–52 (mid to late December) [41]. One of the most useful clinical markers of RSV activity is acute bronchitis in young children aged 0–4 years [42]. Over 90% of all RSV laboratory reports are from children aged less than 5 years. A comparison of RSV reports and acute bronchitis in young children demonstrates a remarkable association (Fig. 2).

During periods of concurrent circulation of influenza and RSV, it can be difficult to disentangle the effects of each virus. We have defined virus active periods of influenza and RSV and introduced a combined period, where we have tried to apportion the effects of each virus. From the studies, it is clear
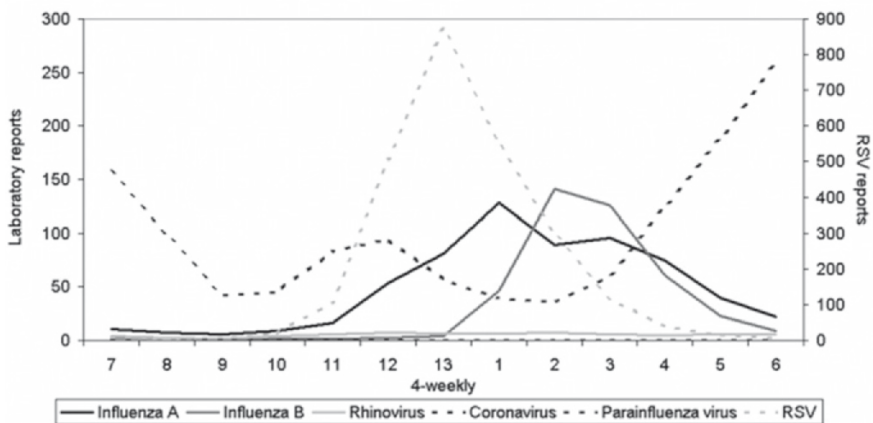


Figure 1. Seasonality of laboratory reports for common respiratory viruses received at the Health Protection Agency; reports per 4-week period with the winter weeks centred on the horizontal axis on mid winter (data averaged over years 1993–2001) [42].
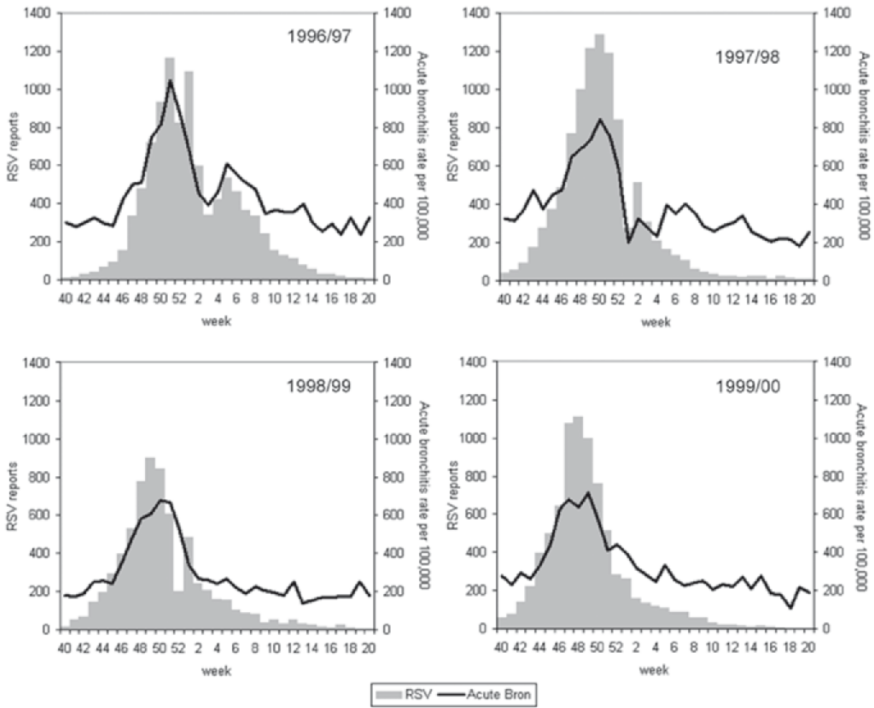
Figure 2. Incidence rate per 100 000 population of acute bronchitis in young children aged 0–4 years compared with laboratory reports for respiratory syncytial virus (RSV) over selected winters [42].

that RSV plays an important role in the burden of a number of commonly diagnosed respiratory infections. In fact, we, and others, believe that RSV plays as great, if not greater role than influenza in causing respiratory tract infections, especially in the oldest and youngest populations. We have also previously studied the contribution of each virus to respiratory hospital emergency admissions and drawn similar conclusions.

## Respiratory infections

### Common cold

Clinical presentation
The diagnosis of common cold is based upon recognition of a loosely defined syndrome rather than specific symptoms. Generally, the term is taken to mean an acute URTI with rhinitis and variable degrees of pharyngitis. Other presenting symptoms may include sneezing, runny nose, sore throat, chills; the presence of a mild fever is common but, except in young
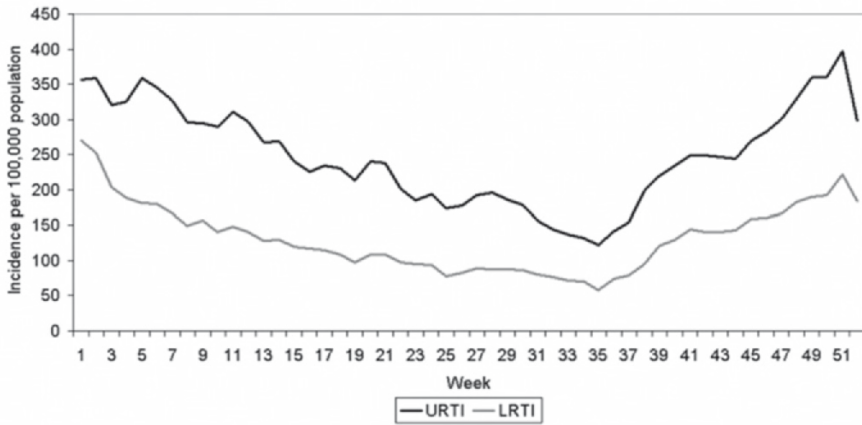
Figure 3. Mean weekly incidence rate per 100 000 population over the period 2002–2007 of upper and lower respiratory tract infections (URTI and LRTI).

children, the fever tends to be less than that associated with influenza. Colds are caused by a range of viruses such as RV, adenovirus and HCoV. Viruses such as influenza and RSV may also cause symptoms that are commonly described as a cold, although we tend to associate these viruses with more severe respiratory symptoms. A plot of the weekly incidence of URTI and LRTI averaged over a 6-year period (2002–2007) shows how the two types of illness show the same trend, suggesting a common aetiology (Fig. 3). The incidence of acute otitis media (AOM) and the common cold in children aged 0–4 years is plotted over 4 selected winters in Figure 4, again suggesting a common aetiology [43]. The common cold is usually a mild self-limiting acute respiratory illness; however, symptoms may be more severe in younger children. The duration of illness is mostly about 7 days but the acute phase lasts 3–4 days. In addition to AOM, the common cold may trigger exacerbations of asthma and cause sinusitis [27]. The mild self-limiting nature of URTI prompts only limited collection of clinical specimens for virological investigation from routine disease management and thus it is difficult to be specific about aetiology in the majority of cases of common cold and URTI.

## Secular trends

Similar to other acute respiratory infections, the incidence of diagnosed common cold infections has gradually fallen over previous years. The reduction in young children is particularly significant and has been accompanied by a similar reduction in AOM. Whereas in older age groups these reductions may be attributable in part to changes in consulting behaviour, the decrease in young children with acute ear problems suggests a real decrease
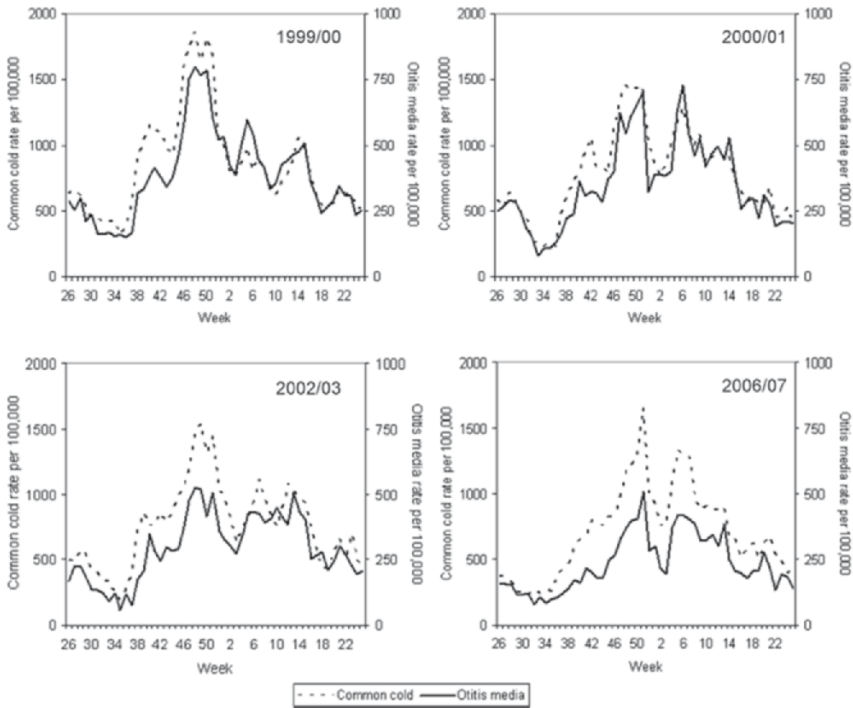
Figure 4. Weekly incidence rate per 100 000 of common cold and acute otitis media in young children aged 0–4 years over selected years (horizontal axes centred on turn of year: note differing scales on vertical axes) [87].

since patient health care expectations on behalf of children are more likely to be higher than lower.

## Seasonality

As with most acute respiratory infections, the common cold is more frequent in winter. Peak incidence rates occur between weeks 48 and 02. Incidence is much higher in young children with the highest incidence recorded in children aged 0–4 years (Fig. 5).

### *Herpes simplex and cold sores*

Cold sores are commonly associated with the common cold but these are due to specific herpes viruses. The constitutional symptoms experienced by persons with cold sores are similar to the common cold and often confused with it. It is possible that a common cold infection increases the likelihood
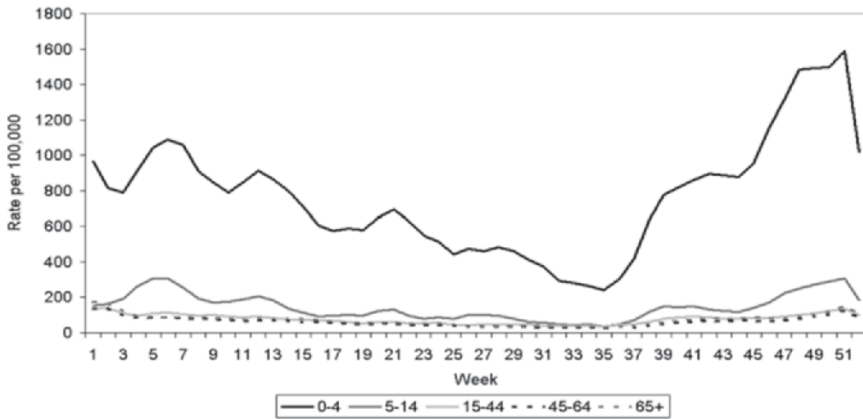
Figure 5. Weekly incidence rate of common cold over the period 1999–2008 by age group.

of a herpes simplex infection and the development of the typical cold sores, particularly on the lips and around the mouth.

There are two types of herpes simplex virus: type 1, which is implicated in the commonly encountered facial cold sore, but less frequently in genital herpes [44]; and type 2, which is more commonly a cause of genital herpes [45]. Both conditions are more common in females than males [46]. There are specific antiviral treatments for herpes simplex infections and they include acyclovir, either given orally or topically applied [47]. The topical application is commonly prescribed for persons with cold sores, but to be effective it must be given immediately the first symptoms appear [48].

## Acute otitis media

### Clinical presentation
AOM is the inflammation of the middle ear involving the Eustachian tube and is a common reason for presentation of young children with earache. AOM may be suppurative or non-suppurative. It is often thought of as a secondary complication of acute respiratory infections: however, data from the RCGP WRS for common cold and AOM demonstrate a close association, suggesting that AOM is as likely a direct result of the respiratory infection rather than an associated complication (Fig. 4).

### Secular trends
Contrary to the trends of influenza-like illness (ILI), the incidence of AOM increased steadily from 1967 to a peak during the late 1990s, since when rates have steadily declined (Fig. 6).
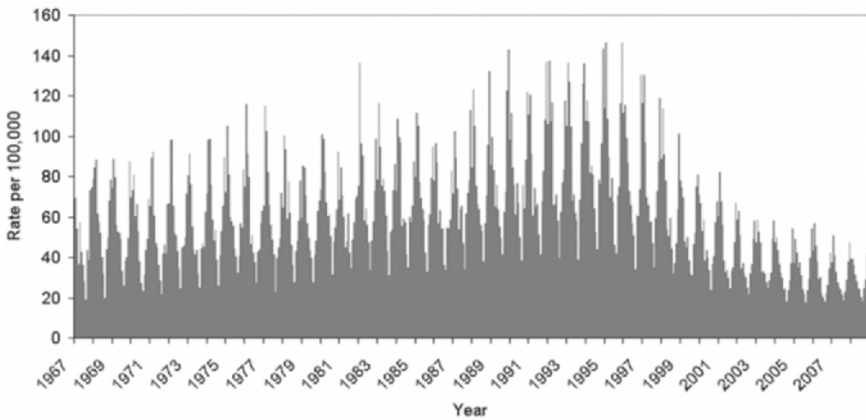
Figure 6. Mean weekly incidence rate in 4-week periods per 100 000 population of acute otitis media over the period 1967–2008 [53].

We have recorded data separately for suppurative otitis media since 1994; incidence of suppurative otitis media is generally lower with rates among all age groups about half those of total non-suppurative otitis media. These data show a similar trend to AOM with incidence falling from 1995 and then stabilising from 2003/2004 onwards. This trend is also seen in data for pneumonia (Fig. 12). The peak of AOM during the 1990s has been recorded for a number of other respiratory infections, including acute bronchitis and asthma.

Although uncommon now, mastoiditis as a complication of AOM was a serious problem fifty and more years ago [49]. The lingering fear of a recurrence of mastoiditis is a major reason for the continued excessive use of antibiotics for the treatment of AOM. Mastoiditis is not always a complication of a viral URTI: it is sometimes a complication of streptococcal infections [49]. Intensive (probably intravenous) treatment with antibiotics and appropriate surgical intervention remains necessary for the treatment of this condition [50]. Clinically, it presents with acute pain and tenderness over the mastoid process usually accompanied by aural discharge.

## Seasonality

The seasonality of AOM demonstrates a close association with the diagnosis of common cold (Fig. 4). In children aged 0–4 years, both clinical diagnoses peak during winter weeks 50–52; the diagnosis of common cold is more frequent than AOM, at a ratio of ~2:1 [43]. It is also interesting that there are six main peaks of AOM during the year, and the troughs between these peaks coincide with school holidays, providing evidence again that infections are concurrent with the increase in acute respiratory

infections associated with the return of children to school after holiday periods.

## Acute sinusitis

### Clinical presentation

Acute sinusitis usually presents with a background of recent URTI [51]. The mucosal lining of the paranasal sinuses is continuous with the upper respiratory tract and is subject to the catarrhal oedema and mucosal congestion affecting the entire upper respiratory tract when subject to infection or to pollen sensitisation. The label acute sinusitis describes infection in any of the paranasal sinuses (frontal, ethmoidal, maxillary) but is usually reserved to describe secondary bacterial infection [52]. This arises because sinus drainage becomes blocked and the relevant sinus fills up with pus that does not drain properly. The increased pressure created causes local pain and tenderness, which is usually readily apparent on percussion of the area. It is commonly accompanied by a sensation of blockage and by pus in the nose. The sense of smell is impaired or lost. The diagnosis is prompted by the history and local tenderness but can be confirmed by X-ray. Treatment includes nasal decongestants and antibiotics with surgical drainage in non-responding cases. Some people get particularly frequent episodes and develop nasal polyps. Nasal polypectomy and surgical measures to improve drainage are sometimes needed for these patients.

### Seasonality

The incidence of acute sinusitis roughly follows that of URTI generally. Experience in the WRS has shown that this condition is reported more frequently in females than males (by a factor of 2 to 1) [2]. At one time we thought this may be part of a well-recognized gender-based consultation bias. However, the magnitude of the difference and the fact that it is not seen in most other respiratory infections suggest that this is not a sufficient explanation for the difference. We speculate that the anatomical architecture in females is more prone to blockage than that in males. It could also be partly explained by the difficulty of distinguishing the head pain from a migraine attack, which is well recognized as commoner in females. Incidence of acute sinusitis is maximal in the 25–64-year age group [53].

## Croup

### Clinical presentation

Croup is an infection associated with inflammation and swelling of the larynx and trachea; it is a clinically distinct illness and is more prevalent

in children under 3 years of age [54]. Clinical presentation is commonly characterised by the sudden onset of the distinctive harsh "barking" cough and sore throat [55]. Symptom onset most usually happens at night and is accompanied by stridor, hoarse voice and respiratory distress [55]. Upon examination of the patient, inspiratory stridor may be present, with prolonged inspiration and chest wall retraction. When considering the diagnosis of croup, it is important to exclude other causes of shortness of breath or stridor such as foreign bodies and epiglottitis.

Epiglottitis is a frightening condition especially in young children where the lumen of the upper airways is small. It can be rapidly progressive leading to virtual asphyxiation from a very swollen epiglottis, obstructing the laryngeal opening [56]. Clinical features are classically those of an acute tonsillitis plus signs of progressive airway obstruction. The condition needs to be recognised as a serious emergency and dealt with promptly. Tracheostomy may well be necessary. *Haemophilus influenzae* type B (HIB) is one of the most common pathogens implicated with this condition and incidence has decreased since the introduction of the HIB vaccine [56, 57].

Pertussis infection or whooping cough can be confused with croup, but, whereas in croup the respiratory obstruction appears almost at the beginning of the illness, it takes some time to build up in whooping cough. In pre-vaccination days whooping cough was described as a condition which was 3 weeks coming, 3 weeks of significant symptoms and 3 months in which symptoms recurred with every respiratory virus infection. Although this was useful advice and a suitable warning for an anxious parent, it is a limited view of this illness in young children (less than 12 months of age), where the illness is particularly serious because of the small airways. The disease in this age group commonly progresses more rapidly than in older children and adults. Clinically, it is diagnosed on hearing the classical paroxysmal cough which leaves the sufferer gasping for breath and often quite cyanosed. The coughing paroxysms and terminal stridor are caused by laryngeal oedema. Retching or sometimes vomiting commonly follows the paroxysm.

Whooping cough is a bacterial infection mainly caused by *Bordetella pertussis*. The organism can be isolated from posterior nasal specimens (per nasal swab) obtained in the early stages of the illness. Management of whooping cough is essentially preventive by immunization [58]. However, the immunisation schedule only starts at 3 months of age and the protective response is variable and wanes with advancing age. Management of the acute condition involves the use of cough and spasm suppressants, plus a course of erythromycin, provided it can be started early in the course of the illness (it is of less use if administered later than 2 weeks after onset). Erythromycin should also be considered in infant contacts who have not yet received primary immunisation. Any decrease in the uptake of pertussis vaccination is likely to lead to an increased possibility of transmission from an older sibling to vulnerable young babies sometimes before there has been an opportunity to offer them immunisation. In older children and adults,

whooping cough may present as an acute spasmodic cough with increasing intensity over 3 weeks, but these symptoms can be very protracted.

## Secular trends

Historically, whooping cough used to occur with a secular trend about every 3 or 4 years [53]. That pattern no longer exists: 1997 was the most recent year in which there were a substantial number of cases reported to the WRS [59].

The long-term complications of *B. pertussis* infection include bronchiectasis, and here it is relevant specifically to mention measles [60]. Most doctors primarily associate measles with its classical morbilliform rash, which incidentally is often preceded by Koplik's spots on the buccal mucosa [61]. However, in terms of the clinical impact of measles the respiratory component is more significant. Indeed, if a suspicious rash is not accompanied by a cough it is very unlikely to be measles. Pre-immunisation, measles was often complicated by pneumonia and to a lesser extent by measles encephalitis. The long-term damage caused by pneumonia as a complication of measles was sometimes further complicated by the development of bronchiectasis [60].

## *Sore throat and tonsillitis*

## Clinical presentation

The presenting symptom of sore throat is often one of a constellation of symptoms associated with almost any viral URTI or LRTI. It is aggravated by any obstruction of the nasal passages. For some patients, however, a sore throat is a very specific symptom. It may be accompanied by substantial fever and difficulty in swallowing. In most viral respiratory infections the patient also complains of cough but the absence of cough and other respiratory symptoms makes bacterial tonsillitis more likely. On examination there is commonly a purulent exudate over the tonsils or pharynx but tender enlarged tonsillar lymph nodes are a clue to bacterial cause (commonly haemolytic streptococcus) [62]. In cases with enlarged or tender tonsillar nodes it is worth trying to confirm the diagnosis by throat swab culture or using one of the streptococcal rapid tests.

In former years streptococcal throat infections were often complicated by a skin rash (scarlet fever or in its mild form scarlatina), arthropathy and cardiac manifestations (rheumatic fever) or by renal problems (acute nephritis) [63]. Although these manifestations are now rare, it does not follow that they will not return and we need to be alert to noticing critical symptoms such as joint pain and swelling or blood in the urine. Occasionally, tonsillitis may progress to cause a peritonsillar abscess which may even require surgical drainage. Although it is no longer fashionable to give

penicillin to everyone with a sore or even streptococcal sore throat, patients with any of these complications should be treated with a 10-day course of Penicillin V administered intramuscularly if there is any difficulty with oral administration [64].

Glandular fever is often confused with acute tonsillitis. It occurs less frequently and is concentrated in the age group 15–24 years. It is caused by the Epstein-Barr virus. Clinically, the throat often has much more extensive exudates but is not always as painful as in streptococcal tonsillitis. It differs from tonsillitis with the extensive distribution of lymphadenopathy and the presence of an enlarged or tender spleen. However, in mild cases it is not always easy to distinguish the two conditions. The diagnosis should be established by the Paul-Bunnell blood test or by culture of the Epstein-Barr virus from a throat swab specimen. Antibiotics do not help in the management of this condition and in particular, the use of amoxicillin or ampicillin can prompt an unpleasant rash.

## Secular trends

Examined over 40 years there has been a decline in the incidence of acute tonsillitis. An all age incidence rate of 100–150 per 100 000 population per week was usual in the 1970s but now this rate is more commonly around 60–80 per 100 000. These trends have been observed separately in all age groups, although rates in childrenof 0–4 and 5–14 are approximately twice those found in adults 15–44 years and five times those seen in older adults. The incidence of glandular fever has also declined [65].

## *Influenza-like illness*

### Clinical presentation

Traditionally, the diagnostic label "influenza-like illness" (ILI) has always been associated with an infection with one of the many influenza viruses circulating in the community. The name 'influenza' originates in Italy and was used to describe epidemics of cough and fever, which were thought to be influenced by the disposition of the planets and heavenly bodies in the winter sky [66]. In the late nineteenth century it was thought to be caused by *Haemophilus influenzae* but in 1933 it was clearly attributed to the influenza virus [67]. ILI as a diagnostic label covers a wide range of symptoms and it is now apparent that these symptoms can be caused by numerous other respiratory pathogens that circulate at the same time as the influenza viruses.

The clinical term ILI is classically defined as a collection of presenting symptoms including myalgia, fever, chills, sore throat and cough, which typically appear with sudden onset [9]. A non-productive cough is more common at a later stage in the illness, and is often the main reason for subsequent consultation with a GP. Other symptoms may be present during the

acute phase of the illness including rhinitis, pharyngitis, conjunctivitis and AOM (especially in children). The acute febrile phase of illness tends to resolve within 3–5 days; however, malaise and general fatigue may persist for several days and sometimes weeks post infection.

The data collected in the WRS for surveillance purposes are not based on a precise case definition of ILI, although GPs are given guidance on the appropriate use of respiratory diagnostic terminology based on their judgement at the time of consultation. The symptomatology differs according to age; the elderly often present without fever; young children may present with AOM; patients immunised with seasonal influenza vaccine may present with less severe symptoms.

## Secular trends

The RCGP WRS has provided continuous monitoring of ILI in the community since 1966 [68]. Figure 7 displays the weekly incidence per 100 000 population of new cases of ILI diagnosed by GPs in the WRS. The clinical impact of the 1968/69 pandemic was felt in the winter of 1969/70 in the United Kingdom (UK), demonstrating the spread of global pandemics and the delay of subsequent waves [69]. During the 1969/70 winter all age rates of ILI reached 1252 per 100 000 in week 1 of 1970. In the following decade, rates of ILI remained relatively high. During subsequent decades the clinical incidence of ILI has gradually fallen, a trend seen with other common respiratory infections [6]. The last major epidemic occurred in 1989/90, when the prevailing influenza A H3 virus infected persons of all ages but particularly children aged 0–4 years in whom the recorded incidence exceeded that seen in the pandemic which hit the UK in the winter of 1969/70 (Fig. 8). During
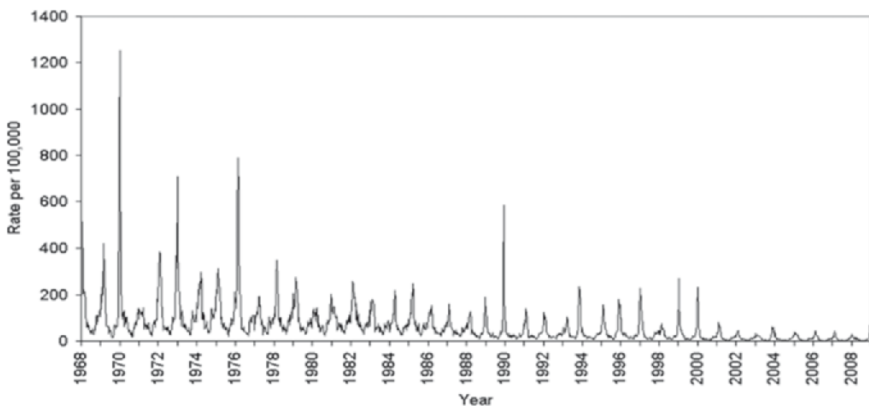


Figure 7. Weekly incidence rate per 100 000 population of influenza-like illness (ILI) over the period 1968–2008 [68].
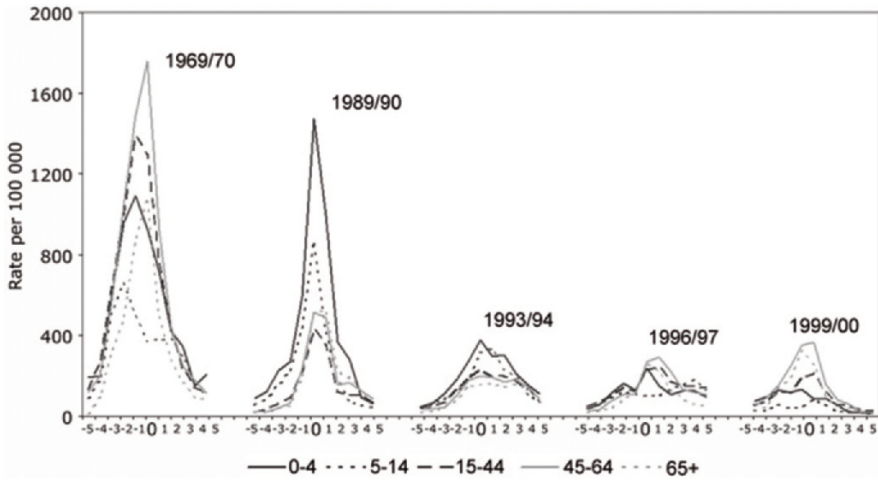
Figure 8. Age-specific incidence rate per 100 000 of influenza-like illness (ILI) over selected winters. Incidence rates are centred around the peak week (week 0) ±5 weeks.

the Millennium winter (1999/00) the National Health Service in England was severely stretched due to an influenza epidemic and there were dramatic news stories of persons spending several hours on trolleys in corridors while a hospital bed could be found [70]. Although the ILI activity was not particularly great in magnitude, it impacted on the 45–64 and 65+ years age groups (Fig. 8): respiratory infections in these age groups are more likely to result in hospital admission, and longer stays in hospital [71]. The hospital admission pressures in the Millennium winter came partly also from persons requiring admission for acute bronchitis, which was likely due to viruses other than influenza, in particular to RSV [70]. During the winter 2003/04 a novel strain of influenza H3N2 spread throughout the UK and other parts of the world [72, 73]. This "Fujian-like" strain was particularly virulent in young children as monitored by GP surveillance data; in contrast, in the winters of 1999/00 and 2007/08 it impacted on older age groups (25–44 and 65+ years, respectively) with a relatively low incidence of ILI recorded in young children (Johnson et al., unpublished results).

Currently, levels of influenza diagnosis in general practice are substantially less than those seen in the period 1970–1999 [68]. Several factors may have contributed to the reduction. In part it may be due to a reduced likelihood of consultation caused for example by changes in the statutory requirements for sickness certification; however, that has no bearing on the consultation rates in children or the elderly. Changes in consulting behaviour for uncomplicated respiratory tract infections may have been instigated by promotional campaigns discouraging patients from consulting doctors for "colds and the 'flu". The introduction of the tele-health service NHS Direct may also have had an effect by, in effect, providing a triage

service, advising uncomplicated and low risk respiratory cases to self-treat at home [74]. Other potential factors reducing the incidence of ILI include: the overall health of the general population has improved in recent decades due to reductions in pollution/smoking, and smaller family sizes, providing less opportunity for virus spread. Viewed over a 40-year period, however, changes in the incidence of respiratory infections are not the same for all conditions, suggesting that the changes are more complex, probably relating to changes in the circulating viruses and in their transmission characteristics [75]. For influenza in particular, the more severe epidemics over the last years have been caused by influenza A H3N2 viruses and have involved numerous mutations [76]: perhaps we are reaching an evolutionary end point.

## Seasonality

In the Northern Hemisphere influenza circulates during the winter months. A feature of influenza epidemics is the unpredictability of its appearance in winter [70]. WRS data demonstrate that annual influenza epidemic periods can range from early November (e.g. 1993) through to late March/April (e.g. 1988), although the most common period of circulation is around December/January. Influenza B tends to appear later in the winter than influenza A. Accordingly, national surveillance systems designed to monitor the burden of ILI in the community have a wide window of enhanced surveillance activities in order to capture any unusually early or late activity. Public health surveillance systems such as the WRS, NHS Direct and QSurveillance® specifically monitor ILI activity from October to May [77].

## *Acute bronchitis*

## Clinical presentation

Acute bronchitis is one of the most common infections reported in general practice, especially in the youngest and oldest age groups. Using routine incidence data collected from the RCGP WRS, we have estimated that 6.2% of children (aged 0–14 years) presented to their GP with one or more episodes of acute bronchitis during 2001. The presentation and diagnosis of acute bronchitis is usually associated with cough as the chief symptom sometimes accompanied by wheeze and pain on coughing and by fever. The diagnosis is usually made when the cough is productive and rales are heard on auscultation of the chest. The diagnosis of acute bronchitis is often problematic due to the difficulty in differentiating from asthma. This differentiation presents the GP with problems, especially in young children, where there is no satisfactory distinction between asthma and acute bronchitis when it first appears. Mostly, the diagnosis of asthma follows a series of ill-
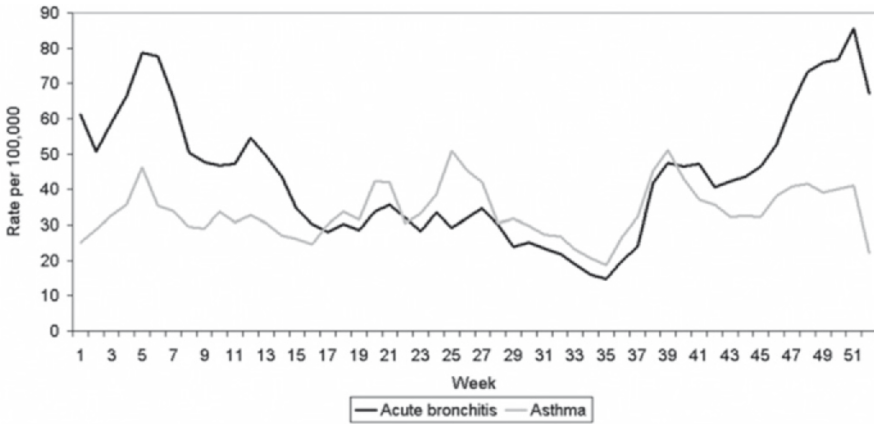
Figure 9. Mean weekly incidence rate per 100 000 of asthma and acute bronchitis over the period 1999–2008 in children aged 5–14 years.

nesses described variously as wheezy or acute bronchitis. For some persons, there is a strong tendency of respiratory infections to prompt attacks of asthma. In Figure 9 a comparison is made between WRS weekly incidence data averaged over 10 years for asthma attacks and for acute bronchitis in children of 5–14 years. These conditions follow the same seasonal pattern. The duration of illness varies considerably and is not clearly related to the causative pathogen.

Acute bronchiolitis is a particular problem in young children where the pathological damage is concentrated at the smaller bronchiole and alveolar level. It cannot be clinically differentiated from broncho-pneumonia. Cough may be less prominent than shortness of breath and respiratory distress may occur. It is commonly caused by RSV and is highly consistent in its seasonal appearance in December in almost all winters. It is very common in children under 5 years; it has been estimated that there are on average 25 respiratory deaths and 79 deaths from all causes attributed to RSV in this age group, estimates similar to those attributed to influenza [78].

The conditions described as trachea-bronchitis and laryngitis imply an emphasis of symptoms based on epithelial damage in the major tracheal and laryngeal airways. Coughing is usually more intense when these parts of the airways are affected and in some cases quite prolonged. Whooping cough and croup are particular examples of such infections.

## Secular trends

The RCGP WRS has collected clinical incidence data on acute bronchitis since 1967. In comparison to ILI, the long-term secular trend of acute bron-chitis is remarkably different (Fig. 10). During the 1990s the incidence of
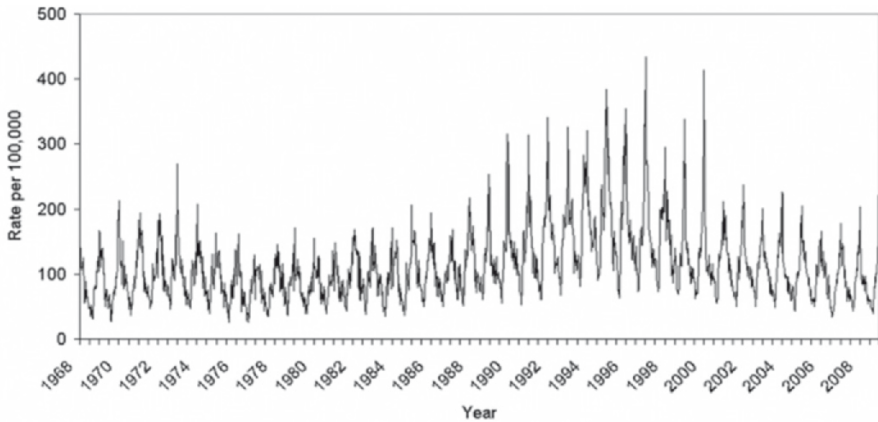
Figure 10. Weekly incidence rate of acute bronchitis per 100 000 population over the period 1968–2008.

acute bronchitis increased, peaking during 1994 and then gradually decreasing to present day. The differences between the two respiratory conditions are indicative of differing aetiologies. Interestingly, the trend of acute bronchitis is mirrored by that of asthma with the peak occurring during the mid-1990s demonstrating the close relationship between the two conditions.

## Seasonality
Acute bronchitis demonstrates a clear seasonal peak during the last weeks of the year. Interestingly, there are differences in the peak between age groups as previously reported. The incidence of acute bronchitis in young children (0–4 years) peaks during week 48; the peak in the elderly (65+ years) is approximately 2–3 weeks later; this finding is consistent from season to season and probably represents the mode of spread from young children to the elderly during the holiday period at Christmas and New Year (Fig. 11). Interestingly, this is not replicated in ILI data; a similar analysis reveals no lag between these age groups suggesting that ILI infections start and spread through all age groups at an equal rate. These findings for ILI have been replicated in other sentinel networks across Europe [79].

## *Pneumonia*

## Clinical presentation
Pneumonia can be defined as an illness of the lung involving alveolar and parenchyma inflammation, which results in abnormalities of alveolar gas exchange. Although often a secondary complication of viral or bacte-
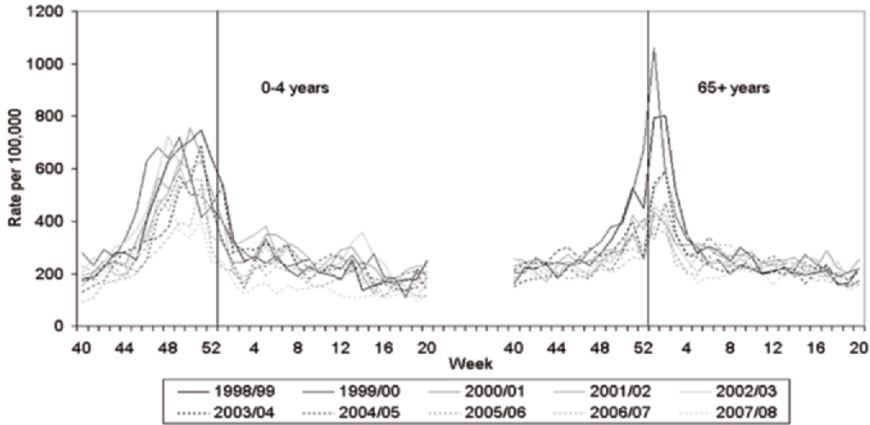
Figure 11. Weekly incidence rate per 100 000 of acute bronchitis in young children aged 0–4 years and the elderly aged 65+ years over selected winter weeks 40–20. The vertical lines mark the year end.

rial infections, primary viral pneumonia is associated with clinical features including non-productive cough, and in more severely ill patients, cyanosis and hypoxemia. Viral causes of pneumonia are mainly associated with influenza and RSV infection, although more recent literature suggest that serious LRTI including pneumonia can be caused by a wide range of viral pathogens and the seasonality of pneumonia suggests that even though caused by a bacterial pathogen it is often consequent on a viral infection [30].

## Secular trends
Incidence rates of pneumonia peaked at their highest rate during the winter of 1969/70; this was when the last influenza pandemic occurred and is most likely a reflection of complications of primary influenza infection. Rates steadily declined over the 1970s, but then stabilised during the 1980s and 1990s. Since the turn of the Millennium, the incidence of pneumonia again decreased, although data from the last couple of years suggest that this decrease has once again stabilised.

## Seasonality
The seasonality of pneumonia as recorded by the RCGP WRS suggests a close association with acute respiratory infections. Comparing the incidence of pneumonia and that of ILI over the last 40 years shows that the highest incidence of pneumonia occurs at the same time as the highest incidence of ILI (Fig. 12). We performed a cross-correlation of the weekly data for pneu-
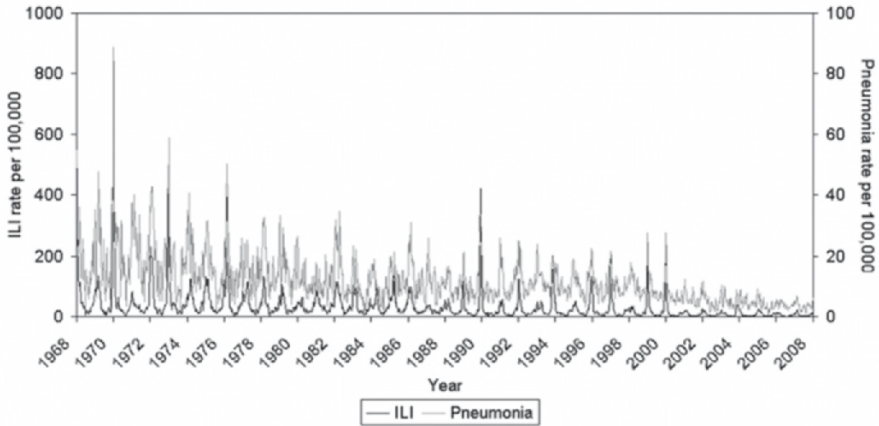
Figure 12. Weekly incidence rate per 100 000 of influenza-like illness (ILI) and pneumonia over the period 1968–2008 in elderly persons aged 65+ years (smoothed 3-week rolling average).

monia and ILI over this 40-year period, demonstrating that the incidence of ILI and pneumonia were maximally correlated in week 0, strongly supporting (although not proving) a casual relationship.

## Hospital admissions

Acute respiratory infections place an annual burden on secondary health care facilities. Although these 'winter pressures' are not a new phenomenon, in the UK they received more prominence during the winter of 1999/2000 when the National Health Service was severely crippled, producing a national crisis during which many hospitals were unable to meet the demand.

Influenza and RSV are the two pathogens most notably associated with the pressures. Although there are numerous other pathogens potentially capable of causing disease severe enough to prompt admission (especially in elderly or other at-risk groups), these two pathogens have previously been associated with hospitalisations for respiratory and other causes [70, 80–82]. Using hospital admission data accessed from the Hospital Episode Statistics database, there were approximately 4.7 million emergency admissions for all causes and all ages to hospitals in England during 2006/07 (May–April), of which approximately 530 000 were labelled as a respiratory cause (J Chapter ICD10) [83].

Admissions due to respiratory causes were estimated over the winters 1989/90 to 1997/98 [84]. During winters where serious influenza epidemics occurred, e.g. 1997/98, there were an estimated 21 000 excess admissions. These estimates were made during influenza epidemic periods, i.e., periods

when influenza viruses were known to be circulating in the community and therefore give a good idea of burden due to the virus. Averaged over the study period, there were 9000 excess admissions per year during the influenza active period.

In addition to respiratory admissions, respiratory viruses are associated with increased hospital admission for other groups of disease. Thompson et al. [82] estimated that in the USA there were more than 200 000 respiratory and circulatory admissions per annum due to influenza. A study using data from England and Wales found increased circulatory deaths contemporary with new episodes of respiratory disease diagnosed by sentinel GPs during influenza epidemic periods [85].

## Deaths

Despite the range of pathogens that circulate in the community causing respiratory tract infections each season, influenza and RSV remain the two main causes of respiratory mortality. Therefore, in respect of estimating numbers of deaths resulting from these infections, this work is predominantly concentrated on these two pathogens. It has been estimated that during the 1990s in England and Wales an average of 12 000 deaths (all-cause mortality) were attributable to influenza each winter [84]. However, it is important to remember that these estimates were made using data collected at a time when there were much higher rates of community-based influenza activity than at present: therefore, current estimates would probably be lower. In the USA, Thompson et al. [76] studied age-specific pneumonia and influenza deaths and estimated those attributable to influenza and RSV. Over the winters 1990/91 to 1998/99 there were 8097 and 2707 underlying pneumonia and influenza deaths associated with influenza and RSV, respectively. In the age-specific analysis, 90% of influenza and 78% of RSV-related respiratory and circulatory deaths occurred in the 65+ years age group [76]: a similar study based on mortality data from England provided similar estimates of deaths [85]. These data highlight the severe impact of respiratory infections, in particular influenza and RSV, on the elderly population. We have recently undertaken an analysis of admissions due to ILI and acute bronchitis with respiratory emergency and all deaths against a background of influenza and RSV 'active periods' [80]. Clinical incidence rates of ILI and acute bronchitis both peak during virus active periods; however, it is clear that the greatest impact occurs during periods of RSV activity. In winters where both virus active periods coincide, e.g. 1999/00, this impact is greatest [70]. In the years where there is good separation between periods of virus activity, it is easier to disentangle the associated effects from each virus, and again it is clear that the clinical, admission and death statistics all increase more during periods of RSV activity (Fig. 13). The active period for RSV, as it affects persons over 65 years, is based on a 3-week lag behind RSV reports
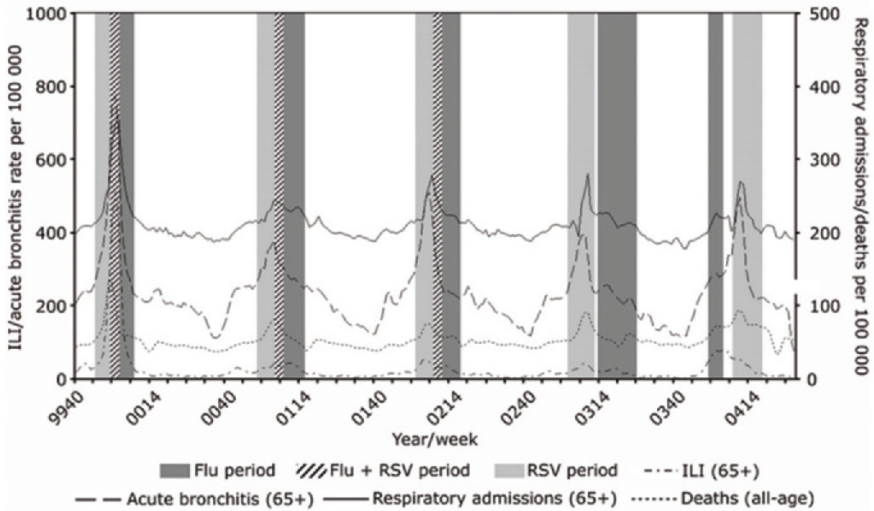
Figure 13. Weekly incidence rate of influenza-like illness (ILI) and acute bronchitis, emergency hospital admissions for respiratory causes and all-cause mortality against influenza and respiratory syncytial virus (RSV) active periods over the period 1999/00–2003/04.

in infants, which in turn is taken from the lag in clinical incidence between acute bronchitis as diagnosed in young children and in adults.

It is important to note that the elderly population is increasing. In England and Wales, the population aged over 65 years has increased from 5.5 million in 1961 to over 8.5 million in 2007, and is projected to increase to over 11 million by 2020 [86]. These population estimates imply that health care services that are particularly pressurised by respiratory infections in the elderly population will come under increasing pressure in the future as this burden increases.

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