Common Cold
ed. by R. Eccles and O. Weber

Epidemiology

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Abstract

The common cold is the result of an upper respiratory tract infection causing an acute syndrome characterised by a combination of non-specific symptoms, including sore throat, cough, fever, rhinorrhoea, malaise, headache, and myalgia. Respiratory viruses, alone or in combination, are the most common cause. The course of illness can be complicated by bacterial agents, causing pharyngitis or sinusitis, but they are a rare cause of cold and flu-like illnesses (CFLIs). Our understanding of CFLI epidemiology has been enhanced by molecular detection methods, particularly polymerase chain reaction (PCR) testing. PCR has not only improved detection of previously known viruses, but within the last decade has resulted in the detection of many divergent novel respiratory virus species. Human rhinovirus (HRV) infections cause nearly all CFLIs and they can be responsible for asthma and chronic obstructive pulmonary disease exacerbations. HRVs are co-detected with other respiratory viruses in statistically significant patterns, with HRVs occurring in the lowest proportion of co-detections, compared to most other respiratory viruses. Some recently identified rhinoviruses may populate an entirely new putative HRV species; HRV C. Further work is required to confirm a causal role for these newly identified viruses in CFLIs. The burden of illness associated with CFLIs is poorly documented, but where data are available, the impact of CFLIs is considerable. Individual infections, although they do not commonly result in more severe respiratory tract illness, are associated with substantial direct and indirect resource use. The product of frequency and burden for CFLIs is likely to be greater in magnitude than for any other respiratory syndrome, but further work is required to document this. Our understanding of the viral causes of CLFIs, although incomplete, has improved in recent years. Documenting burden is also an important step in progress towards improved control and management of these illnesses.

Introduction

The common cold is the result of an upper respiratory tract infection (URTI) resulting in an acute syndrome best described as cold and flu-like illness (CFLI). It is characterised by a combination of non-specific symptoms, including sore throat, cough, fever, rhinorrhoea, malaise, headache

and myalgia. It is usually due to infection by one or more of many viruses detected in the respiratory tract [1]. Bacterial commensals or those causing pharyngitis or sinusitis may complicate clinical CFLI diagnoses due to an overlap in detection or symptoms but overall, bacteria are rare causes of CFLI [2, 3] and are not reviewed here.

In 2001, the first of many divergent novel respiratory virus species were described for the first time with the aid of polymerase chain reaction (PCR)-based molecular techniques. Discovery of human metapneumovirus (HMPV) [4] was followed by other newly identified viruses (NIVs) including the human coronaviruses (HCoVs) NL63 [5] and HKU1 [6], human bocavirus (HBoV) [7] and many new human rhinovirus (HRV) strains [8, 9] populating an entirely new putative HRV species; HRV C [10, 11]. Some NIVs are yet to be clearly associated with specific clinical syndromes, but all have been detected in patients with CFLIs [12]. Because there have been no case-controlled studies of the common cold for some time, it is unclear what the combined impact of molecular diagnostic testing for respiratory viruses and the increasing number of NIVs will be for our understanding of the syndrome, but it is likely to be significant.

In this chapter we review the epidemiology of the common cold. This includes several aspects of the incidence and disease distribution of the common cold by discussing which, when and how the viral causative agents are detected, focussing on the HRVs. We briefly examine causal association of some complications following CFLIs which include asthma [13] and chronic obstructive pulmonary disease (COPD) [14] and describe the impact and cost of CFLIs.

Epidemiology of viral causes of CFLIs

The viruses consistently causing most CFLIs are HRVs [15] comprising 50–80% [3, 16] of relevant symptomatic respiratory illnesses. However, the human influenza viruses (IFVs; IFAV, IFBV and IFCV), the human parainfluenza viruses (HPIVs, 1–4), the HCoVs, 229E and OC43, human respiratory syncytial virus (HRSV), human adenoviruses (HAdV) and human enteroviruses (HEV) [17] have also been associated with 8–15% of CFLIs [18–20], despite some being traditionally considered more ‘serious’ causes of respiratory syndromes, including acute lower respiratory tract illnesses (LRTIs).

Factors affecting the circulation patterns and clinical impact of respiratory viruses

The reported peak activity and rate of different viral infections associated with CFLIs varies with the manner in which illnesses are defined, recorded,

documented aetiologically, and tracked longitudinally [21]. However, historical detection rate data do not comprehensively represent HRV circulation patterns because sequential infections by different strains occur and may appear as unbroken symptomatic episodes during a single observation period [22, 23]; an occurrence which is rarely examined. In other instances, multiple HRV strains can be isolated [24, 25] or detected [26–28] from a single specimen, indicating a capacity for HRV co-infection which is similarly overlooked.

Studies seeking to explain epidemics of the colloquially termed 'respiratory viruses' often attribute them to the season [29]. Commonly, the circulation pattern for each virus that can recur annually is dominated by a different strain or species, which changes each year depending on the nature of pre-existing immunity within that location's population. When we documented the seasonal characteristics of HMPV detections over 4 years, we found that among over 700 HMPV-positive specimens, the four genetically defined HMPV subtypes exchanged dominance each year and detection frequencies cycled up to, or down from, their peak at other times [30, 31]. Herd immunity contributes to controlling epidemics of viruses, especially those which elicit strong and long-lasting immune responses in their hosts. The age of a population is therefore a significant factor in the epidemiology of respiratory viruses. In general terms, adults suffer fewest severe outcomes from respiratory virus infection and children most. In the very young a portion of the pathology of severe illness can be attributed to the small and developing airways. Individual immunity is accrued over time for the adults but is relatively weak among neonates and young children since it is during the early years of life that this response is developed by repeated exposure to infection. A relative increase in the prevalence of symptomatic illnesses is also seen among the elderly, often attributed to the waning of immunity with age.

For some respiratory viruses, including IFV and HRSV, a strict pattern of peak activity occurring with colder or wetter weather is common [33–35]. Exceptions can occur during which higher temperatures and greater daily temperature fluctuations parallel the respiratory virus epidemic period [34]. Some of these epidemic peaks can be seen in Figure 1 exemplified by HRSV, HMPV and IFAV detected in a paediatric hospital-based population during 2003. The defined peaks usually recur at a similar time each year, whereas HEVs and HAdVs are more consistently present and the HRVs, apart from dominating the overall number of detections in this population, often peak in spring and autumn. HRSV activity also correlates with complex interactions of latitude, temperature, humidity and UVB radiance [29]. Apart from weather conditions, cohorting of populations can also occur during return from long school or university holidays, which is a particularly common trigger for HRV epidemics in the young [36–39]. The accompanying increased risk of transmission due to aerosols in close quarters and shared contact with contaminated surfaces are implicated as the cause of

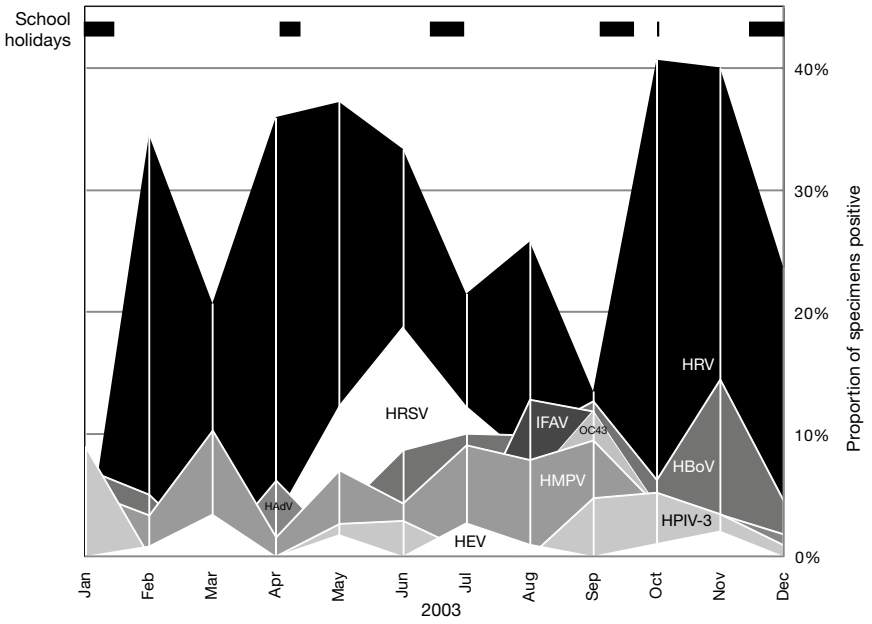

Figure 1. Virus detections plotted by month for 2003. The virus detected is indicated, as are school holidays in Queensland, Australia, during the year of the study at this location. Data were derived from a paediatric hospital-based, in- and outpatient population [8, 32].

rapid increases in the numbers of symptomatic illnesses. Susceptibility to CFLIs may also be directly influenced by weather conditions affecting the respiratory epithelium [40].

HRV detections occur throughout the year but are usually seen to peak in spring and autumn [41–48] depending on the method of detection, the length of the study period and the type of population investigated [22, 49]. One study indicated that HRVs of any given strain might be sporadically detected ahead of an epidemic, providing warning of the impending widespread activity by that strain [50]. Few studies examine whether every strain recurs each year at a single location or whether herd immunity protects against reinfection by a previous epidemic strain, and if so, how long such an effect might last. In Brisbane (Queensland, Australia) during 2003, HRV B strains circulated during winter and HRV C strains predominantly circulated during spring [8]. In contrast, the HRV As occurred in all seasons.

The role of common cold viruses in potentiating bacterial infections

It has long been known that bacterial adherence is enhanced by preceding infection of a respiratory virus [51], particularly HRSV and IFAV [51]. Such

studies began after the influenza pandemic of 1918 [52] during which death due to secondary bacterial infection was a significant contributor to total morbidity. Since then, prior infection by IFAV and HRV has been shown to increase the number of staphylococci, streptococci and pneumococci adhering to a pharyngeal cell line, while measles virus decreased adherence and HAdV had no effect [53]. Possible mechanisms, identified using animal studies, include IFV neuraminidase-mediated removal of sialic acid moieties permitting bacteria access to otherwise hidden receptor molecules [52, 54] on the cell surface, and expression of haemagglutinin which enhances group A streptococcal binding [55]. HRV-14 infection can also increase subsequent bacterial adherence by up-regulating streptococcal receptor expression on human tracheal cells, partly mediated by transcription factor activation after HRV infection [56]. Both infectious HRV-16 and HRV-2 reduced the capacity of human alveolar macrophages to respond to lipopolysaccharide and lipoteichoic acids *in vitro* [57], which may, *in vivo*, permit worsening of an HRV infection *via* concomitant bacterial superinfection. In children, but not adults, peak HRSV activity was significantly and positively correlated with peak *Streptococcus pneumoniae*-mediated pneumococcal disease activity in Australia and New Zealand [58, 59]. In the Netherlands, both children and adults were found to have higher rates of pneumococcal and meningococcal disease during peak IFV and HRSV seasons [35]. Vaccination to prevent pneumococcal disease successfully prevented nearly one third of cases of pneumonia associated with the major respiratory viruses [60], presumably by preventing bacterial super infections.

Methods of detecting viruses in CFLIs

Robust detection methods that are kept up-to-date have been of paramount importance to our evolving understanding of the epidemiology of the CFLIs. Co-culture of patient secretions with "permissive" cells lines has been the longest serving method of detection but it is now well known for being insensitive [48, 61, 62]. Examples of previously unknown respiratory viruses believed to be endemic rather than recently emerged are being reported with increasing frequency. For the HRVs this was exemplified by the molecular identification of a large number of highly divergent, and at writing, unculturable HRV C strains [8, 10, 11, 32]. Insensitive and inefficient testing of the HRV super-group is to be blamed for delaying characterisation of the rhinoviruses, thus leading to a significant underestimation of the total number and nature of strains, which has been undeniably detrimental for all previous epidemiology studies of CFLI. With the introduction of nucleic acid testing and improvements to PCR product detection methods, a quantum leap in respiratory virus detection frequencies has been achieved. Even so, no single assay has been shown to robustly detect all HRVs and no panel of assays has achieved 100% laboratory diagnoses. Time to specimen

delivery was once thought to be a cause for reduced aetiologies but even the use of PCR, not requiring infectious pathogens, still misses a large proportion of suspected infections [63].

Cell culture methods

Cell culture techniques are limited by poor sensitivity due to slow growth or poorly cytopathic viruses, reduced viability due to poor specimen handling, narrow detection windows, complex result interpretation requiring high levels of operator expertise, host immunosuppression, antimicrobial therapies, high levels of background signal and non-specific cross-reactions [64, 65]. Nonetheless, both microbial culture and rapid immunofluorescence assays can be used to produce valuable epidemiological data, reveal new, uncharacterised or atypical microbes and yield intact or infectious organisms for further study [66].

Viruses have been isolated in cell cultures since the 1950s but diagnostic services were limited for a further two decades [67]. Microscopic examination of degenerative changes brought about by virus replication (cytopathic effects), a sometimes slow and always technically demanding skill, was later augmented by haemadsorption tests to identify the extent of haemagglutinating protein expression, which indicates the replication of certain respiratory viruses. Subsequently, shell vial methods were employed, which, when used with specific antibodies, identified viral antigens in 1–2 days compared to 2–10 days for haemagglutination methods [68]. In 1953 Andrewes and colleagues at the Common Cold Unit (Salisbury, UK) described the first isolation of an HRV strain [69, 70]. Later, improved culture systems permitted viral replication to be more easily identified and maintained [71, 72]. Nonetheless, even using cell-culture conditions normally favouring the appearance of cytopathicity, instances of non-cytopathic HRV strains have been found by other methods [73], which may have included HRV C-like viruses.

Because the respiratory tract is a cellularly diverse environment and because a wide variety of viruses with diverse tropism cause CFLIs, cell culture methods require the use of a broad range of cell types. For methods to be useful, they must encompass virus concentrations ranging from 10^1 to 10^5 $TCID_{50}$/ml [74–77]. Additionally, successful isolation and higher viral yields require monitoring of cell age after plating (< 72 h), inoculum volume, culture medium pH (6.8–7.3) and cell density [78–81]. Therefore, culture can be expensive, not just for the labour required to inoculate, maintain under sometimes fastidious conditions [70, 80, 82–84] and monitor the cultures, but also to ensure that the diverse range of cell stocks and culture media are available and fresh. Even with these criteria met, HRVs and most of the respiratory NIVs have proven to be very poor targets for isolation methods based on cell culture [67]. Despite the challenges [85], virus isolation is

reportedly a more sensitive indicator of infection than an antibody rise in paired sera [86].

Antibody-based methods

To date, antibody-based methods have proven the most diversely commercialised and robust diagnostic format either for the indirect detection of a host response to a respiratory virus, or the direct detection of viral antigen in culture or from infected cells present in specimens, such as nasopharyngeal aspirates or bronchoalveolar lavage. Antibody-based results augment both general diagnostic molecular data and those data provided by research studies aiming at better characterising respiratory viruses. Apart from speed, cost-benefit and familiarity, an obvious advantage derived from use of a protein-based system is the existence of conserved antigenic regions among related viruses; regions that do not vary significantly among strains of the same species or other relevant taxonomic grouping. Such conservation is infrequently reflected at the nucleotide level making these regions troublesome targets for nucleic acid-based systems but ideal for antibodies. Unfortunately, antigenic conservation can also be manifested as cross-reaction; difficulty discriminating between infections caused by closely related viruses. Such discrimination is important when searching for the role of each individual respiratory virus in illness [87].

Antigen detection methods may be performed with or without a biological amplification step such as *in vitro* cell culture. If culture is not being employed, then it is necessary to collect cellular specimens since the cells confine virions to a small, easily identified space that aids/allows immunofluorescent detection; but such cellular specimens are not always available. Rapid respiratory virus antigen detection is relatively insensitive and, depending on the clinical priorities for the particular virus, negative results may need to be confirmed using another assay, which largely abrogates the benefits of speed [88, 89]. Furthermore, antibody-based methods have not kept up with the recent flurry of NIVs and so reliable diagnostic reagents are not available for the latest viral discoveries [67].

Seroclassification or 'serotyping' of an HRV infection was once the gold standard for strain identification of the 'common cold viruses' but serotyping became impractical as the number of distinct strains grew beyond convenience [79, 90]. Antibodies are essential for strain-specific neutralisation of infection [91], techniques around which the HRV nomenclature system evolved in 1967 [92]. These determine whether co-incubation of a characterised antibody with a preparation of an unknown virus can preclude its cellular entry and replication. If successful, the antibody chosen confers some degree of identification upon the unknown virus. Such techniques have found that a large number of distinct strains circulate each year and that a selection of them predominate in a given season, replaced by others in

subsequent years [70, 93]. Today, PCR-based sequencing methods can do the same job at the genetic level with increased objectivity and speed compared to the complex and lengthy neutralisation methods [94, 95].

Polymerase chain reaction

The improved sensitivity of PCR-based assays dramatically increased the frequency of viral detection compared to cultivation methods [96], which has meant that many previous studies are incomparable to today's findings. This improvement is especially noticeable for the HRVs [3, 26, 42, 97–99] but also for other viruses that are fastidious or, to date, impossible, to culture. Because of PCR it is becoming commonplace to find reports of HRVs predominating in CFLIs [100–102], despite the incomplete validation of published assays against all picornavirus (HRV and HEV) strains using clinical material. Nonetheless, many assays successfully detect the currently circulating HRV strains at levels as low as 10^2 $TCID_{50}$/sample. This amount is commonly shed during experimental infections [103, 104]. Because HRV strains are now being detected beyond their traditionally understood symptomatic context of the CFLI syndrome [16, 105], it is becoming more important to define a qualitative and quantitative correlation between HRV nucleic acid detection and the presence of infectious virus at the sampling site. Unfortunately, the latter is problematic when using PCR to study respiratory viruses because of the inability to normalise the amount of starting RNA template [106].

Improved detection by PCR compared with traditional methods means that less invasive specimen types can be used for research, and in most circumstances, diagnostic testing. For example, prior to PCR, there were problems with the sensitivity of RSV detection using less-invasive specimen types. Using antigen detection, a reduction in positives by approximately one-third was seen when nasal swabs were used, compared with nasopharyngeal aspirates [107, 108]. Use of PCR has largely overcome this issue [109], to the point where less-invasive specimen types can be easily collected by lay people in community settings for research purposes [47, 110], or used instead of invasive techniques in clinic or outpatient settings [109].

When they are included in the PCR testing menu, HRVs raise the frequency of pathogen detection above one per sample [111]. Studies find that HRV strains are very frequent contributors to co-infections [112] and co-detections [113], sometimes presenting this in terms of their minor contributing role in serious respiratory disease [112, 113]. More likely this reflects the insensitivity of old cell culture-based methods that simply failed to propagate many HRV strains and in the process created paradigms for the HRVs that reduced their profile for further study. In one study, half of all HRV detections were found concurrently with another virus, on the surface, a significant fraction, and yet 80% or more of HRSV, HMPV, HEV

and IFV detections and 71% of HCoV-NL63 detections were found in the company of another virus [114].

The use of a multiplex real-time PCR (m-rtPCR) or a suite of individual rtPCR assays [113] that encompass the majority of regularly detected viral targets is being steadily embraced by diagnostic laboratories that receive respiratory secretions and a number of these panels include a capacity to detect HRVs [115]. Multiplexing PCRs increases result throughput and reduces costs associated with labour and time but also requires significant research and developmental time and may still perform at a reduced clinical sensitivity compared to individual assays.

Innovative, but less well evaluated, multitarget molecular laboratory tools now exist including the MultiCode-PLx system, which employs a synthetic nucleobase pair, multiplex PCR and microsphere flow cytometry [116]. It permits the discrete detection of 17 respiratory viral targets and two assay controls, although it returns an unusually low HRV detection rate. Similar technology also provides a sensitive, 20-target, 2-step RT-PCR-based assay [117]. The Seeplex® respiratory virus detection kit targets 12 respiratory viruses [118] using dual priming oligonucleotides [119] and detecting the amplicon by capillary electrophoresis (Seegene Inc.). It has compared favourably to culture-based testing [120]. The ResPlex II assay (Qiagen) employs a proprietary multiplex RT-nPCR [121] approach followed by amplicon detection using a Luminex suspension array to identify 12 targets [122, 123]. The xTAG™ respiratory viral panel combines PCR and the Luminex array system and detects more than 20 different targets including controls (Luminex Corporation). PCR amplicon detection by MassTag technology can discriminate 20–30 viral and bacterial agents of illness [124] using oligonucleotides tagged with a unique compound that is released *via* a photolabile link (Qiagen). The MassTag approach has been able to detect HRV C strains [9, 26, 125]. Microarrays can detect thousands of viral targets (US$ 30–300 per sample) but still require a pre-hybridisation PCR amplification because of their insufficient sensitivity to directly detect viral nucleic acids from clinical specimens. Arrays are still low-throughput, high-turnaround time diagnostic options. At their most robust, microarrays, like PCR, rely on the existence of conserved regions of sequence to detect unknown viruses and they too can detect previously unknown HRV strains [126], although nothing vastly different from what is already known. Rapid protein- or virion-based assays are not (yet) adequately sensitive [127, 128].

PCR does have some downsides, some of which have been mentioned already. Detection of microbial genomic nucleic acids cannot yield the same information about infectivity as cell culture, but there have been good correlations reported between infectivity and viral genome detection for yellow fever virus [129] and in a comprehensive birth cohort study characterising frequent respiratory infections in which PCR data were found to correlate very well with symptomatic respiratory illness [130]. Despite the ‘closed’

nature of the modern generation of rtPCR techniques, they are PCR-based and as such still subject to contamination by amplicon from previous runs and template from extraction areas or infected technologists. Efficient PCR relies entirely on conserved sequence targets and thus an extensive foreknowledge of each virus is being sought. If the region targeted by oligonucleotides is subject to genetic variation, PCR will continue the diagnostic trend towards underestimating viruses in CFLIs. Even for conserved targets, PCR primer pair designs that yield a single specific amplicon from clinical specimen extracts can be extremely difficult to achieve when faced with the highly variable cellular and microbial content of respiratory tract specimens and the sequence similarities between viruses and humans for some targets. Non-specificity can render quantification methods useless [131] as can the absence of suitable housekeeping gene targets to permit normalisation of viral nucleic acid input. Because the success of PCR has led to an increase in the number of virus detections and a reduction in the number of virions required for a positive result, positive PCR methods are sometimes greeted with scepticism due to them being perceived as too sensitive. Such concerns must be addressed by careful epidemiology.

Questions raised by the co-detection of viruses among CFLIs

When thorough screening is conducted for all relevant viruses in each specimen, multiple virus detections are a frequent result. In particular, this has been the case since the more widespread adoption of PCR as the diagnostic method of choice because it is significantly more sensitive than the traditional methods of culture and direct or indirect fluorescent antibody assays. PCR is also better than other diagnostic methods at rapidly and specifically discriminating multiple targets representing different viral genes or strains, fuelling an increasing number of reports of microbial co-detections in 20% or more of specimens [114, 132–137]. For viral co-detections that include HRSV, interferon gamma (IFN-γ) levels are reduced [100]. This suggests a mechanism of immune intervention that creates a beachhead in the host's innate immune response, which subsequently permits additional viruses to gain a foothold, thereby increasing the frequency of co-detections. Although a description of all of a patient's viruses is necessary before the significance of co-detections can be determined, it does complicate the interpretation of results and the traditional assignation of a "causal" virus. Historically, to save labour and costs, causality has been associated with a "first-past-the-post" approach in which the initial virus to be detected is assigned the causal role [122]. Many laboratories have yet to completely adopt PCR, and so the occurrence of co-detections is not globally acknowledged, further complicating their impact compared to single detections.

What the detection of more than one virus, as well as the particular mix of viruses involved, means to the clinical outcome is controversial, with

studies describing illness severity that is worsened [138–140] or unchanged [137, 141] by multiple detections. Among infants hospitalised with bronchiolitis, there was a 2.7-fold increased likelihood of infants with viral co-detections being admitted to a paediatric intensive care unit than those with single detections [114]. Considering their ubiquity, it is interesting that relatively low numbers of concurrent detections of other respiratory viruses occur with HRV strains [47, 142]. In fact, HRV strains are co-detected with other pathogens in reproducible, but clinically undefined, patterns [111]. Nonetheless, there is an increasing number of single HRV detections being made from patients with significant LRTIs and with acute otitis media [143]: it is becoming clearer that the HRV infection process can directly cause illness and that HRVs are not merely passengers in the clinical outcome of the infection [44].

The increasing proportion of viruses found in the company of other viruses, and also with bacteria, raises some interesting questions. Is it possible that a certain number, or certain mix, of viruses, or both, is necessary to tip the host into a state of symptomatic illness? This question may be especially relevant for viruses traditionally thought of as causing more mild respiratory illness, such as the HAdVs and perhaps HBoV. It is noteworthy that the proportion of asymptomatic episodes decreases with the number of micro-organisms detected and increases with age in children [138]. If not the nature then perhaps it is the order of infection that is important as has been suggested for some viral and bacterial pairings. This is poorly addressed by examining data from the clinical microbiology laboratory since such testing is only a cross-sectional snapshot of the host's condition. To address this question accurately, carefully planned, longitudinal cohort studies are required. In a study of 27 children during the first year of life who contracted five or more moderate-to-severe respiratory illnesses, it was apparent that the same viral species or strain did not usually recur during a 12-month period [130]. Another question is whether infection by one virus or bacterium predisposes the host to infection by one or more others.

The proportion of asymptomatic PCR positives is virus specific and occurs in more than a third of children during a CFLI season [144]. A particularly confounding and relevant issue for viral epidemiology is that raised by the criteria used to define an illness in some studies. Some criteria are so stringent that they may miss mild, but nonetheless common and virally induced CFLI symptoms such as headaches [144]. Such omissions are likely to contribute to the number of 'asymptomatic' cases reported by some investigations [114] and to the severity scores used for studies linking single and multiple detections to clinical outcome. It might be simple coincidence that two or more viruses can be detected in the same specimen, reflecting an overlap of their seasonal peaks [114] when it is more likely that hosts will come into contact with more than one virus in the community. However, we believe this is not the case for two reasons. We have not seen a

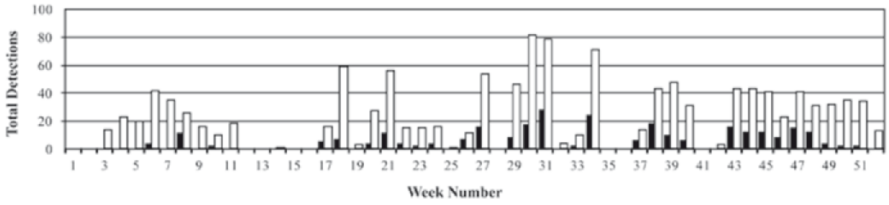

Figure 2. The total number of virus detections (open bars) and co-detections (filled bars) during each week of 2003. Viruses tested included, HRSV, HMPV, IFAV, IFBV, HAdV, HBoV, HPIVs, non-SARS HCoVs and respiratory picornaviruses. Data are derived from [8] and [32].

seasonal trend towards more co-detections in certain seasons (Fig. 2) but we have seen patterns that indicate virus-specific factors drive the association between co-detected viruses.

When we statistically analysed co-detections from earlier studies of HRV-QPM [32], which also included screening for traditional respiratory viruses and NIVs, we identified that patterns existed that particularly involved the association of certain viruses. Specifically, HRVs were the virus or virus group with the lowest statistically significant proportion of co-detections. We believe that this may be an example of a strong HRV interference effect. Others have shown that epidemics of HRSV may be interrupted or apparently staved off by an epidemic of IFV [33, 145]. A possible mechanism for the separation often seen between an epidemic peak due to one virus and that from another could be competition between different viruses for replication in the same host cells or tissues or for use of the same, or very similar, receptor molecules required for infection. Interference may also be due to the nature of the immune response elicited by the infected host in response to infection by the first virus [73, 146]. Seasonal variation in the prevalence of any virus may be influenced by interference, whereby the peak prevalence of one respiratory virus impedes or prevents the processes that let other viruses establish themselves at the same time, in the same host population [145].

Despite extensive investigation of respiratory specimens taken from patients requiring hospitalisation, oxygen therapy and/or drug treatment, we noted the retention of a large proportion (34%) of specimens from which no virus could be detected [8]. Other studies have found similar frequencies of negative specimens and such findings indicate the likely existence of yet-to-be characterised viral causes of respiratory illness. Extrapolating from all the known respiratory viruses and recent research findings, it is reasonable to assume that any new agents of respiratory disease will be associated with CFLIs as well as possibly more severe disease in some populations and also both as sole agents and in the company of other viruses and bacteria.

Associations between acute virus infections and chronic respiratory disease

CFLI is linked with a number of more serious clinical conditions that may require hospitalisation, invasive testing procedures and the use of drugs and other supportive measures. An URTI may develop into a LRTI or it may acutely exacerbate pre-existing chronic conditions including asthma and COPD. Such exacerbations mask CFLI epidemiology by favouring the clinical diagnosis of the LRTI. Acute LRTIs contribute to more morbidity and mortality than HIV infection, malaria, cancer or heart attack [147] worldwide. Because of equivalent isolation frequencies from well and ill children, the presence of potential bacterial pathogens cannot reliably be correlated with LRT symptoms [145].

As we stated earlier in the chapter, many respiratory viruses that are associated with serious disease are also associated with milder common cold-like illnesses; the converse is also true. Viruses, especially the HRVs, that were previously deemed to be capable of causing only mild illness [138] are now being frequently associated with costly and distressing illnesses and CFLI complications. In particular, respiratory viruses often cause more severe LRT symptoms in neonates and infants, because of airway swelling, excessive secretions and smooth muscle contraction in their narrow immature airways resulting from infection [148].

The importance of HRV infection associated with LRT morbidity during the first year of life is both significant [13] and underappreciated [149]. HRVs replicate in non-nasal tissues including smooth muscle [150] and bronchial epithelial cells [151, 152]. In addition, the immunopathological effect of viral replication in the upper airways may be transmitted systemically [148]. If HRVs naturally replicate in the LRT, as has been reported [83], then a local host inflammatory effect is a likely pathogenic mechanism.

In one example, a German birth cohort study found a positive association between repeated LRTI (pneumonia, bronchitis, pertussis, tracheobronchitis, 'flu', croup and bronchitis) before the age of 3 and wheeze at the age of 7 [13]. Nonetheless, the impact of LRTIs on immune development and the contribution of genetic predisposition to LRTIs remain unclear [14, 153, 154]. This study also found a significant inverse relationship between recurrent "runny nose" episodes and subsequent atopic sensitisation, and these repeated infections imparted most of their protective effect during the first year of life [13]. A study of infants found that a sixth of HRV isolate-positive patients exhibited symptoms of LRTIs (mostly wheezing) [155]. In adults ≥40 years of age, the duration of symptoms and frequency of LRTIs associated with HRV isolation starts to increase with age [156].

Although HRVs have been associated with threefold more LRT and wheezy LRT illnesses than HRSV [149], the risk of obstructive airway disease is similar whether an HRV or HRV and HRSV are detected [100].

Studies of children in hospital-based populations usually report more significant clinical outcomes, especially those relating to the LRT [157]. These data can be considered a condensed sampling of illness among community-based populations but conclusions should be interpreted cautiously. LRT illness has also been identified in other age and patient groups [74, 91, 99, 100, 155, 158–161]; nonetheless, hospital-based populations retain importance for probing the potential of a virus to cause severe clinical outcomes, especially due to a first infection. This environment provides cases with the strongest influence on future prioritisation of therapeutic developments [145].

HRVs and expiratory wheezing exacerbations

Acute wheezing episodes (including bronchiolitis and acute asthma, which share similar pathologies) are a common epidemic and seasonal LRT manifestation of respiratory virus infection of the URT and LRT of children from all ages, but especially among males and during the first year of life [145, 158, 162, 163]. The mechanisms underlying the induction or exacerbation of asthma are not yet fully understood [148, 164] but wheezing is blamed for excessive use of antibiotics, for being the primary cause of hospitalisation among children and, rarely, for death [48, 165, 166]. Exacerbations of asthma and COPD are often preceded by a symptomatic rather than asymptomatic HRV episode [166–171], although, in some instances, an exacerbation is the only evidence of symptoms [172]. Reduced peak expiratory volume in children is especially associated with detection of respiratory picornaviruses [170].

Traditionally, it is HRSV infection that is causally associated with expiratory wheezing because of the virus's well-known ability to infect the LRT, but periods of epidemic wheezing unaccompanied by high rates of HRSV detection are common [163, 173]. The Childhood Origins of Asthma Study (COAST) used sampling criteria that were designed to intentionally investigate the role of HRSV in illness, but instead of HRSV, the data indicated that HRVs were the most important predictor of subsequent wheezing in early childhood [174, 175]. Although the total number of symptomatic respiratory illnesses did not differ significantly, asthmatics had more HRV infections, while their siblings had more bacterial infections. Since asthmatics are more often treated with antibiotics, bacterial detection rates may be falsely lowered in some reports [176]. Significantly higher rates of HRV detection with more obvious LRT symptoms are more common in asthmatic children than in non-asthmatic populations [166, 176–178]. History of asthma in children also appears to be a risk factor for more frequent symptomatic viral infections. However, the presence of atopy or allergy does not appear to be a common feature [162, 166] since only a small proportion of allergic children have asthma [179].

Impact and cost of the common cold

For any illness or syndrome, mapping the epidemiology and burden of disease is needed for a number of reasons, but key amongst them is prioritising the need for prevention, treatment, and further research efforts. There are three pieces of evidence required by those developing health policies in assessing whether to recommend or implement a publicly funded prevention or treatment program: epidemiology of the targeted illness, the efficacy of the intervention, and the cost effectiveness of the intervention [180]. Evaluations of cost effectiveness consist of a number of key components, including how common the illness is, the cost associated with illness, and the cost of any intervention, either prevention or treatment [181]. Given the ubiquitous nature of the common cold syndrome, there has been little attention paid to documenting impact. This is a feature colds have in common with the less frequent, but more severe end of the respiratory infection spectrum. Based on estimates from the Global Burden of Disease study, acute respiratory diseases, despite being one of the largest contributors to disability-adjusted life-years (DALYs), receive a discouragingly low proportion of health-related research funds [182].

The value used in cost-effectiveness evaluations is a product of counts of illness and impact of individual illness, often presented as DALYs [181]. Even though CFLIs have lower severity compared with complicated URTIs and LRTIs, due to the frequency their burden cannot be ignored. Acute respiratory infection incidence is highest in the first 2 years of life, with up to 13 episodes per year, and it is not uncommon to average close to one infection per child-month [130, 183]. Whereas illnesses can often be managed in the community with supportive care from parents, complications requiring a medical visit in which antibiotic therapy is prescribed, such as otitis media (30%) and sinusitis (8%), are common [184]. In pre-school aged children, nearly 50% of general practitioner visits are for acute respiratory infections [185], many of which will only involve self-limiting URT symptoms.

The availability of preventive vaccines and therapeutic antivirals means that interpandemic influenza is the most studied of respiratory viruses associated with the cold. Estimates around the cost impact of other respiratory viruses are rare – particularly compared to their relative frequency. Some estimates about the cost impact of non-influenza viruses are available from the US. Using a telephone survey of over 4000 households, researchers collected self-reported incidence and resource use during non-influenza, viral respiratory infections [186]. These figures were extrapolated to the US population and costs attached to resource use. The direct costs associated with viral respiratory infections were US$17 billion annually, with these being outweighed by the indirect cost burden of US$22.5 billion. The indirect cost component was made up of missed workdays due to illness, totalling 70 million days, and missed workdays while caring for a household member, totalling 189 million days [186]. The annual cost burden of antibiotic use for

acute respiratory tract illness in the US is over US$1.3 billion alone [187]. This compares with a recent modelling assessment of seasonal influenza suggesting annual costs US$87.1 billion, with 83% of this cost due to annual deaths [188]. Information about HRSV impact is more common than other non-influenza viruses, but pertains mainly to those groups of children who are currently eligible for preventive interventions: those born prematurely with associated lung disease, or with specific congenital cardiopulmonary malformations [189–191]. A US study using three national databases and an assumption that 15% of all acute otitis media was due to HRSV calculated direct medical costs from HRSV to be over US$1.3 billion (2002 dollars) per annum, with 98% of these costs associated with illness in the less than 5-year age group [192].

Although national data are rare, community-level impact is even less commonly measured. Two recent community-level studies have included an assessment of acute respiratory illness in children using a sensitive definition for influenza-like illness [47, 110, 193–195]. The threshold for burden data collection for study children could be met with a combination of two non-specific symptoms, such as nasal stuffiness and decreased activity [47, 194]. Standard costs were applied to burden data to derive a syndrome cost [193] and a virus-specific cost of illness [195]. A mean cost for community-managed illness from each study was AUD$241 from the 2001 pilot study [193], and AUD$309 from the 2003/2004 main study [195] (average exchange rates during study period: United Kingdom pound £1 = AUD$2.49, Euro €1 = AUD$1.73, and US$1 = AUD$1.50) [196]. The main study included an influenza season of higher than normal activity with H3N2 influenza A (drifted strain subtype A/Fujian/411/2002-like) being the predominant circulating type [197].Virus-specific cost of illness for all viruses other than influenza fell within a relatively narrow band, and picornaviruses (not further differentiated) had an mean cost of AUD$267 per illness [195]. A recent UK study looking at the cost impact of individual cough illnesses in children aged 3–59 months, without detailed recording of indirect costs, reported a mean cost per episode to the National Health Service (NHS) of £27, a mean cost for the family of £15, and an annual cost to the NHS £31.5 million [198].

These findings show that, although there are some data on illnesses associated with more serious outcomes and specific viruses, there continues to be little in the way of targeted research at the national or community level documenting the simple burden associated with the common cold. Future community-based studies into the common cold and associated respiratory tract illness, integrating epidemiology and economic methods, are required [199].

Conclusions

The common cold is the syndromic child of many parents. The nature of the child, its epidemiology, severity, and impact, is determined by interaction of host, pathogen, and environmental effects. HRVs are the agents most commonly associated with CFLIs, but other respiratory viruses, including influenza viruses and HRSV, can be associated with the syndrome. The recent expansion in the use of PCR has brought improved detection of known viruses, but also detection of NIVs. Through these means, the diagnostic gap in all respiratory illnesses is reduced. The contribution of HRV Cs in respiratory illness appears to overshadow that of other known RVs; however, it is difficult to judge given the paucity of data from the other species, and further documentation of HRV epidemiology and impact are research priorities for the coming years. Although our knowledge of the causes of CFLIs has improved in past few years, the collation of impact data is some way behind. Documenting burden is an important step in the progress towards improved control and management of these illnesses.

Acknowledgements.

This work was possible because of funding from NH&RMC project grant 455905 and RCHF Project Seeding grant 10281.

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