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Review

Respiratory viral infections in the elderly

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1. Introduction

This is the first in a series of two articles dealing with viral infections of importance to elderly populations. Respiratory viral infections have long been recognized as important contributors to death and disability in older adults. The specific reasons why these infectious agents, which usually cause self-limited disease in healthy young adults, are associated with enhanced disease with aging are not completely known. Analysis of this problem is complicated by the difficulties in separating the effects of age itself from those of the chronic diseases that often accompany aging. However, more limited physiologic reserves with aging and potentially blunted immune responses may play a role.

Influenza virus has traditionally received the greatest attention and remains a significant problem in aging populations, while respiratory syncytial virus and parainfluenza viruses have also been implicated as potential causes of serious illness in some elderly individuals. In this brief review, the disease impact of infections with influenza, respiratory syncytial, and parainfluenza viruses will be reviewed, and approaches to control of these agents will be outlined.

2. Influenza

2.1. Disease impact

Influenza is unique among respiratory viruses in that epidemics are regularly associated with excess morbidity and mortality (Glezen, 1982), manifested as excess rates of pneumonia and influenza associated hospitalization during influenza epidemics (Glezen, 1982; Perrotta et al., 1985). For older individuals, the yearly estimate is 4.1–4.4 million excess respiratory illnesses associated with influenza each year (Sullivan et al., 1993). Recent, non-pandemic influenza seasons have been associated, on average, with 5600 excess pneumonia and influenza deaths and 21 300 all-cause excess

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deaths in the USA (Simonsen et al., 1997). Both influenza A and B can be associated with severe illness (Blaine et al., 1980), although the highest mortality rates are generally seen during years with significant H3 virus activity. Complications and deaths from influenza are of particular concern in those with certain 'high-risk' medical conditions, primarily the elderly and adults and children with cardiovascular and pulmonary conditions (Barker and Mullooly, 1980) The presence of such conditions significantly increases the risk of influenza-related hospitalizations above that associated with age alone (Barker and Mullooly, 1982; Table 1). Although only about one-fourth of hospitalizations for influenza occur in individuals over the age of 65, three-fourths of influenza-related deaths occur in this age group (Perrotta et al., 1985). It is important to recognize that the majority of elderly high-risk individuals who are hospitalized during influenza epidemics were ambulatory and leading productive lives prior to their acute illness (Barker and Mullooly, 1980).

In addition to causing serious illness and deaths, influenza in the elderly results in significant decreases in functional abilities. In recent studies, 10–12% of individuals over 65 admitted to hospital with acute respiratory disease required a higher level of assistance with daily living then they required prior to illness (Gladman et al., 1991; Falsey et al., 1995a). In one nursing home outbreak, 25% of those surviving acute influenza experienced a significant decline in functional status (Barker et al., 1998).

2.2. Treatment and prevention

2.2.1. Current inactivated influenza vaccine

The most effective measure currently available for the control of influenza is the annual administration of inactivated influenza vaccine. The vaccines are well-tolerated and increases in hemagglutination inhibition (HAI) antibody are seen in most young adult recipients (Cate et al., 1983; LaMontagne et al., 1983; Quinnan et al., 1983). Inactivated influenza vaccine has been shown to be effective in the prevention of influenza A in several controlled studies conducted in young adults, with levels of protection of 70–90% when there is a good antigenic match between vaccine and epidemic viruses (Meiklejohn et al., 1978; Meiklejohn, 1983; Ruben, 1987).

Relatively few prospective trials of protective efficacy have been conducted in elderly populations. In one recent randomized placebo-controlled trial, inactivated vaccine was approximately 58% effective in preventing laboratory-documented influenza in an otherwise healthy elderly population (Fig. 1; Govaert et al., 1994). In addition, retrospective case–control studies have documented the effectiveness of inactivated influenza vaccines in the elderly. For example, the study by Barker and Mulooly documented a 72% reduction in hospitalization and 87% reduction in mortality with influenza vaccine in the elderly (Barker and Mullooly, 1980). A recent meta-analysis of cohort observational studies resulted in pooled estimates of effi-

Table 1
Effect of age and high-risk conditions on deaths during influenza epidemics[a]

Age group	HR status	No. of P and I deaths	P and I deaths per 100(000 ± SEM
15–44	No HR	0	0
	1 HR condition	0	0
	(2 HR conditions	0	0
15–64	No HR	1	2 ± 2
	1 HR condition	7	10 ± 13
	(2 HR conditions	4	377 ± 195
(65	No HR	1	9 ± 9
	1 HR condition	14	217 ± 59
	(2 HR conditions	11	306 ± 257

[a] Adapted from Barker and Mullooly (1982).

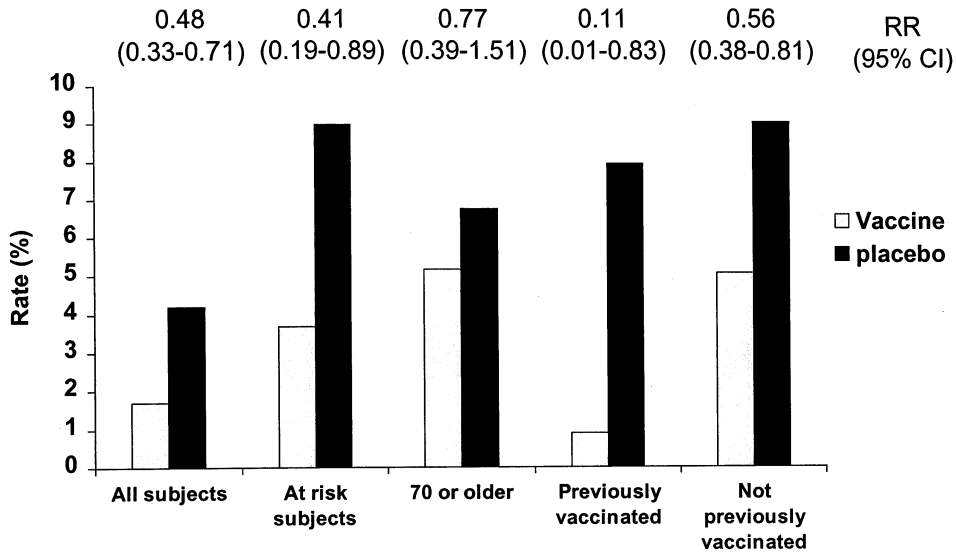

Fig. 1. Rates of serologically documented influenza infection in adults over 60 randomized to receive inactivated influenza vaccine or placebo (data from Govaert et al., 1994).

cacy of vaccine of 56% for prevention of influenza-related respiratory illness, 53% for prevention of pneumonia, 50% for prevention of hospitalization, and 68% for prevention of death (Gross et al., 1995). Vaccination was 43–65% effective in preventing pneumonia and influenza-related hospital deaths, and 27–30% effective in preventing deaths from all causes during influenza outbreak periods in non-institutionalized persons 45 and older in Manitoba (Fedson et al., 1993). It has been estimated that among elderly persons living in the community, influenza vaccination is associated with a direct savings of $117 per year per person vaccinated (Nichol et al., 1994).

However, the protective efficacy of vaccination appears to be lower in individuals over age 65 than it is in younger adults. The explanation for this decreased efficacy in the elderly is not completely clear, but is at least in part related to decreased antibody responsiveness to influenza vaccine in this age group (Quinnan et al., 1983; Coles et al., 1992; Nicholson et al., 1992; Powers and Belshe, 1993; Remarque et al., 1993; Treanor et al., 1994). For example, the antibody responses to inactivated influenza vaccine in two groups of elderly subjects, individuals living independently at home, and residents of chronic care facilities are compared with the responses of healthy adults in Table 2 (unpublished studies). In addition, the levels of antibody associated needed for protection against influenza illness in the elderly may be higher than the 1:40 titer traditionally associated with protection in young adults (Bennett et al., 1994; Betts et al., 1993).

Not all studies have shown diminished responses to influenza vaccination in the elderly, with the affect of the specific antigen occasionally outweighing the effect of age (Glathe et al., 1993). The effect of age may be primarily in effecting the subclass of HA-specific IgG produced (Powers, 1994), consistent with an affect of aging on numbers of naive T cells. In some studies, the presence of chronic disability, rather than age of the subject, appears better able to predict lack of responsiveness (Gross et al., 1989). Malnutrition has been identified as a common problem in the disabled elderly, but does not appear to contribute to the reduced response to vaccination in most people (Pozzetto et al., 1993).

2.2.2. Vaccine development

Efforts to improve the performance of influenza vaccine in the elderly have been focused on three basic areas, improvement in the level and dura-

Table 2
Immunogenicity of inactivated influenza vaccine

Group (*n*)	Mean age (years)	Serum HI antibody responses to the following antigens								
		H1N1 responses			H3N2 responses			B responses		
		Log 2 HI ± SD		% Responding	Log 2 HI ± SD		% Responding	Log 2 HI ± SD		% Responding
		Pre	Post		Pre	Post		Pre	Post	
Healthy adults (52)	34	5.1 ± 2.0	6.7 ± 1.7	50	4.9 ± 1.5	6.7 ± 1.7	48	5.9 ± 1.6	7.9 ± 1.8	54
Healthy elderly (52)	75	4.2 ± 1.3	5.3 ± 1.8	25	4.0 ± 1.3	4.8 ± 1.6	25	5.9 ± 1.4	6.9 ± 1.6	23
Nursing home elderly (46)	85	4.5 ± 1.3	5.5 ± 1.8	33	4.2 ± 1.5	5.3 ± 2.0	32	5.3 ± 1.8	6.3 ± 2.0	26

tion of systemic immune responses to vaccine, improvement in mucosal immune responses, and addition of cellular immune responses to the spectrum of potentially protective responses induced by vaccination. However, two features of the current inactivated vaccines are important to keep in mind while considering new approaches to influenza prevention in any population. First, the current vaccine is very well-tolerated, and any significant increase in local or systemic side-effects over that seen with current vaccine would likely be accepted poorly. Second, the current vaccine is relatively inexpensive, and improvements in efficacy might support only a modest increase in cost.

2.2.2.1. High dose vaccine. Current vaccines are administered at a standard dose of 15 μg of HA per antigen. Recently, improved purification techniques have allowed exploration of much higher doses of vaccine. Administration of 405 μg of highly purified monovalent H1 antigen to healthy young adults, or of trivalent vaccine containing 135 μg of each antigen was well-tolerated and produced 2- to 4-fold higher geometric mean serum HAI and neutralizing antibody titers 4 weeks after vaccination, compared with standard doses (Keitel et al., 1994). Improved nasal secretion antibody responses with high dose vaccines were also seen (Keitel et al., 1994).

Studies of high dose vaccines in elderly subjects have generally demonstrated a less robust dose–response curve than seen in young adults (Gross et al., 1988a; Palache et al., 1993). Evaluation of high dose recombinant HA expressed in baculovirus reached similar conclusions. A dose of 135 μg of an H3 HA resulted in significantly increased post-immunization antibody titers in young adults compared with standard inactivated vaccine (Treanor et al., 1996). However, the dose–response curve was flat in elderly recipients, and there was little increase, even at 135 μg, compared with standard vaccine. The enhancement of protective efficacy, if any, resulting from use of very high doses of HA in this population remains to be evaluated.

2.2.2.2. Adjuvants and alternative formulations. The most commonly used adjuvant for vaccines in humans is alum (aluminum hydroxide or aluminum phosphate), but alum does not adsorb the HA of all influenza viruses efficiently, and alum adjuvants are not used for inactivated influenza vaccine. Other adjuvants that have been evaluated with influenza vaccine in animals or phase I studies have consisted of agents which modify the immune response directly, such as the squalene derivative MF59, monophosphoryl lipid A (MPL), the purified soap-bark derivatives Quil A or QS-21, dihydroepiandosterone (DHEA) (Daynes and Araneo, 1994), or cytokines. Another strategy is to physically modify the vaccine to improve antigen presentation, such as formulation in liposomes (el Guink et al., 1989; Kaji et al., 1992), or multimeric complexes such as ISCOMs (immunostimulating complexes) (Sundquist et al., 1988; Lovgren et al., 1990).

Several studies have been performed in elderly humans which have compared responses between adjuvanted and non-adjuvanted formulations of inactivated influenza vaccine. While some studies have shown enhanced serum antibody responses, no single formulation has emerged as clearly superior. Inactivated influenza vaccine formulated with MF59 (FLUAD, Chiron vaccines) has resulted in slightly higher levels of post-immunization antibody in elderly recipients compared with non-adjuvanted vaccine, but at the expense of higher rates of mild local and systemic side-effects (Martin, 1997; Minutello et al., 1999). This vaccine formulation has been licensed in Italy. Dehydroepiandrosterone (DHEA) has been reported to increase post-vaccination antibody titers in elderly subjects, primarily in those without a history of previous vaccination (Ben-Yehuda et al., 1998). Liposomal inactivated vaccine was well-tolerated and induced more frequent CTL responses but did not enhance antibody responses to vaccine in a small study of elderly subjects (Powers, 1997). In contrast, a virosomal preparation incorporating liposomes with phosphatidylcholine and phosphatidylethanolamine did result in enhanced antibody responses in elderly subjects (Gluck et al., 1994), and has been licensed in Switzerland. Conjugation of the hemagluttinin to a protein carrier has been reported to enhance immune responses and protective efficacy (Gravenstein et

al., 1994). The use of thymosin-alpha 1 has improved antibody responsiveness in elderly men (Gravenstein et al., 1989), as did the cytokine IL-2 (Provinciali et al., 1994). As additional potential adjuvants are described, it is likely that further improvements will be forthcoming.

2.2.2.3. Live virus vaccines. Studies in a variety of animal models have confirmed the importance of mucosal immunity in protection against influenza (Renegar and Small, 1991). More limited studies in humans have also suggested that the very effective protective immunity that is induced by influenza virus infection is mediated predominantly by the local HA-specific IgA (Clements et al., 1986a,b). Thus, methods to induce mucosal immunity are attractive options for improving influenza vaccine performance.

Live, attenuated influenza virus vaccines, generated by genetic reassortment with cold-adapted influenza A and B viruses (Maassab and DeBorde, 1985) have been extensively evaluated in children, young adults, and elderly subjects (reviewed in Murphy, 1993). Safety has also been demonstrated in high-risk individuals who would not be able to tolerate even minor lower respiratory tract inflammation, such as in individuals with cystic fibrosis or asthma (Miyazaki et al., 1993; Gruber et al., 1994). In adults, such 'cold-adapted' vaccines are generally more effective than parenterally administered inactivated influenza vaccine at inducing nasal HA-specific IgA, while inducing levels of serum HAI and HA-specific IgG antibody that are slightly lower than seen with inactivated vaccine. Although not studied extensively, limited data suggests that cold-adapted influenza vaccines may also induce antibody and cytotoxic T cells with more broadened recognition within a subtype than seen after inactivated vaccine (Gorse and Belshe, 1990; Clover et al., 1991).

Field trial evaluations have demonstrated the protective efficacy of ca reassortant influenza vaccines in children and adults. A recently completed field trial in 1600 children ages 18–71 months demonstrated a greater than 90% efficacy of trivalent cold-adapted influenza vaccine in prevention of culture positive influenza A (H3N2) and influenza B (Belshe et al., 1997). In adults, a randomized, double-blind trial conducted in 5210 individuals over 5 years showed that mono- or bivalent cold-adapted vaccines was approximately equal to inactivated vaccine in prevention of laboratory confirmed influenza illness (Edwards et al., 1994). The trivalent formulation of cold-adapted vaccine (FluMist) was of approximately equal effectiveness to inactivated vaccine in prevention of infection-associated illness due to all three components in experimentally infected adults (Treanor et al., 1999). In a recent study, FluMist was 23% effective in preventing febrile upper respiratory tract illnesses during the influenza season in a population of working adults (Nichol et al., 1999). Live, attenuated, cold-adapted influenza vaccines thus represent a promising approach to influenza vaccination.

Studies of cold-adapted vaccines in elderly and high-risk subjects have shown these vaccines to be well-tolerated in these populations also (Gorse et al., 1988, 1991; Powers et al., 1989; Atmar et al., 1990; Gorse and Belshe, 1990; Powers et al., 1991, 1992). No changes in oxygen saturation or pulmonary mechanics have been seen when cold-adapted vaccines have been given to elderly subjects or to those with chronic lung diseases (Gorse et al., 1988, 1991; Atmar et al., 1990). A minority of vaccine recipients shed detectable virus in nasal secretions, generally at low titer and for a short duration.

Serum antibody responses to cold-adapted vaccines in elderly subjects have been less than those seen in younger subjects (Gorse et al., 1988, 1991; Powers et al., 1989, 1991, 1992). Systemic antibody responses to cold-adapted influenza A virus vaccines as measured by hemagglutinin-specific IgG enzyme immunoassays of various types have been observed in from 0 to 48% of subjects, significantly less than the rate of systemic antibody responses to inactivated vaccines in these studies. In addition, geometric mean serum antibody titers are higher following inactivated influenza vaccines than after cold-adapted vaccine. Local HA-specific IgA responses have been seen in up to 60% of elderly recipients of cold-adapted vaccines, while slightly lower rates of local antibody response have been seen following inacti-

vated vaccine. Mean post-vaccination nasal antibody levels have often been difficult to interpret because of a high degree of variability in the level of pre-immunization antibody and the inherent difficulty in making these types of measurements, but appear to be somewhat higher in those receiving cold-recombinant vaccines. Relatively less work has been performed to evaluate cold-adapted influenza B virus vaccines in the elderly. However, one study in ambulatory elderly adults demonstrated that cold-adapted influenza B virus vaccines to be were well-tolerated, but less immunogenic than inactivated vaccine (Treanor et al., 1994). Nasal wash antibody responses were not seen very frequently with any of the vaccines given in that study.

The reasons for the apparently decreased infectivity of cold-adapted influenza vaccine viruses in the elderly may be related to the extensive previous exposure of older adults to influenza virus infections. However, this immunologic experience is not simply reflected by serum HAI titers, because the infectivity of cold-recombinant vaccines in older adults is low even with low pre-vaccination serum HAI antibody titers (Powers et al., 1992). In that study, only 36% of elderly adults with pre-vaccination serum HI titers of $\leq 1{:}8$ responded to vaccination with the CR A/Kawasaki/86 (H1N1) virus, compared with 100% of young adults (Powers et al., 1992).

The relative lack of serum HAI antibody responses to vaccination with cold-adapted influenza vaccines in older adults has suggested that such vaccine may not be optimal when used alone in this population. However, live vaccination does appear to potentially offer a benefit in induction of more frequent local antibody responses than seen with inactivated vaccine. This has led to the hypothesis that the use of both vaccine might have a synergistic effect, with inactivated vaccines providing systemic immunity and the cold-adapted vaccine augmenting the local immune response. Preliminary evaluation of the immunogenicity of parenteral inactivated vaccine given with intranasal cold-adapted vaccine has suggested that combined live and inactivated vaccines resulted in modest, but consistent, increases in the frequency of immune responses compared with either inactivated vaccine or cold-adapted vaccine alone (Powers et al., 1989, 1991; Gorse et al., 1996; Treanor and Betts, 1998).

These promising results were the basis of a small field trial to evaluate the combination of intranasal cold-adapted vaccine and intramuscular inactivated influenza vaccine in the prevention of influenza A in residents of nursing homes (Treanor et al., 1992). All participants received trivalent inactivated influenza vaccine parenterally and were randomly assigned to receive either live attenuated influenza A (H3N2) vaccine or placebo intranasally. Influenza A activity was relatively quiescent during this study, and attack rates of influenza in the participating nursing homes were generally low. However, over the 3-year period of the study, participants who received intranasal vaccine and who were subsequently exposed to influenza A had significantly lower rates of laboratory-documented influenza A and outbreak associated (i.e. temporally related to institutional influenza outbreaks) respiratory illness (Fig. 2; Treanor et al., 1992). A similar study comparing intramuscular trivalent inactivated vaccine combined with intranasal cold-adapted influenza B/Yamagata/88 to inactivated vaccine alone also showed reductions in laboratory-documented influenza B with combined vaccination, but the rates of infection were too low to allow conclusions to be drawn about the efficacy of this approach for influenza B (Treanor and Betts, 1998).

In summary, currently available data suggests that cold-adapted influenza A vaccines are safe in elderly and chronically ill individuals. Both local and systemic antibody responses are clearly less than those seen in young adults, even in elderly individuals with relatively low pre-vaccination serum HAI titers. In addition, systemic antibody responses to cold-adapted vaccines are generally less frequent and of lower magnitude than seen with inactivated vaccine, while local antibody responses are only marginally greater. However, combined intranasal cold-adapted and intramuscular inactivated vaccine provided significantly greater protection in this population than inactivated vaccine alone, despite the very modest apparent increase in immunogenicity. These data are promising, and should be confirmed in a larger

population during a period of more significant influenza activity.

2.2.3. Antiviral agents

2.2.3.1. M2 channel inhibitors. The antiviral drugs amantadine and rimantadine are both licensed in the USA and in some other countries for the treatment and prevention of influenza A in adults. Both drugs act by inhibiting the action of the viral M2 protein, an ion channel that plays an important role in viral uncoating. Because only influenza A viruses contain an M2 protein that interacts with these drugs, amantadine and rimantadine are only active against influenza A viruses.

Studies to demonstrate the efficacy of M2 channel inhibitors in acute influenza A have largely been carried out in younger adult populations and in children. These studies have demonstrated that therapy within 48 h of onset of symptoms is associated with reductions in symptom scores, in more rapid resolution of fever, and return to normal activities, and in some studies, reductions in viral shedding (Van Voris et al., 1981; Younkin et al., 1983; Hayden and Monto, 1986). Efficacy has been demonstrated in infections due to H1N1, H2N2, and H3N2 influenza A viruses. Neither drug has been subjected to extensive efficacy evaluation in high-risk subjects. One placebo-controlled blinded study carried out in nursing home patients showed more rapid reduction in fever and in symptoms in rimantadine recipients. Furthermore, physicians who were caring for these patients, but who were blinded to the study drug status, prescribed significantly fewer antipyretics, antitussives, and antibiotics, and obtained fewer chest X-rays for the rimantadine recipients (Betts et al., 1987). The effectiveness of early therapy of high-risk individuals with amantadine or rimantadine in reducing the frequency of subsequent complications is unknown.

M2 channel inhibitors are also effective in the prevention of influenza. In large-scale studies of seasonal prophylaxis in otherwise healthy adults, the drugs have had efficacy rates of 70–90% against laboratory-documented influenza A (Dolin et al., 1982; Douglas, 1990). Amantadine and rimantadine have similar levels of efficacy in this setting, but rimantadine is associated with significantly fewer side-effects (Dolin et al., 1982). Efficacy has also been demonstrated in post-exposure prophylaxis in the family setting (Galbraith

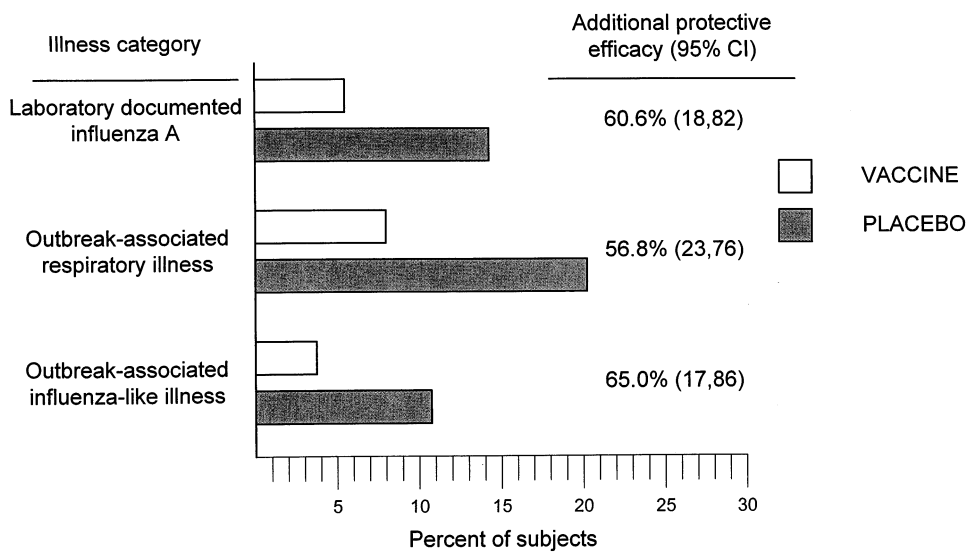

Fig. 2. Rates of laboratory-documented influenza illness, outbreak-associated respiratory illness, and outbreak-associated influenza-like illness in nursing home residents randomized to receive parenteral inactivated influenza vaccine with intranasal cold-adapted influenza vaccine or intranasal placebo (from Treanor et al., 1992).

et al., 1969). These findings suggest that prophylaxis of contacts in other closed settings, such as nursing homes, would also effectively terminate influenza outbreaks. Evidence of the effectiveness of outbreak-initiated prophylaxis in nursing homes is largely observational, but does suggest that early initiation can reduce the rate of influenza in institutions (Atkinson et al., 1986; Arden et al., 1988). Use of such prophylaxis for 14 days is as effective as are longer courses of administration (Drinka et al., 1998). It is currently recommended that when institutional outbreaks of influenza occur, chemoprophylaxis should be administered to all residents, and continued for approximately 2 weeks, or for 1 week after termination of the outbreak (CDC, 1998).

The development of antiviral resistance in treated individuals, with subsequent transmission to contacts, can significantly limit the effectiveness of post-exposure prophylaxis in either the family setting (Hayden et al., 1989) or in institutions (Mast et al., 1991; Degelau et al., 1992). For this reason it is recommended that treated and prophylaxed individuals should be isolated from each other if possible (CDC, 1998). However, resistant influenza A virus has been identified in this setting even before the onset of amantadine or rimantadine administration (Houck et al., 1995).

Both amantadine and rimantadine should be administered at a maximum dose of 100 mg per day in individuals over the age of 65. The daily dose of amantadine may need to be further reduced in individuals with impaired renal function. At 100 mg per day, the incidence of CNS side-effects in the elderly is substantially lower with rimantadine than amantadine (Keyser et al., 1998). However, side-effects of rimantadine in the elderly occur at a higher rate than in young adults (Tominack and Hayden, 1987). Administration of amantadine to individuals with motor seizures has been reported to increase the frequency of seizures (Atkinson et al., 1986). This may also occur with rimantadine, but appears to be less frequent (Soo, 1989). In one study, long-term prophylactic administration of rimantadine in a nursing home population was well-tolerated and had an estimated efficacy of 58% in prevention of flu in a nursing home (Monto et al., 1995).

2.2.3.2. Neuraminidase inhibitors. The determination of the crystal structure of the neuraminidase complexed with sialic acid (Varghese et al., 1983) has allowed the development of a series of analogs with neuraminidase-inhibiting activity (von Itzstein et al., 1993). The first of these compounds to be evaluated in clinical studies, 4-guanidino-2,4-dideoxy-2,3-dehydro-*N*-acetylneuraminic acid, or zanamivir (Relenza) is a highly potent and selective inhibitor of the neuraminidase of influenza A and B viruses. Zanamivir has significant antiviral activity against a wide variety of laboratory and clinical influenza A and B isolates in cell culture, and in the mouse and ferret models (von Itzstein et al., 1993; Woods et al., 1993). The drug is not orally bioavailable and is administered topically. Intranasal zanamivir was effective in the therapy of influenza in experimentally infected adult volunteers in whom both early treatment (beginning 26–32 h after challenge) and late treatment (beginning 50 h after challenge) were effective in reducing virus shedding compared with placebo, and early treatment also reduced symptom scores and reduced the frequency of middle ear abnormalities (Hayden et al., 1996; Walker et al., 1997). Subsequently, inhaled zanamivir was shown to be effective in the early treatment of naturally acquired acute influenza A and B in man, resulting in an approximately 24-h decrease in the duration of symptoms when administered within the first 48 h of illness (Hayden et al., 1997). Zanamivir also reduced the frequency of complications in a small number of high-risk subjects (MIST, 1998). This drug thus represents the first antiviral with clear-cut clinical efficacy against both influenza A and B in man. Zanamivir was recently licensed for treatment of acute, uncomplicated influenza in adults. An oral antineuraminidase inhibitor, oseltamivir (Tamiflu), is in development, and has also demonstrated therapeutic efficacy in experimentally infected adults (Hayden et al., 1999a).

Relatively less information is available regarding the use of zanamivir for prophylaxis. In one study, once daily zanamivir inhalation was associated with a 67% reduction in influenza illness in healthy adults during the epidemic season (Monto et al., 1999) Use in the elderly has not been

evaluated extensively. In one small study in a nursing home which experienced sequential outbreaks of influenza A and B, the use of outbreak-initiated prophylaxis with either rimantadine or zanamivir was compared during the influenza A outbreak, and of zanamivir or no treatment during the influenza B outbreak. One case of laboratory confirmed influenza A influenza occurred in study subjects, in an individual receiving rimantadine, and one case of influenza B, in an individual receiving no treatment (Schilling et al., 1998)

3. Respiratory syncytial virus (RSV)

3.1. Disease impact

Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract infection in infants and young children, causing an estimated 90 000 hospitalizations and 4500 deaths annually in the USA (Glezen et al., 1971; Mufson et al., 1973; Parrott et al., 1973) Immunity to RSV is incomplete and re-infection occurs throughout life, although re-infection has always been considered a mild illness (Hall et al., 1976, 1978) Traditionally, severe RSV infection has been considered a problem of childhood. However, RSV has recently been identified as a common cause of serious disease in a number of adult populations, including immunocompromised persons, frail elderly, and those with underlying cardiopulmonary disease (Englund et al., 1988, 1991; Martin et al., 1988; Hertz et al., 1989; Falsey et al., 1992a, 1995a; Harrington et al., 1992; Whimbey et al., 1995) Despite recent advances in the understanding of RSV infections in infants, three important areas regarding RSV infection in the adult remain relatively unexplored. These include (1) detailed knowledge about the epidemiology and clinical impact of RSV in various adult populations; (2) an understanding of the mechanisms of disease pathogenesis and (3) development of the correlates of immunity to RSV in the adult.

Among elderly adults, RSV is a significant cause of excess morbidity and mortality. RSV infections have been documented in attendees of senior daycare centers, the community-dwelling and institutionalized elderly (Falsey et al., 1992a, 1995a,b). RSV outbreaks are well-documented in nursing homes, with attack rates ranging from 2 to 89% (Mathur et al., 1980; Sorvillo et al., 1984; Agius et al., 1990; Falsey et al., 1990). However, it should also be noted that RSV is consistently identified each winter as a cause of sporadic respiratory illness in nursing homes indicating that RSV infections are not limited to nosocomial outbreaks (Nicholson et al., 1990; Osterweil et al., 1990; Falsey et al., 1992a). Even during documented influenza virus epidemics, RSV infections can be identified in this population (Falsey et al., 1990). In one surveillance study in a 550-bed nursing home in Rochester, New York, RSV caused 27% of 149 acute respiratory tract infections during a single winter season (Falsey et al., 1992a). In this study, rhinovirus (9%) and parainfluenza viruses (6%) were the next most commonly identified agents. Of the 40 RSV infected patients, four (10%) developed pneumonia and two (5%) died.

The severity of RSV infection in institutionalized persons can be quite variable. Serious complications are well-recognized with rates of pneumonia ranging from 5 to 67%, and mortality from 0 to 53% (Mathur et al., 1980; Sorvillo et al., 1984; Agius et al., 1990; Falsey et al., 1990, 1992a). Symptoms are often indistinguishable from those of influenza virus infection, although, the presence of nasal congestion and wheezing are more characteristic of RSV (Mathur et al., 1980).

In addition to the institutionalized elderly, RSV has also been recovered from attendees at adult day care centers (Falsey et al., 1995b). During a 15-month period encompassing two winter seasons in Rochester, NY, RSV was identified in 16 of the 165 participants, slightly less than the 22 influenza A and B virus infections which occurred during the same period. Although there were no deaths directly attributable to RSV, one infected patient required hospitalization for pneumonia. There is little information available on the incidence of RSV infection in the community dwelling elderly, although significant illness clearly occurs each winter. Three cases of culture positive RSV lower respiratory tract infection were identified in one analysis of community ac-

quired pneumonia (Zaroukian et al., 1988), and 57 cases were reported among elderly patients (average age 75) in a retrospective 10-year review of hospitalization for pneumonia in Sweden, representing 2.3% of all pneumonia cases (Vikerfors et al., 1987, 1988). In Rochester, NY, 10% of 1600 admissions of persons 65 years of age or older for acute cardiopulmonary or flu-like illness over a 3-year period were caused by RSV, and 13% were due to influenza virus (Falsey et al., 1995a). Underlying COPD or congestive heart failure was present in 43 and 63% of the RSV infected patients, respectively. Mortality among RSV infected patients was 10%, comparable with the 6% mortality in influenza virus infected patients, and 14% were discharged to a higher level of care. Among 1195 hospitalized adults in Ohio, RSV was the third most common identifiable cause (4.4%), behind *Streptococcus pneumoniae* (6.2%) and influenza virus (5.4%) (Dowell et al., 1996). Of the 57 RSV cases, 55% were over 65 years of age. Slightly more than half had underlying COPD, coronary artery disease or congestive heart failure.

In addition to clinical reports describing acute lower respiratory tract infections, there is growing evidence to implicate RSV as an important contributor to excess morbidity within the geriatric population during the winter, as has been shown for influenza virus. Although the impact of RSV in the elderly is less readily apparent than in the infant, evidence continues to accumulate that among community-dwelling older persons, RSV may be as serious as non-pandemic influenza (Nicholson et al., 1975; Fleming et al., 1993). In the United Kingdom during 1991–1994, excess mortality in older persons was temporally associated with peak RSV activity in children (Fleming et al., 1993). In a detailed statistical analysis of data spanning 1975–1990, also from the UK, RSV had a greater impact than influenza virus on excess morbidity and mortality in persons over age 65 (Nicholson et al., 1975).

3.2. Treatment and prevention

There is little known about immunity and disease pathogenesis in the elderly or high-risk adult. It is not known if the increase in severe RSV infections in this age group is a result of underlying frailty of the host, global immunosenescence, or an age related decline in one or another of RSV-specific immune functions. Very little is known about the role of antibody to RSV in the elderly, with the exception that all adults have detectable serum antibody (Falsey et al., 1992). Elderly adults are capable of mounting a brisk serum IgA and IgG response to RSV infection (Angius et al., 1990). This is important, because relative lack of serum neutralizing antibody was recently found to be a risk factor for RSV disease in a study of frail elderly adults (Falsey et al., 1998). Baseline blood samples were obtained from subjects attending a senior daycare center and volunteers were followed over the next 26 months and evaluated for any acute respiratory tract illness. Samples from 22 subjects who developed symptomatic RSV infection were compared with 22 control subjects who did not become infected with RSV. The mean serum IgG titer to RSV fusion protein (F) was significantly lower in the RSV-infected group compared with the controls as were the neutralizing titers to group A RSV (Fig. 3). These data suggest that older adults with low levels of serum neutralizing antibody may be at greater risk of developing symptomatic RSV and supports the view that boosting titers by vaccination may be beneficial.

Currently, several RSV vaccine candidates are in human trials, with the potential for development of numerous additional vaccine candidates. One approach of potential benefit for the elderly is the use of purified RSV F protein (PFP-2, Wyeth–Lederle vaccines). Results in previously infected children who were vaccinated with PFP-2 demonstrated stimulation of neutralizing antibody to both group A and B strains, although large-scale efficacy studies have not been performed (Belshe et al., 1993). PFP-2 was also safe and reasonably immunogenic in both healthy and frail elderly subjects. Twenty-nine of 33 (87%) healthy elderly recipients of PFP-2 vaccine had a 4-fold or greater rise in serum IgG to the F protein at 8 weeks post-vaccination and twenty of 33 (61%) had a 4-fold or greater rise in serum neutralizing titer to group A or group B RSV. In that study,

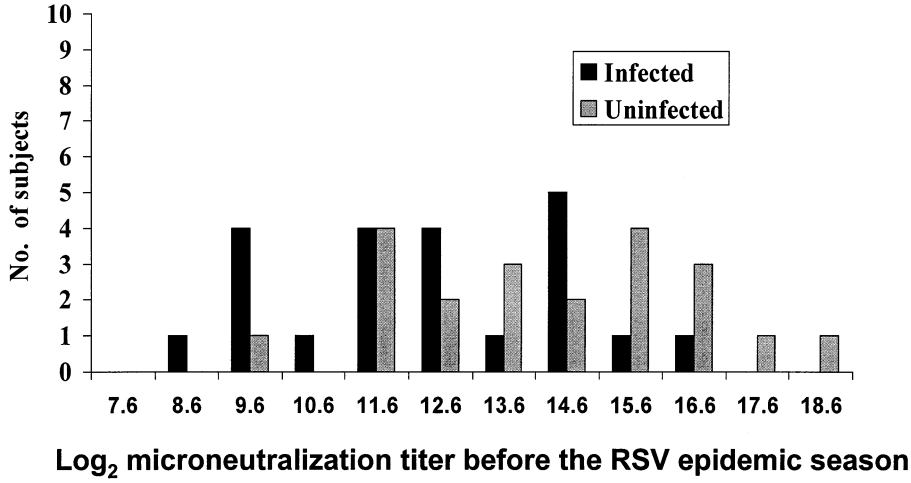

Fig. 3. Pre-illness levels of serum neutralizing antibody to group A RSV in elderly individuals enrolled in adult day care who were or were not subsequently infected with RSV during RSV outbreaks (from Falsey et al., 1995b).

response to vaccination was inversely correlated with pre-immunization serum neutralizing titers. Subjects were followed throughout the ensuing winter, and 3 RSV infections were identified in the placebo group and none in the vaccine group (Falsey and Walsh, 1996). In a second study, PFP-2 was evaluated in 37 institutionalized persons over age 65 (Falsey and Walsh, 1997). Vaccination was well-tolerated and 36 of 37 subjects completed the study. Nineteen of 36 (53%) of vaccinees had a 4-fold or greater rise in IgG to F protein at 4 weeks and 17 (47%) had a significant rise in neutralizing titers to either group A or B virus. The response rate to PFP-2 again correlated with pre-immunization neutralization titers, although PFP-2 appeared to be slightly less immunogenic in the institutionalized elderly than in the healthy elderly

Recent animal studies suggest that adjuvants such as QS-21 and MPL (monophosphoryl lipid A) can alter the primary immune response to FG towards a Th1 pattern rather than the Th2 pattern seen when alum is used as the adjuvant (Neuzil et al., 1997). This vaccine could potentially induce greater neutralizing antibody titers than an F protein vaccine due to the induction of antibody to the G protein.

Incorporation of specific RSV genes, most notably F, into virus vectors, such as vaccinia virus and adenovirus, have been successfully completed and could be used as a vaccine. Although promising in rodents, these vaccines did not reach clinical trials in infants because of lack of immunogenicity and efficacy in subhuman primates (Wertz et al., 1987; Hsu et al., 1992, 1994). However, it is possible that in already primed elderly subjects, these vectored vaccines may be immunogenic.

Live attenuated vaccines represent an attractive approach towards the development of an RSV vaccine because they should restimulate local nasal immunity and a balanced cellular immune response. Initial results with temperature-sensitive (ts) or cold-adapted (ca) mutants were disappointing in infants, as vaccines were either poorly immunogenic, excessively virulent, or genetically unstable (Kim et al., 1973; Wright et al., 1982). Currently, several new live virus vaccines are being evaluated in infants. Genetically stable, attenuated viruses have been produced from previous cold passaged and temperature-sensitive (cpts) mutants by additional chemical mutagenesis and the precise genetic alterations defined by sequence analysis of viral RNA (Crowe et al., 1994; Firestone et al., 1996). The cpts-248/404 virus is one of several candidate temperature-sensitive vaccines and has a shut-off temperature of 38°C (Firestone et al., 1996). Studies in rodents and

chimpanzees show the virus to be phenotypically stable, and despite restricted replication are immunogenic and protective against wild-type challenge (Crowe et al., 1995, 1996). Ts-1C is another live virus vaccine candidate produced by chemical mutagenesis with 5-fluorouracil (McKay et al., 1988; Pringle et al., 1993). Virus replication is shut off at 37°C and, in studies of adult volunteers, the vaccine was found to be stable, attenuated, and modestly immunogenic. The recent development of full length infectious cDNA clones of RSV, which produce live virus upon transfection of cells in tissue culture, offers the potential of a limitless supply of specifically altered live vaccine products (Collins et al., 1995).

4. Parainfluenza virus

4.1. Disease impact

Parainfluenza viruses are common causes of respiratory tract illness in infants and young children. Although each of the serotypes has distinctive epidemiology and clinical characteristics, in individual cases it is generally not possible to distinguish between the viruses. Although the epidemiology of PIV infection is relatively constant on a national level, there is substantial regional variation in the distribution of serogroups each year (Chanock and McIntosh, 1990). Each of the viruses can cause a wide spectrum of disease from mild upper respiratory symptoms to life threatening pneumonia. PIV1 tends to occur in the fall every other year and is associated with half of all croup cases, but also causes bronchiolitis and pneumonia. PIV2, like PIV1 may occur every other year, although also is seen annually, and is associated with croup. Infection with PIV1 and PIV2 can occur at any age, although severe disease is uncommon under age 1 year. Most children demonstrate serologic evidence of infection with PIV1 and PIV2 by the age of 5 years. In contrast, PIV3 tends to infect infants less than 6 months of age and half of all infants are infected in the first year of life, with most of the rest infected by age 2 years. PIV3 is not specifically associated with croup, and is second to RSV as a cause of bronchiolitis and pneumonia in young infants. The virus is endemic and infection occurs throughout the year including winter, spring and summer months.

Although generally considered a disease of childhood, the parainfluenza viruses, like RSV, have recently been recognized as causes of serious respiratory illness in certain adult populations such as the elderly and the severely immunocompromised. Parainfluenza infection in an adult always represents re-infection, and generally symptoms are limited to the upper respiratory tract, or produce mild lower tract symptoms (Cooney et al., 1975). Within families, up to 25% of young adult parents develop evidence of infection when parainfluenza virus is introduced into the household (Cooney et al., 1975). PIV infections have been documented in community dwelling elderly with pneumonia or signs of lower respiratory tract infection (Mufson et al., 1967; Fransen et al., 1969; Cooney et al., 1975; Stanek and Heinz, 1988; Greenberg, 1991; Monto and Sullivan, 1993). However, the incidence and clinical significance of PIV in these groups appears to be variable. In one report of community acquired PIV lower respiratory tract infection, PIV3 was isolated from two of 361 patients and documented seroconversion to PIV in 23 of 346 subjects (6.6%) (Mufson et al., 1967). In persons between 60–70, 70–80, and >80 years of age, seroconversion to PIV was associated with 11, 14 and 21% of the lower respiratory tract illnesses, respectively, in contrast to rates of 3, 4 and 6% in controls without respiratory symptoms. In another serologic study of respiratory illness from Sweden, 69 cases of PIV infection were detected out of 598 patients with pneumonia (Fransen et al., 1969). Of the 189 patients greater than 60 years of age, 20 (11%) had serologic evidence of PIV infection. More recently, PIV infection was identified in 2.1% of acute respiratory illness in persons over age 40 years during 11 years of community surveillance in Tecumseh, MI (Monto and Sullivan, 1993). For comparison, influenza A and B viruses were identified as the cause of illness in 10.3%. However, not all investigators have described parainfluenza virus as a cause of lower respiratory tract illness in adults (Cooney et al.,

1975; MacFarlane et al., 1993; Marrie et al., 1996).

Outbreaks of parainfluenza types 1 and 3 have also been reported from long-term care facilities Anon, 1983. Illnesses were characterized by fever, sore throat, rhinorrhea, and cough. Rates of pneumonia were high (17–29%) with several deaths. Attack rates of 22 and 28% for residents and employees, respectively, were noted in an Alabama nursing home outbreak. In prospective studies in nursing home populations, parainfluenza viruses have been responsible for 5–6% of respiratory illnesses (Arroyo et al., 1988; Gross et al., 1988b; Falsey et al., 1992a, 1995b).

Parainfluenza virus has also been implicated as a cause of exacerbation of chronic obstructive pulmonary disease (COPD) (Carilli et al., 1964; Buscho et al., 1978; Hudgel et al., 1979; Smith et al., 1985). In composite, PIV is generally second or third behind influenza virus and respiratory syncytial virus as a cause of acute deterioration of lung function in this group (Fagan and Chastre, 1996).

4.2. Treatment and prevention

The earliest attempt at immunization for PIV used a formalin inactivated trivalent whole virus vaccine (Fulginiti et al., 1967; Weibel et al., 1967; Fulginiti et al., 1969). Although immunogenic, it was not efficacious in infants and was thus abandoned. However, in contrast to the findings with inactivated RSV vaccine discussed above, there was no evidence of enhanced disease in infants who received the PIV vaccine. Purified HN and F or virus vectors expressing HN or F have provided materials for either parenteral or topical immunization, and have been tested in animal models of parainfluenza virus infection (Blaine et al., 1980; Ray et al., 1985; Spriggs et al., 1987; Ray et al., 1988; Sullivan et al., 1993). Two live attenuated parainfluenza type 3 vaccines have also been developed for use in infants and children (Karron et al., 1995a,b). One is a bovine PIV which has significant antigenic relatedness to human PIV3, and which is attenuated for primates based on its long evolution in a heterologous bovine host. The second is a cold-passaged (cp), cold-adapted (ca), temperature-sensitive (ts) mutant of the JS strain of human PIV3. In seronegative children this vaccine is well-tolerated and highly immunogenic (81% seroconversion) at the highest dose given (105 TCID50). However, in seropositive children who are perhaps more predictive of the performance of such a vaccine in adults, only 4 of 34 (11%) developed 4-fold rises in hemagglutination titers, and only 22% developed nasal IgA responses.

5. Rhinovirus and coronavirus infections

5.1. Disease impact

The common cold is one of the most common disease experiences in all age groups. Although there is no single clinical entity defined as a 'cold', generally colds are considered to be predominantly respiratory illnesses including symptoms of rhinitis with variable degrees of pharyngitis (Gwaltney et al., 1967; Rao et al., 1995). Patients often report chills, but true fever is unusual. Cough and hoarseness are occasionally also part of the illness, but lower respiratory tract signs and symptoms are not characteristics of colds. Recognized complications of colds in adults include secondary bacterial infections of the paranasal sinuses and middle ear, and exacerbations of asthma, chronic bronchitis, and emphysema.

Although there are many viral etiologies of the common cold, two viruses that are often associated with this syndrome, rhinoviruses and coronaviruses, are emerging as potentially important pathogens in the frail elderly. Rhinoviruses infections are extremely common, and in the USA have been observed at rates of 0.74–0.77 infections per person per year in adults (Gwaltney et al., 1966; Hamre and Procknow, 1966). In the USA, RV infections are most prevalent in the early fall and late spring. The major reservoir for RV is school children, who transmit RV infection among their peers in the classroom (Beem et al., 1969) and introduce it into their homes, infecting other family members (Hendley et al., 1969).

In addition to causing cold symptoms, rhinoviruses have been implicated in the develop-

ment of acute sinusitis and in the precipitation of exacerbations of chronic bronchitis and asthma. The virus has been recovered from aspirates obtained by direct puncture of the maxillary sinuses of patients with acute sinusitis (Pitkaranta et al., 1997), and mucosal thickening and/or sinus exudates have been observed in as many as 77% of subjects with acute colds (Turner et al., 1992; Gwaltney et al., 1994). Clinically manifest acute sinusitis is seen in a small (0.5–5%) proportion of individuals with naturally occurring colds (Wald et al., 1991). As many as 40% of exacerbations of chronic bronchitis have been associated with RV infection (Eadie et al., 1966; Stenhouse, 1967; McNamara et al., 1969; Lambert et al., 1972). However, the effect of RV infection on pulmonary function in patients with chronic obstructive pulmonary disease is less marked than that of influenza infection (Smith et al., 1985). It is not known whether rhinovirus invades the bronchial tree directly, but several studies indicate that direct invasion may occur (Halperin et al., 1983; Gern et al., 1999). Rhinovirus is also among the respiratory viruses shown to precipitate attacks of asthma, predominantly in children (Minor et al., 1974, 1976; Horn et al., 1979 but also in adults Teichtahl et al., 1997). Experimental RV infection of varying severity led to the development of wheezing and increased bronchial reactivity, as demonstrated by histamine provocation, in 20% of adults with mild to moderate asthma (Halperin et al., 1985).

Coronaviruses are moderate-sized (100–150 nm), round viruses containing positive-sense single-stranded RNA. Distinctive club-shaped projections are present on the virus surface, giving the virus particle the appearance of having a crown or corona, from which it derives its name. Two antigenic types of human coronavirus have been recognized: the 229E-related strains that have been isolated in cell cultures such as human embryonic lung cell fibroblasts, and the OC43-related strains that require organ culture. The coronavirus group also appears to be an important cause of common colds, although the overall contribution to annual respiratory disease morbidity is uncertain. In longitudinal studies in adults, coronaviruses have accounted for 4–15% of acute respiratory disease annually and up to 35% during peak periods (Hamre and Beem, 1972; Hendley et al., 1972). Annual illness rates in children have been measured at 8%, with peak rates of up to 20% (Kaye et al., 1971; Kaye and Dowdle, 1975). The reported frequency of infection in adults for 229E and OC43 viruses has ranged from 15 to 25 per 100 persons per year, with up to 80% of infections occurring in persons with prior antibody to the infecting virus (Cavallaro and Monto, 1970; Hamre and Beem, 1972; Hendley et al., 1972; Monto and Lim, 1974). Most large peaks of coronavirus activity have occurred in winter and early spring, but infections have been detected throughout the year Macnaughton, 1982; Monto, 1997).

Recent data have implicated these viruses as common causes of moderately debilitating acute respiratory disease in older adults. Prospective studies have identified rhinoviruses as associated with 7% of acute respiratory illnesses in elderly adults attending supervised day care (Falsey et al., 1997) and as many as one-fourth of episodes occurring among ambulatory elderly adults (Nicholson et al., 1997). In the same studies, coronaviruses were identified as responsible for 8 and 10% of episodes, respectively. Rhinovirus outbreaks have also been reported in long-term care settings (Nicholson et al., 1990; Falsey et al., 1992b; Wald et al., 1995).

A striking feature of these illnesses has been significant lower respiratory tract involvement in many cases. Signs and symptoms such as cough, sputum production, dyspnea, and wheezing have been reported in from 40 to 90% of individuals, and are significantly more common in the elderly than in younger health care workers (Table 3) (Falsey et al., 1997). Clinical illness caused by coronavirus and rhinovirus in ambulatory elderly adults was similar to that associated with influenza (Nicholson et al., 1997), and was associated with significant mobidity. Restriction of activity was seen in almost one-fifth of those with rhinovirus illnesses, and 43% of infections resulted in medical consultation. The presence of chronic medical conditions and smoking may be risk factors for the development of lower respiratory tract symptoms from rhinovirus infection (Nicholson et

al., 1996). Of note, however, rhinovirus and coronavirus infections have not yet been established convincingly as causes of increased levels of hospital admission or enhanced mortality among elderly populations.

5.2. Treatment and prevention

The only effective therapy for RV colds currently available is symptomatic treatment of individual complaints. However, because of their high incidence, development of effective antiviral therapy for rhinovirus infections has been an object of considerable interest for many years. A detailed review of all of the efforts over many years to generate such a treatment is beyond the scope of this review, but many such studies have utilized experimental infection of human adult volunteers for this purpose. Benefit has been seen in this model with early treatment with a combination of interferon α2 and ipratroprium bromide given nasally and naproxen given orally (Gwaltney, 1992), and capsid binding agents such as pirodavir (Hayden et al., 1992) and pleconaril. Because 90% of rhinovirus serotypes use the same cellular receptor, receptor blockade with soluble ICAM-1 has also been evaluated with minor benefit (Turner et al., 1999). Pleconaril has been reported to reduce the duration of symptoms by 21% in naturally occuring colds (Hayden et al., 1999). Although serotype-specific immunity does develop after infection (Fleet et al., 1965), prospects for a rhinovirus vaccine are poor because of the multiplicity of rhinovirus serotypes.

Antiviral agents with clinical usefulness for coronavirus infection are currently unavailable, so that treatment of coronavirus colds also depends upon the use of symptomatic therapies. Intranasal interferon is protective against experimental coronavirus colds (Higgins et al., 1983), and intranasal nedocromil sodium was also effective in reducing nasal mucus weights in this model (Barrow et al., 1990). Little attention has been given to the development of coronavirus vaccines. In volunteer experiments, infection with a 229E-like coronavirus induced effective short-term immunity appeared to rechallenge with the homotypic virus, but challenge with other strains of the 229E serotype resulted in infection and illness (Reed, 1984).

6. Summary

Viral respiratory infections represent a significant challenge for those interested in improving the health of the elderly. Influenza continues to result in a large burden of excess morbidity and mortality. Two effective measures, inactivated influenza vaccine, and the antiviral drugs rimantadine and amantadine, are currently available for control of this disease. Inactivated vaccine should be given yearly to all of those over the age of 65, as well as younger individuals with high-risk medical conditions and individuals delivering care to such persons. Live, intranasally administered attenuated influenza vaccines are also in develop-

Table 3
Clinical features of rhinovirus and coronavirus infectoins among staff compared with older participants

Symptom	No. with indicated symptom within the following group (%)		*P* value comparing rates in elderly and younger individuals
	Elderly participants in senior daycare ($n = 66$, mean age: 78.5 years)	Staff members at the daycare center ($n = 44$, mean age: 35 years)	
Nasal congestion	56 (85)	42 (95)	NS
Sore throat	23 (35)	23 (52)	NS
Hoarseness	30 (45)	21 (48)	NS
Cough	61 (92)	28 (64)	<.001
Sputum	38 (58)	10 (23)	<.001
Dyspnea	24 (36)	11 (25)	NS
Constitutional	58 (94	39 (61)	<.001
Fever	15 (23)	10 (23)	NS

ment, and may be useful in combination with inactivated vaccine in the elderly. The antiviral drugs amantadine and rimantadine are effective in the treatment and prevention of influenza A, although rimantadine is associated with fewer side-effects. Recently, the inhaled neuraminidase inhibitor zanamivir, which is active against both influenza A and B viruses, was licensed for use in uncomplicated influenza. The role of this drug in treatment and prevention of influenza in the elderly remains to be determined. Additional neuraminidase inhibitors are also being developed. In addition, to influenza, respiratory infections with respiratory syncytial virus, parainfluenza virus, rhinovirus, and coronavirus have been identified as potential problems in the elderly. With increasing attention, it is probable that the impact of these infections in this age group will be more extensively documented. Understanding of the immunology and pathogenesis of these infections in elderly adults is in its infancy, and considerable additional work will need to be performed towards development of effective control measures.

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