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# Respiratory Syncytial Virus and Other Noninfluenza Respiratory Viruses in Older Adults



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## KEYWORDS

- Respiratory syncytial virus • Noninfluenza respiratory virus • Outbreak • Elderly
- Long-term care facility • Multiplex respiratory viral panel

## KEY POINTS

- Among older adults, the morbidity and mortality of respiratory syncytial virus infections is similar to that of influenza.
- Several other respiratory viruses (human metapneumovirus, parainfluenza virus, rhinovirus, coronavirus and adenovirus) may cause outbreaks among residents of long-term care facilities.
- Supportive care is the mainstay of medical therapy; effective antivirals or vaccinations do not yet exist for noninfluenza respiratory viruses.
- Rapid diagnostic molecular tests will augment our epidemiologic understanding of noninfluenza respiratory viral outbreaks.
- Infection prevention and control measures for contagious individuals includes hand hygiene, cough etiquette, and use of a mask, gown, and gloves by health care workers.

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## INTRODUCTION

Respiratory tract infections are a common cause of morbidity and mortality in older adults. In 2014, influenza and pneumonia accounted for 2.3% of deaths among adults 65 years or older in the United States.<sup>1</sup> Older adults, especially those older than 75 years of age, experience the highest rate of influenza-associated mortality rate among all age groups.<sup>2</sup> The availability of rapid diagnostic tests, antiviral medications, and, most notably, the seasonal influenza vaccine mitigate some of influenza's devastating effects.<sup>3</sup> Respiratory viruses other than influenza also cause significant morbidity and mortality among older adults, particularly those who are residents of long-term care facilities (LTCFs).<sup>4,5</sup> These viruses include respiratory syncytial virus (RSV), human metapneumovirus (HMPV), parainfluenza virus, rhinovirus, coronavirus, and adenovirus. In this article, we review viruses, other than influenza, that are common causes of respiratory infections in older adults and discuss relevant diagnostic tests, transmission, and infection prevention and control measures.

### *Epidemiology*

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In the United States, the National Respiratory and Enteric Virus Surveillance System, a voluntary laboratory-based system affiliated with the Centers for Disease Control and Prevention (CDC), monitors temporal and geographic patterns associated with the detection of RSV, HMPV, parainfluenza viruses, and respiratory adenoviruses.<sup>6</sup> Data from the National Respiratory and Enteric Virus Surveillance System informs reports from the CDC regarding ongoing trends in detection of respiratory viruses. Although comprehensive, the National Respiratory and Enteric Virus Surveillance System data do not include patient demographics and therefore do not specifically provide information about the epidemiology of respiratory viruses in older adults or LTCFs. Additionally, other than to rule out influenza, for which there is effective antiviral therapy, molecular diagnostic tests are not yet widely used in the evaluation of older adults or LTCF residents with respiratory infections. Accordingly, most of our understanding of the epidemiology of noninfluenza respiratory infections among older adults is informed through research studies and descriptions of outbreaks in LTCFs (**Table 1**).

## RESPIRATORY SYNCYTIAL VIRUS

First isolated from chimpanzees in 1956, RSV is a nonsegmented, single-stranded, negative-sense RNA virus within the Paramyxoviridae family (**Table 2**).<sup>7</sup> Most recognized for its effect on children, RSV also causes severe infections among older adults. Similar to influenza, it generally circulates from fall through spring, with a peak in January.<sup>8</sup> A protein on the surface of the virus, dubbed the F protein, causes cell membranes of nearby cells to fuse to form the syncytia for which the virus is named.

### *Epidemiology*

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Among older adults, RSV causes morbidity and mortality that rivals that of influenza. Falsey and colleagues<sup>9</sup> described RSV infections among older adults over 4 consecutive winters from 1999 to 2003. Among older adults hospitalized with a respiratory viral infection ( $n = 1388$ ; age  $75 \pm 12$  years), the authors detected roughly similar proportions of RSV and influenza (142 and 170 cases, respectively). Furthermore, they also found that people with RSV and influenza had similar rates of intensive care stays (15% vs 12%) and mortality (8% vs 7%), respectively. Among this community-dwelling population, for whom the prevalence of vaccination against influenza and *Streptococcus pneumoniae* was greater than 75%, the incidence of RSV was similar to that for nonpandemic influenza.

**Table 1**  
**Reports of outbreaks of noninfluenza respiratory viral infection in long-term care facilities**

<b>Virus</b>	<b>Reference</b>	<b>Date of Outbreak</b>	<b>Location</b>	<b>Description</b>
RSV	Garvie & Gray, <sup>94</sup> 1980	Data not given	United Kingdom	Seventeen of 40 residents aged 69–90 y developed fever, anorexia and a nonproductive cough. Paired sera from 2 cases showed an increase in RSV complement fixation titers from <20–160. One resident died after severe chest infection.
	Sorvillo et al, <sup>10</sup> 1984	Feb–March, 1979	California	Forty-four of 101 residents (40%) affected; 22 (55%) had pneumonia and 8 (20%) died. Serologic evidence of RSV infection in 13 of 16 patients from whom blood was obtained.
	Caram et al, <sup>12</sup> 2009	Jan–Feb, 2008	North Carolina	Routine surveillance detected an RSV outbreak in a 56-room, 120-bed long-term care facility; 22 of 52 residents (42%) developed symptoms of a respiratory tract infection. RSV was detected by RT-PCR in 7 (32%) of the 22 cases. 1 patient was admitted to the hospital and died.
	Meijer et al, <sup>95</sup> 2013	Winter, 2012–2013	The Netherlands	The Sentinel Nursing Home Surveillance Network in the Netherlands identified an outbreak of RSV-B. Of 10 residents tested for RSV, 4 had RSV-B positive. Two residents had pneumonia and 8 were diagnosed with the common cold. All 10 residents recovered within 2 wk after the onset of symptoms.
	Doi et al, <sup>96</sup> 2014	Winter, 2013–2014	Japan	Twenty-four of 99 residents aged from 68 to 97 y developed respiratory symptoms in winter; 5 cases (20.8%) were diagnosed with pneumonia. RSV was detected from 7 of 10 nasopharyngeal samples by RT-PCR. No other pathogens were isolated.
	Spires et al, <sup>87</sup> 2017	Jan, 2015	Tennessee	During a 16-d outbreak, 30 of 41 (73%) of residents infected. High attack rate among staff. From 14 specimens, 6 positive for RSV-B, 7 for HMPV, 1 for influenza; 15 residents hospitalized, 10 with pneumonia; 5 deaths.

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**Table 1**  
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Virus	Reference	Date of Outbreak	Location	Description
HMPV	Honda et al, <sup>97</sup> 2006	Jan, 2005	Japan	Eight inpatients developed respiratory tract illness in a 23-bed ward. HMPV detected using RT-PCR in nasal swabs from all patients. Two developed secondary bacterial pneumonia with <i>Klebsiella pneumoniae</i> ; all patients recovered.
	Boivin et al, <sup>23</sup> 2007	Jan–Feb, 2006	Quebec, Canada	Ninety-six of 364 residents (27%) presented with respiratory or constitutional symptoms during 6 wk in winter of 2006. Of 13 samples nasopharyngeal samples, real-time multiplex RT-PCR showed HMPV in 6 and RSV in 1 subject. Three of 6 confirmed cases died; a total of 9 people died during the outbreak.
	Louie et al, <sup>48</sup> 2005	June–July, 2003	California	Twenty-six of 148 residents (18%) developed respiratory symptoms. Five of 14 respiratory specimens were positive by PCR for HMPV. Eight residents developed pneumonia, and 2 were hospitalized; no deaths.
	Omura et al, <sup>98</sup> 2011	Sept–Oct, 2009	Japan	Twenty-seven of 99 residents became symptomatic. RT-PCR detected HMPV detected from 9 of 9 throat swabs collected.
	Te Wierik et al, <sup>99</sup> 2012	Jan–March, 2010	The Netherlands	Five of 18 clinical cases tested positive for HMPV by RT-PCR. A 5% attack-rate for laboratory-confirmed cases, 13% for clinical cases. Three deaths; at least 1 believed to be owing to HMPV infection.
	Liao et al, <sup>24</sup> 2012	Spring–Summer, 2011	Oregon	Sixteen of 44 residents met case definition of severe respiratory tract infection. Six of 10 nasopharyngeal swab specimens from case patients were positive for HMPV; 5 diagnosed with pneumonia, 4 hospitalized, and 2 died.
	Ibrahim et al, <sup>25</sup> 2013	Dec, 2011–Feb, 2012	West Virginia and Idaho	Among 57 cases of respiratory illness from 2 facilities (28 of 83 residents in West Virginia, 29 of 80 residents in Idaho), 45 (79%) patients had lower respiratory tract infections. Of these, 25 (56%) had pneumonia, 5 (9%) had upper respiratory tract infection, and 6 patients (11%) died.

HPIV	Glasgow et al, <sup>36</sup> 1995	May, 1993	Ontario, Canada	Twenty-six (6 definite, 2 probable, and 18 suspected) of total 84 residents had respiratory symptoms. Six of 10 paired sera obtained from ill residents showed a 4-fold or greater increase to HPIV type 3. One resident had pneumonia; 1 was hospitalized. No deaths.
	Faulks et al, <sup>37</sup> 2000	Sept, 1999	Wisconsin	Of 49, 25 residents developed new respiratory symptoms. Of 18 who had chest film, 11 showed new infiltrates. Three residents were hospitalized; 4 died. Four of 10 viral cultures were positive with HPIV type 3.
	Ryan et al, <sup>39</sup> 2017	Jan, 2016	Australia	Eleven residents presented with respiratory symptoms in a 30-bed residential aged care facilities. Nine of 10 nasopharyngeal swabs were positive with HPIV type 3 by PCR; 2 residents were hospitalized. No deaths.
Rhinovirus (HRV)	Wald et al, <sup>49</sup> 1995	Aug–Sept, 1993	Wisconsin	One hundred twenty-eight residents developed a new respiratory illness. Throat and nasopharyngeal virus cultures of 67 ill residents yielded 33 culture-positive with rhinovirus. One resident died owing to respiratory failure.
	Louie et al, <sup>48</sup> 2005	June–July, 2003	California	In a 99-bed facility, 56 residents and 26 staff developed a respiratory illness. Twelve residents died. Seven of 13 respiratory specimens were culture positive for rhinovirus.
	Hicks et al, <sup>47</sup> 2006	July–Aug, 2002 (A); July–Sept, 2003 (B)	Pennsylvania	In nursing home A, 40 of 170 residents (24%) had a respiratory illness; 4 of 10 specimens from symptomatic patients tested positive for rhinovirus. In nursing home B, 77 of 124 residents (62%) had a respiratory illness; 6 of 19 respiratory specimens from symptomatic patients tested positive for rhinovirus. Five of 10 (50%) rhinovirus-positive cases in both facilities showed clinical and radiographic evidence of pneumonia. There were 7 deaths from both facilities.
	Longtin et al, <sup>50</sup> 2010	July, 2009	Ontario, Canada	Thirty-two of 60 (53%) residents and 21 of 100 (21%) staff developed respiratory symptoms. HRV was identified in 5 of 14 nasopharyngeal swabs from symptomatic residents; no other pathogens were detected. Seven deaths occurred during the outbreak (6 owing to pneumonia or respiratory infection and 1 owing to failure to thrive).
	Mubareka et al, <sup>100</sup> 2013	Aug–Oct, 2012	Canada	Of 71 residents screened, 56 were positive for an HRV during an outbreak that lasted 5.5 wk. 3 different rhinovirus genotypes were identified suggesting presence of cocirculation of multiple genotypes during a large outbreak.

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**Table 1**  
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<b>Virus</b>	<b>Reference</b>	<b>Date of Outbreak</b>	<b>Location</b>	<b>Description</b>
Human Coronavirus (HCoV)	Birch et al, <sup>58</sup> 2005	Aug–Sept, 2002	Melbourne, Australia	Outbreaks of influenza-like illness occurred in 3 geographically distinct aged-care facilities. HCoV-OC43 RNA was detected in 16 of 27 nasopharyngeal swabs obtained from the 92 symptomatic residents; no other viruses isolated.
	Patrick et al, <sup>59</sup> 2006	Jul–Aug, 2003	British Columbia, Canada	Ninety-five of 142 residents (67%) and 53 of 160 staff members (33%) experienced symptoms of respiratory infection. Eight residents died. Initially misdiagnosed as SARS-CoV owing to antibody cross-reactivity. Subsequently, diagnosis corrected as HCoV-OC43 by RT-PCR.
Adenovirus	Kandel et al, <sup>64</sup> 2010	April–May, 2006	Massachusetts	Twelve of 40 residents had acute respiratory disease (4 confirmed, 8 suspected cases). Three positive cultures for HAdV type 4. Deaths in 3 of 4 confirmed cases and 1 of 4 suspected cases.

*Abbreviations:* HAdV, human adenovirus; HCoV, human coronaviruses; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; RSV, respiratory syncytial virus; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome coronavirus.

**Table 2****Taxonomy of noninfluenza respiratory viruses**

<b>Virus</b>	<b>Family</b>	<b>Genome</b>	<b>Subtypes</b>	<b>Seasonality<sup>a</sup></b>
Respiratory syncytial virus	Paramyxoviridae	Single-stranded negative sense RNA	A, B	Fall through Spring
Human metapneumovirus	Paramyxoviridae	Single-stranded negative sense RNA	A, B	Winter through Spring
Parainfluenza virus	Paramyxoviridae	Single-stranded negative sense RNA	HPIV-1, HPIV-2, HPIV-3, HPIV-4	Spring through Winter
Rhinovirus	Picornaviridae	Single-stranded positive sense RNA	More than 100 serotypes	Fall through Spring
Coronavirus	Coronaviridae	Single-stranded positive sense RNA	HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV <sup>b</sup> MERS-CoV <sup>b</sup>	Fall through Spring
Adenovirus	Adenoviridae	Double-stranded DNA	More than 50 serotypes; Major groups A-G	Winter through Spring

*Abbreviations:* HCoV, human coronaviruses; HPIV, human parainfluenza virus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

<sup>a</sup> Based on temperate climates.

<sup>b</sup> SARS-CoV and MERS-CoV are outside of the scope of this review.



The rates of RSV infections and death parallel that of influenza among LTCF residents as well. An LTCF in California reported a 6-week outbreak of RSV in 1979 with an attack rate of 40% and a case fatality rate of 20%.<sup>10</sup> Among 381 nursing homes in Tennessee, during 4 consecutive years (1995–1999), RSV contributed to an average of 15 hospitalizations, 76 antibiotic courses, and 17 deaths per 1000 persons each year.<sup>11</sup> In comparison, influenza caused an average of 28 hospitalizations, 147 antibiotic courses, and 15 deaths per 1000 persons each year. In 2008, active surveillance for symptomatic and asymptomatic respiratory viral infections detected an RSV outbreak in a 56-room, 120-bed LTCF in North Carolina.<sup>12</sup> Among 52 residents, 22 (42%) developed respiratory tract infections and, of those, 7 (32%) had an RSV infection confirmed using reverse transcriptase polymerase chain reaction (RT-PCR). One resident required hospitalization and subsequently died. This study in particular is notable for using RT-PCR to support timely and accurate recognition of an RSV outbreak. Although active surveillance for RSV may be useful in early diagnosis and, therefore, in outbreak prevention, the expense and resource use involved may render them impractical for most LTCFs.

### **Clinical Disease**

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As with influenza, the spectrum of clinical disease caused by RSV infections is diverse and heterogeneous (**Table 3**). Younger adults may be reinfected every 5 to 7 years, and may manifest symptoms of a mild cold or sinus infection or remain asymptomatic. In older adults, RSV may cause self-limiting upper respiratory tract infections, pharyngitis, rhinosinusitis, pneumonia, respiratory failure, and death. Unfortunately, clinical manifestations do not permit identification of specific viral pathogens, including RSV.<sup>5,13</sup> In a prospective study, Walsh and colleagues<sup>13</sup> assessed the clinical characteristics of older adults living in the community or retirement homes who were admitted to the hospital with an acute respiratory illness. Using culture, RT-PCR, serologic analysis, or a combination of these tests, they identified 132 patients with RSV infection and 144 with influenza A virus. They reported that RSV, compared with influenza A, was more commonly associated with nasal congestion (68% vs 55%;  $P = .03$ ), lower temperature at admission (37.7°C vs 38.1°C;  $P = .004$ ) and wheezing by history (73% vs 53%;  $P = .002$ ) or on physical examination (82% vs 68%;  $P = .02$ ). Although these factors were independent predictors for RSV infection persons, none were sufficiently sensitive or specific to accurately discriminate between illnesses caused by RSV versus influenza.

Among RSV-infected adults, disease severity correlates with increased levels of interleukin-6 (IL-6) and viral shedding. IL-6 is a proinflammatory cytokine associated with physical function decline and chronic disease.<sup>14</sup> A study of RSV-infected adults showed that hospitalized patients, compared with outpatients, had greater nasal IL-6 levels and shed RSV longer ( $13.1 \pm 6.3$  days vs  $9.8 \pm 4.8$  days, respectively).<sup>15</sup> Furthermore, hospitalized adults who required mechanical ventilation for RSV-related respiratory failure manifested higher peak RSV viral loads compared with those who did not ( $\log_{10} 3.7 \pm 1.7$  PFUs/mL vs  $\log_{10} 2.4 \pm 1.1$  PFUs/mL, respectively;  $P = .02$ ).<sup>16</sup> Similarly, among adults hospitalized with PCR-confirmed RSV infections ( $n = 123$ ; age  $78 \pm 15$  years), increasing concentrations of viral RNA were associated with respiratory insufficiency and risk of complications (adjusted odds ratio 1.40 per increase in  $\log_{10}$  copies/mL, 95% CI, 1.03–1.90;  $P = .034$ ).<sup>17</sup> Together, these studies indicate that high RSV viral loads correlate with disease severity.

Age-related immune senescence may increase older adults' risk for developing RSV infection and for subsequent hospital admission. Older adults with lower serum RSV neutralizing antibodies are more likely to become infected with RSV and to require

**Table 3**  
**Frequency of clinical manifestation of noninfluenza respiratory viral infections among older adults<sup>a</sup>**

	Fever	Headache	Nasal Congestion	Dyspnea	Wheezing	Cough	Sputum	Sore Throat	Myalgia	Fatigue	Hoarseness	Chest Pain
Influenza	+++	++++	+++	+++	++++	++	++++	++	++	+++	+++	++
Respiratory syncytial virus	++	+++	+++	+++	+++	+++	++++	++	++	++	+++	+
Human metapneumovirus	++	++	++	++++	+++	++	++++	++	++	++	+++	++
Parainfluenza virus	–	++	–	++	++	++	++	–	+	–	–	++
Rhinovirus	+	++	++	++	++	++	+++	++	+++	+	+++	++
Coronavirus	++	++	+++	+++	++	–	+++	–	++	++	++	–

<sup>a</sup> Adenovirus is excluded owing to the limited number of reports.

Frequencies are shown with symbols; + = 0%–25%, ++ = 26%–50%, +++ = 51%–75%, ++++ = 76%–100%; – = Frequency unknown owing to insufficient data.

Data from Refs. [4,5,13,26,27,36,44–47,101–106](#)

hospital admission. A prospective study of adults enrolled in day care programs compared serum anti-RSV antibody titers between an infected subgroup ( $n = 22$ ) and controls matched for age, exposure, and recent respiratory illness.<sup>18</sup> The mean titers of neutralizing antibodies against RSV were significantly lower in RSV-infected patients compared with controls for both group A ( $12.4 \pm 2.2$  vs  $14.2 \pm 2.2$ ,  $P = .008$ , respectively) and group B virus ( $9.1 \pm 2.1$ , vs  $10.3 \pm 1.5$ ,  $P = .01$ , respectively). A similar study evaluated antibody titers among a prospective cohort of adults with RSV infection ( $n = 130$ ), 61 of whom were hospitalized for RSV.<sup>19</sup> Multivariate analysis showed an increased risk for hospitalization (odds ratio, 5.89; 95% CI, 1.69–20.57;  $P = .04$ ) among adults with low serum anti-RSV antibody levels, defined as less than a 1:100 dilution.

After infection, RSV-specific antibodies provide some protection from reinfection, but levels usually decrease within months. A study evaluating 20 adults reported an 8-fold increase in RSV antibody titers after RSV infection. Within 1 year, however, the RSV antibody titers decreased by at least 4-fold in 15 of the adults studied (75%).<sup>20</sup> Because immunity is not complete after preceding infections, reinfection can occur throughout life.<sup>21</sup>

## HUMAN METAPNEUMOVIRUS

HMPV, first described in 2001, is a common cause of respiratory infections among all age groups and circulates from winter through spring in temperate climates. Like RSV, HMPV is a member of the Paramyxoviridae family and is divided into genotypes A and B, each of which includes subtypes. Given the variety of genotypes, a seasonal shift of predominant genotype can occur each year, similar to influenza virus.<sup>22</sup>

### *Epidemiology*

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A prospective study in Tennessee found similar rates of infection by HMPV and influenza among hospitalized adults.<sup>4</sup> Over 3 consecutive winters, Widmer and colleagues<sup>4</sup> enrolled 508 individuals 50 years and older, more than 90% of whom lived in the community, who were hospitalized with respiratory symptoms or nonlocalizing fever. RT-PCR testing on nasal swabs detected HMPV in 4.5% (23/508) and influenza virus in 6.5% (33/508) of hospitalized individuals. Patients with HMPV, compared with those with laboratory-confirmed influenza, were older (median age, 76.2 vs 60.0), had more cardiovascular disease (78.3% vs 51.5%), and were more likely to have received the influenza vaccination (87.0% vs 51.5%). Notably, they were also less likely to report a fever (51.2% vs 87.9%).

Several reports describe notable morbidity and mortality associated with HMPV outbreaks in LTCF residents. In 2006, 27% of residents (96/364) at an LTCF in Quebec City, Canada, presented with respiratory or constitutional symptoms.<sup>23</sup> Of 13 samples obtained by nasopharyngeal swab or nasopharyngeal aspirate, real-time multiplex RT-PCR detected HMPV in 6 residents. The fatality rate was 50% (3 of 6 patients) among confirmed HMPV cases. In 2011, 36% of residents (16/44) at an LTCF in Oregon met the case definition of severe respiratory tract infection and, of those, 5 had pneumonia, 4 were hospitalized, and 2 died. Six of 10 nasopharyngeal swab specimens collected from the 16 afflicted residents tested positive for HMPV.<sup>24</sup> Similarly, in the winter of 2011 to 2012, 2 skilled nursing facilities in Idaho and Washington also experienced HMPV outbreaks.<sup>25</sup> Among the residents with lower respiratory tract infections, 56% (25/45) had pneumonia, and 11% (6/45) died. For 3 of the HMPV outbreaks described, the outbreak investigation queried about the staff caring for the

residents and found that some of them also experienced symptoms of acute respiratory illness.

### **Clinical Disease**

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The clinical manifestations of HMPV infection in adults, similar to those in children, are nonspecific upper respiratory symptoms including cough and nasal congestion, although asymptomatic infection is common.<sup>26–28</sup>

Several prospective studies assessed the symptoms manifested by older adults. Older adults developed dyspnea and wheezing more frequently than younger adults,<sup>26</sup> although these symptoms are not specific to HMPV.<sup>4</sup> Compared with influenza, however, fever is reported less frequently (51.2% vs 87.9%).<sup>4</sup> In a prospective study of adults hospitalized for community-acquired pneumonia, Johnstone and colleagues<sup>29</sup> used RT-PCR on nasopharyngeal swabs to detect HMPV in 4% of cases (8/193) during influenza season; concomitant blood, sputum, and assays for other virus and atypical bacterial pathogens were negative. Specific risk factors for HMPV infection for older adults and residents of LTCF are not yet known.

### **PARAINFLUENZA VIRUS**

Human parainfluenza virus (HPIV), a single-stranded negative sense RNA virus, is yet another member of the Paramyxoviridae family. First detected in the 1950s, this virus has 4 major serotypes, HPIV-1, HPIV-2, HPIV-3, and HPIV-4.<sup>30</sup> Parainfluenza virus generally circulates from spring through winter, with different seasonality and peaks depending on serotypes.<sup>31</sup> In children, HPIV-1 and HPIV-2 cause croup and HPIV-3, the most prevalent serotype, is associated with bronchiolitis and pneumonia.

### **Epidemiology**

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Two reports describing large, population-based studies detail the morbidity and mortality of HPIV in older adults. Between 1976 and 1982, the Communicable Disease Surveillance Center in the United Kingdom received 5781 laboratory reports of HPIV infection.<sup>32</sup> Although just 2% of positive HPIV samples (121/5781) came from older adults, 46% (56/121) of those individuals had pneumonia or other lower respiratory tract infection. A population-based study of adults aged 65 or older in the Netherlands estimated the numbers of deaths attributable to HPIV between 1999 and 2007. The authors reported lower rates of mortality caused by HPIV (0.9%) compared with influenza A (1.5%) or RSV (1.4%).<sup>33</sup>

Several reports describe HPIV outbreaks in LTCFs, most owing to HPIV-3.<sup>32,34,35</sup> In 1993, 30% of residents (26/84) and 6% of staff (5/78) at an LTCF in Ontario, Canada, developed respiratory tract infections.<sup>36</sup> Paired sera from 6 of 10 ill residents showed a 4-fold or greater increase in antibodies to HPIV-3. One resident was hospitalized, although none died. In 1999, 51% of residents (25/49) at a 50-bed skilled nursing unit at a Wisconsin Veterans Home developed new respiratory symptoms.<sup>37</sup> Viral cultures from 4 of 10 residents tested grew HPIV-3. Because viral cultures are typically less sensitive than PCR-based detection methods, this likely underestimated the true prevalence of HPIV-3.<sup>38</sup> Three residents required hospitalization and 4 died. In 2016, 11 residents presented with respiratory symptoms in a 30-bed residential aged care facility in Australia. Nine of 10 nasopharyngeal swabs tested positive for HPIV-3 by PCR. Two residents were hospitalized and none died.<sup>39</sup> These outbreaks indicate that compared with RSV and HMPV, HPIV outbreaks in LTCF have similar rates of attack and morbidity.

### **Clinical Disease**

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In healthy immunocompetent adults, HPIV infections are usually asymptomatic or cause mild respiratory symptoms indistinguishable from other common respiratory viruses.<sup>30</sup> A prospective study of the etiology of community-acquired pneumonia among adults in the Netherlands identified HPIV in 6% of cases.<sup>40</sup> Reported in 1998, an investigation of an outbreak of lobar pneumonia at a 70-bed LTCF in Massachusetts suggests a possible association between *S pneumoniae* pneumonia and preceding HPIV infection.<sup>35</sup> Over 10 days, 10 residents developed lobar pneumonia; 9 had serum available. The study used 18 matched controls. Of those, 5 had both serologic evidence of recent HPIV-1 infection and upper respiratory infection symptoms in the preceding month, compared with 2 of 18 controls (matched odds ratio, 9.0; 95% CI, 1.2–208). Ultimately, 2 of the 10 residents with pneumonia died; both of them had evidence of *S pneumoniae* infection. The authors note that only 3 of the 67 residents had documentation of pneumococcal vaccination. After identification of the eighth case of pneumonia, all nursing home residents received influenza and pneumococcal vaccines.

### **RHINOVIRUS**

A single-stranded, positive-sense RNA virus, the human rhinovirus (HRV) accounts for 30% to 50% of common colds each year.<sup>41</sup> There are more than 100 serotypes of HRV, which is divided into 3 genotypes, A, B, and C; the severity of illness does not seem to be associated with a particular genotype.<sup>42</sup> In temperate climates, HRV circulates year round and are more likely to cause illness in the warmer months; infections caused by influenza and RSV predominate in the winter months.<sup>41</sup> HRV causes respiratory infections in every age group, and recurrent infection can occur throughout life.<sup>43</sup>

### **Epidemiology**

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Rhinovirus infection is one of the most common noninfluenza respiratory viruses in older adults. A prospective study in the Netherlands evaluated community-dwelling older adults with acute respiratory symptoms for viral infections.<sup>44</sup> PCR on nasopharyngeal swabs or serology detected rhinovirus in 32% of cases (34/107), followed by coronavirus 17% (18/107) and influenza A 5% (5/107). Among symptom-free controls, these rates were 2% (2/91), 2% (2/91), and 0% (0/91), respectively. A similar prospective surveillance study in England found similar results with rhinovirus identified in 24% of respiratory infections (121/497) in adults aged 60 to 90 years.<sup>45</sup> Coronavirus (12%; 59/497) and influenza A or B (3%; 17/497) were the next most common pathogens. Multiple logistic regression analysis showed that current smoking (odds ratio, 1.47; 95% CI, 1.14–1.90) and chronic medical conditions (odds ratio, 1.40; 95% CI, 1.17–1.68) were independently associated with lower respiratory complications. Chronic medical conditions included regular treatment for heart disease, respiratory illness, or another high-risk condition designated by the Department of Health. Similarly, a prospective study in Italy assessed people over 65 years of age who presented to the emergency department with a fever and a respiratory illness in February and March of 2009 and 2010.<sup>46</sup> PCR performed on nasopharyngeal washes detected HRV in 16% of samples (17/103) in 2009 and 8% (11/135) in 2010. In comparison, influenza A was more prevalent than HRV in 2009 (24%, 25/103) and absent in 2010, likely because the pandemic H1N1 influenza circulated through the region in October through December 2009.

HRV is a frequent cause of outbreaks in LTCFs that are notable for high attack rates and mortality.<sup>47–49</sup> From July through December 2009, 269 LTCFs in Ontario, Canada,

reported 297 respiratory outbreaks; all LTCFs submitted samples to the Ontario Public Health Laboratory.<sup>50</sup> Molecular-based methods implicated HRV as the cause of 59% of the outbreaks (174/297). The next most prevalent virus was influenza A, which caused 7.0% of the outbreaks (22/297).

In the summers of 2002 and 2003, two nursing homes in Pennsylvania reported severe respiratory disease outbreaks associated with HRV.<sup>47</sup> In facilities A and B, 24% (40/170) and 62% of residents (77/124) experienced a respiratory illness. Specimens collected from symptomatic residents at facility A and B tested positive for HRV in 4 of 10 and 6 of 19 samples, respectively. Of the 10 rhinovirus-positive cases, 5 residents had clinical and radiographic evidence of pneumonia. Between the 2 facilities, a total of 7 residents died of severe respiratory illness concurrent with the HRV. In June 2003, a 99-bed LTCF in California experienced a similar outbreak.<sup>48</sup> Notably, 21% of the residents (12/56) died, possibly owing to a secondary bacterial infection. Of 13 respiratory specimens collected, 7 (54%) were culture positive for rhinovirus. Furthermore, 2 of 3 sputum cultures grew nontypeable *Haemophilus influenzae*. The high attack rate associated with HRV may render large numbers of residents vulnerable to secondary bacterial infection, ultimately resulting in both morbidity and mortality from a virus regarded as a cause of the common cold.

### **Clinical Disease**

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Usually regarded as a pathogen with low virulence, HRV may cause asymptomatic infection among younger adults.<sup>51</sup> Asymptomatic infection is less common in older adults. In addition to the common cold symptoms such as rhinorrhea, cough, and sore throat, HRV infection may cause asthma exacerbations in children and younger adults and, as discussed, may cause or predispose LTCF residents to bacterial pneumonia.<sup>52,53</sup>

### **HUMAN CORONAVIRUS**

First described in 1965, human coronaviruses (HCoV) also cause common colds among all age groups, with infections occurring more often in winter and spring compared with summer and fall.<sup>54</sup> The Coronaviridae family, composed of single-stranded positive-sense RNA viruses, also includes severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, both of which are beyond the scope of this review. Strains HCoV-229E and HCoV-OC43 seem to be most frequently associated with human respiratory diseases.

### **Epidemiology**

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HCoV causes upper respiratory infections in elderly people living in the community. Two prospective studies in Rochester, New York, and England used a 4-fold increase in antibody titers between the acute and convalescent phase to indicate infection<sup>55,56</sup> They found evidence for infection with HCoV-229E in 51% (31/61) and HCoV-229E or HCoV-OC43 in 30% (69/231), respectively, of community-dwelling older adults with acute respiratory illnesses.

Although HCoV is also one of the most common respiratory viruses in LTCFs to our knowledge, only 2 reports describe HCoV outbreaks in LTCFs.<sup>57</sup> Birch and colleagues<sup>58</sup> reported outbreaks of respiratory disease and influenza-like illness in August and September 2002 among 3 geographically distinct LTCFs in Melbourne, Australia. From 92 symptomatic residents at the 3 institutions, staff obtained 27 nasopharyngeal swabs. PCR-based testing detected HCoV-OC43 RNA in 59% of the specimens (16/27); no other viruses were isolated. Additionally, among 85 staff members,

37 developed respiratory symptoms, indicating an attack rate of 44%. Not surprisingly, epidemiologic investigations determined that LTCF staff members were the index case in 2 of the 3 LTCFs. The second report also describes an outbreak of HCoV-OC43. In the summer of 2003, an LTCF in British Columbia, Canada, reported that 67% of their residents (95/142) and 33% of their staff members (53/160) developed respiratory infections.<sup>59</sup> Eight residents died. Interestingly, the outbreak was initially attributed to severe acute respiratory syndrome coronavirus owing to cross-reactivity to antibodies against nucleocapsid proteins from both viruses. Subsequently, RT-PCR confirmed HCoV-OC43. Together, these 2 outbreaks suggest that HCoV-OC43 represents a virulent pathogen for older adults in LTCFs. Additionally, they also highlight the role that ill health care workers may have in transmitting illnesses to LTCF residents.

### ***Clinical Disease***

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Similar to HMPV, HPIV, and HRV, HCoV infections often manifest as common colds without specific or defining characteristics. A large, prospective, cohort study by Walsh and colleagues<sup>60</sup> details clinical features of HCoV infection in adults. In Rochester, New York, adults who developed an acute respiratory illness in the winter months from 1999 to 2003 underwent surveillance with RT-PCR and serologic studies. The adults included 4 cohorts: healthy older adults ( $n = 611$ ; age  $75 \pm 6$  years), high-risk adults with underlying cardiopulmonary disease ( $n = 511$ ; age  $70 \pm 11$  years), healthy young adults ( $n = 291$ ; age  $33 \pm 5$  years), and a hospitalized group ( $n = 1388$ ; age  $75 \pm 12$  years). During the study period, testing identified 398 HCoV infections from all cohorts, 214 of which (54%) were symptomatic. Of those, 10% (21/214) of them had evidence of viral infection. Manifestations of HCoV infection among prospective cohorts excluding the hospitalized group were congestion (98%–100%), constitutional symptoms (53%–74%), and cough (40%–79%). Fever was not common; the mean temperature ranged  $36.4^{\circ}\text{C}$  to  $36.8^{\circ}\text{C}$ . Asymptomatic infection, defined as a 4-fold or greater increase in HCoV-specific serum IgG in the absence of respiratory symptoms, was common, ranging from 33% to 44% in prospective cohorts. Among 71 HCoV infections in the hospitalized group, 23 (32.3%) had infiltrate on chest radiography and 3 (4.2%) died. Although capable of causing acute exacerbations of chronic obstructive pulmonary disease or community-acquired pneumonia, most HCoV infections seem to be less severe than those caused by RSV, HMPV, and PIV.<sup>61,62</sup>

### **ADENOVIRUS**

Human adenoviruses (HAdV), members of family Adenoviridae, was first isolated from human adenoid tissue in 1953. These double-stranded DNA viruses, of which there are now more than 50 serotypes identified, cause a variety of illnesses, most commonly respiratory infections, conjunctivitis, and gastroenteritis.<sup>63</sup>

### ***Epidemiology***

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Only limited descriptions specifically focus on HAdV infection in older adults, Kandel and colleagues<sup>64</sup> reported an outbreak of HAdV type 4 among residents of an LTCF in Boston, Massachusetts, in April and May 2006. Acute respiratory infections developed in 30% of residents (12/40), and 4 of those 12 died. Nasopharyngeal aspirates from 7 specimens initially tested negative using a rapid antigen test. PCR-based testing subsequently confirmed HAdV type 4 in 3 of the 7 tests, highlighting the low sensitivity of the rapid test.



### ***Clinical Disease***

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Although most people recover without complications, infection by some HAdV serotypes may cause severe pneumonia and significant morbidity and mortality, even among immunocompetent young adults.<sup>62,65–69</sup> From a population health perspective, however, HAdV is perhaps a less important pathogen in older adults compared with influenza and the other respiratory viruses described.

### **DIAGNOSTIC TESTING**

A wide range of diagnostic tests may identify the cause of viral respiratory infections. Serologic testing compares acute and convalescent specimens collected weeks apart. Although useful for epidemiologic research, serologic testing is not practical for clinical care. Rapid antigen tests have an advantage of quick results, but are limited in their usefulness owing to poor sensitivity and specificity. When clinical suspicion of a disease is high, negative tests should be confirmed with another testing method.<sup>70</sup> Viral cultures are neither sensitive nor timely in their outcomes, rendering these unhelpful in clinical practice. Some laboratories may offer enzyme immunoassay testing. For most respiratory viruses, these also lack sensitivity.<sup>38</sup>

The US Food and Drug Administration has approved several nucleic acid amplification tests for clinical use, with tests for influenza representing the most commonly used single virus assay. Multiplex panels use PCR to test for several respiratory viruses at once, a practical strategy because clinical manifestations do not permit the identification of specific viral pathogens. The number of respiratory viruses tested, sensitivity, and specificity in detection of each virus are different depending on which multiplex PCR test is used.<sup>71</sup> Other than for influenza, the lack of effective antiviral medications combined with the costs associated with nucleic acid amplification test make routine use of these studies impractical for most clinical settings. A potential benefit to more routine use of nucleic acid amplification tests for acute respiratory infections, however, may be the early detection of viral outbreaks in LTCFs through active surveillance, which may confer further benefits by reducing unnecessary antibiotic use.<sup>12</sup> The Infectious Diseases Society of America endorsed this approach in their 2008 clinical practice guidelines addressing fever and infection in LTCF residents.<sup>72</sup> Finally, identification of viral pathogens among older adults with community-acquired pneumonia may support decisions to stop antibiotics and thus support antibiotic stewardship practices.<sup>73</sup>

### **PREVENTION AND MANAGEMENT**

As demonstrated for influenza, vaccines are a safe and at least partially effective approach to preventing illness caused by respiratory viral pathogens. Although a detailed discussion of vaccines is beyond the scope of this article, of the pathogens discussed, RSV is a high priority for vaccine development, although none are yet available for clinical use. In the meantime, the most effective prevention measures include the use of transmission-based precautions, including hand hygiene and social distancing, as part of broader infection prevention and control activities.

### ***Infection Prevention and Control***

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The prevalence and sheer number of respiratory viral pathogens means that, despite our best efforts, most adults will have 2 to 3 viral infections each year.<sup>74</sup> Understanding the transmission of respiratory viruses informs the foundation for infection prevention and control. We focus here on applying these principles to residents of LTCFs.<sup>75</sup>



### **Transmission**

People may become infected with respiratory viruses through direct contact (person to person), indirect contact (via fomites), and droplets containing respiratory secretions. Direct physical contact with an infected person is the most common, efficient, and important form of noninfluenza respiratory virus transmission.<sup>76</sup> Indirect contact occurs via exposure to viable viral particles on fomites contaminated by infected individuals. Finally, susceptible individuals may breathe in droplets of respiratory secretions from an infected person who sneezes or coughs. The CDC defines droplets as respiratory secretions larger than 5  $\mu\text{m}$  and advises using a surgical mask to prevent exposure.<sup>77</sup> Gralton and colleagues<sup>78</sup> evaluated the size of particles produced by 12 adults and 41 children with symptomatic respiratory infections. They reported that with breathing or coughing, 80% of the participants produced airborne particles less than 5  $\mu\text{m}$  in diameter that contained viral RNA. These findings, and those of other investigators,<sup>79,80</sup> support consideration of airborne precautions for outbreaks with severe respiratory viral illnesses, including influenza. However, association with clinical outcomes is still lacking. In addition, airborne precautions are not possible outside of hospital settings and thus are not currently recommended.

### **Hand hygiene**

Hand hygiene remains the most important measure to prevent infections in health care settings. Just as in acute care, health care workers in LTCFs demonstrate deficiencies in their hand hygiene practice<sup>81,82</sup> and alcohol-based hand rub improves adherence.<sup>83</sup> Schweon and colleagues<sup>84</sup> described a comprehensive hand hygiene program involving alcohol-based hand rub use by both health care workers and residents at an LTCF in Pennsylvania. Lower respiratory tract infections decreased among the residents. Although the outcomes did not differentiate between viral and bacterial infections, they clearly support the important role of basic hand hygiene practices to prevention infections.

### **Isolation precautions**

In 2007, the CDC last updated guidelines for isolation precautions in health care setting including LTCFs.<sup>77</sup> In general, they recommend droplet precautions in addition to standard precautions during the care of individuals with a possible respiratory viral infection. Notably, they call for the use of personal protective equipment, including gowns, gloves, and a mask, for entry into rooms of people on droplet precautions. They also introduced respiratory hygiene and cough etiquette, asking symptomatic people to cover their mouth and nose when sneezing or coughing, to use tissues and dispose of them in no-touch receptacles, to perform hand hygiene after soiling of hands with respiratory secretions, and to wear a surgical mask if tolerated or maintain spatial separation of at least 3 feet when possible. Although not specifically mentioned in the 2007 CDC guidelines, social distancing also reduces the risk of respiratory virus transmission. Social distancing includes avoiding people who are sick, canceling group activities, and staying home from work when ill. This approach is readily implemented in long-term care and other communal settings.

### **Work restriction of health care personnel**

Guidelines addressing infection control among health care personnel recognize that staff may transmit respiratory viral infections to others and indicate that people with acute viral respiratory infections should not care for high-risk individuals, particularly during community outbreaks of influenza and RSV.<sup>85</sup> The same document also acknowledges that restriction of infected health care personnel from all patient care duties may not be possible because large numbers of personnel may have viral

respiratory illnesses during the winter. A prospective study of health care workers at a tertiary care children's hospital detected respiratory virus in 16.7% of nasal swabs collected from asymptomatic individuals during influenza season (November through April).<sup>86</sup> Perhaps of greater concern was that 46% of the subjects reported working while ill with an influenza-like illness. Although these findings may be representative of people working in long-term care, several of the descriptions of noninfluenza viral outbreaks in LTCFs suggest strong parallels. Accordingly, employers might consider strategies to help health care workers with respiratory illnesses minimize their contact with LTCF residents as part of resident safety. When this is not possible, cohorting sick staff and residents may help augment infection control efforts.<sup>87</sup>

### **Treatment**

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Unlike influenza, which may be treated with specific and effective antiviral agents, supportive care remains the mainstay of management for older adults with respiratory illnesses caused by the viruses discussed. Supportive care is an active process that includes frequent monitoring until the patient's clinical status improves.<sup>88</sup> Additional features of supportive care for people with respiratory viral infections include hydration, treatment of fever with acetaminophen, albuterol, supplemental oxygen, and perhaps nebulized saline.

Viral infections may precede or occur concurrently with bacterial pneumonia. When concomitant or secondary bacterial lower respiratory infection is suspected in patients with respiratory viral infection, empirical antibiotics should be used. Falsey and colleagues<sup>89</sup> investigated 771 adults hospitalized with respiratory illness, finding that 348 (41%) had a viral infection and, of those, 136 (39%) had evidence of bacterial coinfection, as assessed using procalcitonin and specific bacterial tests. Ideally, among older adults in whom a viral pneumonia is suspected, procalcitonin results that confirm the absence of a bacterial infection should help clinicians to stop antibiotics. A recent systematic review concluded that using procalcitonin to guide initiation and duration of antibiotic treatment in patients with acute respiratory infections reduced antibiotic consumption and was not associated with higher mortality rates or treatment failure.<sup>90</sup> Procalcitonin is not yet available as a point-of-care test and is, therefore, still relegated primarily for use in research and acute care settings.

Even with the recent introduction of procalcitonin, determining if a patient has a mixed viral-bacterial infection or bacterial superinfection after a viral respiratory illness presents a significant clinical challenge. In adults, typical clinical signs and symptoms suggestive of pneumonia (eg, temperature  $\geq 38^{\circ}\text{C}$  or  $< 35^{\circ}\text{C}$ , cough, dyspnea, tachypnea, hypoxia, abnormal percussion or altered breath sounds on auscultation, leukocytosis, or leukopenia) are not sufficient to accurately predict whether community-acquired pneumonia is owing to viral and/or bacterial etiologies.<sup>91</sup> Additional consideration of atypical signs and symptoms of infection common to frail older adults, such as decreased appetite, lethargy, delirium, and age-appropriate definitions of fever only adds to diagnostic uncertainty about pneumonia in general, let alone the specific etiology. Molecular testing improves detection for bacterial and viral pathogens, but the implications of test results for clinical care are not yet clear. Gadsby and colleagues<sup>92</sup> collected sputum (96%) and endotracheal aspirates (4%) from 323 adults hospitalized for community-acquired pneumonia. Based on multiplex PCR, they detected viruses in 30% of patients (98/323), with 82% of viruses (80/98) codetected with bacteria. These results suggested potential deescalation of antibiotics in 77% of cases, but the authors did not specifically describe stopping antibiotic therapy.

The minimum criteria developed by Loeb and colleagues<sup>93</sup> for the initiation of antibiotics in residents of LTCFs may offer some guidance to help differentiate between viral and bacterial bronchitis and pneumonia. Developed mainly based on observational studies and expert opinion, the intent of these recommendations is to reduce unnecessary antibiotic use among LTCF residents. For residents with respiratory infections, the Loeb minimum criteria for initiation of antibiotics call for assessment of vital signs (temperature, heart rate, and respiratory rate), symptoms (cough, sputum, and rigors), delirium, and medical history of chronic obstructive pulmonary disease. These criteria do not require blood tests or imaging studies, permitting them to help inform clinical decisions about active monitoring versus initiating antibiotics in resource-limited settings. For settings with more robust resources, diagnostic tests may provide more specific guidance.

## SUMMARY

The majority of clinical knowledge about noninfluenza respiratory viruses comes from pediatric studies. As demonstrated, these viral pathogens also have an important influence on the health of older adults. RSV, in particular, causes infections that rival the morbidity and mortality caused by influenza. Outbreaks of any of the viruses discussed, when they occur in LTCFs, also have grave consequences for frail older adults, especially among those with chronic cardiopulmonary diseases. Unlike influenza, effective vaccines and antiviral medications are not yet available, even for RSV. Accordingly, infection prevention and control measures remain the best protection against these pathogens. Hand hygiene is important in all settings; within health care facilities, the use of masks, gowns, and gloves may reduce the risk of infection transmission among health care workers and patients or residents.

Recent advances in rapid molecular diagnostic tests may permit greater recognition of the consequences of respiratory viral infections among older adults. In acute care settings, early recognition of viral infections among hospitalized patients may promote more judicious use of antibiotics. Within LTCFs, routine surveillance using multiplex PCR tests may rapidly identify viral outbreaks and foster swift implementation of infection prevention and control measures. Finally, a better assessment of the overall influence of noninfluenza respiratory pathogens may support innovations leading to effective antiviral therapy and vaccinations with the potential to improve the health of people of all ages.

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