Coronaviruses contribute to the burden of respiratory diseases in children, frequently manifesting in upper respiratory symptoms considered to be part of the "common cold." Recent epidemics of novel coronaviruses recognized in the 21st century have highlighted issues of zoonotic origins of transmissible respiratory viruses and potential transmission, disease, and mortality related to these viruses. In this review, we discuss what is known about the virology, epidemiology, and disease associated with pediatric infection with the common community-acquired human coronaviruses, including species 229E, OC43, NL63, and HKU1, and the coronaviruses responsible for past world-wide epidemics due to severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus.

**Keywords.** coronavirus; SARS; MERS; COVID-19; pediatric respiratory viruses.

Understanding the history and epidemiology of the common community human coronaviruses (HCoVs) and those responsible for recent past epidemics is crucial to the control and treatment of novel coronaviruses. The epidemiology of previously described community coronaviruses in children is relatively well known from surveillance studies. However, important clinical and laboratory details of these viruses, such as duration of shedding, transmission rates, viral load over time, immunity, and morbidity in high-risk populations, are not well characterized. Such information becomes more important and clinically relevant as we consider world-wide pandemics such as the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak.

Coronaviruses are already known to be ubiquitous viruses and recognized as pathogens in both humans and animals. A coronavirus was first isolated as a causative agent of bronchitis in birds in 1937 [1] and was originally discovered in humans during studies that evaluated the common cold. The history of the discovery of HCoVs is shown in Table 1 [2–20]. The common human coronaviruses known today include the species 229E, OC43, NL63, and HKU1. These 4 viruses are primarily viewed as relatively benign respiratory pathogens in humans, typically causing upper respiratory tract disease and common cold symptoms. By contrast SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) are highly pathogenic in humans, with high rates of severe pneumonia and fatal outcomes [21]. Currently, the novel coronavirus SARS-CoV-2 is spreading worldwide, causing anxiety, disease, and mortality [22, 23]. Despite the heightened interest, limited pediatric data are available regarding either the community HCoVs or the newer pathogenic species in children. Here, we review what is known about HCoV infections in children in the pre-coronavirus disease 2019 (COVID-19) era.

**VIROLOGY**

Coronaviruses belong to the *Coronaviridae* family in the *Nidovirales* order. The coronavirus subfamily is further classified into 4 genera known as the alpha, beta, gamma, and delta coronaviruses. These viruses cause a wide variety of generally species-specific illness in mammals and birds, including chickens, turkeys, bats, rats, dogs, cats, piglets, and whales [21]. Coronaviruses were named for their characteristic crown-like surface projections seen in electron micrographs that correspond to large surface spike proteins. These viruses are enveloped, nonsegmented, positive-sense RNA viruses and have the largest identified viral RNA genomes, with an approximate length of 30 kilobases [24].

Only alpha and beta coronaviruses are known to infect humans. Both HCoVs 229E and NL63 are alpha coronaviruses and HCoV-HKU1, HCoV-OC43, MERS-CoV, and SARS-CoV are beta coronaviruses (Table 1) [24, 25]. Phylogenetic analysis has revealed that SARS-CoV-2 also falls within the beta coronavirus in the same subgenus as the SARS-CoV, but in a different clade [26]. All 7 coronaviruses that infect humans are believed to have originated in bats [27, 28]. Based on modeling, it is speculated that HCoV-OC43 was transmitted to humans around 1890 [29].
Bats also appear to be the original host of SARS-CoV-2, and it is hypothesized that currently unknown wild animal(s) sold at the Huanan seafood market in Wuhan, China, might have played a role as an intermediate host to humans [26].

HCoVs OC43 and 229E were isolated from nasal cavities of people with the common cold in the 1960s. In the 1970s, studies that used serology and viral culture linked HCoVs 229E and OC43 with 8% of cases of lower respiratory tract infection (LRTI) in hospitalized infants [30, 31]. Poor replication in tissue culture and a lack of cytopathic effect in early attempts at culture were major obstacles in making further progress in the field. The development and widespread use of molecular diagnostics as well as the emergence of SARS-CoV in 2003 significantly accelerated coronavirus research. Subsequently, new HCoVs NL63 and HKU1 were identified and are frequently seen in children. Additional pathogenic coronavirus species and outbreaks with MERS-CoV and, recently, SARS-CoV-2 have led to increased interest, research, and concern [21, 23].

EPIDEMIOLOGY OF COMMON HCOVS: OC43, NL63, HKU1, AND 229E

Community-acquired HCoVs species OC43, NL63, HKU1, and 229E are found worldwide in temperate and tropical countries, as well as low-, middle-, and high-income countries [32, 33]. HCoV infection can occur at any time of the year, with unpredictable year-to-year patterns, and outbreaks are reported in some years and in certain parts of the world. All 4 species may circulate yearly and even simultaneously [34], with the highest rates of HCoV infection seen in winter and spring months in temperate climates [21]. Almost all surveillance data indicate HCoV-OC43 is the most common species. A large prospective surveillance study conducted in Norway from 2006 to 2015 that enrolled all hospitalized children aged ≤16 years with respiratory tract infections revealed that HCoVs OC43 and NL63 were detected most frequently and were epidemic every second winter [35]. HCoV-HKU1 was prevalent every second winter during the year when detection rates for HCoVs OC43 and NL63 were low; HCoV-229E was the least common.

Sero-prevalence data suggest that exposure is common in early childhood [36]. More than 90% of adults are seropositive for at least 1 HCoV species [37]. A recent prospective active surveillance study of young infants in Nepal that used multiplex polymerase chain reaction (PCR) showed that HCoVs are less common in neonates compared with older infants [32]. Outbreaks of variable sizes have been reported sporadically in medical students, young asthmatic children, and neonatal intensive care units [38–41]. For example, an outbreak of HCoV-229E was reported in a neonatal intensive care unit where 92% of infected preterm neonates developed symptoms, including worsening respiratory conditions and bradycardia [42]. Potential nosocomial transmission by staff members was speculated.

Large surveillance studies of children and adults to evaluate the prevalence of all major respiratory viruses using multiplex PCR have been conducted in many settings, showing that HCoV infections are the fourth or sixth most common virus detected overall and across all age groups [33, 43]. Coinfections are relatively common, especially in children aged ≤5 years. A prospective surveillance study in Norway demonstrated that annual hospitalization rates of children with LRTI associated with HCoV detection were 1.5 and 2.8 per 1000 children aged <5 years and aged <1 years, respectively [35].

SHEDDING AND TRANSMISSION OF COMMON HCOVS: OC43, NL63, HKU1, AND 229E

The mode(s) of HCoV transmission is not known [21, 25]. It is assumed that transmission occurs via a combination of droplet and direct/indirect contact, similar to other respiratory viruses. HCoVs OC43 and 229E appear to be primarily transmitted during the first
few days of illness when symptoms and viral load in the respiratory tract are highest. The incubation period of HCoV-229E was 2 to 5 days (median, 3 days) in adults in challenge studies and has not yet been clearly defined for other HCoVs or in children [25, 44].

The transmission of HCoV in community epidemics is impacted by the characteristics of HCoV infection and shedding in children. Children have higher attack rates, as high as 78% within households, compared with adults, as shown in an active surveillance study in Kenya [45]. These data complement community studies in the 1960s that showed a higher frequency of HCoV-229E in families with children aged <15 years [36], a higher rate of HCoV-OC43 infection in children aged <5 years [46], and frequent clustering of infections within families [46]. The attack rate of HCoV in childcare settings has also been shown to be higher with younger age [47].

Children may shed HCoVs for extended periods of time after infection, potentially leading to additional transmissions within close-contact settings. There are very limited data regarding duration of shedding in children. In prospective childcare studies, 34% of children with HCoV had detectable virus at 1 week or more following symptom onset, with shedding documented for up to 18 days (Figure 1) [47, 48]. A longitudinal study of weekly nasal swabs taken from symptomatic and asymptomatic adults and children similarly found that viral detection extended beyond 1 week [49]. Children aged <5 years with HCoV detection were frequently asymptomatic, especially with HCoV-229E. These findings reinforce serologic-based findings of asymptomatic infection in 7% of children with HCoV-229E in the 1960s [50].

Figure 1. Examples of HCoV shedding patterns in young children attending child care centers [47, 48]. Children attending group childcare were tested prospectively for respiratory viruses at each acute respiratory illness (ARI). Swabs were collected weekly from ARI onset until symptoms were nonworsening and swabs were negative by real-time-polymerase chain reaction [47]. Human coronavirus (HCoV)-positive swabs (for all species) are represented by filled circles, and negative swabs are represented by open circles. Weeks on x-axis were calculated as weeks since symptom onset with an HCoV (+) acute respiratory illness. The lower limit of positivity was set at 1000 copies/mL for this analysis. Sequencing of HCoV isolates was not performed.

CLINICAL MANIFESTATIONS OF COMMON HCOVS: OC43, NL63, HKU1, AND 229E

Clinical symptoms associated with the 4 common HCoVs generally appear to be indistinguishable from cold symptoms or influenza-like illness (rhinorrhea, sore throat, cough, wheezing, and fever) associated with other respiratory viruses [21, 25, 51] and generally are similar in children and adults.

Respiratory Tract Infections

HCoVs 229E and OC43 were shown to be pathogenic in adult human volunteer studies. Cold symptoms (eg, sore throat, rhinorrhea, cough) are very similar to those caused by other respiratory viruses [39, 44]. It is assumed that HCoVs NL63 and HKU1 have similar pathogenicity, although this has not been proven in challenge studies. The frequent detection of HCoVs in asymptomatic patients as well as coinfection with other respiratory viruses make the interpretation of HCoV pathogenesis and clinical findings challenging. A multicenter, prospective surveillance study conducted in the United States evaluated the prevalence of HCoVs among hospitalized children with acute respiratory illness and demonstrated that the prevalence of HCoVs was similar in both asymptomatic and symptomatic groups of children [52]. In contrast, a prospective community surveillance study of respiratory viruses in Utah showed HCoV detection was often associated with symptoms in all age groups, suggesting HCoV infection might have been previously underestimated as an etiology of respiratory tract infection [49].

An analysis of new and old data reveals, not surprisingly, that viral coinfections are less common in children with influenza virus (9% of influenza in Seattle, Washington; 27% in Seoul, South Korea) than in children infected with a community HCoVs (43% of HCoV infections in Seattle and 42% in Seoul; Table 2). A Norwegian prospective surveillance study compared children hospitalized with respiratory tract
infections vs asymptomatic children admitted for elective surgery [35]. Multivariable analyses suggest that higher viral load (cycle threshold <28 by PCR), codetection of generally symptomatic viruses (respiratory syncytial virus [RSV], human metapneumovirus, influenza, and parainfluenza virus), younger age (<2 years), being female, and high-risk underlying conditions (lung, heart, or neurologic disorder) were associated with symptomatic children. Children with only HCoV detected were more likely to have a higher viral load compared with those with viral coinfection.

Associations of HCoVs with LRTI or asthma exacerbation in children have been reported [21, 31, 34, 38, 53, 54]. Clearly, respiratory distress and pneumonia have been well documented in children with only HCoV detected as a potential pathogen [34, 55]. Specific HCoV species and associated risk factors for disease severity have been evaluated, although some studies did not address potential confounders, such as the presence of coinfection [56]. One retrospective study of 212 hospitalized children with HCoV (54 with and 158 without viral coinfection) showed that similar numbers of children received respiratory support and intensive care [57]. Bivariate analyses showed that younger age (<2 years) and chronic complex medical conditions (cardiovascular, respiratory, genetic, or congenital) were associated with increased disease severity. No specific species were associated with severity of illness. Although the presence of viral coinfection was not associated with increased disease severity, the analysis did not assess the impact of specific types of coinfections. A retrospective analysis of 1237 children who presented to Seattle Children's Hospital (Washington) for acute care with detected HCoVs showed that disease severity did not vary by HCoV species [58]. Younger age, presence of underlying pulmonary disorder, and presence of coinfection, particularly RSV, were associated with increased likelihood of LRTI in multivariable models. The impact of RSV coinfection with HCoV has been described in other studies [59].

Like other respiratory viruses, HCoVs have been detected in middle ear effusions and nasal secretions in children with otitis media, and its possible etiology of acute otitis media has been implicated [60, 61]. The significant association between HCoV-NL63 and croup has been reported, with evidence suggesting that HCoV-NL63 is the second most common etiology of croup following parainfluenza virus type 1 [62, 63].

### Immunocompromised Host

HCoV has been described as a possible etiology of severe pneumonia in immunocompromised hosts [64–67]. Data are limited for this high-risk population and particularly are lacking in pediatric hematopoietic cell transplantation (HCT) recipients [68]. Among 404 children aged <18 years who underwent allogeneic HCT from April 2008 to September 2018 at Seattle Children's Hospital, HCoVs were the third most common respiratory viruses detected post-HCT following rhinovirus and parainfluenza virus (preliminary data). The cumulative incidence of HCoVs in children during the first 365 days following HCT are shown in Figure 2. HCoVs were detected in bronchoalveolar lavage (BAL) specimens from 2 young children in this cohort. The detection of HCoV in BAL specimens among HCT recipients and patients with hematologic malignancy was also evaluated, but only 1 of 35 patients was a child [69]. Among 16 patients in that study (15 adults, 1 child) with HCoV and without other coinfections identified by BAL, 10 required oxygen support, suggesting a role of HCoV as a significant

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**Table 2. Rates of Human Coronavirus and Influenza Infection With or Without Viral Coinfection by Polymerase Chain Reaction Testing in Symptomatic Patients**

| Institution | Seattle Children's Hospital, Seattle, Washington (<18 years) | Samsung Medical Center Seoul, Korea (<18 years) |
|-------------|-------------------------------------------------------------|-------------------------------------------------|
| Test used   | FilmArray (Biofire, Merieux)                                 | LG AdvanSure RV-plus real-time polymerase chain reaction (LG Life Science) |
| Number of specimens tested | 2052 | 918 |
| HCoV detected, N (overall %) | 115 (6) | 86 (9.4) |
| HCoV+ only, N (% of all HCoV+) | 66 (57) | 50 (58) |
| HCoV coinfection: HCoV and another virus(es) detected simultaneously | 49 (43% of all HCoV-positive specimens; 2.4% overall) | 36 (42% of all HCoV-positive specimens; 3.9% overall) |
| Both HCoV+ and influenza+ | 3 (3% of all HCoV+) | 10 (12% of all HCoV+) |
| Both HCoV+ and RSV+ | 25 (22% of all HCoV+) | 8 (9% of all HCoV+) |
| Both HCoV+ and RhV/Ent+ or adenovirus+ | 15 (13% of all HCoV+) | 14 (15% of all HCoV+) |
| Influenza detected, N (overall %) | 161 (8) | 63 (7) |
| Influenza+ only, N (% of all influenza+) | 146 (91) | 46 (73) |
| Influenza coinfection: influenza and another virus(es) detected simultaneously | 15 (9% of all influenza-positive specimens; 0.7% overall) | 17 (27% of all influenza-positive specimens; 1.9% overall) |
| Both influenza+ and RSV+ | 5 (3% of all influenza+) | 1 (2% of all influenza+) |
| Both influenza+ and RhV/Ent+ | 7 (4% of all influenza+) | 5 (8% of all influenza+) |
| Both influenza+ and HCoV+ | 3 (2% of all influenza+) | 10 (15% of all influenza+) |

These data are from patients seen in hospitals (Seattle, Washington, using FilmArray, and Seoul, Korea, using LG AdvanSure RV-plus real-time polymerase chain reaction) from November 2019 through January 2020.

Abbreviations: Ent, enterovirus; HCoV, human coronavirus; RhV, rhinovirus; RSV, respiratory syncytial virus.
respiratory pathogen. In a retrospective study of immunocompromised and nonimmunocompromised children with HCoV detected in nasal specimens in Seattle, the prevalence of LRTI that required oxygen supplementation (severe LRTI) was 15% (13/85) and 11% (122/1152), respectively [58]. Multivariable models showed that immunocompromised state, presence of RSV, and underlying pulmonary disorder were associated with increased risk of severe LRTI.

A prospective surveillance study with weekly nasal sampling in 215 allogeneic HCT recipients of all ages demonstrated that the median shedding duration of HCoVs was 3 weeks (range, 0–22 weeks) [70]. Our follow-up study suggests that high viral load, high-dose steroids, and myeloablative conditioning are associated with prolonged shedding (≥21 days) of HCoV in allogeneic HCT recipients (2 pediatric and 42 adult patients) [71]. Using available nasal samples from patients with prolonged shedding, we performed whole-genome sequencing, which revealed only small and slow genomic changes, consistent with previously estimated evolution rates. This is in contrast to more rapid genomic changes associated with influenza infections [72]. In addition, an 18-year-old pediatric patient had 3 HCoV species (OC43, HKU1, 229E) detected sequentially over a 5-month period without an associated poor outcome.

Possible Associations With Other Diseases
The role of HCoVs as enteric pathogens in humans has been debated, perhaps in part because of the known enteric disease associated with coronavirus in animals, including dogs. Risku et al investigated the presence of HCoVs in stool of children with and without gastroenteritis. All 4 species were found in 2.5% of stool samples (22/878) from children with gastroenteritis, whereas 1.7% of stool samples (2/112) from controls were positive for HCoVs. However, other known enteric pathogens, such as rotavirus or norovirus, were also found in 18 of 22 stool samples in children with gastroenteritis. Among 4 patients with only HCoV detected in stool, 3 had respiratory symptoms [73]. Another study examined both stool and nasopharyngeal swabs in hospitalized children with acute gastroenteritis and in controls [74]. HCoVs were more frequently detected in patients with gastroenteritis than in controls (23/260, 8.8% vs 4/151, 2.6%, respectively). Interestingly, in patients with gastroenteritis, more than half (13/23) had respiratory symptoms and HCoVs were more frequently found in nasopharyngeal samples than in stool samples (22/256, 8.6%, vs 6/260, 2.3%, respectively). Based on these studies, the significance of HCoVs as enteric pathogens appears minor.

HCoV-OC43 has been detected in the central nervous system of children with acute disseminated encephalomyelitis or fatal encephalitis [75, 76]. A prospective study investigated associations between HCoVs detection and various clinical manifestations [77]. This latter study proposed an etiological role of HCoVs in febrile seizures given that children with febrile seizures had higher rates of HCoVs detection with higher viral load in nasopharyngeal swabs than those with bronchiolitis or gastroenteritis and healthy controls. However, an etiologic connection between HCoVs and neurologic diseases remains unproven [78]. Carefully conducted epidemiological studies have not demonstrated an association between HCoVs and Kawasaki disease [21, 25].

SARS-COV
An outbreak of SARS-CoV occurred in East and Southeast Asia in early spring of 2003. This international outbreak began in a hotel in Hong Kong and ultimately spread to more than 20 countries.

Etiology and Epidemiology
The etiologic agent of SARS-CoV is a novel coronavirus identified by multiple investigators [10–12, 79]. The virus was classified as a beta-coronavirus, lineage B. This virus uses angiotensin-converting enzyme 2 as a functional cellular receptor. The virus also binds to the C-type lectin CD209L (also known as L-SIGN) and DC-SIGN [80–82]. During the outbreak, approximately 8098 cases occurred with 774 deaths, resulting in an overall mortality rate of 9% [24]. In Hong Kong, about 5% of the cases were children and adolescents [83]. Young children appeared to have a milder form of the disease [84–87].

Clinical Manifestation and Outcome
Among laboratory-confirmed and probable pediatric SARS-CoV cases, the most common symptoms included fever (98%), cough (60%), nausea or vomiting (41%), and constitutional
Clinical manifestations of SARS-CoV in children are nonspecific, and it can be very difficult to differentiate SARS-CoV from other respiratory tract infections without laboratory testing in the outbreak setting. However, certain features may provide a clue. A comparison of 15 pediatric patients with laboratory-confirmed SARS-CoV and 15 age- and sex-matched patients with culture-confirmed influenza in Taiwan revealed that rates of fever, cough, and constitutional symptoms such as chills and myalgia were similar between the 2 groups, but patients with SARS-CoV had significantly less rhinorrhea, sputum production, and sore throat than those with influenza [88]. In general, respiratory and constitutional symptoms are similar in the beginning of the illness in children and adults. However, a much higher proportion of adult patients progress to severe pneumonia, even acute respiratory distress syndrome. In fact, despite a high mortality rate in adults (9.6%–16.7%) [83], there were no fatalities documented in the pediatric population [84–87].

**SARS-CoV Infection During Pregnancy**

A study reported outcomes of 5 pregnant women infected with SARS-CoV [89]; the gestational ages of their infants ranged from 26 weeks to 32 weeks. In 3 of these 5 pregnant women, cesarean section was needed because of maternal conditions, including hypotension and worsening pulmonary function. However, a systematic search for perinatal transmission of the SARS-CoV did not detect the virus in any of the 5 babies.

**MERS-COV**

The first case of MERS-CoV was reported in a man hospitalized in Jeddah, Saudi Arabia, in June 2012. He died of severe pneumonia and renal failure, and a novel coronavirus was isolated from his sputum [14].

**Etiology and Epidemiology**

This new beta-coronavirus was named MERS-CoV [13]. It belongs to lineage C and is closely related to Tylonycteris bat coronavirus HKU4 (Ty-BatCoV HKU4) and Pipistrellus bat coronavirus HKU5 (Pi-BatCoV HKU5) [13]. The dromedary camel is known to be the intermediate host of MERS-CoV. The widely expressed cell-surface protease dipeptidyl-peptidase 4 (also known as CD26) was identified as a functional receptor for host cell entry [90].

As of November 2019, the World Health Organization reported 2494 laboratory-confirmed cases of MERS-CoV infection in 27 countries with 858 deaths globally, resulting in an approximate 34% mortality rate [91]. All known MERS-CoV infections can be traced to countries in the Middle East, primarily Saudi Arabia. Most cases have been in adults with underlying chronic diseases or immunosuppression who live or travel in the Arabian Peninsula. Among 1351 confirmed cases between 2012 and 2019, cases aged <18 years were less than 5% of all confirmed cases [92]. MERS-CoV infection in adults usually occurs as sporadic cases, healthcare-associated infection, or transmission within families [93]. However, most confirmed pediatric cases were secondary cases after exposures to others within the same family [94].

The proportion of children among those infected with MERS-CoV has consistently been reported as being relatively low compared with the general population. From June 2012 to April 2016, the proportion of pediatric patients was 1.6% (9 of 552) of all positive cases in Saudi Arabia [94]. Among patients hospitalized in Riyadh, Saudi Arabia, from April 2014 to November 2016, the proportion of 295 confirmed pediatric patients (aged <18 years) was 2.4%, with age ranging from 9 months to 17 years (Supplementary Table 1).

**Clinical Manifestation and Outcome**

Clinical manifestations in pediatric patients have not been systematically described. Among the 31 pediatric patients with MERS-CoV infection documented from June 2012 to April 19, 2016, 13 patients (42%) were asymptomatic [94]. In another study, among 7 pediatric patients identified from April 2014 to November 2016, 3 were asymptomatic; fever, cough, shortness of breath, diarrhea, and vomiting were observed in 4 patients [95]. Although pediatric patients typically have mild disease, high-risk children with underlying conditions, including cystic fibrosis, nephrotic syndrome, and unidentified underlying conditions, died of MERS-CoV infection, with a fatality rate of 12% (4/33) (see Supplementary Table 1) [96, 97].

**MERS-CoV Infection in the Fetus**

A recent study summarized MERS-CoV infection in 11 pregnant women [98]. The gestational ages ranged from 6 weeks to 38 weeks. Among those 11 pregnant women, 7 (64%) were admitted to intensive care units and 3 (27%) died. Of the 11 births, 3 (27%) died, 2 had documented intrauterine death at 34 weeks and 5 months of gestation, and 1 was delivered at 24 weeks but did not survive.

**CONCLUSIONS**

Recognition of the importance of community coronavirus disease due to 4 established HCoVs has increased over the past 20 years, with widespread availability of molecular diagnostic methods. However, detailed information on pathogenesis, immunity, and viral characteristics of disease in children remains limited. Recent and ongoing epidemics of novel coronaviruses in the 21st century have highlighted issues of zoonotic origins of transmissible respiratory viruses and potential transmission, disease, and mortality related to these viruses. The role of children in the spread of disease with these novel viruses remains unclear. As the current pandemic with SARS-CoV-2 unfolds, more information regarding the role of children in viral transmission and their clinical...
presentation and outcome will become more evident. Further study of coronaviruses in humans is imperative.

Supplementary Data
Supplementary materials are available at Journal of the Pediatric Infectious Diseases Society online.

Notes
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