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Clinical presentation of Enterovirus D68 in adults with acute respiratory infections consulting in emergency departments in Quebec, Canada

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ABSTRACT

Objectives: Enterovirus D68 (EV-D68) is mainly studied in children, while data in adults are limited. We described the clinical presentation of EV-D68 in adults, compared with other enterovirus/rhinovirus (EV/RV) infections.
Methods: We used clinical and laboratory data from 1143 adults visiting four emergency departments in Quebec, Canada, for acute respiratory infections (February 2022 to March 2023). We analyzed nasopharyngeal swabs using a multiplex polymerase chain reaction; positive EV/RV samples were further tested with EV-D68–specific polymerase chain reaction assays. We calculated the Pandemic Medical Early Warning Score (PMEWS) to assess severity.
Results: Of 155 (14%) EV/RV samples, 19 (12%) were EV-D68 and occurred from July to October, 2022. Patients with EV-D68 more frequently lived with other people (100% vs 73%, $P = 0.02$) and tended to have more underlying chronic respiratory diseases (26% vs 20%) and respiratory symptoms (e.g., dyspnea: 84% vs 75%; wheezing: 63% vs 44%; and chest pain: 63% vs 49%), although these differences were not statistically significant. PMEWS, hospitalizations, and median time spent in the emergency department did not differ significantly between the EV-D68 and the other EV/RV group.
Conclusions: Respiratory symptoms tended to be more common among participants with EV-D68 than those with other EV/RV, although disease severity was similar. Larger studies are needed to better characterize EV-D68 infections in adults.

Introduction

Enteroviruses (EVs) and rhinoviruses (RVs) are among the most common pathogens responsible for acute respiratory infections (ARIs) in humans worldwide [1–3]. Both EVs and RVs belong to the *Enterovirus* genus of the *Picornaviridae* family [1–3]. Enterovirus D68 (EV-D68) is a unique genotype of this family, as it shares features of EVs and RVs [3]. EV-D68 infections previously occurred sporadically [4]. However, EV-D68 has increasingly gained attention since 2014 due to a large outbreak that affected the United States, Canada, Europe, and Asia,

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followed by biennial outbreaks, typically during the summer and fall [2,3,5–8]. EV-D68 is now considered as a re-emerging infectious pathogen of concern that is associated with a range of clinical manifestations: mild to severe ARI and neurological complications [4,5]. Although the case fatality rate is low (0-4.4%) [4], severely affected individuals often require emergency care, hospitalization, and intensive care unit (ICU) admission [2,6,9].

EV-D68 has mainly been reported in children, especially those with respiratory comorbidities such as asthma [2,9–11]. EV-D68 has also been reported in adults, particularly those with underlying conditions (e.g., respiratory diseases and immunosuppression). Adults with EV-D68 reported several symptoms such as cough, rhinorrhea, dyspnea, wheezing, malaise, and fever. Clinical presentation ranged from mild illness, necessitating only outpatient management, to respiratory failure requiring ICU admission [12–14]. However, studies in adults with EV-D68 were limited in several ways: they were often retrospective with selection bias (focusing on severely ill or hospitalized individuals), had small sample sizes (typically <15 patients), had limited clinical data, had data of adults and children analyzed together, or lacked comparison with other EVs and RVs to assess relative severity [2,4,9,12–21]. As presenting symptoms of EV-D68 can resemble those of other viral respiratory infections, diagnosing EV-D68 is challenging, especially given the limited clinical knowledge of this infection in adults [2]. Additionally, as commercial rapid diagnostic tests to help distinguish EV-D68 from other EVs and RVs are lacking, and testing for EV-D68 is not routine practice, the availability of epidemiological data is further limited [2,5]. Given the lack of approved antiviral treatment and vaccines for EV-D68 and its potential to cause widespread outbreaks of severe respiratory illnesses, improved understanding of its epidemiology and clinical characteristics is needed to better prepare for and control future outbreaks [2,4,10].

Using data from a large multicenter study of adults presenting with ARI to emergency departments (EDs) in Quebec, Canada, we aimed to determine the frequency of EV-D68 infections and to analyze the sociodemographic characteristics, clinical presentation, management, and outcomes of those infected with EV-D68 compared with other EVs and RVs. We hypothesized that adults infected with EV-D68 would have more severe respiratory symptoms and be hospitalized more often than those infected with other EVs and RVs, similar to what has been observed in children.

Methods

Study design and population

This study is nested in a large multicenter clinical study of adult patients presenting with ARI to EDs. Participants were recruited prospectively between February 2022 and March 2023 from the EDs of four university hospitals in Quebec, Canada, namely the Centre Hospitalier de l'Université Laval (CHUL) and Hôpital de l'Enfant-Jésus in Quebec City, and the Centre Hospitalier de l'Université de Montréal (CHUM) and the Jewish General Hospital in Montreal. Participants were enrolled if they (i) had at least one respiratory symptom suggestive of ARI (i.e., cough, purulent sputum, sore throat, nasal congestion, rhinorrhea, ageusia) for ≤10 days, (ii) were aged ≥18 years, (iii) were able and willing to consent, (iv) had a triage score of 3 (urgent), 4 (less urgent), or 5 (non-urgent) according to the Canadian Triage and Acuity Scale [22], (v) were fluent in French or English, (vi) resided in the province of Quebec, (vii) were reachable by phone, and (viii) were covered by Quebec public health insurance. We excluded participants if they resided in long-term care facilities, had cognitive impairment, or refused nasopharyngeal swab sampling. The CHU de Québec-Université Laval ethics board approved this study (MP-20-2022-6152). This clinical study is registered in the ClinicalTrials.gov database (NCT05322694).

Study procedures and data collection

After triage, trained research staff invited eligible participants to participate in the study and obtained informed consent. The research staff systematically collected nasopharyngeal swabs from all participants. Additionally, a rectal swab was collected from participants who also had acute infectious diarrhea, defined as at least three loose stools within 24 hours with symptoms lasting ≤7 days. These swabs were frozen and later analyzed using a point-of-care respiratory multiplex polymerase chain reaction (PCR) assay (BIOFIRE RP2.1 Panel, bioMérieux, Marcy-l'Étoile, France) for the nasopharyngeal swabs and gastrointestinal PCR assay (BIOFIRE FILMARRAY GI panel, bioMérieux) for the rectal swabs. The respiratory multiplex PCR panel can detect a wide range of pathogens (18 viruses and four bacteria) (Figure 1), including EVs and RVs, but cannot differentiate between these two and cannot identify EV-D68. The research staff also collected the following demographic and clinical information directly from the participants during the ED visit or from their medical records: age, sex, gender, ethnicity, living conditions, triage score, symptoms (respiratory and other), comorbidities, vital signs, initial ED orientation, investigations and treatment administered, disposition after physician assessment, ED discharge diagnosis, and treatment(s) prescribed. Subsequently, a follow-up phone call to participants was made to collect information on events that occurred within 7 days of ED discharge. These events included consultation in the ED or other clinics, and hospitalization if any. All the data collected were entered into REDCap (Research Electronic Data Capture), a secure web-based platform.

The present study was part of an observational multicenter study whose primary objective was to evaluate the validity of an experimental clinical triage decision rule (consisting of a rapid molecular test and a self-administered patient questionnaire) and to compare it with standard care. Thus, the respiratory multiplex PCR panel was not performed in real time, and results were not disclosed to the treating team. After the completion of study procedures, the participants followed the care pathway they would have taken outside the research project.

EV-D68 detection

In this nested study, we analyzed participants with a nasopharyngeal swab sample that tested positive for EVs and RVs based on the respiratory multiplex PCR assay. The samples were stored and tested with two different in-house amplicon-based EV-D68–specific PCR assays, designed on the basis of the PCR assay developed by Ikuse et al. [23], which distinguish EV-D68 from other EVs and RVs. We then excluded participants who were coinfected with other viral or bacterial respiratory pathogens identified using the respiratory multiplex PCR assay. We did not exclude EV- and RV-positive participants who tested positive for other bacterial respiratory pathogens based on additional microbiology tests (i.e., hemoculture, throat and/or sputum culture), as these tests were not systematically done in all participants. Similarly, we did not exclude EV- and RV-positive participants with acute infectious diarrhea who tested positive for an enteric pathogen, since (i) rectal swabs were not collected systematically for all participants and (ii) acute infectious diarrhea may be associated with EV-D68.

Statistical analysis

We calculated the Pandemic Medical Early Warning Score (PMEWS), a score based on vital signs, age, social isolation, performance status, and presence of comorbidities to assess severity and the risk of complications [24]. We defined a score of 0-2 as low-risk and a score of ≥3 as high-risk [25]. We reported information on sociodemographic characteristics, clinical presentation, management, and outcomes using proportions and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables. We compared EV-D68 with the other EVs and RVs (hereafter collectively referred to as "other EV/RV")

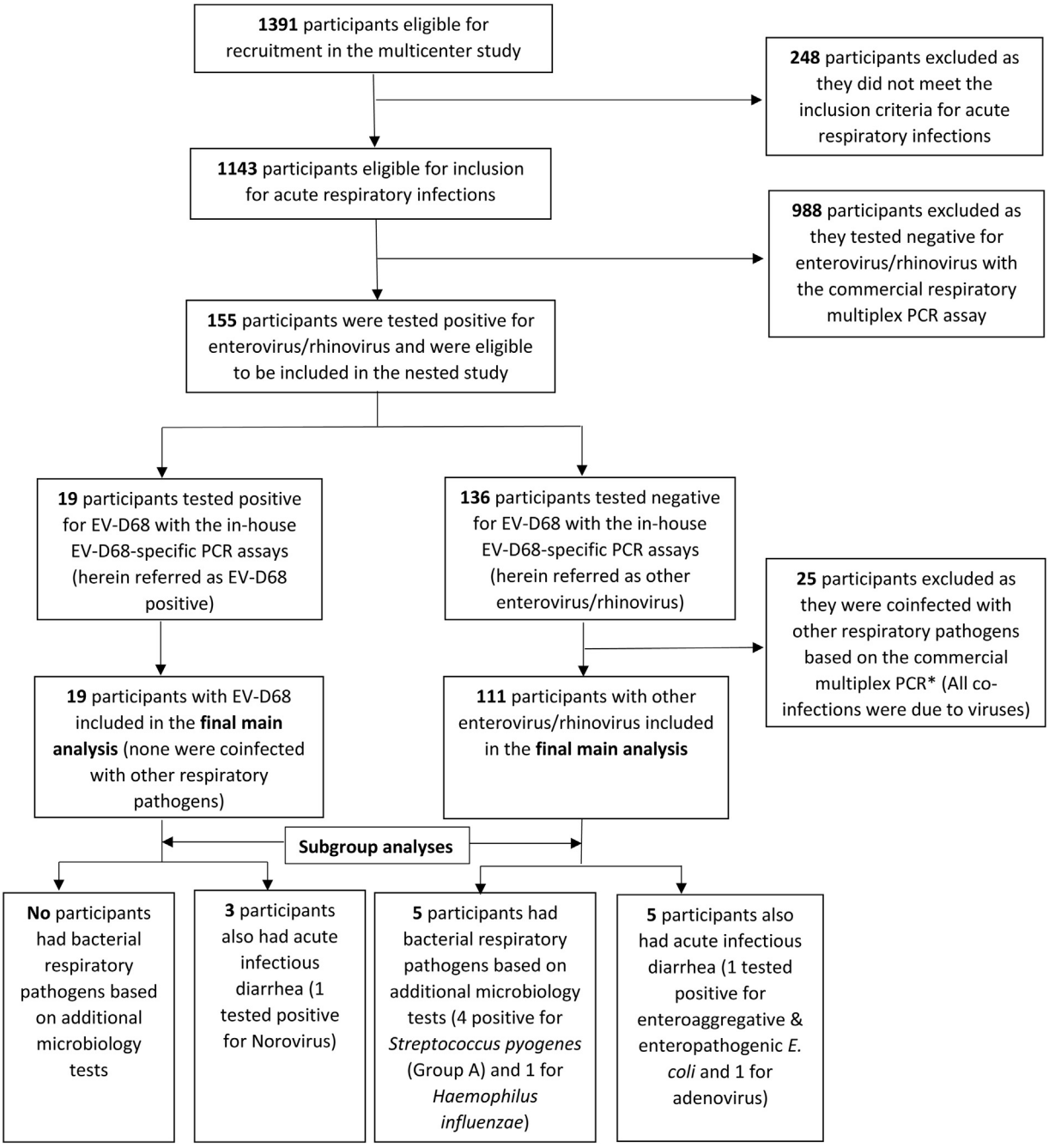

Figure 1. Flowchart of included participants.
EV, enterovirus; PCR, polymerase chain reaction.
* The viruses which can be detected with the respiratory multiplex PCR assay (BioFire RP2.1 Panel, bioMérieux, Marcy-l'Étoile, France) include: Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A virus, Influenza A virus A/H1, Influenza A virus A/H3, Influenza A virus A/H1-2009, Influenza B virus, Parainfluenza virus 1, Parainfluenza virus 2, Parainfluenza virus 3, Parainfluenza virus 4, Respiratory syncytial virus.
The bacteria which can be detected with the respiratory multiplex PCR assay (BioFire RP2.1 Panel, bioMérieux, Marcy-l'Étoile, France) include *Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae*.

using Fisher's exact test for categorical variables and the Wilcoxon rank sum test (Mann-Whitney test) for non-normally distributed continuous variables. In subgroup analyses, we assessed the severity of EV-D68 and other EV/RV infections in (i) participants who were positive for bacterial respiratory pathogens based on the additional microbiology tests (excluding the respiratory multiplex PCR assay) and (ii) those who also had acute infectious diarrhea. We used STATA, Version 18.0 (StataCorp, College Station, TX) for statistical analysis.

Results

Study population and characteristics

Among the 1143 participants with ARI recruited in the EDs, we identified 155 (14%) cases of EVs and RVs, of which 19 (12%) were EV-D68 (Figure 1). EV-D68 infections were more likely to be monomicrobial (i.e., without coinfection with other viral or bacterial respira-

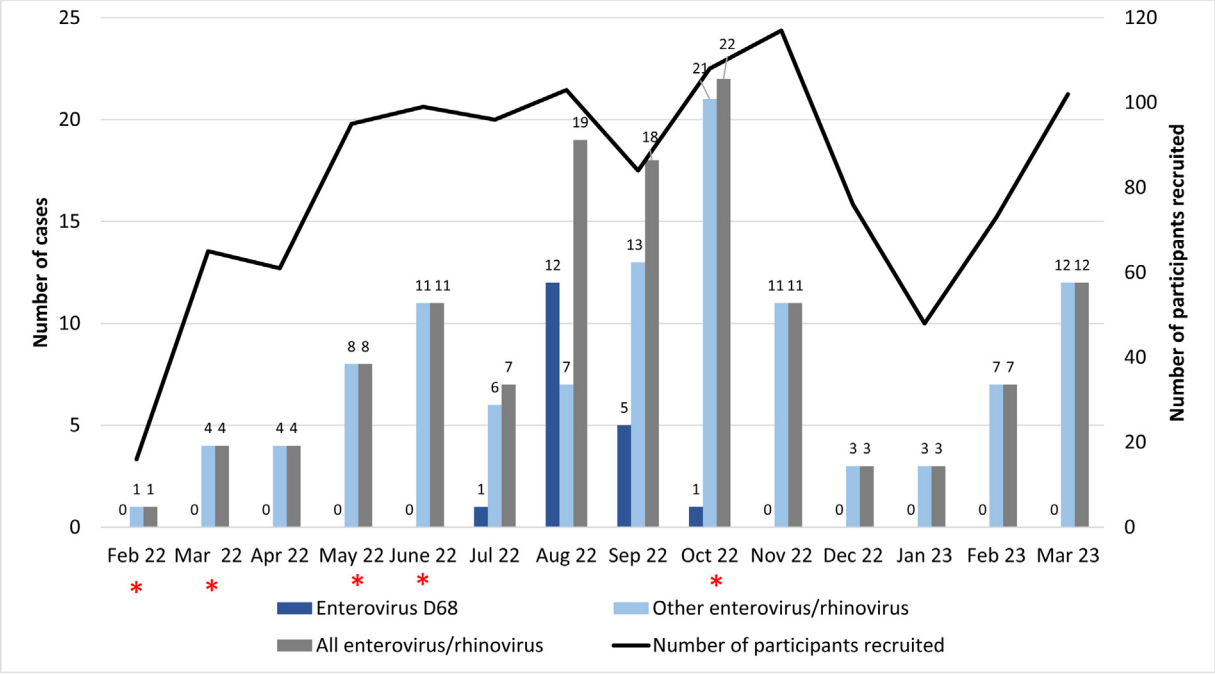

Figure 2. Monthly frequency of cases of enterovirus D68, other enterovirus/rhinovirus, and total enterovirus/rhinovirus (bar graphs) against total recruitment (solid black line) in emergency departments between February 2022 and March 2023 in Quebec, Canada. The months during which major COVID-19 measures were lifted are indicated by an asterisk and described as follows:
February 2022: COVID-19 vaccination passport not required for some places.
March 2022: COVID-19 vaccination passport not required in most public places and health facilities.
May 2022: Wearing a mask in public places no longer mandatory except in public transportation and health care facilities.
June 2022: Wearing a mask no longer mandatory in public transportation.
October 2022: COVID-19 border measures and travel requirements in Canada lifted.

tory pathogens) than other EV/RV infections (100% vs 82%, $P = 0.04$). Among those with other EV/RV, we excluded 25 who were coinfected with other respiratory pathogens. Hence, the analyses were based on a total of 130 cases of EVs and RVs (19 EV-D68 and 111 other EV/RV). All EV-D68 cases occurred during summer and fall (July to October 2022), with most in August (n = 12, 63%), followed by September (n = 5, 26%) (Figure 2).

Participants' characteristics are presented in Table 1 and the frequency of missing variables in Table S1. Few data were missing (mostly sociodemographic characteristics), while they were almost complete for clinical information. There was a predominance of female participants in both the EV-D68 (68%) and other EV/RV (59%, $P = 0.61$) groups. The median age of the EV-D68 group (32 years, IQR 25-56) was similar to that of the other EV/RV group (33 years, IQR 25-51, $P = 0.88$). Those infected with EV-D68 more frequently reported being in a couple (88% vs 53%, $P = 0.01$), living with other people (100% vs 73%, $P = 0.02$), and sharing a household with children (44% vs 34%, $P = 0.57$) compared with those with other EV/RV. Other sociodemographic characteristics were comparable between the two groups. In the EV-D68 group, participants more often smoked (68% vs 50%, $P = 0.21$) or had underlying chronic respiratory diseases (26% vs 20%, $P = 0.55$) such as asthma (21% vs 14%, $P = 0.49$) and chronic obstructive pulmonary disease (11% vs 5%, $P = 0.33$), but none of these findings were statistically significant.

Clinical presentation

Most participants (95%) arrived to the ED by foot, and more than half had a triage score of 3 (urgent) in both groups (Table 1). A wide range of respiratory, general, and other symptoms was reported for EV-D68 and other EV/RV infections (Figure 3 and Table S2). Cough was the most frequent symptom in both groups (EV-D68: 89%; other EV/RV: 87%; $P = 1.00$). Participants with EV-D68 presented more frequently with dyspnea/shortness of breath (84% vs 75%, $P = 0.56$), wheezing (63% vs 44%, $P = 0.14$), and chest pain (63% vs 49%, $P = 0.32$) compared with those with other EV/RV, although these differences did not reach statistical significance. In contrast, sputum production was less frequent in the EV-D68 group (47% vs 73%, $P = 0.03$). Less than half of the participants in the two groups had fever. The proportion of other symptoms did not differ markedly between EV-D68 and other EV/RV.

Vital signs measured in the ED are shown in Table S3. In a slightly higher proportion of those with EV-D68 infections, oxygen saturation was decreased (16% vs 10%, $P = 0.43$) and respiratory rate was increased (26% vs 19%, $P = 0.54$) compared with those with other EV/RV infections. However, the median PMEWS was lower in the EV-D68 group (1, IQR 0-4) compared with the other EV/RV group (3, IQR 1-4; $P = 0.07$). Similarly, the proportion of participants with a high-risk PMEWS (i.e., score ≥3) was lower among those with EV-D68 than those with other EV/RV infections (37% vs 51%, $P = 0.32$), but the differences were not statistically significant.

Management in the ED and at discharge

After triage, most participants (≥98%) in the two groups were either placed on a stretcher or redirected to the waiting room (Table 2). Fewer chest x-rays were performed in the EV-D68 group than in the other EV/RV group (32% vs 50%, $P = 0.21$). A similar proportion of those with EV-D68 and other EV/RV received inhaled bronchodilator therapy in the ED (16% and 19%, respectively, $P = 1.00$). The discharge diagnoses from the ED are presented in Table 2. Two (11%) patients were hospitalized among those infected with EV-D68. Both were older adults and had underlying comorbidities: the first patient, aged 64 years, had heart disease and asthma and was hospitalized for 14 days; the second patient, aged 75 years, had heart disease, asthma, chronic obstructive

Table 1
Sociodemographic information, medical history, and presentation at the emergency department of participants with Enterovirus D68 infections vs participants with other enterovirus/rhinovirus infections.

	Enterovirus D68–positive (N = 19) n (%)	Other enterovirus/rhinovirus–positive without coinfections (N = 111) n (%)	*P*-value
Sociodemographic characteristics			
Sex (female)	13 (68)	66 (59)	0.61
Gender			
Men	4 (25)	35 (39)	0.49
Women	12 (75)	53 (60)	
Other	0 (0)	1 (1)	
Age, years			
Range	19-75	18-92	
Median (interquartile range)	32 (25-56)	33 (25-51)	0.88
Race (white/Caucasian)	13 (81)	67 (75)	0.76
Civil status (married or in a relationship)	14 (88)	47 (53)	**0.01**
Live with at least one person	16 (100)	65 (73)	**0.02**
Live with children	7 (44)	30 (34)	0.57
Urban residence	14 (88)	71 (80)	0.73
Highest educational level[a]			
Primary	0 (0)	3 (3)	0.90
Secondary	12 (75)	57 (64)	
Tertiary	4 (25)	27 (30)	
Other	0 (0)	2 (2)	
Employed	13 (81)	67 (75)	0.76
Annual income of household			
<40,000$	3 (19)	26 (30)	0.14
≥40,000$	12 (75)	42 (48)	
Prefer not to answer	1 (6)	20 (23)	
Comorbidities/chronic medical history			
Current or past smoking (any)[b]	13 (68)	56 (50)	0.21
Current cigarette smoking	5 (26)	26 (23)	0.78
Take medication on a regular basis	13 (68)	72 (65)	1.00
History of self-reported COVID-19	9 (47)	68 (61)	0.32
Has at least one underlying condition[c]	6 (32)	50 (45)	0.32
Chronic heart or vascular disease	3 (16)	24 (22)	0.76
Chronic respiratory disease	5 (26)	22 (20)	0.55
Asthma	4 (21)	16 (14)	0.49
Chronic obstructive pulmonary disease	2 (11)	6 (5)	0.33
Rheumatic or connective tissue disease	0 (0)	2 (2)	1.00
HIV or immunodeficiency	0 (0)	1 (1)	1.00
Cancer	0 (0)	4 (4)	1.00
Previous stroke or transient ischemic attack	1 (5)	0 (0)	0.15
Diabetes	2 (11)	11 (10)	1.00
Endocrine disease	1 (5)	4 (4)	0.55
Renal disease	0 (0)	1 (1)	1.00
Hepatic disease	0 (0)	0 (0)	-
Ongoing pregnancy	1 (5)	4 (4)	0.55
Presentation at ED			
Arrival at ED			
By foot	18 (95)	105 (95)	1.00
Ambulance	1 (5)	5 (5)	
Triage score at ED			
P3 (urgent)	10 (53)	68 (61)	0.53
P4 (less urgent)	9 (47)	38 (34)	
P5 (non-urgent)	0 (0)	5 (5)	

As there are missing data for some variables (Table S1), the total N may differ.
ED, emergency department.
[a] Educational level: primary, secondary (includes high school, college, professional diploma, CEGEP), and tertiary (includes university certificate, bachelor degree, master degree, doctorate)
[b] Any current or past smoking includes cigarettes, vaping, cannabis, and cigars
[c] At least one underlying condition includes cardiac, respiratory, rheumatic, HIV or immunodeficiency, cancer, diabetes, stroke, liver disease, renal disease, or endocrine diseases.

Table 2
Management in the emergency department (orientation, investigations performed in ED, treatment prescribed in ED, physician diagnosis, disposition after assessment, treatment prescribed at discharge) of participants with Enterovirus D68 infections vs participants with other enterovirus/rhinovirus infections.

	Enterovirus D68–positive (N = 19) n (%)	Other enterovirus/ rhinovirus–positive without coinfections (N = 111) n (%)	*P*-value
Orientation after triage			
Stretcher	5 (26)	49 (44)	0.28
Waiting room	14 (74)	60 (54)	
Redirected to a clinic	0 (0)	2 (2)	
Returned home	0 (0)	0 (0)	
Investigations performed in ED			
Radiological examination			
Computed tomography scan of thorax	1 (5)	6 (5)	1.00
Chest x-ray	6 (32)	55 (50)	0.21
Spirometry	1 (5)	3 (3)	0.47
Laboratory examination	15 (79)	71 (64)	0.30
Treatment prescribed in ED			
Any inhalation treatment	3 (16)	21 (19)	1.00
Type of inhalation treatment			
Salbutamol (metered-dose aerosol with aerochamber)	2 (11)	19 (17)	0.74
Ipratropium (metered-dose aerosol with aerochamber)	0 (0)	9 (8)	0.36
Salbutamol (nebulized)	1 (5)	4 (4)	0.55
Ipratropium (nebulized)	1 (5)	4 (4)	0.55
Other	0 (0)	8 (7)	0.60
Physician diagnosis at discharge[a]			
Asthma, asthmatic bronchitis, bronchial hyperactivity, bronchospasm	1 (5)	13 (12)	0.69
COPD/acute exacerbation of COPD/superinfected COPD	3 (16)	8 (7)	0.20
Pneumonia	3 (16)	12 (11)	0.46
Chest pain	0 (0)	1 (1)	1.00
Other respiratory-related diagnosis[b]	9 (47)	49 (44)	0.81
Other enteritis-related diagnosis[c]	2 (11)	3 (3)	0.16
Patient disposition after emergency physician assessment[a]			
Discharge to home	17 (89)	93 (84)	0.74
Specialist or hospital consultation	2 (11)	17 (15)	0.74
Admission to hospital	2 (11)	8 (7)	0.64
Patient was not seen by physician	0 (0)	8 (7)	0.60
Treatment prescribed at ED discharge (excluding hospitalized patients)			
Antibiotics	5 (26)	34 (31)	0.79
Antipyretic or pain reliever	2 (11)	5 (5)	0.28
Oral corticosteroids	4 (21)	12 (11)	0.26
Intranasal corticosteroids	0 (0)	3 (3)	1.00
Inhaled corticosteroids	2 (11)	10 (9)	1.00
Antiviral treatment	0 (0)	0 (0)	-
Total time spent in ED, in hours			
Range	3.3-31.0	1.0-45.3	
Median (interquartile range)	6.8 (5.0-13.7)	6.4 (4.1-11.4)	0.27

As there are missing data for some variables (Table S1), the total N may differ.
COPD, chronic obstructive pulmonary disease; ED, emergency department.
[a] Several answers are possible
[b] Other respiratory-related diagnoses include otitis media, acute sinusitis, acute tonsillitis, pharyngitis, acute laryngitis, acute bronchitis, upper respiratory tract infection/common cold/nasal congestion, flu/influenza illness, viral infection, viremia
[c] Other enteritis-related diagnoses include colitis, abdominal pain/colic, enteritis, and gastroenteritis.

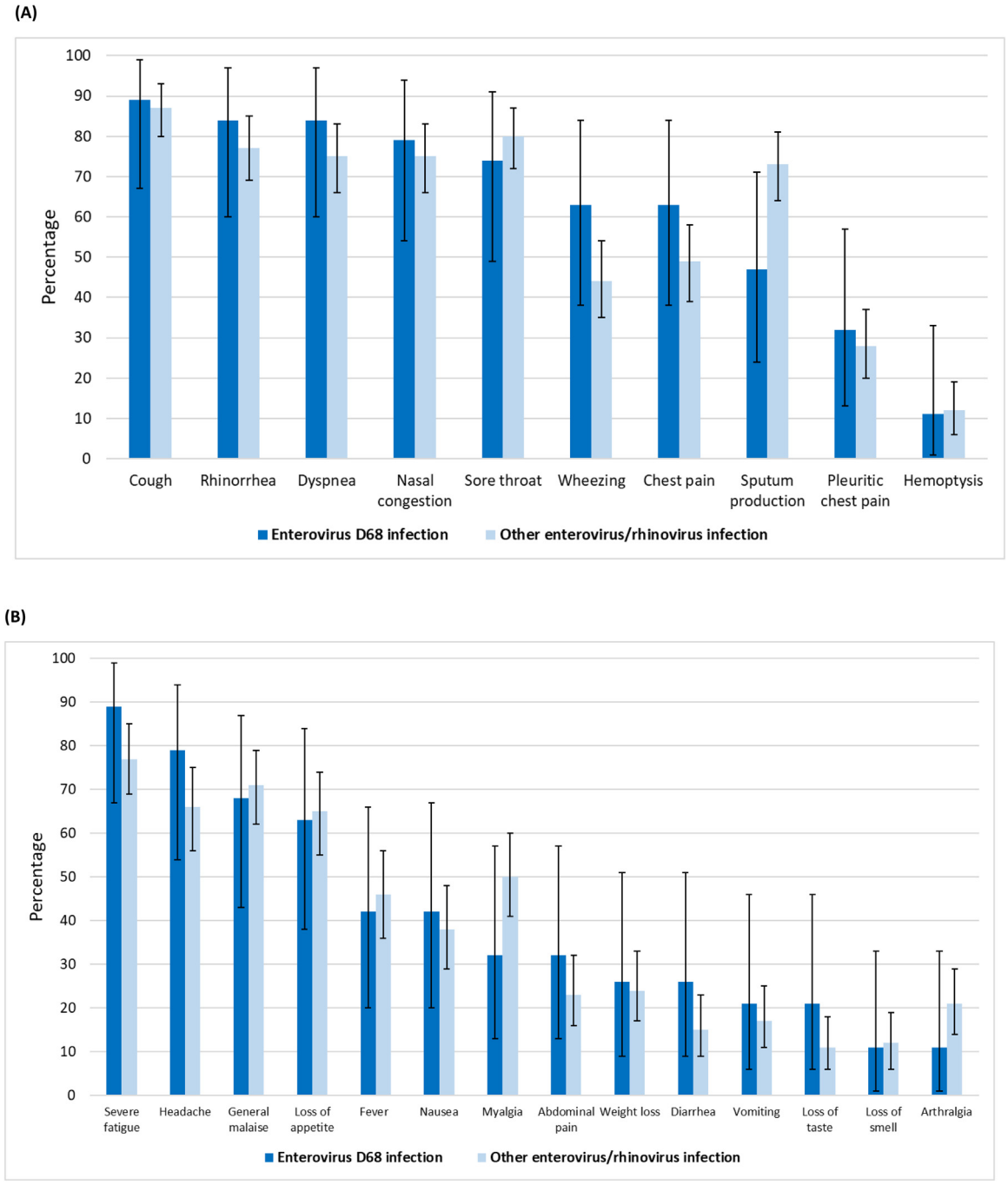

Figure 3. (a) Frequency of respiratory symptoms with 95% confidence intervals and (b) frequency of other/general symptoms with 95% confidence intervals among participants with enterovirus D68 infections vs participants with other enterovirus/rhinovirus infections.

pulmonary disease, and diabetes, and was hospitalized for 4 days. In the other EV/RV group, eight (7%) patients were hospitalized. Their median age was 70 years (IQR 27-75), the median length of hospitalization was 3 days (IQR 2-5), and three of these eight patients had underlying co-morbidities: all three had heart disease, one had asthma, and one had chronic obstructive pulmonary disease.

Antibiotics were prescribed in similar proportions in both groups (EV-D68: 26%; other EV/RV: 31%; $P = 0.79$) at discharge from the ED. Detailed information on antibiotic prescription is available in Table S4. Antipyretics or pain relievers were prescribed twice as often to those with EV-D68 (11% vs 5%, $P = 0.28$); a similar pattern was observed for oral corticosteroids (21% vs 11%, $P = 0.26$). The time spent in the ED did not differ between EV-D68 (median: 6.8 hours, IQR 5.0-13.7) and other EV/RV (median: 6.4 hours, IQR 4.1-11.4, $P = 0.27$) (Table 2).

Outcomes within 7 days after ED discharge

Three (16%) participants with EV-D68 and 22 (20%) with other EV/RV could not be contacted to collect information on events occurring within 7 days after the initial ED visit. Three participants (19%) in the EV-D68 group and 10 (11%) in the other EV/RV group consulted again in an ED, family medicine clinic, or walk-in clinic ($P = 0.41$). Excluding those who were hospitalized at the initial visit, none of the participants with EV-D68 were hospitalized within 7 days, while in the other EV/RV group, four were hospitalized but none were admitted to the ICU.

Subgroup analysis

Only one participant in the EV-D68 group had an additional microbiology test (hemoculture); no bacterial respiratory pathogen was detected. In the other EV/RV group, 18 had additional microbiology tests, of whom five tested positive for bacterial respiratory pathogens (Figure 1). Of these five participants, four had high-risk PMEWS, one was hospitalized, one received antibiotics at discharge (Table S4), and none had to re-consult within 7 days of ED discharge.

Three (16%) participants with EV-D68 also had acute diarrhea, and one tested positive for norovirus (Figure 1). All three participants had high-risk PMEWS. However, none were hospitalized at the initial ED visit, nor did they re-consult within 7 days. Five (5%) participants with other EV/RV also had acute diarrhea. Of these five participants, two tested positive for enteric pathogens (Figure 1), two had high-risk PMEWS, and none were hospitalized at the initial visit nor had to consult again within 7 days.

Discussion

In this study, we identified 19 cases of EV-D68 in the summer and fall of 2022 among 155 EV/RV patients, from a total of 1143 adult patients presenting with ARI to EDs in Quebec, Canada. Given this small sample size, the statistical power was insufficient to detect significant differences between groups. We found that those with EV-D68 more often lived with other people compared with those with other EV/RV. Other sociodemographic characteristics did not differ between the two groups. Adults with EV-D68 tended to have more underlying chronic respiratory diseases, respiratory symptoms (particularly wheezing, dyspnea, and chest pain), and abnormal oxygen saturation and respiratory rate compared with those with other EV/RV, although none of these features differed significantly. In fact, EV-D68 infections did not appear to be more severe according to the PMEWS and the number of hospitalizations.

The small number and proportion of adults with EV-D68 in our study is consistent with findings from other studies, although comparisons are limited because of several differences across studies (e.g., in the selective testing of severely ill participants, study duration, study period, number of countries and centers involved, and the definition of adults) [2,9,13,14,16–18,20,26]. We believe that the number of EV-D68 cases may be underestimated in our study. First, several potentially at-risk people, such as those living in long-term care facilities or having a triage score of 1 (resuscitation) or 2 (emergent), were excluded. Second, those with milder forms of EV-D68 infections might not have been captured, as they did not seek medical care. It is thought that most cases of EV-D68 are mild or asymptomatic and remain undiagnosed [2,7]. Furthermore, given the continued presence of the COVID-19 pandemic during the study period, we speculate that patients with respiratory symptoms consulted in COVID-19 clinics or stayed home rather than visiting EDs.

All EV-D68 cases in our study were detected in summer and fall (July to October 2022), aligning with the typical seasonality (June to December) and the previously reported biennial surge patterns in even-numbered years [3,8–11,13,14,16]. As we did not recruit participants before summer/fall of 2021 and after summer/fall of 2023, we cannot assess the validity of the EV-D68 biennial pattern in Quebec, especially in the context of the COVID-19 pandemic. It has been noted that the biennial pattern of EV-D68 was disrupted following an upsurge of cases in Europe in 2019 and COVID-19–related public health interventions [7,9,17]. Interestingly, we observed that EV/RV cases, including EV-D68, peaked shortly after most COVID-19 measures (e.g., wearing of face masks in most public places) were lifted in June 2022 in Quebec (Figure 2) [27]. This suggests that COVID-19 public health interventions might have played a role in the dynamics of EV-D68 and other EV/RV transmission.

Similar to our findings, other studies also observed a slight female predominance among adults with EV-D68 [13,16]. We do not know whether this is due to chance or differences in health-seeking behaviors [28]. It is also thought that female individuals, as primary caregivers, are more exposed to young children, who are usually the main source of transmission for EV-D68 in a household [3]. In addition, we found that all those infected with EV-D68 lived with at least one other person, and they more often lived with children, suggesting that close-contact settings might play a role in the transmission of EV-D68. It has indeed been demonstrated that EV-D68 transmits within households between children and parents, although symptoms are milder in adults [29]. The possibly higher infectivity of EV-D68 compared with other EV/RV should be further explored.

Respiratory symptoms such as wheezing, dyspnea, and chest pain were more often reported among those with EV-D68, but the proportions were not significantly higher compared with those with other EV/RV. Other studies in adults also found that similar symptoms such as wheezing and dyspnea (including asthma-like presentation) were reported with EV-D68 infections [12–14]. To our knowledge, no other studies exclusively conducted in adults have compared the respiratory symptoms of EV-D68 with those of other EV/RV. However, studies conducted in children or both adults and children (analyzed together) found that wheezing and/or dyspnea were more frequently reported in EV-D68 infections than in other EV/RV infections [2,10,11,26,30]. Respiratory symptoms such as wheezing, dyspnea, and chest pain may help differentiate EV-D68 from other EV/RV, although we could not demonstrate any statistical significance, possibly because of our limited sample size. Wheezing, as a symptom of bronchial hyperreactivity, could suggest that EV-D68 leads to more inflammation of the lower airways compared with other EV/RV. Larger studies are needed to better highlight the distinguishing features between EV-D68 and other EV/RV.

Few participants were hospitalized among those with EV-D68 (11%) in our study, in contrast to findings in other studies [13,16]. For instance, in a French study, adults with EV-D68 (n = 20) were hospitalized six times more often than those in our study (65% vs 11%). There could be several reasons for this: their population was older (median age: 53.7 vs 32.0 years in our study), had more underlying chronic lung diseases (60% vs 26%), and possibly included the full range of clinical severity, unlike in our study, where we excluded participants with a triage score of 1 (resuscitation) and 2 (emergent) [16]. Additional reasons could be differences in admission practices or accessibility of primary care. Similarly, another French study gathering respiratory samples from 11 laboratories found that of those infected with EV-D68 (n = 21), 67% were hospitalized; three of them were admitted in the ICU and had underlying conditions [13]. Other studies, although limited by size or selective testing of respiratory samples of more severely ill or hospitalized patients, generally found that adults with underlying diseases were commonly and more severely affected [12,14,17]. Although our small sample size lacks statistical power and limits our interpretation, we observed that among those with EV-D68, one-third had at least one underlying condition, and both of the hospitalized patients had underlying cardiac and respiratory diseases. Given these observations, scientific communities, public health authorities, and decision-makers should be aware of the role of EV-D68 as a potential cause of severe complications not only in children but also in adults, especially those with underlying comorbidities. To date, such communiqués have mostly focused on children with asthma, with little to no information about adults [31–33].

Our study is one of the few studies characterizing EV-D68 infections with extensive sociodemographic, symptom, and clinical information in adults seeking medical care in the ED, and adds valuable insights about this re-emerging pathogen. As we systematically collected nasopharyngeal swabs and tested for EV-D68 in all eligible participants, our study population is less subject to selection bias. However, our study also has several limitations. First, with a study duration of 14 months, we could not adequately assess seasonality nor demonstrate if EV-D68 displayed a biennial pattern; thus, the frequency and dynamics of EV-D68 in adults remain uncertain. Second, the small number of EV-D68 cases limited its characterization (e.g., multivariable logistic regression to identify risk

factors was not feasible), and analyses comparing EV-D68 with other EV/RV need to be interpreted cautiously given the lack of statistical power. Third, we did not genotype other EVs and RVs because of technical complexity and small sample size. Hence, we could not characterize and compare how the clinical presentation of non–EV-D68 strains and RVs differed from that of EV-D68. Finally, the study population is representative of only Quebec residents visiting the EDs of tertiary hospitals in two cities with a triage score of 3 (urgent) to 5 (non-urgent). As we excluded more ill participants with a triage score of 1 (resuscitation) and 2 (emergent), we might have missed the more severe cases of EV-D68. Additionally, our results might not be generalizable to other health care settings.

Conclusion

Adults with EV-D68 had a wide range of symptoms; some of them tended to be more prevalent than in other EV/RV infections, such as wheezing, dyspnea, and chest pain. Overall, EV-D68 infections did not appear to be more severe compared with other EV/RV infections. As EV-D68 still has the potential to cause severe respiratory diseases, awareness and a deeper understanding of EV-D68 are essential. Larger studies covering a longer time frame with systematic screening of respiratory samples of patients from diverse health care settings and including the full range of disease severities are needed to better understand the full spectrum of EV-D68 infections in adults. With the growing uncertainties about the seasonality and biennial pattern of EV-D68, yearly surveillance is warranted for future outbreak preparedness and tracking viral evolution.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

The CHU de Québec-Université Laval ethics board approved this study (MP-20-2022-6152), and written informed consent was obtained from the participants.

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Author contributions

M.C.M., S.I., S.B., and P.D. conceptualized this analysis. M.C.M. processed and analyzed the data. S.B., M.-L.V., S.T., M. Boissinot, M.G.B., C.T., Y.L., A.H., and R.G. set up the multicenter cohort study. S.I., M. Baz, I.R., R.K., and V.R.D. contributed to the virus detection assays. M.C.M. drafted the manuscript. All authors interpreted the data, critically reviewed the manuscript, and approved the final version.

Data availability

The data sets generated and/or analyzed during this study are available from the corresponding author upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2025.100669.

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