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World-Wide Prevalence and Genotype Distribution of Parechovirus A

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ABSTRACT

Members of species *Parechovirus A* (PeV-A) are among the most prevalent human viruses worldwide. Studies on PeV-A prevalence and epidemiology have been conducted in separate countries, describing variations in PeV-A prevalence across continents. There is no overview on global PeV-A prevalence, hampering global insights in viral dynamics. We conducted a literature search on PeV-A prevalence and PeV-A genotype distribution, and summarized the findings of 106 included articles. We found that PeV-A prevalence was higher in Africa as compared to other continents, higher in fecal samples as compared to other sample types, and higher in young children as compared to older children and adults. The diversity of PeV-A types in Asia, Africa and South-America is wide, while it is narrower in Europe and North-America. PeV-A1 seems to be associated mainly with gastro-enteritis, but is also detected regularly in stool samples of healthy study participants, indicating asymptomatic carriage. PeV-A3 is associated with neurological symptoms and is the predominant type found in cerebrospinal fluid samples. Although the reports on seasonality are diverse, PeV-A infections seem to occur mainly in summer and fall.

INTRODUCTION

Members of the species *Parechovirus A* (PeV-A), formerly known as *Human Parechovirus*, within the *Picornaviridae* family, are highly prevalent globally, and associated with a variety of clinical symptoms, among which central nervous system (CNS) infection in young children [1,2]. Echovirus 22 and 23, now known as types PeV-A1 and PeV-A2, were reclassified as members of a distinct genus in 1994 [3]. Since then, many new PeV-A types have been identified, with PeV-A19 being the type most recently classified [4]. During the past decades, the PeV-A prevalence and type distribution have been determined in specific geographical regions and/or study populations. To date, no overview regarding PeV-A prevalence is available, while only a single review reporting PeV-A genotype distribution has been published [5]. The aim of this review was to organize the currently available literature to determine the PeV-A prevalence in different continents and sample types, and in patients reporting different clinical symptoms, as well as the distribution of the 19 known PeV-A genotypes.

METHODS

Literature search

We performed a literature search in the PubMed database on November 17th 2018 and in the Embase/OVID database on December 12th 2018 to identify all publications on PeV-A prevalence - which was defined as the detection of viral RNA in clinical or surveillance samples - and PeV-A genotype distribution (Table 1). To reduce bias due to variation in the methods used for PeV-A detection and typing, only articles published after 2009 were considered for inclusion. All hits were screened on title and abstract and subsequently on full text using in- and exclusion criteria as summarized in Table 1.

Data extraction

Of all included articles, data on the following topics was extracted: country and time period of the sample collection, number of samples (if number of samples was not specified, number of included participants was taken as a proxy), sample type (e.g., stool samples, respiratory samples and cerebrospinal fluid (CSF)), symptoms of the participants (e.g., gastro-intestinal (GE), respiratory and CNS symptoms), age of the participants (when no age was specified in a pediatric population, it was assumed that participants up to 18 years of age were included), PeV-A prevalence and the distribution of PeV-A genotypes. For case-control studies, the results for the case- and control- group were recorded separately. For studies that mentioned seasonality of PeV-A infection, information on this topic was recorded.

Statistical analysis

Weighted average PeV-A prevalences were calculated for each continent, sample type, symptom group and age group, such that the contribution of each study was proportional to the number of included samples. The distribution of the PeV-A genotypes were determined overall, and for the specific sample types and symptom groups, by calculating the weighted average of the proportion of each genotype. All statistical analyses were performed using R version 3.5.2.

Table 1: The searches as performed in the PubMed Database on November 17th, 2018 and in the Embase/OVID Database on December 12th, 2018, and the in- and exclusion criteria used for article selection.

Search in PubMed database
""Parechovirus""[Mesh] OR HPeV* [tiab] OR parecho* [tiab] AND (((""Genotype""[Mesh] OR ""Serogroup""[Mesh] OR *type* [tiab] OR ""Prevalence""[Mesh] OR ""Epidemiology""[Mesh]) OR (""Public Health Surveillance""[Mesh] OR prevalen* [tiab] OR frequen* [tiab] OR surveillan* [tiab]))
Search in Embase/OVID database
parechovirus/ OR human parechovirus/ OR parecho*.ti,ab,kw OR HPeV*.ti,ab,kw AND ((genotype/ OR serotype/ OR type*.ti,ab,kw) OR (prevalence/ OR epidemiology/ OR frequency/ OR epidemiolog*.ti,ab,kw OR surveill*.ti,ab,kw OR frequen*.ti,ab,kw))
Inclusion criteria
Studies reporting PeV-A prevalence and/or PeV-A genotype distribution in a specified population
Studies using molecular methods to detect and type PeV-A's
Exclusion criteria
Studies reporting PeV-A detection in environmental or wastewater samples
Studies reporting PeV-A detection in animals
Case reports/case series
<100 included samples for determining PeV-A prevalence*
<10 successfully typed strains for determining genotype distribution*
Studies reporting PeV-A prevalence in participants with specific medical conditions (e.g. Diabetes Mellitus, immunocompromised patients)
Studies reporting on only one specific PeV-A genotype
Papers published before 2009
Papers not available in full length in English

*Studies meeting only one of these exclusion criteria were excluded from analysis of PeV-A prevalence or PeV-A genotype distribution only respectively.

RESULTS

The included studies

The search in the PubMed database resulted in 354 hits and the search in the Embase/OVID database resulted in 551 hits. After removal of duplicates, 566 articles were left for the screening. Of the 566 articles, 377 were excluded based on title and abstract, and 84 were excluded based on full text, leaving a total of 105 studies. One accepted manuscript [4] was also included, resulting in 106 included studies in total (S1). Of the106 studies, the majority was conducted in Europe (36/106,34%) or Asia (43/106, 41%), while 13/106 (12%)

were conducted in North-America, 10/106 (9.4%) in Africa and only two (1.9%) and one (0.9%) in Oceania and South-America respectively. One study was conducted in multiple countries and continents (Figure 1A, S1). Most studies had a total sampling period of < one year (35/106, 33%), < three (40/106, 38%) or < five years (17/106, 16%) (Figure 1B, S1), and most of the studies were conducted in the last ten years, after 2008 (Figure 1C, S1). The most frequently collected samples included stool samples (37/106, 35%), respiratory samples (23/106, 22%) and CSF (22/106, 21%), while 24/106 (23%) studies tested several sample types or other sample types, e.g., urine, blood, middle ear fluid and biopsies (Figure 1D, S1). In studies reporting PeV-A prevalence in patients with specific symptoms, GE symptoms were most often the symptoms of interest, (24/106, 23%), followed by respiratory symptoms (13/91, 12%), CNS symptoms (12/106, 11%) and fever without source (FWS) (3/106, 2.8%). A total of 26/106 (25%) studies included patients with a selection of symptoms or other symptoms, e.g., sepsis-like illness, herpangina and parotitis. While 6/106 (5.7%) studies had included only healthy participants, 10/106 (9.4%) had included a control group of healthy participants (Figure 1E, S1). The majority of studies (78/106, 74%) were conducted in children. Only 19/106 (18%) studies had included adults, while data on participants' ages were not mentioned in 9/106 (8.5%) studies (Figure 1F, S1).

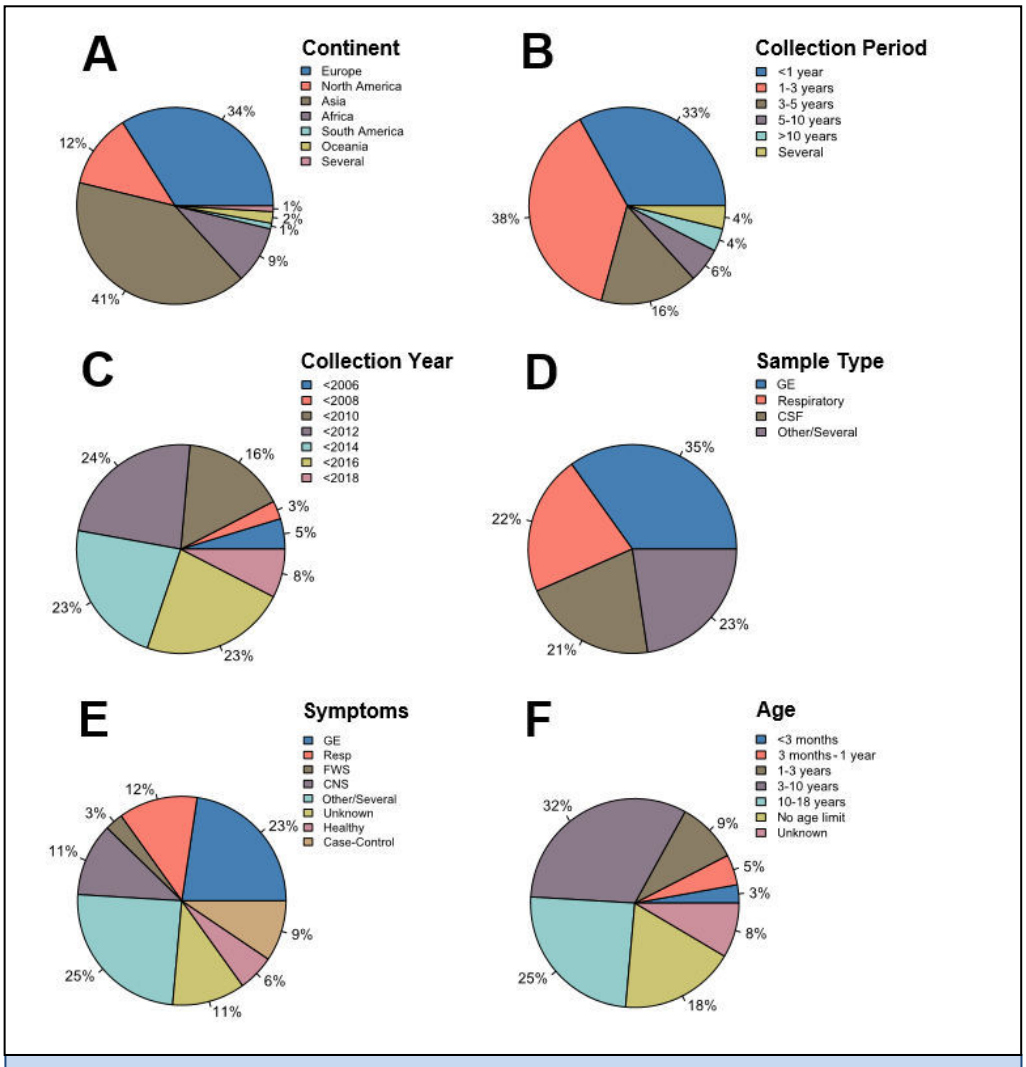


Figure 1: Pie charts displaying the characteristics of the included studies; Continent of sample collection (1A), duration of collection period (studies that collected samples in multiple, temporally separated periods were labeled as 'several') (1B), (last) year of sample collection (1C), sample types (GE = gastro-intestinal (stool), CSF = cerebropinal fluid) (1D), symptoms (GE = gastro-intestinal, FWS = fever without source, CNS = central nervous system) (1E) and age (1F).

PeV-A prevalence

PeV-A prevalence in a minimum of 100 samples was reported in 102 of the included studies (95%, S1). Only 4/102 (4.0%) studies that screened for PeV-A, did not find any positive samples (S1). Average PeV-A prevalence was highest in Africa (12%), while it remained <6% in Europe, North-America and Asia (2.7%, 5.7% and 3.1% respectively) (Figure 2A). In both Asia and Africa, a wide range of PeV-A prevalence was found across the studies (0%-55% and 0%-59%, respectively), while the highest prevalence found in Europe and North-America was 24% and 27% respectively. Weighted average PeV-A prevalence was higher in stool samples (11%), while it remained <4% for other sample types; 2.0%, 2.9% and 1.7% for respiratory samples, CSF samples and other/several sample types respectively (Figure 2B). PeV-A prevalence was highest in studies including only children up to three months of age (23%), lower in studies including children up to one, three or ten years, and was lowest in studies including children up to 18 years of age (1.7%) and adults (1.2%) (Figure 2C). Studies including adults only (S1), reported even lower prevalences, ranging between 0% and 0.5% (S1). Studies that had included participants with a wide age range reported PeV-A infections predominantly or exclusively in young age groups, often <1 year of age [6-16]. Additionally, several studies reported that PeV-A infected participants were significantly younger than non-infected participants [4,17,18]. Studies including participants with GE or CNS symptoms, with FWS, or healthy participants found high prevalences (8.9%, 6.2%, 7.1% and 6.8%, respectively), while lower prevalences were found in patients with respiratory symptoms (1.5%) (Figure 2D). Ten of the studies were case-control studies, that had included patients with varying symptoms in the case group and healthy controls in the control group. While three case-control studies found a higher PeV-A infection rate in the case group, four case-control studies, all testing PeV-A prevalence in stool samples, found a higher rate in the control group. The remaining three studies found comparable PeV-A infection rates in the case- and control group (S1).

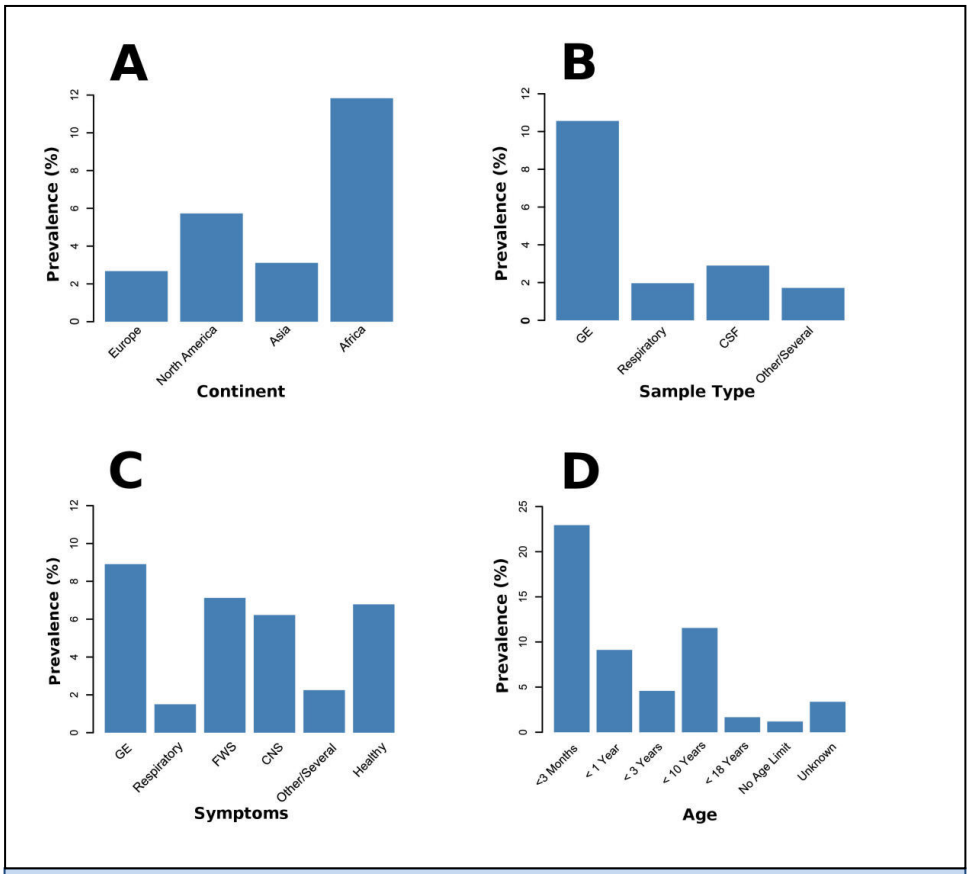


Figure 2: Bar graphs displaying the weighted average PeV-A prevalence in different continents (2A), sample types (GE = gastro-intestinal, CSF = cerebrospinal fluid) (2B), symptoms (GE = gastro-intestinal, FWS = fever without source, CNS = central nervous system) (2C) and age (2D).

PeV-A type distribution

A total of 53 included studies (50%, S1) reported PeV-A genotypes in a minimum of ten successfully typed strains. PeV-A1 and PeV-A3 were the most prevalent genotypes, with 40% and 38% of the viral strains typing as PeV-A1 or -A3 respectively (Figure 3A). In Europe, PeV-A1 through PeV-A6 were identified, while in North-America, only PeV-A1 through PeV-A4 were found. PeV-A7 through PeV-A19 were identified exclusively in Asia, Africa and South-America. In stool samples and patients with GE symptoms, PeV-A1 was the most prevalent genotype (55% and 60% respectively) (Figure 3A and 3B). In CSF samples and patients with CNS symptoms, PeV-A3 was most prevalent (86% and 87%, respectively) (Figure 3A and 3B).

Pev-A Seasonality

Some studies reported that they did not see any seasonal patterns in PeV-A infection (S1). However, 17 studies reported more infections in summer and 12 more infections in fall, while only four studies reported more infections in winter and three more infections in spring (S1). Some reported seeing biannual (i.e., twice a year) or biennial (i.e., every two years) PeV-A infection peaks, while others reported genotype-specific peaks in different seasons (S1).

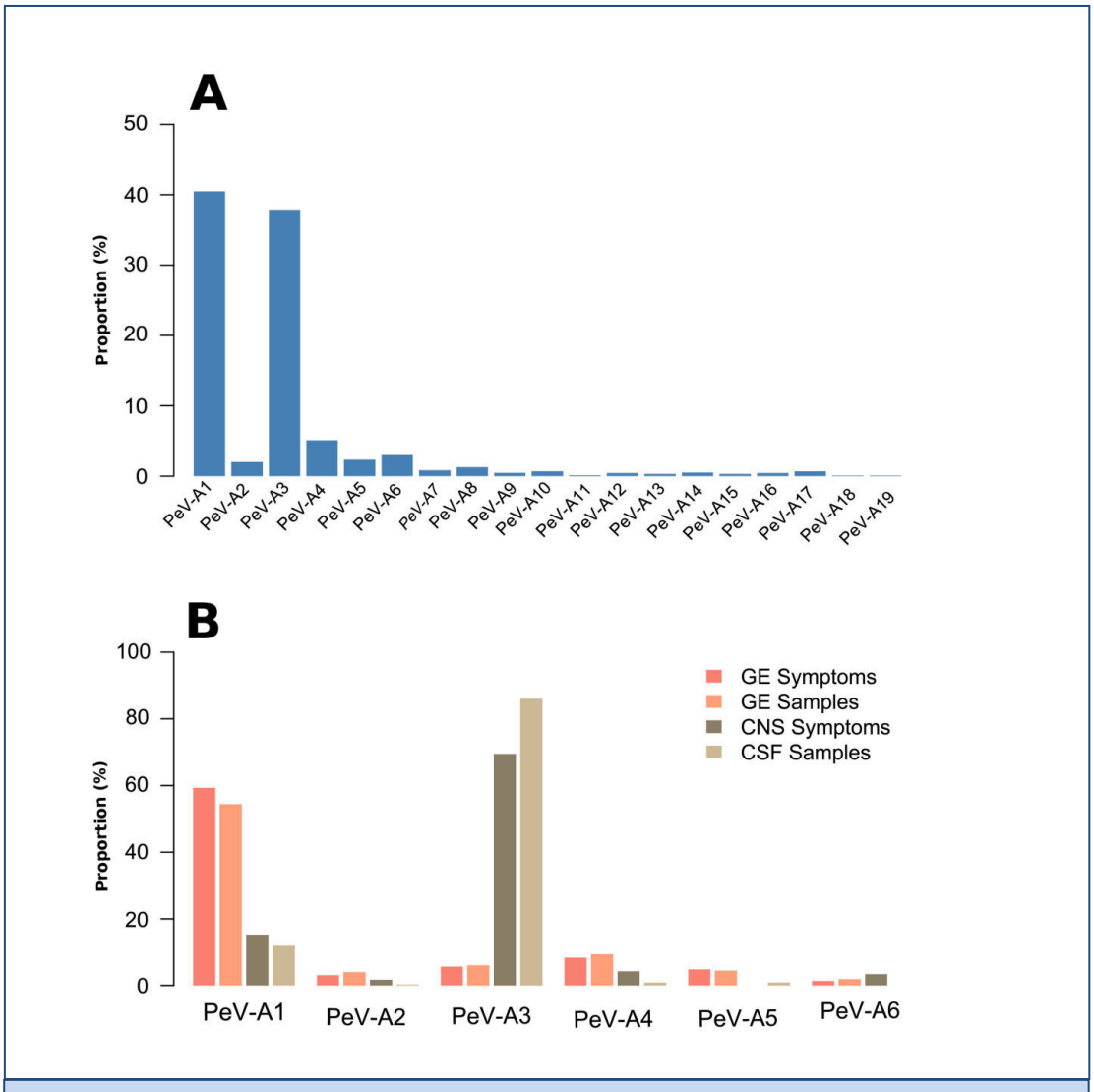


Figure 3: Distribution of the PeV-A genotypes. Percentages represent the weighted average proportion of the type among all typed strains. Bars represent the distribution in the total database (3A) and in subsets, including only gastro-intestinal (GE) samples, cerebrospinal fluid (CSF), GE symptoms and central nervous system (CNS) symptoms (3B).

DISCUSSION

This review described the PeV-A prevalence in different continents, patient groups and sample types, and reported the distribution of the 19 known PeV-A genotypes.

PeV-A was found across all continents, in the vast majority of the studies. It was apparent that Africa had the highest PeV-A prevalence, while prevalences in Europe, North-America and Asia appeared to be comparable.

The prevalence in stool samples was high compared to the prevalence in other sample types. The most likely explanation for this is that PeV-A1 is highly prevalent, often asymptomatic, and predominantly eliciting gastro-intestinal symptoms. The high prevalence in healthy participants and patients with GE symptoms further supports this, as stool was the sample type most often collected in both groups. The high PeV-A prevalence in patients with FWS is mainly derived from high PeV-A prevalences found in studies including children under three months of age with FWS (S1) [19,20]. Many studies observed a higher PeV-A prevalence in young children, indicating that PeV-A infections, mainly occur in (early) childhood, while they are rare among older children and adults.

While PeV-A1 and PeV-A3 were by far the most prevalent genotypes across all continents, we could see that there is a greater diversity of PeV-A genotypes in Africa and Asia, compared to Europe and North-America. South-America seems to have a wider diversity as well, although we could only include one study from this continent. The two studies included for Oceania reported only PeV-A3 infections. However, as these studies were conducted during a PeV-A3 outbreak, these results might not represent the normal diversity of PeV-A in this continent. We are uncertain about the reason for the variety in PeV-A diversity worldwide, but we speculate that differences in climate might influence PeV-A diversity. PeV-A1 is mainly found in stool samples and in patients with GE-symptoms, while PeV-A3 is more often found in CSF samples and patients with CNS symptoms worldwide. This supports the findings from several specific papers, in which associations between PeV-A1 and gastro-intestinal infections, and between PeV-A3 and CNS infections were reported [21,22].

The reports on PeV-A infection and seasonality varied widely. The vast majority of the studies reporting seasonality in all continents reported more PeV-A infections during summer and/or fall, leading to the hypothesis that these are the prime seasons for PeV-A infections worldwide.

An important limitation of this study was the lack of comparability between the included studies. We could not perform statistical analyses using the current data set, because of the large variety in study characteristics (the age and symptoms of the included participants and the type of sample collected). We chose to describe our findings only correcting for the amount of included samples in each study. In the future, more comparable studies might allow us to calculate more precisely the contribution of several factors such as age, continent and symptoms to PeV-A prevalence. The searching of the databases, the evaluation of in- and exclusion of the studies and the data extraction for the current review were performed by one author only, which might have potentially introduced bias.

This is the first review describing the global PeV-A prevalence and PeV-A genotype distribution. Although we currently have reasonable knowledge on PeV-A circulation in Europe, North America, Asia, and Africa, data on South America and Oceania is lacking. Data on PeV-A epidemiology in these continents, and more elaborate data on PeV-A epidemiology in the other continents, could help us in further understanding the differences in PeV-A prevalence and type distribution and the clinical relevance of PeV-A and its specific genotypes.

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All authors declare not to have any conflict of interest regarding this study.

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Supplementary Material 1: All included studies, their characteristics and reported PeV prevalence. For articles without a DOI, the PMCID or PMID is given.

No.	Author	DOI	Continent	Sampling Periodlength	Sample	Sample type	Symptoms	Age	Seasonality	IncludedforPrevalence	Includedfor type distribution	PeV prevalence
1	Aizawa et al.	10.1016/j.jinf.2015.10.010	3	1	6	3	4	7		Yes	Yes	52
2	Alam et al.	10.3390/v7010378	3	2	4	1	1	4		Yes	Yes	21
3	Alam et al.	10.1371/journal.pone.0078377	3	1	3	1	1	4	7	Yes	Yes	24
4	Altan et al.	10.1371/journal.pone.0202054	4	6	7	1	5	4		Yes	Yes	4.5
5	Barskey et al.	10.1093/infdis/jit408	2	2	4	4	5	7		Yes	No	0
6	Baumgarte et al.	10.1128/JCM.01468-07	1	1	1	1	1	6		Yes	No	1.6
7	Benet et al.	10.4269/ajtmh.16-0733	7	3	6	4	2	4		Yes	No	0.7
8	Benschop et al.	10.1016/j.diagmicrobio.2010.05.016	1	2	3	1	5	7	4	Yes	Yes	8.6
9	Biscaro et al.	10.1016/j.meegid.2018.02.011	1	1	7	1	1	5		Yes	No	2.6
10	Bozkurt et al.	PMID: 26613223	3	2	5	1	1	5		Yes	No	8.8
11	Braun et al.	10.1093/jpids/pis005	2	1	3	1	8	2		Yes	Yes	Case: 21 Control: 27
12	Breiman et al.	10.1186/s12879-015-0827-x	4	2	4	2	8	4		Yes	No	Case: 1.9 Control: 2.1
13	Brini et al.	10.1371/journal.pone.0188325	4	2	6	2	2	4		Yes	No	8.1
14	Brouwer et al.	10.1007/s00705-018-04131-7	4	2	1	1	8	4		Yes	Yes	Case: 55.3 Control: 59.4
15	Bubba et al.	10.1097/INF.0000000000001344	1	3	6	4	5	4	2; 3	Yes	Yes	5.2
16	Bubba et al.	PMC4718355	1	1	4	1	1	4		Yes	No	6.3
17	Cabrerizo et al.	10.1002/jmv.24658	1	2	5	4	5	6	1	Yes	Yes	2
18	Cabrerizo et al.	10.1097/INF.0b013e31828bbe46	1	1	4	2	2	5	3; 4	Yes	Yes	3.6
19	Calvo et al.	10.1016/j.jcv.2016.10.020	1	2	6	3	3	1		Yes	No	24
20	Chaimongkol et al.	PMID: 22372354	1	1	2	1	1	4		Yes	No	1.9
21	Chakrabarti et al.	10.1007/s00431-018-3209-8	1	1	7	3	5	4	1; 2	Yes	No	10
22	Chang et al.	10.7883/yoken.JJID.2018.019	3	4	7	4	5	5	8	Yes	Yes	0.4
23	Chen et al.	10.1007/s00705-013-1915-0	3	1	6	1	1	4		Yes	Yes	13.4
24	Chen et al.	10.1002/jmv.25222	3	2	5	1	8	6		Yes	Yes	Case: 12 Control: 6.5
25	Chhabra et al.	10.1093/infdis/jit254	2	1	3	1	8	4	2	Yes	No	Case: 4.8 Control: 4.4
26	Chiang et al.	10.1371/journal.pone.0184533	3	2	7	4	5	3	3; 4	Yes	Yes	2.3
27	Chieochansin et al.	10.1016/j.virol.2011.09.021	3	2	4	2	5	6	2; 4; 6	Yes	Yes	1.6
28	Chuchaona et al.	10.1016/j.meegid.2015.02.003	3	1	5	1	1	5		Yes	No	1.8
29	Colvin et al.	10.1542/peds.2012-1391	2	3	4	4	8	3		Yes	No	Case: 7.8 Control: 0
30	Cordey et al.	10.1016/j.jcv.2015.05.003	1	1	6	4	5	5		Yes	No	2.6
31	Cristanziano et al.	10.1016/j.jcv.2015.08.004	4	2	6	1	6	6		Yes	No	5.2
32	Cui et al.	10.1186/s12879-015-0863-6	3	2	5	2	2	5		Yes	No	0
33	De Crom et al.	10.1016/j.jcv.2016.01.014	1	3	4	4	5	5	2	Yes	Yes	15
34	Do et al.	10.1371/journal.pone.0160606	3	2	4	2	2	3		Yes	No	2
35	Elfving et al.	10.1097/INF.0000000000001876	4	1	4	2	8	4		Yes	No	Case: 1.5 Control: 0
36	Feikin et al.	10.1093/infdis/jis530	4	3	4	4	8	6		Yes	No	Case: 0.5 Control: 0.5
37	Felsenstein et al.	10.1097/INF.0000000000000112	2	3	5	3	5	5		Yes	No	2.7
38	Fischer et al.	10.3201/eid2001.130569	1	3	5	4	5	7	2; 3	Yes	Yes	3.0
39	Ghanem-Zoubi et al.	10.1016/j.jcv.2013.06.001	3	2	3	3	4	4	2	Yes	Yes	3.5
40	Gong et al.	10.1371/journal.pone.0151495	3	3	5	4	5	7		No	Yes	-
41	Graul et al.	10.1016/j.jcv.2017.10.008	4	2	3	1	8	4	8	Yes	Yes	Case: 21 Control: 26
42	Guo et al.	10.1371/journal.pone.0068321	3	1	4	1	1	4	2; 3	Yes	Yes	25
43	Han et al.	10.1016/j.jcv.2013.05.023	3	2	5	3	5	5		Yes	Yes	6.5
44	Harvala et al.	10.2807/1560-7917.ES2014.19.15.20772	1	4	5	3	5	7	5	Yes	Yes	1
45	Harvala et al.	10.1016/j.jinf.2014.02.017	1	1	5	4	5	3		Yes	No	5.5
46	Harvala et al.	10.1002/jmv.22023	1	3	4	3	5	6	5	Yes	Yes	0.8
47	Hassan et al.	10.1093/jpids/piy077	2	1	5	1	8	3		Yes	No	Case: 11 Control: 16
48	Hoffmann et al.	10.1371/journal.pone.0043666	4	2	4	2	2	4		Yes	No	0.4
49	Huang et al.	10.1016/j.jmii.2014.06.013	3	4	5	4	5	7		Yes	Yes	5.7
50	Itta et al.	10.1080/23744235.2016.1218045	3	1	6	1	1	4		Yes	Yes	8.8
51	Janahi et al.	10.1186/s12879-017-2225-z	3	2	4	2	2	3		Yes	No	3
52	Jeziorski et al.	10.1002/jcla.21737	1	1	5	3	5	2		Yes	No	7.5
53	Jung et al.	10.1093/ofid/ofw172.21	3	2	6	3	5	5		Yes	No	5.9
54	Karsch et al.	10.1097/INF.0000000000000802	1	2	5	1	4	6	2	Yes	Yes	4.2
55	Khamrin et al.	10.1016/j.jviromet.2011.02.012	3	2	3	1	1	4		Yes	No	6.4

56	Khatami et al.	10.1093/cid/ciu784	6	1	6	4	5	2		No	Yes	-
57	Kolehmainen et al.	10.1097/INF.0000000000000401	1	6	5	4	5	3		Yes	No	3
58	Kolehmainen et al.	10.1016/j.jcv.2012.02.006	1	5	4	1	6	3	3	Yes	Yes	6.4
59	Kool et al.	10.3109/13814788.2014.907267	1	1	2	2	3	4		Yes	No	2.3
60	Kurz et al.	10.1007/s00431-015-2583-8	1	3	5	4	5	1		Yes	Yes	25
61	Lau et al.	10.1016/j.jcv.2012.01.008	3	1	1	1	1	5		Yes	No	0.3
62	Lekana-Douki et al.	10.1186/1471-2334-14-373	4	2	4	2	5	6		Yes	No	0.5
63	Ljubin-Sternak et al.	10.1155/2016/2168780	1	6	6	2	2	5		Yes	No	1.3
64	Malhotra et al.	10.4103/ijmr.IJMR_22_15	3	2	5	2	2	4		Yes	No	0
65	Malhotra et al.	10.1186/s12985-016-0549-8	3	2	6	2	2	4		Yes	No	0.3
66	Masse et al.	10.1155/2017/1423718	1	3	7	2	2	6*		Yes	No	0
67	McNeale et al.	10.1016/j.jcv.2017.12.003	6	1	6	4	4	5		No	Yes	-
68	Memish et al.	10.1016/j.cmi.2015.02.008	3	1	5	2	6	6*		Yes	No	0.04
69	Messacar et al.	10.1002/jmv.24119	2	2	4	3	4	2	2; 3	No	Yes	2.9
70	Midgley et al.	10.1093/jpids/pix010	2	1	6	3	5	2		No	Yes	-
71	Mladenova et al.	10.1016/j.meegid.2015.10.004	1	1	4	1	4	4		Yes	No	4.8
72	Moe et al.	10.1371/journal.pone.0159196	1	2	6	2	2	4		Yes	No	9
73	Momoki et al.	10.7883/yoken.JJID.2017.490	3	5	7	4	5	7	2; 3	Yes	Yes	12
74	Morikawa et al.	10.1016/j.jcv.2015.01.006	3	2	6	2	6	4		Yes	No	2.8
75	Morikawa et al.	10.1016/j.jcv.2015.10.001	3	1	6	2	5	5	2; 3	Yes	No	3.7
76	Nielsen et al.	10.1016/j.jviromet.2013.06.038	1	2	3	4	5	7	2	Yes	Yes	3
77	Nix et al.	10.1099/vir.0.053827-0	5	2	1	1	4	6		No	Yes	-
78	Parisi et al.	10.1016/j.ijid.2016.01.012	1	2	6	3	4	6*		Yes	No	0
79	Parisi et al.	10.1016/j.ejpn.2016.04.002	1	2	6	3	4	5		Yes	No	1.5
80	Patil et al.	10.1017/S095026881700262X	3	3	4	1	1	4		Yes	Yes	14
81	Pellegrinelli et al.	10.1099/jgv.0.000937	1	4	7	2	5	4		Yes	Yes	5.4
82	Pham et al.	10.1016/j.jviromet.2010.07.038	3	2	3	1	1	5		Yes	No	8.1
83	Pham et al.	10.3201/eid1601.091105	3	1	2	1	1	5		Yes	Yes	8.3
84	Pham et al.	10.1002/jmv.21740	3	1	3	1	1	5		Yes	Yes	8.1
85	Piralla et al.	10.1002/jmv.23197	1	2	4	4	5	6	3	Yes	Yes	0.4
86	Rahimi et al.	10.1007/s13365-013-0221-7	3	2	4	3	4	4		Yes	Yes	43.2
87	Renaud et al.	10.1016/j.jcv.2011.02.010	2	2	5	4	5	6		Yes	Yes	3.4
88	Rovida et al. et al.	10.1016/j.diagmicrobio.2013.07.020	1	2	5	1	1	6		Yes	No	0.3
89	Saikruang et al.	10.1007/s00705-014-2191-3	3	1	3	1	1	6*		Yes	No	0.3
90	Sano et al.	10.1111/ped.13467	3	4	6	4	3	1	2	Yes	Yes	20
91	Schuffenecker et al.	10.1016/j.jcv.2012.04.016	1	2	4	3	5	4		Yes	Yes	2.9
92	Sedmak et al.	10.1086/649863	2	5	1	4	5	3		Yes	Yes	4.2
93	Seo et al.	10.3345/kjp.2015.58.3.102	3	2	5	3	4	4		Yes	No	3.4
94	Seo et al.	10.14776/kjpid.2012.19.1.28	3	1	3	1	1	4		Yes	No	16
95	Sharp et al.	10.1097/INF.0b013e318276b328	2	1	3	3	5	5	2; 3	Yes	Yes	17
96	Sharp et al.	10.1128/JCM.01680-12	2	1	3	2	6	5	2	Yes	Yes	2.8
97	Thongprachum et al.	10.1002/jmv.24155	3	3	5	1	1	5		Yes	No	6.6
98	van den Bergh et al.	10.1371/journal.pone.0047711	1	3	3	2	6	2		Yes	No	9
99	Van Someren et al.	10.1097/CCM.0000000000002752	1	1	6	2	2	6*		Yes	No	0.1
100	Vollbach et al.	10.1186/s12985-015-0427-9	1	5	3	3	4	5		Yes	No	0.6
101	Walters et al.	10.1016/j.jcv.2011.07.008	2	4	4	3	5	5	2; 3	Yes	Yes	2.4
102	Yamamoto et al.	10.1099/jmm.0.000167	3	1	6	4	5	6	7	Yes	Yes	10
103	Yip et al.	10.1186/1743-422X-11-182	3	6	5	1	1	5		Yes	Yes	3
104	Zhao et al.	10.1186/s13099-016-0135-z	3	3	6	1	1	4		Yes	Yes	13
105	Zhong et al.	10.1002/jmv.23449	3	3	4	3	5	5		Yes	Yes	8.7
106	Zhong et al.	10.1002/jmv.22114	3	2	3	1	1	4	1; 2; 3	Yes	Yes	55

Continent: 1,Europe; 2, North-America; 3, Asia; 4, Africa; 5, South-America; 6, Oceania; 7, multiple continents

Sampling Period: 1, ≤ 1 year; 2, ≤ 3 years; 3 ≤ 5 years; 4, ≤ 10 years; 5, > 10 years; 6, several separated inclusion periods

Sample collection (last year): 1, ≤ 2006; 2, ≤ 2008; 3, ≤ 2010; 4, ≤ 2012; 5, ≤ 2014; 6, ≤ 2016; 7 ≤ 2018

Sample type: 1, gastro-intestinal (GE); 2, respiratory; 3, cerebrospinal fluid (CSF); 4, several/otherincluded sample types; 5, unknown

Symptoms: 1, gastro-intestinal (GE); 2, respiratory; 3, fever without source (FWS); 4, central nervous system (CNS); 5, several/other included symptoms; 7, unknown; 8, case-control

Age: 1, ≤ 3 months; 2, ≤ 1 year; 3, ≤ 3 years; 4,, ≤ 10 years; 5, ≤ 18 years; 6, No age limit (6*, only adults); 7, unknown

Seasonality: 1, spring; 2, summer; 3, fall; 4, winter; 5, biennial; 6, biannual; 7, different seasonality per type; 8, no seasonality observed