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REVIEW

Prevalence of human bocavirus infections in Europe. A systematic review and meta-analysis

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Abstract

Human bocaviruses (HBoVs) are recently described as human emergent viruses, especially in young children. In this study, we undertook a systematic review and meta-analysis to estimate their prevalence in Europe. PubMed, Web of Science and Scopus databases were systematically screened for clinical studies, up to October 2020. Study eligibility criteria were primary full-text articles from clinical studies, conducted using valid screening test methods and published in peer-reviewed journals, in English or Spanish and from European countries. The overall pooled prevalence, prevalence by country as well as the prevalence of HBoV as a single or co-pathogen were estimated using a random-effects model. Sub-group and meta-regression analyses explored potential sources of heterogeneity in the data. A total of 35 studies involving 32,656 subjects from 16 European countries met the inclusion criteria. Heterogeneity ($I^2 = 97.0\%$, $p < .01$) was seen among studies; HBoV prevalence varied from 2.0 to 45.69% with a pooled estimate of 9.57% (95%CI 7.66-11.91%). The HBoV prevalence both as a single infection (3.99%; 95%CI 2.99-5.31%) or as co-infection with other viruses (5.06%; 95%CI 3.88-6.58%) was also analysed. On a geographic level, prevalence by country did not show statistical differences, ranging from 3.24% (Greece) to 21.05% (Denmark). An odds ratio analysis was also included in order to evaluate the relevance of the variable 'age' as a risk factor of HBoV infection in children <5 years old. The OR value of 1.77 (95%CI 1.13-2.77; $p < .01$) indicated that being <5 years old is a risk factor for HBoV infection. This study showed that HBoV has a moderate prevalence among European countries.

KEYWORDS
gastrointestinal tract infection, hospitalized children, Human bocavirus, prevalence, respiratory tract infection

1 | INTRODUCTION

The twenty-first century has led to the discovery of several new and emergent respiratory viruses, being among them human bocaviruses (HBoVs). HBoVs are recently described viruses belonging to the genus *Bocaparvovirus* (family *Parvoviridae*, subfamily *Parvovirinae*) which comprise four genotypes (HBoV1-4). HBoV1 was first identified in 2005 in nasopharyngeal aspirates from children with respiratory tract infection (RTI) (Allander et al., 2005). Since 2009, genotypes HBoV2-4 were subsequently identified (Arthur et al., 2009; Kapoor et al., 2009, 2010).

HBoV are small non-enveloped viruses (~25 nm in diameter), with icosahedral T = 1 capsid symmetry and a linear ssDNA genome of approximately 5 kb in length and negative- or positive-sense, organized in three open reading frames (Guido et al., 2016). Intra-species recombination has been shown for all four HBoVs, and a recombination event between HBoV1 and a common ancestor of HBoV2 and HBoV4 has been suggested to led to the formation of HBoV3 (Cheng et al., 2011; Kapoor et al., 2010). HBoVs are commonly detected in children, while in adults and the elderly, their detection is infrequent (Qiu et al., 2017).

From a clinical perspective, HBoV1 is the most important of HBoVs and one of the most commonly detected respiratory viruses, causing mild to severe upper or lower RTI in children (mainly between 6 months and 5-year-old). HBoV1 is most likely transmitted by the respiratory route and can be detected in very high loads in the respiratory tract during the acute phase, after which it may persist at low viral loads for months (Martin et al., 2010; Qiu et al., 2017).

HBoV2-4 are mainly detected in faecal samples, being HBoV2 the most frequent genotype followed by HBoV1, HBoV3 and HBoV4 (Qiu et al., 2017). The general lack of HBoV2-4 genotypes in respiratory samples and their presence in faeces suggest that these genotypes are enteric and spread most likely via faecal–oral route. However, the occurrence of HBoVs in faeces is similar among patients with or without symptoms of respiratory or gastrointestinal infection, so the causal role of HBoV in gastrointestinal disease is still unclear (Arthur et al., 2009; Kapoor et al., 2009, 2010).

Besides respiratory and stool samples, HBoVs have also been detected in urine (Wang et al., 2010), saliva (Martin et al., 2009), blood (Li et al, 2015; Tozer et al., 2009), tonsils (Lu et al., 2008), cerebrospinal fluid (Mitui et al., 2012), as well as in environmental samples like river water (Hamza et al., 2009), sewage (Iaconelli et al., 2016) and shellfish (La Rosa et al., 2018). The implications of these non-respiratory findings are uncertain.

Since their discovery in 2005, HBoVs have gained considerable attention due to its global distribution in clinical samples. The prevalence of HBoVs has been reported ranging from 1 to 56.8% of respiratory tract samples and from 1.3 to 63% of stool samples, depending on the country. Globally, the HBoVs total prevalence was estimated around 6% (Guido et al., 2016). However, high prevalence does not necessarily mean high clinical relevance, and proving its causative role has been difficult, in part because the virus is often detected along with other respiratory and enteric viruses at co-detection rates as high as 75% (Christensen et al., 2010; Guido et al., 2016; Martin et al., 2010). These facts raise the question about the true contribution and significance of HBoV as a causative agent in human infections. In this study, a systematic review and meta-analysis on the pooled estimates of the HBoV infections were conducted to gain knowledge on the overall prevalence of HBoV in Europe, detected both as a single pathogen or in the presence of other viruses, as well as to determine whether this prevalence vary across European countries. We also performed an odds ratio (OR) analysis to determine if age is a risk factor for HBoV infection.

2 | MATERIALS AND METHODS

2.1 | Study design and article searching strategy

The protocol of this systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P 2015) Guidelines (Shamseer et al., 2015). The literature search strategy, selection of studies, data extraction and result reporting were also done in accordance with the PRISMA guidelines (Moher et al., 2009). A comprehensive literature search was done in PubMed, Web of Science and Scopus using keywords and Boolean logic operators. The keywords used were: '*human bocavirus*', '*HBoV*', '*respiratory tract infection*', '*gastrointestinal tract infection*', '*prevalence*' and '*hospitalized children*'. The detailed search strategy is provided in Supporting information. Additionally, related articles were retrieved manually from Google Scholar and critically evaluated.

2.2 | Eligibility criteria

Only primary full-text articles (clinical studies), from 2005 to October 2020, conducted using valid screening test methods (PCR or ELISA) and published in peer-reviewed journals, in English or Spanish and from European countries were considered. Studies with unclear epidemiological information (e.g., lacking age range or number of analysed individuals) or methodological inconsistencies were not included in the study.

2.3 | Article selection and data extraction

All articles were imported into Mendeley Desktop software (version 1.19.4) and duplicated articles were removed. Remaining articles were later screened independently by three authors (DP, AL and EG) to identify eligible studies according to the eligibility criteria. After the screening of published articles for eligibility, relevant data and information were extracted from each eligible study and curated in a Microsoft Excel (version 16.43; 2020) sheet including name of the first author, year of publication, country, detection technique (RT-qPCR, ELISA), age of the patients, sample type, sample size, number of HBoV positive cases, number of HBoV positive cases as a single virus, number of HBoV positive cases in co-detection with other viruses and study population. Two authors (D.P., A.L.) independently collated data from the eligible studies and evaluated the data. Any inconsistencies or disagreement

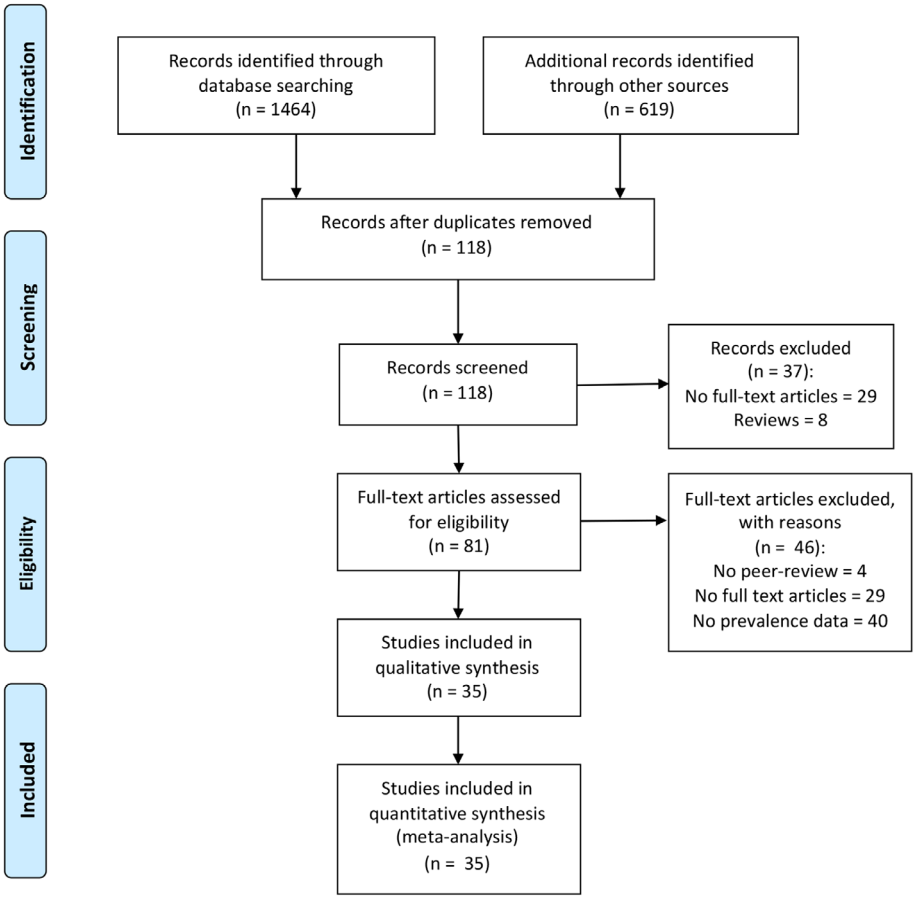

FIGURE 1 PRISMA flow diagram for the identification and selection of articles for inclusion in the systematic review and meta-analysis

were discussed with a third author (J.L.R.) and was resolved by consensus.

2.4 | Statistics and meta-analysis

Data manipulation and meta-analysis to calculate the pooled estimates of HBoV prevalence were done using R software (version 3.6.3) and its IDE Rstudio software (RStudio Team, Boston, MA; version R v3.6.3) using 'readxl' (version 1.3.1) (Wickham & Bryan, 2019), 'meta' (version 4.15-1) (Balduzzi et al., 2019) and 'metafor' (version 2.4-0) (Viechtbauer, 2010) packages. A random-effects (RE) model (DerSimonian and Laird method) at 95% CI was used to estimate the pooled prevalence. The use of RE models is recommended (instead of the fixed-effects model) when there is a high degree of heterogeneity between studies, to adjust this observed variability (Borenstein et al., 2009; Veroniki et al., 2016). The Cochrane's Q statistic and the I^2 index statistic were calculated for each analysis to check the proportion of the overall variation that was attributable to the heterogeneity between studies. Its value can range from 0 to 100%, where a value of >75% represents high degree of heterogeneity. The sources of heterogeneity were further analysed using the sensitivity analysis, outlier detection, sub-group analysis and meta-regression. Egger's test and Funnel plots were used to investigate publication bias and small-study effects. Comparative analyses of the HBoV prevalences among countries were conducted by Kruskal–Wallis non-parametric test. The OR and the 95% confidence interval (CI) was also calculated for the variable age <5 years old as a risk factor for the infection with HBoV.

3 | RESULTS

3.1 | Study selection

A total of 2083 studies were identified from the databases and manual searching. After removing duplicated articles and articles outside Europe, 118 studies were critically screened by their title and abstract and 81 studies were identified for full-text evaluation. After applying the eligibility criteria, 46 studies were excluded due to the lack of detailed data or their potential for introducing bias. The remaining 35 studies fulfilled the inclusion criteria and were used for the meta-analysis (Figure 1).

3.2 | Descriptive characteristics of included studies

A total of 35 articles were enrolled in the study to be used in this systematic review and meta-analysis, with a total of 32,656 cases. The

sample size across the studies ranged from 32 (Bajolle et al., 2014) to 9098 (Bagasi et al., 2020) samples. Regarding the geographic distribution of the studies, nine studies were obtained from Italy (Don et al., 2010; Esposito et al., 2008; Gerna et al., 2007; Guido et al., 2011; Maggi et al., 2007; Midulla et al., 2010; Nicolai et al. 2017; Pierangeli et al., 2008; Principi et al., 2015;), four studies from Spain (Calvo et al., 2008, 2016; García-García et al., 2007; Pozo et al., 2007), four studies from France (Bajolle et al., 2014; Brieu et al., 2008; Foulogne et al., 2006; Jacques et al., 2008), three studies from Germany (Kleines et al., 2007; Volz et al., 2007; Weissbrich et al., 2006), three studies from Finland (Kantola et al., 2010; Paloniemi et al., 2014; Risku et al., 2012), two studies from UK (Bagasi et al., 2020; Nawaz et al., 2012), two studies from Slovenia (Praznik et al., 2018; Ursic et al., 2012) and one study from Sweden (Allander et al., 2007), Norway (Christensen et al., 2008), Denmark (von Linstow et al., 2008), Greece (Haidopoulou et al., 2010), Albania (La Rosa et al., 2016), Bulgaria (Korsun et al., 2019), Belgium (Verbeke et al., 2019) and Poland (Sobkowiak et al., 2020) (Table 1).

3.3 | Meta-regression and sensitivity analysis

A meta-regression analysis was done on the variables 'year of study', 'country', 'co-infections', 'technique', 'HBoV mono-infection'. Only the variable 'year of study' resulted significantly associated with HBoV pooled prevalence, with a significant regression coefficient of 9.25 ($p = .027$; SD 0.03). Sensitivity analysis was also performed by removing a single study from the analysis in order to ensure the stability of the overall effect estimate. The result indicated that removing a single study from the analysis did not significantly influence the pooled estimate.

3.4 | Publication bias and small study effects

The presence of publication bias was evaluated using funnel plots and Egger's test. The regression test for funnel plot asymmetry shows the symmetry between the studies so we can accept that there is no publication bias. First, studies' effect sizes were plotted against their standard errors and the visual evaluation of the funnel plot indicated no publication bias as the graph appear symmetrical (Supporting information Figure S1). The subjective evidence from the funnel plot was objectively confirmed using the Egger's weighted regression statistics. According to the symmetry assumption, the *p*-value of .1659 indicates the absence of small study effects among the included studies.

3.5 | Meta-analysis of HBoV prevalence in Europe

HBoV prevalence in Europe among included studies ranged from 2% in Finland (Kantola et al., 2010) to 46% in Italy (Guido et al., 2011), although most of the studies ranged between 2 and 22% (Table 1). The overall pooled prevalence among the total 32,656 cases based on the REs model was 9.57% (95% CI: 7.66-11.91) with a heterogeneity index I^2 of 97% (95% CI: 95.52-98.40) ($p < .001$) (Supporting information Figure S2). However, the occurrence of HBoV as single pathogen decrease to 3.99% (95% CI: 2.99-5.31) (Figure 2A) while the frequency of co-detection was 5.06% (95% CI: 3.88-6.58) (Figure 2B). Results of the prevalence pooled by countries were as follow: Albania (9.15%), Belgium (6.68%), Bulgaria (6.99%), Denmark (21.05%), Finland (9.84%), France (8.48%), Germany (8.35%), Greece (3.24%), Italy (7.77%), Norway (11.97%), Poland (11.88%), Slovenia (19.87%), Spain (11.60%), Sweden (18.92%) and UK (3.78%) (Figure 3). Kruskall–Wallis test, performed to compare the prevalence between countries, was not significant.

3.6 | Sub-group analysis

Since the meta-analysis exhibited a high degree of heterogeneity ($I^2 = 97\%$; $p < .001$), a sub-group analysis using the variable 'age' (younger and older of 5-year-old) as a potential source of heterogeneity among the 35 included studies was performed. The sub-group analysis indicated that the overall prevalence of HBoV slightly increased among children younger than 5-year-old (9.70%; CI: 7.34-12.73) while in patients older than 5-year-old was reduced (9.30%; CI: 6.27-13.60). On the other hand, the heterogeneity was reduced in patients older than 5-year-old ($I^2 = 91\%$; $p < .001$), indicating that the variable 'age' can explain part of the heterogeneity in this group (Supporting information Figure S3, Table 2).

3.7 | Risk ratio analysis

In order to evaluate the relevance of the variable 'age' as a risk factor for HBoV infection in children <5 years old, we pooled a total of five studies that indexed the discrete number of positives samples for HBoV in children under this age and also included a control group. The analysis showed a RR value of 1.77 (95% CI: 1.13-2.77; $p = .01$) by a RE model, indicating that less than 5 years old is a risk factor for HBoV infection (Figure 4).

4 | DISCUSSION

The emergence of novel respiratory viruses is being of a particular concern during the beginning of this century and it is expected to increase in the next years. The estimation of an accurate prevalence for these viral infections is of public health importance but relies on huge and epidemiologically representative surveys. In the absence of such information, this study provides a retrospective systematic review and meta-analysis for the overall prevalence of HBoV infection in Europe. We included 35 studies from 16 different European countries, which makes us think that the data can be reasonably extrapolated to the European continent.

The rigorous methodological and statistical procedures employed give robustness to the estimations present here. Nevertheless, findings

TABLE 1 Characteristics and summary of outcomes from the 35 included studies in this systematic review and meta-analysis

Authors (Ref)	Year	Country	N[a]	N+[b]	P (%)[c]	Mono- Inf (%)[d]	Co-inf (%)[e]	Other viruses[f]	Sample[g]	Study population[h]
Foulogne et al.	2006	France	589	26	4.41	17 (65.38)	9 (34.62)	RSV, AdV, hMPV	NS	AH
Weissbrich et al.	2006	Germany	835	87	10.42	53 (60.92)	34 (39.08)	RSV, IFV-A, IFV-B, AdV, HPIV 1, 2, 3	NS	AH
Allander et al.	2007	Sweden	259	49	18.92	12 (24.49)	37 (75.51)	Yes, not specified	NS, SE	SA
García-García et al.	2007	Spain	301	49	16.28	13 (20.41)	39 (79.59)	RSV, RhV, AdV, hMPV, EV, HPIV	NS	AH
Gerna et al.	2007	Italy	426	42	9.86	16 (30.95)	29 (69.05)	RSV, RhV	NS, BAL	AH
Kleines et al.	2007	Germany	94	12	12.77	7 (58.33)	5 (41.67)	RSV	NS, BAL	AH
Maggi et al.	2007	Italy	284	9	3.17	6 (55.56)	4 (44.44)	RhV	NS, ST, SE	AH
Pozo et al.	2007	Spain	730	115	15.75	49 (35.65)	74 (64.35)	RSV, AdV, RhV	NS, ST, UR	AH
Volz et al.	2007	Germany	389	11	2.83	7 (63.64)	4 (36.36)	RSV, NoV	NS, SE	AH
Brieu et al.	2008	France	507	55	10.85	23 (60.00)	22 (40.00)	RSV, hMPV	NS	AH
Calvo et al.	2008	Spain	710	99	13.94	80 (80.81)	19 (19.19)	RSV, AdV, RhV, HPIV, EV	NS, BAL	AH
Christensen et al.	2008	Norway	376	45	11.97	10 (22.22)	35 (77.78)	AdV, CoV-OC43, CoV-NL63, EV, hMPV, IFV-A, HPIV-3, RhV, RSV, CMV	NS	AH
Esposito et al.	2008	Italy	1332	99	7.43	49 (49.49)	50 (50.51)	RSV, hMPV	NS	SA
Jacques et al.	2008	France	192	24	12.50	14 (58.33)	10 (41.67)	RV, AdV, RSV, RV, HMPV, IFV-A, EV	NS	AH
Pierangeli et al.	2008	Italy	415	34	8.19	13 (38.82)	21 (61.18)	RSV	NS	AH
von Linstow et al.	2008	Denmark	228	48	21.05	21 (43.75)	27 (56.25)	RhV, CoV OC43, AdV, RSV, hMPV, HPIV-1	NS, ST	PCS
Midulla et al.	2010	Italy	182	22	12.09	7 (31.82)	15 (68.18)	RSV	NS	AH
Don et al.	2010	Italy	101	12	11.88	7 (66.67)	4 (33.33)	RhV, AdV, hMPV	BLO, NS	AH
Haidopoulou et al.	2010	Greece	370	12	3.24	8 (66.67)	4 (33.33)	IFV-A, CoV-OC43	NS	AH
Kantola et al.	2010	Finland	250	5	2.00	NA	NA	not specified	ST	SA
Guido et al.	2011	Italy	116	53	45.69	27 (50.94)	26 (49.06)	hMPV, IFV-A, IFV-B	NS	SA
Nawaz et al.	2012	UK	4380	324	7.40	175 (54.00)	149 (46.00)	Yes, not specified	ST	CCS
Risku et al.	2012	Finland	990	92	9.29	22 (23.91)	70 (76.09)	RV, NoV, SaV, AdV, AiV, CoV	ST	SA
Uršič et al.	2012	Slovenia	760	158	20.79	66 (37.97)	98 (62.03)	RSV, RhV, IFV-A, CoV, AdV, HPIV-3, hMPV	NS, BAL	AH
Bajolle et al.	2014	France	32	7	21.88	6 (85.71)	1 (14.29)	Yes, not specified	NS, SE	AH
Paloniemi et al.	2014	Finland	955	119	12.46	NA	NA	RV, NoV, AsV	NS, ST	SA
Principi et al.	2015	Italy	1823	104	5.70	57 (54.81)	47 (45.19)	EV, RV and RSV	NS	SA
La Rosa et al.	2016	Albania	142	13	9.15	0 (0.00)	13 (100.00)	RhV, AdV	ST	AH
Calvo et al.	2016	Spain	3275	319	9.74	80 (25.08)	239 (74.92)	RSV, RhV, AdV	NS	AH
Nicolai et al.	2017	Italy	273	10	3.66	6 (60.00)	4 (40.00)	hMPV, RV, RSV	NS	AH
Korsun et al.	2019	Bulgaria	515	36	6.99	20 (55.56)	16 (44.44)	RSV, HPIV-1, HPIV-3, RV, AdV, RhV	NS	SA
Praznik et al.	2018	Slovenia	473	87	18.39	NA	NA	not specified	NS	AH
Verbeke et al.	2019	Belgium	1153	77	6.68	6 (6.49)	72 (93.51)	RV, AdV	NS	AH

(Continues)

TABLE 1 (Continued)

Authors (Ref)	Year	Country	N[a]	N+[b]	P (%)[c]	Mono- Inf (%)[d]	Co-inf (%)[e]	Other viruses[f]	Sample[g]	Study population[h]
Bagasi et al.	2020	UK	9098	185	2.03	43 (23.24)	142 (76.76)	Yes, not specified	NS, BAL, SPU	RCS
Sobkowiak et al.	2020	Poland	101	12	11.88	5 (41.67)	7 (58.33)	Yes, not specified	NS	AH
Total			32,656	2451	9.57	9255 (45.90)	1326 (54.10)			

[a]N, total cases involved in each study.
[b]N+, number of HBoV positive cases.
[c]P (%), HBoV prevalence for each study calculated as the ratio between N and N+.
[d]Mono-inf (%), number (percentage) of positive cases detecting HBoV as a single virus.
[e]Co-inf (%), number (percentage) of positive cases detecting HBoV along with other viruses.
[f]Other viruses: AiV, aichivirus; AsV, astrovirus; AdV, adenovirus; EV, CoV, coronavirus; CMV, cytomegalovirus; enterovirus; hMPV, human metapneumovirus; HPIV, human parainfluenza virus type 1, 2 and 3; IFV-A, influenza virus type A; IFV-B, influenza virus type B; NoV, norovirus; RV, rotavirus; RhV, rhinovirus; SaV, sapovirus; RSV, respiratory sincitial virus.
[g]Sample type analyzed: NS, nasopharyngeal sample; SE, serum; BAL, bronchoalveolar lavage, ST, stool; UR, urine; BLO, boold; SPU, sputum.
[h]AH, admitted to hospital; SA, seeking assistance; PCS, prospective cohort study; CCS, case control study; RCS, retrospective cohort study.

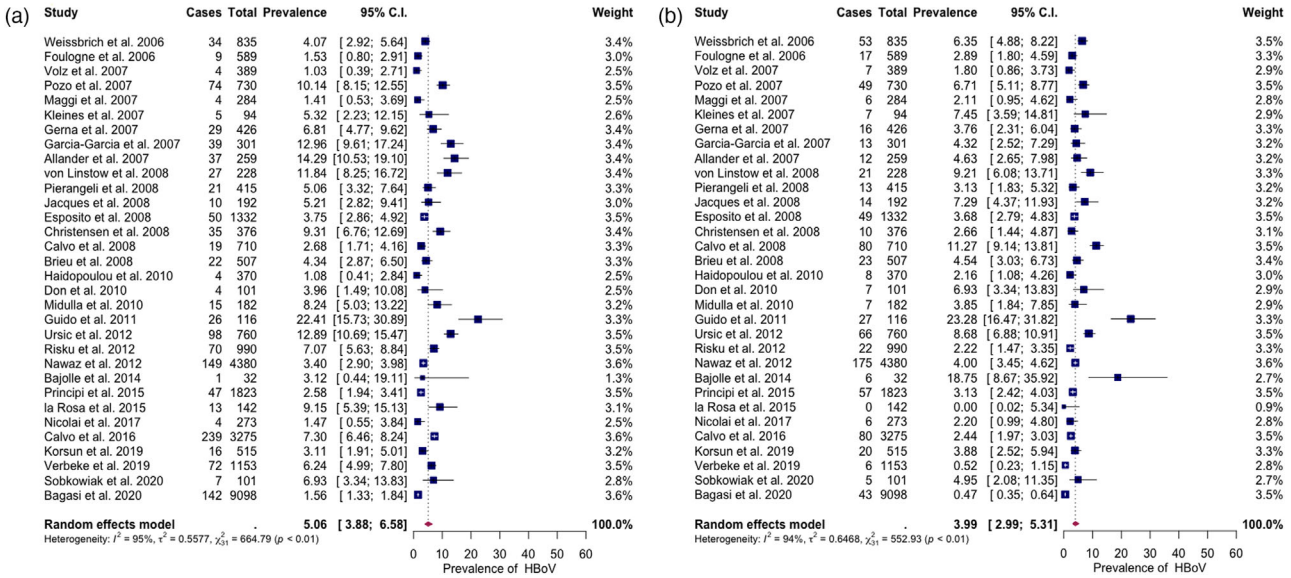

FIGURE 2 Forest plot showing the prevalence of HBoV in Europe as a single infection (A) and co-infection (B) from the 35 included studies and using random-effects model (DL method). The study-specific prevalence and 95% CIs are denoted by blue boxes and black lines. The size of squares proportional to the weight assigned to the study in the meta-analysis. The overall estimate is represented by the diamond, where diamond width corresponds to 95% CI bounds. Box and diamond heights are inversely proportional to precision of the proportion estimate

should be interpreted considering some limitations, mainly related to the way the data are presented in the included studies.

The inclusion of the number of total cases and positive cases for each group of age is crucial to better exploit the results and for a meta-analysis of prevalence. However, we found that age grouping was highly variable in published reports, which made difficult to sub-group study populations into finite age groups and the assignment of their respective prevalence.

A high degree of heterogeneity between studies was founded, which is very common in meta-analyses of prevalence (Veroniki et al., 2016). In this regard, sub-group analysis was undertook to identify sources of heterogeneity, however, the source of this heterogeneity was not found and some characteristics that may further explain it were not reported in the original studies. For instance, the seasonal occurrence of HBoV is still a subject of debate. Although HBoV infection is diagnosed throughout the year and no clear seasonality has been observed in several epidemiological studies (Christensen et al., 2010; Martin et al., 2015), there are increasing evidences suggesting the higher frequencies of the viral infection in the cold months of the year. Most of the studies included in this review reported a HBoV seasonality during fall and winter. This could be a factor contributing to the heterogeneity among the studies and should be considered in the meta-analysis. However, most of these studies did not included detailed information about the distribution of the HBoV infections by months, so a

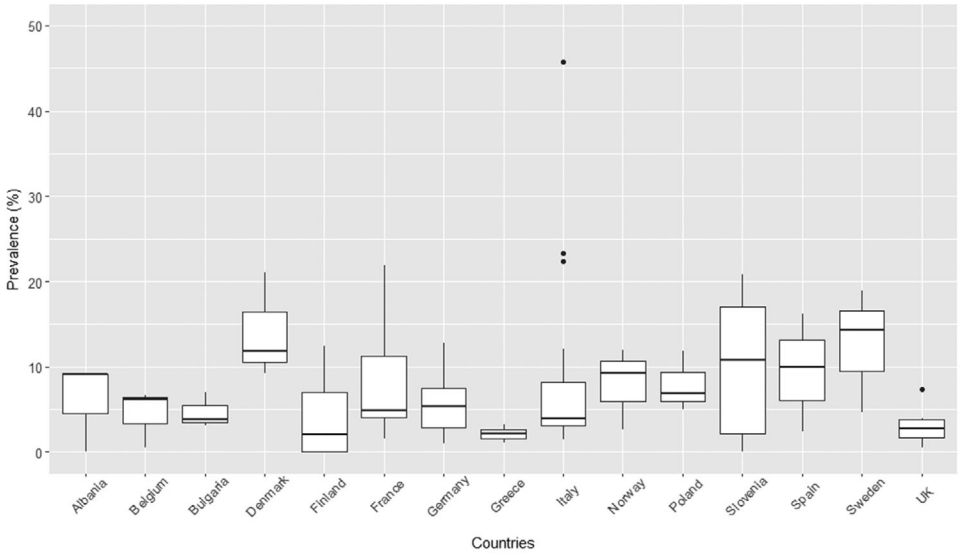

FIGURE 3 Box-plot diagram showing the pooled prevalence of HBoV by each country represented in the meta-analysis

TABLE 2 Pooled prevalence and meta-analysis statistics of HBoV in Europe using the included studies

Group	Prevalence (95% CI)	I^2 (95% CI)	t^2 (95% CI)	*p*-value ($p < .05$)
Overall	9.57 (7.66-11.91)	96.77 (95.52-98.40)	0.50 (0.36-1.03)	1.00E-04
<5 years old	9.70 (7.34-12.73)	98.00 (95.20-98.10)	0.52 (0.4-1.00)	1.00E-04
>5 years old	9.30 (6.27-13.60)	91.00 (90.12-95.42)	0.52 (0.4-1.00)	1.00E-04
HBoV mono-detection	3.99 (2.99-5.31)	94.40 (93.00-95.50)	0.65 (0.40-1.36)	1.00E-04
HBoV co-detection	5.06 (3.89-6.58)	95.30 (94.20-96.20)	0.56 (0.33-1.13)	1.00E-04

seasonality analysis could not be performed. On the other hand, performing sub-group and regression analysis, the variable 'age < 5 years old' was identified as the cause of part of the heterogeneity. However, other part of the heterogeneity could not be completely eliminated possibly due to clinical and methodological diversity of the included studies or to statistical heterogeneity.

In this study, different countries were variably represented, some of them with only one study. Geographical location has been previously reported as variable between countries and may also be one of the factors contributing to the heterogeneity (De et al., 2017). Although this may weaken to some extent the generalizability of our findings for every single country, the meta-regression model did not find any statistical difference. In this sense, more epidemiological studies are needed in these regions. For 2011 and 2018, the prevalence by year is only represented by a single study. However, more important than the number of studies is the cohort involved. In that sense, the year 2011 has included an extremely low number of cases hampering the accurate estimation of the prevalence for that year.

The study presented here estimates the overall prevalence for HBoV infection without distinguishing between genotypes. Previous

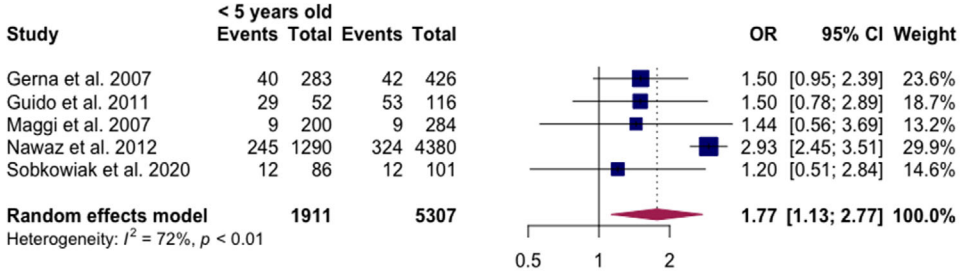

FIGURE 4 Forest plot on analysis on odd ratio (OR) and 95% confidence interval (CI) according to HBoV prevalence using the variable 'age' younger than 5-year-old

studies have reported that the genotypes of HBoVs most frequently detected are, in descending order, HBoV1, HBoV2, HBoV3 and HBoV4 (Söderlund-Venermo, 2019). Among the included studies, only a few differentiate between the four HBoV genotypes, so the detection rate for each genotype could not be reported. In this respect, testing simultaneously at least HBoV1 and HBoV2, the most frequent genotypes according to literature, would allow to obtain a better analysis of the prevalence and the epidemiology of HBoV (Kantola et al., 2010).

Besides these limitations, we estimated a pooled overall prevalence of HBoV of 9.57%. This relatively high prevalence is in accordance with previous studies. Guido et al. (2016) estimated a global HBoV prevalence of 6.3 and 5.9% in respiratory and gastrointestinal infection, respectively. Other large-scale studies have detected HBoV from 9 to 19.3% of all samples (Bronzel et al., 2008; Christensen et al., 2010; Franz et al., 2010; Martin et al., 2010). The absence of statistical differences for the pooled prevalence by country suggests a homogeneous distribution of HBoV among European countries.

One important strength of the present systematic review and meta-analysis is that HBoV prevalence as mono-infection and co-infection were analysed separately. This is important because multiple viral detections are common in young children and HBoV is frequently detected together with other respiratory and enteric viruses both in respiratory and gastrointestinal samples from symptomatic or asymptomatic infants (Christensen et al., 2010; Martin et al., 2010; Schildgen et al., 2008). Even in respiratory samples containing actively transcribing HBoV1, other viruses have been detected in almost 60% of the cases (Christensen et al., 2013).

Guido et al. (2016) estimated the rate of HBoV co-infections with other viruses at 52.4% (respiratory infections) and 46.7% (gastrointestinal infections) and HBoV is typically found as the second or third most commonly detected virus, after RSV and RhV (Christensen et al., 2010; Martin et al., 2010). In the present study, the overall co-detection rate of HBoV with other viruses was 54.1% (Table 1). The studies included here also reported RSV, AdV and RhV as the other viruses more commonly detected along with HBoV. These facts strongly suggest that HBoV is an important respiratory pathogen in children but also that it may exist in the respiratory or gastrointestinal tract as a bystander virus.

Some explanations for these high co-detection rates are the prolonged shedding of HBoV, that can last for months after the primary infection (Martin et al., 2010, 2015; von Linstow et al., 2008; Wagner et al., 2016) and the fact that children can have up to ten respiratory infections per year (Kusel et al., 2006). Other questions that remain poorly understood are whether HBoV1 has a more active or synergetic role in multiple respiratory infections and if it can establish latency by integration into the host cell genome or as an episome (Schildgen et al., 2012). Until the mechanisms of HBoV persistency, reactivation and reinfection are unravelled, occurrence values as a single- and co-pathogen should be reported. In this regard, this study adds valuable data for this porpoise.

At the time of this writing, COVID-19 pandemic continues to run its course. In this new context, viral prevalence studies conducted before the onset of the pandemic will be very useful to evaluate how the control measures against SARS-CoV-2 (wearing masks, hand hygiene, social distancing, lockdowns, travel restrictions) can impact the prevalence of other respiratory viruses.

Conducting a retrospective epidemiological study, Chiu et al. (2020) found a significant decrease in cases of influenza, enterovirus and all-cause pneumonia during the COVID-19 pandemic (Chiu et al., 2020). In this sense, we provide here a pre-COVID-19 snapshot of the HBoV prevalence in Europe. Further studies are warranted to evaluate if HBoV prevalence, as the other emergent respiratory viruses, decrease as a result of the implemented measures against SARS-CoV-2 or if other factors, such as virus competition, may contribute as well (Latorre-Margalef et al., 2017; Lin et al., 2020; Pinky & Dobrovolny, 2016; Trinh & Zeng, 2017).

5 | CONCLUSIONS

In summary, this systematic review and meta-analysis provides a clear summary of the existing knowledge on the European prevalence of HBoV infection. Data presented here show that HBoV infection is relatively frequent in children admitted to hospital and should be incorporated as part of the standard diagnostic panels, especially for children under 5 years old. This meta-analysis also emphasizes the importance of analysing the presence of this virus both as a single pathogen or in co-infection with other viruses and supports the need for further research on the discrimination between genotypes and respiratory and gastrointestinal samples.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interest.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

AUTHOR CONTRIBUTIONS

D.P.: Conceptualization; methodology; investigation; formal analysis; writing-original draft; writing-review and editing. A.L.: Methodology; investigation; formal analysis. E.G.: Investigation; formal analysis. J.L.R.: Conceptualization; methodology; formal analysis; writing-review and editing; funding acquisition; supervision.

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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