Influenza and Other Respiratory Viruses

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Impact of Respiratory Viral Codetections on RSV Disease Burden in Young Children in Primary Care

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ABSTRACT

Background: Young children with respiratory syncytial virus (RSV) often have viral coinfections. This study assessed the impact of respiratory viral codetections on RSV disease burden in children < 5 years and whether this varies by specific codetected viruses.

Methods: Retrospective analyses were performed using data from the RSV ComNet study prior to implementation of passive immunisation. Children < 5 years with acute respiratory infection (ARI) were eligible for testing for RSV and other viruses (multiplex real-time Polymerase Chain Reaction). Primary care physicians completed a short report on day 1, and parents completed follow-up questionnaires (digital or by phone) on days 14 and 30. Disease burden was measured by healthcare resource utilisation, clinical course, and parental work absence.

Results: Of the 2637 children tested, 822 (31%) were RSV-positive, of which 585 (52%) had completed day 1 data. There were 378 (65%) children with RSV monoinfection and 207 (35%) with RSV codetection. Rhinovirus/enterovirus was most frequently codetected (60%). Healthcare resource utilisation, clinical course, and parental work absence did not significantly differ between children with RSV codetection and RSV monoinfection. Hospitalisation rate was 7% (CI: 5%–10%) versus 8% (CI: 5%–13%) and mean duration of illness 11 (CI: 10.6–11.9) versus 12 days (CI: 11.4–13.4), respectively.

Conclusion: RSV-infections with viral codetections were generally not associated with increased healthcare resource utilisation, symptomatology, or parental work absence in children in primary care, suggesting that viral codetection alongside RSV disease does not impose a greater burden on patients or society. Further research is needed to determine whether specific RSV codetected viruses differentially impact disease burden.

1 | Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute respiratory infections (ARI) in infants and causes 33 million lower respiratory tract infections, 3.6 million hospitalisations and 101.400 deaths annually in children under 5 years of age [1]. Nearly all children are infected with RSV by the age of 2 [2]. RSV is typically associated with symptoms such as cough, wheezing and fever and can lead to more severe ARIs such as bronchiolitis and pneumonia [3, 4]. RSV infection leads to a substantial yearly number of primary care visits, emergency department visits and hospitalisations among young children [5, 6]. Treatment options for RSV infection (e.g., bronchodilators and mechanical ventilation) are primarily supportive and have limited impact on symptom severity or disease course [7]. In Western countries mortality due to RSV remains low [1, 8, 9]. Since 2022 several long-acting monoclonal antibodies (mAb) and a maternal RSV vaccine (RSVpreF) have been market-approved or are awaiting market approval in Europe [10, 11]. Both immunization strategies offer passive protection against RSV during the first months of life [12, 13]. In Italy, the mAB 'Nirsevimab' is administered to infants under 12 months of age during their first RSV season in selected regions of Italy during the 2024/2025 season and a maternal RSV vaccine was approved in 2023 but is not yet widely available [14]. In Spain, 'Nirsevimab' is also administered to infants under 12 months of age during their first RSV season during the 2023/2024 season; however, no maternal RSV vaccination programme is currently in place [15]. In the United Kingdom, a maternal vaccination programme has been in place since September 2024, and the implementation of 'Nirsevimab' occurred in autumn 2025, but 'Nirsevimab' is limited to specific high-risk groups: preterm born babies (before 32 weeks) and those that have medical conditions [16–18].

Respiratory viruses cause disease in some hosts while persisting as asymptomatic infections in others [19, 20]. With the increasing use of multiplex real-time PCR (RT-PCR) testing, it has become evident that many children test positive for multiple respiratory viruses. Codetection of respiratory viruses occurred in 10% of swabs collected from infants in a prospective birth cohort from 1 month of age, followed during the first year of life, and was more frequently present in swabs from children with ARI symptoms than in children without these symptoms [21]. Previous studies have shown that codetection in RSV-positive children ranged from approximately 30% to 40%, with rhinovirus (RV) being the predominant viral codetection [22, 23].

The role of viral codetections in respiratory infections remains poorly investigated. Previous studies show that RSV, human metapneumovirus (hMPV) and parainfluenza virus (PIV) Types 2 and 4 are strongly correlated with symptomatic ARI, whereas RV is often found asymptomatically [21]. Mixed results were found as to whether RSV codetected with another respiratory virus was associated with a higher disease burden compared to RSV monoinfection. A 2020 meta-analysis found no overall link between viral codetections and RSV disease severity, except for RSV/hMPV codetection, which was associated with higher disease severity regarding their risk of intensive care unit admission and length of hospitalisation [24]. More recent studies also reported no significant differences in disease burden between children with RSV monoinfection and most types of viral codetections [25–27], except for a protective effect against hospitalisation for parainfluenza or adenovirus codetection [28]. In addition, one study suggested that RSV monoinfection is associated with a higher disease burden [29]. This implies more large-scale studies are recommended to understand the connection between disease severity and respiratory codetected viruses alongside RSV.

The RSV ComNet study measured disease burden in children < 5 years in primary care in five European countries before the introduction of passive immunisation strategies [30]. This study showed that RSV infections cause a considerable burden in terms of symptoms, healthcare utilisation and parental work absence, leading to substantial economic costs [30, 31]. The objective of the current study was to conduct a retrospective analysis to evaluate the impact of respiratory viral codetections on RSV disease burden in children < 5 years of age and to assess whether the impact varies between specific respiratory viruses or age groups.

2 | Methods

2.1 | Study Design and Setting

The RSV ComNet study is a primary care-based, prospective cohort study with a follow-up of 30 days. The development of the study protocol and the clinical and economic burden outcomes were published previously [30–32]. The study was conducted in five European countries: Italy, Spain, the Netherlands, the United Kingdom (England only [33]) and Belgium (Flanders only). Data were collected between 1 January 2021 and 1 June 2023, before the implementation of passive immunization programmes in the participating countries. Children with ARI symptoms were enrolled during RSV seasons in Italy and Spain. In the United Kingdom, however, children with ARI symptoms were included year-round. In each participating country, the RSV ComNet study was performed across multiple regions (≥ 2 regions) and primary care sites (≥ 6 sites). Participating primary care physicians (PCP) were primary care paediatricians in Italy, Spain and Belgium and general practitioners (GP) in the United Kingdom and the Netherlands [21–23]. Children recruited in Belgium and the Netherlands were excluded from this retrospective study because testing for other respiratory viruses was not routinely performed in all enrolled children.

2.2 | Study Population

Children under 5 years of age that presented with an ARI to participating PCPs were eligible for RSV testing. The WHO ARI case definition guided primary care surveillance (sudden onset of symptoms with having at least one of the following: shortness of breath, cough, sore throat or coryza) [34]. An additional criterion was added for the purpose of this study: The physician judged that the current illness of the child was caused by an acute respiratory tract infection. PCPs were instructed to obtain nasopharyngeal or oropharyngeal swabs.

2.3 | Virological Testing

Swabs taken from children participating in the RSV ComNet study arms in Italy, Spain and the United Kingdom were tested by multiplex RT-PCR assays, allowing for the detection of other respiratory viruses in addition to RSV. The commercial Allplex Respiratory Panel Assay of Seegene was used in Italy and Spain, whereas the United Kingdom used an in-house assay from the UK Health Security Agency (UKHSA) reference laboratory. A complete overview of respiratory viruses tested in these three countries can be found in Table S1. More details about the testing procedures can be found in the publication from Hak et al. [30].

2.4 | Data Collection Procedures

Children who tested positive for RSV were followed for 30 days after the initial primary care visit, and data were collected at 3 points in time to mitigate potential recall bias: Days 1, 14 and 30. On Day 1, the initial visit, a short clinical report with relevant medical history and presenting clinical symptoms was completed by the PCP. On Days 14 and 30, parents were asked to fill in a questionnaire (digital or by phone) covering healthcare utilisation, medication use, symptoms, duration of illness, parental work absence, day care/school absence and complications such as physician-diagnosed pneumonia and otitis media. The questionnaires were published previously [30].

2.5 | Outcome Definitions and Analysis

In this study the data collected within the prospective RSV ComNet study were retrospective analysed. Patient demographics and characteristics (i.e., medical history and day care attendance) were compared between children with RSV monoinfection and RSV viral codetection by using chi-squared (X^2) tests and independent samples Student's *t*-tests, respectively. Disease burden was defined by various metrics capturing clinical course (illness duration, symptoms and complications), healthcare resource utilisation (primary care visits, emergency department visits, hospitalisation and prescribed and over-the-counter medication use) and societal impact (day care or school absence and parental work absence). Primary care visits included regular visits to a PCP, home visits and out-of-hours consultations. All healthcare visits were restricted to those associated with the RSV episode. Disease burden outcomes were presented as proportions for categorical variables and means with corresponding 95% confidence intervals for continuous variables. For children with missing or incomplete Day 30 questionnaires ($n = 55$, 10%), it was conservatively assumed that no healthcare utilisation, medication use and day-care/school or work absences occurred beyond Day 14.

Additional (post hoc) analyses were performed after it became apparent that some of the baseline variables (i.e., age, prematurity and day care attendance) were different between the RSV monoinfection group and the RSV viral codetection group. Therefore, generalized linear models were applied to each disease burden outcome variable in which *country*, *age*, *prematurity* and *day care attendance* were added as confounders and having a viral codetection as explanatory variable. Each model resulted in six tests, resulting in a total of 102 tests performed. To account for multiple testing, Bonferroni correction was applied to all *p*-values.

Codetected viruses were grouped together by virus families to create analysis groups of sufficient size. Rhinovirus and enterovirus are genetically similar, making it sometimes difficult for PCR assays to distinguish between the two viruses. Therefore, these viruses were treated as a single group in the analyses. Although hMPV and PIVs belong to different viral families—Pneumovirus and Paramyxovirus, respectively—both are negative sense, nonsegmented RNA viruses within the order mononegavirales, reflecting a shared broader phylogenetic context. Given the limited number of codetections for these two viruses and their related evolutionary background, both hMPV and PIVs were combined into the category 'other' for analysis. A *p*-value < 0.05 was deemed statistically significant. All analyses were performed using R version 4.3.2 [35].

3 | Results

3.1 | Study Population

A total of 2637 children were tested during the study period, of whom 822 (31%) were positive for RSV. Among the RSV-positive cases, 585 children (71%) had complete Day 1 data (Figure 1).

Codetection of RSV with other respiratory viruses was found in 207 children (35%), whereas 378 children (65%) had an RSV monoinfection. The proportion of children with RSV codetection was similar in Italy (117/314, 37%) and Spain (62/173, 36%), whereas the United Kingdom showed a somewhat lower proportion (28/98, 29%). Nine types of respiratory viruses were codetected with RSV (Table 1); the most common codetection was RSV with RV and/or enterovirus (EV) (60%), followed by RSV/human bocavirus (HBoV) (14%) and RSV/adenovirus (AdV) (12%). The least common codetection observed was RSV/hMPV (3%). A total of 32/207 (15%) RSV-positive children had more than one viral codetection.

Median age did not significantly differ between children with RSV monoinfection and RSV codetection (14 months: IQR 6–27 vs. 16 months: IQR 8–29, respectively) (Table 2). Premature birth was significantly more common among children with RSV monoinfection (9% vs. 4%, $p < 0.05$) and day care/school attendance among children with RSV codetection (74% vs. 80%, $p < 0.05$). All patient characteristics are shown in Table 2.

3.2 | Disease Burden Outcomes

Symptoms at Days 1, 14 and 30 did not differ statistically significant between children with RSV monoinfection and those with RSV viral codetection after correction for multiple testing (Figure S1). The most common symptom for both groups at Day

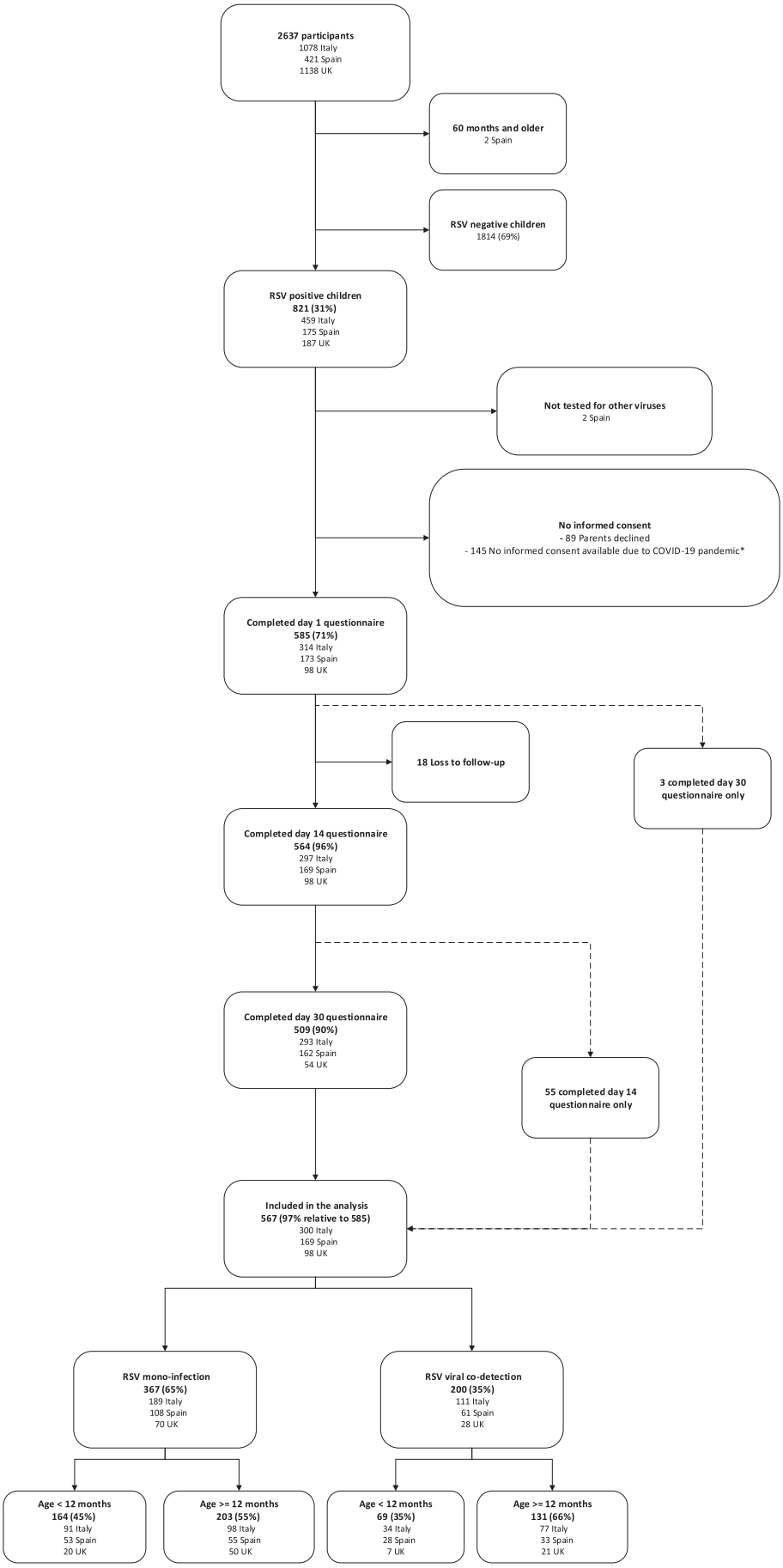

FIGURE 1 | Legend on next page.

FIGURE 1 | Flow chart of patient recruitment. RSV = respiratory syncytial virus. *In one Italian region (Lombardy), the COVID-19 pandemic resulted in insufficient personnel to collect informed consent during the 2021–2022 season, resulting in a random loss to follow up of 62% (145 of 234) among patients without informed consent, other reasons for no informed consent were not monitored.

TABLE 1 | Children with RSV codetection ($n = 207$, 35% of total study population): respiratory viral codetections identified.

Species	Family	Total	Italy	Spain	United Kingdom
Rhinovirus/enterovirus[a]	Picornavirus	124/207 (60%)	71/117 (61%)	35/62 (56%)	18/28 (64%)
Human bocavirus	Parvovirus	29/207 (14%)	12/117 (10%)	17/62 (27%)	n/t
Adenovirus	Adenovirus	25/207 (12%)	17/117 (15%)	3/62 (5%)	5/28 (18%)
Seasonal coronavirus (OC43, HKU1, 229E, NL63)	Coronavirus	23/207 (11%)	18/117 (15%)	4/62 (6%)	1/28 (4%)
Sars-CoV-2	Coronavirus	9/207 (4%)	3/117 (3%)	6/62 (10%)	0/28 (0%)
Influenza virus (all types)	Orthomyxovirus	16/207 (8%)	8/117 (7%)	5/62 (8%)	3/28 (11%)
Influenza virus type A	Orthomyxovirus	8/207 (4%)	1/117 (1%)	4/62 (6%)	3/28 (11%)
Influenza virus type B	Orthomyxovirus	5/207 (2%)	4/117 (3%)	1/62 (2%)	0/28 (0%)
Influenza virus unknown	Orthomyxovirus	3/207 (1%)	3/117 (3%)	0/62 (0%)	0/28 (0%)
Parainfluenza virus Type 1, 2, 3 and 4	Paramyxovirus	10/207 (5%)	5/117 (4%)	5/62 (8%)	n/t
Human metapneumovirus	Pneumovirus	7/207 (3%)	3/117 (3%)	1/62 (2%)	3/28 (11%)

Note: Percentages may sum to > 100% because children can have more than one respiratory viral codetection.
Abbreviation: n/t = not tested.
[a]Rhinovirus was detected in 88 RSV-positive children and enterovirus in 25 RSV-positive children; in 11 RSV-positive children, both rhinovirus and enterovirus were detected.

1 was coryza, in 76% and 79% of the children, respectively. An overview of clinical symptoms in children with RSV codetection at Day 1 categorised by codetection virus family is available in Table S2.

Table 3 presents a summary of disease burden outcomes. In total, 62% (95% CI: 57–67) of children with RSV monoinfection had one or more repeat primary care visit(s), compared to 65% (95% CI: 58–71) of children with an RSV viral codetection. Across the RSV codetections with different respiratory viruses, the percentage of children with a repeat primary care visit ranged from 45% to 77% (Tables 3 and 4). The proportion of children visiting the ED was 23% for children with RSV viral codetection (95% CI:17–29), varying from 14% to 29% for virus-specific RSV codetections, compared to 17% (95% CI:13–21) for children with RSV monoinfection (Tables 3 and 4). On average, children with RSV monoinfection had a duration of illness of 11.3 days (95% CI: 10.6–11.9) compared to 12.4 days (95% CI 11.4–13.4) for children with RSV viral codetection, varying between 9.6 and 15.7 days for virus-specific RSV codetections. Mean parental work absence was 3.2 days (95% CI: 2.2–4.2) for parents of children with RSV viral codetection, with virus-specific codetections ranging from 2.2 to 5.1 days, compared with 2.2 days (95% CI: 1.7–2.7) for children with RSV monoinfection (Tables 3 and 4). Complications including otitis media and pneumonia were observed more often in children with RSV viral codetections than in those with RSV monoinfection (9% vs. 5% and 6% vs. 2%, respectively), but these differences were not statically significant and involved small numbers (Table 3). After adjustment for country, age, prematurity and day care attendance and correction for multiple testing no outcome variables in Table 3 statistically significantly differed between children with RSV monoinfection and those with RSV viral codetections. Disease burden outcomes among children < 12 months and among those ≥ 12 months were not affected differently by the presence of respiratory viral codetections alongside RSV (Table S3).

4 | Discussion

Overall, no substantial differences in healthcare utilisation, clinical course of disease, medication use, complications and day care/school and parental work absence were observed between children with RSV monoinfection and those with RSV viral codetections. Children with RSV/RV/EV codetection did not show substantial differences in disease burden outcomes compared to children with RSV monoinfection. For the other virus-specific codetections, although some numerical differences in outcome measures were observed, the sample sizes were too small to support definitive conclusions about differences in disease burden outcomes.

The current finding that the disease burden is not substantially different for RSV monoinfection and RSV codetection is consistent with previous studies showing that respiratory viral codetections generally do not increase disease severity or clinical outcomes [24, 28, 36–38]. A previous meta-analysis suggests that RSV/hMPV codetection may lead to higher clinical severity in children compared to RSV monoinfection, in terms of their risk

TABLE 2 | Patient characteristics at Day 1.

	Total ($N=585$)	RSV monoinfection ($N=378$)	RSV viral codetection ($N=207$)	p
Demographics				
Median age (IQR) in months	14 (7–28)	14 (6–27)	16 (8–29)	0.39
Age category in months, n/N (%)				
0–5	110/585 (19%)	81/378 (21%)	29/207 (14%)	0.11
6–11	131/585 (22%)	87/378 (23%)	44/207 (21%)	
12–23	166/585 (28%)	101/378 (27%)	65/207 (31%)	
24–59	178/585 (30%)	109/378 (29%)	69/207 (33%)	
Gender, n (%)				
Male	297/585 (51%)	196/378 (52%)	101/207 (49%)	0.53
Female	288/585 (49%)	182/378 (48%)	106/207 (51%)	
Medical history, n/N (%)				
Prematurity (< 37 weeks of gestation)	43/583 (7%)	35/377 (9%)	8/206 (4%)	< 0.05
Any major comorbidity[a]	11/568 (2%)	9/369 (2%)	2/199 (1%)	0.39
Any minor comorbidity[b]	44/568 (8%)	29/369 (8%)	15/199 (8%)	1.00
Household characteristics, n/N (%)				
Attendance day care/school	429/563 (76%)	270/365 (74%)	159/198 (80%)	< 0.01
Parental employment, n/N (%)				
One parent	240/515 (47%)	146/330 (44%)	94/185 (51%)	0.08
Both parents	155/515 (30%)	97/330 (29%)	58/185 (31%)	
No parental employment	120/515 (23%)	87/330 (26%)	33/185 (18%)	

Abbreviations: IQR = interquartile range; RSV = respiratory syncytial virus.
[a]Major comorbidities included: bronchopulmonary disease, congenital heart disease, immunodeficiency, Down syndrome and 'other'.
[b]Minor comorbidities included: atopic conditions (defined as: physician-reported recurrent wheeze, asthma, atopic eczema and/or food allergy), recurrent respiratory tract infections, malnutrition and 'other'.

for intensive care unit admission and length of hospital stay [24]. Although the small number of RSV/hMPV codetections in the current study ($n=7$; 3% of RSV viral codetections) limits firm conclusions, a higher proportion of children with RSV/hMPV and RSV/PIV codetections visited the emergency department compared with those with RSV monoinfection (29% vs. 17%). Furthermore, a single-centre retrospective cohort study found that RSV/RV/EV and RSV/PIV codetections had a significantly lower hospitalisation rate compared to RSV monoinfection (OR: 0.74; $p=0.001$ and OR: 0.55; $p=0.014$, respectively) [39]. In the current study, hospitalisation rates were similar for RSV monoinfection (7%, 5–10) and RSV/RV/EV codetection (8%; 95% CI: 4–14), but overall hospitalisation rate was low because this study was conducted in an outpatient setting, whereas 62% of samples in the retrospective study were obtained from inpatients. As mentioned above, the number of RSV/PIV cases in the current study was too low for analysis by subgroup.

Previously, the RSV ComNet study showed that RSV infections in young children seen in primary care impose a substantial burden on healthcare systems and society across Europe, [30], leading to considerable costs largely driven by healthcare visits and parental work absence and that this burden is higher in infants [31] than in children aged 1–5 years [30]. The present study showed that these age-related differences in disease burden outcomes were not influenced by the presence of viral codetections, suggesting that viral codetection does not substantially modify the effect of age on RSV disease burden.

Two main differences were found in patient characteristics between RSV monoinfection and RSV viral codetection. First, a higher proportion of children who had RSV viral codetection attended day care/school compared to children with RSV monoinfection. This finding was likely attributable to increased exposure to circulating viruses in day care/school settings. Consistent with the current findings, a birth cohort study on the presence of respiratory viruses in relation to susceptibility to respiratory tract infections found that codetection of two or more viruses was statistically significantly associated with higher day care attendance compared to single-virus detections [21]. Second, premature birth was more common in children with RSV monoinfection than in children with RSV viral codetection,

TABLE 3 | Healthcare utilisation, medication use and day care/school and parental work absence of RSV monoinfected children and RSV codetected children.

	Total ($N=567$)	RSV monoinfection ($N=367$)	RSV viral codetection ($N=200$)
Healthcare utilisation, *n/N* % (95% CI)			
≥1 repeat primary care visit[a]	355/563	227/365	128/198
	63% (37–63)	62% (57–67)	65% (58–71)
Primary care visits, mean (95% CI)	2.4 (2.1–2.6)	2.3 (2.0–2.5)	2.5 (2.1–2.9)
Emergency department visits	106/561	61/364	45/197
	19% (16–22)	17% (13–21)	23% (17–29)
Hospitalisation	42/559	26/363	16/196
	8% (5–10)	7% (5–10)	8% (5–13)
Days of illness, *n/N*	548/567	356/367	192/200
Mean (95% CI)	11.7 (11.1–12.2)	11.3 (10.6–11.9)	12.4 (11.4–13.4)
Prescribed medication, *n/N* % (95% CI)			
Any prescribed medication	368/562	230/365	138/197
	65% (61–69)	63% (58–68)	70% (63–76)
Antibiotics	145/562	91/365	54/197
	26% (22–30)	25% (21–30)	27% (21–34)
Bronchodilators	278/562	173/365	105/197
	49% (45–54)	47% (42–53)	53% (46–60)
Corticosteroid inhalers	91/562	52/365	39/197
	16% (13–20)	14% (11–18)	20% (14–26)
Over-the-counter medication, *n/N* % (95% CI)			
Any over-the-counter medication	249/544	146/354	103/190
	46% (42–50)	41% (36–47)	54% (47–61)
Paracetamol	197/562	113/365	84/197
	35% (31–39)	31% (26–36)	43% (36–50)
Complications, *n/N* % (95% CI)			
Otitis media	23/352	12/223	11/129
	7% (4–10)	5% (3–9)	9% (4–15)
Pneumonia	12/352	4/223	8/129
	3% (2–6)	2% (1–5)	6% (3–12)
Day care or school absence[b], *n/N* % (95% CI)			
	261/429	151/270	110/159
	61% (56–65)	56% (50–62)	69% (61–76)
Number of days, mean (95% CI)	7.0 (6.2–7.7)	6.3 (5.3–7.2)	8.1 (6.8–9.4)
Parental work absence[c], *n/N* % (95% CI)			
	169/500	98/321	71/179
	34% (30–38)	31% (26–36)	40% (32–47)
Number of days, mean (95% CI)	2.5 (2.1–3.0)	2.2 (1.7–2.7)	3.2 (2.2–4.2)

Note: If day 30 data were missing, the assumption was made that no additional healthcare utilisation, medication use or day care or parental work absence occurred after Day 14.

Abbreviations: CI = Confidence Interval; RSV = respiratory syncytial virus.

[a]Primary care visits were defined as physical visits to, or home visits by, a community paediatrician or general practitioner, including out-of-hours primary care consultations.

[b]Day care, preschool or school absence was reported per half-day, calculated among children who normally attend day care, preschool or school.

[c]Work absence was reported per half-day and calculated for both parents combined among all children (including those for whom no parental work absence was reported); if data for one parent was missing, the data of the other parent (if available) were used for both parents.

TABLE 4 | Healthcare utilisation, medication use and day care/school and parental work absence of RSV codetected children, stratified by codetected virus family group.

	RV and EV (*N* = 121)	Coronaviruses (*N* = 31)	Bocavirus (*N* = 28)	Adenovirus (*N* = 23)	Influenza A and B (*N* = 15)	Other[a] (*N* = 17)
Healthcare utilisation, *n*/*N* % (95% CI)						
≥1 repeat primary care visit[b]	72/119	24/31	21/28	10/22	9/15	13/17
	61% (51–69)	77% (59–90)	75% (55–89)	45% (24–68)	60% (32–84)	76% (50–93)
Primary care visits, mean (95% CI)	2.4 (2.0–2.8)	2.3 (1.5–3.0)	2.1 (1.6–2.6)	4.8 (0.6–9.0)	1.9 (1.0–2.8)	2.2 (1.4–3.0)
Emergency department visits	28/118	7/31	6/28	3/22	3/15	5/17
	24% (16–32)	23% (10–41)	21% (8–41)	14% (3–35)	20% (4–48)	29% (10–56)
Hospitalisation	9/117	3/31	4/28	1/22	0/15	2/17
	8% (4–14)	10% (2–26)	14% (4–33)	5% (NE)	0%	12% (1–36)
Days of illness, *n*/*N*	116/121	30/31	26/28	22/23	15/15	16/17
Mean (95% CI)	12.0 (10.8–13.3)	13.1 (10.8–15.3)	9.6 (7.6–11.7)	14.8 (10.4–19.1)	15.7 (10.2–21.1)	9.9 (7.6–12.2)
Prescribed medication, *n*/*N* % (95% CI)						
Any prescribed medication	86/118	18/31	23/28	13/22	11/15	12/17
	73% (64–81)	58% (39–75)	82% (63–94)	59% (36–79)	73% (45–92)	71% (44–90)
Antibiotics	34/118	10/31	8/28	4/22	6/15	1/17
	29% (21–38)	32% (17–51)	29% (13–49)	18% (5–40)	40% (16–68)	6% (NE)
Bronchodilators	63/118	13/31	20/28	11/22	8/15	9/17
	53% (44–63)	42% (25–61)	71% (51–87)	50% (28–72)	53% (27–79)	53% (28–77)
Corticosteroid inhalers	24/118	6/31	4/28	5/22	4/15	1/17
	20% (13–29)	19% (7–37)	14% (4–33)	23% (8–45)	27% (8–55)	6% (NE)
Over-the-counter medication, *n*/*N* % (95% CI)						
Any over-the-counter medication	56/116	18/30	17/27	11/20	7/14	12/17
	48% (39–58)	60% (41–77)	63% (42–81)	55% (32–77)	50% (23–77)	71% (44–90)
Paracetamol	45/118	13/31	13/28	10/22	6/15	10/17
	38% (29–48)	42% (25–61)	46% (28–66)	45% (24–68)	40% (16–68)	59% (33–82)
Complications, *n*/*N* % (95% CI)						
Otitis media	8/76	3/22	1/22	0/14	0/9	1/10
	11% (5–20)	14% (3–35)	5% (0.1–23)	0%	0%	10% (0.3–45)

(Continues)

TABLE 4 | (Continued)

	RV and EV ($N=121$)	Coronaviruses ($N=31$)	Bocavirus ($N=28$)	Adenovirus ($N=23$)	Influenza A and B ($N=15$)	Other[a] ($N=17$)
Pneumonia	4/76	1/22	4/22	1/14	0/9	0/10
	5% (1–13)	5% (0.1–23)	18% (5–40)	7% (0.2–34)	0%	0%
Day care, preschool or school absence[c], *n/N* % (95% CI)	59/90	20/26	17/22	13/18	10/13	9/15
	66% (55–75)	77% (56–91)	77% (55–92)	72% (47–90)	77% (46–95)	60% (32–84)
Number of days, mean (95% CI)	7.7 (5.9–9.4)	9.1 (5.7–12.4)	8.7 (5.5–12.0)	11.0 (5.6–16.4)	8.7 (3.5–13.9)	3.7 (1.3–6.1)
Parental work absence[d], *n/N* % (95% CI)	40/107	12/28	9/23	9/22	5/13	6/16
	37% (28–47)	43% (25–63)	39% (20–62)	41% (21–64)	39% (14–68)	38% (15–65)
Number of days, mean (95% CI)	2.9 (1.8–4.1)	2.8 (0.8–4.9)	2.5 (0.4–4.6)	4.8 (0.2–9.4)	5.1 (0–10.6)	2.2 (0–5.0)

Abbreviations: CI = confidence interval; EV = enterovirus; NE = not estimable; RV = rhinovirus.

Note: If day 30 data were missing, the assumption was made that no additional healthcare utilisation, medication use or day care or parental work absence occurred after Day 14.

[a]Other includes hMPV and PIV 1234.

[b]Primary care visits were defined as physical visits to, or home visits by, a community paediatrician or general practitioner, including out-of-hours primary care consultations.

[c]Day care, preschool, or school absence was reported per half-day, calculated among children who normally attend day care, preschool or school.

[d]Work absence was reported per half-day and calculated for both parents combined among all children (including those for whom no parental work absence was reported); if data for one parent was missing, the data of the other parent (if available) were used for both parents.

but the small number of children born prematurely suggests this difference may be due to random variation and should be interpreted with caution. One possible explanation is that parents of preterm born children may be more likely to delay or avoid enrollment in childcare during early childhood, due to concerns about their child's relatively increased vulnerability to infections compared with term-born children.

In our study around one-third (35%) of young children with an RSV infection had one or more respiratory viral codetections. In Italy and Spain, diagnostic testing was performed primarily during the RSV season, whereas in the UK testing occurred year-round as part of routine primary care surveillance. The proportion of viral codetections in RSV-positive children is in line with other prospective and retrospective studies in in- and outpatient settings reporting proportions ranging from 27% to 39% [27, 39–41]. These studies also reported RSV/RV or RSV/RV/EV as the most frequent codetections with RSV/hMPV among the least frequent [14, 19, 30, 31]. Temporal and spatial variations in virus circulation are likely to influence the probability of codetection, with greater overlap in seasonal peaks increasing the likelihood of concurrent infections. The relatively low codetection of RSV and hMPV suggests that simultaneous acquisition of both viruses in young children occurs less frequently. This observation is consistent with previous studies reporting that hMPV circulation typically extends several weeks beyond the RSV season, with peak hMPV activity occurring outside the usual RSV peak period [42–44]. Furthermore, surveillance data indicate that the highest proportion of RSV cases among young children (1–5 years) is detected at the start of RSV seasons [45], well before the hMPV peak. Greater overlap in circulation may explain the patterns observed for other virus-specific codetections in this study. In temperate regions (i.e., most of Europe), influenza and seasonal corona viruses also circulate from autumn through winter, overlapping with the RSV season, whereas rhinovirus, adenovirus and bocavirus circulate year-round [46]. These year-round circulating viruses were the most frequently found in combination with RSV in this study. However, even among countries with similar climates, seasonal dynamics can differ, warranting careful consideration of regional and temporal context when interpreting codetection patterns.

Complications to RSV disease, such as otitis media, often arise from bacterial coinfections secondary to viral respiratory infections in children under 5 years [47]. In our study, 10% of the children developed a complication, and this was marginally more common in children with RSV viral codetection than in children with RSV monoinfection. However, from the findings of this study, it cannot be concluded that children with RSV viral codetections have a higher chance of acquiring bacterial coinfections as the total numbers were relatively small and we did not include bacterial testing in our analyses (i.e., we cannot be certain that bacteria were the causative pathogen of the complications). Overall, 26% of the children received an antibiotic, and antibiotic use was similar between children with respiratory viral codetections and those with RSV monoinfection. Notably, antibiotic use appeared relatively high among children with RSV/influenza codetection compared with other types of RSV codetections.

The outcomes of this study provide unique insights from the primary care perspective. Another strength of this study included the large population of RSV-positive children recruited across

multiple European countries, providing a representative sample of children with ARI symptoms attending primary care and yielding a substantial number of RSV codetections with other respiratory viruses. Importantly, all included children were classified as having RSV as the primary cause of their current illness; none were considered to have RSV merely as an incidental codetected virus. Therefore, the comparisons are likely to reflect true RSV infection with codetection versus RSV monoinfection. In addition, in Italy and Spain RSV patients were enrolled outside of a sentinel-surveillance scheme, with inclusion of all children presenting with ARI symptoms, thereby avoiding selection bias towards children with more severe (RSV) disease.

This study also had limitations. First, methodological differences in PCR testing practices across countries may have affected the current findings. The PCR assays used in Italy and Spain differed from the assay used in the United Kingdom, which did not test for HBoV and PIV. Moreover, the UK sample size was relatively small compared with the other two countries, resulting in an overrepresentation of children recruited outside the typical RSV season in the United Kingdom, and providing a potential bias in the overview of the full spectrum of RSV codetections. Moreover, case numbers for most virus-specific RSV codetections were too small to draw robust conclusions, which is why we pragmatically defined the 'other' group to include hMPV and PIVs. In addition, it was not possible to differentiate true coinfection from mere codetection as the identification of other respiratory viruses did not necessarily imply active replication at the time of testing. Ideally, serial sampling across multiple time points, combined with viral load measurements for all detected viruses, would have allowed to track the infection over time and better understand the pathogenic contributions of codetected virus(es). Consequently, reliance on a single sampling point also made our outcomes more sensitive to viral interference. As a result, the specific contribution of RSV to the disease burden in young children with viral codetections cannot be fully established from this study. Finally, because follow-up data were only collected for RSV-positive children, we were unable to compare the disease burden of RSV monoinfection with that of other non-RSV monoinfections.

In conclusion, respiratory viral codetections were common among young children with RSV, even in primary care, and were not associated with worsened clinical course and increased healthcare resource utilisation, complications or parental work absence, indicating that viral codetections in the context of RSV disease may not impose a greater burden on patients and society than RSV monoinfection. The current findings provide descriptive insights into virus-specific disease burden among RSV viral codetections; however, small sample sizes for most specific codetected viruses limited definitive interpretation. Further research is needed to assess whether specific RSV codetected viruses differentially influence disease burden, disentangle the individual contributions of RSV and codetected viruses to overall burden, and assess the influence of multiple codetections.

Author Contributions

Levi Duijst: investigation, writing – original draft, methodology, validation, visualisation, software, formal analysis, data curation. **Valérie Sankatsing:** investigation, writing – original draft, conceptualisation, methodology, funding acquisition, validation, visualisation, software, formal analysis, supervision, data curation. **Caterina Rizzo:** conceptualisation, methodology, writing – review and editing, data curation. **Francesco Baglivo:** writing – review and editing, data curation. **Elizabeth Button:** writing – review and editing, data curation. **Marta Carballal Mariño:** writing – review and editing, data curation. **María Garcé Sánchez:** data curation, writing – review and editing. **Christine Hagemann:** writing – review and editing. **Simon de Lusignan:** writing – review and editing, data curation. **Oliver Martyn:** writing – review and editing. **Marc Raes:** writing – review and editing. **Daan Van Brusselen:** writing – review and editing. **Joanne Wildenbeest:** writing – review and editing. **Sarah Hak:** writing – review and editing, data curation, formal analysis, software. **Foekje Stelma:** writing – review and editing, funding acquisition, supervision, conceptualisation, project administration. **Johanneke van Summeren:** writing – original draft, conceptualisation, investigation, funding acquisition, validation, methodology, visualisation, software, formal analysis, project administration, data curation, supervision.

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Ethics Statement

Ethical approval or a waiver for full ethical review was obtained from the respective medical ethics committees in each country: the English National Research Ethics Committees (Integrated Research Application System: 285025; Research Ethics Committees: 20/PR/0704) Comité de Ética de la Investigación del Principado de Asturias (ref SAS/3470/2009), Bambino Gesù Children's hospital Rome (ref 1936_OPBG_2019) and Comitato Etico di Area Vasta Nord Ovest per la Sperimentazione clinica Tuscany (ref. prot. 22871_Dini). Parents of all included children provided informed consent.

Conflicts of Interest

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Data Availability Statement

After termination of the ComNet RSV project, anonymised data are available on reasonable request. Inquiries to obtain anonymised data can be sent to the corresponding author (v.sankatsing@nivel.nl).

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1111/irv.70272.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Assay was used during the RT-PCR to test the presence of viruses per country. **Figure S1:** Clinical symptoms in RSV-positive children. $N = 567$ children who completed Day 14 and/or Day 30 questionnaire. **Table S2:** Symptoms in children with RSV codetection, categorised by codetected virus family. **Table S3:** Healthcare utilisation, medication use and day care/school and parental absence of RSV codetected children, stratified by age group.