Prevalence of Bacterial Codetection and Outcomes for Infants Intubated for Respiratory Infections

OBJECTIVES: To determine the prevalence of respiratory bacterial codetection in children younger than 2 years intubated for acute lower respiratory tract infection (LRTI), primarily viral bronchiolitis, and identify the association of codetection with mechanical ventilation duration.

DESIGN: Prospective observational study evaluating the prevalence of bacterial codetection (moderate/heavy growth of pathogenic bacterial plus moderate/many polymorphonuclear neutrophils) and the impact of codetection on invasive mechanical ventilation (IMV) duration.

SETTING: PICUs in 12 high and low/middle-income countries.

PATIENTS: Children younger than 2 years old requiring intubation and ICU admission for LRTI and who had a lower respiratory tract culture obtained at the time of intubation between December 1, 2019, and November 30, 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of the 472 analyzed patients (median age 4.5 mo), 55% had a positive respiratory culture and 29% ($n = 138$) had codetection. 90% received early antibiotics starting at a median of 0.36 hours after respiratory culture. Median (interquartile range) IMV duration was 151 hours (88, 226), and there were 28 deaths (5.3%). Codetection was more common with younger age, a positive respiratory syncytial virus test, and an admission diagnosis of bronchiolitis; it was less common with an admission diagnosis of pneumonia, with admission to a low-/middle-income site, and in those receiving vasopressors. When adjusted for confounders, codetection was not associated with longer IMV duration (adjusted relative risk 0.854 [95% CI 0.684–1.065]). We could not exclude the possibility that codetection might be associated with a 30-hour shorter IMV duration compared with no codetection, although the CI includes the null value.

CONCLUSIONS: Bacterial codetection was present in almost a third of children younger than 2 years requiring intubation and ICU admission for LRTI, but this was not associated with prolonged IMV. Further large studies are needed to evaluate if codetection is associated with shorter IMV duration.

KEYWORDS: bronchiolitis; child; coinfection; intensive care units; respiratory syncytial virus

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Viral lower respiratory tract infection (LRTI) is a common cause of hospitalization and critical illness for infants worldwide, with increasing need for PICU admission and mechanical ventilation even as overall hospitalization rates decline (1, 2). Clinicians often term these illnesses "bronchiolitis" regardless of whether infants have primarily airways (obstructive) or parenchymal (restrictive) disease (3). In children with acute LRTI, older studies and reviews carried out up to 2010 indicated that bacterial coinfections are

DOI: 10.1097/PCC.0000000000003500

RESEARCH IN CONTEXT

- In under 2-year-olds, acute lower respiratory tract infections (LRTIs) are a common reason for invasive mechanical ventilation and are mostly attributed to viral pathogens.
- Although treatment is primarily supportive, systemic antibiotics are frequently used for intubated infants with the premise that more severe illness might be due to bacterial coinfection.
- In this study, we evaluated the prevalence of respiratory bacterial codetection in under 2-year-olds intubated for acute LRTI and its impact on outcomes in the current era of high noninvasive respiratory support usage.

uncommon among moderately ill children cared for in the general wards (4–8). Studies performed 10–30 years ago show that 20–40% of children undergoing endotracheal intubation for bronchiolitis have bacteria detected in the respiratory tract, which was often associated with worse outcomes (9–12). Over the last decade, usage of noninvasive respiratory support has increased markedly, but it is unknown if this approach has impacted the rate at which bacteria are present in the airways of those children still ill enough to warrant endotracheal intubation. Furthermore, a study using the 2012–2016 Pediatric Health Information System (PHIS) database suggests that early antibiotic use may be associated with better overall outcomes of intubated children with bronchiolitis, suggesting a high frequency of bacterial coinfection in the contemporary era (13).

Understanding the frequency and clinical impact of bacterial codetection in infants intubated for LRTI can have major implications on the management of these patients, especially as it relates to antibiotic usage (14). Our prior clinical suspicion was that patients with bacterial codetection, a surrogate for coinfection, would have more severe lung disease than those with LRTI due solely to a virus. Because of uncertainty as to the prevalence and associated clinical outcomes of bacterial codetection in infants requiring invasive mechanical ventilation (IMV) for bronchiolitis, we designed the Bronchiolitis And COdetectioN (BACON) study. Our study objectives were to determine the prevalence of bacterial codetection in children younger than 2 years intubated for LRTI (including bronchiolitis and pneumonia), to understand the association of codetection with clinical outcomes, and to identify clinical factors that may modify that association. Our hypothesis was that respiratory bacterial codetection is more common in the current era of widespread noninvasive support and that it is associated with longer IMV duration.

MATERIALS AND METHODS

The BACON study was designed as a multinational observational cohort study carried out in 47 PICUs between December 1, 2019, and November 30, 2020. The Lead/Coordinating Site for the BACON study was the Nationwide Children's Hospital, and its institutional review board (IRB) approved STUDY00000599, on September 28, 2019. Subsequently, the study was approved by each participating center's IRB or ethics committee, and informed consent was waived or obtained based on local site regulations. All study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as most recently amended. Due to administrative and clinical reasons related to COVID-19 and other extenuating circumstances, there was an unanticipated delay in data analysis and completion of the write-up from study completion to 2023.

The participating centers (see Acknowledgments) included a range of economic regions (low-/middle-income country [LMIC] or high-income country) and for the purpose of analysis, these classifications were checked, post hoc, using the 2022 World Bank categories (15). Forty-six centers identified subjects prospectively; one center enrolled retrospectively because the local IRB restricted prospective recruitment. All treatment, including ventilator management and extubation practices, was at the discretion of the clinical team, though the reported standard of care at all participating PICUs was to obtain, promptly, after intubation a lower respiratory tract culture from all patients who were intubated for suspected LRTI. All microbiologic testing was performed based on each site's standard practice and included the of obtaining samples, sample processing, and reporting of results. There were no shared study-wide treatment protocols.

Patient Population

At all sites, we included and enrolled children aged younger than 2 years with any of the following: signs and/or symptoms of an LRTI (e.g., wheezes, rales, crackles, rhonchi, cough); admission diagnosis of bronchiolitis, pneumonia, or LRTI; and, endotracheal intubation for acute respiratory failure. Patients were excluded if they met any of the following criteria: cardiac arrest within 6 hours of intubation; a do-not-resuscitate order or other similar limitations of care; postconceptual age younger than 38 weeks; intubation only for surgery or other procedure; upper respiratory symptoms (e.g., rhinorrhea, stridor) without lower respiratory symptoms; intubation solely for apnea without lower respiratory symptoms; intubation greater than 24 hours before admission to hospital; and, prior inclusion in the BACON study. Patients with preexisting tracheostomy were also excluded.

Data Collection

Data were collected through medical record review by local site investigators. Deidentified data were entered into a secure Research Electronic Data Capture (REDCap) database hosted by Nationwide Children's Hospital (16, 17). Collected data included: demographics; comorbidities; family history; home medications; presenting signs and symptoms; intubation details; laboratory, microbiologic, and radiographic results; antibiotics; and outcomes. In addition, daily data were collected for the first 3 full days after intubation, including: ventilator settings and blood gas results closest to noon on each study day; respiratory therapies (e.g., inhaled nitric oxide other pulmonary vasodilators, prone positioning, mucolytics, and chest physiotherapy); medications; fluid balance; and feeding details. Admission diagnoses of bronchiolitis, pneumonia, and LRTI (not mutually exclusive) were obtained from the attending physician's documentation at the time of admission.

Definitions

We defined codetection as requiring both of the following conditions to be met: 1) identification of moderate or heavy growth (i.e., equivalent to $\geq 10^4$ cfu/mL if quantitative culture obtained) of at least one pathogenic bacterium from a lower respiratory culture, and 2) moderate or many neutrophils (PMNs; equivalent to ≥ 10 per high power field if quantitative measure used) on the Gram stain of the same lower respiratory culture. Both endotracheal aspirates and bronchoalveolar lavage were allowed, consistent with common clinical practice, prior studies of bacterial coinfection in bronchiolitis, and existing pneumonia guidelines (4, 11, 18).

We defined the duration of IMV as the number of hours from intubation until successful extubation, which was defined as not requiring reintubation for at least 24 hours (19). If a patient required multiple IMV courses, we used the duration from the initial course after study eligibility. To define pediatric acute respiratory distress syndrome (PARDS), we used the oxygenation and radiographic data collected by the investigators and applied the Second Pediatric Acute Lung Injury Consensus Conference guidelines (20). We used a post hoc rather than clinical diagnosis due to the inconsistent recognition of PARDS in these patients and opted to use the current definition to make the analysis more generalizable to current practice. For PARDS on day 1, we used oxygenation and ventilator parameters from day 1 for the oxygenation portion plus the chest radiograph results either immediately after intubation or from day 1, which was the first full calendar day after intubation. The oxygenation index was calculated if an arterial blood gas was available; the oxygen saturation index was an alternative measure as long as the clinically obtained oxygen saturation was less than 98%; no adjustments were made for skin color.

We defined the use of early antibiotics as receiving systemic antibiotics within the first 48 hours of PICU admission (13). We considered prednisone, prednisolone, methylprednisolone, and dexamethasone to be anti-inflammatory corticosteroids; these are termed "steroids" throughout the remainder of this article.

Statistical Analysis

The outcomes of interest included duration of IMV, length of stay (LOS) in the PICU, and mortality. Data are shown as *n* (%) or median (interquartile range [IQR]). Univariable analyses between those with and without codetection were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square or Fisher exact test for categorical variables. Because mortality was rare and the length of PICU stay

was highly correlated with IMV duration, the latter-most was selected as the primary outcome of interest. Since this was a prevalence study, there was no a priori sample size estimate.

A gamma regression with a log link was selected as the model to relate IMV duration to the covariates. To select covariates for model inclusion, we first added variables that were, a priori believed to be associated with IMV duration based on previous literature, including age, presence of comorbidities, respiratory syncytial virus-positive status, and PARDS on day 1. After including those variables in the model, to identify other strong associations between IMV duration and the remaining potential factors, we used the Least Absolute Shrinkage and Selection Operator (LASSO) analysis to select variables (21, 22). Further details about the LASSO selection process are included in the **Supplemental Materials** (http://links.lww.com/PCC/C503). Data splitting was used to ensure valid inferential metrics. Risk ratios (RRs) and corresponding CIs were computed from the coefficient and SE estimates of this model. Univariable risk ratios and corresponding 95% CIs were also computed to characterize the unadjusted relationship between the duration of IMV and each patient characteristic. RRs for longer IMV duration are reported for the presence of variable compared with absence (categorical) or for 1-unit change in a variable (continuous). Multivariable model results reflect RR when adjusted for all other variables in the multivariable model. We did not make any adjustments for multiple comparisons so results of all analyses other than the primary outcome model should be considered exploratory. All analysis was conducted using R statistical software (23, 24).

RESULTS

A total of 556 patients were enrolled from 47 sites in 12 countries from North America, South America, and Europe. After excluding 21 children due to missing data (**Fig. 1**), 535 patients were included for analysis. For the primary analyses, we also excluded 63 that did not have a lower respiratory tract culture obtained after intubation, leaving 472 for the primary analysis. Their median (IQR) age was 4.1 (1.5, 10) months, 35% were cared for in an LMIC PICU, 31% were born prematurely and 50% had no identified comorbidity (**Table 1**). Patient details for the entire cohort, including those who did not have a respiratory culture obtained, are shown in **Supplemental Table 1** (http://links.lww.com/PCC/C503). Subjects were initially ventilated with a median (IQR) positive end-expiratory pressure level of 7 cm H_2O (6, 8), peak inspiratory pressure of 25 cm H_2O (22, 28), tidal volume of 7.2 mL/kg (6.2, 8.9) and FIO_2 of 0.5 (0.4, 0.8) (**Supplemental Table 2**, http://links.lww.com/PCC/C503). Other treatments on the first day of intubation included steroids in 21%, vasoactive medications in 20%, and diuretics in 37% (Supplemental Table 2, http://links.lww.com/PCC/C503). There were 207 patients (44%) who met criteria for PARDS on day 1. Median (IQR) PICU LOS was 10 days (6, 14) days, and hospital LOS was 15 days (9.7, 21.8). There were 28 deaths (5.3%).

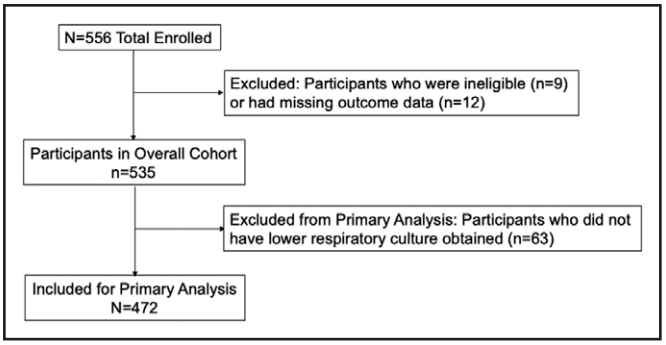

Figure 1. Consolidated Standards of Reporting Trials style diagram of study subjects.

Codetection and Associated Factors

Lower respiratory cultures were collected in 472 children (88% of the entire cohort) with a median (IQR) of 1.95 hours (0.7, 6.2) after intubation. Of those children, 60% (282/472) had moderate or many PMNs on Gram stain, 55% (258/472) had growth of bacteria, and 42% (196/472) had moderate or heavy growth of pathogenic bacteria. Organisms identified from respiratory cultures were most commonly *Haemophilus influenzae* and *Moraxella catarrhalis* (**Supplemental Table 3**, http://links.lww.com/PCC/C503). A complete list of viral pathogens is shown in (**Supplemental Table 4**, http://links.lww.com/PCC/C503). A total of 29% (138/472) had codetection including 37% of children with an admission diagnosis of bronchiolitis, 13% with pneumonia and 15% with LRTI. As shown in Table 1 and **Table 2**, codetection was associated with younger age, high-income country, an admission diagnosis of bronchiolitis, a positive viral test, and not receiving

TABLE 1.
Patient Characteristics Including Demographics, Comorbidities, and Initial Clinical Findings

Variable	Primary Cohort (*n* = 472)	Codetection (*n* = 138)	No Codetection (*n* = 334)
Age, mo; median (IQR)	4.1 (1.5, 10)	2.9 (1.5, 6.5)	5.0 (1.5, 12.0)
Male sex *n* (%)	294 (62.3%)	90 (65.2%)	204 (61.1%)
Low-/middle-income country, *n* (%)	166 (35.2%)	30 (21.7%)	136 (40.7%)
Comorbidities			
None	238 (50.4%)	69 (50%)	165 (49.4%)
Prematurity[a]	147 (31.1%)	49 (35.5%)	98 (29.3%)
<28 wk	18 (3.8%)	6 (4.3%)	12 (3.6%)
28 to <32 wk	16 (3.4%)	4 (2.9%)	12 (3.6%)
32 to <37 wk	113 (23.9%)	39 (28.3%)	74 (22.1%)
Chronic lung disease	54 (11.4%)	13 (9.4%)	41 (12.3%)
Congenital heart disease	33 (7%)	9 (6.5%)	24 (7.2%)
Admission diagnosis[b,c]			
Bronchiolitis	310 (65.7%)	114 (82.6%)	196 (58.7%)
Pneumonia	135 (28.6%)	18 (13%)	117 (35%)
Lower respiratory tract infection	34 (7.2%)	5 (3.6%)	29 (8.7%)
Day of illness; median (IQR)	3 (2, 4)	3 (2, 4)	3 (2, 5)
Clinical findings *n* (%)			
Fever	206 (43.6%)	53 (38.4%)	154 (46.1%)
Cough	183 (38.8%)	48 (34.8%)	135 (40.4%)
Wheeze	148 (31.4%)	41 (29.7%)	107 (32%)
Rales	40 (8.5%)	11 (8%)	30 (9%)
Crackles	103 (21.8%)	21 (15.2%)	82 (24.6%)
Retractions	283 (60%)	99 (71.7%)	184 (55.1%)
Coarse	117 (24.8%)	47 (34.1%)	70 (21%)
Diminished	84 (17.8%)	25 (18.1%)	59 (17.7%)
Viral testing			
Done	447 (94.7%)	133 (96.4%)	314 (94%)
Positive	352 (74.6%)	121 (87.7%)	231 (69.2%)
Respiratory syncytial virus	240 (50.8%)	88 (63.8%)	152 (45.5%)
Rhinovirus	86 (18.2%)	32 (23.1%)	54 (16.2%)
Other virus	54 (11.4%)	14 (10.1%)	40 (12%)
>1 virus	76 (16.1%)	30 (21.7%)	46 (13.8%)

CHD = congenital heart disease, IQR = interquartile range.

[a]<37 wk gestation.

[b]From the attending physician documentation.

[c]Diagnoses not mutually exclusive. Forty-four of 472 patients had none of these diagnoses documented.

TABLE 2.
Associations With Codetection in Univariate Logistic Regression

Variables	OR (95% CI)
Age (per 1-mo increase)	**0.942 (0.908–0.977)**
Male sex	1.195 (0.790–1.807)
Comorbidities	
None	0.976 (0.657–1.452)
CLD (no daily treatment)	0.442 (0.127–1.541)
CLD (daily treatment)	0.966 (0.451–2.068)
Unrepaired acyanotic CHD	1.009 (0.349–2.919)
Repaired acyanotic CHD	0.804 (0.160–4.033)
Unrepaired cyanotic CHD	0.602 (0.067–5.44)
Repaired cyanotic CHD	0.805 (0.083–7.810)
Mild developmental delay	0.274 (0.062–1.203)
Major developmental delay	0.615 (0.245–1.544)
Prematurity	
Prematurity < 28 wk	1.326 (0.483–3.640)
Prematurity 2 to < 32 wk	0.884 (0.2778–2.813)
Prematurity from 32 to < 37 wk	1.398 (0.884–2.210)
No prematurity	Reference
Day of illness (per 1-d increase)	0.952 (0.895–1.012)
History of fever	0.729 (0.486–1.093)
Clinical findings	
Wheeze	0.897 (0.582–1.380)
Rales	0.878 (0.427–1.805)
Crackles	**0.552 (0.326–0.934)**
Ronchi	0.831 (0.514–1.343)
Retractions	**2.069 (1.348–3.177)**
Cough	0.786 (0.520–1.188)
Coarse	**1.948 (1.255–3.024)**
Diminished	1.031 (0.615–1.728)
Day 1 chest radiograph infiltrate	1.170 (0.714–1.917)
Admission diagnosis bronchiolitis	**3.344 (2.047–5.465)**
Admission diagnosis pneumonia	**0.278 (0.161–0.479)**
Viral results	
Any virus +	**3.129 (1.790–5.470)**
Respiratory syncytial virus +	**2.107(1.401–3.171)**
Rhinovirus +	1.565 (0.958–2.558)
Day 1 acute respiratory distress syndrome	1.480 (0.994–2.205)
Day 1 vasoactive medication	**0.436 (0.244–0.779)**
Low-/middle-income country study site	**0.404 (0.255–0.640)**

CHD = congenital heart disease, CLD = chronic lung disease, OR = odds ratio.
Variables significantly associated with codetection are highlighted in boldface font.

WHAT THIS STUDY MEANS

- Respiratory bacterial codetection was common and not significantly associated with mechanical ventilation duration; an association with shorter ventilation duration could not be ruled out and warrants further investigation.
- High antibiotic use, including courses longer than 4 days, is common even among those without codetection or with negative respiratory cultures and may explain why codetection was not associated with longer invasive mechanical ventilation duration.
- Better diagnostic testing and criteria for antibiotic use are needed to help limit unnecessary antibiotics while still appropriately treating true bacterial coinfection.

vasoactive medication on day 1. An admission diagnosis of pneumonia was associated with lower odds of codetection. Nearly all subjects (422/472, 89.4%) received early antibiotics starting at a median (IQR) of 0.36 hours (–5.0, 5.8) before and after the respiratory culture, with no association between usage and codetection (125/138 [91%] with codetection vs. 297/334 [89%] without codetection, $p = 0.6$). Patients with codetection were more likely to have had initial antibiotic treatment continued greater than 4 days compared with those without codetection (110/138 [80%] vs. 213/334 [64%]; $p < 0.001$).

Duration of IMV and Associated Factors

Overall, median (IQR) IMV duration was 151 (88, 226) hours and the associated explanatory factors in the univariate analyses included admission diagnosis, comorbidities, ventilator settings, and use of neuromuscular blockade infusion on day 1 (**Table 3**). When adjusted for confounders, only the absence of comorbidities and meeting PARDS criteria on day 1 were associated with IMV duration (Table 3). Codetection was not associated with longer IMV duration (adjusted RR 0.854 [95% CI, 0.684–1.065]), and we cannot exclude the possibility that it is associated with a shorter IMV duration. We explored the possibility that there was a statistical interaction between codetection and PARDS but we failed to identify one. To obtain estimates of the effect size of each model variable on IMV duration, we calculated average marginal means in an exploratory analysis (**Fig. 2**), which provides the impact of a variable when all other model variables are held constant. The effect of having no comorbidities corresponds to a 54-hour shorter IMV course and having PARDS on day 1 corresponds to a 51-hour longer IMV course when adjusted for model items. Having codetection corresponds to a 30-hour shorter IMV duration compared with no codetection although the 95% CI includes the null value so the true effect could range from a 72-hour shorter to a 12-hour longer IMV course. In an exploratory analysis, we repeated model construction with variable selection and forced receipt of early antibiotics into the model, the association between codetection and IMV duration was unchanged.

DISCUSSION

Between December 2019 and November 2020, we carried out a large multicenter, prospective, observational study of children aged under 2 years old receiving IMV for LRTI and found that nearly one-third of children had bacterial codetection on a lower respiratory tract sample obtained promptly after endotracheal intubation. Codetection was not associated with unfavorable outcomes although nearly all children were treated with antibiotics that may have impacted the disease course. Although our adjusted results included the null value, we were unable to exclude as much as a 15% lower IMV duration with codetection (adjusted RR 0.854), a finding that would be consistent with our single-center study that informed the design of this study (25). Our definition of codetection does seem to reflect the clinical belief that these patients may have true bacterial infections since the majority of those with codetection had antibiotics continued beyond 4 days. Further, our observed association between bacterial codetection and a clinical diagnosis of "bronchiolitis" (as opposed to "pneumonia" or "LRTI") in this heterogeneous cohort, along with the substantial use of antibiotics in children without codetection, shows that novel approaches to diagnosing bacterial coinfection and prescribing antibiotics are needed since the clinical suspicion frequently conflicts with microbiologic data (26–28).

TABLE 3.
Associations With Duration of Mechanical Ventilation in Univariable and Multivariable Gamma Regression

Variable	Univariable RR (95% CI)	Multivariable aRR (95% CI)
Age (mo)	1.004 (0.989–1.019)	0.995 (0.979–1.012)
Male sex	0.839 (0.700–1.004)	
No comorbidities	**0.756 (0.637–0.897)**	**0.751 (0.615–0.917)**
CLD (no treatments)	0.958 (0.586–1.567)	
CLD (daily treatments)	**2.028 (1.407–2.920)**	
Unrepaired acyanotic CHD	**2.416 (1.496–3.901)**	
Repaired acyanotic CHD	2.155 (0.910–5.104)	
Unrepaired cyanotic CHD	0.744 (0.282–1.962)	
Repaired cyanotic CHD	0.896 (0.228–3.527)	
Prematurity (< 37 wk)	1.192 (0.976–1.455)	
Day of illness	1.014 (0.996–1.033)	
Admit diagnosis Bronchiolitis	**0.778 (0.654–0.925)**	0.915 (0.731–1.146)
Admit diagnosis Pneumonia	1.053 (0.858–1.291)	
Day 1 pediatric acute respiratory distress syndrome	1.107 (0.915–1.339)	**1.313 (1.082–1.594)**
Day 1 mean airway pressure	**1.048 (1.022–1.076)**	
Day 1 delta P[a]	**1.018 (1.007–1.029)**	
Day 1 vasoactive medication	1.280 (0.999–1.638)	
Day 1 neuromuscular blockade infusion	**1.343 (1.068–1.689)**	
Day 1 steroids	0.946 (0.754–1.187)	
Respiratory syncytial virus positive	0.981 (0.817–1.178)	1.069 (0.864–1.323)
Day 1 net fluid balance	1.000 (0.9999–1.000)	
Cumulative fluid balance[b]	1.000 (1.000–1.0001)	1.000 (0.9998–1.000)
Codetection	0.920 (0.756–1.120)	0.854 (0.684–1.065)

aRR = adjusted relative risk, CHD = congenital heart disease, CLD = chronic lung disease, RR = adjusted relative risk.
[a]Delta P = pressure difference between peak inspiratory pressure and positive end-expiratory pressure (or amplitude on high frequency oscillatory ventilator).
[b]Through day 3.
Boldface font denotes statistically significant values.

Despite the fact that viral bronchiolitis and other acute LRTIs cause high pediatric morbidity and mortality, are the most common reason infants require ICU admission and are increasingly prevalent in the ICU resulting in significant economic impact, care for these children is supportive and largely lacks evidence (1, 29–34). The role of bacterial coinfections in these patients remains unclear. The two largest prior PICU studies of bacterial codetection were conducted at single centers in 2002–2005 and 2006–2014 and reported codetection rates of 22% and 38%, respectively (9, 10). Although we hypothesized that we would observe a higher codetection rate because only more severely ill children require IMV now, we found a similar codetection rate with similar pathogens, albeit in a larger, contemporary, and multinational cohort that represents international practice. Some studies suggest that the number of infants treated with IMV for bronchiolitis has remained largely unchanged despite a significant rise in noninvasive support, but none of these prior studies can adequately control for any changes in baseline epidemiology or risk of intubation that have

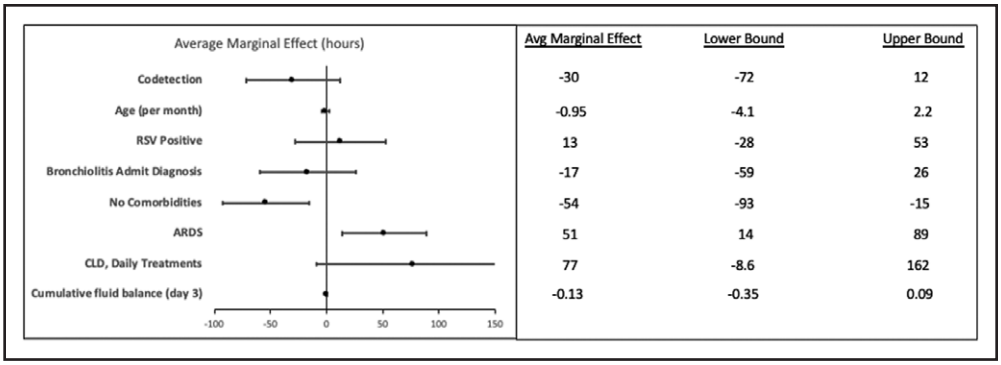

Figure 2. Average marginal mean effect on invasive mechanical ventilation duration for variables included in adjusted gamma regression. ARDS = acute respiratory distress syndrome, CLD = chronic lung disease, RSV = respiratory syncytial virus.

evolved over the last two decades (32, 35, 36). It is likely that many children currently supported noninvasively would have been intubated in prior eras given that the percentage of infants in the ICU receiving IMV for bronchiolitis appears to have decreased dramatically (35, 37). We show that changes in clinical practice may have not impacted the rate of bacterial codetection among IMV bronchiolitis patients.

In contrast to smaller single-center studies that reported codetection was associated with a longer duration of IMV, we found that codetection is not associated with prolonged IMV duration but might be associated with shorter IMV duration (9–12). Because nearly all subjects received early antibiotics, this may reflect that the detrimental impact of bacterial coinfection may be mitigated by prompt treatment, although most infants in prior studies also received early antibiotics. Another interpretation is that our definition of codetection, while similar to others and based on published guidelines, does not accurately identify children with true bacterial coinfection (4, 11, 18). Intriguingly, we found that the odds of codetection were three-fold higher in children diagnosed with "bronchiolitis"—classically a viral disease—than they were in children diagnosed with "pneumonia"—commonly assumed to be due to bacteria. Findings such as fever, crackles on examination, infiltrates on chest radiograph, and the presence of shock either had no association with codetection or were associated with a lower codetection rate. A prior PHIS study showed similar diagnostic uncertainty as antibiotic usage was associated with improved IMV duration in children both with and without a diagnosis of pneumonia (13). Given the widespread use of antibiotics in this population, more precise methods to identify patients who would truly benefit from antibiotic treatment are needed. The complex interactions of bacteria, viruses, inflammation and the host immune response in the lower respiratory tract combined with the lack of a gold standard to diagnose "bacterial pneumonia" may necessitate novel approaches.

Strengths of this study include prospectively enrolling the largest number of children with bronchiolitis in any study of bacterial codetection to date across a geographically and economically diverse group of centers, improving the generalizability of our results; an explicit and objective definition for codetection that did not rely on clinician interpretation; granular data collection to enable adjusting for multiple confounders; and including all children intubated for LRTI and all viral pathogens to reflect the heterogeneity of diagnosis and pathogens typically encountered in critical bronchiolitis. Our study also has some important limitations. First, because this was an observational study, we are unable to determine causality. Second, bacterial codetection may not always represent true infection. Third, specimens were collected via tracheal aspirate or bronchoalveolar lavage based on local practices, which could impact the diagnosis of codetection. However, our findings better reflect actual practice and may be more generalizable to sites with varying diagnostic approaches. Fourth, our respiratory testing was primarily performed on endotracheal aspirates. While these samples may have less specificity compared with bronchoalveolar lavage specimens, bronchoalveolar lavage specimens are frequently not feasible in small, critically ill infants, plus tracheal aspirates represent the common practice in the PICU and are consistent with existing pneumonia guidelines (18). Fifth, we did not standardize ventilator management or extubation practice, but this should have minimal impact on our outcome of IMV duration as there is no reason to expect that patients with codetection would be weaned from the ventilator differently than those without. We also only considered IMV duration as an outcome rather than the total duration of respiratory support; the duration of

ICU-level respiratory support (including both invasive and noninvasive modalities) may be a preferred outcome for future studies given the increasing use of noninvasive support. Sixth, we used the term codetection even in the absence of a confirmed viral pathogen due to the fact that existing evidence suggests that the overwhelming majority of pediatric LRTIs have a viral etiology, particularly in this age group (14). Seventh, because our study period overlapped with the beginning of the COVID-19 pandemic, it is possible that this may have altered the prevalence of codetection and its impact on outcomes (38). Eight, as a study designed primarily to measure the incidence of codetection, our sample size may have been insufficient to detect an association with duration of ventilation, and we cannot rule out that codetection is truly associated with shorter duration as suggested by our analyses. Lastly, because of the very high rate of antibiotic use, we were unable to evaluate the impact of antibiotics on the codetection-outcome association, and it is possible that antibiotic pretreatment may have altered our codetection rate even with the short interval between intubation and respiratory culture.

CONCLUSIONS

In a large multinational cohort of children younger than 2 years intubated for acute LRTI, bacterial codetection was observed in nearly one-third of children but was not associated with longer IMV duration. Given the widespread use of antibiotics regardless of codetection status, and the fact that an admission diagnosis of "pneumonia" was associated with less codetection, more studies are needed to determine the prevalence of true bacterial infection in children with LRTI and to better guide antibiotic decisions in this very common pediatric critical illness.

ACKNOWLEDGMENTS

The Bronchiolitis And COdetectioN (BACON) Study Investigators and centers are listed as follows (low-/middle-income country sites are denoted by *): *Adriana Yock-Corrales (Hospital Nacional de Ninos Dr. Carlos Saenz Herrera, San Jose, Costa Rica), Alex Rotta (Duke Children's Hospital, Durham, NC), Andrew Prout (Children's Hospital of Buffalo, Buffalo, NY), Andrew Wen (Lucile Packard Children's Hospital, Palo Alto, CA), Anna Camporesi (Children's Hospital Vittore Buzzi, Milan, Italy), *Arieth Figueroa Vargas (Fundacion Clinica Infantil Club Noel, Cali, Colombia), Bria Coates (Lurie Children's Hospital, Chicago, IL), *Byron Enrique Piñeres-Olave (Hospital Pablo Tobón Uribe, Medellín, Colombia), Casey Stulce (Comer Children's Hospital, Chicago, IL), Christopher Watson (Medical College of Georgia at Augusta University, Augusta, GA), Conall Francoeur (CHU de Quebec, Quebec City, Quebec, Canada), *Edwin Mauricio Cantillano (Hospital Regional del Norte, Instituto Hondureño de Seguridad Social, San Pedro Sula, Honduras), *Eliana Zemanete (Hospital Susana Lopez de Valencia, Popayan, Colombia), Francisca Castro (Hospital Padre Hurtado, Santiago, Chile), Gema Perez Yague (Hospital Gregorio Maranon, Madrid, Spain), *Goktug Ozdemir (Dokuz Eylul University Hospital, Izmir, Turkey), Harsha Chandnani (Loma Linda University Children's Hospital, Loma Linda, CA), Ilana Harwayne-Gidansky (Stony Brook Children's Hospital, Stony Brook, NY), *Karina Cinquegrani (Hospital El Cruce, Buenos Aires, Argentina), *Ledys Izquierdo (Hospital Militar, Bogota, Colombia), Lee Polikoff (Hasbro Children's Hospital, Providence, RI), *Leonardo Valero (Hospital Universitario San Jorge, Pereira, Colombia), Mary Gaspers (Banner University Medical Center, Phoenix, AZ), Mia Maamari (UT Southwestern Medical Center, Dallas, TX), *Murat Kangin (Saglik Bilimleri University Gazi Yasargil Training and Research Hospital, Diyabakir, Turkey), *Nils Casson Rodriguez (Hospital Regional San Juan de Dios, Tarija, Bolivia), *Nilufer Ozturk (Marmara University, Istanbul, Turkey), *Pablo Castellani (Hospital Sor Ludovica, La Plata, Argentina), *Pablo Vasquez-Hoyos (Hospital de San Jose, Bogota, Colombia), Paras Khandhar (Beaumont Children's Hospital, Royal Oak, MI), *Roberto Jabornisky (Juan Pablo II Hospital, Corrientes, Argentina), *Rosa Arana (Hospital Cayetano Heredia, Lima, Peru), *Rosalba Pardo (Clinica Colsubsidio, Bogota, Colombia), *Rubén Lasso Palomino (Fundacion Valle del Lili, Cali, Colombia), Ryan Nofziger (Akron Children's Hospital, Akron, OH), *Santiago Ayala Torales (Hospital Materno Infantil, San Isidro, Argentina), Sebastian Gonzalez-Dambrauskas (Hospital Casa de Galicia, Montevideo, Uruguay), Shashikanth Ambati (Albany Medical Center, Albany, NY), Shira Gertz (Saint Barnabas Medical Center, Livingston, NY), Simi Jeyapalan (University of Miami, Miami, FL), Srinivas Murthy

(British Columbia Children's Hospital, Vancouver, British Columbia, Canada), Steven Pon (NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY), Steven Shein (Rainbow Babies and Children's Hospital, Cleveland, OH), Teddy Muisyo (University of Oklahoma Health Sciences Center, Oklahoma City, OK), Todd Karsies (Nationwide Children's Hospital, Columbus, OH), Weerapong Lillitwat (Texas Tech University, Lubbock, TX), and *Yurika Lopez-Alarcon (Hospital General de Medellín, Medellín, Colombia).

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Dr. Shein received funding from Ceribell. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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