


# In-hospital respiratory viral infections for patients with established BPD in the SARS-CoV-2 era

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## Abstract

**Objective:** Our objective was to test the hypothesis that in-hospital respiratory viral infections (RVI) would be significantly lower in a cohort of patients with established bronchopulmonary dysplasia (BPD) exposed to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection prevention protocol when compared to historical controls.

**Study Design:** On April 1, 2020, we implemented a universal infection prevention protocol to minimize the risk of nosocomial SARS-CoV-2 transmission in a dedicated BPD intensive care unit. We performed a retrospective cohort study and included patients with established BPD, as defined by the 2019 Neonatal Research Network criteria, admitted to our center who underwent real-time polymerase-chain-reaction RVI testing between January 1, 2015 and March 31, 2021. We excluded patients readmitted from home. We compared the proportion of positive tests to the number of tests performed and the distribution of viral respiratory pathogens in the pre- and post-SARS-CoV-2 eras.

**Results:** Among 176 patients included in the study, 663 RVI tests were performed and 172 (26%) tests were positive. The median number of tests performed, measured in tests per patient per month, in the SARS-CoV-2 era was not significantly different compared to the pre-SARS-CoV-2 era (0.45 vs. 0.34 tests per patient per month,  $p = .07$ ). The proportion of positive RVI tests was significantly lower in the SARS-CoV-2 era when compared to the pre-SARS-CoV-2 era (0.06 vs. 0.30,  $p < .0001$ ). No patients tested positive for SARS-CoV-2 in the SARS-CoV-2 era.

**Conclusions:** Infection prevention measures developed in response to the SARS-CoV-2 pandemic may reduce the risk of RVIs in hospitalized patients with established BPD.

## KEYWORDS

bronchopulmonary dysplasia, neonatology, respiratory tract, viral infections

**Abbreviations:** ADC, average daily census; BPD, bronchopulmonary dysplasia; IQR, interquartile range; MRSA, methicillin resistant staphylococcus aureus; NCH, Nationwide Children's Hospital; nCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; NREVSS, National Respiratory and Enteric Virus Surveillance System; NRN, Neonatal Research Network; PICU, pediatric intensive care unit; PMA, postmenstrual age; PPE, personal protective equipment; PUI, person under investigation; RSV, respiratory syncytial virus; RT-PCR, real-time polymerase chain reaction; RVI, respiratory viral infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

## 1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common morbidity of preterm birth and results in lifelong respiratory insufficiency.<sup>1</sup> Despite preventative efforts, the incidence of BPD is increasing due to the increased survival of extremely preterm infants.<sup>2</sup> Exposure to respiratory viral infections (RVI) is an important contributor to respiratory morbidity in early childhood in preterm infants,<sup>3</sup> and in particular former preterm infants with established BPD.<sup>4,5</sup> Among patients with BPD, RVIs may first occur in the neonatal intensive care unit (NICU)<sup>6–8</sup> and are associated with increased length of stay, severe disease course, unnecessary exposure to antibiotics, nosocomial viral outbreaks in the NICU, and death.<sup>7</sup> Though nosocomial RVIs in the NICU are relatively infrequent, multiple reports suggest that viral transmission to infants may occur in the setting of routine interactions with medical staff, families, and visitors.<sup>3,8–10</sup>

In response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, NICUs have adopted policies to prevent the nosocomial transmission of SARS-CoV-2 to vulnerable preterm infants, including those with established BPD.<sup>11,12</sup>

Outside of the NICU, public health measures including social distancing and mask use have been thought to reduce the transmission not only of SARS-CoV-2 but of RVIs of any type.<sup>13,14</sup> It is, therefore, plausible that NICU infection prevention policies designed to prevent the transmission of SARS-CoV-2 are associated with reduced transmission of RVIs of any type to patients with established BPD in the NICU, but this has not been studied. The objective of this study was therefore to test the hypothesis that in-hospital RVIs would be significantly lower in a cohort of patients with established BPD admitted during the global pandemic who were exposed to a SARS-CoV-2 infection prevention protocol when compared to historical controls admitted before the global pandemic.

## 2 | METHODS

### 2.1 | Study design

This retrospective cohort study was performed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines, which were developed to provide guidance in how to report observational research.<sup>15</sup> Our study population included infants admitted to our center with an established diagnosis of BPD, as defined by 2019 Neonatal Research Network (NRN) criteria.<sup>16</sup> The 2019 NRN criteria stratify patients into BPD grades at 36 weeks post-menstrual age (PMA) where grade 1 corresponds to patients requiring nasal cannula  $\leq 2$  L/min (lpm), grade 2 corresponds to patients requiring noninvasive positive airway pressure (includes nasal cannula  $> 2$  lpm, nasal continuous positive airway pressure [nCPAP], and noninvasive positive pressure ventilation), and grade 3 corresponds to patients requiring invasive mechanical ventilation.<sup>16</sup> We included patients with BPD who underwent clinical RVI testing between January 1, 2016, and March 31, 2021. We excluded patients born  $\geq 32$  weeks gestation and patients re-admitted from home. A formal sample size was not

determined as the cohort included all patients who met the criteria in the study period.

RVI testing data were abstracted from the electronic health record. RVI diagnostic data were then joined to clinical data in a prospectively maintained database. Abstracted clinical data included maternal and infant demographics, perinatal exposures including prenatal steroids and chorioamnionitis, postnatal exposures including intubation in the delivery room, and respiratory support data at 36 weeks PMA. The Nationwide Children's Hospital (NCH) institutional review board approved this study with a waiver of consent.

### 2.2 | Study location and infection surveillance policy

We performed this study in the BPD unit at NCH, a 24-bed ward dedicated to the care of infants with established BPD.<sup>16</sup> The BPD unit is in a different building than the level IV NICU and consists of 10 single rooms and 7 double rooms. Single rooms are generally reserved for patients with anticipated prolonged lengths of stay and infants who have a history of colonization with methicillin resistant staphylococcus aureus (MRSA). Our unit policy is to screen for MRSA via nasal swab on all patients admitted from an outside hospital at the time of admission. We do not perform routine MRSA, RVI, or tracheal aspirate surveillance. RVI testing is performed in symptomatic infants if a clinical index of suspicion for RVI is present as detailed below. If a patient develops an RVI in a double room, our policy is to keep both patients in the same room and place both patients on contact and droplet precautions to prevent the spread of infection across the unit. For patients who are RVI positive, precautions are maintained for a total of 28 days but continued longer if a patient remains symptomatic.

Our BPD unit has two negative pressure rooms. During the SARS-CoV-2 era, patients would be transferred to a negative pressure room if they were symptomatic and underwent RVI and SARS-CoV-2 testing. Additionally, patients would be transferred to a negative pressure room if there was concern for a potential exposure and the patient was on a level of respiratory support that could generate aerosolized secretions, which included patients on nCPAP and invasive mechanical ventilation.

### 2.3 | Study exposure: Universal infection prevention protocol

In the pre-pandemic era, we practiced standard infection control practices (Table 1). To prevent community transmission of SARS-CoV-2 to patients in our center, on April 1, 2020, we implemented an infection prevention protocol that was part of the overall hospital infection control response to the SARS-CoV-2 pandemic. This protocol (Table 1) consisted of vigilant hand hygiene combined with universal droplet precautions for all patients and use of surgical masks with plastic eyeshields as personal protective equipment (PPE) for all staff. For persons under investigation (PUI), defined as any patient undergoing SARS-CoV-2 testing for any reason, we

**TABLE 1** SARS-COV2 universal precautions protocol

Standard measures	SARS-COV2 precautions protocol
Vigilant hand hygiene	Universal surgical masking
Contact precautions for MRSA positive patients	Universal eye shield use
Contact and droplet precautions for PUI	PUI: Airborne and contact precautions including N-95 mask use and gowning during patient care Socially distanced rounds Visitation restrictions (only 2 caregivers allowed to visit throughout duration of hospital stay and only 1 caregiver to visit bedside in a 24-h period. Additionally, siblings were restricted from visiting.) Revised medical leave policies for staff to encourage staying at home in setting of respiratory symptoms

Abbreviation: PUI, persons under investigation.

employed aerosol precautions including the use of N-95 masks, plastic eyeshields, and contact precautions for all staff caring for PUI.

To augment our PPE use, we practiced social distancing throughout the unit. Socially distanced rounds were limited to 4 multidisciplinary team members who maintained 6 feet of separation. As our multidisciplinary teams historically consisted of physicians, advanced practice providers, bedside nurses, respiratory therapists, nutritionists, psychologists, social workers, and care coordinators, we developed a rotation schedule in which one multidisciplinary team member would be physically present on rounds each day of the week with the remainder of the team participating virtually using Microsoft Teams (Microsoft Corporation). We transitioned our weekly comprehensive multidisciplinary team meetings, traditionally held in person, to bi-weekly virtual formats using Microsoft Teams. Hospital policy was revised to encourage staff to monitor for symptoms consistent with viral illness and sick leave policies were revised such that staff would not be required to use sick days if they developed viral symptoms. Lastly, NCH developed a hospital wide policy of limiting family visitation to only one family member at the patient's bedside per 24-h period and only two family members to visit during the entire duration of the patient's hospitalization. For this study, we defined the primary exposure as the "SARS-CoV-2 era," defined as a dichotomous (yes/no) variable between April 1, 2020 (when we implemented the universal infection prevention protocol) and March 21, 2021. Patients undergoing RVI testing before April 1, 2020, defined as the "pre-SARS-CoV-2" group, were categorized as negative exposures while patients who underwent testing after April 1, 2020, defined as the "SARS-CoV-2" group, were categorized as positive exposures.

## 2.4 | Determination of positive RVI

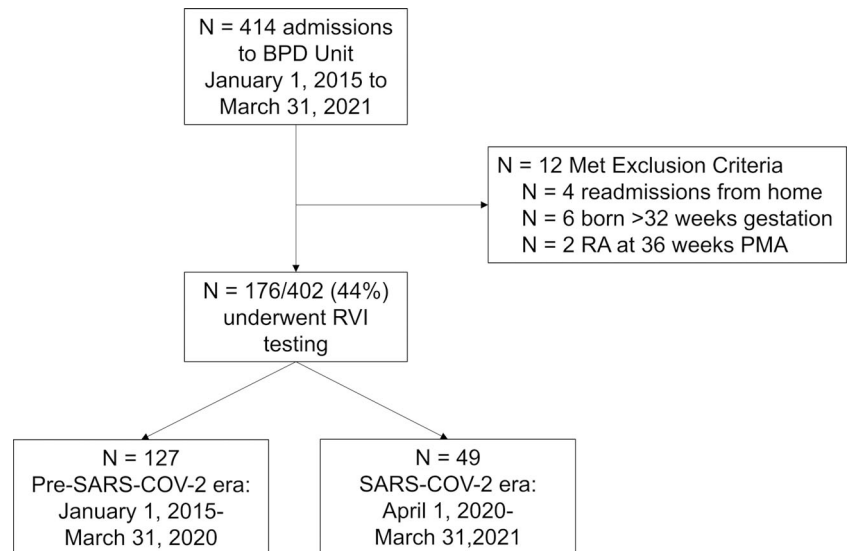
During the study period, patients underwent RVI and SARS-CoV-2 testing if symptomatic and if a clinical index of suspicion for an RVI, including SARS-CoV-2, was present. The diagnosis of RVI is difficult

to make in patients with BPD because many of the diagnostic criteria for RVI (i.e., changes in oxygen saturation, changes in sputum production, abnormal radiographic findings) are part of the natural progression of BPD. To encourage consistent RVI testing in our center, we developed clinical practice guidelines that restrict testing to the following criteria: fever without clear source of infection, deterioration in respiratory status that cannot be explained by BPD alone and recent exposure to sick contacts. Though the criteria for RVI testing in the pre- and SARS-CoV-2 eras did not change, asymptomatic patients undergoing routine elective procedures in the later era, such as tracheostomy placement, did undergo SARS-CoV-2 testing before the procedure in accordance with hospital policy.

Among infants who underwent RVI testing, bedside nurses collected nasopharyngeal swabs for nonintubated patients and tracheal secretions for patients with an endotracheal tube or established tracheostomy. Patient samples were then placed in a universal viral transport medium (BD) and delivered to the clinical laboratory where they were stored, processed, and tested. During the study period, RVI testing for common respiratory viral pathogens was performed using the BioFire Respiratory Panel 2.1, a real-time polymerase chain reaction (RT-PCR) based array respiratory panel that detects 22 viral pathogens (Biofire Defense). SARS-CoV-2 testing was performed on one of four RT-PCR-based assays (1) NCH SARS-CoV-2 Assay<sup>17</sup> (Centers for Disease Control, Atlanta, GA) (2) BioGx assay using the BDMax analyzer (Becton Dickenson) (3) Xpert<sup>®</sup> Xpress SARS-CoV-2 (Cepheid) or (4) isothermal amplification by IDNow (Abbott Laboratories). Positive RT-PCR tests were determined by threshold cycle time values as recommended by the manufacturer.

## 2.5 | Study outcomes

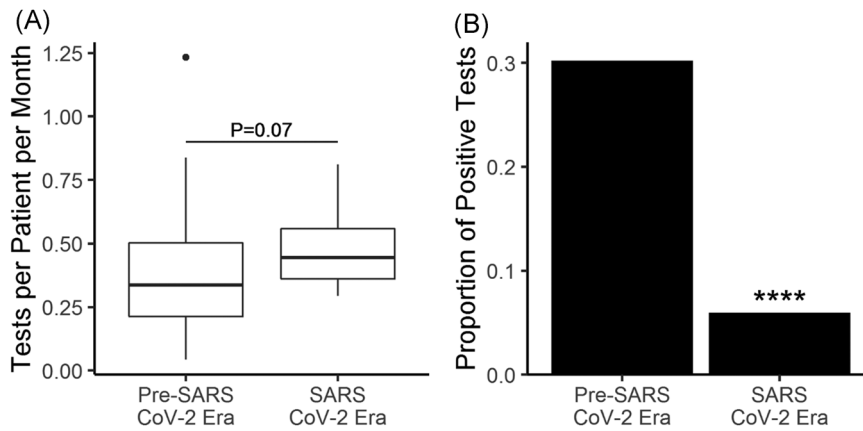
The primary study outcome was a positive RVI, which we defined as a dichotomous outcome based on the presence or absence of a clinical RT-PCR test detecting one or more viral respiratory pathogens. Disposition, tracheostomy, length of stay (defined as birth to initial NICU discharge in days), supplemental oxygen use at discharge, and gastrostomy placement were reported as secondary outcomes.

**FIGURE 1** Flow diagram for study**TABLE 2** Demographics and neonatal characteristics of cohort

Characteristic	All	Pre-SARS-CoV-2 era	SARS-CoV-2 era	<i>p</i>
<i>n</i>	176	127	49	
Maternal Hispanic ethnicity, <i>n</i> (%)	3 (2)	3 (2)	0 (0)	.7
Maternal race				
American Indian or Alaskan native, <i>n</i> (%)	1 (0.6)	1 (0.8)	0 (0)	.4
Asian, <i>n</i> (%)	7 (4)	6 (5)	1 (2)	
Black, <i>n</i> (%)	50 (28)	33 (26)	17 (35)	
Native Hawaiian or Pacific Islander, <i>n</i> (%)	1 (0.6)	0 (0)	1 (2)	
White, <i>n</i> (%)	112 (64)	84 (66)	28 (57)	
Other, <i>n</i> (%)	5 (3)	3 (2)	2 (4)	
Complete antenatal steroids, <i>n</i> (%)	115/146 (79)	87/108 (81)	26/38 (68)	.5
Cesarean delivery, <i>n</i> (%)	129 (73)	87 (69)	42 (86)	<b>.04</b>
Male, <i>n</i> (%)	109 (62)	83 (65)	26 (53)	.2
Gestational age (weeks), median (IQR)	25 (24–27)	26 (24–27)	25 (24–27)	.9
Birth weight (g), median (IQR)	710 (584–915)	695 (581–943)	739 (600–890)	.7
1-min APGAR, median (IQR)	3 (1–5)	3 (2–5)	3 (1–6)	1
5-min APGAR, median (IQR)	6 (4–8)	6 (4–8)	7 (4–8)	.8
Intubation in delivery room, <i>n</i> (%)	132/172 (77)	96/126 (76)	36/48 (75)	1
BPD grade at 36 weeks postmenstrual age				
1, <i>n</i> (%)	20 (11)	18 (14)	2 (4)	.2
2, <i>n</i> (%)	56 (32)	39 (31)	17 (35)	
3, <i>n</i> (%)	100 (57)	70 (55)	30 (61)	

Note: Bold value indicates statistical significance, *p* < .05.

Abbreviations: BPD, bronchopulmonary dysplasia; IQR, interquartile range.



**FIGURE 2** Comparisons of RVI testing frequency and proportion of positive RVI tests in the pre-SARS-CoV2 era and the SARS-CoV2 era. The median number of RVI tests performed per patient per month did not differ significantly between eras (A) but the proportion of positive RVI tests decreased significantly in the SARS-CoV2 era, \*\*\*\* $p < .0001$  (B). RVI, respiratory viral infection

## 2.6 | Statistical analysis

Descriptive data are presented as median with interquartile range (IQR) for nonparametric continuous data and number with percentage for categorical data. Demographics and clinical characteristics were compared by the primary study exposure using the Wilcoxon rank sum test or  $\chi^2$  testing, where appropriate. We compared the proportion of positive RVI tests in patients between the pre- and SARS-CoV-2 eras using  $\chi^2$ . The number of tests performed per patient per month was calculated by dividing the total number of tests performed per month by the average daily census (ADC) by month for our unit, measured in patients per day. The distribution of viral respiratory pathogens identified on clinical testing are presented as number with percentage and stratified by the study exposure. We used R version 4.1.0 (R Institute for Statistical Programming) for statistical analysis. All  $p$  values are two sided and a threshold of  $<.05$  was used for statistical significance.

## 3 | RESULTS

Among 414 consecutive admissions to our BPD unit during the study period, 402 patients met inclusion criteria, of whom 176 patients (44%) underwent RVI testing. (Figure 1) Demographics and neonatal characteristics of the cohort are presented in Table 2. Patients who underwent RVI testing were predominantly male (109, 62%) and born to white (112, 64%), non-Hispanic (173, 98%) mothers (Table 1). In general, members of the cohort were born extremely preterm and with extremely low birth weights. The majority of patients in the study cohort (100, 57%) were treated with invasive mechanical ventilation at 36 weeks PMA and therefore had Grade 3 BPD (Table 2). Patients who underwent RVI testing in the SARS-CoV-2 era were more likely to be born via cesarean section when compared to patients who underwent RVI testing in the pre-SARS-CoV-2 era (86% vs. 69%,  $p = .04$ ). Demographics, neonatal characteristics and BPD grade at 36 weeks PMA otherwise did not differ significantly between patients who had respiratory viral testing in the different eras (Table 2).

**TABLE 3** Distribution of RVIs in pre-SARS-CoV-2 era and SARS-CoV-2 eras

Respiratory viral infection	Pre-SARS-CoV-2 era	SARS-CoV-2 era
<i>n</i>	161	7
Rhino/enterovirus, <i>n</i> (%)	135 (84)	7 (100)
Adenovirus, <i>n</i> (%)	7 (4)	0 (0)
Common coronavirus, <i>n</i> (%)	5 (3)	0 (0)
Parainfluenza, <i>n</i> (%)	4 (2)	0 (0)
Respiratory syncytial virus, <i>n</i> (%)	5 (3)	0 (0)
Parainfluenza virus 3, <i>n</i> (%)	3 (2)	0 (0)
Parainfluenza virus 4, <i>n</i> (%)	1 (1)	0 (0)
Human metapneumovirus, <i>n</i> (%)	1 (1)	0 (0)

For the entire cohort, 172/663 (26%) tests were positive. The median monthly ADC was significantly lower in the SARS-CoV-2 era (20 patients per day vs. 23 patients per day,  $p < .0001$ ), but the median number of respiratory viral tests performed per patient per month was not significantly different in the SARS-CoV-2 era (0.45 tests per patient per month vs. 0.34 tests per patient per month,  $p = .07$ ) (Figure 2A). In the pre-SARS-CoV-2 era 165/546 (0.30) respiratory viral tests were positive compared to 7/117 (0.06) in the SARS-CoV-2 era,  $p < .0001$  (Figure 2B).

In Table 3, we present the distribution of respiratory viral pathogens identified by clinical testing. During the study period, no patients tested positive for SARS-CoV-2. In the pre-SARS-CoV-2 era, rhino/enterovirus was the most common viral respiratory pathogen identified (135/161, 84%), followed by adenovirus (7/161, 4%), and common coronavirus (5/161, 3%) (Table 3). In the pre-SARS-CoV-2 era, 10 patients had coinfections with multiple viral respiratory pathogens. In the SARS-CoV-2 era, only seven positive rhino/enterovirus RVIs were identified by clinical testing (Table 3). Six of the positive RVIs in the SARS-CoV-2 era were associated with an isolated

**TABLE 4** In-hospital outcomes of patients stratified by pre-SARS-CoV-2 era and SARS-CoV-2 eras

Outcome	All	pre-SARS-CoV-2 era	SARS-CoV-2 era	<i>p</i>
<b>N</b>	<b>176</b>	<b>127</b>	<b>49</b>	
Disposition				
Discharge home, <i>n</i> (%)	132 (75)	95 (75)	37 (76)	.01
Reverse transfer to referral hospital, <i>n</i> (%)	26 (15)	21 (17)	5 (10)	.4
Death after 36 weeks postmenstrual age, <i>n</i> (%)	13 (7)	11 (9)	2 (4)	.5
Ongoing NICU care, <i>n</i> (%)	5 (3)		5 (10)	Null
Tracheostomy, <i>n</i> (%)	40 (23)	26 (20)	14 (29)	.3
Length of stay (days) for <i>n</i> = 158 discharged survivors, median (IQR)	247 (158-361)	264 (163-453)	221 (158-361)	.2
Supplemental oxygen use at discharge for <i>n</i> = 158 discharged survivors, <i>n</i> (%)	150 (95)	109 (94)	41 (98)	.6
Gastrostomy for <i>n</i> = 158 discharged survivors, <i>n</i> (%)	107 (68)	75 (65)	32 (76)	.2

Abbreviations: IQR, interquartile range; NICU, neonatal intensive care unit.

nosocomial outbreak in October 2020. All six patients tested positive within 5 days of one another. Review of this outbreak by the hospital acquired infection committee did not identify a clear source for this nosocomial outbreak. One parent reported allergic rhinitis symptoms before the first positive case and a second parent reported having a child at home with respiratory symptoms. Two staff members caring for rhino/enterovirus positive patients during this outbreak developed respiratory symptoms and appropriately followed the hospital's pandemic leave policy.

In-hospital outcomes are presented in Table 4. Thirteen (7%) of the cohort died and 40 (23%) members of the cohort had tracheostomy placement during the study period (Table 4). The median length of stay in the cohort was 247 days (IQR, 158–361, Table 4). Most surviving patients were discharged home on supplemental oxygen (150/158, 95%) and 107/158 surviving discharged members of the cohort received a gastrostomy tube for enteral feedings (Table 4). There were no significant differences in adverse in-hospital outcomes observed for cohort members between eras (Table 4). No RVI positive patients required extra-corporeal membrane oxygenation therapy in either era.

## 4 | DISCUSSION

We report a significant decrease in the number of in-hospital RVIs in a cohort of patients with established BPD in the SARS-CoV-2 era. Additionally, we observed no SARS-CoV-2 infections in this cohort of patients. These findings are important because viral respiratory infections are major sources of respiratory morbidity in patients with established BPD and preventative strategies are not well described. It is plausible that the infection preventative measures we developed in

response to the SARS-CoV-2 pandemic including universal masking, in-hospital social distancing, and prophylactic use of contact precautions, N-95 masking, and eyeshields in the care of PUIs contributed to the significant reduction of RVIs observed in this study.

To our knowledge, this is the first study reporting a reduction in in-hospital viral infections following the adoption of a universal infection prevention protocol for patients with established BPD. Several studies have described strategies that reduced nosocomial viral infections in the NICU following outbreaks.<sup>18–20</sup> These strategies include: cohorting of infected patients, universal use of contact and droplet precautions by staff caring for patients, hand hygiene policies, and restriction of visitors during periods of high community loads of common RVIs.<sup>18–20</sup> None of these studies specifically studied the impact of these interventions on NICU patients with established BPD in the SARS-CoV-2 era. A Cochrane Review of virus mitigation interventions across pediatric and adult medical centers did not show any reduction of influenza-like illness with the use of surgical masks versus no surgical mask or with the use of N95 respirators versus surgical masks when used in health care settings, although it should be noted that the reviewed studies occurred in heterogeneous settings and compliance with interventions was variable.<sup>21</sup> Additionally, none of the studies included in this Cochrane Review were conducted during the SARS-CoV-2 pandemic.<sup>21</sup>

An important finding of our study is that no SARS-CoV-2 infections were observed in this cohort of patients with established BPD. To our knowledge, this is the first study to report the results of RVI testing in the SARS-CoV-2 era among patients with established BPD during their initial NICU hospitalization. Though SARS-CoV-2 infections have been described in neonates,<sup>22–25</sup> we know of no reported cases of positive SARS-CoV-2 among patients with established BPD that occurred before initial NICU discharge. In a survey of the

Paediatric Assembly of the European Respiratory Society, Moeller et al.<sup>26</sup> identified nine children with BPD infected with SARS-CoV-2 following initial NICU discharge, of whom two required no treatment, five required inpatient care with supplemental oxygen and two were admitted to the pediatric intensive care unit (PICU) and treated with invasive mechanical ventilation. In Moeller et al.'s<sup>26</sup> study all nine patients with BPD infected with SARS-CoV-2 survived. Kalyanaraman et al.<sup>27</sup> also reported the case of a former 28 week male with grade 2 BPD who developed severe acute respiratory distress syndrome two weeks following initial NICU discharge. This patient was treated with invasive mechanical ventilation, solumedrol, and hydroxychloroquine in the PICU and discharged home on room air after a 27 day hospital stay.<sup>27</sup>

Although the reported incidences of RVIs of any type in the NICU are relatively low,<sup>8,28,29</sup> preterm infants with established BPD are highly susceptible to in-hospital RVIs due to their immature immune system<sup>30</sup> and need for prolonged initial NICU hospitalization.<sup>31</sup> Given the underlying pulmonary insufficiency that characterizes lung function in infants with established BPD,<sup>32,33</sup> exposure to RVIs can cause major short- and long-term respiratory morbidities. For example, Taylor et al.<sup>5</sup> showed that among patients with moderate or severe BPD, intercurrent RVIs during the initial NICU hospitalization have negative short-term impacts and are independently associated with an increased odds of oxygen, diuretic, and inhaled corticosteroid use. Of note, we found a marked reduction on the burden of in-hospital rhino/enterovirus RVIs (Table 3). This is of particular importance for high-risk preterm infants, given the relatively high occurrence of rhino/enterovirus RVIs in this population, which are associated with increased need for respiratory support, nursing care, and medical resources.<sup>3,8,18,19</sup> A recent report by Sánchez García et al.<sup>29</sup> suggested that any symptomatic RVI in the NICU was associated with a significantly increased odds of respiratory morbidity in early childhood. Following discharge from the NICU, multiple studies have identified the increased susceptibility of BPD patients to adverse respiratory outcomes following RVIs in early childhood, particularly with respiratory syncytial virus (RSV) infection.<sup>4,34-36</sup> Given the increased respiratory morbidity associated with RVIs in patients with BPD, identifying interventions that prevent RVIs during the initial NICU hospitalization is critically important. Though we did not observe significant differences in in-hospital outcomes between the pre-SARS-CoV-2 and SARS-CoV-2 eras, the relatively low number of patients in the SARS-CoV-2 era likely limited our power to detect differences in the secondary outcomes assessed in this study. Nonetheless, the results of our study suggest that enhanced infection prevention measures that are systematically applied and followed, including universal masking, eyeshield use, and social distancing may decrease the burden of RVIs for patients with established BPD during their initial NICU hospitalization. Given the marked reduction in RVIs we observed in patients with established BPD following implementation of the SARS-CoV-2 prevention protocol, we anticipate continuing a number of these interventions, including universal masking,<sup>37</sup> once the pandemic subsides. Nonetheless, further studies are needed to systematically test the impact of these targeted

interventions on reduction of RVIs and in-hospital outcomes in patients with established BPD.

Our study has important limitations. Most notably, the retrospective, observational design of the study limits our ability to determine the causation of the decrease in RVIs observed in this cohort. For example, an important source of potential confounding was the prevalence of respiratory viral pathogens in the community, which would likely impact the risk of RVI in our patients. In Australia, positive detections of RSV and influenza were significantly lower in the winter of 2020, following the widespread adoption of public health prevention measures in response to the SARS-CoV-2 pandemic when compared to historical cases.<sup>14,38</sup> Preliminary reports from the Centers for Disease Control and Prevention suggest a lower burden of detected RVIs including RSV and influenza when compared to historical controls.<sup>39</sup> The National Respiratory and Enteric Virus Surveillance System (NREVSS) monitors temporal and geographic circulation patterns of RSV, influenza, human metapneumovirus, parainfluenza, common coronavirus, and respiratory adenovirus. Community rates for each of these viruses were historically low in Ohio during the study period.<sup>39</sup> The low rates of community transmission of these common RVI pathogens may plausibly explain the observed decrease in RVIs in our study, particularly since none of these pathogens were observed in the SARS-CoV-2 era (Table 3). Most notably, RSV community transmission in Ohio was surprisingly low during the study period with a 3 week moving average of positive RSV PCR tests ranging from 0% to 0.67% during the study period with little fluctuation observed during the traditional RSV season.<sup>40</sup> Since NREVSS does not track rhino/enterovirus infections, which was the most common RVI pathogen observed in this study and the only RVI pathogen identified during the study period (Table 3), it remains unclear as to what impact community transmission of rhino/enterovirus had on the results of our study. Nonetheless, Central Ohio experienced a significant burden of community SARS-CoV-2 infections during the study period<sup>41</sup> and it is notable that none of our cohort members tested positive for SARS-CoV-2. Though we found that the number of RVI tests performed per patient per month did not differ significantly between eras, this finding may be biased by Type 2 error given the lower number of patients and tests performed in the SARS-CoV-2 era when compared to the pre-SARS-CoV-2 era.

Our study was further limited to a cohort of patients with established BPD cared for in a specialized BPD NICU and therefore may not be generalizable to other level IV NICUs that typically have a larger ADC, with a greater number of visitors and staff that are potential sources of nosocomial RVI spread than our BPD unit. Like other studies, the changes tested in our study were made in response to an outbreak, the global SARS-CoV-2 pandemic, and therefore were not tested systematically. Additionally, our prevention measures were developed as a bundle and therefore we could not test the independent effect of specific prevention measures on the reduction of RVIs observed in this study. This limitation is particularly important because our infection prevention protocol included visitation restrictions for families, which may or may not have had any impact on the reduction of RVIs observed in this study but may have

negatively impacted family-patient bonding during the critical period when a patient with BPD is preparing for initial NICU discharge.<sup>42-44</sup> Prospective randomized control trials may more precisely identify specific interventions that result in significant decrease in RVIs<sup>21</sup> but the feasibility of such trials may be limited by ethical and practical considerations. Alternatively, quality improvement methodologies may allow for the assessment of targeted interventions aimed at decreasing nosocomial transmission of RVIs to vulnerable BPD patient populations.

## 5 | CONCLUSIONS

We observed a significant reduction in the number of RVIs among infants with established BPD during their initial NICU hospitalization following the adoption of a SARS-CoV2 infection prevention protocol developed in response to the global pandemic. Given the high risk of respiratory morbidity and mortality associated with RVIs for patients with established BPD, continued use of enhanced infection prevention practices after resolution of the SARS-CoV-2 pandemic, including universal masking and eyeshield use, may further decrease the risk of nosocomial viral infection for patients with established BPD during their initial NICU hospitalization. Further prospective studies are needed to systematically test specific interventions that reduce the risk of RVI exposure to patients with established BPD.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Matthew J. Kielt conceptualized and designed the study, collected, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the final manuscript. Angela Murphy, Jodi Smathers, and MaLeah Bates contributed to study design, analysis and interpretation of the data, and reviewed and revised the final manuscript. Leif D. Nelin contributed to study design, analyzed and interpreted the data, and reviewed and revised the final manuscript. Edward G. Shepherd conceptualized and designed the study, coordinated and supervised data collection, assisted in statistical analysis, contributed to initial drafts of the manuscript, and reviewed and revised the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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