Brief Summary of Findings on the Association Between Underlying Bronchopulmonary Dysplasia (BPD) and Severe COVID-19 Outcomes

Prepared and Reviewed by:

Mylaica Conner Henry, MPH; Communications Specialist/Technical Writer; Eagle Global Scientific

David Weissman, MD, Director Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (CDC)

Jacek Mazurek, MD, MS, PhD, Branch Chief, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Girija Syamlal, MBBS, MPH, Research Epidemiologist, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Katelynn Dodd, MPH, Associate Service Fellow, Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, CDC

Jill Kumasaka; ORISE Fellow; Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, CDC

Devon L. Okasako-Schmucker, MPH; Program Analyst; Eagle Global Scientific

Tashika M. Robinson, MPH; Program Analyst III; Eagle Global Scientific

Christine Nam So, MPH; Program Analyst III; Eagle Global Scientific

Kristen Tansil Roberts, MSW, Behavioral Scientist, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC

Marwan Wassef, MPH; Data Analyst; Chenega Corporation

Erin C. Stone, MPH, MA; Public Health Analyst; Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, CDC

David A Siegel, MD MPH, Core Clinical Unit, Clinical Disease and Health Services Team, Health Systems and Worker Safety Task Force, CDC COVID-19 Response, CDC

Emily Koumans, MD MPH, Clinical Disease and Health Services Team Lead, Health Systems and Worker Safety Task Force, CDC COVID-19 Response, CDC

Kanta Devi Sircar, PhD, MPH, Epidemiologist, Underlying Conditions, Core Clinical Unit, Clinical Disease and Health Services Team, Health Systems and Worker Safety Task Force, CDC COVID-19 Response

Contact: CDC Info contact us form

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One cohort study was retrieved that reported prevalence of severe COVID-19 outcomes for children with BPD.

- Limited evidence[1] was suggestive of an increase in the risk of severe COVID-19 outcomes for children with BPD. Descriptive data from one study[1] is insufficient to definitively conclude an increase in risk in children with this underlying condition; New evidence may change these conclusions.

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A. Methods

The aim of this review was to identify and synthesize the best available evidence on the association between Bronchopulmonary Dysplasia (BPD) and severe COVID-19 in order to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions for a consumer and a provider-specific website with more rigorous information.

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcomes (PECO) question. Clinical experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter from the end of the previous literature search on chronic lung disease (December 2020). The detailed search strategies for identifying primary literature and the search results are provided in Section B.1. Subject matter experts supplemented the literature search results by recommending relevant references published before December 2020. References were included if retrieved by the chronic lung disease literature search and reported exposures and outcomes relevant to this review.

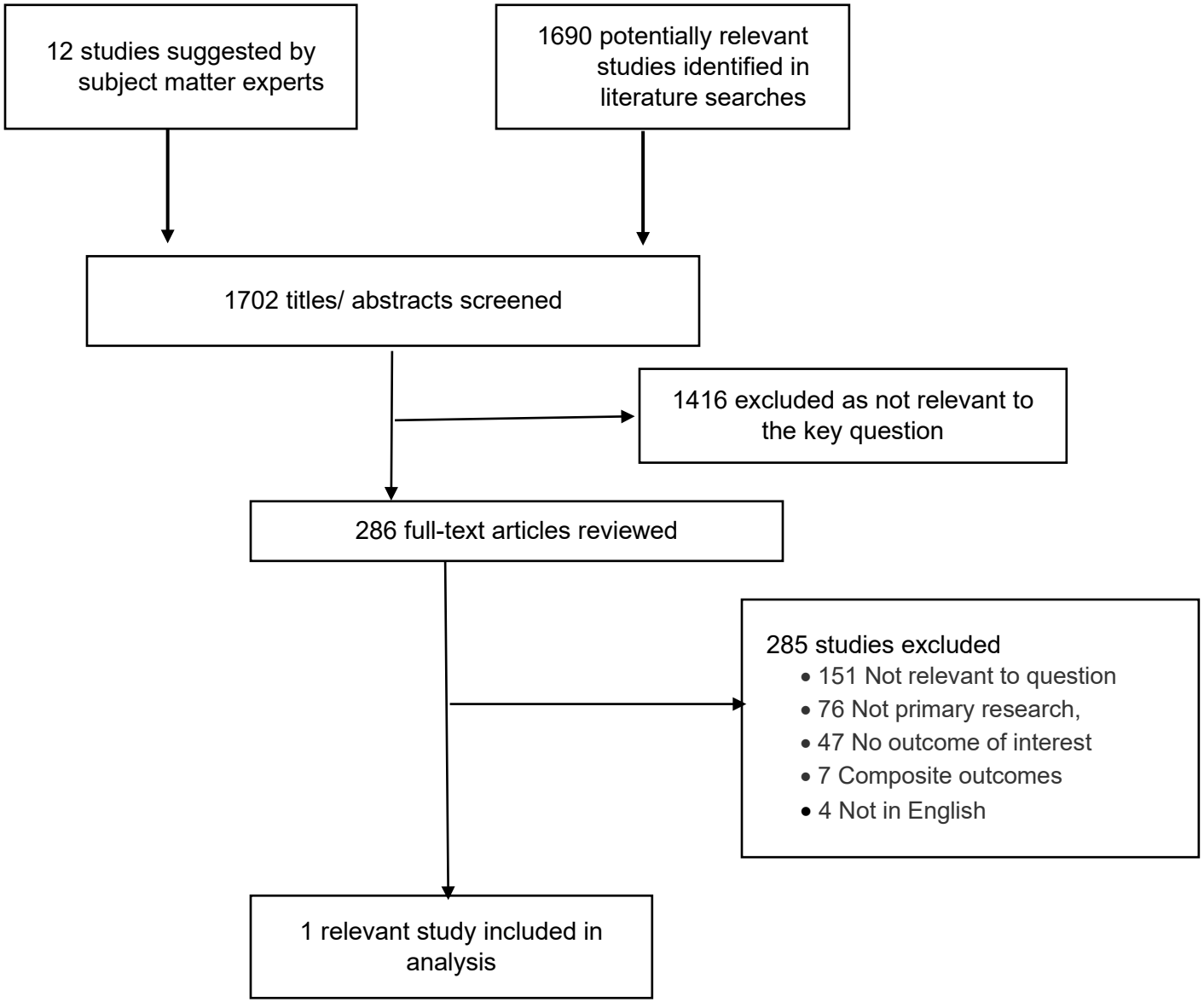
A.2. Study Selection

Titles and abstracts from references were screened by dual review (review initials: M.C., J.K.K., C.O., D.O.S., T.R., C.S., E.C.S., or M.W.). Full-text articles were retrieved if they were:

1. relevant to the PECO question;
2. primary research; and
3. written in English.

Section B.2 presents the full list of exclusion criteria. The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (J.K.K., C.O., D.O.S., K.T.R., C.S., E.C.S., or M.W.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in Figure 1.

Figure 1. Results of the Study Selection Process



A.3. Data Extraction and Synthesis

Methodologic data and results of relevant outcomes from the study meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the study. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

A.4. Aggregation of the Evidence

The internal validity associated with the study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. Table 4 in Section B.3.c. includes the signaling questions used to assess the quality of the study design. The strength, magnitude, precision, consistency, and applicability of results were assessed for all comparators. The overall confidence in the evidence base is reported in the aggregation tables in Section B.3.a.

A.5 Reviewing and Finalizing the Systematic Review

Draft findings, aggregation tables, and evidence tables, are presented to CDC subject matter experts for review and input. Following further revisions, the summary will be published on the CDC website.

B. Systematic Literature Review Results

B.1. Search Strategies and Results

Table 1 Chronic Lung Disease search conducted March 17, 2021

#	Search History
1	chronic lung disease
2	respiratory system disease*
3	reactive airway disease*
4	emphysema
5	chronic bronchitis
6	COPD
7	Chronic obstructive pulmonary disease
8	Asthma *
9	allergic asthma
10	irritant asthma
11	Interstitial lung disease
12	Pulmonary fibrosis
13	idiopathic pulmonary fibrosis
14	nonspecific interstitial pneumonitis
15	hypersensitivity pneumonitis
16	sarcoidosis
17	pneumoconiosis
18	asbestosis
19	coal workers pneumoconiosis
20	silicosis
21	bronchiectasis
22	cystic fibrosis
23	pulmonary vascular disease
24	pulmonary hypertension
25	bronchopulmonary dysplasia
26	bronchiolitis obliterans
27	asthma*
28	reactive airway disease*
29	CF

30	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	Limit 30 to covid-19
32	(202012* or 2021*).dt
33	(202012* or 2021*).dc
34	32 or 33
35	31 and 34
36	Deduplicate

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were included at the title and abstract screen if they:

- were relevant to the key question "what is the association between bronchopulmonary dysplasia and severe COVID-19?";
- were primary research;
- were written in English (can be seen as [language] in title); and
- examined humans only.

Exclusion Criteria: Studies were excluded at full text review if they:

- were not available as full-text;
- were a conference abstract, poster, letter to the editor, or reply letter;
- examined lung transplant, cancer, or immunocompromised populations;
- reported autopsy results; and
- reported only composite outcome measures for "severe COVID-19".

B.3. Evidence Review: Bronchopulmonary Dysplasia (BPD) and Severe COVID-19 Outcomes

B.3.a. Strength & Direction of Evidence

Table 2. Evidence examined for associations with BPD and severe COVID-19

Outcome	Results
Mortality	Overall, the evidence is limited but suggests a low proportion of pediatric inpatients with underlying bronchopulmonary dysplasia (BPD) died. Aggregation indices cannot be measured when only one study[1] is retrieved, and this study was found to have a high threat to internal validity. • One retrospective cohort study[1] (N = 185) of pediatric inpatients in multiple European countries suggested that underlying BPD is not associated with an increase in mortality in patients with COVID-19; of note, no deaths were reported among the nine patients with underlying BPD, however at the end of the study period, one patient had not yet been discharged.
ICU admission	The evidence is limited but suggests a notable proportion of pediatric inpatients with underlying BPD are admitted to the intensive care unit (ICU). Aggregation indices cannot be measured for one study[1], which was found to have a high threat to internal validity. • One retrospective cohort study[1] (N = 185) of pediatric inpatients in multiple European countries reported two of nine patients (22.2%) with BPD were admitted to the ICU.
Ventilation	The evidence is limited but suggests a high proportion of pediatric inpatients with underlying BPD receive non-invasive ventilation. Aggregation indices cannot be measured for one study, which was found to have a high threat to internal validity. • One retrospective cohort study[1] (N = 185) of pediatric inpatients in multiple European countries reported four infants of nine children (44.4%) with BPD received noninvasive ventilation.
Hospitalization	The evidence is limited but suggests a high proportion of pediatric inpatients with underlying BPD are hospitalized. Aggregation indices cannot be measured for one study, which was found to have a high threat to internal validity. • One retrospective cohort study[1] (N=185) of pediatric inpatients in multiple European countries reported seven of the nine (77.7%) pediatric inpatients with BPD were hospitalized, and at the end of the study period, one patient remained hospitalized.

B.3.b. Extracted Evidence

Table 33. Extracted Study Reporting the Association between Bronchopulmonary Dysplasia and Severe COVID-19 Outcomes

Study	Population and Setting	Intervention	Definitions	Results
Author: Moeller[1] **Year:** 2020 **Data Extractor:** MW **Reviewer:** DOS **Study Design:** Retrospective cohort **Study Objective:** To determine the number of COVID-19 cases of children with pre-existing chronic respiratory conditions and whether they have exacerbations associated with SARS-CoV-2 virus. **Internal Validity Assessments (IVA) Score:** 16 (High)	**Population:** N=185 cases with data on underlying conditions **Setting:** 180 centers **Location:** Multiple European countries **Study dates:** March 30 – May 3, 2020 **Inclusion criteria:** Survey responses from members of the ERS Pediatric Assembly on children who tested positive for SARS-CoV-2 at an institution. Additional data was collected on children with pre-existing chronic respiratory conditions. **Exclusion criteria:** NR	**Health Condition Category:** Chronic lung disease **Medical Condition, n/N (%):** Bronchopulmonary dysplasia (BPD): 9/185 (4.8%) **Control/Comparison group, n/N (%):** No BPD: 176/185 (95.1%)	**Medical Condition(s):** *BPD:* ND (Not defined) **Severity Measure(s):** NR (Not reported) **Clinical marker:** NR **Treatment/ Associated Therapy:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* Pediatric intensive care unit *Intubation:* NR *Ventilation:* Supplemental oxygen, noninvasive ventilation (NIV) or invasive ventilation *Hospitalization:* Pediatric ward and other unspecified wards *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *Mortality, n/N (%):* Bronchopulmonary dysplasia: • No deaths reported *ICU admission, n/N (%):* Bronchopulmonary dysplasia: • ICU: 2/9 (22.2%) • No ICU: 7/9 (77.7%) *Ventilation, n/N (%):* Bronchopulmonary dysplasia: • Oxygen use was reported in three children and noninvasive ventilation in four infants *Hospitalization, n/N (%):* Bronchopulmonary dysplasia: • Hospitalized: 7/9 (77.7%) • Not hospitalized: 2/9 (22.2%) **Severity of Condition:** NR **Duration of Condition:** NR **Treatment/ Associated Therapy:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR

B.3.c. Internal Validity Assessments (IVA) of Extracted Study

Table 4. Internal Validity Assessments of Extracted Study reporting the Association between Bronchopulmonary Dysplasia and Severe COVID-19 Outcomes

	Author Year	Moeller 2020[1]
	Outcome	Mortality, ICU admission, hospitalization, ventilation

Domain	Signaling question	Data from survey
Study Elements	Design appropriate to research question	1
	Well described population	1
	Well described setting	1
	Well described intervention/ exposure	1
	Well described control/ comparator	1
	Well described outcome	1
	Clear timeline of exposures/ interventions and outcomes	1
Selection Bias: Sampling	Randomization appropriately performed	0
	Allocation adequately concealed	0
	Population sampling appropriate to study design	1
Selection Bias: Attrition	Attrition not significantly different between groups	0
	Attrition <10-15% of population	1
	Attrition appropriately analyzed	1
Information Bias: Measurement and Misclassification	Measure of intervention/ exposure is valid	0
	Measure of outcome is valid	0
	Fidelity to intervention is measured	0
	Fidelity to intervention is valid	0
	Prospective study	1
	Adequately powered to detect result	0
Information Bias: Performance & Detection	Outcome assessor blinded	0
	Study participant blinded	0
	Investigator/ data analyst blinded	0
	Data collection methods described in sufficient detail	1
	Data collection methods appropriate	0
	Sufficient follow up to detect outcome	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	0
	Appropriate statistical analyses are conducted correctly	0
	Confidence interval is narrow	0
Confounding	Potential confounders identified	0
	Adjustment for confounders in study design phase	0

	Adjustment for confounders in data analysis phase	0
Reporting Bias	All pre-specified outcomes are adequately reported	1
Other Bias	No other sources of bias	1
COI	Funding sources disclosed and no obvious conflict of interest	1
SCORE	Threat to internal validity	16
	Low, Moderate, High	High

C. References

1. Moeller A, Thanikkel L, Duijts L, et al. COVID-19 in children with underlying chronic respiratory diseases: Survey results from 174 centres. *ERJ Open Research*. 2020;6(4):1-8. doi:http://dx.doi.org/10.1183/23120541.00409-2020

D. Abbreviations

Acronym	Full
BPD	bronchopulmonary dysplasia
CF	cystic fibrosis
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
ERT	evidence review team
ICU	intensive care unit
IVA	internal validity assessments
ND	not defined
NIV	noninvasive ventilation
NR	not reported
PECO	population, exposure, comparator, and outcomes