

**Assessing the Impact of Provider-Ordered Viral Diagnostic Testing and Feasibility of Applying a
Viral Acute Respiratory Infection Diagnostic Prediction Model in a Pediatric Population Across
Healthcare Settings**

By

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LIST OF ABBREVIATIONS

ARIs	Acute respiratory infections
RSV	Respiratory syncytial virus
NVSN	New Vaccine Surveillance Network
CDC	Centers for Disease Control and Prevention
ED	Emergency department
PACCARB	Presidential Advisory Council on Combatting Antibiotic-Resistant Bacteria
AAP	American Association of Pediatrics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
CHARMS	CHecklist for Critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MIS-C	Multisystem inflammatory syndrome in children
REDCap	Research Electronic Data Capture
PROBAST	Prediction model risk of bias assessment tool
AUC/AUROC/c-statistic/c-index	Area under the receiver operating characteristic
EPV	Events per variable
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Guidelines
GEE	Generalized estimated-equations
NPV	Negative predictive value
PPV	Positive predictive value
RCT	Randomized clinical trial

Yrs	Years
LRI	Lower respiratory infection
URI	Upper respiratory infection
U.S.	United States
NAAT	Nucleic acid amplification tests
VUMC	Vanderbilt University Medical Center
PCA	Principal components analysis
PCs	Principal components
ORs	Odds ratios
CI	Confidence intervals
ICD-10	International Classification of Diseases, Tenth Revision
DAGs	Directed acyclic graphs
aORs	Adjusted odds ratios
COVID-19	Coronavirus 2019
ROC	Receiver operating characteristic

I. SPECIFIC AIMS

Acute respiratory infections (ARIs) are typically viral in origin and are the most common reason for unwarranted antibiotic use in children.^{1,2} Antibiotic exposure for a viral infection—a self-limiting illness—poses risks for the development of antibiotic resistance, unnecessary costs, and avoidable adverse drug events.² In the United States, pediatric ARIs account for more than 70% of healthcare visits resulting in an antibiotic each year, with the outpatient setting (i.e., emergency departments and outpatient clinics) attributing toward the most unwarranted antibiotic prescriptions.³ Tennessee ranks the sixth highest antibiotic prescribing state the nation.^{4,5} In response, national organizations have prioritized nationwide antibiotic stewardship across healthcare settings. Despite national actions, solutions to minimizing unwarranted antibiotics in the youth of America is multifaceted. The complexities include:

- ARI viral and bacterial pathogens have overlapping clinical presentations
- Rapid molecular diagnostic testing is not available across all healthcare settings
- Rapid molecular diagnostic testing is costly
- Diagnostic test results take time to process
- Testing guidelines for clinical management differ by viral pathogen and are not routinely performed

Diagnostic certainty may be improved by applying prediction modeling intended to discriminate viral ARIs.⁶ Clinical prediction models exist but have primarily focused on pneumonia (condition cause by bacterial ARIs) and two have been viral-specific (i.e., respiratory syncytial virus and influenza). These models have had good discriminative ability, yet their use in a clinical setting has been narrow.⁶ Limitations of these models include: 1) small sample sizes; 2) limited to one healthcare setting; 3) restricted to one respiratory season; 4) developed outside of the United States; 5) defined outcome using older clinical recommendations (i.e., chest x-ray findings); and 6) pneumonia models leave clinicians questioning whether the pathogen causing illness is of viral or bacterial etiology. Updated and

reliable tools are needed to aid clinicians in settings where diagnostic testing to distinguish respiratory viruses may not be feasible or rapidly available.

Understanding the clinical mechanisms influencing provider-ordered viral diagnostic testing across settings may identify gaps and barriers to address before introducing new diagnostic tools/tests. After understanding the nuances of provider-ordered viral testing, we can develop a clinical prediction model specific to the acuity of care and future research can focus on optimally integrating the model into the clinical practice. Using data collected from the New Vaccine Surveillance Network; a prospective, active acute respiratory virus surveillance platform funded by the Centers for Disease Control and Prevention (CDC).^{7,8} Children (≥ 30 days to 17 years) who sought medical attention for fever and/or respiratory symptoms from an ED ($n=2,616$) or hospitalized ($n=1,491$) at the Monroe Carell Jr. Children's Hospital at Vanderbilt between November 2017 to February 2020 are included in the study population to achieve the following aims:

Specific Aim 1. Conduct a systematic review to evaluate existing models predicting respiratory viral infections in children. This aim will serve as a platform for informing the candidate predictors, interaction terms, and case definitions of subsequent aims.

Specific Aim 2. Evaluate patterns of patient characteristics of provider-ordered viral diagnostic testing for acute respiratory infections and assess the association of viral diagnostic testing and antibiotic administration/prescribing in children seen in an emergency department or admitted to an academic hospital.

Specific Aim 2A. Understand the clinical characteristics of provider-ordered viral diagnostic testing for acute respiratory viruses in children by healthcare setting.

Specific Aim 2B. Assess the association of a provider-ordered, positive viral diagnostic test for acute respiratory infections and antibiotic administration/prescribing practices by healthcare setting. We hypothesize children with a positive viral diagnostic test will be

less likely to be administered/prescribed an antibiotic during their visit than children who were viral negative and/or not tested for respiratory viruses during their visit.

Specific Aim 3. Develop and calibrate a diagnostic prediction model(s) for discriminating viral acute respiratory infections from probable bacterial infections in children seen in an outpatient clinic, emergency department, or admitted at an academic hospital.

The Presidential Advisory Council on Combatting Antibiotic-Resistant Bacteria, the Food and Drug Administration, CDC, and Health and Human Services have made antibiotic stewardship interventions, understanding the barriers in antibiotic prescribing, and development of rapid diagnostic tests a top research priority.⁹ Using a large prospective, active viral surveillance study across four respiratory season across three distinct healthcare settings, we will be able to sufficiently evaluate the clinical characteristics of children who receive diagnostic testing and develop, calibrate, and validate a clinical prediction model to optimize the ability to discriminate viral ARIs with precision.

II. BACKGROUND

Acute Respiratory Infections

Acute respiratory infections (ARIs), such as pneumonia and bronchiolitis, are the leading cause of morbidity and mortality in children under five years outside the neonatal period.¹⁰ Characteristically, ARIs are caused by viral pathogens—human rhinovirus, influenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, and parainfluenza—but can also be caused by bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.¹⁰ Infections can be attributed to a single pathogen (virus or bacteria) or multiple pathogens [co-viral or viral and bacterial (co-detection)]; and range from asymptomatic shedding to severe illness^{11,12} with the majority of ARIs occurring in young and previously healthy children.¹³ Viral and bacterial co-detection causing ARI with co-detection up to 20%. Viral respiratory pathogens occur year-round but have epidemic peaks that predominate during the winter months in temperate regions¹⁴, with RSV, influenza, and human rhinovirus being the most common etiologies of illness.^{11,15-17}

In the United States, there are 12 to 32 million respiratory infections among infants (children <1 year) and approximately 200 million for older children¹⁸. As a result, millions of healthcare visits are sought for ARIs.¹⁴ Among children under five years of age with RSV, approximately 57,527 (3%) are hospitalized, 517,747 (25%) are provided care in the emergency department (ED), and 1,534,064 (73%) are treated in an outpatient clinic.¹⁹ Similarly, influenza hospitalization rates are attributed to 45 per 10,000 infants 0 to 5 months, 9 per 10,000 infants 6 to 23 months, and 3 per 10,000 children 24 to 59 months of annual hospitalization rates.²⁰ However, RSV and influenza are not the only viruses causing ARI-associated healthcare visits. In a study of children hospitalized or seen in an outpatient facility with bronchiolitis, 79% had RSV, 39% had rhinovirus, 10% had influenza, 2% had coronavirus, and 1% had parainfluenza, with some patients having co-viral infections.^{21,22} In another viral surveillance study of infants (<1 year) across three distinct healthcare settings, 42% (124/295) had rhinovirus/enterovirus, 34% (101/295) had RSV, 15% (44/295) had influenza, and 9% (31/295) had another respiratory virus.²³ Although we have general estimates from surveillance studies from select

states in the US, the burden, distribution, and clinical presentation of viral pathogens across clinical settings remain largely underreported.²³ This may be posited to the lack of systematic clinical diagnostic testing²³ and/or because ARI viruses are not reported/tracked by local public health for surveillance purposes, with the exception of influenza-associated pediatric deaths.²⁴

The Ripple-Effect of Decades of Diagnostic Uncertainty

Rapid detection of the causative ARI pathogen provides direct patient benefits. Although this task appears simple, clinical symptoms of viral ARIs are non-specific and resemble bacterial respiratory infections.²⁵ Given clinical symptoms are hard to differentiate the pathogen inflicting illness, clinicians are faced with deciphering whether symptoms are consistent with a serious bacterial infection that would benefit from antibiotic therapy. Research has shown diagnostic uncertainty has led to an increase in antibiotic administration and prescriptions.

In the United States, children younger than two are prescribed antibiotics at a higher rate than older children (1,287 prescriptions/1,000 children aged ≤ 2 years versus 1,018 and 691 prescriptions per 1,000 children aged 3-9 or 10-19, respectively)⁴, specifically, the South census region has the highest prescribing rate (1,605/1,000 children) than any other region in the nation.^{4,5} Among Southern states, Tennessee ranks as the sixth highest outpatient prescribing state.^{4,5} Exposure to antibiotics for a viral infection poses risks for the development of antibiotic resistant infections, contributes to unnecessary costs, and avoidable medication-related adverse events.^{2,26-28}

Globally, antimicrobial resistance results in 700,000 deaths per year across all ages, with approximately 200,000 among children; and nearly 50,000 occurring in the United States and Europe.^{29,30} Proportion of pediatric antibiotic resistant infections varies by country and region, ranging from 20% of cases in the U.S. to 90% of newborn hospitalizations in the Middle East.²⁹

Due to these alarming rates, national organizations [i.e., Centers for Disease Control and Prevention, the Department of Human and Health Services, and the Presidential Advisory Council on Combatting Antibiotic-Resistant Bacteria(PACCARB)], launched a National Action Plan for Combating Antibiotic-Resistant Bacteria which aimed to reduce inappropriate antibiotic use by 20% in hospitals and 50% in outpatient setting by 2020⁹ and to maintain and focus on outpatient settings by 2025.³¹ In 2014, actions to meet these goals in hospitals included the development and implementation of antibiotic stewardship programs; and by 2016, these efforts were expanded to include outpatient settings (ED and outpatient).⁹ To benchmark antibiotic stewardship programs across healthcare settings, CDC released the *Core Elements of Antibiotic Stewardship*,³² which provides domains for optimizing antibiotic prescribing (e.g., tracking and monitoring of antibiotic prescribing, antibiotic formulary restrictions, patient education, etc.). Despite improvements in antibiotic stewardship, diagnostic challenges discriminating between viral and bacterial acute respiratory infections persist, with more than 70% of pediatric respiratory infections receiving an antibiotic each year,³ of which 30% were for conditions of viral origin, for which antibiotics provide no clinical benefit.³³

The solutions to improving diagnostic uncertainty are multifaceted and have been recognized by the PACCARB 2025 national goals of developing new diagnostic testing to provide real-time support for antibiotic prescribing.³¹ However, before new testing can be developed and integrated into our healthcare systems, we need research to directly focus on the current use of clinical diagnostic tools and provider testing guidelines across healthcare settings. In turn this research can supplement the assimilation of newer diagnostic testing and help determine potential barriers and opportunities for interventions.

Current Diagnostic Testing & Clinical Guidelines

The current landscape for distinguishing viral respiratory pathogens includes point-of-care and novel molecular diagnostic testing.^{25,34} Point-of-care tests are widely available across healthcare settings but are limited to detecting influenza and RSV and have limitations in sensitivity.³⁵⁻³⁷ Conversely, molecular

diagnostic testing for respiratory viruses enables expedited and accurate microbiologic diagnoses,^{35,38} but are not optimally integrated into all clinical care settings nor are recommended for routine use by clinical management guidelines.^{22,39,40} Indications for the limited use of molecular testing varies by healthcare setting and primarily impacts outpatient clinics and EDs. In outpatient clinics, test results are needed within minutes to influence clinical decisions and management. Current automated molecular technologies are too expensive and do not meet the time constraints of outpatient clinicians.³⁵ Thus, forcing outpatient settings to rely on point-of-care testing and/or clinical presentation. Clinicians in the ED often manage sicker children than outpatient clinics and have access to more complex diagnostic testing.³⁵ But in the ED, empiric antibiotics and hospitalization are in question. Sometimes the decision to administer empiric antibiotics is for the concern of a serious bacterial infection and is given before molecular testing results are available.³⁵ Another added layer of complexity is the guidelines set by the American Association of Pediatrics (AAP), which recommends pediatricians to diagnose bronchiolitis (condition often caused by RSV) and assess for disease severity based on the child's history and physical examination without routinely using laboratory or radiography.²² For influenza, guidelines recommend clinicians not rely on rapid diagnostics—which is more widely available but lacks sensitivity—but use molecular diagnostics for patient care decisions.³⁹ Posited explanations for the lack of promoting molecular viral testing may be attributed to the lack of past studies demonstrating improvements in outcomes and/or cost.⁴⁰⁻⁴² The variability of study findings stems from the heterogeneity and quality of studies, such as small sample sizes and lack of multiple respiratory seasons.⁴⁰ Methods identifying bacterial pathogens are considerably more limited as they rely on traditional culture methods or novel molecular assays. These types of tests are typically available to inpatient settings but may be ordered from a physician in the ED prior to hospitalizing the patient. Of note, traditional culture is not routinely performed due to the invasive nature of specimen collection and molecular panels include limited number of bacterial pathogens.^{34,43,44}

Costs, time, and accessibility are barriers to precise diagnosis for clinicians providing care outside the inpatient setting (i.e., outpatient and EDs).²³ Thus, creating a black box atmosphere with diagnostic

uncertainty for ARIs,²³ leaving clinicians with only clinical features to make a judgement call on whether the pathogen is of viral or bacterial etiology. Further, this scenario leads to possible misclassifications and administration of an antibiotic that is not beneficial for the child's infection. This everyday problem may not seem critical, but in reality, this is a "Tragedy of the Commons".³³ As explained by Spellberg, this phenomenon applies to scenarios where an individual acts to significantly benefit themselves, and as a consequence accepts a tradeoff of a small amount of overall harm to society at large.^{33,45} When everyone in society undertakes the same actions—in this case antibiotic administration as a precaution or hedge—the collective harm to society becomes enormous (antibiotic resistance and adverse reactions).^{33,45}

Shifting the Paradigm to Clinical Diagnostic Models

Although the solution is complex, more diagnostic certainty can be attained by applying prediction modeling and clinical prediction rules intending to discriminate ARIs caused by only a virus.⁶ Multiple prediction models for childhood pneumonia have been developed; however, their use in clinical practice is limited.⁴⁶⁻⁵⁴ Current models have focused on condition outcomes (i.e., pneumonia), been limited to one respiratory season, included biomarkers that may be influenced by resources in varying settings, and present findings in a risk classification scale rather than probability.⁴⁶⁻⁵⁴ In addition, the current models on predicting childhood pneumonia have used radiography to discern their outcome. The use of radiography to determine the outcome is problematic because clinical guidelines do not indicate the use of radiography for children presenting to the ED or outpatient clinic with mild lower respiratory tract infection and without hypoxemia or a focal lung examination. Although these prediction models add insights into the factors that have high predictability for pneumonia, they still leave clinicians with the same amount of diagnostic uncertainty about the causative pathogen of the condition at hand and do not provide clinicians outside of the inpatient setting additional aid.

Apart from childhood pneumonia, two prediction models have been developed to predict the risk of 1) RSV²⁵ and 2) influenza.⁴⁶ The RSV model was developed in Germany among 1545 hospitalized

children using age, sex, weight, illness duration, and symptoms as candidate predictors.²⁵ Multiple imputation was performed for missing data and final predictors were selected using the Akaike information criterion.²⁵ The influenza model was developed in Canada on 1241 children <18 years of age from a prospective influenza vaccine study.⁴⁶ Candidate predictors included sex, history of influenza vaccination, age (dichotomized: 0-5 vs. 6-17 years), and clinical symptoms.⁴⁶ A complete case analysis was performed and forward stepwise was used to select final predictors.⁴⁶ Neither of the viral-specific prediction models used methods for shrinkage or optimism-corrected bias, and authors used a split-sample to develop and internally validate their models.^{25,46} Shrinkage and optimism-corrected bias penalizes the model by adjusting for the regression coefficients,⁵⁵ in turn, discounting the variation for regression to the mean⁵⁶ and allows for optimal model performance in subsequent validations and applications.⁵⁵ Nevertheless, these models provide clarity that diagnostic prediction models help shift the paradigm of diagnosing viral infections in children.

Given the past and current circumstances of ARIs, the need for diagnostics with more robust methods for distinguishing between causative pathogens have never been greater.³⁵ Early, accurate detection can improve the well-being of a child and initiate antivirals or antibiotic therapy when indicated. However, currently there is a gap in our technical abilities to solely rely on diagnostic testing to provide answers. As stated by Sir William Osler, MD, *"Medicine is a science of uncertainty and art of probability"*.³³ Goals to develop a prediction model that allows physicians to assess and manage diagnostic uncertainty without passing that burden to the patient is timely and important. Building a prediction model across healthcare settings in a prospective cohort of more than 4,000 children may help inform future antibiotic stewardship guidelines and have a direct impact to patients and antibiotic administration practices.

III. Diagnostic Prediction Models Distinguishing Pediatric Viral Acute Respiratory Infections: A Systematic Review

INTRODUCTION

Globally, acute respiratory infections (ARIs) such as pneumonia and bronchiolitis are the leading cause of morbidity and mortality in children under five years outside the neonatal period.¹⁶ Prior to the introduction of vaccines, bacterial pathogens (i.e., *Streptococcus Pneumoniae* and *Haemophilus influenzae*) were the leading etiologies for ARIs.⁵⁷ However, respiratory viruses have been shown to predominately cause ARIs^{19-21,57} with an estimated global burden of 156 million new infections per year.¹⁶ Currently, viral ARIs are often identified with point-of-care antigen tests or novel molecular diagnostic assays, but, these tests can be costly and not readily accessible to all healthcare settings worldwide.³⁵⁻³⁷ This challenge requires clinicians to infer ARI etiologies based on clinical features, which is prone to diagnostic uncertainty as viral and bacterial ARI symptoms overlap.^{58,59} In an attempt to increase diagnostic certainty, researchers have developed several prediction models to facilitate diagnosis of viral ARIs.

Previous systematic reviews have assessed clinical prediction models for diagnosing childhood pneumonia using radiography⁶⁰ and diagnostic models of influenza-specific outcomes.⁶¹ However, to date, no systematic reviews have formally synthesized diagnostic models distinguishing viral ARIs from bacterial ARIs in children. In this systematic review, we identified and evaluated published diagnostic prediction models developed to predict viral ARIs [e.g., virus versus no virus; or viral-specific (i.e., influenza, RSV, adenovirus, parainfluenza, human metapneumovirus, endemic human coronaviruses, rhinovirus, enterovirus.)] among children.

METHODS

Article screening, selection, data extraction, and reporting were conducted in adherence

to guidelines set by Cochrane Prognosis Methods Group and Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA, **Appendix File A1**].^{62,63} Our systematic review is registered on the international prospective register of systematic reviews⁶⁴ (PROSPERO: CRD42022308917; **Appendix File A2**).

Study Eligibility Criteria

Our review question was defined using the CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) modified version of the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Setting) system (**Appendix Table A1**).⁶⁵ Our goal was to identify previously published diagnostic models developed to predict viral ARIs in children. Studies included in this systematic review had the following criteria: 1) reported development of diagnostic models, with or without external validation; 2) study population included children (<18 years) seeking medical attention at either an ambulatory (i.e., ED or outpatient clinic) and/or inpatient setting; 3) were written in English; 4) were published by February 3, 2022; and 5) examined any of the following viral outcomes (either in aggregate or viral-specific): adenovirus, non-pandemic coronavirus strains (229E, HKU1, NL63, OC43), human metapneumovirus, influenza, parainfluenza (1-4), rhinovirus, enterovirus, and/or RSV.

Study exclusion criteria were: 1) study population excluding children (i.e., ≥18 years) or restricted to children with immunocompromised conditions (i.e., cystic fibrosis, Down's syndrome, cancer, etc.); 2) model outcome specific to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019, or multisystem inflammatory syndrome in children (MIS-C, sequelae of severe acute respiratory syndrome coronavirus 2).

Search Strategy and Article Selection

We searched PubMed and Embase electronic databases on February 3, 2022, using a strategy developed with assistance from a reference librarian (**Appendix Table A2**). Articles selected from the

search strategy were imported into Covidence, a web-based platform streamlining systematic reviews, where article deduplication, abstract screening, and full text review were conducted.⁶⁶ Manual abstract screening and full text review were conducted by two independent reviewers (DAR and LSP); and discordance was discussed and resolved between reviewers. Excluded studies were reported according to PRISMA guidelines.⁶³

Data Extraction and Data Analysis

Data from final selected studies were recorded in a standardized collection form designed in REDCapTM (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA).⁶⁷

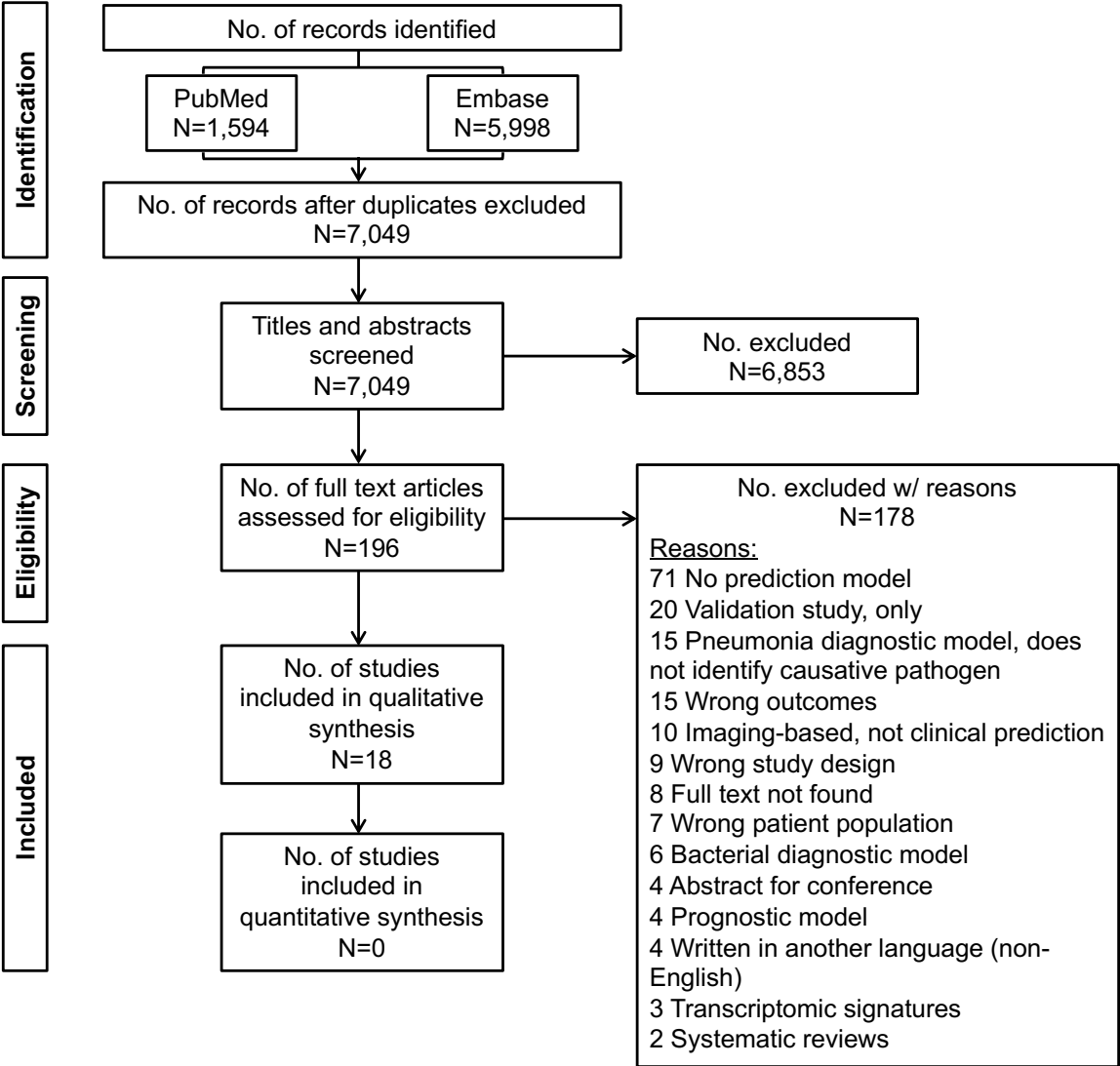
Studies were critically appraised and evaluated for risk of bias and applicability using the CHARMS checklist⁶⁵ (**Appendix File A3**) and the prediction model risk of bias assessment tool (PROBAST),^{68,69} respectively. Data extraction included the data source, sample size, missing data methods, outcomes, predictors, model development techniques, model performance measures (i.e., calibration and discrimination), model evaluation (internal and external validation), and model results [final model/presentation (e.g., nomogram, beta coefficients, odds ratios, etc.)].

Studies that presented multiple models with different predictors (e.g., symptom combinations, biomarkers), the model with the best sensitivity and specificity cut-off was analyzed. Multiple models were included from studies using different model development approaches (e.g., logistic regression and machine learning) or developed multiple models for specific respiratory viruses or age groups. A meta-analysis was not conducted due to the heterogeneity of different predictors (i.e., symptoms, biomarkers, illness diaries, etc.) examined, heterogeneity of outcomes, varying methods of respiratory virus detection (i.e., immunofluorescent assay, culture, polymerase chain reaction), lack of internal validation, and lack of reporting calibration and discrimination measures.

RESULTS

Our search in PubMed and Embase identified 7,049 unique studies, of which 6,853 studies were excluded after title and abstract screening. Full text review was conducted on 196 articles and 18 studies were included in our qualitative synthesis (**Figure 3.1**). Most studies were prospective cohorts

Figure 3.1. PRISMA Flow Chart of Final Study Inclusion Criteria. PRISMA, Preferred Reporting Items for Systematic Reviews



(44%), with the remaining studies using data from retrospective cohorts (22%) and cross-sectional designs (22%, **Tables 3.1-3.3, Appendix Table A2**). Forty percent of studies took place in an inpatient setting; and 4 studies developed more than one model. One-half (2/4) of studies that developed multiple diagnostic models used the same methodology for development with the exception of 2 studies (e.g., logistic regression and machine learning).^{46,70} Of the two remaining studies, one developed separate models based on age (i.e., <2 years and ≥2 years)⁷¹ and the other developed three models,⁷² which consisted of an aggregated virus model, an adenovirus-specific model, and an RSV-specific model.

Diagnostic Prediction Model Characteristics

Most diagnostic prediction models (61%) were developed with the intent of predicting a specific respiratory virus, with influenza as the most common viral target (**Table 3.4**). Viral outcomes were primarily determined by single- or multi-plex polymerase chain reaction assays (10/18; 56%). Supplemental Table 4 includes each individual study's outcome and measurement (e.g., RSV detected by multi-plex polymerase chain reaction assays).

Clinical symptoms and demographic characteristics were the most frequent predictors considered in model development, with cough, age, sore throat, fever, sex, myalgia, rhinorrhea, and wheezing as the most common candidate predictors (**Figure 3.2**). Common predictors retained in final models included: cough, age, fever, and rhinorrhea.

Logistic regression was the predominate method used to develop diagnostic models (76%), with the remaining 4 models using machine learning approaches (n=2) and both logistic regression and machine learning (n=2, **Table 3.4**). Nearly three-quarters of studies used either forward or backwards selection to retain final predictors in models, with most using a p-value criterion of <0.05 (6/10; 60%).

Table 3.1. Study Characteristics for Influenza-Specific Clinical Diagnostic Prediction Model Studies (n=7)

First Author, Year	Study Location(s)	Sample Size/ Study Duration	Study Population Age(s)	Data Source	Validation	Outcome/ no. with outcome/ sample size	Predictors in Final Model(s)	Model Performance	Risk of bias- Population; Predictor; Outcome; Analysis
^a Monto A.S., <i>et al.</i> , 2000 ⁷³	North America; Europe; Southern Hemisphere	N=3,744 5 months over 4 yrs	Patients from 8 clinical trials with influenza-like illness ≥18 yrs (1 site); ≥12 yrs (3 sites); ≥13 yrs (4 sites)	Retrospective cohort	None	<u>Influenza, all models:</u> 2470/3744= 66.0%	Fever; Cough; Myalgia	Sensitivity: 61.5% Specificity: 68.5%	Low; Low; High; High
Friedman M.J., <i>et al.</i> , 2004 ⁷⁴	United States	N=118 3 months	All patients (<18 yrs) with febrile illness at an emergency department of a suburban pediatric center	Prospective cohort	None	<u>Influenza:</u> 58/118= 49.2%	Cough; Headache; Pharyngitis	Sensitivity: 80% (95% CI: 69%-91%); Specificity: 78% (95% CI: 67%-89%); HL test: <i>P</i> =0.25	Low; Low; Low; High
Keijzers G.B., <i>et al.</i> , 2011 ⁷⁵	Australia	N=117 3 months	Children (<18 yrs) admitted from the emergency department with acute respiratory illness	Cross-sectional	None	<u>Influenza:</u> 39/117= 33.3%	Cough; Headache; History of fever; Wheeze; Temperature at presentation; Rhinorrhea	Sensitivity: 93% Specificity: 60% PPV: 59% NPV: 94%	Low; Low; Low; High
Lin C.Y., <i>et al.</i> , 2012 ⁷⁶	Taiwan	N=506 1 month	Children (<18 yrs) who received a rapid	Prospective cohort	Internal (split-sample)	<u>Influenza:</u> 187/506= 37.0%	Family members w/ influenza; Fever; Age; Classmates	<u>Derivative set, score ≥5:</u> Sensitivity: 69.5% Specificity: 63.6%	Low; Low; Low; High

			influenza test at the emergency department				w/ influenza A; Sore throat; Cough; Headache; Myalgia; Lethargy	<u>Validation set, score ≥ 5:</u> Sensitivity: 68.9% Specificity: 57.8% PPV: 52.0% NPV: 73.8%	
Vuichard-Gysin D., <i>et al.</i> , 2019 ⁴⁶	Canada	N=1241 2.8 yrs	Children (<18 yrs) enrolled in a RCT from 3 communities and later had signs and symptoms of ARI	Retrospective cohort	Internal (split-sample)	<u>Influenza:</u> 152/1241= 12.2%	<u>GEE Model:</u> Age; Chills; Cough; Fever <u>Classification Tree Model:</u> Chills; Cough; Runny nose; Sex	<u>GEE Model:</u> <u>Derivative Set:</u> AUC: 0.76 (95% CI: 0.72, 0.80); <u>Validation Set:</u> AUC: 0.70 (95% CI: 0.63, 0.77); <u>Classification Tree Model:</u> <u>Derivative Set:</u> AUC: 0.77 (95% CI: 0.73, 0.81); <u>Validation Set:</u> AUC: 0.74 (95% CI: 0.67, 0.80)	Low; Low; Low; High
Evers P., <i>et al.</i> , 2020 ⁷¹	United States	N=818 0.5 yrs	Children (<18 yrs) seen for influenza like illness at an emergency department or urgent care clinic affiliated with a tertiary pediatric hospital	Retrospective cohort	None	<u>Influenza, all models:</u> 284/818= 34.7% <u>Model 1, <2 yrs:</u> 75/359= 20.9% <u>Model 2, ≥ 2 yrs:</u> 211/459= 46.0%	<u>Model 1, <2 yrs:</u> Influenza contact; Influenza immunized; Influenza incidence; Cough <u>Model 2, ≥ 2 yrs:</u> Influenza incidence; Influenza immunized; Myalgia; Diarrhea	<u>Model 1 (<2 yrs):</u> AUC: 0.64 Sensitivity: 84% Specificity: 46% PPV: 29% NPV: 92% <u>Model 2 (≥ 2 yrs):</u> AUC: 0.59 *No other measures reported for this model.	Low; Low; Low; High

Monamele C.G., <i>et al.</i> , 2020 ⁷⁰	Cameroon	N=11,816 10 yrs	Patients presenting to 16 sites with influenza like illness or severe acute respiratory illness and had a respiratory specimen collected and sent for influenza diagnosis	Surveillance study	Internal (split-sample)	<u>Influenza, all models:</u> 2838/11816= 24.0%	<u>Logistic regression model:</u> Cough; Rhinorrhea Asthenia; Headache; Sore throat; Vomiting; Arthralgia; Noisy breath; Myalgia; Shortness of Breath; Diarrhea; Conjunctivitis Ear pain; Skin rash <u>Random forest model:</u> Myalgia; Arthralgia; Headache; Rhinorrhea; Sore throat; Noisy breath; Asthenia; Cough; Shortness of breath; Diarrhea; Ear pain; Conjunctivitis Vomiting; Skin rash	<u>Logistic regression model:</u> <u>Derivation set:</u> Not reported <u>Validation set:</u> AUC: 0.67 Sensitivity: 75.6% Specificity: 46.6% <u>Random forest model:</u> OOB: 25.9%	Low; Low; Low; High
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Footnote:

^aMonto *et al* developed multiple models with 3-symptom combinations, but we only present the model with the best sensitivity and specificity cut-off in this table.

Abbreviations: ARI, acute respiratory infection; AUC, area under the receiver operating curve; GEE, generalized estimated-equations; NPV, negative predictive value; OOB, out-of-bag predictions; PPV, positive predictive value; RCT, randomized clinical trial; RSV, respiratory syncytial virus; Yrs, years

Table 3.2. Study Characteristics for Aggregated Viral versus No Virus or Bacterial Infection Clinical Diagnostic Prediction Model Studies (n=7)

First Author, Year	Study Location(s)	Sample Size/ Study Duration	Study Population Age(s)	Data Source	Validation	Outcome/ no. with outcome/ sample size	Predictors in Final Model(s)	Model Performance	Risk of bias- Population; Predictor; Outcome; Analysis
Moreno L., <i>et al.</i> , 2006 ⁷⁷	Argentina	N=175 1.5 yrs	Children (1 mth-5 yrs) hospitalized for community acquired pneumonia at two tertiary children's hospitals	Prospective cohort	Internal (split-sample)	<u>Bacterial Pneumonia</u> : 48/175= 27.4%	Axillary temperature; Age; Absolute neutrophil count; Bands; White blood cells	<u>Derivation set</u> : AUC: 0.996 (95% CI: 0.99, 1.00); Sensitivity: 100% (95% CI: 97.3-100); Specificity: 93.7% (95% CI: 88.7-96.7) <u>Validation set</u> : AUC: 0.98 (95% CI: 0.97, 1.00); Sensitivity: 100% (95% CI: 84.6-100); Specificity: 93.9% (95% CI: 87.8-97.5)	Low; Low; Low; High
Taylor J.A., <i>et al.</i> , 2010 ⁷⁸	United States	N=108 5 months	Children (2-11 yrs) enrolled in a clinical trial with symptoms of URI seeking healthcare from a pediatric outpatient clinic	Prospective cohort	None	<u>Viral upper respiratory infection</u> : 62/108= 57.4%	Runny nose at day 1; Runny nose at day 4; Cough at day 4; Fever at day 3	Sensitivity: 81.4% (95% CI: 69.1-90.3); Specificity: 94.3% (95% CI: 80.8-99.3); Accuracy: 73.3% (95% CI: 63.5-81.6)	Low; Low; Low; High
Kool M., <i>et al.</i> , 2015 ⁷²	Netherlands	N=257 1 yr	Children (>3 mths-6 yrs) presenting to a general practitioner (outpatient) during out of	Cross-sectional	None	<u>Any respiratory virus</u> , Model 1: 136/257= 53% <u>Adenovirus</u> .	<u>Any respiratory virus</u> , Model 1: Temperature; Cough	<u>Any respiratory virus</u> , Model 1: AUC: 0.64 (95% CI: 0.58-0.71) <u>Adenovirus</u> .	Low; Low; Low; High

			service hours			<u>Model 2:</u> 28/257= 10.9%	<u>Adenovirus.</u> <u>Model 2:</u> Temperature; Rhinitis	<u>Model 2:</u> AUC: 0.71 (95% CI: 0.62-0.80)	
Mistik S., <i>et al.</i> , 2015 ⁷⁹	Turkey	N=624 1 yr	Patients (≥3 yrs) presenting to a family physician (outpatient) with a sore throat	Prospective cohort	Internal (split-sample)	<u>Viral Sore Throat:</u> 277/624= 44.4%	Headache; Stuffy nose; Sneezing; Temperature; Tonsillar exudate/swelling	Validation set/score: Sensitivity: 60.2% Specificity: 72.5% PPV: 62.5% NPV: 70.5%	Low; High; Low; High
Zhu G., <i>et al.</i> , 2015 ⁸⁰	China	N=96 1.6 yrs	Children (4-7 yrs) hospitalized at a pediatric center with suspected LRI	Cross-sectional	45/96= 46.9%	<u>Bacterial Lower Respiratory Tract Infection:</u> 45/3=15.0%	C-reactive protein; CD35; CD64	AUC: 0.97 (95% CI: 0.93, 1.00)	Low; Low; Low; High
Naydenova E., <i>et al.</i> , 2016 ⁸¹	Gambia	N=84 3 yrs	Children (2 mths-5 yrs) hospitalized with LRI	Cross-sectional	None	<u>Bacterial Pneumonia:</u> 22/84= 26.2%	Respiratory rate; Heart rate; Oxygen saturation; and lipocalin 2	AUC: 0.92% (95% CI: 0.90-0.93) Sensitivity: 81.8% (95% CI: 81.8-81.8); Specificity: 90.6% (95% CI: 89.1-92.2); MCC: 70.5% (95% CI 68.1-73.0)	Unclear; Low; High; High
Tagarro A., <i>et al.</i> , 2021 ⁸²	N=262 Spain	N=262 3yrs	Children (1 mth-16 yrs) hospitalized at one of 17 hospitals and diagnosed with community acquired pneumonia via radiography	Prospective cohort	Internal (split-sample)	<u>Bacterial pneumonia:</u> 124/262= 47.3%	Chest x-ray consolidation; Age; lack of worker breathing; Wheezing; Temperature; PCV; Leukocytosis; Neutrophilia; Hemoglobin; C-reactive protein	<u>Derivative set:</u> AUC: 0.81 Sensitivity: 97.3%, Specificity: 48.8%, PPV: 63.2%, NPV: 95.2% <u>Validation set:</u> AUC: 0.81 Sensitivity:	Low; Low; Low; High

								97.3%, Specificity: 48.8%, PPV: 63.2%, NPV: 95.2%	
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Abbreviations: AUC, area under the receiver operating curve; LRI, lower respiratory infection, negative; NPV, negative predictive value; PPV, positive predictive value; URI, upper respiratory infection; Yrs, years

Table 3.3. Study Characteristics for Respiratory Syncytial Virus (RSV)-Specific Clinical Diagnostic Prediction Model Studies (n=5)

First Author, Year	Study Location(s)	Sample Size/ Study Duration	Study Population Age(s)	Data Source	Validation	Outcome/ no. with outcome/ sample size	Predictors in Final Model(s)	Model Performance	Risk of bias- Population; Predictor; Outcome; Analysis
Weigl J.A., et al., 2003 ⁸³	Germany	N=700 4 yrs	Children (0-2 yrs) hospitalized with LRI	Nested case-control	None	RSV: 217/700= 31%	Age; Disease Diagnosis; Site/center; Intercostal retractions; Underlying condition; C-reactive protein; Illness duration prior to enrollment; Prematurity	Accuracy: 73.0%	Low; Low; Low; High
Durani Y., et al., 2008 ⁸⁴	United States	N=197 1 month	Children (≤ 3 yrs) with clinical suspicion of RSV in the emergency department at a suburban tertiary care pediatric hospital	Prospective cohort	None	RSV: 126/197= 64.0%	Cough; Wheezing; Retractions	AUC: 0.66 (95% CI: 0.56-0.74); Sensitivity: 80% (95%CI: 71-87%); Specificity: 68% (95%CI: 54-79%); PPV: 82% (95%CI: 74-89%); NPV: 66% (95%CI: 52-77%)	Low; Low; Low; High
Kool M., et al., 2015 ⁷²	Netherlands	N=257 1 yr	Children (> 3 mths-6 yrs) presenting to a general practitioner (outpatient) during out of service hours	Cross-sectional	None	RSV, Model 3: 36/257= 14.0%	RSV: Model 3: Daycare; Temperature; Cough; Rhinitis	RSV, Model 3: AUC: 0.73 (95% CI: 0.63-0.83)	Low; Low; Low; High

Manuel B., et al., 2019 ²⁵	Germany	N=1085 Nov-Dec over 4 yrs	Children (<18 yrs) hospitalized with ARI	Prospective cohort	Internal (split- sample)	RSV: 447/1085= 41.2%	Age; Cough; Rales; Lower respiratory tract infection; Duration of clinical symptoms; Admission date	<u>Derivation set:</u> AUC: 0.79 <u>Validation set:</u> AUC: 0.73	Low; Low; Low; High
Gebremed hin A.T., <i>et</i> <i>al.</i> , 2022 ⁸⁵	Australia	N=37,784 13 yrs	Children (<5 yrs) in a data registry hospitalized with testing records for RSV	Retrospective cohort	Internal (cross- validation)	RSV: 8,604/37,784 =22.8%	Acute bronchiolitis; bronchitis; pneumonia; acute lower respiratory infection; upper respiratory tract infection; age; time of year; residence type; asthma; other infections; whooping cough; Method of birth; Mother's age; Sex; Mother smoke status; severity score; number of siblings; Mother asthma;	AUC: 0.87 (95% CI: 0.86, 0.88); Sensitivity: 58.4% (95% CI: 57.3-59.6); Specifcity: 92.2% (95% CI: 91.8-92.5); PPV: 68.6% (95% CI: 67.5-69.7); NPV: 88.3% (95% CI 87.9-88.7)	Low; High; Low; High

							length of stay; mechanical ventilation; ICU admission; Birth season; Admission year		
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Abbreviations: ARI, acute respiratory infection; AUROC, area under the receiver operating curve; LRI, lower respiratory tract infection, negative; NPV, negative predictive value; PPV, positive predictive value; RSV, respiratory syncytial virus; Yrs, years

Table 3.4. Study Outcome and Diagnostic Prediction Model Development Methods (n=18)

Characteristics	No. of studies reporting characteristic	Categories	N(%) or median (IQR)
Outcome Type	18 (100)	Aggregate of multiple viruses Virus-specific ^a Influenza RSV ^a Adenovirus ^a Bacterial & Viral Both aggregate of multiple viruses and viral-specific ^a	2 (11) 11 (61) 7 (58) 5 (42) 1 (8) 4 (22) 1 (5.6)
Candidate Predictor Type(s)	18 (100)	Demographic Clinical Symptoms Vital Signs Clinical Biomarkers	10 (56) 15 (83) 6 (33) 8 (44)
Missing data	10 (56)	Complete case analysis Single imputation Multiple imputation Other	5 (50) 0 4 (40) 1 (10)
Analysis Method	17 (94)	Logistic regression Machine learning Multiple models w/ both logistic regression and machine learning	13 (76) 2 (12) 2 (12)
Method for considering predictors in multivariable models	17 (94)	All candidate predictors Unadjusted association Clinical relevance/ <i>a priori</i>	10 (59) 4 (24) 3 (18)
Selection of predictors during modeling ^b	17 (94)	Full model approach Forward/Backwards stepwise selection Statistical significance in MV model Recursive partitioning/Random Forest Backwards Bootstrap	1 (6) 12 (71) 1 (6) 3 (18) 1 (6)
P-value for predictor selection	8 (44)	<0.01 <0.05 0.20	1 (12) 6 (75) 1 (12)
P-value for retainment in model	10 (71)	<0.05 0.10 0.30 Not reported	6 (75) 1 (12) 1 (12) 2 (20)

Internal Validation	8 (44)	Internal (split-sample) Cross-validation	7 (88) 1 (12)
External Validation	0 (0)		--
Calibration	4 (22)	Calibration plot Hosmer-Lemeshow goodness of fit p-value	1 (25) 4 (100)
Discrimination Measures	10 (56)	C-index (AUROC)	10 (100)
Classification	15 (83)	Sensitivity Specificity Predictive values Likelihood ratios Accuracy Post-test Probability Matthew's Correlation Coefficient	14 (78) 14 (78) 12 (67) 3 (17) 2 (11) 2 (11) 1 (6)
Model presentation ^c	17 (94)	Risk score Model coefficients Odds ratios Classification	5 (28) 5 (28) 10 (56) 1 (6)

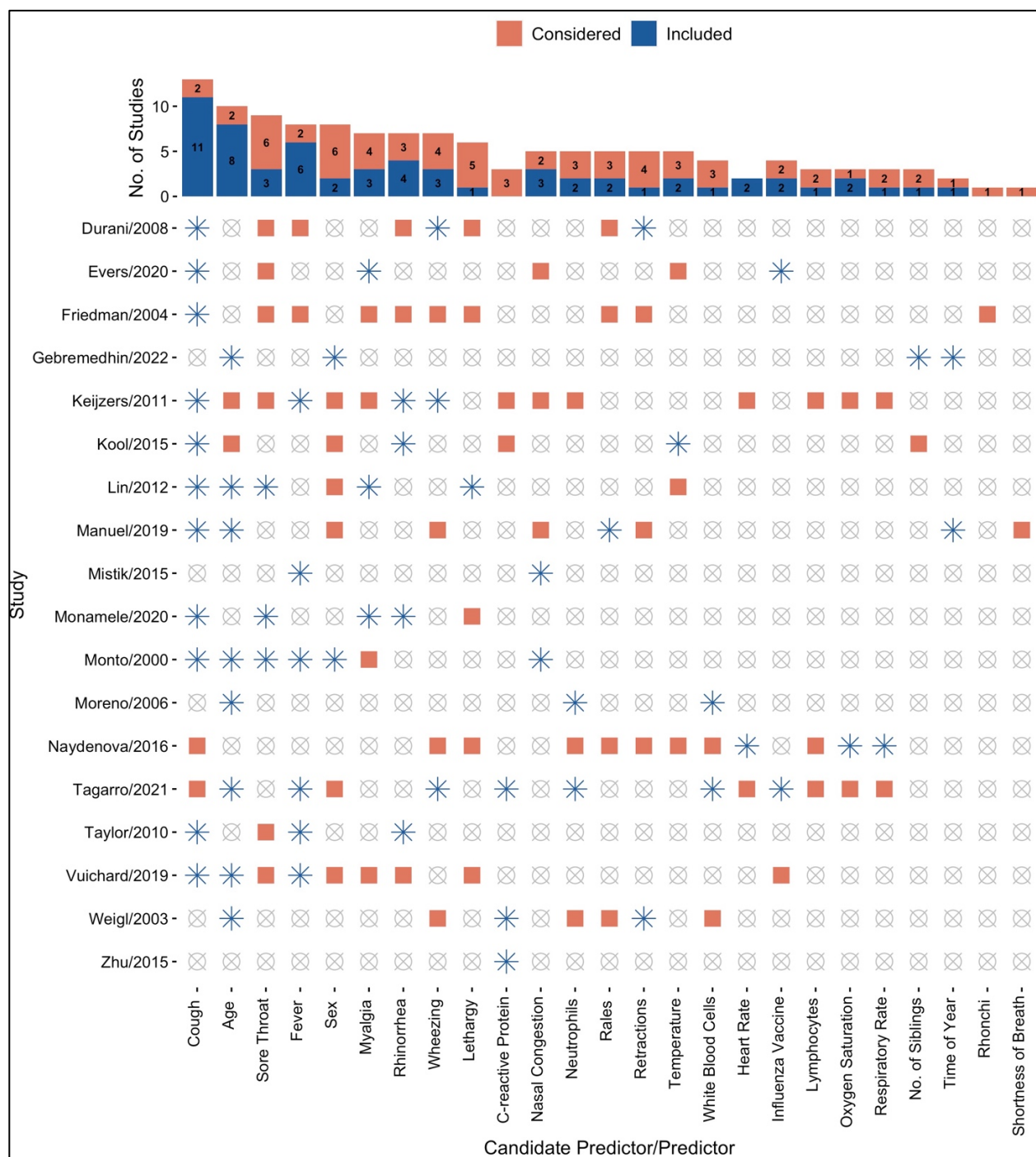
Footnote:

^adenotes the viral-specific models developed in one study that developed three total models

^bone study is counted twice as they performed both forwards/backwards selection and random forest for the development of two separate models

^cmodel presentations are included for the studies that developed multiple models

Figure 2. Common Predictors Considered and Included in the Development of Viral Diagnostic Models, by Study (n=18)



Overall, 8 (44%) models were internally validated, with 7 studies using split-sample and 1 (12%) using cross-validation; and no models were externally validated (**Table 3.4**). Ten studies reported discrimination measures (summary estimate used to determine the prediction model's ability to distinguish between patients having and not having the disease/outcome of interest⁶²) with the area under the receiver operating characteristic (AUROC or c-statistic). Instead, most studies reported classification measures (83%), such as sensitivity, specificity, and positive and negative predictive values. A total of 4 (22%) studies reported calibration measures (model's accuracy of predicting risk probabilities⁶²), with 100% assessing calibration using Hosmer-Lemeshow tests. One study also provided a calibration plot, which is considered best practice for prediction model studies.⁸⁶ Final models were predominantly reported with odds ratios (without intercepts) (n=10; 56%). Supplemental Table 5 includes each study's final model presentation.

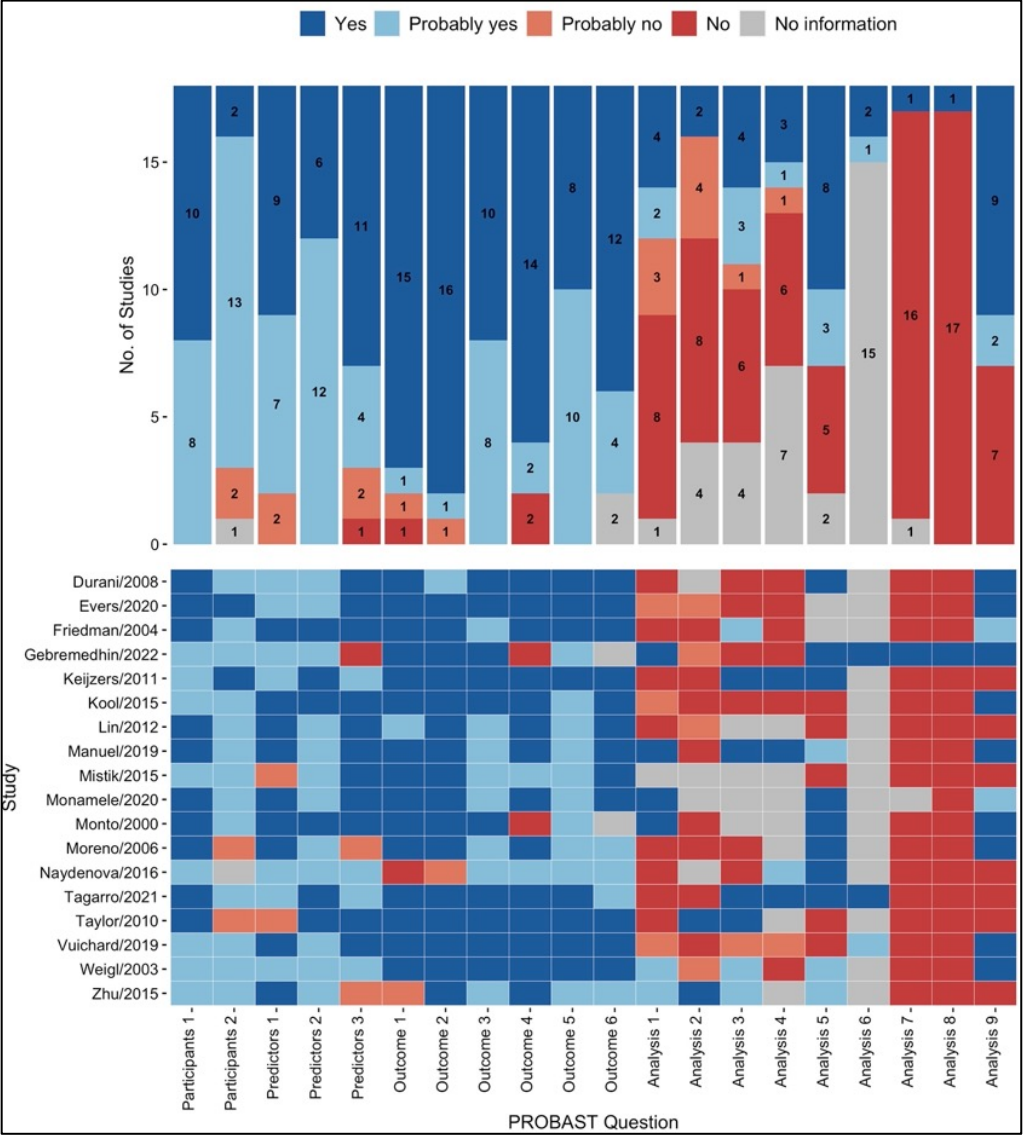
Risk of Bias

Risk of bias assessment for each PROBAST signal question by study is displayed in **Figure 3.3** and overall risk of bias and applicability is shown in **Figure 3.4**. Most studies had a low risk of bias in population, predictors, and outcome domains, but all studies had high risk of bias in the analysis domain (**Figure 3.3-3.4**).

Unclear risk of population bias was attributed to a lack of details provided in the inclusion and exclusion criteria.⁸⁷ Common sources of predictor bias included a lack of standardized collection and/or operational definitions for predictors⁷⁹ and the timing/availability of data that would inhibit the model diagnostic intent.⁸⁵ In the outcome domain, sources of bias were attributed to inconsistent⁷³ and non-standard⁸¹ measurement methods to discern the outcome.

Analytic bias was extensive across all studies. Overall, 10 studies (56%) reported missing data, of which 4 (40%) reported performing multiple imputation to handle missing data (**Figure 3.3, Table 3.4**).^{25,75,78,81} Continuous and categorical variables were primarily dichotomized, but were appropriately

Figure 3.3 Heatmap of Individual Signaling Questions from PROBAST Assessing Risk of Bias for Each Study (n=18)

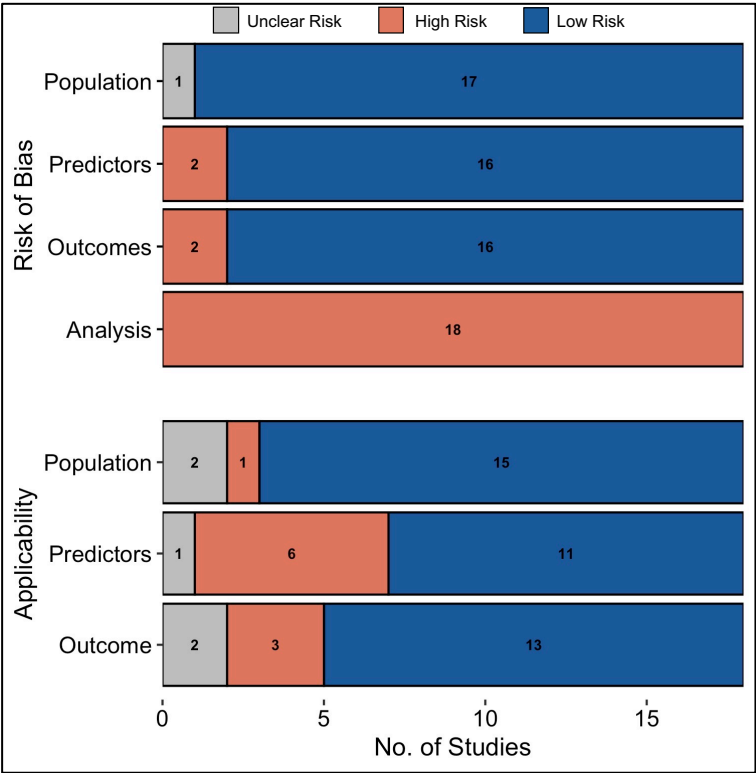


Footnote: Full details on PROBAST signaling questions are provided in **Supplemental Table 2**).
Participants 1: What study design was used and was it appropriate? Participants 2: Were the inclusion and exclusion criteria appropriate? Predictors 1: Were predictors assessed the same way for all participants? Predictors 2: Were predictor assessments used without knowledge of the outcome? Predictors 3: Are all predictors available at the time the model was intended to be used? Outcome 1: Was the outcome determined appropriately? Outcome 2: Was the outcome specified or standard? Outcome 3: Were predictors excluded from the outcome definition? Outcome 4: Was the outcome defined and determined in a similar way for all participants? Outcome 5: Was the outcome determined without predictor information? Outcome 6: Was the time interval between predictor assessment and outcome determination appropriate? Analysis 1: Were there a reasonable number of participants with the outcome? Analysis 2: Were continuous and categorical variables handled appropriately? Analysis 3: Were all enrolled participants included in the analysis? Analysis 4: Were participants with missing data handled appropriately? Analysis 5: Was univariable analysis avoided in the selection of predictors? Analysis 6: Were complexities in the data (e.g., censoring, sampling of controls) accounted for appropriately? Analysis 7: Were relevant model performance measures evaluated appropriately? Analysis 8: Were model overfitting, underfitting, and optimism in the model performance accounted for? Analysis 9: Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?^{68,69}

handled (i.e., considered non-linearity or did not dichotomize continuous variables) in 2 studies (11%)^{25,75,78,80,81} and 11 studies (61%) avoided univariable analysis to select key predictors. Sixty-one percent of studies (n=11) had a low events per variable ratio (EPV), indicating models were likely overfit [EPV, median: 8 (IQR: 6-15); Figure 3]. Only one study corrected for overfitting or penalization for model optimism.⁸⁵ The same study was the only one to report both discrimination and calibration measures from their model.⁸⁵ Overall, 11 studies (61%) reported their final models with model coefficients which reduces bias from rounding or transforming coefficients to develop a risk score.^{25,46,70,71,73-75,77,83,84,88}

Forty-four percent (n=8) of studies were applicable to our review question in all domains. Several studies were not applicable because predictors included laboratory biomarkers that are not routinely available in healthcare settings (e.g., c-reactive protein, CD35, lipocalin 2).^{77,80-83} In addition, studies with imprecise or non-standardized inclusion criteria across sites⁷³ or varying methods of outcome ascertainment were also considered high risk of lacking applicability.^{81,84,85}

Figure 3.4. Overall Risk of Bias and Applicability for Each Study Using PROBAST (n=18).



DISCUSSION

In this systematic review, we identified 18 studies that developed diagnostic prediction models intended to viral ARIs in children. Across studies, minimal concern for bias was found in the study population, predictors, and outcome ascertainment. However, high concern for bias was observed in the analytical approaches undertaken for prediction model development in all studies. Key drivers of analytic bias were attributed to lack of reporting model performance measures (discrimination or calibration), limited validation, dichotomizing continuous variables, omitting missing data, overfitting, and lack of accounting for overfitting and model optimism. Despite analytic shortcomings, our findings suggest clinical diagnostic prediction models have the potential to serve as an alternative diagnostic tool for clinicians in situations where testing is not routinely available.

Predictors frequently considered and retained in models included clinical symptoms and demographic characteristics, such as cough, fever, rhinorrhea, and age, which are well-known factors associated with viral ARIs.^{19-21,89-92} In addition to these predictors, models commonly incorporated clinical biomarkers (e.g., c-reactive protein, neutrophils, lymphocytes, leukocytes, and genes).^{77,80-83,92} Inclusion of these biomarkers may impede the clinical utility and generalizability of the diagnostic prediction model as these biomarkers are not routinely captured in pediatric ambulatory care settings (e.g., outpatient, emergency department, urgent care) in developed and developing countries; and in inpatient settings, results are often not timely. Future diagnostic prediction models should consider candidate predictors more readily available at the time of presentation/diagnosis, such as symptom duration, time of year (i.e., prevalence of respiratory viruses), and vital signs.

Among studies reporting model discrimination measures (model's ability to distinguish between patients having and not having the disease/outcome of interest⁶²), most reported good discriminative ability with a c-statistic greater than 0.7 [ranges from 0.5 (no discriminative ability) to 1.0 (perfect discriminative ability)]. Less than a quarter of studies reported model calibration measures (agreement between observed and predicted outcomes);⁴⁵ with all studies reporting the Hosmer-Lemeshow goodness-of-fit

test. Historically, only reporting the Hosmer-Lemeshow test was common practice but has disadvantages due to its inability to detect miscalibration or overfitting of predictors.⁴⁵ Modern-day methods suggest newly developed models should report calibration plots, slopes, and intercepts in combination with the Hosmer-Lemeshow test.⁴⁵ Studies included in this systematic review rarely performed internal validation and among those who did, the majority were validated with split-sample techniques, and none were externally validated. It is well known that using split-sample approaches typically lead to a less stable model with unreliable assessment of model performance (i.e., overly optimistic).⁹³⁻⁹⁵ In these circumstances, bootstrapping is the recommended strategy for internal validation of prediction models,⁹³⁻⁹⁵ which reflects sampling the underlying population by drawing samples with replacement from the original sample (without holding out any data in the model development phase) and estimates bias due to overfitting or “optimism” in the final model fit.⁵⁵ In turn, a shrinkage factor is used to adjust regression coefficients.^{55,56,96} This approach discounts for variation for regression to the mean⁵⁶ and allows for better performance in subsequent external validations and applications.⁵⁵ Future external validation studies should be performed on rigorously internally validated models and in a similar setting to the development prediction model.⁹³

Although high analytic bias was widespread across studies, Manuel *et al*²⁵ and Gebremedhin *et al*⁸⁵ had notable model development characteristics worth highlighting. Both studies developed an RSV diagnostic prediction model in hospitalized children (Germany²⁵ and Western Australia⁸⁵). Manuel *et al*²⁵ clearly stated multiple imputation with chained equations was used to handle missing data, selected candidate predictors using prior knowledge, and performed multiplex-polymerase chain reaction testing on all children to determine RSV positivity. Advantages of using multiplex-polymerase chain reaction to detect RSV provides for the ability to simultaneously detect multiple viral targets and is more sensitive than immunofluorescence assays.⁹⁷ In addition, Manuel and colleagues²⁵ presented their final model with unrounded beta coefficients, along with the model intercept. Model presentation of both the intercept and unrounded beta coefficients allows for other research teams to externally validate the model. Gebremedhin *et al*⁸⁵ selected candidate predictors based on prior knowledge, appropriately

handled repeated ARI episodes with robust standard error estimators, conducted internal validation using ten-fold cross-validation methods, presented model discrimination measures and a calibration plot, and reported prediction model results in accordance with TRIPOD guidelines (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Guidelines).⁵⁵ Ten-fold cross-validation is a better alternative than split-sample validation because data is not sacrificed/split in the stages of model building and validation. However, limitations of ten-fold cross-validation compared to the preferred bootstrapping methods aforementioned include: only validates nine-tenths of the model (not full model validation), has lower precision, and precludes full variability of variable selection.⁹⁵ Presentation of a calibration plot in model development is robust and provides the model's accuracy of predicting risk probabilities and information regarding the extent of agreement between expected and observed outcomes.⁶² Of note, both models require external validation prior to use in clinical practice.

Our systematic review has limitations that should be considered. First, due to the heterogeneity between study outcome measurements (i.e., different assays to detect viruses) and the scarcity of reporting both discrimination and calibration measures we were unable to conduct a meta-analysis. However, we were able to qualitatively assess 18 studies and identified opportunities for improvement in the analytical methods of diagnostic model development. Second, we excluded four studies that were not available in English. All four studies had abstracts available in English and did not report any model performance metrics, thus, these studies may have been excluded from our systematic review for an alternative reason (e.g., not a prediction model, wrong population, etc.). Finally, we excluded diagnostic prediction models that were developed for SARS-CoV-2 or MIS-C. Rationale for excluding these models are attributed to SARS-CoV-2 being less prevalent in children than adults,⁹⁸ changes in healthcare seeking behaviors during the pandemic response,⁹⁹ and the suppression of other respiratory virus circulation during this era.¹⁰⁰

Diagnostic prediction models may be an impactful tool in clinical diagnoses of viral ARIs. Rapid detection of the etiologic cause of ARIs may lead to direct patient benefits and may help guide clinical management decisions including administration of therapeutics, additional laboratory testing for bacterial pathogens, or radiography. Although the existing ARI diagnostic models are not ready for clinical application, we believe the critical appraisal of published findings will be invaluable towards the development and validation of future prediction models.

IV. PATTERNS OF PROVIDER-ORDERED VIRAL DIAGNOSTIC TESTING PRACTICES AND THE IMPACT ON ANTIBIOTIC PRACTICES ACROSS HEALTHCARE SETTINGS

IV.A PATTERNS OF PROVIDER-ORDERED VIRAL DIAGNOSTIC TESTING

INTRODUCTION

Outside the neonatal period, acute respiratory infections (ARIs) are the leading cause of childhood morbidity and mortality worldwide.¹⁰¹ In the United States (U.S.), ARIs account for 41% and 40% of annual infectious disease-related emergency department (ED) visits and hospitalizations, respectively.¹⁰² ARIs are most often caused by respiratory viruses, such as respiratory syncytial virus (RSV), rhinovirus, and influenza, but can also be caused by bacteria.^{58,59,103} Given the overlapping clinical presentations of viral and bacterial ARIs, clinicians frequently order viral diagnostic tests to discriminate viral and bacterial etiologies.^{58,59} Viral diagnostics testing includes rapid antigen (influenza and RSV) and most recently, nucleic acid amplification tests (NAAT). Differentiating between viral and bacterial ARIs may help clinicians target their treatment choices (e.g., antivirals, antibiotics, or only symptomatic management).

Despite the potential advantages of distinguishing ARIs of viral or bacterial origin, national guidelines discourage routine viral diagnostic testing for bronchiolitis²² and advise against relying on rapid antigen testing for diagnosing influenza if there is a high clinical suspicion.³⁹ In spite of this recommendation, a study which included 42 U.S. children's hospitals, noted that viral testing was performed in 45% of children hospitalized with bronchiolitis, and testing practices varied across institutions.¹⁰⁴ Pediatric hospitals tend to more often utilize molecular testing, whereas in ED viral diagnostics have primarily focused on rapid influenza antigen testing.^{103,104} However, no studies have examined the clinical factors influencing provider-ordered viral testing across healthcare settings. Our aim was to assess clinical presentation patterns that prompt clinicians to obtain viral testing on children presenting to an ED and among those hospitalized with an ARI.

METHODS

Study Design in the Emergency Department and Inpatient Setting

We used data collected from an ARI viral surveillance study as part of the Centers for Disease Control and Prevention funded New Vaccine Surveillance Network (NVSN)^{8,91} in Nashville, Tennessee between November 2, 2017, and February 28, 2020. Year-round recruitment occurred 4 days/week in the ED and 5 days/week in the inpatient setting at the Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center (VUMC). Institutional Review Boards at VUMC and the CDC reviewed and approved this study.¹⁰⁵

Study Design in the Outpatient Setting

We used data collected from an active, prospective viral surveillance study among children (>30 days to <12 months) in Davidson County, Tennessee from December 16, 2019, to February 28, 2020. Surveillance was conducted at four distinct outpatient clinics,²³ with recruitment occurring ≥4 days per week.²³ This study was approved by the Institutional Review Board at VUMC.

Study Population in the Emergency Department and Inpatient Setting

Eligible children were younger than 18 years, resided within the catchment/surveillance area (e.g., Davidson, Williamson, Cheatham, Dickson, Rutherford, Montgomery, Roberson, and Sumner counties), and presented to an ED or were hospitalized within 48 hours of enrollment (**Appendix Figure B1**). Children were required to have at least one of the following symptoms within 14 days of onset: fever, cough, earache, nasal congestion, runny nose, sore throat, post-tussive vomiting, wheezing, shortness of breath/rapid or shallow breathing, myalgia, apnea, apparent-life threatening event, or brief resolved unexplained event (e.g., unresponsive, etc.).^{8,91} A child was ineligible if any of the following criteria were met: chemotherapy-associated fever and neutropenia (absolute neutrophil count <500/μL), newborns never discharged since birth, transferred to VUMC from another hospital >48 hours after initial admission, recently hospitalized (≤5 days), or previously enrolled in the study within the past 14 days.^{8,91}

We further excluded infants <30 days old, due to the increased risk of serious bacterial infections compared to other groups^{22,47} (e.g., group B *Streptococcus*) and unique clinical management/practices. Children with multiple ARI visits were considered susceptible to a new ARI infection (either viral or bacterial) if each visit was ≥ 90 days from the previous visit.

Study Population in the Outpatient Setting

Eligible children were required to present with a fever ($\geq 100.4^{\circ}\text{F}$) and/or at least one of the following respiratory symptoms: wheezing, crackles, rales, diminished breath sounds, shortness of breath, cough, earache, nasal congestion, rhinorrhea, coryza, and/or sore throat within 14 days of illness onset.²³ Exclusion criteria included: presenting with both fever and neutropenia (absolute neutrophil count $< 500 \times 10^3/\mu\text{L}$), having a known non-infectious cause for their symptoms, or a prior study enrollment in the past seven days.²³ Duplicate ARI enrollments <90 days apart from the prior enrollment were excluded from this study.

Interviews & Medical Chart Abstractions

After informed consent, trained research personnel interviewed the child's parent/guardian to collect demographic information (age, sex, race, and ethnicity), clinical symptoms, and past medical history using a standardized case report form. Physical exam findings, vital signs at the time of presentation, and provider-ordered viral testing (i.e., rapid antigen and NAAT) were abstracted from medical charts. Final clinical disposition was determined by the highest level of care provided to the child during their visit (i.e., children enrolled in the ED and later hospitalized were considered an inpatient). During the study period, providers at VUMC and outpatient clinics could order the following viral tests: rapid influenza antigen, rapid RSV antigen, and NAAT testing. Demographic, interview, medical record, and laboratory results were maintained in a secure REDCapTM (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database.⁶⁷

Provider-Ordered Viral Tests

Our main outcome was a provider-ordered viral test, which included at least one of the following: rapid influenza antigen, rapid RSV antigen, and/or NAAT; dichotomized into tested versus not tested.

Principal Components Analysis (PCA)

PCA was used to derive different clinical presentation patterns using the following variables: age (years), illness duration (days), maximum temperature [none, moderate ($\geq 100.4^{\circ}\text{F}$ to $< 102.0^{\circ}\text{F}$), or severe ($\geq 102.0^{\circ}\text{F}$)], pulmonary symptoms (cough, nasal congestion, rhinorrhea, self-reported wheezing, and shortness of breath; yes or no), number of non-pulmonary symptoms (fatigue, earache, myalgia, diarrhea, vomiting, sore throat), respiratory rate (breaths/minute), heart rate (beats/minute), oxygen saturation on room air (%), wheezing (yes or no), retractions (yes or no), time of year [respiratory season (October-April) or non-respiratory season], any underlying medical condition (yes or no), underlying respiratory condition (yes or no), underlying asthma/reactive airway disease (yes or no), underlying cardiovascular condition (yes or no), underlying neurologic condition (yes or no), underlying oncologic/immunosuppressive condition (yes or no), prematurity (yes or no), public insurance (yes or no), private insurance (yes or no), none/self-pay insurance (yes or no), and prior antibiotic use in past 14 days (yes or no). Continuous variables were standardized to have a mean of zero and standard deviation equal to one.

Clinical presentation patterns were derived for children in each healthcare setting (i.e., ED and hospitalized). The different principal components derived from the PCA analysis were rotated to maximize the variance explained by each pattern. Screeplots were generated to summarize the total number of principal components (PCs) with the greatest amount of variance explained. The strongest PCs whose eigenvalues were greater than 1 were chosen to represent the independent clinical presentation patterns. Final PCs were dichotomized at the median using cut-points among children who did not receive a provider-ordered test (n=1,322).

Validation of Clinical Diagnostic PC Patterns

PCs were validated using test results from our research specimens. Research specimens (e.g., nasal, oropharyngeal, and/or tracheal aspirates) were collected from all enrolled children and placed in viral transport medium by study personnel. All research specimens were transported to the VUMC research laboratory and stored at 4°C until processed, within 48-hours. Testing was performed using (quantitative reverse transcription-polymerase chain reaction) assays for the following viruses: adenovirus, human metapneumovirus, influenza (A, B, and C), parainfluenza (types 1-4), respiratory syncytial virus (RSV), rhinovirus, and endemic coronaviruses (OC43, 229E, NL63, and HKU1). Research specimen collection and molecular testing were performed in accordance with the NVSN study protocol.^{8,91}

Statistical Analysis

Sociodemographic and clinical characteristics of children by setting were summarized using frequency (percent) for categorical variables and mean (standard deviation) for continuous variables. We performed multiple imputation for 266 children with ≥ 1 missing covariates, using predictive mean matching with 10 imputation samples (**Appendix Figure B2**).⁵⁶ Our final analytic sample size consisted of 4,107 children. Sensitivity analysis and justification for using selecting 10 imputation sample sets were conducted across various imputation sample sets (e.g., 10, 25, 50, 100, 500, 1000) and are provided in **Appendix Table B1**.

PC-specific models were built using unconditional logistic regression with robust sandwich estimators (to account for repeat visits) to estimate odds ratios (ORs) and 95% confidence intervals between different clinical presentation patterns and provider-ordered viral testing. All analyses were performed in R (version 3.6.1).

Outpatient, Exploratory Analysis

Due to small sample sizes, we conducted an exploratory principal components analysis in the outpatient setting with the same PCA methods used in the ED and inpatient setting. Multiple for 6 children with ≥ 1 missing covariate was performed using predictive mean matching with 5 imputation samples (**Appendix Figure B2**).⁵⁶ *A priori* predictors included: age (months), illness duration (days), maximum temperature [none, moderate ($\geq 100.4^{\circ}\text{F}$ to $<102.0^{\circ}\text{F}$), or severe ($\geq 102.0^{\circ}\text{F}$)], pulmonary symptoms [yes or no; cough, nasal congestion, rhinorrhea, wheezing (self-reported), shortness of breath], number of non-pulmonary symptoms (i.e., fatigue, earache, myalgia), wheezing (yes or no), retractions (yes or no), crackles (yes or no), rales/rhonchi (yes or no), underlying medical condition (yes or no), underlying respiratory condition (yes or no), underlying asthma/reactive airway disease (yes or no), underlying cardiovascular condition (yes or no), underlying neurologic condition (yes or no), underlying oncologic/immunosuppressive condition (yes or no), prematurity (yes or no), public insurance (yes or no), private insurance (yes or no), none/self-pay insurance (yes or no), and prior antibiotic use in past 14 days (yes or no).

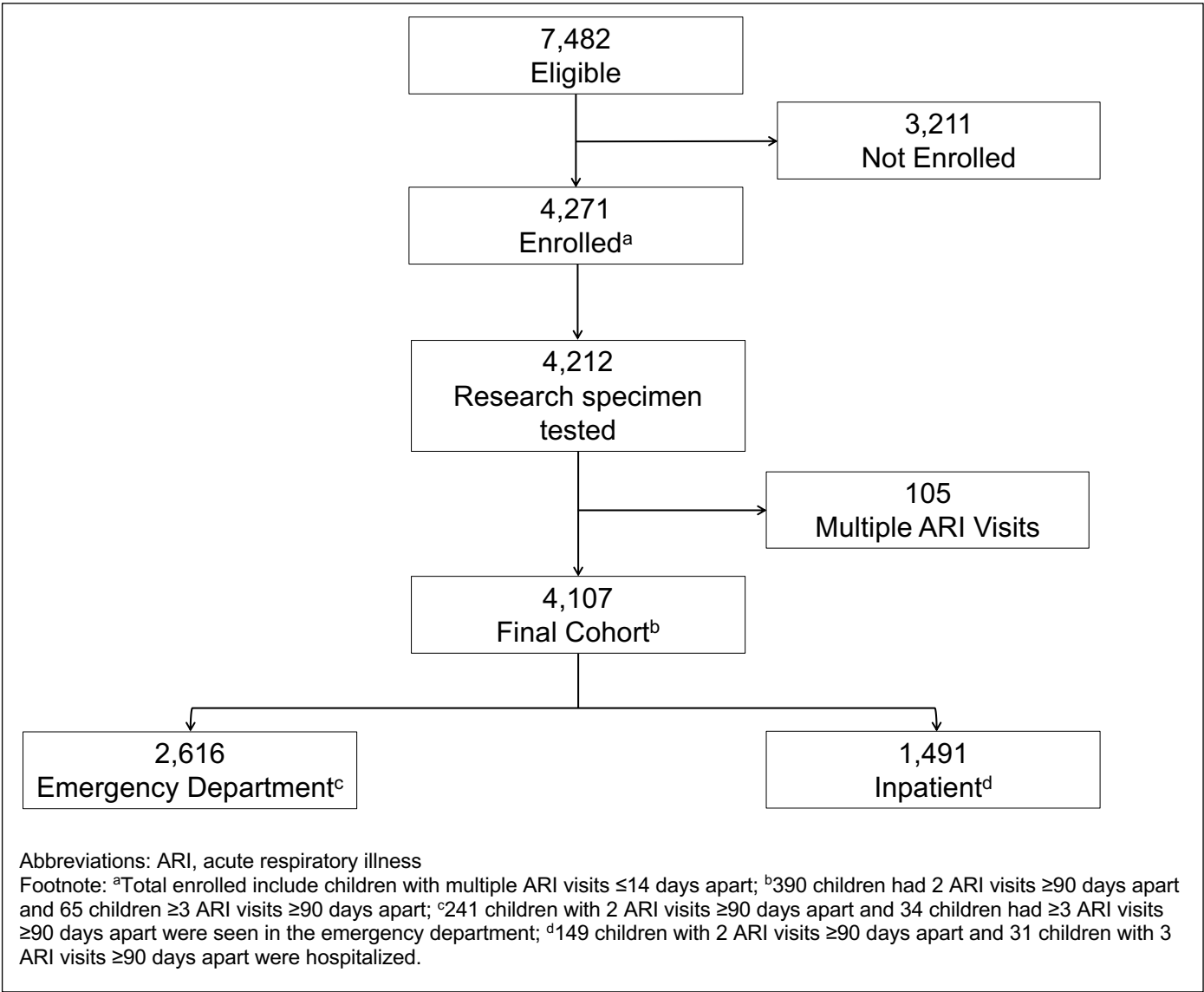
PCs were further evaluated using research specimen test results. Nasal swabs (research respiratory specimen) were collected and placed in viral transport medium and further aliquoted into tissue lysis buffer (ATL Lysis Buffer, QIAGEN), snap-frozen, and stored at -80°C .²³ Testing was performed using Luminex® NxTAG Respiratory Pathogen Panel for: influenza, adenovirus, RSV, endemic coronaviruses (OC43, 229E, NL63, and HKU1), human metapneumovirus, rhinovirus/enterovirus, bocavirus, parainfluenza (types 1-4), *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.²³

RESULTS

From November 2017 to February 2020, 4,271 (57%) of 7,482 children eligible were enrolled, among whom 4,212 (99% of enrolled) had a research specimen tested. A total of 151 enrollments were excluded based on a prior enrollment occurring within <90 days. Our final cohort included 4,107 children, of which 2,616 (64%) were from the ED and 1,491 (36%) were hospitalized (**Figure 4.A.1**). A

total of 455 children from our final cohort had multiple ARI visits ≥ 90 days apart, with some children incurring multiple visits in both healthcare settings (n=12).

Figure 4.A.1. Consort Diagram of Children (>30 days - 17 years) Enrolled in an Emergency Department and Hospitalized with Acute Respiratory Illness, Nashville, Tennessee, November 2017-February 2020.



Provider-Order Viral Testing by Setting

Emergency Department

Children were a median age of 3 years, predominately black, non-Hispanic, and 31% had at least one underlying medical condition (**Table 4.A.1**). Cough, nasal congestion/runny nose, and fever were the

most frequently reported symptoms. A provider-ordered viral test occurred in 49% (1,294/2,616) of children with an ARI-related ED visit, with 97% (1,255/1,294; 87% rapid influenza; 1% rapid RSV; 13% NAAT) with one-test, 3% (38/1,294; 100% rapid influenza; 42% rapid RSV; 58% NAAT) with two-tests, and <1% (1/1,294) had three-tests. In total, 64% of children had at least one virus detected from their research specimen, with influenza most common (**Table 4.A.1**).

Inpatient

Of the 1,491 hospitalized children, the median age was 1.6 years, with higher proportion white, non-Hispanic, 47% of children had at least one underlying medical condition and had a mean length of stay of 3 days. Twenty percent were admitted to the intensive care unit. Cough, nasal congestion/runny nose, and shortness of breath were the 3 most common symptoms reported; 51% and 36% had retractions and wheezing, respectively, found on physical exam (**Table 4.A.1**). A provider-ordered test occurred in 64% (955/1,491) of the children with an ARI-related hospitalization, with 82% (784/955; 22% rapid influenza, 3% rapid RSV, 75% NAAT) with one-test, 15% (143/955; 95% rapid influenza; 46% rapid RSV; 59% NAAT) with two-tests, and 3% (28/955) with three-tests. Overall, 61% of children had at least one virus detected from their research specimen, with RSV and rhinovirus most common.

Outpatient, Exploratory

A total of 174 children were enrolled from the outpatient setting. Children from the outpatient setting were racially and ethnically diverse, had a median age of 7 months, and 24% had at least one underlying medical condition (**Table 4.A.2**). A provider-ordered test occurred in 33% (58/174) of the children with 76% (44/58; 75% rapid influenza; 23% rapid RSV; 2.3% NAAT) with one-test and 24% (14/58; 100% rapid influenza; 93% rapid RSV; 7% NAAT) two-tests. Overall, 84% of children had at least one respiratory virus detected from their research specimen, with rhinovirus/enterovirus and RSV most frequent.

Table 4.A.1. Sociodemographic and Clinical Characteristics of Children (>30 days-17 years)
Enrolled in Emergency Departments and Hospitalized with Acute Respiratory Illness, Nashville,
Tennessee, November 2017-February 2020

Characteristic(s)	Emergency Department N=2,616	Inpatient N=1,491
Age, years—mean (SD)	4.6 (4.4)	3.4 (4.1)
Age, years—median (IQR)	3.0 (1.1, 7.0)	1.6 (0.5, 4.9)
0 to <2 years—no. (%)	1,028 (39.3)	832 (55.8)
2 to <5 years—no. (%)	662 (25.3)	293 (19.7)
≥5 to <18 years—no. (%)	926 (35.4)	366 (24.5)
Sex, male—no. (%)	1,405 (53.7)	873 (58.6)
<i>Race/ethnicity—no. (%)</i>		
White, Non-Hispanic	353 (13.5)	676 (45.4)
Black, Non-Hispanic	1,115 (42.6)	355 (23.8)
Other Non-Hispanic	182 (7.0)	135 (9.1)
Hispanic	940 (35.9)	310 (20.8)
Unknown	26 (1.0)	15 (1.0)
<i>Insurance type—no. (%)</i>		
Public	2,093 (80.0)	968 (64.9)
Private	219 (8.4)	395 (26.5)
Both	13 (0.5)	27 (1.8)
None/Self Pay	262 (10.0)	80 (5.4)
Unknown	29 (1.1)	21 (1.4)
<i>Social exposures—no. (%)</i>		
Daycare/School attendance ^a	1,419 ^b (54.3)	677 (45.4)
Smoke exposure	687 ^b (26.3)	392 ^c (26.3)
E-cigarette exposure	95 ^b (3.6)	114 ^d (7.6)
<i>Underlying medical conditions—no. (%)</i>		
≥1 Underlying medical condition	869 (33.2)	765 (51.3)
Respiratory	471 (18.0)	406 (27.2)
Asthma/RAD, only	433 (16.6)	292 (19.6)
Cardiovascular	52 (2.0)	127 (8.5)
Neurological/Neuromuscular	120 (4.6)	220 (14.8)
Oncologic/Immunosuppressive	318 (12.2)	267 (17.9)
Renal	4 (0.2)	15 (1.0)
Gastrointestinal/Hepatic	64 (2.4)	156 (10.5)
Endocrine	9 (0.3)	38 (2.5)
Other	76 (2.9)	88 (5.9)
Prematurity, <37 weeks ^e —no. (%)	109 (4.2)	144 (9.7)
<i>Time of illness^f—no. (%)</i>		
Respiratory season	2,002 (76.5)	1,148 (77.0)
Antibiotic consumption ≤14 days prior to visit/hospitalization—no. (%)	158 (6.0)	257 (17.2)
<i>Clinical symptoms at enrollment—no. (%)</i>		
Fever, >100.2 °F	1,997 (76.3)	1,069 (71.7)
Maximum temperature, °F—mean (SD)	101.3 ^g (2.1)	101.3 ^h (2.2)
Cough	2,146 (82.0)	1,267 (85.0)
Nasal congestion/runny nose	2,100 (80.3)	1,182 (79.3)
Lethargy	1,643 (62.8)	1,124 (75.4)
Earache	663 (25.3)	202 (13.5)
Sore throat	1,107 (42.3)	377 (25.3)
Myalgia	608 (23.2)	224 (15.0)
Wheezing	1,115 (42.6)	943 (63.2)
Shortness of breath	1,219 (46.6)	1,139 (76.4)
Illness duration, days—mean (SD)	2.8 ⁱ (2.3)	3.3 ^j (2.6)

<i>Vital signs at presentation—mean (SD)</i>		
Heart rate, bpm	135.6 ^k (28.5)	150.3 (27.2)
Respiratory rate, bpm	28.5 ^l (9.2)	38.5 ^m (13.7)
Oxygen Saturation, capillary	98.4 ⁿ (1.9)	95.5 (5.3)
<i>Physical assessment—no. (%)</i>		
Wheezing	278 (10.6)	539 (36.2)
Retractions	232 (8.9)	767 (51.4)
<i>Research laboratory results—no. (%)</i>		
Virus, positive	1,689 (64.6)	917 (61.5)
Adenovirus	101 (6.0)	26 (2.8)
Influenza	464 (27.5)	101 (11.0)
RSV	252 (14.9)	288 (31.4)
Rhinovirus	247 (14.6)	184 (20.1)
Parainfluenza (Types 1-4)	172 (10.2)	77 (8.4)
Human metapneumovirus	84 (5.0)	62 (6.8)
Coronaviruses (OC43, 229E, NL63, HKU1)	106 (6.3)	41 (4.5)
≥ 2 respiratory viruses	263 (15.6)	138 (15.0)

Footnote:

^a reported attending daycare/school ≥4 times/week;

^bn=2615; ^cn=1489; ^dn=1488;

^eHistory of prematurity was reported for children aged <2 yrs;

^fRespiratory season, October-April;

^gn=2511; ^hn=1465; ⁱn=2615; ^jn=1489; ^kn=2603; ^ln=2602; ^mn=1490; ⁿn=2605

Abbreviations: RAD, reactive airway disease; RSV, respiratory syncytial virus

Table 4.A.2. Clinical Characteristics of Children (>30 days-11 months) Enrolled in Three Distinct Outpatient Clinics with Acute Respiratory Illness, Nashville, Tennessee, December 2019-February 2020

Characteristic(s)	Outpatient N=174
Age, months—mean (SD)	6.7 (3.0)
Age, months—median (IQR)	6.8 (4.4, 9.0)
Sex, male—no. (%)	87 (50.0)
Race—no. (%)	
White, Non-Hispanic	66 (37.9)
Black, Non-Hispanic	57 (32.8)
Other Non-Hispanic	16 (9.2)
Hispanic	34 (19.5)
Unknown	1 (0.6)
Insurance type—no. (%)	
Public	85 (48.9)
Private	83 (47.7)
None/Self Pay	4 (3.4)
Social Exposures—no. (%)	
Daycare attendance ^a	63 (36.2)
Smoke exposure	18 (10.3)
E-cigarette exposure	3 (3.5)
Underlying medical conditions—no. (%)	
≥1 Underlying medical condition	41 (23.6)
Respiratory	2 (1.1)
Cardiovascular	4 (2.3)
Neurological/Neuromuscular	3 (1.7)
Oncologic/Immunosuppressive	17 (9.8)
Renal	0
Gastrointestinal/Hepatic	7 (4.0)
Endocrine	1 (0.6)
Other	15 (8.6)
Prematurity, <37 weeks—no. (%)	9 (5.2)
Antibiotic consumption ≤14 days prior to visit—no. (%)	8 (4.6)
<i>Clinical Symptoms—no. (%)</i>	
Fever, >100.2 °F	111 (63.8)
Maximum temperature, °F—mean (SD)	100.5 ^b (1.7)
Cough	151 (86.8)
Nasal Congestion/Runny nose	164 (94.3)
Lethargy	67 (38.5)
Earache	59 (33.9)
Sore throat	20 (11.5)
Myalgia	9 (5.2)
Wheezing	88 (50.6)
Shortness of Breath	63 (36.2)
Illness duration, days—mean (SD)	3.6 (2.7)
<i>Physical assessment—no. (%)</i>	
Wheezing	18 (10.3)
Retractions	9 (5.2)
Rales/rhonchi	11 (6.3)
Accessory muscle use	2 (1.1)
Crackles	12 (6.9)
<i>Research Laboratory Results—no. (%)</i>	
Virus, positive	146 (83.9)

Adenovirus	4 (2.7)
Influenza	17 (11.6)
RSV	35 (24.0)
Rhinovirus/enterovirus	47 (32.2)
Parainfluenza (Types 1-4)	1 (0.6)
Human metapneumovirus	6 (4.1)
Coronaviruses (endemic)	5 (3.4)
Bocavirus	1 (0.7)
≥ 2 respiratory viruses	31 (21.2)

Footnote:
^a reported attending daycare/school ≥4 hours/week
^b n=168

PC Patterns by Setting

Emergency Department

A total of 4 PCs accounting for 63% cumulative proportion of variance were identified in the ED (**Table 4.A.3, Appendix Figure B3**). PC1_{ED} described 26% of variance and had a pattern mimicking RSV: younger children with a higher temperature, more likely to have respiratory symptoms, short illness duration, high respiratory rate and heart rate, lower oxygen saturation, no underlying medical conditions, and not regularly attending daycare. PC2_{ED} had a pattern resembling rhinovirus-like presentation: older children than PC1_{ED}, no fever present, more likely to present with respiratory symptoms, have wheezing and retractions present on physical exam, and no underlying medical conditions. PCs 3_{ED}-4_{ED} each accounted for 12% and 11% of variance, and both patterns were comprised of older children. PC3_{ED} represented either influenza or rhinovirus infections with a pattern of a short illness duration, high temperature, more likely to present with respiratory symptoms, low respiratory rate, and low oxygen saturation. PC4_{ED} closely followed an influenza-like presentation with a pattern of longer illness duration, respiratory symptoms present, high respiratory rate and low oxygen saturation, and underlying medical conditions dominated by respiratory disorders. Univariable summary statistics for PCs can be found in **Appendix Table B2**.

children with symptoms representing the rhinovirus-like pattern ($\geq$ median, PC2_{ED}) had 71% (OR: 0.29; 95% CI: 0.24, 0.34) decreased odds of receiving a provider-ordered viral test compared to those with symptoms less representative of the rhinovirus-like pattern ($<$ median, PC2_{ED}). **Table 4.A.4**). In contrast, children with symptoms representing the rhinovirus-like pattern ($\geq$ median, PC2_{ED}) had 71% (OR: 0.29; 95% CI: 0.24, 0.34) decreased odds of receiving a provider-ordered viral test compared to those with symptoms less representative of the rhinovirus-like pattern ($<$ median, PC2_{ED}). No associations were observed for the patterns of PC3_{ED} (RSV-like) and PC4_{ED} (influenza-like) with provider-ordered testing.

Inpatient

A total of 3 PCs accounting for 49% cumulative proportion of variance were identified among hospitalized children (**Table 4.A.3, Appendix Table B2, Appendix Figure B3**). PC1_{IP} explained 22% of observed ordering variation and resembled influenza-like illness. These children were older (school-aged) and characterized by short illness duration, high temperature, increased frequency of non-respiratory symptoms (i.e., myalgia, vomiting, diarrhea, etc.), low respiratory rate and heart rate, and underlying conditions. PC2_{IP} described 15% variance and consisted of children with rhinovirus-like illness. These patients were younger than PC1_{IP} (influenza-like) and presented with a short illness duration, no fever, greater likelihood of respiratory symptoms, low heart rate, low oxygen saturation, wheezing on physical exam, and underlying conditions dominated by respiratory disorders (i.e., asthma/reactive airway disease). PC3_{IP} mimicked RSV-like illness and captured young children presenting with a high respiratory rate, low oxygen saturation, and wheezing and retractions on physical exam.

Among hospitalized children, children with symptoms representing the rhinovirus-like pattern ($\geq$ median, PC2_{IP}) had 39% (OR: 0.61; 95% CI: 0.49, 0.76) decreased odds of receiving a provider-ordered viral test during their stay than those with dissimilar symptoms ($\leq$ median, PC2_{IP}; **Table 4.A.4**). An association was not observed for the patterns of PCs 1 (influenza-like) and 2 (rhinovirus-like) with provider-ordered testing.

Outpatient, Exploratory

Overall, 2 PCs accounting for 47% cumulative proportion of variance were identified (**Appendix Figure B3, Appendix Table B3**). PC1_{OP} described 28% of variance and resembled RSV-like illness. These children were extremely young with no known underlying medical conditions, had a short illness duration, no fever, presenting with respiratory symptoms, and no wheezing, retractions, crackles, or accessory muscle use was identified on physical exam. PC2_{OP}, included children older than PC1_{OP}, but these children were more likely to have non-respiratory symptoms, a short illness duration, fever, and

no wheezing or retractions found on physical exam, potentially mimicking more of a co-viral illness (i.e., RSV and influenza).

In the outpatient setting, children with symptoms consistent with a co-viral-like pattern ($\geq$ median, PC2_{OP}) had 2.6-fold (OR: 2.60; 95% CI: 1.36, 5.07) increased odds of receiving a provider-ordered viral test during their stay than children with dissimilar symptoms ($\leq$ median, PC2_{OP}; **Table 4.A.4**). An association was not observed for the patterns of PC1_{OP} (RSV-like).

Validation of PCA Patterns with Research Specimens by Setting

Emergency Department

Among children who were tested, the frequency of viral detection from a research specimen was highest in PCs_{ED} 1 and 4 (68% and 67%, respectively, **Figure 4.A.2**). RSV (20%) and ≥ 2 respiratory viruses (20% [RSV/coronavirus codetection=9%;17/182]) were the most often detected in PC1_{ED} (RSV-like), while influenza was most common in PC3_{ED} (30%; influenza/rhinovirus-like) and PC4_{ED} (30%; influenza-like). In PC2_{ED} (rhinovirus-like), rhinovirus (25%) and RSV (19%) were the two most frequent viruses detected.

Inpatient

Among children who had a provider-ordered viral test, positivity was highest in PC3_{IP} (RSV-like), with RSV accounting for 36% of all virus-positive detections (**Figure 4.A.2**). In PC2_{IP} (rhinovirus-like), rhinovirus (30%) and RSV (29%) were the two most common detected viruses. Rhinovirus and influenza were identified in 22% and 21% of virus-positive specimens, respectively, associated with PC1_{IP} (influenza-like).

Outpatient, Exploratory

In PC1_{OP} (RSV-like), rhinovirus and RSV were the most common viruses detected among children (**Figure 4.A.2**).

Table 4.A.3. Principal Components of Children (>30 days-17 years) Enrolled in Emergency Departments and Hospitalized with Acute Respiratory Illness, Nashville, Tennessee, November 2017-February 2020

Covariate(s)	Emergency Department (n=2,616)				Inpatient (n=1,491)		
	PC1 ^{ED}	PC2 ^{ED}	PC3 ^{ED}	PC4 ^{ED}	PC1 ^{IP}	PC2 ^{IP}	PC3 ^{IP}
	<i>RSV-like pattern</i>	<i>Rhinovirus- like pattern</i>	<i>Influenza & rhinovirus- like pattern</i>	<i>Influenza- like pattern</i>	<i>Influenza- like pattern</i>	<i>Rhinovirus- like pattern</i>	<i>RSV-like pattern</i>
Age, years	-0.56	-0.05	0.16	0.15	0.54	0.24	0.14
Antibiotic consumption ≤14 days prior to visit/hospitalization	0.00	-0.02	-0.03	0.01	0.05	-0.07	0.04
Illness duration, days	-0.04	0.03	-0.89	0.21	0.06	-0.30	0.41
Temperature	0.18	-0.72	0.14	-0.02	0.15	-0.63	0.06
Fever	0.06	-0.25	0.03	0.00	0.04	-0.24	0.02
Respiratory symptoms	0.00	0.01	-0.04	0.03	-0.02	0.02	0.05
No respiratory symptoms	-0.17	-0.57	-0.26	0.22	0.22	-0.42	0.30
Respiratory rate	0.51	0.20	-0.11	0.11	-0.52	0.06	0.22
Heart rate at presentation	0.55	-0.16	0.06	-0.03	-0.51	-0.21	0.02
Oxygen saturation at presentation	-0.13	-0.07	-0.23	-0.91	0.09	-0.26	-0.77
Wheezing on physical exam	0.02	0.08	0.02	0.08	-0.04	0.14	0.12
Retractions on physical exam	0.05	0.06	0.00	0.07	-0.14	0.10	0.16
Respiratory season	-0.01	-0.02	-0.04	0.01	-0.02	-0.01	0.05
Underlying medical conditions	-0.06	0.05	0.05	0.11	0.11	0.15	0.07
Respiratory	-0.07	0.04	0.06	0.10	0.10	0.15	0.09
Asthma/RAD, only	-0.07	0.04	0.05	0.09	0.09	0.12	0.06
Cardiovascular	0.00	0.00	0.01	0.02	0.01	0.03	0.04
Neurological/neuromuscular	-0.01	0.00	0.01	0.02	0.06	0.05	0.02
Oncologic/immunosuppressive	-0.03	0.02	0.02	0.04	0.08	0.06	0.00
Prematurity, <37 weeks	0.01	0.01	0.00	0.01	-0.02	0.02	0.00
Public insurance	0.01	0.01	-0.02	-0.02	-0.03	0.02	0.00
Private insurance	0.00	0.00	0.01	0.02	0.04	-0.01	0.01
Self-pay insurance	0.01	0.00	0.00	-0.00	0.00	0.00	-0.01
Sex	0.03	0.01	0.00	0.01	0.00	0.01	-0.04
Daycare	-0.19	-0.01	0.07	0.05	0.16	0.03	0.08
Proportion of Variance Explained (%)	26.02	14.19	11.53	11.11	22.35	15.08	11.34
Eigenvalue(s)	2.39	1.31	1.06	1.02	2.25	1.52	1.14

Table 4.A.4. Association of Principal Components and Clinical Provider-Ordered Viral Testing, by Healthcare Setting, Nashville Tennessee, November 2017-February 2020

Pattern(s)	PC-value	No. with Provider-Ordered Testing	No. w/o Provider-Ordered Testing	Odds Ratio	95% CI	P-Value
Emergency Department^b (n=2,616)						
<i>RSV-like pattern</i>						
PC 1 _{ED} , <median	<0.17	650	661	Ref	Ref	Ref
PC 1 _{ED} , ≥median	≥0.17	644	661	0.99	0.85, 1.15	0.906
<i>Rhinovirus-like pattern</i>						
PC 2 _{ED} , <median	<0.41	1004	661	Ref	Ref	Ref
PC 2 _{ED} , ≥median	≥0.41	290	661	0.29	0.24, 0.34	<0.001
<i>Influenza & rhinovirus-like pattern</i>						
PC 3 _{ED} , <median	<0.04	530	661	Ref	Ref	Ref
PC 3 _{ED} , ≥median	≥0.04	764	661	1.44	1.24, 1.68	<0.001
<i>Influenza-like pattern</i>						
PC 4 _{ED} , <median	<-0.18	627	661	Ref	Ref	Ref
PC 4 _{ED} , ≥median	≥-0.18	667	661	1.06	0.91, 1.24	0.429
Inpatient^c (n=1,491)						
<i>Influenza-like pattern</i>						
PC 1 _{IP} , <median	<-0.08	525	268	Ref	Ref	Ref
PC 1 _{IP} , ≥median	≥-0.08	430	268	0.82	0.66, 1.01	0.065
<i>Rhinovirus-like pattern</i>						
PC 2 _{IP} , <median	<0.24	592	268	Ref	Ref	Ref
PC 2 _{IP} , ≥median	≥0.24	363	268	0.61	0.49, 0.76	<0.001
<i>RSV-like pattern</i>						
PC 3 _{IP} , <median	<0.08	481	268	Ref	Ref	Ref
PC 3 _{IP} , ≥median	≥0.08	474	268	0.99	0.80, 1.22	0.892
Outpatient^d (n=174)						
<i>RSV-like pattern</i>						
PC 1 _{OP} , <median	<0.05	31	56	Ref	Ref	Ref
PC 1 _{OP} , ≥median	≥0.05	27	60	0.81	0.43, 1.53	0.520
<i>Co-Viral-like pattern</i>						
PC 2 _{OP} , <median	<0.20	20	67	Ref	Ref	Ref
PC 2 _{OP} , ≥median	≥0.20	38	49	2.60	1.36, 5.07	0.004

Footnote:

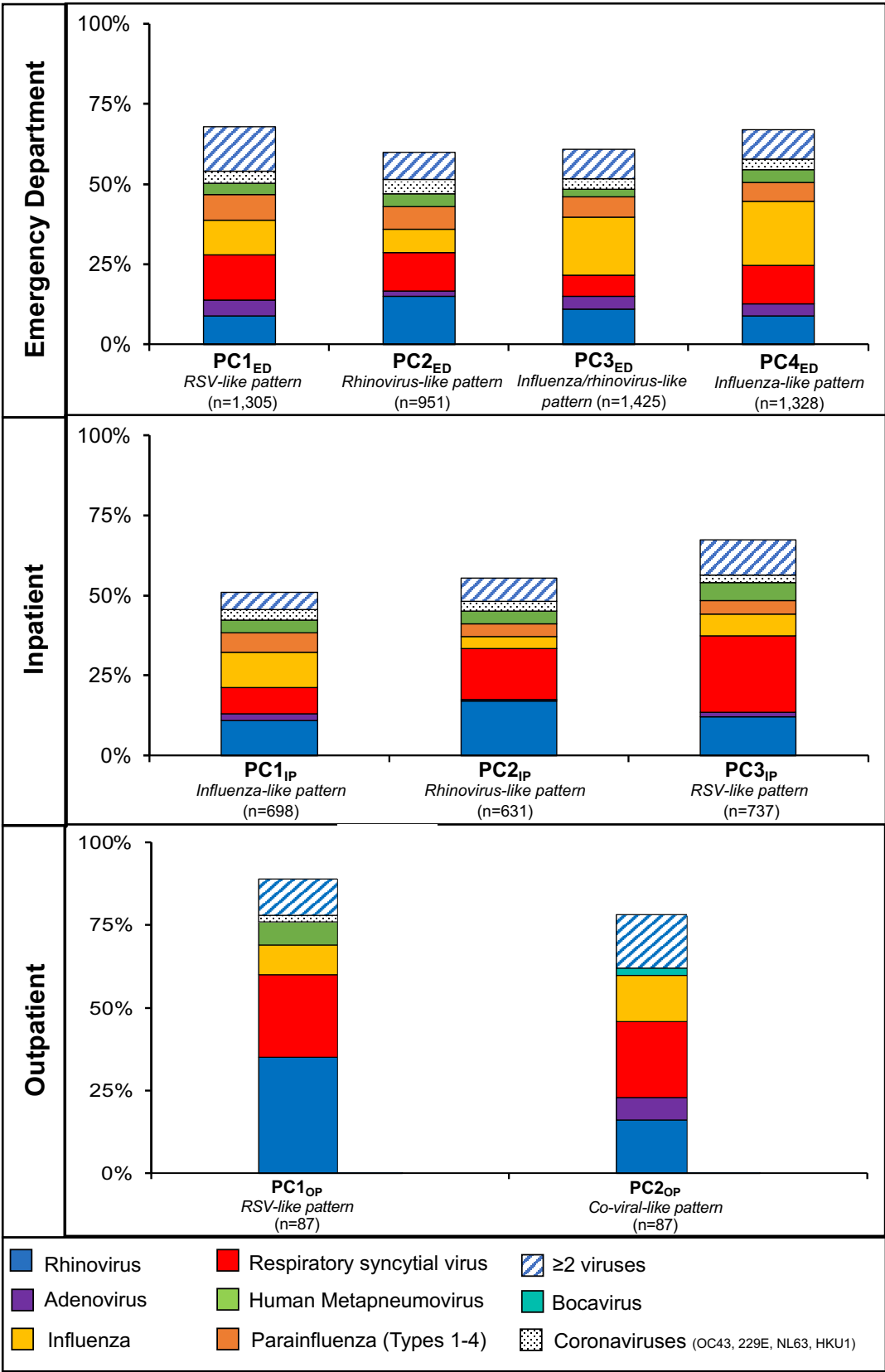
^aincludes rapid influenza, rapid RSV, and RT-qPCR

^bTotal no. of tests performed=1,294/2,616 (rapid influenza=1,126; RT-qPCR=157; rapid RSV=11)

^cTotal no. of tests performed=955/1,491 (rapid influenza=339; RT-qPCR=593; rapid RSV=23)

^dTotal no. of tests performed=58/174 (rapid influenza=47; rapid RSV=23; RT-qPCR=2)

Figure 4.A.2. Validation of Principal Components Respiratory Virus Distribution using Research Specimen Results, by Healthcare Setting, November 2017-February 2020.



DISCUSSION

In our prospective study of 4,107 ARI-related ED visits and hospitalizations in Nashville, Tennessee, we demonstrate provider-ordered viral testing practices vary across healthcare settings. In the ED, nearly one-half of children with an ARI-related illness were administered a provider-ordered viral test, with rapid influenza accounting for 87% of all tests performed. In comparison, two-thirds of hospitalized children underwent viral testing with more than 60% receiving a molecular test. Influenza/rhinovirus-dominant clinical presentation patterns were more likely to receive provider-ordered testing in the ED, while rhinovirus-like patterns were less likely to receive testing in either setting. Thus, clinical presentation patterns among children with ARI vary by healthcare setting and influence decisions to initiate viral testing.

In the ED, we found that the influenza/rhinovirus-like clinical presentation pattern was associated with provider-ordered viral test. Rapid influenza tests accounted for more than three-quarters of all tests administered while 66% of virus-positive research specimens in the influenza/rhinovirus-like pattern were non-influenza viruses. The abundance of rapid influenza tests may be attributed to the decision of initiating prompt antiviral therapy, which was only available for influenza prior to the SARS-CoV-2 pandemic. Further, these findings suggest that non-influenza-like clinical presentation patterns, such as RSV (common cause bronchiolitis), were not targeted with appropriate diagnostic testing. The limited use of RSV testing adheres to the American Academy of Pediatrics clinical practice guidelines for bronchiolitis, which recommends clinicians diagnose children based on history and physical exam and advises against routine viral testing.²² In the pediatric guidelines for community-acquired pneumonia (common viral ARI condition), rapid influenza testing is strongly recommended as a first-step to reduce additional diagnostic testing, initiate antiviral therapy, and minimize unnecessary antibiotic therapy.¹⁰⁶ From a diagnostic standpoint, the clinical patterns and associated viral testing practices we identified in the ED appear to be well aligned with the common ARI condition(s) guidelines. However, the confluence of clinical factors, laboratory findings, and institutional practices that shape management of

children seen in the ED with a non-influenza ARI and a negative influenza rapid test deserves systematic analysis.

The proportion of provider-ordered viral tests for hospitalized children were nearly 20% more compared to the ED, with the majority performed using NAAT. This difference might be attributed to time allowance for testing results in the inpatient setting, potential antiviral use, the need to rule out serious bacterial infections, insurance reimbursement, or decision-making about further laboratory evaluation, such as blood tests, cerebral spinal fluid assessment, or radiography.^{44,58}

Despite the availability of NAAT to our ED clinicians, this resource was sparingly used, perhaps a reflection of the influence of a positive result on the clinical management plan. A meta-analysis assessing the use of rapid viral tests in the ED revealed null effects of viral testing on provider decisions about clinical management.¹⁰³ In a retrospective study using the National Hospital Ambulatory Medical Care Survey, rapid influenza testing in U.S. emergency departments decreased the use of antibiotics and ancillary testing.¹⁰⁷ Most studies assessing rapid viral testing and its impact on clinical management in the ED are methodologically aimed at influenza,¹⁰³ and findings have not been uniformly replicated in hospitalized patients.⁵⁹ Discordant results across settings could be due to variability in patient acuity, provider practices, or the prevalence of viral testing performed. Studies evaluating pathogen-appropriate testing and influence of results on patient management and outcomes are needed to define the true clinical impact of testing on pediatric ARIs.

In our study, rhinovirus was detected in nearly a quarter of children with a research specimen (23%, including co-detections). Despite being common in both the ED and inpatient settings, children with rhinovirus-like patterns were less likely to receive a provider-ordered test. Rhinovirus is often associated with asthma exacerbations, bronchiolitis, and community-acquired pneumonia in children, particularly among those with underlying respiratory conditions (i.e., asthma/reactive airway disease).^{90,108,109} Limited use of viral testing in both the ED and inpatient settings for rhinovirus-like

clinical presentation might be ascribable to clinical management guidelines, as previously mentioned, or specific clinical presentations observed in children with rhinovirus ARIs.¹⁰⁹ Of note, in a prospective multi-center study assessing differences among children younger than 2 years hospitalized with bronchiolitis caused by RSV and rhinovirus, patients with rhinovirus ARI presented similarly to older children with asthma.¹¹⁰ Differences in clinical presentation may underlie variations in patient management, including viral testing, highlighting opportunities for improvement initiatives and standardization of care across settings.

A major strength of our study is systematic, active, prospective enrollment and molecular viral testing conducted over consecutive years among children with ARI in both the ED and inpatient settings. However, certain limitations apply. First, our study only included children enrolled prior to March 2020, and does not reflect practices during the coronavirus 2019 pandemic. Second, we used principal components, a data-driven approach, to understand the clinical presentation patterns influencing provider-ordered viral testing. Third, our findings represent a single center and may not be generalizable to other states or regions.¹⁰² Fourth, we were unable to assess clinician years of experience in either setting, which may affect viral testing practices. Fifth, due to small sample sizes we were restricted to performing an exploratory analysis in the outpatient setting. Our findings revealed children presenting with a co-viral-like pattern had nearly 3 times increased odds to receive viral testing. We posit this finding to the potential for a more severe clinical presentation (i.e., shortness of breath/wheezing). However, due to small sample sizes our effect confidence intervals are imprecise (confidence interval ratio: 3.73), and therefore should be interpreted with caution. Additional research in the outpatient setting is needed. Finally, our study focused on testing practices for viral ARIs and did not assess clinical testing for bacterial ARIs.

CONCLUSION

Variability in provider-ordered viral testing was observed across clinical presentation patterns and testing options by healthcare setting. Rapid influenza testing was the most common test performed in

the ED, while utilization of NAATs were more common in the inpatient setting. Future research should target identification of individual drivers of pediatric viral testing practices and policies and impact of those decisions on ARI management and outcomes.

IV.B ASSOCIATION OF PROVIDER-ORDERED VIRAL TESTING & ANTIBIOTIC ADMINISTRATION PRACTICES

INTRODUCTION

In the United States, acute respiratory infections (ARIs) are reported in 12 to 32 million infants (<1 year old) and nearly 200 million children (≥ 1 year old) per year,¹⁸ annually accounting for 41% of emergency department (ED) visits and 40% of hospitalizations.¹⁰² Since the introduction of pneumococcal and *Hemophilus influenza* vaccines, viruses have become the primary cause of ARIs,⁵⁷ but bacterial infections do still occur, making clinical diagnosis and management challenging. Children with ARIs often present with fever or shortness of breath, further leading to empiric antibiotic therapy—typically broad-spectrum—and diagnostic testing.¹¹¹ Mounting evidence has shown broad-spectrum antibiotics are used in situations where narrow-spectrum antibiotics or no antibiotics are warranted (inappropriate antibiotic use), with prescribing rates highest across Southern ambulatory care settings (i.e., EDs and outpatient clinics).^{3,5,112-114}

Advancements in rapid diagnostic viral testing have made testing options more accurate, faster, less expensive, and more readily accessible.^{111,115,116} However, the impact of viral diagnostic testing on antibiotic administration for children with ARI remains unclear due to conflicting results, with some studies reporting that viral diagnostics are associated with lower antibiotic use, while others report no impact.^{59,103} Likewise, studies examining viral testing and antibiotic prescribing and administration practices in both EDs and inpatient settings are limited. Therefore, in this prospective study, we aimed to evaluate the association of 1) provider-ordered viral testing and antibiotic prescribing/administration, and 2) provider-ordered viral test result (i.e., positive, negative) and antibiotic prescribing/administration among children presenting to an ED or hospitalized with an ARI at major tertiary care children's hospital in Nashville, Tennessee. We hypothesized that a provider-ordered test, regardless of the result, would be associated with reduced antibiotic prescribing/administration among children in both the ED and inpatient settings.

METHODS

Study Design

We used data collected from November 2, 2017, to February 28, 2020, from the New Vaccine Network (NVSN). NVSN study is a multi-center, active, prospective ARI surveillance study in children (<18 years), funded by the Centers for Disease Control and Prevention (CDC).^{8,91} This study only includes data collected from the Nashville, Tennessee site. Year-round recruitment occurred 4 days per week in the ED and 5 days per week in the inpatient setting at the Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center (VUMC). Institutional Review Boards at VUMC and the CDC reviewed and approved this study.¹⁰⁵

Study Population

Children were eligible if they presented to an ED or were hospitalized within 48 hours of enrollment and had at least one of the following symptoms in the 14 days prior to enrollment: fever, cough, earache, nasal congestion, runny nose, sore throat, post-tussive vomiting, wheezing, shortness of breath/rapid or shallow breathing, myalgia, apnea, apparent-life threatening event, or brief resolved unexplained event (e.g., unresponsive, etc.).^{8,91} In addition, eligible children had to live within the catchment/surveillance area (e.g., Davidson, Williamson, Cheatham, Dickson, Rutherford, Montgomery, Roberson, and Sumner counties). Children were excluded if they met any of the following criteria: chemotherapy-associated fever and neutropenia (absolute neutrophil count $<500 \times 10^3/\mu\text{L}$), newborns never discharged since birth, transferred to VUMC from another hospital >48 hours after initial admission, recently hospitalized (≤ 5 days), or were previously enrolled in the study in the past 14 days.^{8,91}

We additionally excluded children younger than 30 days to minimize the inclusion of serious bacterial infections due to differences in clinical management practices, and children with multiple ARI enrollments <90 days apart. We considered children with multiple ARI enrollments (≥ 90 days from the prior visit) as susceptible to a new viral or bacterial ARI, thus allowing for the potential for additional provider-ordered viral testing and antibiotic use.

Illness History, Clinical Characteristics, & Provider-Ordered Testing

After obtaining informed consent, the parents/guardians of enrolled children were interviewed by trained research personnel to collect demographic (age, sex, race, and ethnicity) information, clinical symptoms, and past medical history using a standardized form. Provider-ordered viral testing (i.e., influenza antigen, respiratory syncytial virus (RSV) antigen, and molecular respiratory testing), vital signs at time of presentation, physical exam findings, other clinical lab testing (i.e., rapid *Streptococcus* antigen testing and bacterial cultures), the first five discharge diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10]), and active and completed antibiotics were abstracted from each child's medical record. Final clinical disposition was determined by the highest level of care provided to the child during their visit (i.e., children enrolled in the ED and later hospitalized were considered inpatient). At VUMC, molecular respiratory testing is performed using BioFire® FilmArray Respiratory Pathogen Panel 2.0 and consists of the following targets: adenovirus, non-pandemic coronavirus strains (229E, HKU1, NL63, OC43), human metapneumovirus, influenza, parainfluenza (types 1-4), rhinovirus/enterovirus, and RSV, and respiratory bacterial pathogens (i.e., *Bordetella pertussis*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*).^{23,117} Our exposure was defined as receipt of at least one provider-order viral test, including rapid influenza antigen, rapid RSV antigen, and/or nucleic acid amplification test (NAAT); dichotomized as tested versus not tested (referent).

Interview, medical record, and laboratory results were maintained in a secure REDCap™ (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database.⁶⁷

Antibiotic Administration & Tiered Discharge Diagnoses

Our outcome variable was defined as antibiotic prescribed during the child's ED visit or administered during hospitalization. Antibiotics were categorized in three main groups: 1) None administered; 2) Narrow-spectrum (e.g., penicillins, tetracyclines, first-generation cephalosporins, and sulfonamides); and 3) Broad-spectrum [e.g., macrolides (azithromycin), amoxicillin-clavulanate, advanced-generation

cephalosporins, quinolones, and clindamycin].^{118,119} In the instance both narrow- and broad-spectrum antibiotics were administered/prescribed during the child's healthcare visit/stay, broad-spectrum was assigned (**Appendix Table B4**).

ICD-10 discharge diagnoses were classified based on the indication for an antibiotic using CDC's tiered diagnosis system (Tier 1-antibiotics almost always indicated; Tier 2-antibiotics may be indicated; Tier 3-antibiotics are not indicated or indications are unclear).¹¹² If a child's visit had ICD-10 codes in multiple tiers, priority was given to Tier 1 diagnoses, followed by Tier 2 and Tier 3 diagnoses.¹¹² Tiered diagnoses were further compared to antibiotic prescribing/administration and provider-ordered viral testing by healthcare setting.

Statistical Analysis

Children's sociodemographic and clinical characteristics by setting were summarized using frequency (percent) for categorical variables and mean (standard deviation) for continuous variables. We performed multiple imputation for 265 children with ≥ 1 missing covariate information, using predictive mean matching with 10 imputation samples (**Appendix Figure B4**).⁵⁶

For each healthcare setting, confounders were assessed through directed acyclic graphs (DAGs, **Appendix Figure B5-6**) generated using priori knowledge. Setting-specific models were built using unconditional polytomous logistic regression with robust sandwich estimators (to account for repeat enrollments) to estimate adjusted odds ratios (aORs) and 95% confidence intervals between provider-ordered viral testing (i.e., tested versus not tested) and provider-ordered viral test result (i.e., positive test versus not tested and negative test versus not tested) and three-level antibiotic administration (i.e., no antibiotics prescribed/administered [referent], narrow-spectrum, or broad-spectrum). Restricted cubic splines were generated for continuous covariates (**Appendix Table B5, Appendix Figure B7**) and determined based on non-linearity evaluated by plotting the risk of being administered/prescribed an antibiotic for each continuous variable (**Appendix Figure B8**). Models were adjusted for pulmonary

symptoms (cough, nasal congestion, rhinorrhea, self-reported wheezing, and shortness of breath; yes or no), wheezing (yes or no), retractions (yes or no), time of year (respiratory season [October-April] or non-respiratory season), any underlying medical condition (yes or no), insurance (none/self-pay, private, or public), temperature ($<100.4^{\circ}\text{F}$, $\geq 100.4^{\circ}\text{F}$ - $<102.0^{\circ}\text{F}$, $\geq 102.0^{\circ}\text{F}$), age, heart rate, respiratory rate, oxygen saturation, illness duration, and multiplicative interactions between age and heart rate and age and respiratory rate. Statistical tests were based on two-tailed probability with a significance level (α) set at 5%. All analyses were performed in R (version 3.6.1).

Exploratory Analysis, Outpatient

Due to small sample sizes (power calculations; **Appendix Figure B9**), we conducted an exploratory analysis in the outpatient setting with the same statistical methods used in the ED and inpatient setting. Comprehensive study design, population, interview, and laboratory testing details are provided in **Appendix File C1**). We performed multiple imputation for 6 children with ≥ 1 missing covariate information, using predictive mean matching with 5 imputation samples (**Appendix Figure B4**).⁵⁶ Unconditional polytomous logistic regression adjusting for age (months), illness duration (days), insurance type (none/self-pay, private, or public), temperature ($<100.4^{\circ}\text{F}$, $\geq 100.4^{\circ}\text{F}$ - $<102.0^{\circ}\text{F}$, $\geq 102.0^{\circ}\text{F}$), pulmonary symptoms (cough, nasal congestion, rhinorrhea, self-reported wheezing, and shortness of breath; yes or no), and underlying medical condition (yes or no) to estimate adjusted odds ratios (aORs) and 95% confidence intervals between provider-ordered viral testing (i.e., tested versus not tested) and provider-ordered viral test result (i.e., positive test versus not tested and negative test versus not tested) and three-level antibiotic administration (i.e., no antibiotics prescribed/administered [referent], narrow-spectrum, or broad-spectrum).

RESULTS

From November 2017 to February 2020, a total of 4,107 enrollments were included, of which 2,616 (64%) were from the ED and 1,491 (36%) were hospitalized. Of the 4,107 enrollments, 455 (11%) children represented multiple ARI enrollments ≥ 90 days apart, which were not mutually exclusive to one

healthcare setting. Overall, 49% (1,294/2,616) and 64% (955/1,491) of children received at least one provider-ordered viral test in the ED and inpatient setting, respectively (**Table 4.B.1**).

Patient Characteristics, by Setting

No sociodemographic differences between receiving and not receiving a provider-ordered viral test were observed among children in either the ED or inpatient setting (**Table 4.B.1**). Overall, children were predominately younger than 5 years and had public health insurance (i.e., Medicaid). In the ED, children were predominantly Black, non-Hispanic and approximately one-third reported at least one underlying medical condition. Children hospitalized were primarily white, non-Hispanic and about one-half had a known underlying medical condition, with respiratory conditions being the most common. In both settings, provider-ordered tests during respiratory season (October-April) were more frequent than in non-respiratory season. In contrast, for children seen in the ED and hospitalized with an ARI, a provider-ordered test was less commonly ordered if wheezing and retractions were found on physical examination (**Table 4.B.1**).

Children seen in the ED most often presented with fever, cough, and nasal congestion/rhinorrhea. Those who presented with myalgia, lethargy, or fever were less likely to have provider-ordered viral testing ordered (**Figure 4.B.1A**). Among hospitalized children, cough, nasal/congestion, lethargy, and shortness of breath were the most common symptoms (**Figure 4.B.1B**); more patients with fever had a provider-ordered viral test. Of note, symptoms in Figure 4.B.1B are not mutually exclusive.

A total of 174 children were enrolled in the outpatient setting, of which 33% (n=58) were administered a provider-ordered viral test. No sociodemographic differences were observed between receiving and not receiving a provider-ordered viral test. Provider-ordered viral tests were more often given to children with private insurance, those in daycare, those with an earache, and if wheezing or crackles were present on physical exam (**Appendix Table B6**). In contrast, children with shortness of breath, wheezing, and fever were less likely to be administered a provider-ordered viral test (**Figure 4.B.1B**).

Table 4.B.1. Sociodemographic and Clinical Characteristics of Children (>30 days-17 years) Enrolled in an Emergency Department and Hospitalized with Acute Respiratory Illness, by Provider-Ordered Viral Testing, Nashville, Tennessee, November 2017-February 2020

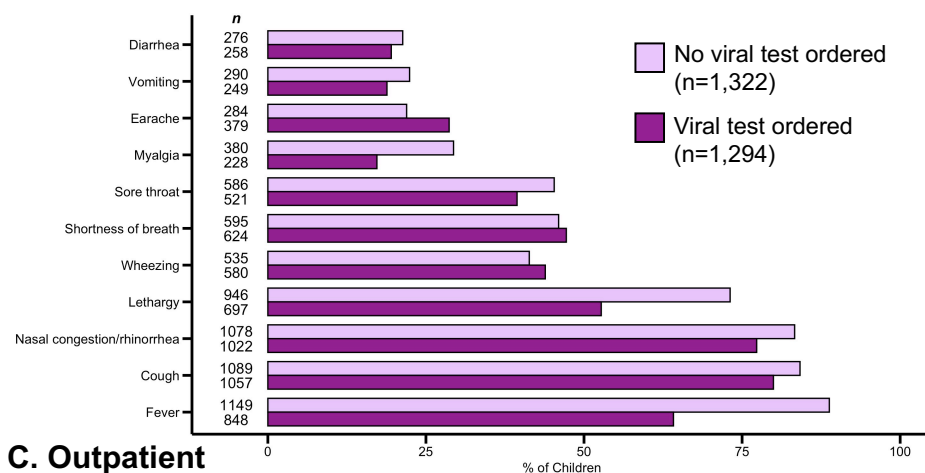
Characteristic(s)	Emergency Department		Inpatient	
	Viral Test Ordered N=1,294	No Viral Test Ordered N=1,322	Viral Test Ordered N=955	No Viral Test Ordered N=536
Age, years—mean (SD)	4.8 (4.5)	4.4 (4.3)	3.2 (4.1)	3.8 (4.2)
Age, years—median (IQR)	3.3 (1.2, 7.3)	2.8 (1.0, 6.5)	1.4 (0.4, 4.1)	2.0 (0.6, 6.0)
0 to <2 years—no. (%)	483 (37.3)	545 (41.2)	565 (59.2)	267 (49.8)
2 to <5 years—no. (%)	321 (24.8)	341 (25.8)	181 (19.0)	112 (20.9)
≥5 to <18 years—no. (%)	490 (37.9)	436 (33.0)	209 (21.9)	157 (29.3)
Sex, male—no. (%)	690 (53.3)	715 (54.1)	552 (57.8)	321 (59.9)
Race—no. (%)				
White, Non-Hispanic	172 (13.3)	181 (13.7)	436 (45.7)	240 (44.9)
Black, Non-Hispanic	517 (40.0)	598 (45.2)	221 (23.1)	134 (25.0)
Other Non-Hispanic	84 (6.5)	98 (7.4)	90 (9.4)	45 (8.4)
Hispanic	509 (39.3)	431 (32.6)	197 (20.6)	113 (21.1)
Unknown	12 (0.9)	14 (1.1)	11 (1.2)	4 (0.7)
Insurance type—no. (%)				
Public	1,049 (81.1)	1,044 (79.0)	630 (66.0)	338 (63.1)
Private	104 (8.0)	115 (8.7)	149 (27.8)	246 (25.8)
Both	6 (0.5)	7 (0.5)	12 (2.2)	15 (1.6)
None/Self Pay	121 (9.1)	141 (10.7)	31 (5.8)	49 (5.1)
Unknown	14 (1.1)	15 (1.1)	6 (1.1)	15 (1.6)
Underlying medical conditions—no. (%)				
≥1 Underlying medical condition	415 (32.1)	454 (34.3)	492 (51.5)	273 (50.9)
Respiratory	225 (17.4)	246 (18.6)	242 (25.3)	164 (30.6)
Asthma/RAD, only	206 (15.9)	227 (17.2)	154 (16.1)	138 (25.7)
Cardiovascular	28 (2.2)	24 (1.8)	104 (10.9)	23 (4.3)
Neurological/Neuromuscular	65 (5.0)	55 (4.2)	168 (17.6)	52 (9.7)
Oncologic/Immunosuppressive	141 (10.9)	177 (13.4)	158 (16.5)	109 (20.3)
Renal	2 (0.2)	2 (0.2)	11 (1.2)	4 (0.7)
Gastrointestinal/Hepatic	39 (3.0)	25 (1.9)	127 (13.3)	29 (5.4)
Endocrine	5 (0.4)	4 (0.3)	28 (2.9)	10 (1.9)
Other	20 (1.5)	56 (4.2)	61 (6.4)	27 (5.0)
Prematurity, <37 weeks ^a	63 (4.9)	46 (3.5)	107 (11.2)	37 (6.9)
Time of Illness ^b —no. (%)				
Respiratory season	1,150 (88.9)	852 (64.4)	766 (80.2)	382 (71.3)
Antibiotic consumption ≤14 days prior to visit/hospitalization—no. (%)	66 (5.1)	92 (7.0)	171 (17.9)	86 (16.0)
Illness duration, days (mean [SD])	2.6 (2.1)	3.0 ^c (2.4)	3.4 ^d (2.6)	3.3 (2.5)
Vital Signs at presentation—mean (SD)				
Maximum temperature, °F (mean [SD])	101.9 ^e (2.0)	100.6 ^f (2.1)	101.5 ^g (2.2)	100.8 ^h (2.1)
Heart rate, bpm	139 ⁱ (28.6)	132.3 ^j (28.0)	152.1 ^k (27.4)	147 (26.7)
Respiratory rate, bpm	28 ^l (8.7)	29 ^m (9.8)	38.4 ^k (13.5)	38.7 (14.2)
Oxygen Saturation, capillary	98.4 ⁿ (1.9)	98.4 ^o (1.9)	95.3 (5.9)	95.7 (3.8)
Physical assessment—no. (%)				
Wheezing	89 (6.9)	189 (14.3)	289 (30.3)	250 (46.6)
Retractions	67 (5.2)	165 (12.5)	460 (48.2)	307 (57.3)
Rapid <i>Streptococcus</i> antigen, positive—no. (%)	77 (6.0)	69 (5.2)	10 (1.0)	5 (0.9)
Clinical Laboratory Cultures—no. (%)				
Bacterial culture, positive	39 (3.0)	29 (2.2)	67 (7.0)	14 (2.6)
Blood	0	0	3 (0.3)	0

Cerebral spinal fluid	0	1 (0.1)	9 (0.9)	2 (0.4)
Respiratory	23 (1.8)	11 (0.8)	19 (2.0)	6 (1.1)
Urine	14 (1.1)	13 (1.0)	33 (3.5)	4 (0.7)
Other	2 (0.2)	4 (0.3)	3 (0.3)	2 (0.4)

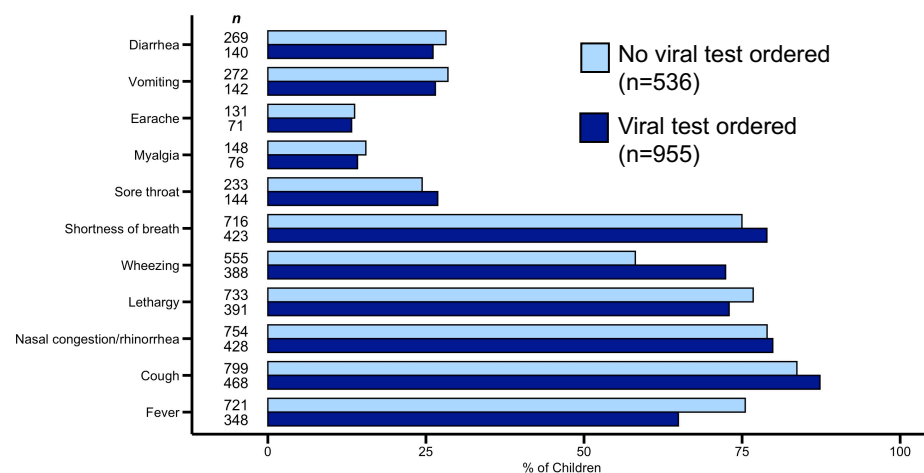
Footnote: ^aHistory of prematurity was reported for children aged <2 yrs; ^bRespiratory season, October-April; ^cn=1,321; ^dn=953; ^en=1,219; ^fn=1,261; ^gn=923; ^hn=522; ⁱn=1,290; ^jn=1,313; ^kn=954; ^ln=1,288; ^mn=1,314; ⁿn=1,289; ^on=1,316

Figure 4.B.1. Symptom Presentation of Children Enrolled in an Emergency Department (A), Hospitalized (B), or Outpatient Clinic (C) with Acute Respiratory Illness, by Provider-Ordered Viral Testing, Nashville, Tennessee

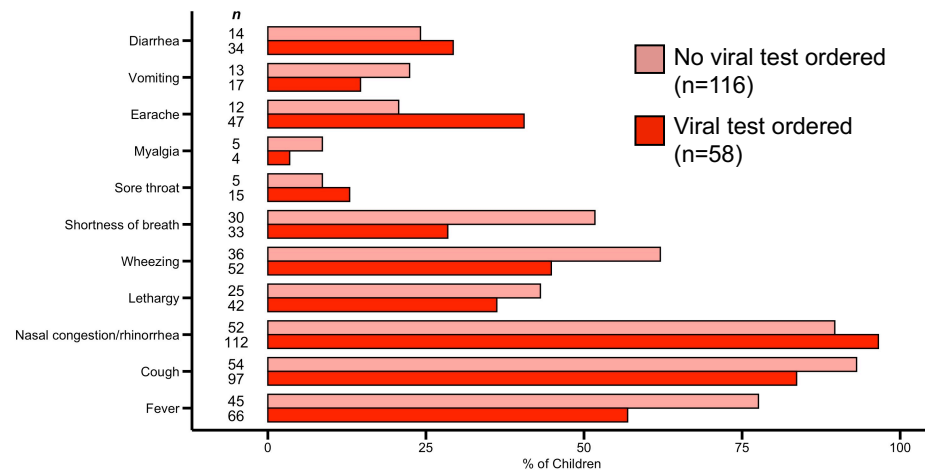
A. Emergency Department



B. Inpatient



C. Outpatient



Provider-Ordered Testing, by Setting

Children with and without provider-ordered viral tests were more often given a rapid *Streptococcus* antigen test in the ED (22%; 573/2,616) than in the inpatient setting (5%; 68/1,491; **Table 4.B.1**).

Among children in the ED, no differences in clinical culture orders were observed between those with and without provider-ordered viral testing. Compared to children hospitalized without a provider-ordered viral test, those with viral testing were more likely to also have bacterial cultures performed, of which 7% detected a bacterial pathogen (**Table 4.B.1**). Bacterial pathogens were most frequently identified from urine and respiratory (e.g., sputum, throat) sources in both the ED and inpatient setting.

In the ED, 87% (1,126/1,294) of viral tests were a rapid influenza antigen, whereas 73% (698/955) of tests in children hospitalized were a molecular respiratory panel (**Table 4.B.2**). The two most common viral pathogens detected from molecular testing were rhinovirus/enterovirus and parainfluenza in the ED and rhinovirus/enterovirus and RSV in the inpatient setting.

Among children in the outpatient setting, only 2 children were administered a rapid *Streptococcus* antigen test. Overall, 48% (28/58) of viral tests administered in the outpatient setting were positive, with the majority influenza (**Table 4.B.2**). Of note, outpatient clinics had the highest proportion of rapid RSV antigen testing compared to the ED and inpatient setting (40% vs. ED: 2% and inpatient: 12%). Nearly half of the rapid RSV tests were RSV positive.

Table 4.B.2. Provider-Ordered Viral Testing Results among Children with Acute Respiratory Illness, by Setting, Nashville, Tennessee

Provider-Ordered Viral Testing ^a	Emergency Department (n=1,294) no. (%)	Inpatient (n=955) no. (%)	Outpatient (n=58) no. (%)
Any Provider-Ordered test, positive	854 (66.0)	694 (72.7)	28 (48.0)
<i>Rapid Antigen Test(s)</i>			
Rapid influenza antigen performed	1,126 (87.0)	339 (35.5)	47 (81%)
Rapid influenza antigen, positive	701/1,126 (62.3)	213/339 (62.8)	18/47 (38%)
Rapid RSV antigen performed	28 (2.2)	117 (12.3)	23 (40%)
Rapid RSV antigen, positive	16/28 (57.1)	64/117 (12.3)	11/23 (48%)
<i>Molecular Test(s) performed</i>	180 (13.9)	698 (73.1)	2 (3.8)
Adenovirus	20/180 (11.1)	58/698 (8.3)	0
Influenza	17/180 (9.4)	51/698 (7.3)	0
RSV	23/180 (12.8)	150/698 (21.5)	1/2 (50.0)
Rhinovirus/enterovirus	63/180 (35.0)	224/698 (32.1)	1/2 (50.0)
Parainfluenza (Types 1-4)	29/180 (16.1)	45/698 (6.4)	0
Human metapneumovirus	8/180 (4.4)	45/698 (6.4)	0
Coronaviruses (endemic)	16/180 (8.9)	35/698 (5.0)	0
<i>Mycoplasma pneumoniae</i>	2/180 (1.1)	21/698 (3.0)	0
<i>Bordetella parapertussis</i>	0	0	0
<i>Legionella pneumophila</i>	0	0	0
<i>Chlamydophila pneumoniae</i>	0	0	0

Footnote: ^amultiple provider-ordered tests may have been administered to a single child during their visit/hospitalization.

Provider-Ordered Viral Testing and Antibiotic Administration

Antibiotics were prescribed in 16% (201/1,294; 74% narrow-spectrum; 26% broad-spectrum) of children with a provider-ordered test in the ED and administered in 25% (239/955; 25% narrow-spectrum; 75% broad-spectrum) of children hospitalized with viral testing. In the ED, receipt of provider-ordered viral testing, regardless of the result (e.g., positive or negative), resulted in a decreased odds of narrow-spectrum antibiotic prescriptions. Specifically, children who received a provider-ordered viral test had 25% lower odds (aOR: 0.75; 95% CI: 0.54, 0.98) of being prescribed a narrow-spectrum antibiotic than no antibiotic during their visit than those who did not receive a viral test (**Table 3**). Conversely prescription of broad-spectrum antibiotics was dependent on the result of the provider-ordered viral test, where we observed a positive result led to a decrease in broad-spectrum therapy, but a negative result showed an increase in broad-spectrum therapy. However, results for these estimates were imprecise to draw strong inferences.

In the inpatient setting, receipt of provider-ordered testing had no effect on narrow-spectrum antibiotics; but a positive result showed a slightly lower odds of narrow-spectrum therapy, where a negative result indicated a higher odds of narrow-spectrum therapy. Strong inferences from these estimates were unable to be drawn due to imprecision. Overall, regardless of the viral test results, receipt of provider-ordered viral test resulted in a increased odds of broad-spectrum antibiotic administration. Children with a negative provider-ordered viral test had 57% increased odds (aOR: 1.57; 95% CI: 1.01, 2.44) of being administered a broad-spectrum antibiotic compared to children with no viral testing (**Table 4.B.3**).

In our exploratory analysis in the outpatient setting, receipt of a provider-ordered viral test, regardless of its result, showed decreased odds of narrow-spectrum antibiotic prescriptions. However, we observed a positive viral test had 28% increased odds of prescribing broad-spectrum antibiotics, but the sample size (n=2) is too small to observe whether this effect is representative of the true estimates in a larger population (**Table 4.B.3**).

Administration of antibiotics by tiered discharge diagnoses and setting are shown in **Figure 4.B.2**. In the ED, 74% (1,923/2,616) of children had a tier 3 discharge diagnosis, with unspecified fever (467/1,932; 24%) and unspecified acute upper respiratory infection (409/1,932; 21%) as the two most common diagnoses. In tier 1 and 2, *Streptococcal* pharyngitis (125/283; 58%) and acute otitis media (214/463; 46%) were the most frequent diagnoses, respectively. Among children in the ED with a tier 3 diagnosis, 96% were not prescribed an antibiotic, regardless of provider-ordered viral testing status. Narrow-spectrum (73%; 315/432) antibiotics were most frequently prescribed in the ED, with 35% in tier 1, 50% in tier 2, and 16% in tier 3 (**Figure 4.B.2**).

Among children hospitalized, 69% (1,031/1,491) were assigned a tier 3 diagnosis, followed by tier 2 and then tier 1 (**Figure 4.B.2**). The most common discharge diagnoses were pneumonia (73/275; 27%), acute otitis media (81/139; 58%), and acute bronchiolitis due to RSV (195/1,077; 18%) for tiers 1, 2, and 3, respectively. Overall, 87% of children hospitalized and assigned a tier 3 discharge diagnosis were not administered an antibiotic. In the inpatient setting, broad-spectrum (72%; 241/334) were the most common antibiotics administered, with 39% of broad-spectrum antibiotics administered to patients with discharge diagnoses in tier 1, 15% in tier 2, and 46% in tier 3 (**Figure 4.B.2**).

Table 4.B.3. Polytomous Logistic Regression of the Association of Provider-Ordered Viral Testing and Antibiotic Administration among Children with Acute Respiratory Illness, by Setting

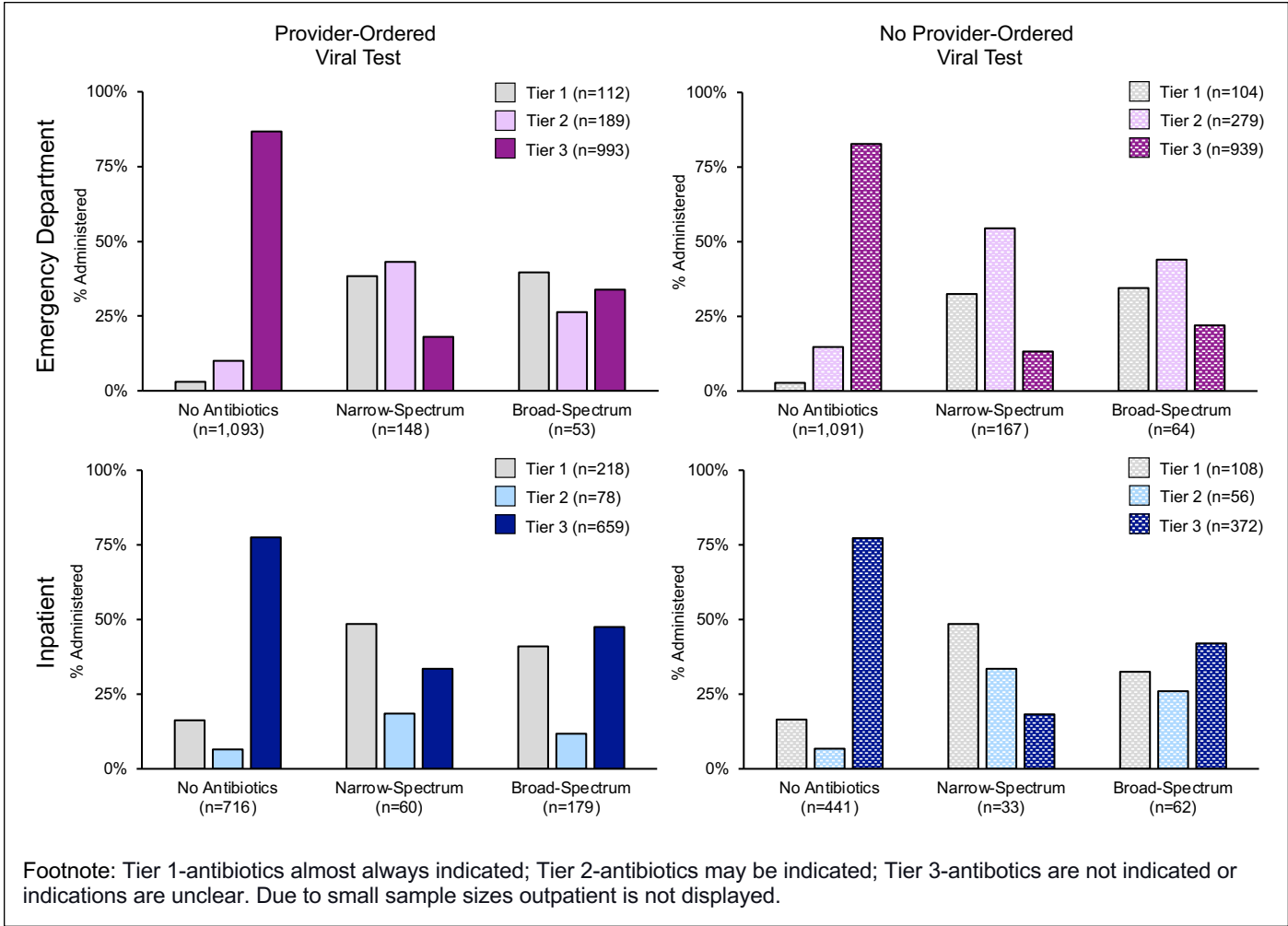
Setting	Provider-Ordered Viral Test	No Antibiotic(s)	aOR (95% CI)	P-value	Antibiotics					
					Narrow-Spectrum	aOR (95% CI)	P-value	Broad-Spectrum	aOR (95% CI)	P-value
ED ^a (n=2,616)	Viral Test/No Viral Test	1093/1091	Ref.	Ref.	148/167	0.75 (0.54, 0.98)	0.035	53/64	0.89 (0.58, 1.36)	0.577
	Positive Viral Test/No Viral Test	723/1091	Ref.	Ref.	101/167	0.75 (0.56, 1.01)	0.062	30/64	0.72 (0.44, 1.19)	0.205
	Negative Viral Test/No Viral Test	370/1091	Ref.	Ref.	47/167	0.74 (0.51, 1.07)	0.111	23/64	1.11 (0.65, 1.89)	0.696
Inpatient ^a (n=1,491)	Viral Test/No Viral Test	716/441	Ref.	Ref.	60/33	1.00 (0.62, 1.62)	0.989	179/62	1.27 (0.90, 1.80)	0.180
	Positive Viral Test/No Viral Test	538/441	Ref.	Ref.	41/33	0.90 (0.53, 1.51)	0.683	115/62	1.16 (0.79, 1.68)	0.448
	Negative Viral Test/No Viral Test	178/441	Ref.	Ref.	19/33	1.34 (0.71, 2.53)	0.369	64/62	1.57 (1.01, 2.44)	0.046
Outpatient (n=174) ^b	Positive Viral Test/No Viral Test	20/80	Ref.	Ref.	6/27	0.72 (0.21, 2.50)	0.601	2/9	2.15 (0.23, 19.8)	0.500
	Negative Viral Test/No Viral Test	26/80	Ref.	Ref.	3/27	0.25 (0.06, 0.97)	0.045	1/9	0.41 (0.03, 4.99)	0.484

Footnote:

^a models were adjusted for pulmonary symptoms (cough, nasal congestion, rhinorrhea, self-reported wheezing, and shortness of breath; yes or no); age (restricted cubic spline, 4-knots), maximum temperature (<100.4°F, ≥100.4°F -<102.0°F, ≥102.0°F), illness duration (restricted cubic spline, 3-knots), respiratory rate (restricted cubic spline, 4-knots), heart rate (restricted cubic spline, 4-knots), oxygen saturation (restricted cubic spline, 3-knots), wheezing (yes or no), retractions (yes or no), insurance (none/self-pay, private, or public), underlying medical condition (yes or no); time of year [respiratory season (October-April) or non-respiratory season]; age*heart rate (restricted cubic spline, 4-knots each), age*respiratory rate (restricted cubic spline, 4-knots each).

^bmodel was adjusted for pulmonary symptoms (cough, nasal congestion, rhinorrhea, self-reported wheezing, and shortness of breath; yes or no); age (restricted cubic spline, 4-knots), maximum temperature (<100.4°F, ≥100.4°F -<102.0°F, ≥102.0°F), illness duration (restricted cubic spline, 3-knots), wheezing (yes or no), retractions (yes or no), insurance (none/self-pay, private, or public), underlying medical condition (yes or no).

Figure 4.B.2. Antibiotic Administration Practices Among Children (>30 days-17 years) Enrolled in an Emergency Department and Hospitalized with Acute Respiratory Illness, by Tiered Discharge Diagnosis Classification and Provider-Ordered Viral Testing, Nashville, Tennessee, November 2017-February 2020.



DISCUSSION

In this active ARI surveillance study of 4,107 children in Nashville, Tennessee, we evaluated the association of provider-ordered viral testing and viral test results with antibiotic prescribing and administration in the ED and inpatient settings. In the ED, influenza rapid antigen tests were administered in 87% of all tests performed. The most common antibiotics prescribed were narrow-spectrum, and receipt of provider-ordered viral testing decreased narrow-spectrum antibiotic use. In the inpatient setting, 73% of all tests performed were a molecular respiratory panel, broad-spectrum antibiotics (empiric therapy) were the most frequently administered, and a negative provider-ordered viral test increased broad-spectrum antibiotic administration. Regardless of setting, a positive provider-ordered viral test did not impact antibiotic administration practices and children primarily had a tier 3 discharge diagnosis. Our findings demonstrate that provider-ordered viral testing and antibiotic administration practices differ by setting.

In the ED, we found provider-ordered viral testing decreased the use of narrow-spectrum antibiotics, which may reflect the high prevalence of influenza antigen testing and tier 3 diagnoses. Concordant with our findings, *Bonner et al.*,¹²⁰ conducted a randomized prospective trial in an Alabama pediatric ED and reported a 34% decreased risk (RR: 0.66; 95% CI: 0.45, 0.96) of receiving an antibiotic among children with rapid influenza antigen testing.¹⁰³ We also found provider-ordered viral testing in the ED did not lead to a decreased use of broad-spectrum antibiotics, and positive viral tests were not associated with antibiotic administration practices. These findings mirror three of four studies included in a meta-analysis,^{103,121-123} along with a single-center study in Colorado,¹²⁴ and a multi-center study in Europe¹²⁵ evaluating the effect of respiratory viral testing and antibiotic prescribing in EDs. Discordant results may be ascribed to the various test options available, or the sensitivity and specificity of testing platforms used across institutions. We also showed nearly three-quarters of antibiotics prescribed in the ED were narrow-spectrum and were most frequently administered to children with a tier 2 diagnosis—where more than one-half of diagnoses were attributed acute otitis media. Prior studies have revealed broad-spectrum antibiotics account for more than half of antibiotics prescribed in ED's for respiratory

tract infections in children.^{3,27,126} However, these studies included non-pediatric EDs, which prescribed macrolides (broad-spectrum antibiotic) more often than pediatric EDs.¹²⁶ The use of narrow-spectrum antibiotics is in compliance with the American Academy of Pediatrics clinical management guidelines for acute otitis media, which recommends amoxicillin (narrow-spectrum) as the first-line defense when an antibiotic is indicated.¹²⁷ Discrepancies across studies also may be attributed to varying practices and adherence to antimicrobial stewardship programs. Core elements of antimicrobial stewardship are set by the Centers for Disease Control and Prevention,¹²⁸ but program components are developed and implemented by each individual institution/center. Further studies evaluating correlations between antibiotic stewardship in the outpatient settings and provider-ordered viral testing on antibiotic prescribing practices are needed.

Among hospitalized children, the lack of a provider-ordered tests was associated with a higher frequency of broad-spectrum antibiotics. This finding is not surprising and may be explained by the practice of administering empiric antibiotics (broad-spectrum) when there is suspicion of a bacterial infection, but the bacterial etiology is not yet known. Studies evaluating provider-ordered testing and antibiotic practices in hospitalized children have heterogeneous findings,¹²⁹⁻¹³¹ and a meta-analysis concluded viral testing did not influence antibiotic practices in hospitals.⁵⁹ Similar to the ED, testing platform options and antimicrobial stewardship practices and adherence might explain the variable impact of viral testing on antibiotic practices across studies. In our study, broad-spectrum antibiotics were the most common type of antibiotic used in the inpatient setting, with administration in both tier 1 and 3 diagnoses. Because we only assessed active and completed antibiotics, we were unable to determine whether empiric antibiotics were stopped among children with a tier 3 diagnosis once provider-ordered viral and bacterial test results were reported. Additional studies assessing the impact of provider-ordered testing on halting empiric antibiotic treatment of patients are needed to define and optimize the value of respiratory pathogen testing on antibiotic use in these settings.

Our study results should be considered in context of some limitations. First, our study findings are from one ED and hospital and may reflect antibiotic stewardship strategies implemented at our institution. Thus, our results may not be generalizable to practices across other institutions or settings, such as outpatient or urgent care facilities. Second, in the ED, we did not measure whether antibiotic prescriptions were filled and completed appropriately. However, we believe this limitation minimally impacted our study as our goal was to evaluate the clinical practices of viral testing and antibiotic prescribing. Third, in our study we restricted antibiotics to those that were active or completed and did not evaluate the association between viral testing and halting of empiric (broad-spectrum) antibiotic therapy. Therefore, our results may underestimate the total number of antibiotics ordered during a child's ED visit/hospitalization. Fourth, we were unable to assess whether clinician years of experience or provider type (e.g., attending physician, resident, physician assistant, nurse practitioner) impacted the prevalence of viral testing and antibiotic administration practices. Prior studies have shown both years of experience and provider type to be associated with differences in antibiotic prescribing practices.¹³² Fifth, our study was unable to fully interpret the association of provider-ordered viral testing and antibiotic prescribing practices in the outpatient setting. Our findings in the outpatient setting suggest clinical practices are similar to what we observed in the ED, but due to small sample sizes we cannot be certain. Additional studies focusing on viral testing practices in the outpatient settings are needed. Finally, the study period reflects clinical viral testing and antibiotic prescribing and administration practices prior to the coronavirus disease 2019 (COVID-19) pandemic. Studies have recently reported that during the COVID-19 pandemic, changes in healthcare seeking behaviors (i.e., decreases in visits) led to a dramatic reduction of antibiotic prescriptions (31.6 to 6.4 prescriptions per 1000 visits) in children for respiratory tract infections.¹³³ However, reports from April to June 2021 have shown a rebound in both respiratory tract infections and antibiotic prescriptions.¹³³ Additional studies are needed to evaluate the relative impact of viral testing for severe acute respiratory syndrome coronavirus 2 on antibiotic administration practices among children.

CONCLUSION

In conclusion, the influence of provider-ordered viral testing on antibiotic administration practices differs by setting and may be heavily influenced by the components of and adherence to antimicrobial stewardship strategies within individual institutions. Future research should address the impact of provider-ordered testing on halting of empiric antibiotics in inpatient settings and assess the combination of antimicrobial stewardship strategies and viral testing on antibiotic administration practices across settings.

V. DEVELOPMENT AND EXTERNAL VALIDATION OF A DIAGNOSTIC VIRAL ARI MODEL IN CHILDREN

INTRODUCTION

Acute respiratory infections (ARIs), commonly caused by respiratory viruses, are the leading cause of global childhood morbidity, with approximately 156 million new infections per year.¹⁶ In addition to respiratory viruses, ARIs are also caused by bacteria, which have overlapping clinical presentation inducing diagnostic uncertainty. Current diagnostic platforms distinguishing viral ARIs include point-of-care tests for influenza and respiratory syncytial virus (common viral ARIs) and novel molecular assays capable of detecting multiple viruses and common respiratory bacteria on one test platform. Yet, these diagnostic tools are not widely accessible to developing countries or integrated into all healthcare settings in developed countries (resource-limited settings), including the United States (U.S.).¹³⁴ Reasons for limited accessibility include cost, complexity, requirement of advanced laboratory infrastructure, and turnaround time.^{35,134}

The hedge of diagnostic accessibility further confines clinicians to determine etiologic ARI causes from clinical symptoms, shown to be associated with increased empiric antibiotic administration and prescriptions. Antibiotic treatment for viral infections has been shown to influence future infection resistance patterns.²⁹ Globally, antimicrobial resistance results in 700,000 deaths per year across all ages, with approximately 200,000 among children.²⁹ Diagnostic certainty of ARI etiologies can improve misdiagnosis and antibiotic misuse.^{29,30} In effort target diagnostic challenges, researchers have strived to develop diagnostic prediction models for ARIs. In our recent systematic review (**Chapter III**), we identified 18 diagnostic models predicting the probability of a child having a viral ARI.¹³⁵ Among these studies, 44% of models were developed in an inpatient setting, 72% were developed outside the U.S, and analytic bias was extensive across all studies. The most common analytic domains receiving a high risk of bias included lack of reporting model performance measures (e.g., discrimination or calibration), limited internal validation, dichotomizing continuous predictors, using complete case analysis to handle missing data, and overfitting (**Chapter III**).

Therefore, we aimed to develop two diagnostic prediction models in the ED and inpatient settings, using data available at the time of clinical presentation to distinguish viral ARIs among symptomatic children. In addition, we externally validated setting-specific models using a U.S. outpatient dataset and a hospital dataset from Jordan.

METHODS

Study Design & Population of Model Development Settings

We used data collected from a prospective ARI viral surveillance study as part of the Centers for Disease Control and Prevention funded New Vaccine Surveillance Network (NVSN)^{8,91} in Nashville, Tennessee between November 2, 2017, and February 28, 2020. Year-round recruitment occurred 4 days/week in the ED and 5 days/week in the inpatient setting at the Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center (VUMC). Institutional Review Boards at VUMC and the CDC reviewed and approved this study.¹⁰⁵

Children were eligible if they were younger than 18 years, resided within the catchment/surveillance area, and presented to an ED or were hospitalized within 48 hours of enrollment (**Appendix Figure B1**). Children were required to have at least one of the following symptoms in the 14 days prior to enrollment: fever, cough, earache, nasal congestion, runny nose, sore throat, post-tussive vomiting, wheezing, shortness of breath/rapid or shallow breathing, myalgia, apnea, apparent-life threatening event, or brief resolved unexplained event (e.g., unresponsive, etc.).^{8,91} A child was ineligible if any of the following criteria were met: chemotherapy-associated fever and neutropenia (absolute neutrophil count <500/ μ L), newborns never discharged since birth, transferred to VUMC from another hospital >48 hours after initial admission, recently hospitalized (≤ 5 days), or previously enrolled in the study within the past 14 days.^{8,91}

Study-Specific Exclusion Criteria

In this study for all settings, we further excluded children younger than 30 days to minimize the inclusion of serious bacterial infections due to differences in clinical management practices, and children with multiple ARI enrollments <90 days apart. We considered children with multiple ARI enrollments (≥ 90 days from the prior visit) as susceptible to a new viral or bacterial ARI. Methods and results are reported in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Guidelines¹³⁶ (TRIPOD, **Appendix Table C1**).

Data Collection & Viral Laboratory Testing

After obtaining informed consent, trained research personnel interviewed the parents/guardians of enrolled children to collect demographic (age, sex, race, ethnicity, insurance type), clinical symptoms, and past medical histories using a standardized form. Vital signs at the time of presentation (respiratory rate, heart rate, oxygen saturation), physical exam findings, bacterial testing (i.e., rapid *Streptococcus* antigen testing and bacterial cultures), and the first five discharge diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10]) were abstracted from each child's medical record. Final clinical disposition was determined by the highest level of care provided to the child during their visit (i.e., children enrolled in the ED and later hospitalized were considered inpatient).

Research specimens (e.g., nasal, oropharyngeal, and/or tracheal aspirates) were collected from all enrolled children and placed in viral transport medium by study personnel. All research specimens were transported to the VUMC research laboratory and stored at 4°C until processed, within 48-hours. Testing was performed using (quantitative reverse transcription-polymerase chain reaction) assays for the following viruses: adenovirus, human metapneumovirus, influenza (A, B, and C), parainfluenza (types 1-4), respiratory syncytial virus (RSV), rhinovirus, and endemic coronaviruses (OC43, 229E, NL63, and HKU1). Research specimen collection and molecular testing were performed in accordance with the NVSN study protocol.^{8,91}

Interview, medical record, and research specimen results were maintained in a secure REDCapTM (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database.⁶⁷

Model Outcome-Viral ARI versus Other ARI

Our primary outcome was viral ARI dichotomized as: 1) viral ARI; and 2) other ARI [probable bacterial or viral and probable bacterial co-detection (mixed infection)]. Probable bacterial and mixed infections are collapsed into one category because the clinical management (e.g., antibiotic therapy) for both groups are the same.

Due to the potential of a child presenting with ARI, but not having a viral or bacterial pathogen detected from clinical cultures or viral research assays, we further used the CDC's tiered diagnosis system [Tier 1-antibiotics almost always indicated (e.g., pneumonia, sepsis, etc.); Tier 2-antibiotics may be indicated (e.g., acute otitis media); Tier 3-antibiotics are not indicated or indications are unclear (e.g., bronchiolitis, influenza, etc.)]¹¹² to classify the first five ICD-10 discharge diagnosis codes into categories that would correspond to the clinical management of a child. Children with a tier 1 or 2 ICD-10 code were categorized into other ARI [probable bacterial ARI (ED: 728; inpatient: 452)]; and children with tier 3 diagnoses and no viruses detected from research assays were categorized into viral ARI (ED:607; inpatient=376). If a child's visit had ICD-10 codes in multiple tiers, priority was given to Tier 1 diagnoses, followed by Tier 2 and Tier 3 diagnoses.¹¹²

Comprehensive details on final viral and other ARI ascertainment are provided in **Appendix Table C2**. In brief, viral ARI was defined as a child having at least one virus detected from their research respiratory specimen and no bacterial pathogen detected or a Tier 1 or 2 discharge diagnosis. In addition, those with a Tier 3 diagnosis not meeting a probable bacterial ARI and had no virus detected from their respiratory research were also classified into viral ARI. Whereas children with a bacterial pathogen detected from rapid Streptococcus antigen tests or clinical cultures or had a Tier 1 or 2 discharge diagnosis were categorized into other ARI.

Candidate Predictors for Model Development

Candidate predictors for each setting were selected based on prior knowledge, clinical input, and the likelihood of availability to other healthcare institutions. Sample size calculations using the three sample size criteria proposed by Riley et al¹³⁷ were conducted for each setting by the total number of candidate predictor and final predictor parameters (**Appendix Table C3**). The three criteria assess adequate sample size for: 1) overfitting defined by an expected shrinkage of predictor effects by 10% or less; 2) absolute difference of 0.05 in the model's apparent and adjusted R-squared value; 3) precise estimation (within +/- 0.05) of the average outcome risk in the population.¹³⁷ In the ED, our sample size of 2,616 meets all three criteria requirements in the candidate predictor and final model predictor domains. However, our sample size in the inpatient setting is sufficient to fulfill criterion 2-3, but with our sample size have small overfitting by an expected shrinkage of predictor effects by 10% or less. Full details are provided in **Appendix Table C3**.

Twenty-two candidate predictors (total 27 parameters) were considered: age, temperature, respiratory rate, heart rate, oxygen saturation, illness duration, household size, health insurance, respiratory season, cough, nasal congestion/rhinorrhea, lethargy, earache, sore throat, myalgia, wheezing present on physical exam, and the following underlying medical conditions: respiratory, cardiovascular, neurologic, oncologic, and other (**Appendix Table C2**).

Model Development & Internal Validation

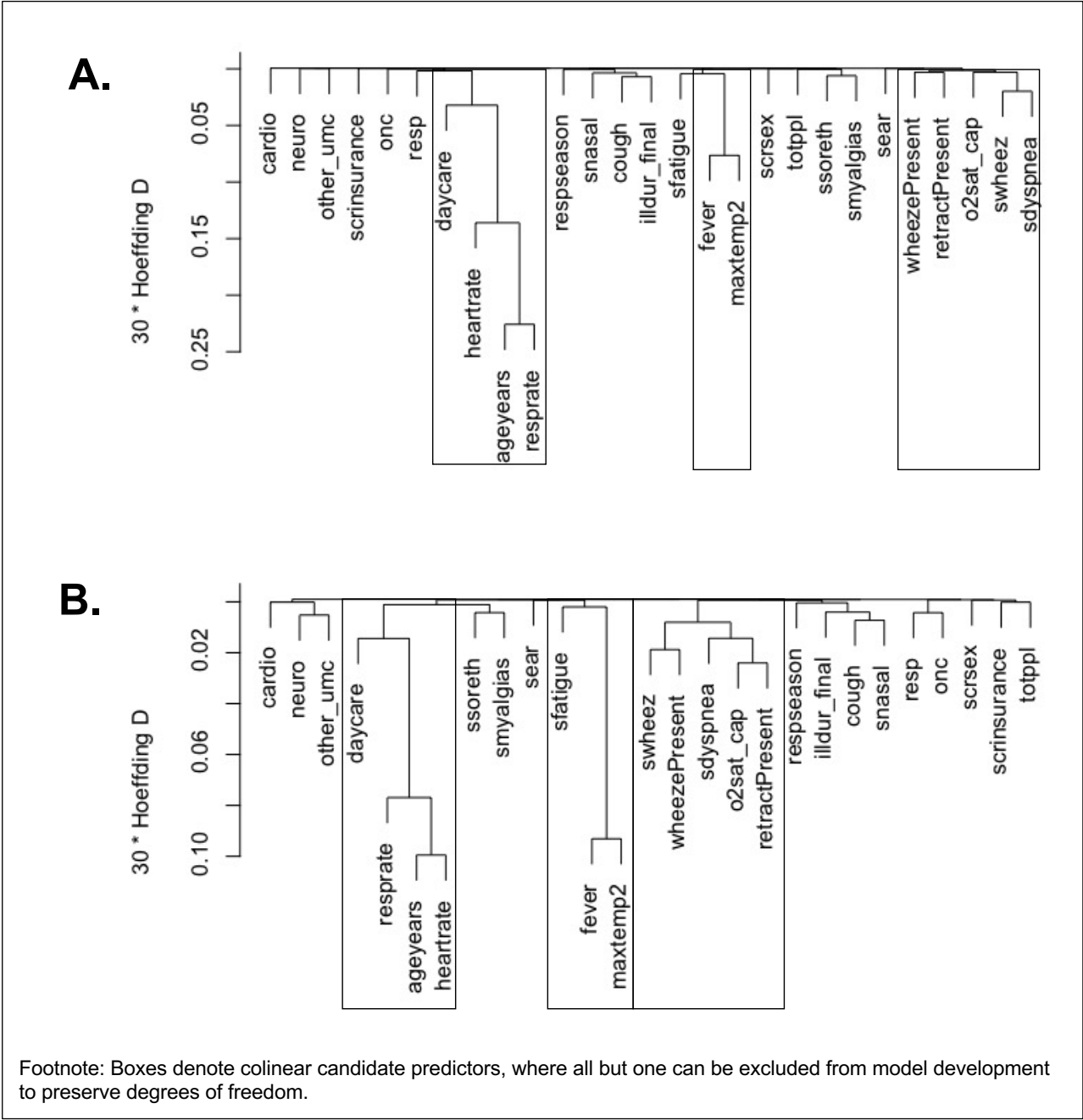
We performed multiple imputation for 265 children with ≥ 1 missing covariate (ED: 194 missing; inpatient: 71 missing), with 10 imputation samples.⁵⁶ Imputed values were averaged using the median for continuous variables and mode for categorical variables and summarized into one complete dataset. Our final analytic sample size in the ED and inpatient settings consisted of 4,107 children (ED: 2,616; inpatient: 1,491).

Redundancy analyses evaluating collinearity across candidate predictors was performed using Hoeffding D statistic for each setting (**Figure 5.1**).⁹⁵ From the redundancy analysis daycare, fever, and self-reported shortness of breath and wheezing, and retractions identified on physical exam were removed in both healthcare settings. Non-linearity was assessed by setting with a global chunk test using restricted cubic splines with various knots per continuous covariate (3-knots: temperature, oxygen saturation, illness duration; 4-knots: respiratory rate and heart rate; 5 knots: age). In the ED, age was the only non-linear variable and was modeled using a restricted cubic spline with 5-knots. In the inpatient setting, temperature and age were found to be non-linear and modeled with 3- and 5-knots. Knot values are provided in **Appendix Table C2**.

Each setting-specific model was developed using logistic regression for a binary outcome. Bootstrap backwards selection was used to identify the most important predictors for viral, ARI. Variables selected in $\geq 87\%$ of the 500 bootstrap repetitions in each setting-specific model were included.^{138,139} Bootstrap frequency thresholds were determined based on model performance measures.

Model performance was evaluated with discrimination and calibration measures. Discrimination, measures the model's ability to distinguish viral ARI from non-viral ARI, was calculated using the concordance index (c-index) and shown graphically with a receiver operating characteristic (ROC) curve. The C-index ranges from 0.5 (no discriminative ability) to 1.0 (perfect discrimination). Agreement between each model's observed and predicted outcomes (i.e., calibration) were assessed with a calibration plot, slope, and intercept.¹⁴⁰ Overall fit for each setting-specific model was evaluated using the Brier score [ranging from 0 (perfect accuracy) to 1 (inaccuracy)]. Internal validation using enhanced bootstrapping with 200 replications was used to estimate the optimism-corrected performance measures for each setting-specific model.⁹⁵ Final model predictions for each setting-specific model account for shrinkage according to the heuristic shrinkage $[(X^2 - df) / X^2]$ factor to correct for overfitting and uncertainty induced by the variable selection process.⁹⁵

Figure 5.1. Redundancy Analysis Evaluating Collinearity Across Candidate Predictors using Hoeffding D Statistic in the Emergency Department (A) and Inpatient Setting



Sensitivity Analysis

We developed an additional model for each setting excluding all children with a tier 3 discharge classification and no virus detected from research assays. Redundancy analyses and non-linearity assessment were re-evaluated, and model development was conducted using the same methods as the initial models. In the inpatient setting, no continuous variables were non-linear and were left as continuous; whereas age remained non-linear in the ED and was modeled using a restricted cubic spline with 5-knots. Model performance measures (discrimination, calibration, and Brier scores) were compared to the initial model developed in each setting.

Model External Validation, by Setting

Emergency Department Validation Populations

The initial ARI model developed in the ED was externally validated through geographic and spectrum transportability (i.e., validating a model among patients who are on average more [or less] advanced in their disease process).⁹⁶ Spectrum transportability is relevant and important when a model is developed in a secondary care setting.⁹⁶ Specifically, spectrum transportability was conducted among the 1,491 children hospitalized from the Nashville NVSN dataset and an outpatient viral surveillance study from December 2019-February 2020 among 174 children (≥ 30 days- < 11 months). **Appendix File C1**, provides comprehensive details study design, population, data collection, and laboratory testing methods for the outpatient setting.

Inpatient Validation Populations

The initial inpatient ARI model was tested (geographic and temporal external validation) in validation samples of children younger than two years with ARI hospitalized in a government-run hospital in Amman, Jordan. The validation sample includes 362 children hospitalized between January-February 2020.¹⁴¹ Study design, population, data collection, and laboratory testing details are provided in **Appendix File C1**.

External Validation Statistical Evaluation

Patient characteristics from the initial setting-specific models were descriptively compared to the characteristics of external validation samples. Model performance measures were compared with discrimination and calibration plots, intercepts, and slopes.

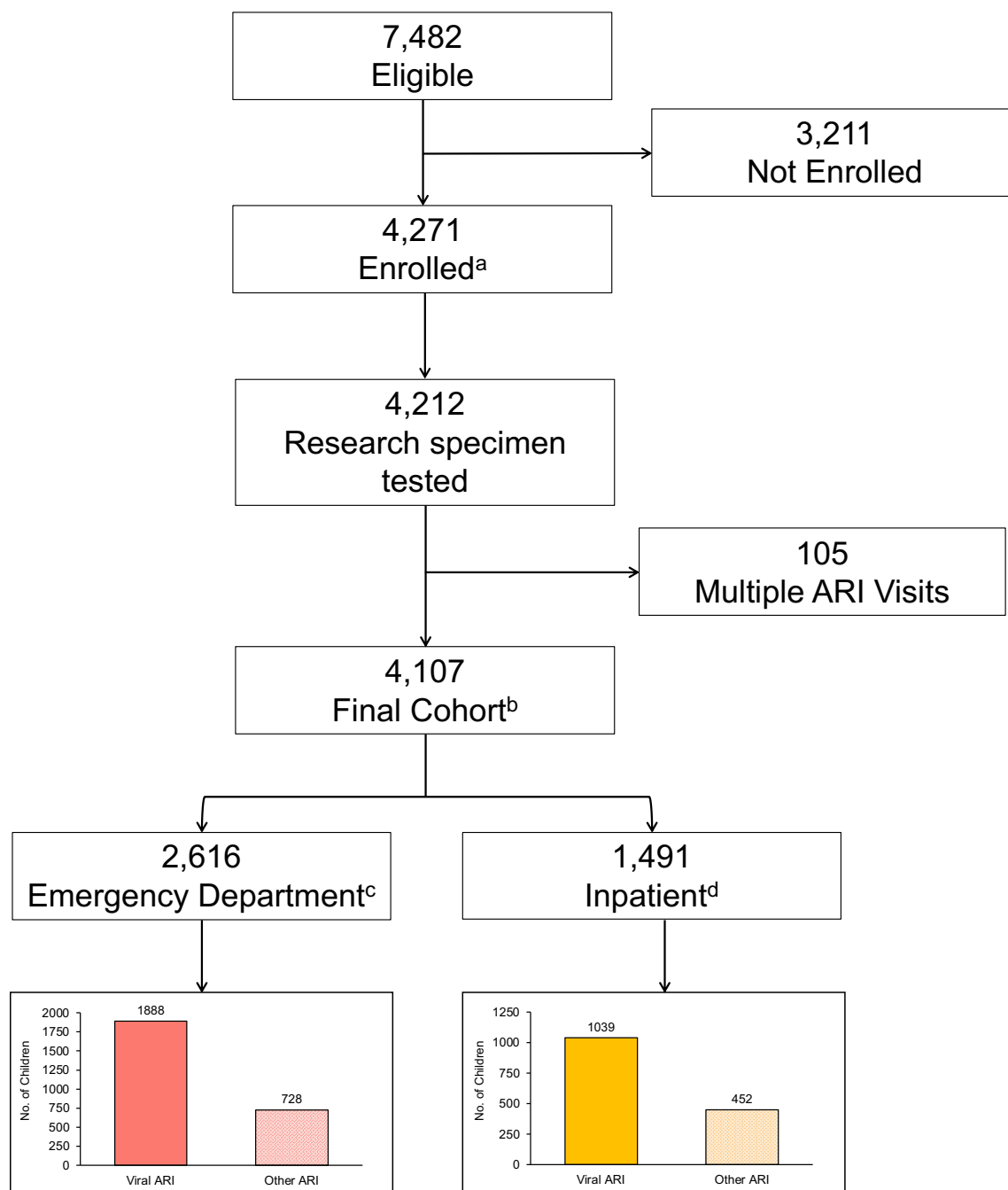
RESULTS

During our study period, 4,107 children were enrolled, with 455 (11%) children having multiple ARI visits ≥ 90 days apart, with 12 children incurring multiple visits in both healthcare settings (**Figure 5.2**). Overall, 2,616 (64%) visits were incurred in the ED and 1,491 (36%) were hospitalized, with 1,888 (72%) and 1039 (70%) classified as viral ARIs, respectively.

Sociodemographic and Clinical Characteristics

In both settings, most children were male, had public health insurance (i.e., Medicaid), were seen during respiratory season (October-April), and presented with cough and/or rhinitis (nasal congestion/rhinorrhea; **Appendix Table C4**). Compared to the ED, children hospitalized were younger, had higher heart and respiratory rates, more often had wheezing or retractions present on physical exam, and more likely to have an underlying medical condition.

Figure 5.2. Consort Diagram of Children (>30 days-17 years) Enrolled in an Emergency Department and Hospitalized with Acute Respiratory Illness, Nashville, Tennessee, November 2017-February 2020



Viral ARI Model Performance by Setting

Emergency Department

After bootstrap backwards selection, the most important predictors for viral ARI were illness duration, earache, sore throat, age, wheeze present on physical exam, cough, myalgia, and nasal congestion (**Table 5.1**). The diagnostic prediction model for viral ARI demonstrated good discrimination with a c-index of 0.74 (95% CI: 0.72, 0.76; **Figure 5.3A**) and good calibration with a near-diagonal curve from 0.2 to 1.0 (**Figure 5.3B**). Calibration departure between 0.2 to 0.4 are likely attributed to lack of children with other ARIs. The Brier score was 0.17 (good overall model accuracy, **Appendix Table C5**). After internal validation, the optimism-corrected c-index was 0.74 (95% CI: 0.71, 0.76) and optimism-corrected slope and intercept were 0.97 and 0.02, indicating minimal to no overfitting (**Appendix Table C5**).

After applying heuristic shrinkage factor of 0.97, predicted risks from the final model can be applied to an external population by using a nomogram (**Figure 5.4**). Based on the clinical symptoms and physical exam findings at the time of presentation, a sum of the total points for each important predictor is added to determine the risk a child has for a viral ARI. For example, if a child has illness duration of 3 days (points=52), no earache (points=100), no sore throat (points=28), is two years old (points=40), wheezing present on physical exam (points=62), cough (points=35), no myalgia (points=0), and rhinitis (points=25); the risk a child has a viral ARI is approximately 0.93 (total points=52+100+28+40+62+35+0+25=342). In addition to the nomogram, predicted risks can also be calculated with the following formula:

$$\text{logit}[E(\text{viral ARI} = 1)|\beta_i] = \alpha + \beta_1(\text{illness duration}) + \beta_2(\text{earache}) + \beta_3(\text{sore throat}) + \beta_4(\text{age}') + \beta_5(\text{wheeze on physical exam}) + \beta_6(\text{cough}) + \beta_7(\text{myalgia}) + \beta_8(\text{rhinitis}),$$

$i = 11 \text{ parameters}$

Using the expit function:

$$\begin{aligned} 1/[1 + \exp [-E(\text{viral ARI} = 1 * [0.97, \text{heuristic shrinkage}])]] \beta_i \\ = 5.9934 + (-0.0841) * (\text{illness duration}) + (-1.5621) * (\text{earache}) + (-0.4083 \\ * (\text{sore throat}) + 0.0102 * (\text{age}) + (-7.3262) * (\text{age}') + 12.2861 * (\text{age}'') + (-5.3187) \\ * (\text{age}''') + 0.7301 * (\text{wheeze present on physical exam}) + 0.4512 * (\text{cough}) + 0.3247 \\ * (\text{myalgia}) + 0.3337 * (\text{rhinitis}) \end{aligned}$$

Inpatient

After bootstrap backwards selection, the most important predictors for viral ARI were maximum temperature, earache, wheeze present on physical exam, age, respiratory rate, and illness duration (**Table 5.1**). The diagnostic prediction model for viral ARI demonstrated good discrimination with a c-index of 0.71 (95% CI: 0.68, 0.74; **Figure 5.3A**) and good calibration with a near-diagonal curve from 0.2 to 1.0 (**Figure 5.3B**) and a Brier score of 0.19 (good overall model accuracy, **Appendix Table C5**). After internal validation, the optimism-corrected c-index was 0.70 (95% CI: 0.67, 0.73) and optimism-corrected slope and intercept were 0.94 and 0.03, indicating minimal to no overfitting (**Appendix Table C5**). After applying heuristic shrinkage factor of 0.94, predicted risks from the final model can be applied to an external population by using a nomogram (**Figure 5.4**) or with the following formula:

$$\text{logit}[E(\text{viral ARI} = 1)|\beta_i] = \alpha + \beta_1(\text{maximum temperature})' + \beta_2(\text{earache}) + \beta_3(\text{wheeze on physical exam}) + \beta_4(\text{age})''' + \beta_5(\text{respiratory rate}) + \beta_6(\text{illness duration})$$

$i = 10 \text{ parameters}$

Using the expit function:

$$\begin{aligned} 1/[1 + \exp [-E(\text{viral ARI} = 1 * [0.94, \text{heuristic shrinkage}])|\beta_i] \\ = 44.7728 + (-0.4253) * (\text{maximum temperature}) + 0.2632 * (\text{maximum temperature}') \\ + (-0.9759) * (\text{earache}) + 0.6007 * (\text{wheeze present on physical exam}) + 0.3397 * (\text{age}) \\ + (-60.8689) * (\text{age}') + 89.2862 * (\text{age}'') + (-29.7840) * (\text{age}''') + (-0.0169) \\ * (\text{respiratory rate}) + (-0.0588) * (\text{illness duration}) \end{aligned}$$

Sensitivity Analysis

Final models requiring a respiratory virus to be detected from a research respiratory specimen are shown in (**Appendix Tables C5-6, Appendix Figure C1**). Overall, both setting-specific models had similar discrimination to our initial final models with an optimism-corrected c-index of 0.75 (95% CI: 0.73, 0.78) in the ED and 0.71 (95% CI: 0.68, 0.74) in the inpatient setting. However, Brier scores indicate our initial final models perform slightly better than the models restricting to research respiratory testing.

External Validation by Setting

Across external validation datasets, children were predominantly male and less than one-quarter of children had a known underlying medical condition. Children seen in the outpatient clinics had an average age of 7 months, were racially and ethnically diverse (**Appendix Table C7**) and the prevalence of viral ARI was 74% (133/174). In the Jordan hospital sample, children had a mean age of 6 months and a viral ARI prevalence of 93% (336/352).

Emergency Department External Validation

Our viral ARI model in the outpatient setting performed well with a good discrimination with a c-index of 0.73 (95% CI: 0.63, 0.82) and good calibration (slope: 0.65; intercept:0.29) with a near-diagonal curve between 0.6 to 0.9 (**Figure 5.5.A**) and a Brier score of 0.17. We also used the inpatient setting to externally validate our ED viral ARI model. In the inpatient setting, our model had decent discrimination (c-index=0.66; 95% CI: 0.63, 0.69) and good calibration (slope: 0.91; intercept: 0.06, **Figure 5.5.B**); and a Brier score of 0.20.

Inpatient External Validation

Applying our inpatient ARI model to another hospital sample in Amman, Jordan, the model had poor discrimination with a c-index of 0.64 (95% CI: 0.54, 0.74) and poor calibration with extreme departures throughout (slope: 0.79; intercept: 0.66). Despite poor discrimination and calibration, a nearly perfect Brier score of 0.07 was observed (**Figure 5.5.C**).

Table 5.1. Final Viral, ARI Prediction Model Results^a in the Emergency Department and Inpatient Setting from Bootstrapped Backwards Selection^b after Multiple Imputation for Missing Values^c

Emergency Department N=2,616			
Characteristic(s)	Bootstrap Inclusion Frequency (%)	Coefficient	Standard Error
Intercept	100.0	5.9934	2.5488
Illness duration	100.0	-0.0841	0.0214
Ear pain (yes/no)	100.0	-1.5261	0.1037
Sore throat (yes/no)	99.4	-0.4083	0.1058
Age, years (RCS,5 knots)	99.0	0.0102	0.2319
Age, years (RCS,5 knots)'	99.0	-7.3262	9.0382
Age, years (RCS,5 knots)''	99.0	12.2861	14.9700
Age, years (RCS,5 knots)'''	99.0	-5.3187	6.7715
Wheeze, physical exam (yes/no)	98.6	0.7301	0.2124
Cough (yes/no)	98.0	0.4512	0.1341
Myalgia (yes/no)	88.0	0.3247	0.1205
Rhinitis (yes/no)	87.6	0.3337	0.1275
Maximum temperature, °F	62.8	--	--
Heart rate, bpm	60.6	--	--
Respiratory season ^b (yes/no)	59.8	--	--
Insurance			
Private	56.2	--	--
Both, Public & Private	56.2	--	--
None/Self-pay	56.2	--	--
Total people in household	55.4	--	--
Respiratory rate, bpm	50.6	--	--
Respiratory underlying condition (yes/no)	41.6	--	--
Neurological underlying condition (yes/no)	40.6	--	--
Other underlying condition ^c (yes/no)	29.8	--	--
Cardiovascular underlying condition (yes/no)	20.0	--	--
Oxygen saturation, %	19.2	--	--
Hematologic/Oncologic/Immunosuppressive underlying condition (yes/no)	16.4	--	--
Fatigue	15.4	--	--
Inpatient N=1,491			
Intercept	100.0	44.7228	7.9686
Maximum temperature, °F (RCS, 3 knots)	100.0	-0.4253	0.0796
Maximum temperature, °F (RCS, 3 knots)'	100.0	0.2632	0.0889
Earache (yes/no)	100.0	-0.9759	0.1684
Wheeze, physical exam (yes/no)	98.6	0.6007	0.1431
Age, years (RCS,5 knots)	98.4	0.3397	0.5091
Age, years (RCS,5 knots)'	98.4	-60.8689	64.9068
Age, years (RCS,5 knots)''	98.4	89.2862	95.5789
Age, years (RCS,5 knots)'''	98.4	-29.7840	32.6378
Respiratory rate, bmp	98.4	-0.0169	0.0054
Illness duration	87.4	-0.0588	0.0232
Insurance			
Private	85.2	--	--
Both, Public & Private	85.2	--	--
None/Self-pay	85.2	--	--
Neurological underlying condition (yes/no)	67.8	--	--
Sore throat (yes/no)	43.0	--	--
Total people in household	35.8	--	--

Respiratory underlying condition (yes/no)	33.6	--	--
Cough (yes/no)	31.0	--	--
Other underlying condition ^c (yes/no)	30.6	--	--
Respiratory season ^b (yes/no)	27.4	--	--
Heart rate, bpm	26.4	--	--
Fatigue	25.4	--	--
Rhinitis (yes/no)	23.4	--	--
Oxygen saturation, %	19.4	--	--
Myalgia (yes/no)	17.6	--	--
Cardiovascular underlying condition (yes/no)	16.8	--	--
Hematologic/Oncologic/Immunosuppressive underlying condition (yes/no)	15.8	--	--

Footnote:

^aFinal model is based on 80% inclusion frequency in the bootstrapped backwards selection.

^bBootstrapped backwards selection included 500 repetitions.

^c3,842 complete cases; 265 children missing ≥ 1 covariate (ED: 194; inpatient: 71)

Figure 5.3. Viral Acute Respiratory Infection Prediction Model Characteristics Depicting Model Discrimination with a Receiver Operating Characteristic Curve (A) and Calibration Plot of Observed and Predicted Outcome Probabilities in the Emergency Department (B) and Inpatient Setting (C)

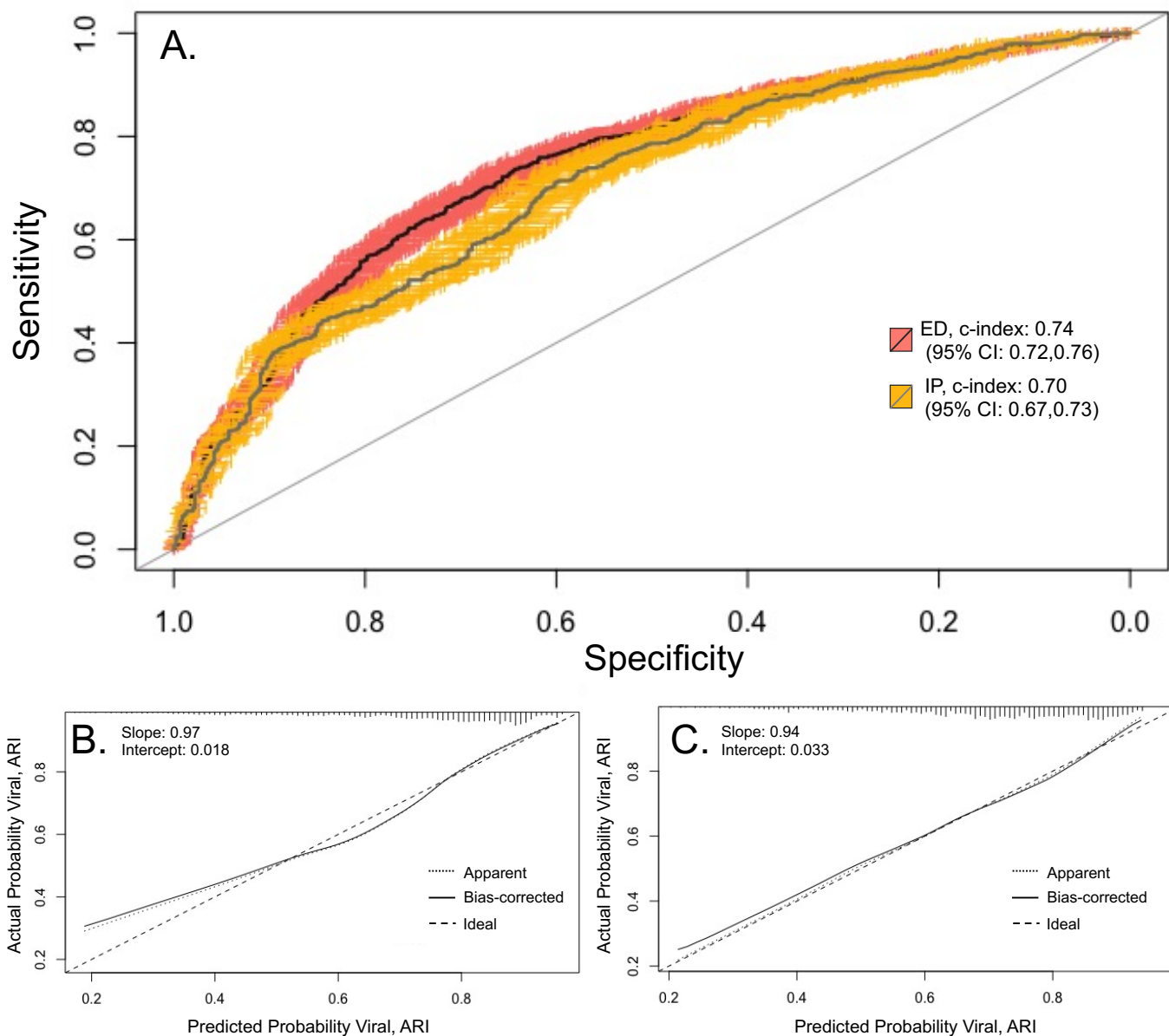


Figure 5.4. Nomogram to Estimate a Patient's Risk of Viral Acute Respiratory Infection Seen in the Emergency Department or Inpatient Setting

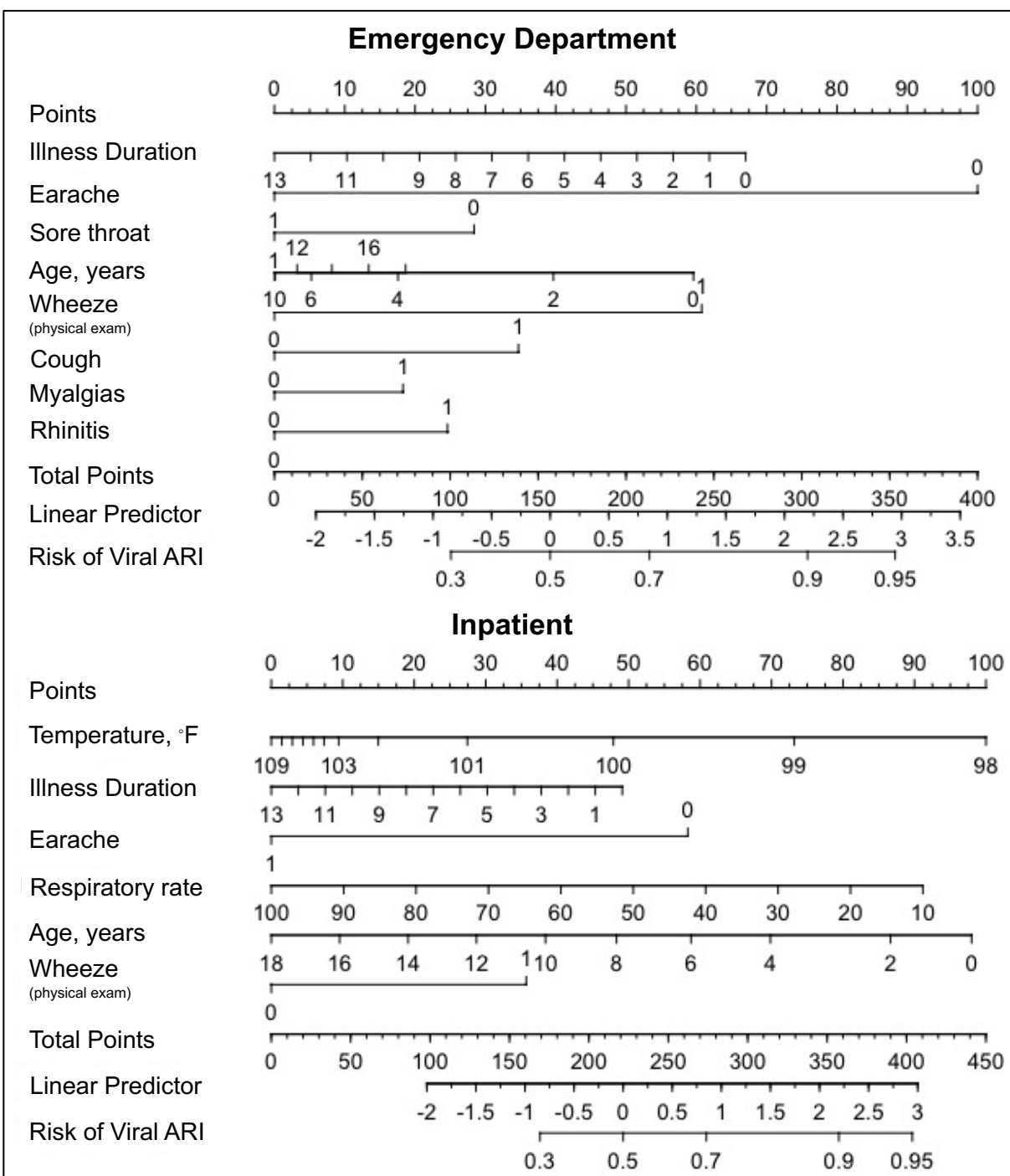
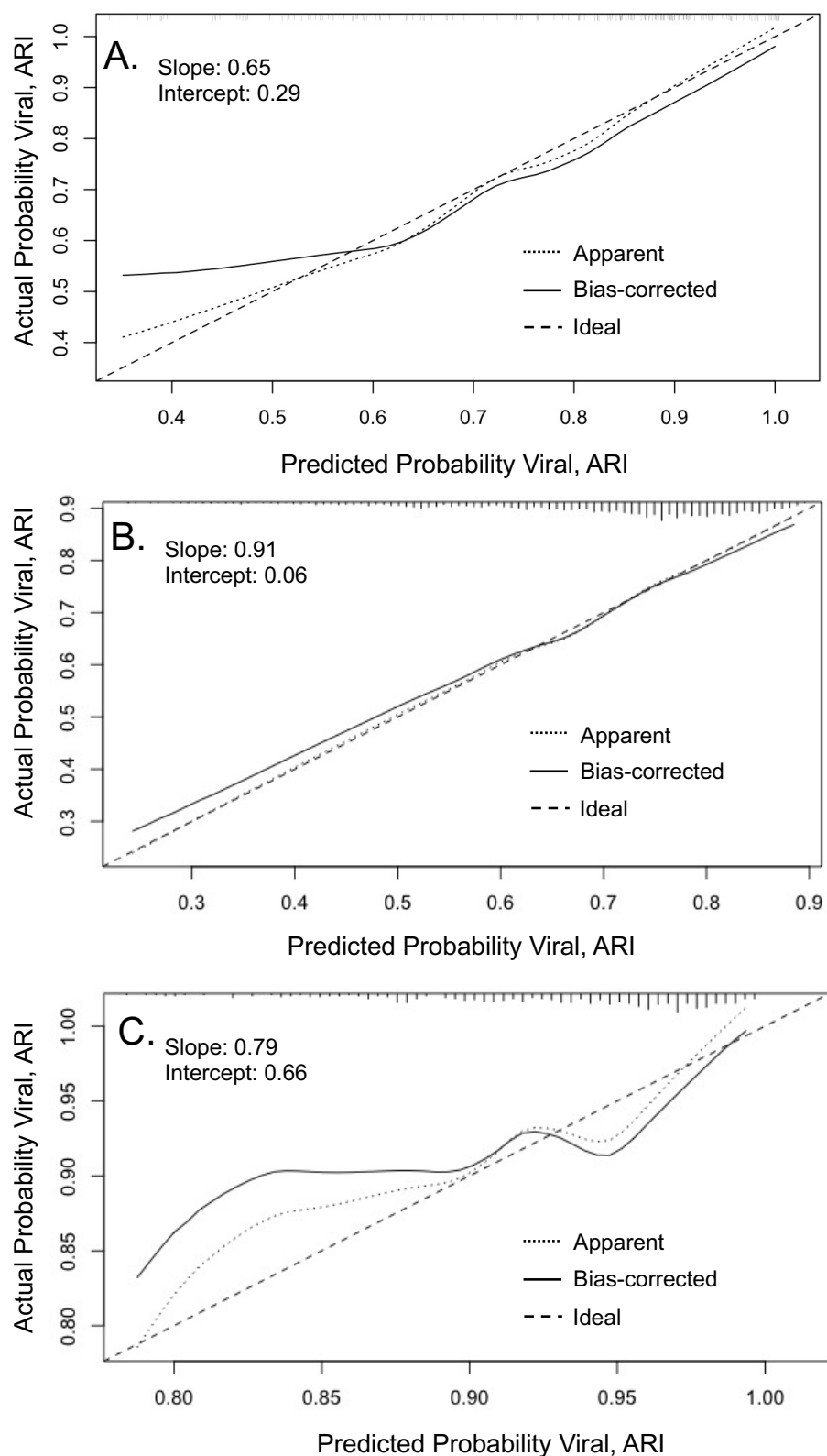


Figure 5.5. External Validation Calibration Plots for the Viral ARI Diagnostic Prediction Model Developed in the Emergency Department and Inpatient Setting: Emergency Department to Outpatient Validation (A), Emergency Department to Inpatient Validation (B), and Inpatient to Inpatient in Jordan Validation (C)



DISCUSSION

We used clinical data available at the time of presentation to develop and internally and externally validate two setting-specific diagnostic prediction models distinguishing viral ARIs from other ARIs among symptomatic children seeking medical attention. Our ED-specific viral ARI model included a total of 8 predictors, performed well with a c-index of 0.74 and was slightly better than our inpatient-specific model with 6 predictors and a discrimination ability of 0.70. We externally validated our ED model to an outpatient viral surveillance study, which revealed consistent discrimination to our initial model and good calibration with some departures observed among risk probabilities under 50%. External validation of our ED model in the inpatient setting resulted in poorer discrimination than the outpatient setting but did have excellent calibration. Conversely, applying our inpatient model to a hospital dataset in Amman, Jordan resulted in poor external validation. Nevertheless, both our ED and inpatient models should undergo additional external validation by independent investigators to truly determine the consistency and general applicability of our models in other states, regions, and countries. Overall, this study initiates a framework for aiding clinicians' diagnostic certainty in distinguishing viral ARIs from other ARIs, which could further impact direct patient management.

In our internally validated ED model, younger age, shorter illness duration, absence of an earache or sore throat, and presence of cough, myalgia, rhinitis, or wheezing on physical exam, were the strongest predictors of viral ARI. Cough, temperature, or rhinitis are commonly included in prior influenza-specific and respiratory virus models developed in ambulatory care settings (EDs/outpatient clinics).^{71,72,74,75} However, these models were developed using suboptimal analytical methods which can lead to overly optimistic results, concerns for bias, and poor external validation.^{93,135} Nevertheless, our model outperformed prior models with discrimination enhancements (c-index: 0.74 vs. 0.64); and inclusion of calibration measures for continued external validation among independent researchers.

Younger age, shorter illness duration, lower respiratory rate, presence of wheezing on physical exam, and absence of earache and fever (normal temperature) were key predictors of viral ARI in the inpatient

setting. Age, wheezing, illness duration, and respiratory rate have all separately been included across other hospital prediction models for viral ARIs.^{25,81,82,84} Often, inpatient models have included laboratory biomarkers that are not regularly collected on every hospitalized child (i.e., c-reactive protein, leukocytes, neutrophils, lipocalin 2, etc.).⁸⁰⁻⁸³ In addition, only two models have performed internal validation and provided discrimination measures. Compared to an RSV-specific model, which used predictors available at the time of clinical presentation, our model had similar discrimination ability (c-index: 0.70 vs. 0.73).²⁵ The other internally validated model developed to predict bacterial pneumonia used blood biomarkers (leukocytes, neutrophils, hemoglobin), chest x-ray findings, along with age and wheezing reported better discrimination (c-index: 0.81).⁸² Despite having better discriminatory ability, blood biomarkers tests are more invasive and are not regularly performed among all hospitalized children. Thus, to ensure clinical utility and generalizability we selected candidate predictors that are available at the time of presentation.

To our knowledge these are the first viral ARI diagnostic prediction models to be externally validated in other settings and populations.¹³⁵ The external validation of our ED model in a separate outpatient surveillance study in Nashville, Tennessee and the inpatient setting had favorable performance outcomes. Despite the good outcomes in the outpatient setting, the sample size was small and is apparent by our optimism-corrected intercept (0.29). Excellent calibration was observed in the inpatient setting but did not have as good of discriminative ability. This finding is not surprising but may be explained by the acuity differences of children hospitalized compared to those only seen in the ED. For example, in our study population, we see children hospitalized are more likely to have signs of respiratory distress (i.e., higher respiratory rate, lower oxygen saturation, presence of retractions or wheezing) than children in the ED. In addition, roughly 20% more of children hospitalized have an underlying medical condition. Similarly, the poor external validation of our inpatient-specific viral ARI model in hospitalized cohort of children with ARI in Amman, Jordan may be attributed to population differences and acuity of patients. This population was on average around three years younger than our initial inpatient model, less than one-quarter reported having an underlying medical condition, and the

prevalence of viral ARI was about 20% higher. Despite the poor external validation identified through discrimination and calibration, the Brier score had nearly perfect accuracy at 0.07. The Brier score is a quadratic scoring rule which provides the squared differences between actual outcomes and predictions; but is influenced by the incidence of the outcome.⁹⁶ This result suggests the model accuracy is excellent but may require some additional modification to address calibration and discrimination, specifically in this external population. For instance, in Jordan 93% of children had a viral ARI outcome and the prevalence of earache, myalgia, and sore throat were minimal. These differences in clinical characteristics may be attributed to the age of the patients, the regional prevalence of viral circulation, differences in healthcare seeking behaviors, or varying diagnostic practices in Jordan compared to the U.S. Nevertheless, additional external validation of both our ED and inpatient viral ARI models are needed to determine the overall generalizability and whether models should be developed by country or region.

Our study has some important limitations. First, we used a composite of research laboratory, clinical bacterial testing, and ICD-10 discharge diagnoses to determine our endpoint of viral and other ARIs. All children in our study had research testing performed to detect respiratory viruses; however, bacterial cultures were ascertained from medical chart abstractions and were deemed by the child's clinical provider. Using CDC's tiered diagnosis classification system,¹¹² we classified children without research or clinical etiologic confirmation into the appropriate clinical suspicion category. We believe this composite endpoint leads to less misclassification as not all infections deem laboratory testing or may be present from the clinical sample retrieved. To address this limitation, we performed a sensitivity analysis excluding discharge diagnoses from the viral ARI endpoint, which showed consistent discrimination ability but overall was inferior to our initial models with composite endpoints. Second, our external validation populations had relatively small sample sizes and still require additional rigorous validation by independent researchers before these models can be used in clinical practice. Finally, we did not include coronavirus 2019 (COVID-19) pandemic years in our initial model development or external validation. Exclusion of the COVID-19 era is attributed to the various clinical presentations of

COVID-19 associated with emergence of new variants, the prevalence of COVID-19 infections among children, and the current lack of seasonality.

CONCLUSIONS

We developed two setting-specific diagnostic prediction models for clinical use in estimating the individual risk a child has a viral ARI. Our model includes predictors that are widely available to clinical providers in any setting or country and can be implemented with a nomogram or pen and paper.

Although our models require additional rigorous external validation before widespread clinical implementation, preliminary external validation results are promising for further clinical distribution in resource-limited settings.

VI. CONCLUSIONS & FUTURE DIRECTIONS

Summary of Study Aims and Results

Among 4,107 children with an ARI seeking medical attention from an ED or hospitalized in Nashville, Tennessee, we aimed to 1) systematically reviewed the existing literature for studies that developed a diagnostic model to predict the risk of viral or bacterial ARIs; 2) understand patient clinical characteristics influencing clinicians to order viral diagnostic testing; 3) evaluated the association between ordering a viral diagnostic test and antibiotic prescription/administration and viral diagnostic test results and antibiotic prescription/administration; 4) developed setting-specific diagnostic prediction models (in the ED and inpatient setting) to calculate the probability of a child having a viral ARI; and 5) externally validated both setting-specific diagnostic prediction models in separate ARI surveillance datasets. From these analyses we identified opportunities to address methodological gaps in developing a diagnostic prediction model, differences in provider-ordered viral testing and variability of antibiotic administration practices across healthcare settings, and developed and validated a viral ARI model.

We performed a principal components analysis to determine clinical patterns in children with ARIs to understand the factors that influence a provider to order a viral diagnostic test across healthcare settings (**Chapter IVA**). We found differences in the use and selection of viral tests across settings. In the inpatient setting viral diagnostic testing in children was conducted more frequently than any other setting (i.e., 64% versus 49% in the ED, and 33% in outpatient clinics). However, both the ED and outpatient clinics had a higher usage of rapid antigen testing, specifically for influenza. These findings indicated clinicians are following AAP guidelines of ruling out influenza but using clinical judgement to determine other common ARI conditions, such as bronchiolitis. In our principal components analysis, we observed that children presenting with symptoms and characteristics representative of rhinovirus-like presentation had 71% and 39% decreased odds of being tested with a viral test in the ED and inpatient setting, respectively. These results highlight the need for studies focusing on the clinical

management and outcomes of children with ARIs caused from rhinovirus, specifically in the inpatient setting, to understand whether rhinovirus is a main contributor to the judicious use of antibiotics.

After understanding the clinical features influencing provider-ordered viral testing, we further evaluated the association between viral testing and antibiotic administration practices across settings (**Chapter IVB**). Motivation for this study was driven by the heterogeneity of findings suggesting viral testing may not dictate antibiotic prescription/administration practices. In the ED, we found receipt of a viral test decreases the odds of being administered a narrow-spectrum antibiotic compared to children without viral testing. Whereas in the inpatient setting odds of being administered a narrow-spectrum antibiotic is dependent on the result of the test (i.e., positive test, decreased odds; negative test, increased odds). Narrow-spectrum antibiotics are primarily used when the causative pathogen is known; and is recommended to be used as first-line defense treatment for illnesses such as strep throat¹⁴² or acute otitis media.¹²⁷ We postulate the differences in viral testing influences between settings may be due to the acuity of patients seen in the ED versus hospitalized. When further assessing the association of viral testing and broad-spectrum antibiotics, the results of viral tests were associated with the odds of being administered a broad-spectrum antibiotic. However, in the inpatient setting, regardless of receipt of testing or the results children were at increased odds of being administered broad-spectrum antibiotics compared to children without testing. This finding is likely explained by inpatient providers empirically prescribing antibiotics, but may stop them based on test results, which we did not assess in our study. Overall, our findings show that providers practicing in both the ED and inpatient setting at VUMC are not frequently administering antibiotics to children with illnesses that do not warrant antibiotic therapy.

From our systematic review, we identified 18 studies that developed diagnostic prediction models for ARIs (**Chapter III**). Across studies, minimal concern of bias was identified in the methodologies of study recruitment (i.e., population), ascertainment of outcome, and use of predictors. High risk of analytic bias was found in all studies and was attributed to the use of outdated model development methodologies,

lack of handling missing data, and the development in small sample sizes (raising concern for overfitting). In addition, no studies externally validated their developed models. Despite the analytic shortcomings and lack of external validation, our systematic review identified the potential impact prediction models may have in aiding clinicians with diagnosing viral ARIs, especially in resource-limited settings. In addition, our findings showed opportunities for prediction model enhancements and the need for external validation. Keeping these findings in mind, we developed two diagnostic models for the ED and inpatient setting (**Chapter V**). To ensure widespread applicability of our models we only included candidate predictors available at the time of presentation, regardless of setting or country. Both models after internal validation had good discriminative ability (i.e., c-index: ≥ 0.70) and calibration and accuracy. Our ED viral ARI model, externally validated well in the inpatient and outpatient surveillance studies conducted in Nashville, Tennessee. However, when validating our inpatient viral ARI model in a hospital in Jordan resulted in poor discrimination and calibration. Further indicating additional external validation studies are needed prior to widespread clinical use of either developed model.

Summary of Public Health Impact

The findings of our research may have several public health implications to future research and clinical ARI management and guidance documents. In our systematic review, we identified outdated analytic approaches such as internally validating models using a split-sample method. Split-sample internal validation is a method where the sample population is randomly divided into two groups (i.e., derivation and validation sets) and internally validated.⁹³⁻⁹⁵ Because this approach uses half of the sample to develop the model this often leads to less stable model results and unreliable assessment of model reliability.⁹³⁻⁹⁵ In addition to identifying gaps in model development methods, we provided suggestions on best model development approaches for future studies in hopes to change the rigor of prediction models developed in pediatric infectious diseases. Suggestions included using bootstrapping methods for internal validation, performing external validation, presenting final unrounded model coefficients and calibration plots. In our two studies focusing on the influences and impact of provider-ordered viral

testing across healthcare settings, we show clinical management guidance and antibiotic stewardship directly influence clinical practice at our institution. These findings emphasize healthcare settings should evaluate the influences impact of viral testing in their institutions to identify opportunities to strengthen clinical management practices. After understanding the implications of viral testing, we developed a diagnostic model intended to aid clinicians in resource-limited settings, such as outpatient clinics, urgent cares, and healthcare facilities in developing countries. In turn, we believe in the future, these models may help settings (e.g., outpatient) or countries limit the use of antibiotics when not indicated.

Study Strengths

A major strength of our study includes the active, prospective ARI surveillance study which systematically enrolls, interviews, and performs testing for 15 viral targets among all patients over consecutive years in both the ED and inpatient setting. The study design and process of data collection allowed for the use self-reported clinical symptoms and sociodemographic characteristics across all analyses. Further permitting us to develop a prediction model using symptom characteristics reported by parents at the time of presentation. Systematic research viral testing provided the opportunity to assess the virus frequency among children with and without clinical test results. Typically, clinical studies are only able to provide viral test results on children who were tested.

Study Limitations

Overall, our study has some notable limitations worth mentioning. First, throughout the study period (**Chapters IV-V**), we included children who had multiple ARI enrollments in either healthcare setting with at least 90 days between each enrollment. Including children with multiple ARI visits (N=390) may have introduced selection bias into our study. For example, children more likely to have an underlying medical condition may have an increased risk for acquiring ARIs annually and clinicians may be more inclined to have them seek medical attention from the ED or more likely to hospitalize these children. To account for potential selection bias, we excluded multiple enrollment visits <90 days from the prior

visit. This exclusion criteria ensured that each ARI enrollment represented a new illness because we allowed for more than six incubation periods (average incubation period: ~14 days for respiratory viruses¹⁴³). Not only did we extend out six incubation periods, but also ensured those children with underlying medical conditions seeking medical care had a new ARI, given immunocompromised children are known to shed respiratory viruses for as long as 30 days.¹⁴⁴ In addition to these exclusion criteria, we also descriptively compared demographic and clinical characteristics of children included in our study with one-, two-, and three-enrollments for each healthcare setting. Regardless of the number of enrollments, differences between sex, race, and ethnicity were not observed in either healthcare setting; and most enrollments occurred during respiratory season (**Appendix Tables D1-2**). In both healthcare settings, children with multiple enrollments (i.e., >1 visit) were younger at their first visit compared to children with a single enrollment. In the ED, children with multiple enrollments were observed to have higher proportion of underlying medical conditions at the second and third enrollment (**Appendix Table D1**). However, in the inpatient setting, more than 70% of children with multiple ARI enrollments had an underlying medical condition across settings (**Appendix Table D2**). Although children with multiple ARI enrollments are more likely to have underlying medical conditions compared to those children with only one ARI enrollment, we thought excluding these individuals would limit the generalizability of our findings as individuals remain susceptible to ARIs throughout life. As individuals age, they are more at risk for developing underlying medical conditions, which may put them at increased risk for ARIs and thus should also be represented in ARI study populations. From our descriptive evaluation and strict exclusion criteria, we believe our study population is representative of the general population at risk for ARIs.

Second, we were unable to draw conclusions from the exploratory analyses conducted in the outpatient setting due to small sample sizes (**Chapter IV**). The outpatient setting is understudied but has been shown to be a primary contributor to prescribing antibiotics for viral illnesses that do not warrant an antibiotic.¹⁴⁵ Therefore we encourage researchers with datasets specific to outpatient clinics replicate our analyses to better understand the implications of viral testing.

Third, in **Chapter V**, we initiated external validation in three separate datasets [ED: 2 (outpatient and inpatient); Inpatient: 1 (Jordan)]. External validation of diagnostic prediction models is essential to determine the generalizability of the model. In our study, we performed geographic and spectrum transportability (i.e., using population less sick or sicker than the population developed from) in the ED and geographic validation in the inpatient setting. Hypothetically, if we had unlimited resources and were able to design a study to develop diagnostic prediction models for each setting, we would systematically include outpatient ARI visits and would externally validate our models using other NVSN sites. Including the outpatient would help viral ARIs in a setting that is known to overprescribe antibiotics, which are attributed to a lack of widespread testing in this setting. Externally validating our models using all NVSN sites would ensure all candidate predictors were collected and measured in a systematic manner. Validating our models in other NVSN sites would help identify whether the model needs to be adjusted (i.e., include additional variables) or if it is adequate to use in a clinical situation. Ideally our model will aid clinicians in settings with limited viral testing to determine viral ARIs and in turn decrease inappropriate use of antibiotics. Nevertheless, in our study we initiated external validation with the data we had available. However, additional external validation studies are needed as literature shows validation should be performed in large datasets from multiple locations and time-periods by independent investigators to be deemed generalizable and applicable for clinical use.^{93,95,96}

Finally, we excluded study periods during the circulation of SARS-CoV-2. During the study proposal phase, incidence of SARS-CoV-2 in children was lower than in adults and often caused asymptomatic infection, followed by a sequelae of a multisystem inflammatory syndrome. The response of COVID-19 further led to changes in healthcare-seeking behaviors which would need to be accounted for in all statistical analyses. In addition, circulation of other respiratory viruses during the COVID-19 pandemic were suppressed¹⁰⁰ and until recently have returned to rates observed prior to the pandemic. Therefore, due to nuances of the COVID-19 pandemic related changes, we believe data collected during this

period would not be fully representative of viral ARIs in children nor reflective of the current and future clinical management of SARS-CoV-2 in children.

Future Directions

In this study, we attempted to understand the influences, clinical utility, and outcomes of viral diagnostic testing in a pediatric population. Additional studies are needed to assess the factors associated with provider-ordered viral testing in outpatient settings, including outpatient clinics, urgent care facilities, and telehealth. Based on our exploratory analysis, we assume the outpatient setting will have lower usage of provider-ordered viral testing than the ED and test selection will primarily be influenza antigen testing. Determining the factors associated with testing in the outpatient settings may provide insight for intervention opportunities, such as policy and procedure updates or education. In addition, studies in outpatient settings evaluating the association between provider-ordered viral testing and antibiotic prescriptions could have a sizeable impact on barriers or gaps in antibiotic stewardship that may not be currently included in antibiotic stewardship guidance.

We also developed, internally validated, and conducted external validation of a diagnostic model predicting the risk of a child having a viral ARI in the ED and inpatient setting. To determine the generalizability of our model, future research is needed. External validation of our setting-specific models should be performed by independent researchers from the same setting in other regions, states, or countries. In addition, another study could be performed to validate our external validation results in the outpatient setting by conducting a pilot study among outpatient clinics in Tennessee. External validation of various regions, states, and countries will help indicate whether models are in part driven by the viral prevalence in each community. For example, in our external validation of a Jordanian hospitalized cohort, 93% of children had a viral ARI and we found our model had poor discrimination and calibration but excellent overall accuracy. This finding points towards the potential influence of viral prevalence across communities. If this is true, then it provides infectious disease and public health

officials with the knowledge that viral ARI diagnostic prediction models should be developed not only according to healthcare setting but also developed within specific communities.

Lastly, once SARS-CoV-2 reaches a seasonal circulation pattern, studies could focus on updating our analyses (**Chapters IV-V**) to include SARS-CoV-2 with other seasonal respiratory viruses. Including and updating viral ARIs in children with SARS-CoV-2 may reveal changes to the use of provider-ordered viral testing across settings. However, future researchers should consider in additional confounding or time-varying covariates to appropriately analyze the influences and impact of provider-ordered testing because of the frequent changes to protocols and clinical management for SARS-CoV-2.

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Appendix File A1. PRISMA Checklist



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Appendix File A2. PROSPERO-Registered Systematic Review Protocol

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PROSPERO

Systematic review

Please select one of the options below to edit your record. Either option will create a new version of the record - the existing version will remain unchanged.

A list of fields that can be edited in an update can be found [here](#)

1. * Review title.

Give the title of the review in English

Evaluation of Prediction Models Distinguishing Pediatric Viral Acute Respiratory Infections: Protocol for a Systematic Review/Meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

03/02/2022

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/04/2022

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No

Review stage	Started	Completed
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Danielle Rankin

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Ms. Rankin

7. * Named contact email.

Give the electronic email address of the named contact.

danielle.a.rankin@vanderbilt.edu

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information, i.e. personal home address

Give the full institutional/organisational postal address for the named contact.

1161 21st Ave South, D7232 MCN, Nashville, TN 37232

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

4077666169

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Vanderbilt University Medical Center

Organisation web address:

<https://www.vumc.org/main/home>

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

NOTE: email and country now **MUST** be entered for each person, unless you are amending a published record.

Ms Danielle A. Rankin. Vanderbilt University Medical Center, Division of Epidemiology

Dr Lauren Peeluk. Vanderbilt University Medical Center, Division of Epidemiology

Dr Stephen Deppen. Vanderbilt University Medical Center, Division of Epidemiology

Dr Christopher Slaughter. Vanderbilt University Medical Center, Department of Biostatistics

Dr Sophie E. Katz. Vanderbilt University Medical Center, Department of Pediatrics

Dr Natasha B. Halasa. Vanderbilt University Medical Center, Department of Pediatrics
 Dr Nikhil K. Khankari. Vanderbilt University Medical Center, Division of Genetic Medicine

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

This project was supported by CTSA award No. TL1TR000447 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Grant number(s)

State the funder, grant or award number and the date of award

CTSA award No. TL1TR000447, July 2020

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

The goal of our systematic review is to summarize existing diagnostic prediction models developed to predict the probability of having a respiratory virus (i.e., virus/no virus) or viral-specific (i.e., respiratory syncytial virus [RSV], influenza, etc.) among children (<18 years) seeking medical attention at an ambulatory (i.e., emergency department or outpatient clinic) or inpatient setting. The diagnostic prediction models should be intended to inform clinical providers of the causative viral pathogen and used at the time of clinical presentation.

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search studies published from January 1, 1975, to February 3, 2022, that have developed (or updated) and internally validated a diagnostic prediction model with the goal of identifying respiratory viral pathogens by searching PubMed/MEDLINE, EMBASE, reference lists of included papers, and relevant systematic reviews.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible.

Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/308917_STRATEGY_20220215.pdf

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

We will examine diagnostic prediction models of viral illnesses (respiratory syncytial virus, influenza, adenovirus, etc.) among children seeking medical attention for an acute respiratory illness.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Diagnostic prediction models with an outcome of viral respiratory pathogens and developed among children (<18 years of age) will be included. Models can be developed among children seeking medical attention from an outpatient clinic, emergency department, or hospitalization. We will exclude all studies that focused model development specific to an immunocompromised pediatric population (i.e., cystic fibrosis, stem cell transplantation, Down syndrome, etc.).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Not applicable.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Comparison of candidate predictors, final predictors, model performance, model validation, and predictive accuracy will be conducted across studies/models.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Inclusion Criteria:

- 1) Diagnostic prediction models with or without external validation
- 2) Study population including children (<18 years) seeking medical attention at either an ambulatory (i.e., emergency department or outpatient clinic) and/or inpatient setting
- 3) Written in English
- 4) Published by February 3, 2022
- 5) Model outcome of: aggregated respiratory virus [i.e., including any of the following viruses: adenovirus, non-pandemic coronavirus strains (229E, HKU1, NL63, OC43), human metapneumovirus, influenza, parainfluenza (1-4), rhinovirus, enterovirus, and/or respiratory syncytial virus] or viral-specific (i.e., RSV, influenza, etc.)

Exclusion Criteria:

- 1) Study population excluding children (≥ 18 years) or restricted to children with immunocompromised conditions (i.e., cystic fibrosis, Down's syndrome, cancer, etc.)
- 2) Model outcome specific to severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, or multisystem inflammatory syndrome in children (sequelae of severe acute respiratory syndrome coronavirus 2)
- 3) Written in non-English languages
- 4) Published after February 3, 2022

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies will be included if they developed, internally validated, or updated a diagnostic prediction model in children (<18 years) for viral acute respiratory infections.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The primary outcome of interest is the probability of acute viral respiratory infection among children seeking medical attention. Included studies may define the outcome collectively (i.e., virus/no virus) or viral-specific (i.e., RSV, influenza, etc.). Studies should evaluate at least one of the following viral outcomes: adenovirus, non-pandemic coronavirus strains (229E, HKU1, NL63, OC43), human metapneumovirus, influenza, parainfluenza (1-4), rhinovirus, enterovirus, and/or RSV.

Measures of effect

We will collect measures of model performance, such as:

- Calibration
- Discrimination
- C-statistic/index
- Area under the receiver operating characteristics curve
- Classification
- Sensitivity
- Specificity
- Positive and negative predictive values
- Validation
- Internal
- External

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Measures of effect

Not applicable.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Article selection will be conducted in four steps by two independent reviewers: 1) Deduplication of articles selected from the multiple electronic systems; 2) Two reviewers will screen titles and abstracts of articles; 3) Full-text review of remaining articles will be conducted by the same two reviewers. Discordance will be discussed between reviewers, and if a consensus is not reached, the final resolution will be handled by a third party; 4) Data extraction from final articles will be conducted and qualitatively and quantitatively analyzed.

Data extracted from the selected studies will be recorded in a standardized collection form designed in REDCapTM (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA). Studies will be critically appraised and evaluated for risk of bias and applicability using the CHARMS checklist and the prediction model risk of bias assessment tool (PROBAST), respectively. Data extraction will include the source of the data, sample size, missing data methods, outcomes, predictors, model development techniques, model performance measures (i.e., calibration and discrimination), model evaluation (internal and external validation), and model results (final model/presentation).

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Risk of bias will be assessed using the PROBAST tool, which assesses deficiencies in study design, methods, and analyses that may lead to inaccurate measures of model performance.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data.

If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Using the CHARMS checklist and PROBAST tool, key elements of included studies will be synthesized. Data synthesis will include target population, sample size, setting, participants, missing data methods, outcome(s), candidate predictor(s), model development techniques, model performance (calibration and discrimination), model evaluation, and model results. The results will be summarized using descriptive statistics.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If warranted given the number of relevant studies identified, we will conduct a random-effects meta-analysis to summarize performance measures (e.g., discrimination and calibration). If needed, performance measures will be harmonized on the same scale prior to conducting a random-effects meta-analysis.

Models developed in sub-populations, such as age groups, will be qualitatively assessed. If an adequate number of studies within these sub-populations exist, we will conduct a stratified random-effects meta-analysis to summarize performance measures within sub-populations.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness	No
Diagnostic	Yes
Epidemiologic	Yes
Individual patient data (IPD) meta-analysis	No
Intervention	No
Living systematic review	No
Meta-analysis	No
Methodology	No
Narrative synthesis	No
Network meta-analysis	No
Pre-clinical	No
Prevention	No
Prognostic	No

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Prospective meta-analysis (PMA)	No
Review of reviews	No
Service delivery	No
Synthesis of qualitative studies	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	No
Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	No
Child health	Yes
Complementary therapies	No
COVID-19	No
Crime and justice	No
Dental	No
Digestive system	No
Ear, nose and throat	No
Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	Yes
International development	No

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Mental health and behavioural conditions	No
Musculoskeletal	No
Neurological	No
Nursing	No
Obstetrics and gynaecology	No
Oral health	No
Palliative care	No
Perioperative care	No
Physiotherapy	No
Pregnancy and childbirth	No
Public health (including social determinants of health)	Yes
Rehabilitation	No
Respiratory disorders	No
Service delivery	No
Skin disorders	No
Social care	No
Surgery	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	No
Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

United States of America

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them.

If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Yes I give permission for this file to be made publicly available

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Manuscript on findings will be submitted to a journal for publication.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Diagnostic prediction of acute respiratory viruses; systematic review of predicting respiratory viruses

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.

New registrations must be ongoing so this field is not editable for initial submission.

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission).

List authors, title and journal details preferably in Vancouver format.

Appendix Table A1. CHARMS Guide to Framing the Review Aim, Search Strategy, and Study Inclusion and Exclusion Criteria of a Prediction Model Systematic Review⁶⁵

Items	Comments and Strategy
1. Prognostic versus diagnostic prediction model	<i>Define whether the aim is to review models to predict: Future events (prognostic) or current status (diagnostic).</i> Strategy: Diagnostic prediction model, we are aiming to identify models discriminating respiratory viruses in children with acute respiratory infections.
2. Intended scope of review	<i>Define the intended scope of the review and intended purpose of the models reviewed in it.</i> Strategy: Models aimed to inform physicians whether the pathogen causing a child's acute respiratory infection is a virus.
3. Type of prediction modeling studies to be included	<i>Define the type of prediction modeling studies to include.</i> Strategy: Include prediction models without external validation in internal data but must be internally validated.
4. Target population to whom the prediction model applies	<i>Define the target population relevant to the review scope.</i> Strategy: Children (<18 years of age) with acute respiratory symptoms.
5. Outcome to be predicted	<i>Define the outcome of interest to be predicted.</i> Strategy: A collective outcome of any respiratory viruses (i.e., virus/no virus) or viral-specific (i.e., RSV, influenza, etc.) that cause ARIs in children
6. Time span of prediction	<i>Define over what specific time period the outcome is predicted (prognostic models only).</i> Strategy: None needed, we are reviewing diagnostic models.
7. Intended moment of using the model	<i>The systematic review may focus on models to be used at a specific moment in time.</i> Strategy: Models intended to be used at the time of diagnosis and therapeutic decision making.

Footnote: Adapted from the CHARMS Checklist for Systematic Reviews of Prediction Modeling Studies⁶⁵

Appendix Table A2. Search Criteria Developed to Conduct a Systematic Review/Meta-Analysis on Diagnostic Prediction Models

Database	Search Terms
PubMed (N=1594)	1. (respiratory tract infections[tiab] OR acute respiratory infections[tiab] OR respiratory viral infection*[tiab] OR respiratory viruses[tiab] OR respiratory virus*[tiab] OR "Pneumonia, Viral/diagnosis"[Mesh] OR "Influenza, Human/diagnosis"[Mesh] OR "Common Cold/diagnosis"[Mesh] OR "Respiratory Syncytial Virus Infections/diagnosis"[Mesh]) 2. (prediction [tiab] OR decision [tiab] OR clinical prediction model*[tiab] OR diagnostic model*[tiab] OR "Decision Support Systems, Clinical"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Nomograms"[Mesh] OR nomogram*[tiab] OR "Diagnosis, Differential"[Mesh] OR validat*[tiab] OR "Calibration"[Mesh] OR "Validation Study"[Publication Type] OR "Validation Studies as Topic"[Mesh]) 3. ("Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR "Infant, Newborn"[Mesh] OR newborn[tiab] OR newborns[tiab] OR neonat*[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR teen-ager[tiab] OR teen-agers[tiab] OR youth[tiab] OR youths[tiab]) 4. NOT(COVID-19[MESH] OR SARS-CoV-2[tiab] OR COVID-19[tiab] OR MIS-C[tiab]) 5. 1 AND 2 AND 3 AND 4 6. Filter: 1975-2021
EMBASE N=5998	1. (respiratory tract infections or acute respiratory infections or respiratory viral infection\$ or respiratory viruses or respiratory virus\$).ti,ab. 2. *pneumonia/di [Diagnosis] 3. *influenza/di [Diagnosis] 4. *common cold/di [Diagnosis] 5. *Human respiratory syncytial virus/ 6. 1 OR 2 OR 3 OR 4 OR 5 7. (predict* or decision* or diagnos* or nomogram or validat*).ti,ab. 8. *decision support system/ 9. *nomogram/ 10. *calibration/ 11. *validation study/ 12. 7 OR 8 OR 9 OR 10 OR 11 13. (infant* or newborn* or neonat* or child* or pediatric* or paediatric* or adolescent* or teen* or youth*).ti,ab. 14. *child/ 15. *adolescent 16. 13 OR 14 OR 15 17. 6 AND 12 AND 16 18. Limit 17 to yr="1975-2021"

Appendix File A3. CHARMS Checklist

CHARMS 2014 Relevant items to extract from individual studies in a systematic review of prediction models

Domain	Key items	Reported on page #
SOURCE OF DATA	Source of data (e.g., cohort, case-control, randomized trial participants, or registry data)	
PARTICIPANTS	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)	
	Participant description	
	Details of treatments received, if relevant	
	Study dates	
OUTCOME(S) TO BE PREDICTED	Definition and method for measurement of outcome	
	Was the same outcome definition (and method for measurement) used in all patients?	
	Type of outcome (e.g., single or combined endpoints)	
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?	
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?	
CANDIDATE PREDICTORS (OR INDEX TESTS)	Time of outcome occurrence or summary of duration of follow-up	
	Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)	
	Definition and method for measurement of candidate predictors	
	Timing of predictor measurement (e.g., at patient presentation, at diagnosis, at treatment initiation)	
	Were predictors assessed blinded for outcome, and for each other (if relevant)?	
SAMPLE SIZE	Handling of predictors in the modelling (e.g., continuous, linear, non-linear transformations or categorised)	
	Number of participants and number of outcomes/events	
MISSING DATA	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)	
	Number of participants with any missing value (include predictors and outcomes)	
	Number of participants with missing data for each predictor	
MODEL DEVELOPMENT	Handling of missing data (e.g., complete-case analysis, imputation, or other methods)	
	Modelling method (e.g., logistic, survival, neural network, or machine learning techniques)	
	Modelling assumptions satisfied	
	Method for selection of predictors for inclusion in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)	
	Method for selection of predictors during multivariable modelling (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)	
MODEL PERFORMANCE	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)	
	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals	
MODEL EVALUATION	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used	
	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)	
RESULTS	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)	
	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	
	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	
INTERPRETATION AND DISCUSSION	Comparison of the distribution of predictors (including missing data) for development and validation datasets	
	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	
	Comparison with other studies, discussion of generalizability, strengths and limitations.	

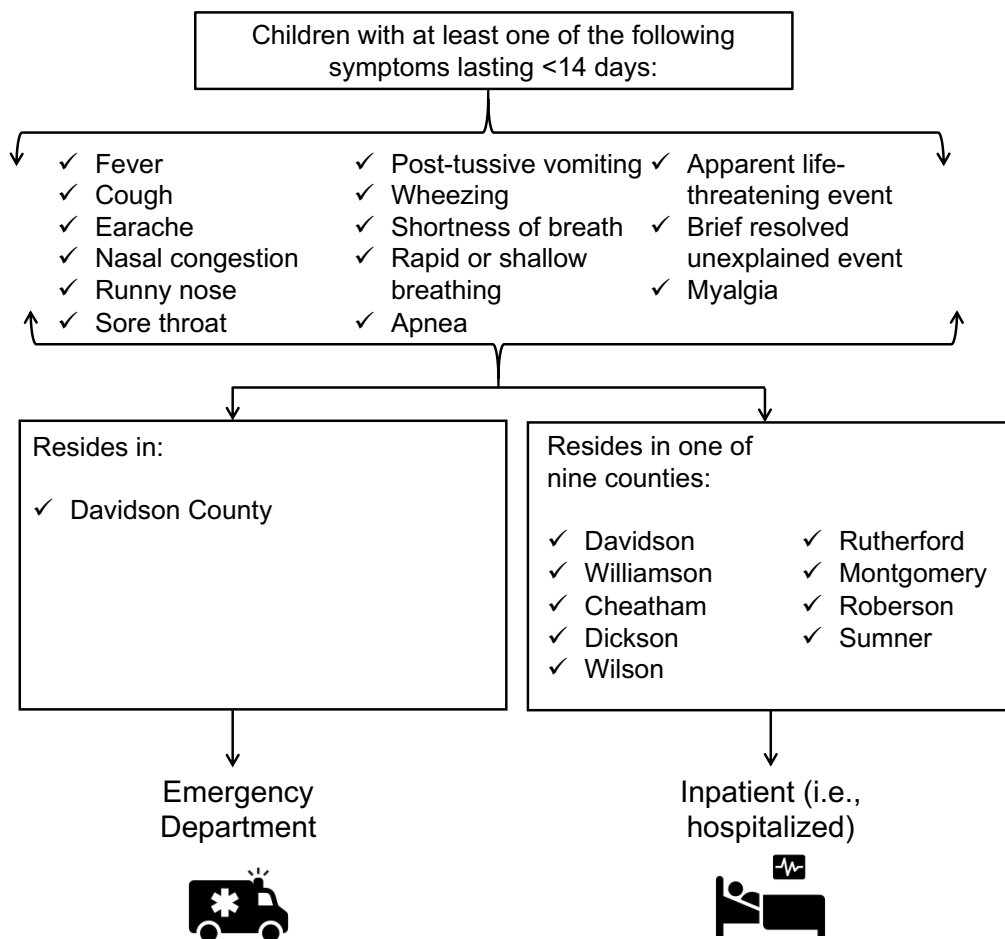
Appendix Table A3. Summary of Study Design and Source Population Characteristics (n=18)

Characteristics	Categories	N(%) or median (IQR)
Study design	Prospective cohort	8 (44.4)
	Retrospective cohort	4 (22.2)
	Nested case-control	1 (5.6)
	Cross-sectional	4 (22.2)
	Surveillance study	1 (5.6)
Healthcare Setting	Inpatient	8 (44.4)
	Emergency Department	3 (16.7)
	Outpatient clinics	3 (16.7)
	Emergency Department and Urgent Care	1 (5.6)
	Other ^a	3 (16.7)
Study region	North America	5 (28)
	South America	1 (5.6)
	Europe	5 (28)
	Africa	2 (11)
	Asia	2 (11)
	Australia/Oceania	2 (11)
	Global	1 (5.6)
Number of models developed	1	14 (77.8)
	2	3 (16.7)
	3	1 (5.6)

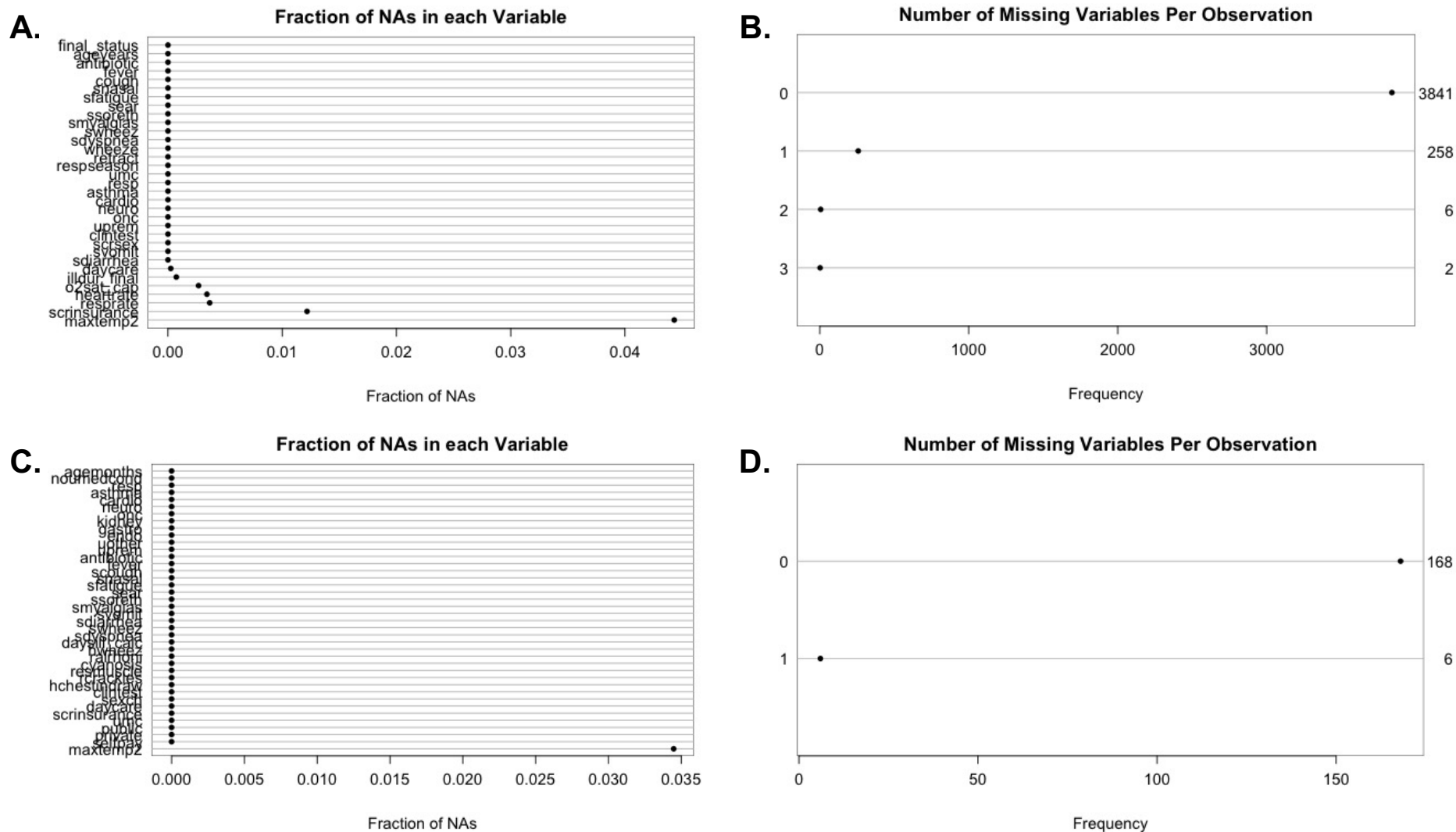
Footnote:

^aOther includes surveillance sites, communities, and clinical trial sites

Appendix Figure B1. Eligibility Criteria for Enrollment into the Acute Respiratory Infection Surveillance Study in Nashville, Tennessee, November 2017-February 2020



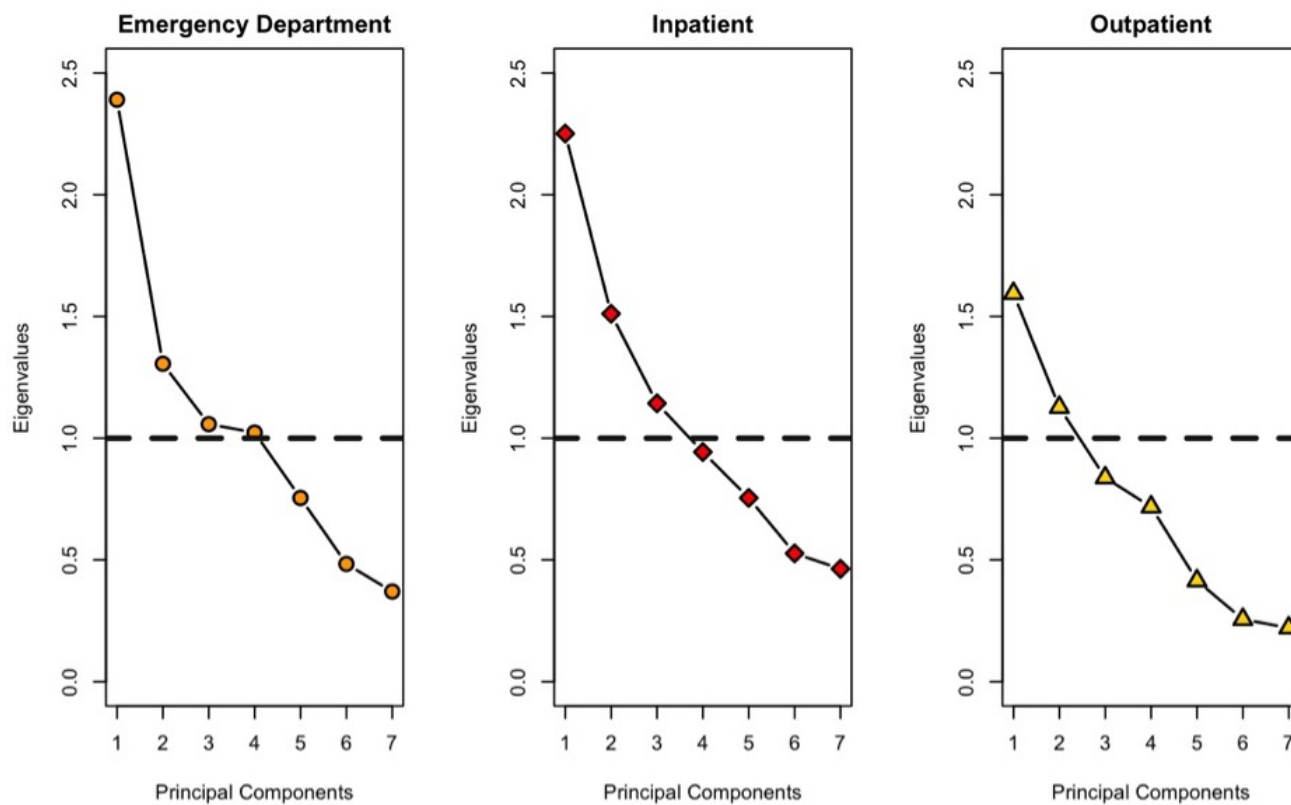
Appendix Figure B2. Total Missingness for the Emergency Department and Inpatient Setting (A-B) and Outpatient Setting (C-D)



Appendix Table B1. Evaluation of R-Squared Values for Imputation Sets

Covariates	10X	25X	50X	100X	500X	1000X
Illness duration	0.150	0.142	0.141	0.135	0.137	0.148
Maximum temperature	0.599	0.583	0.585	0.573	0.582	0.577
Respiratory rate	0.579	0.583	0.591	0.591	0.594	0.575
Heart rate	0.536	0.548	0.543	0.560	0.577	0.541
Oxygen saturation	0.246	0.251	0.245	0.290	0.234	0.267
Insurance	0.078	0.109	0.104	0.111	0.102	0.103

Appendix Figure B3. Screeplots of Principal Components, by Healthcare Setting



Appendix Table B2. Univariable Summary Statistics for Principal Components, by Healthcare Setting

Pattern(s)	Mean (SD)	Median (IQR)
Emergency Department (n=2,616)		
PC1 _{ED} , RSV-like pattern	0 (1.6)	0.2 (-1.1, 1.2)
PC2 _{ED} , Rhinovirus-like pattern	0 (1.1)	-0.1 (-0.9, 0.9)
PC3 _{ED} , Influenza & rhinovirus-like pattern	0 (1.0)	0.2 (-0.5, 0.7)
PC4 _{ED} , Influenza-like pattern	0 (1.0)	-0.2 (-0.7, 0.5)
Inpatient (n=1,491)		
PC1 _{IP} , Influenza-like pattern	0 (1.5)	-0.2 (-1.1, 1.0)
PC2 _{IP} , Rhinovirus-like pattern	0 (1.2)	-0.1 (-0.9, 0.9)
PC3 _{IP} , RSV-like pattern	0 (1.1)	-0.1 (-0.7, 0.5)
Outpatient (n=174)		
PC1 _{OP} , RSV-like pattern	0 (1.3)	0.05 (-1.7, 0.9)
PC2 _{OP} , Co-viral-like pattern	0 (1.1)	0.20 (-1.5, 0.8)

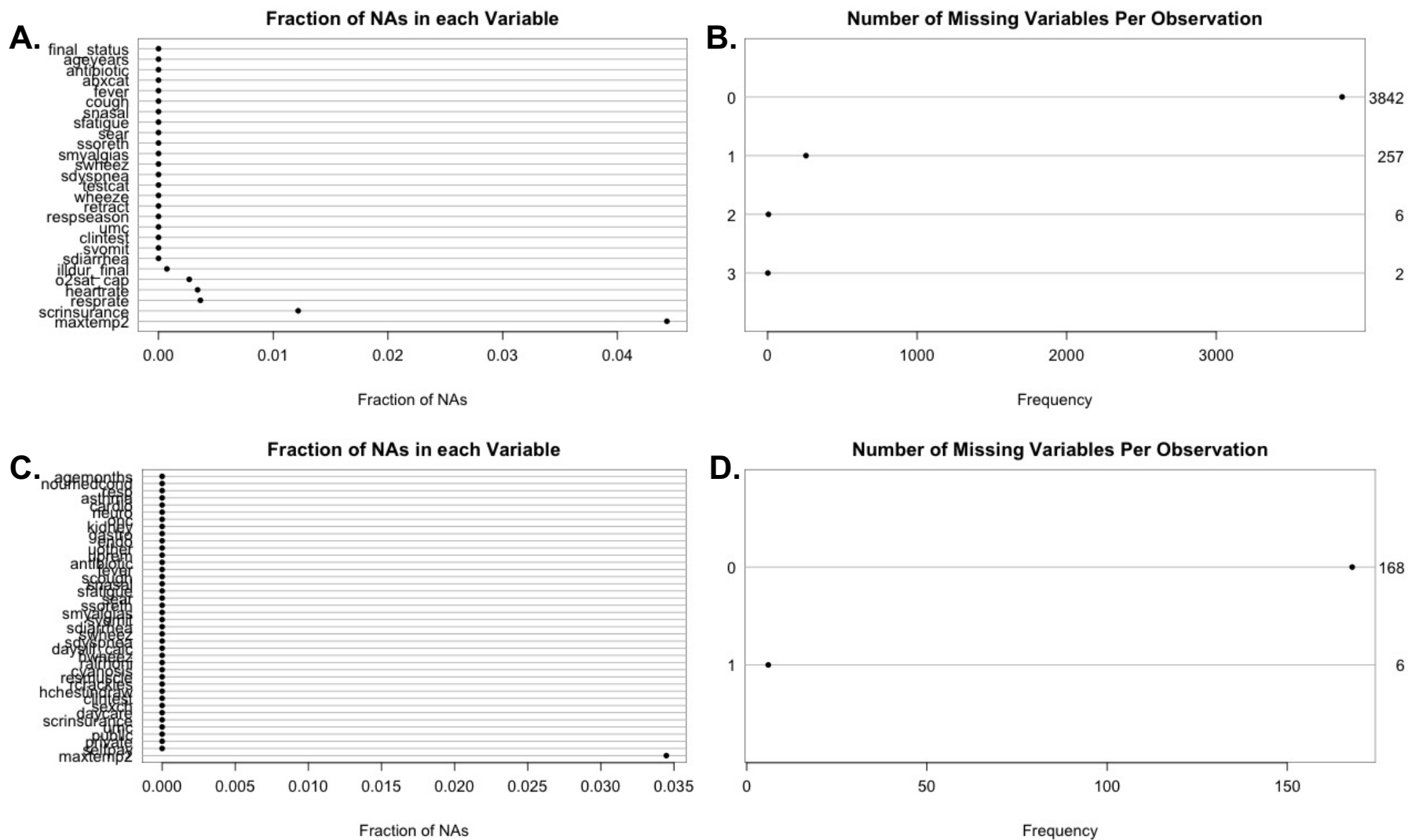
Appendix Table B3. Principal Components among Children (>30 days-11 months) Enrolled in Three Distinct Outpatient Clinics with Acute Respiratory Illness, Nashville, Tennessee, December 2019-February 2020

	PC1_{OP}	PC2_{OP}
Covariate(s)	<i>RSV-like pattern</i>	<i>Co-Viral-like pattern</i>
Age, months	-0.56	-0.34
Illness duration, days	-0.13	-0.79
Temperature	-0.54	0.46
Fever	-0.22	0.17
Respiratory symptoms	-0.00	-0.01
No respiratory symptoms	-0.56	0.01
Cyanosis	0.00	0.01
Wheezing	0.02	0.00
Retractions	-0.03	0.00
Crackles	-0.01	0.02
Accessory muscle use	0.00	0.01
Underlying medical conditions	-0.06	0.01
Public insurance	0.06	-0.02
Private insurance	-0.06	0.01
Self-pay insurance	0.00	0.01
Sex	0.06	-0.05
Daycare	-0.06	-0.04
Proportion of Variance (%)	27.63	19.52
Explained (%)	27.63	47.15
Eigenvalue(s)	1.63	1.11

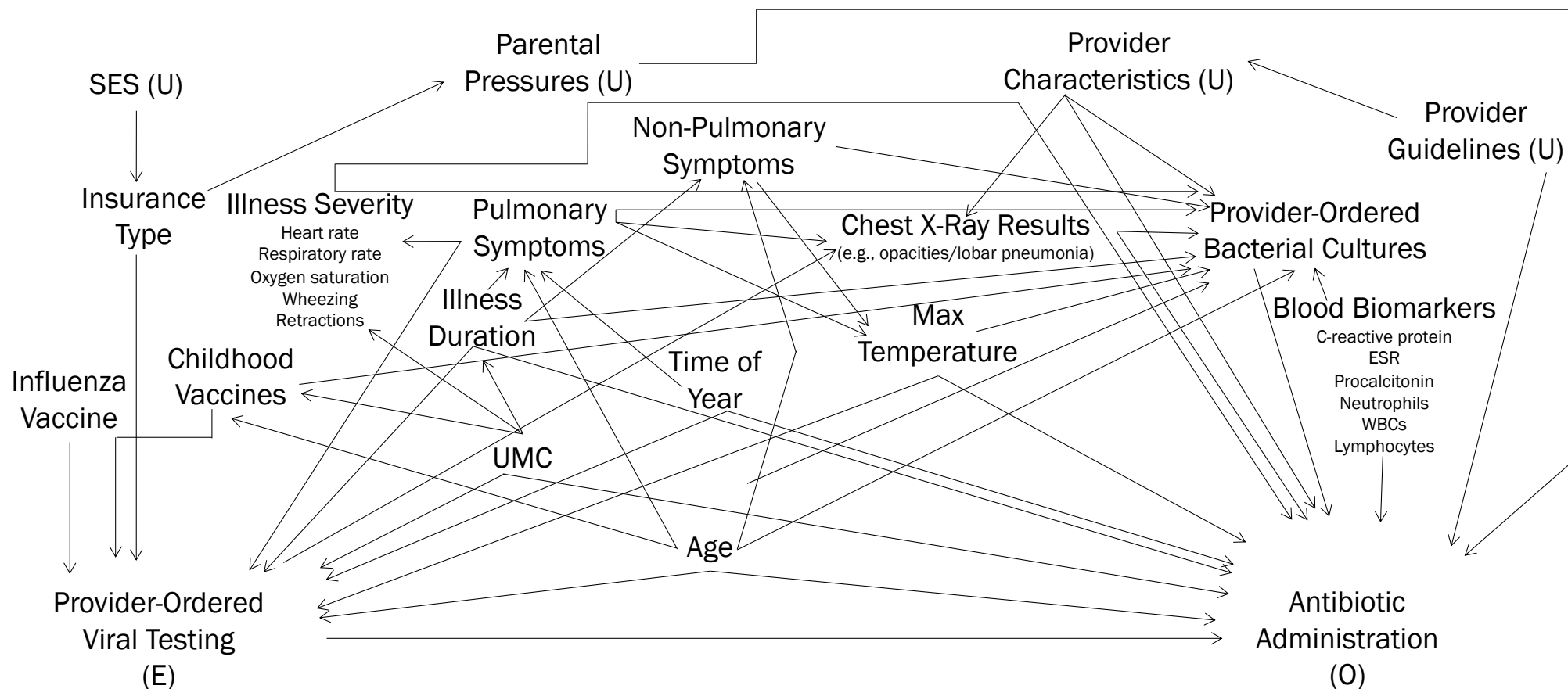
Appendix Table B4. Classification of Antibiotics Administered During a Child's Healthcare Visit, Nashville, Tennessee

None Administered	No antibiotics were prescribed/administered during the child's ED visit/hospital stay
Narrow-Spectrum	Penicillin • Penicillin, Amoxicillin, Ampicillin, Nafcillin 1st generation cephalosporins: • Cefazolin, Cefadroxil, Cephalexin, Cephalothin, Cephapirin, Cephadrine Sulfonamides • Bactrim, Bactrim DS, Cotrim, Septra, Sulfadiazine, Pediazole, Trimethoprim/Sulfamethoxazole, Erythromycin/Sulfisoxazole, Septra DS, Sulfatrim Tetracyclines • Minocycline, Doxycycline, Sarecycline, Eravacycline, Oxytetracycline, Tetracycline Gentamicin Metronidazole
Broad-Spectrum	Amoxicillin-Clavulanate Advanced generation cephalosporins: • Cefoxitin, Cefotetan, Cefmetazole, Cefprozil, Cefaclor, Cefuroxime, Ceftriaxone, Cefepime, Cefotaxime, Ceftazidime, Cefixime, Cefdinir Clindamycin Quinolones • Ciprofloxacin, Levofloxacin, Ofloxacin, Moxifloxacin, Gemifloxacin Macrolides • Erythromycin, Azithromycin, Clarithromycin, Fidaxomicin, Vancomycin, Tobramycin Linezolid Piperacillin/Tazobactam Daptomycin

Appendix Figure B4. Total Missingness for the Emergency Department and Inpatient Setting (A-B) and Outpatient Setting (C-D)



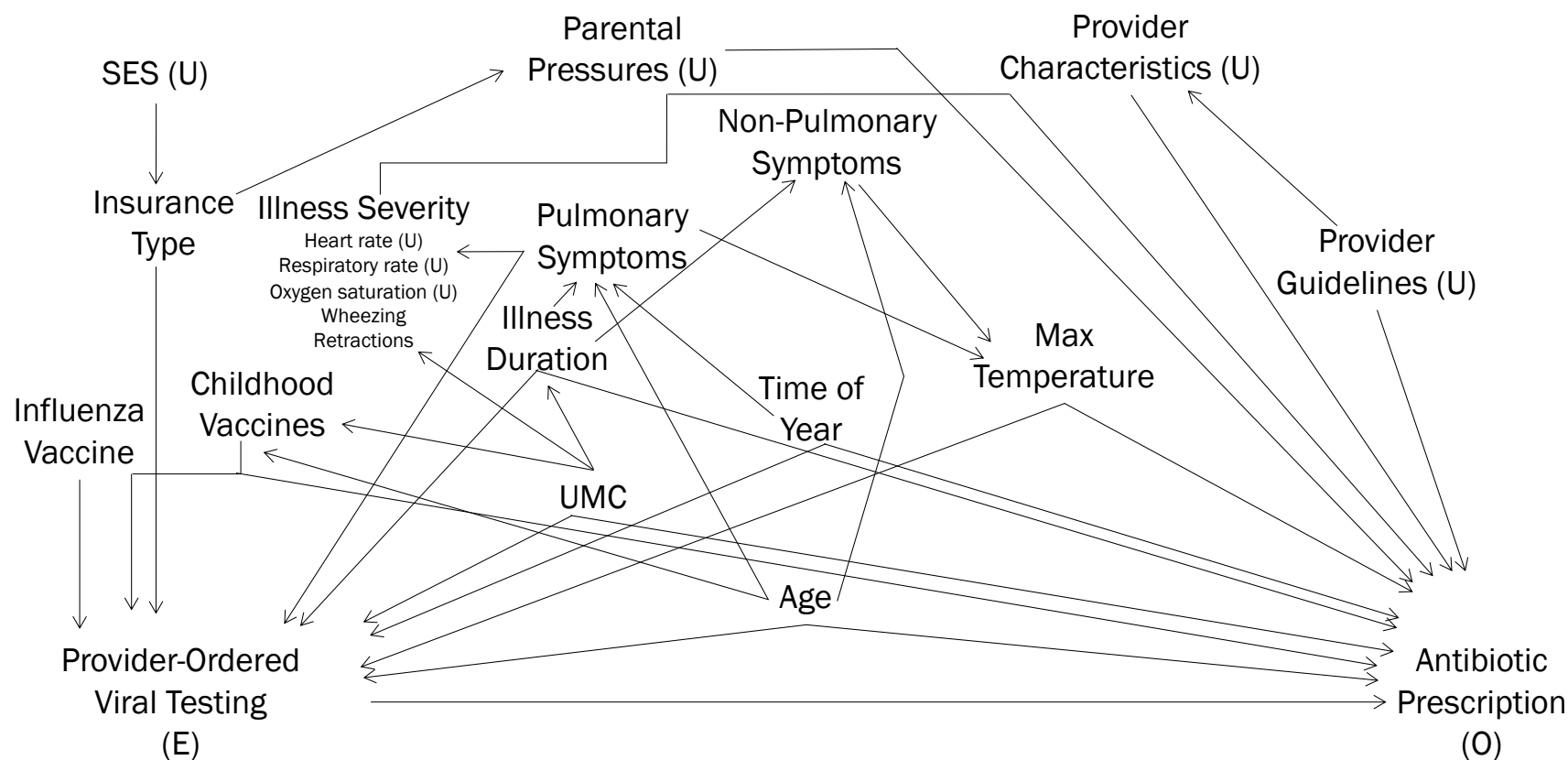
Appendix Figure B5. Assessment of Confounders in the Emergency Department and Inpatient Setting using Directed Acyclic Graph (DAG) Theory



Footnote: The minimally sufficient adjustment set for estimating the total effect of provider-ordered viral testing on antibiotic administration included: age, illness duration, illness severity, insurance, maximum temperature, pulmonary symptoms, time of year, and underlying medical conditions.

Abbreviations: E, exposure; ESR, erythrocyte sedimentation rate; O, outcome; U, unmeasured; UMC, underlying medical conditions; WBCs, white blood cell count

Appendix Figure B6. Assessment of Confounders in the Outpatient Setting using Directed Acyclic Graph (DAG) Theory



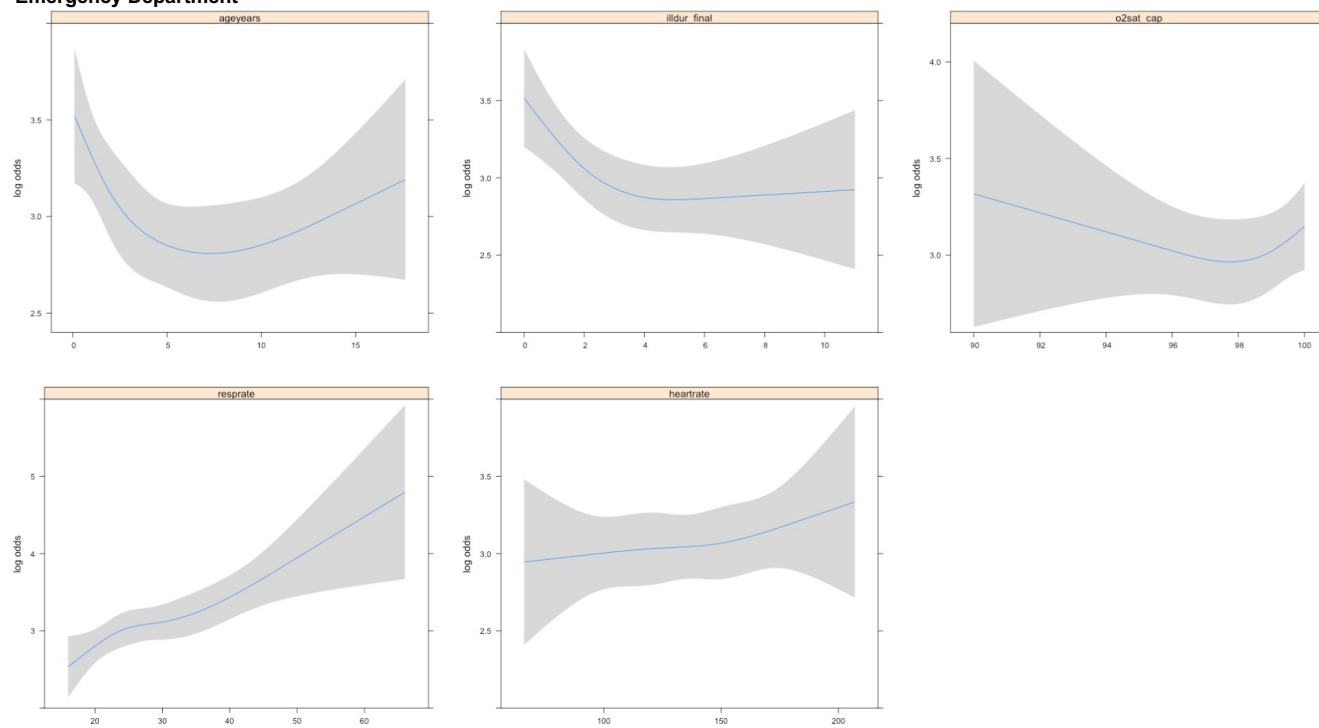
Footnote: The minimally sufficient adjustment set for estimating the total effect of provider-ordered viral testing on antibiotic administration included: age, illness duration, illness severity, insurance, maximum temperature, pulmonary symptoms, time of year [controlled for in this population, (i.e., enrollment was from December 2019-February 2020)], and underlying medical conditions.
Abbreviations: E, exposure; ESR, erythrocyte sedimentation rate; O, outcome; U, unmeasured; UMC, underlying medical conditions; WBCs, white blood cell count

Appendix Table B5. Knot Placements for Continuous Variables with Restricted Cubic Splines, by Healthcare Setting

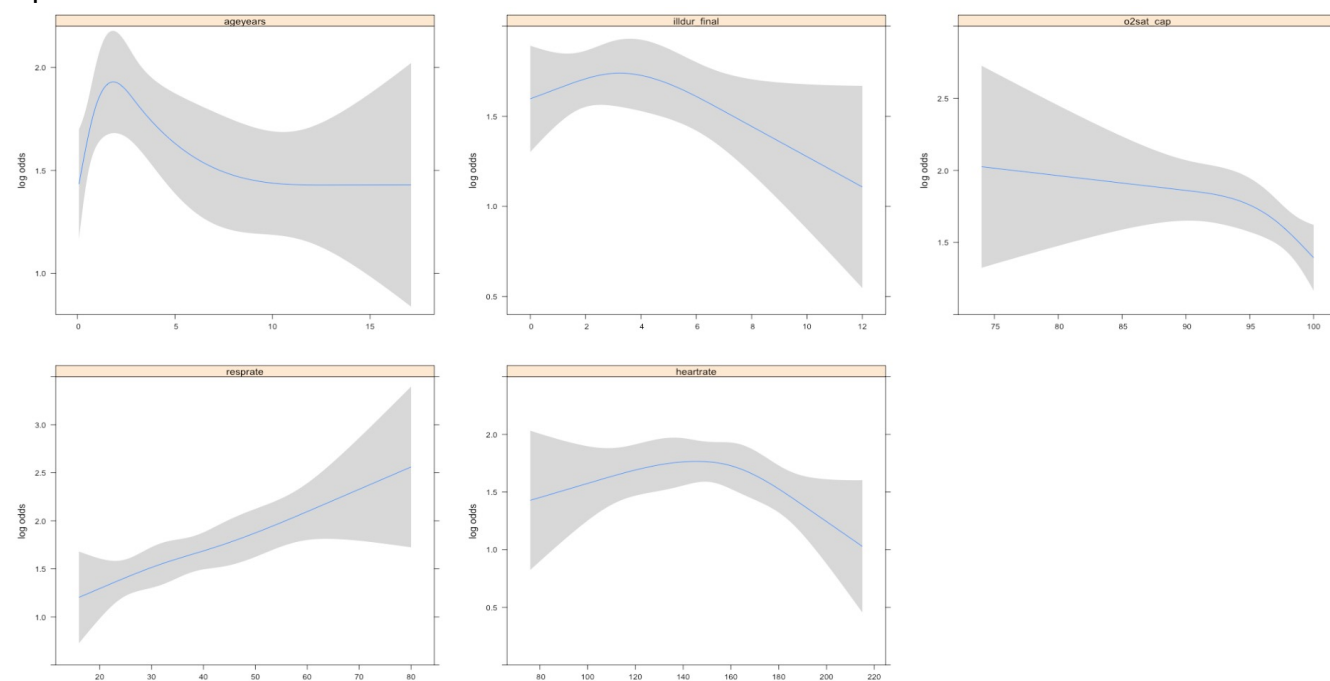
Covariate	No. of Knots	Knot Values for ED	Knot Values for Inpatient
Age, years	4	0.32 1.69 5.05 14.06	0.11 0.8 3.02 12.83
Illness Duration, days	3	0 2 6	1 3 7
Respiratory Rate	4	18 24 30 48	20 32 42 64
Heart Rate	4	88 125 148 182	102 141 162 191
Oxygen Saturation	3	96 99 100	90 97 100

Appendix Figure B7. Shapes of Continuous Variables Modeled with Restricted Cubic Splines, by Healthcare Setting

Emergency Department

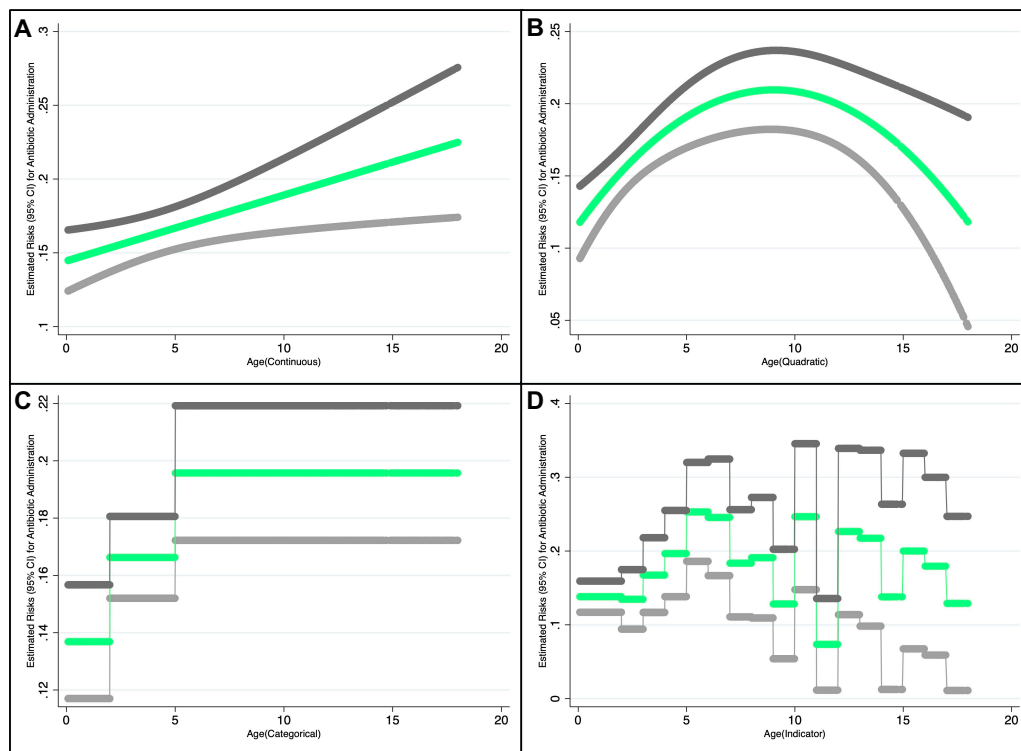


Inpatient

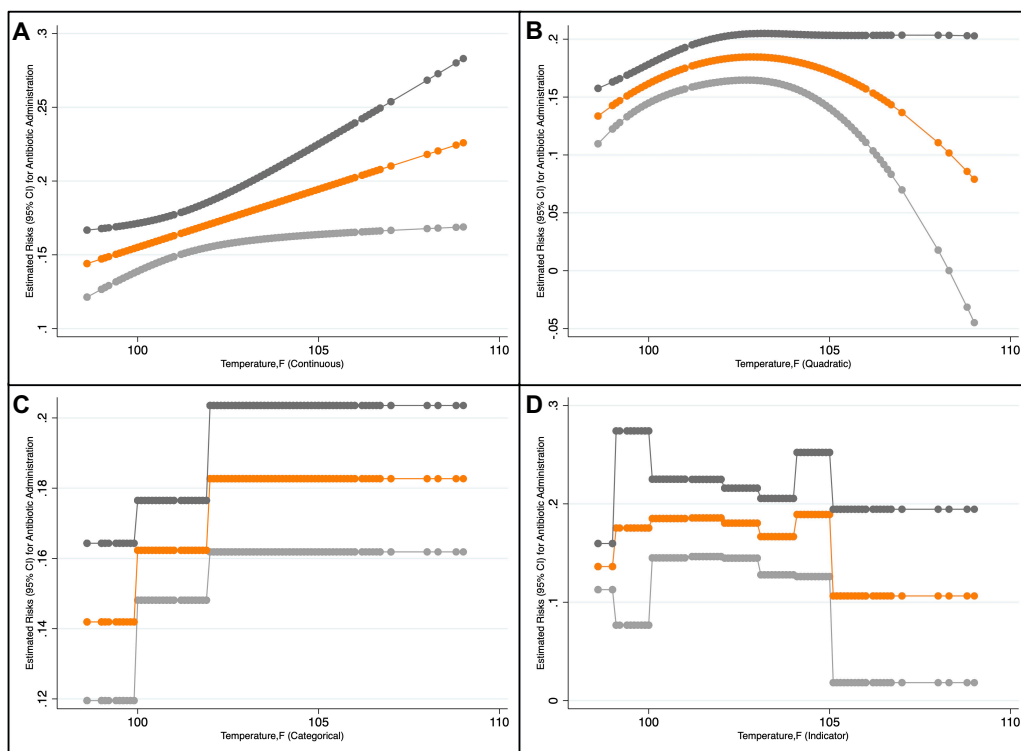


Appendix Figure B8. Assessing the Risk of Antibiotic Administration in Association with Continuous Covariates, by Variable and Healthcare Setting: Continuous (A), Quadratic (B), Categorical (C), Indicator (D)

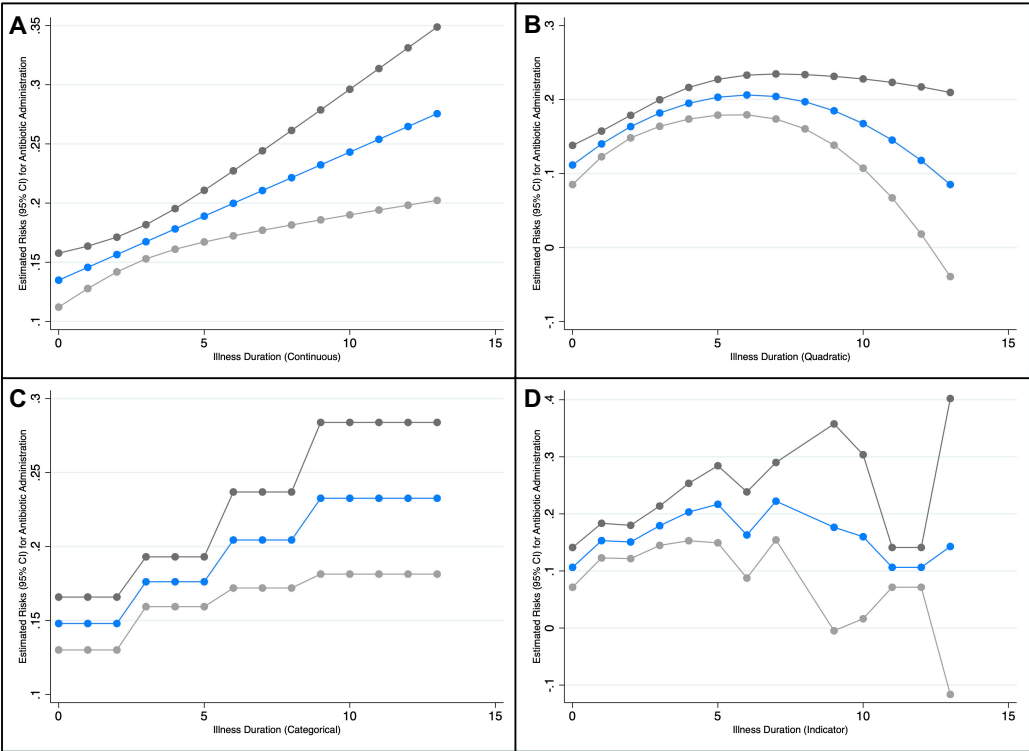
Emergency Department, Age



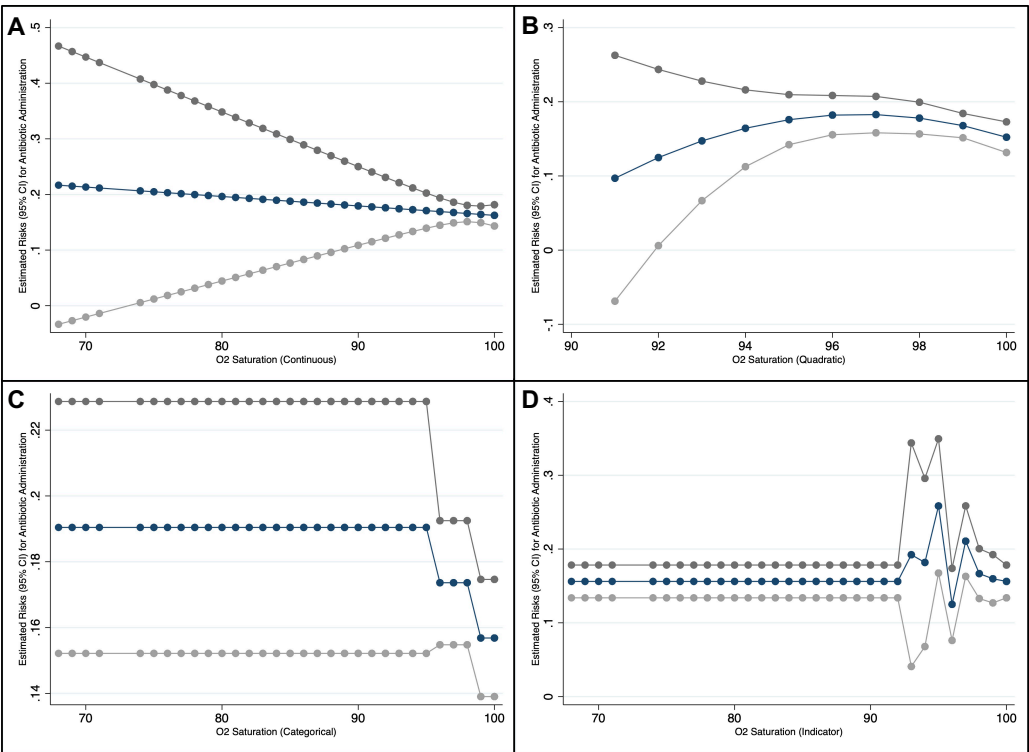
Emergency Department, Temperature



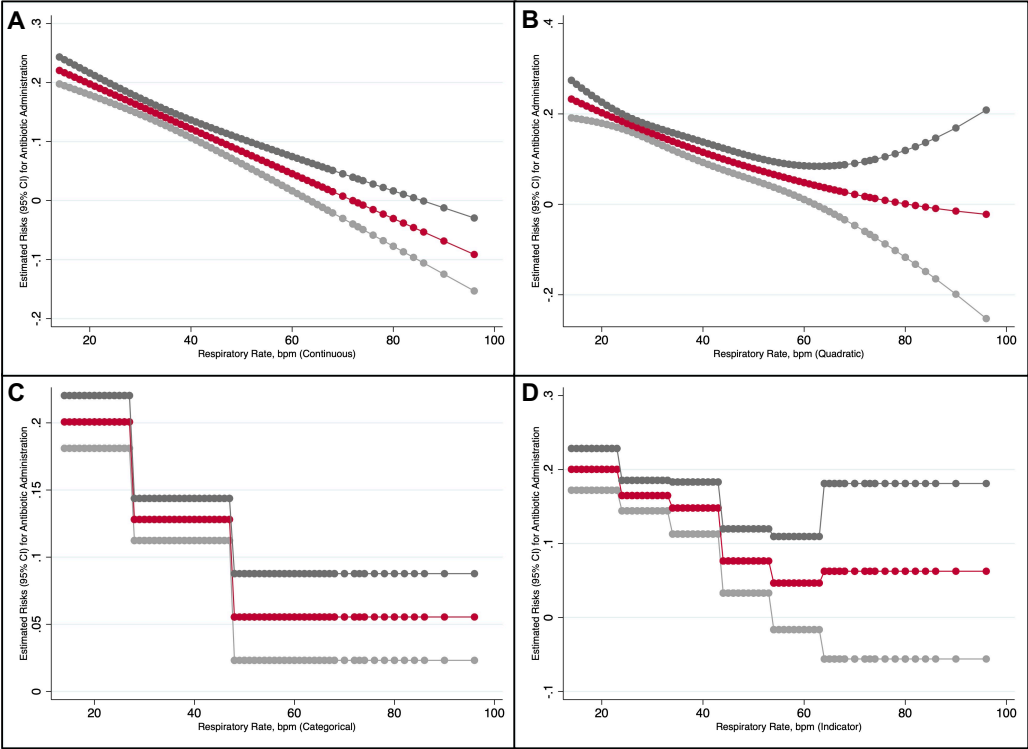
Emergency Department, Illness Duration



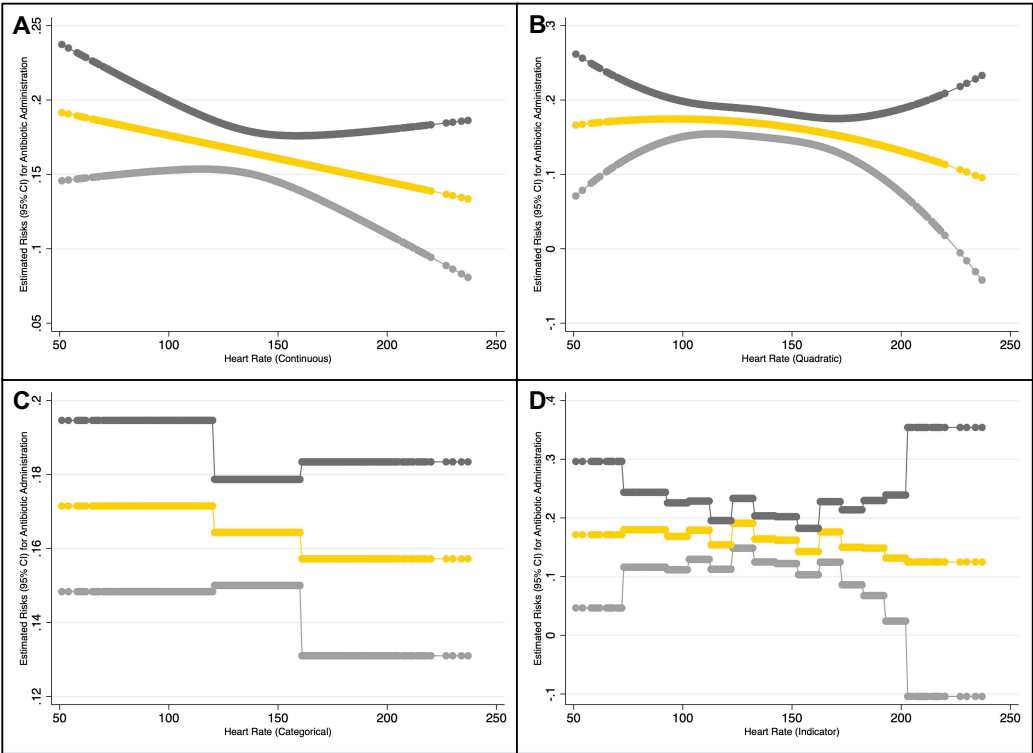
Emergency Department, Oxygen Saturation



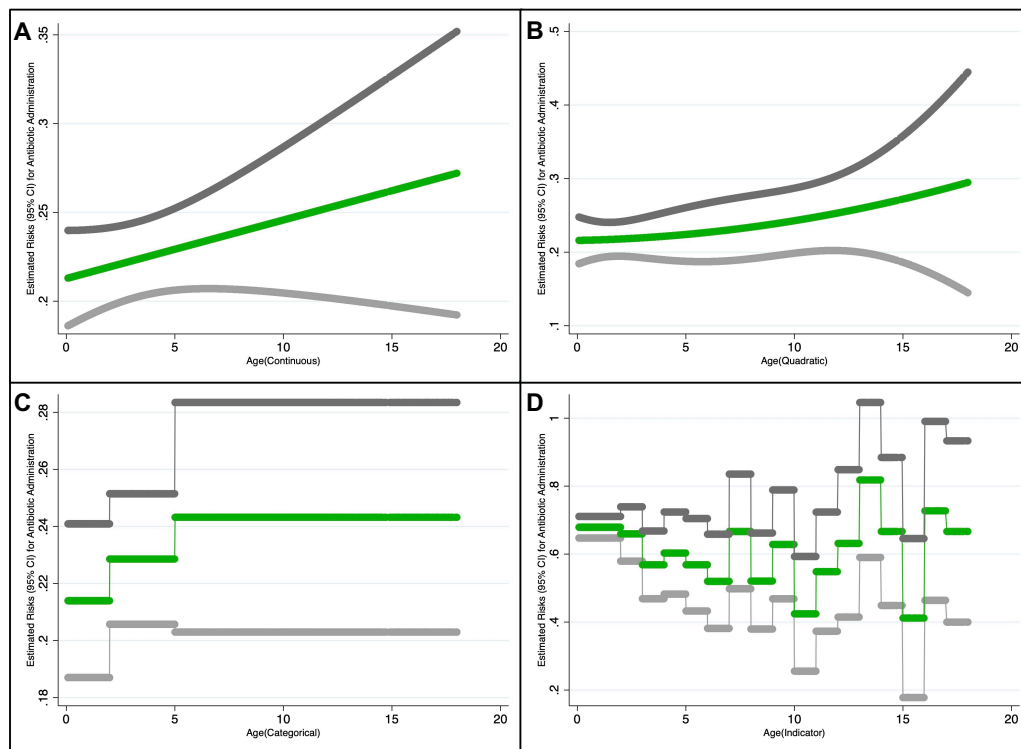
Emergency Department, Respiratory Rate



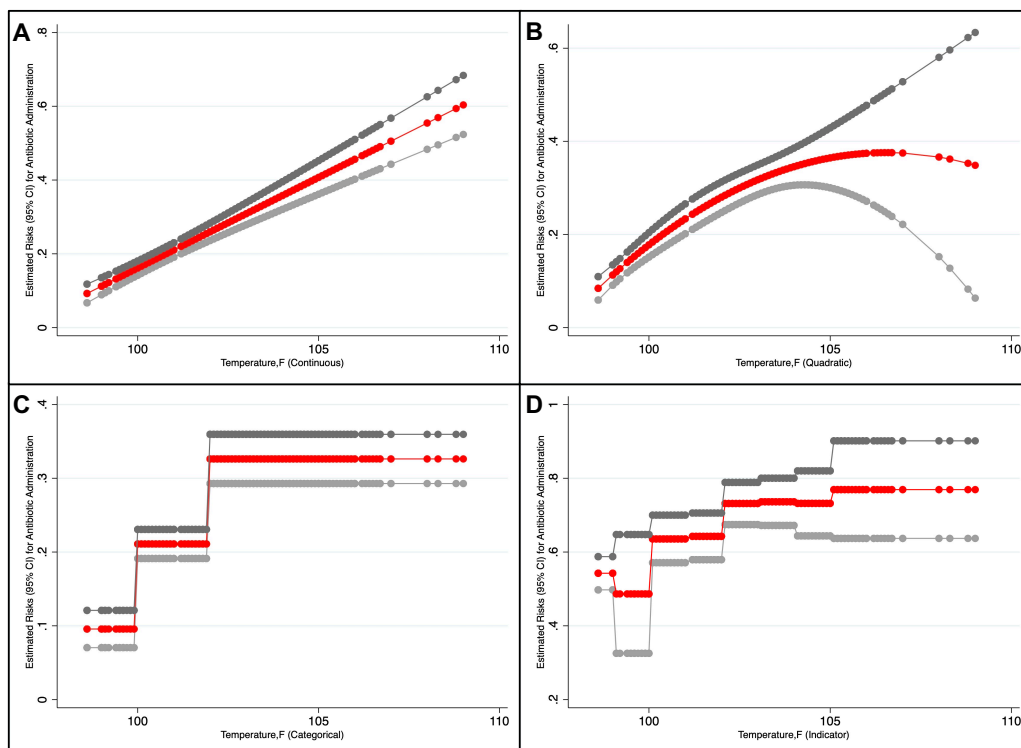
Emergency Department, Heart Rate



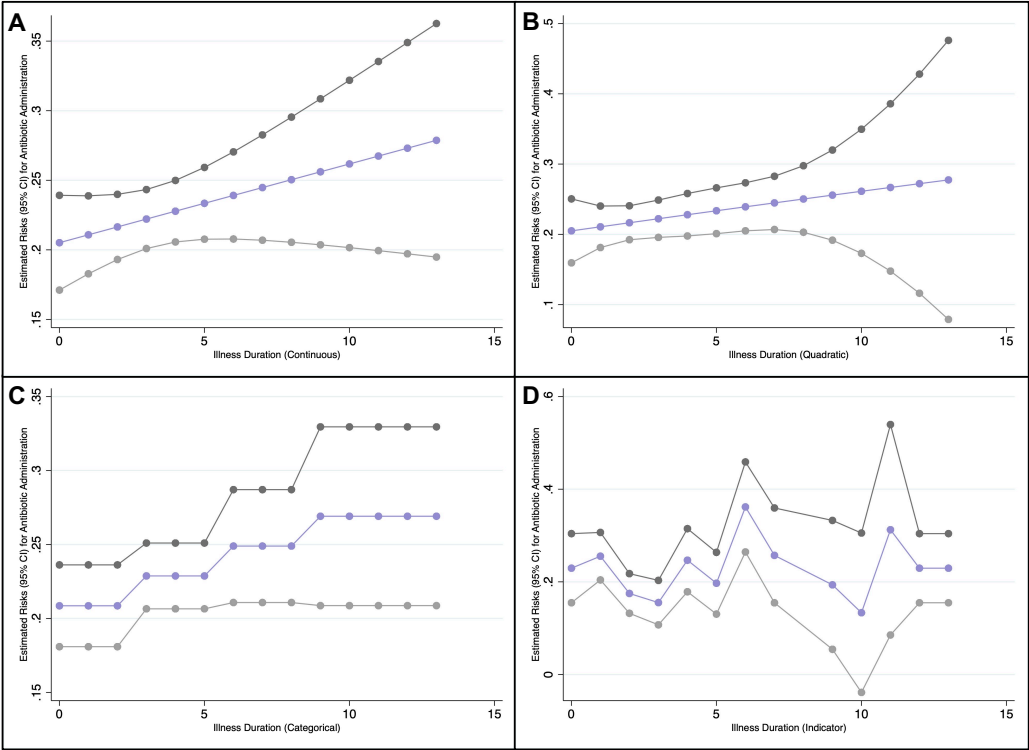
Inpatient, Age



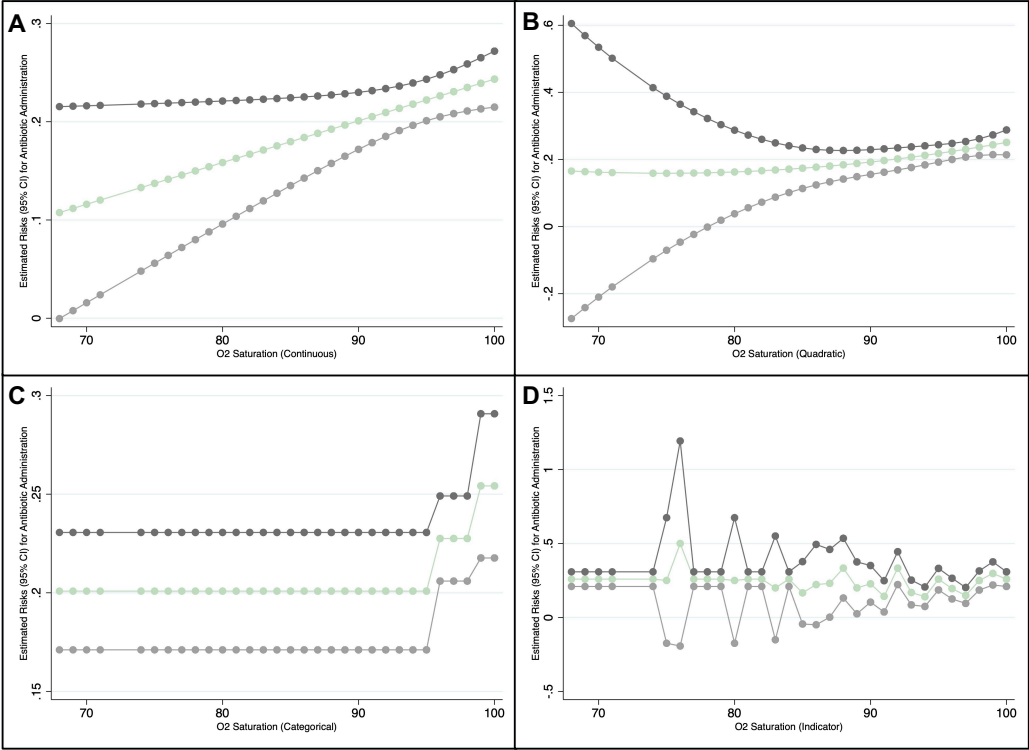
Inpatient, Temperature



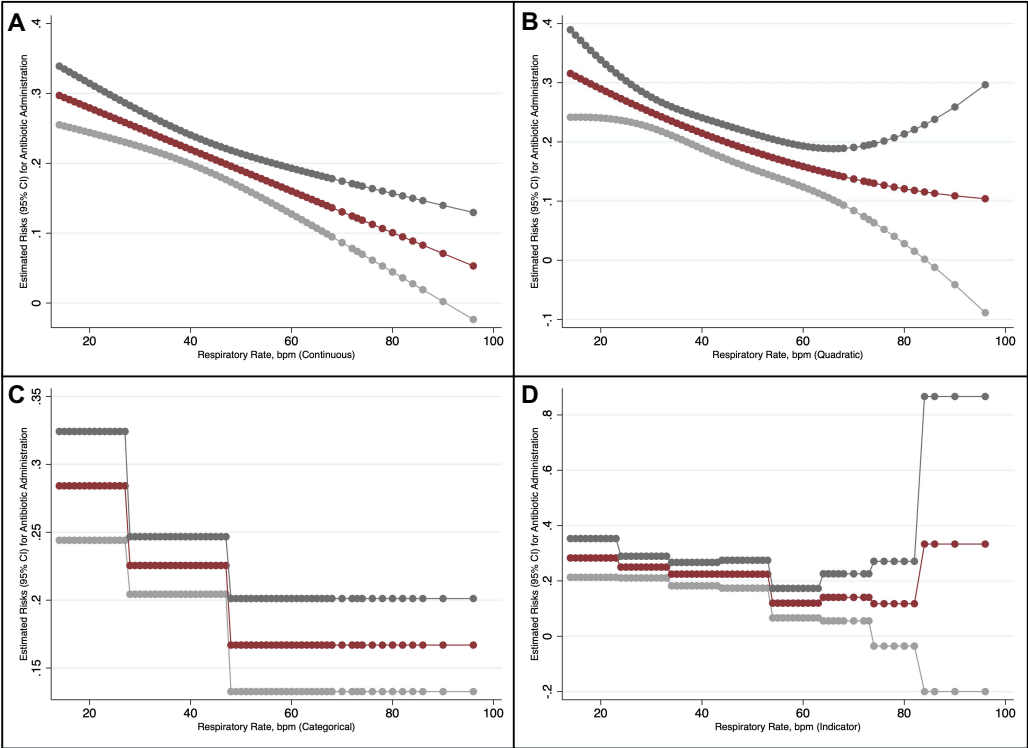
Inpatient, Illness Duration



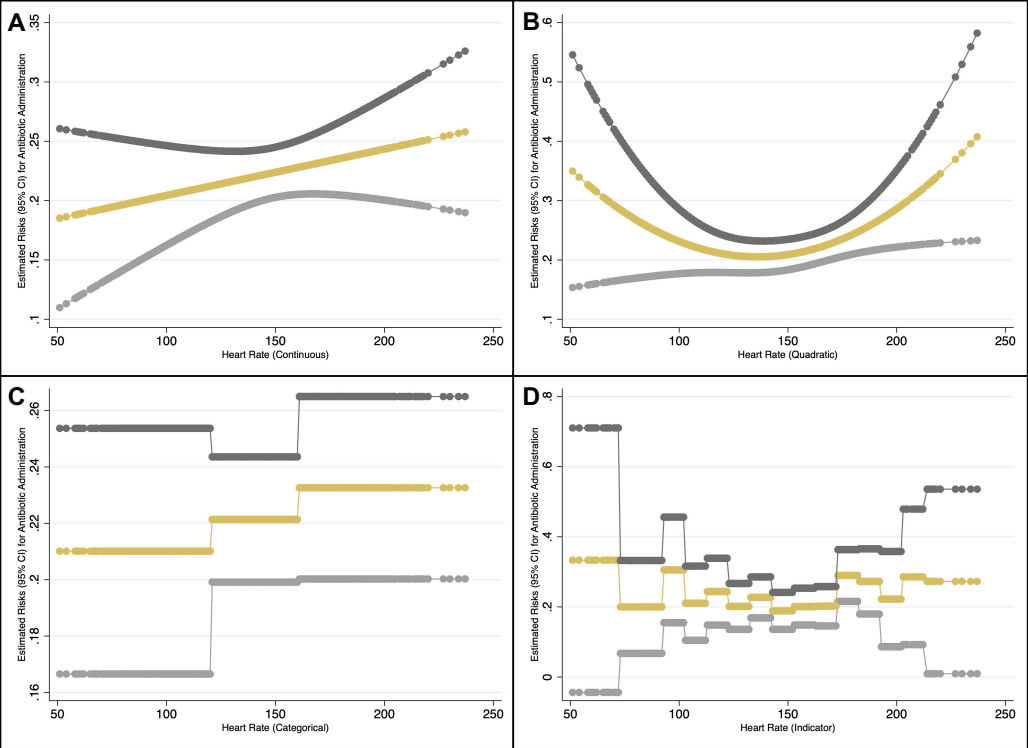
Inpatient, Oxygen Saturation



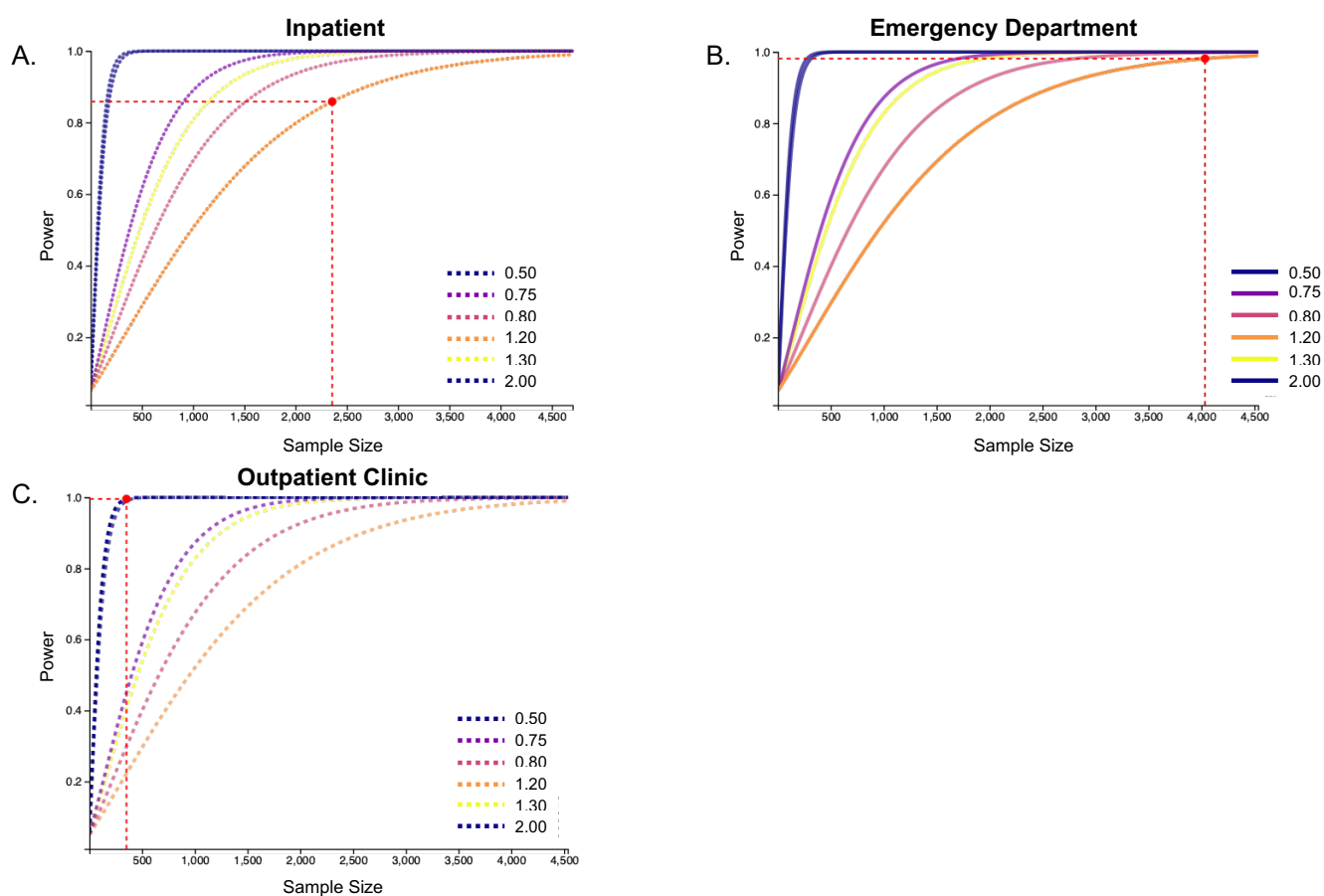
Inpatient, Respiratory Rate



Inpatient, Heart Rate



Appendix Figure B9. Power Calculations for Evaluation of Provider-Ordered Viral Diagnostic Testing and Antibiotic Administration/Prescribing in the Inpatient (A), Emergency Department (B), and Outpatient Clinic (C)



Appendix Table B6. Sociodemographic Characteristics of Children (>30 days-11 months) Enrolled from Three Distinct Outpatient Clinics with Acute Respiratory Illness, by Provider-Ordered Viral Testing, Nashville, Tennessee, December 2019-February 2020

Characteristics	Viral Test Ordered N=58	No Viral Test Ordered N=116
Age, months—mean (SD)	6.6 (3.1)	6.8 (3.0)
Age, months—median (IQR)	6.1 (3.9, 8.9)	6.9 (4.4, 9.1)
Sex, male—no. (%)	24 (41.4)	63 (54.3)
<i>Race—no. (%)</i>		
White, Non-Hispanic	21 (36.2)	45 (38.8)
Black, Non-Hispanic	22 (37.9)	35 (30.2)
Other Non-Hispanic	6 (10.3)	10 (8.6)
Hispanic	9 (15.5)	25 (54.3)
Unknown	0	1 (0.9)
<i>Insurance type—no. (%)</i>		
Public	24 (41.4)	61 (52.6)
Private	33 (56.9)	50 (43.1)
None/Self Pay	1 (1.7)	5 (4.3)
<i>Underlying medical conditions—no. (%)</i>		
≥1 Underlying medical condition	16 (27.6)	25 (21.6)
Respiratory, including asthma/RAD	1 (1.7)	1 (0.9)
Cardiovascular	0	4 (3.4)
Neurological/Neuromuscular	1 (1.7)	2 (1.7)
Oncologic/Immunosuppressive	6 (10.3)	11 (9.5)
Renal	0	0
Gastrointestinal/Hepatic	3 (5.2)	4 (3.4)
Endocrine	0	1 (0.9)
Other	7 (12.1)	8 (6.9)
Prematurity, <37 weeks	8 (13.8)	1 (0.9)
Daycare attendance ^a	28 (48.3)	35 (30.2)
Maximum temperature, °F—mean (SD)	101.2 ^b (1.8)	100.2 ^c (1.6)
Illness duration, days—mean (SD)	2.9 (2.1)	3.9 (2.9)
<i>Physical assessment—no. (%)</i>		
Wheezing	10 (17.2)	8 (6.9)
Retractions	5 (8.6)	4 (3.4)
Rales/Rhonchi	3 (5.2)	8 (6.9)
Crackles	7 (12.1)	5 (4.3)
Rapid <i>Streptococcus</i> antigen performed—no. (%)	0	2 (1.7)

Footnote:

^a reported attending daycare/school ≥4 hours/week;

^b n=55;

^c n=113

Appendix Table C1. TRIPOD Checklist: Prediction Model Development



TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	Explain how to use the prediction model.	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Appendix Table C2. Study Outcome and Candidate Predictor Operational Case Definitions

Variable(s)	Operational Definition	Use in Model Development
Viral ARI	A child having at least one of the following: - Viral pathogen detected from research respiratory specimen detected on RT-qPCR: - Adenovirus - Human metapneumovirus - Influenza (A, B, and C) - Parainfluenza (types 1-4) - Respiratory syncytial virus - Rhinovirus - Endemic coronaviruses (OC43, 229E, NL63, and HKU1) - Tier 3 ICD-10 discharge diagnosis only (i.e., no Tier 1 or 2 discharge diagnoses)¹¹²	Outcome variable, dichotomized: Viral ARI vs. Other ARI
Other ARI	A child having at least one of the following: - Bacterial culture, positive - Positive rapid strep antigen test - Bacterial pathogen detected on RT-qPCR from nasal bacterial testing: <i>Bordetella pertussis</i> <i>Bordetella parapertussis</i> <i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i> - Any Tier 1 or 2 ICD-10 discharge diagnosis code¹¹²	
Age, years	Age at time of enrollment	ED, 5-knot values: 0.32; 1.24; 3.01; 6.42; 14.062 Inpatient, 5-knot values: 0.11 0.53 1.56 4.1825 12.83
Temperature, °F	Maximum temperature, self-reported by parents at the time of enrollment interview. If a child's parent reported no fever was present, their temperature was recorded as normal=98.6°F.	ED, continuous Inpatient, 3 knot values: 98.6; 101.3; 104
Respiratory rate, bpm	First recorded in vital signs at the time of clinical presentation	ED and Inpatient, continuous
Heart rate	First recorded in vital signs at the time of clinical presentation	ED and Inpatient, continuous
Oxygen saturation	First recorded in vital signs at the time of clinical presentation	ED and Inpatient, continuous
Illness duration	Self-reported at the time of enrollment interview.	ED and Inpatient, continuous
Household size	Self-reported at the time of enrollment interview.	ED and Inpatient, continuous
Health insurance	Self-reported at the time of enrollment interview.	ED and Inpatient, Categorical: Public, private, both, none/self-pay
Respiratory season	Based on the date of enrollment	ED and Inpatient, dichotomous: October-April vs. May-September
Cough	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no
Nasal congestion/rhinorrhea	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no
Lethargy	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no

Earache	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no
Sore throat	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no
Myalgia	Self-reported at the time of enrollment interview.	ED and inpatient, dichotomous: Yes vs. no
Wheezing	Determined by child's clinician on physical exam	ED and inpatient, dichotomous: Present vs. not present
Underlying medical conditions	Self-reported at the time of enrollment interview. Conditions were separated into the following categories: • Respiratory • Cardiovascular • Neurologic • Hematologic/Oncologic/Immunosuppressive Other (i.e., renal, gastrointestinal, endocrine, prematurity, other)	ED and inpatient, dichotomous: Yes vs. no

Appendix Table C3. Minimum Sample Size Required to Develop a Multivariable Prediction Model for a Binary Outcome using *pmsampsize* package in RStudio¹³⁷, by Setting

	Emergency Department (n=2,616)			Inpatient (n=1,491)		
	Minimum Sample Size Required	Shrinkage	Cox-Snell R ²	Minimum Sample Size Required	Shrinkage	Cox-Snell R ²
Candidate Predictors (n=27)						
Criteria 1 ^a	2293	0.90	0.100	2166	0.90	0.106
Criteria 2 ^b	724	0.74	0.100	706	0.75	0.106
Criteria 3 ^c	310	0.90	0.100	329	0.90	0.106
Final Model Predictors (n=10)						
Criteria 1 ^a	850	0.90	0.100	803	0.90	0.106
Criteria 2 ^b	269	0.74	0.100	262	0.75	0.106
Criteria 3 ^c	310	0.90	0.100	329	0.90	0.106

Footnote:

^aCriteria 1: small overfitting defined by an expected shrinkage of predictor effects by 10% or less

^bCriteria 2: small absolute difference of 0.05 in the model's apparent and adjusted R-squared value

^cCriteria 3: precise estimation (within +/- 0.05) of the average outcome risk in the population

Using *pmsampsize* in R, we estimated the minimum sample size we would need to meet all three sample size criteria proposed by Riley et. al¹³⁷ for the development of viral ARI models in both the emergency department and inpatient setting. In the ED, our sample size of 2,616 meets all three criteria requirements in the candidate predictor and final model predictor domains. In the inpatient setting to meet all three criteria we would need a minimum sample size of 2,166 with 1,495 events, assuming an outcome prevalence of 69%. Our sample size in the inpatient setting is sufficient to fulfill criterion 2-3, but with our sample size have small overfitting by an expected shrinkage of predictor effects by 10% or less. However, we address this sample size limitation in the inpatient setting by applying a heuristic shrinkage to our model for external validation. In addition, we believe our inpatient model to be of unique importance and interest because our development methods adhere to rigorous prediction model guidelines.

Appendix File C1. Study Population and Data and Laboratory Collection Methods from External Validation Datasets

Study Design and Population by Setting

Outpatient

We used data collected from an active, prospective viral surveillance study among children (<1 year) in Davidson County, Tennessee from December 16, 2019, to February 28, 2020. Surveillance was conducted in four distinct outpatient clinics,²³ with recruitment occurring ≥ 4 days per week.²³

Children were eligible if they presented with one of the following symptoms 14 days prior to enrollment: fever, wheezing, crackles, rales, diminished breath sounds, shortness of breath, cough, earache, nasal congestion, rhinorrhea, coryza, and/or sore throat.²³ Exclusion criteria included: presenting with both fever and neutropenia (absolute neutrophil count $<500 \times 10^3/\mu\text{L}$), having a known non-infectious cause for their symptoms, or a prior study enrollment in the past seven days.²³ This study was approved by the Institutional Review Board at Vanderbilt University.

Government-run Hospital in Amman, Jordan

We used data from a prospective ARI surveillance study in Amman, Jordan from January-February 2020, with recruitment occurring five days per week (Sunday-Thursday).¹⁴¹ The participating hospital is one of three government-run hospitals in Amman, which is the largest city and capital in Jordan (population >2 million).¹⁴⁶

Children were eligible if they were younger than two years and had one or more of the following admission diagnoses: ARI, apnea, asthma exacerbation/reactive airway disease (RAD), bronchiolitis, bronchopneumonia, croup, cystic fibrosis exacerbation, febrile seizure, fever without localizing signs, respiratory distress, pneumonia, pertussis, pertussis-like cough, rule out sepsis, upper respiratory infection (URI), or other respiratory diagnosis. Children were required to have fever or respiratory symptoms occur within 72 hours.¹⁴¹ Children were ineligible if they met one of the following criteria: fever and neutropenia and newborns never discharged from the hospital. Written informed consent was obtained from parents or guardians prior to enrollment and study procedures. Approval was obtained from the Institutional Review Boards of the Jordanian Ministry of Health and Vanderbilt University Medical Center.

Study-Specific Exclusion Criteria

For consistency with our model development studies, we excluded children younger than 30 days to minimize the inclusion of serious bacterial infections due to differences in clinical management practices.

Data Collection

Outpatient

After obtaining informed consent, trained research personnel interviewed the parents/guardians of enrolled children to collect demographic (age, sex, race, ethnicity, insurance type), clinical symptoms, and past medical histories using a standardized form in commonly spoken languages (i.e., English, Spanish, or Arabic).²³ Physical exam findings, bacterial testing (i.e., rapid *Streptococcus* antigen testing and bacterial cultures), and the first five discharge diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10]) were abstracted from each child's medical record.

Government-run Hospital in Amman, Jordan

After consent, trained research personnel interviewed the parents/guardians of enrolled children to collect demographics (age and sex), clinical symptoms, and past medical histories using a standardized form. Interviews were conducted in Arabic (Jordan's primary language) by bilingual research staff and information was transcribed and documented in English on standardized forms. After discharge, medical records were extracted for each child for vital signs at time of presentation (heart rate,

respiratory rate, oxygen saturation), physical exam findings, bacterial cultures, and discharge diagnoses.

Laboratory Testing

Outpatient

Research nasal swabs collected from all enrolled children and placed in viral transport medium and further aliquoted into a tissue lysis buffer (ATL Lysis Buffer, QIAGEN), snap-frozen, and stored at -80°C.²³ All specimens were tested for respiratory syncytial virus (RSV), adenovirus, endemic coronaviruses (OC43, 229E, NL63, and HKU1), human metapneumovirus, human rhinovirus/enterovirus, influenza (A and B), bocavirus, and parainfluenza virus (1, 2, 3, and 4), *Mycoplasma pneumonia* and *Chlamydia pneumoniae* using Luminex® NxTAG Respiratory Pathogen Panel.²³

Government-Run Hospital Amman, Jordan

Research specimens (i.e., nasal and throat swabs) were collected from all enrolled children and placed in viral transport medium (M4RT®, Remel, USA), aliquoted into MagMAX™ Lysis/Binding Solution Concentrate (Life Technologies, USA), snap-frozen, stored at -80°C, and shipped on dry ice to Nashville, TN, USA.^{15,147} Testing of original and lysis buffer aliquots were performed through real-time reverse transcriptase polymerase chain reaction (RT-qPCR) for twelve respiratory viruses: adenovirus, human metapneumovirus, influenza (A, B, and C), parainfluenza (types 1-4), respiratory syncytial virus (RSV), rhinovirus, and endemic coronaviruses (OC43, 229E, NL63, and HKU1).^{92,148,149}

Interview, medical record, and research specimen results from all three studies were maintained in separate and secure REDCap™ (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) databases.⁶⁷

Model Outcome-Viral ARI versus Other ARI

In external validation studies, the same ARI outcome definition was used: 1) viral ARI; and 2) other ARI [probable bacterial or viral and probable bacterial co-detection (mixed infection)].

In the outpatient and NVSN inpatient datasets, ICD-10 codes were classified into tiered diagnoses and categorized in the same manner as the initial ED model. The two hospital Jordan datasets, ICD-10 codes were not collected, therefore discharge diagnoses were categorized into tiers based on the best ICD-10 diagnosis match.

Appendix Table C4. Sociodemographic Characteristics of Children (>30 days-17 years) Enrolled in Emergency Departments and Hospitalized with Acute Respiratory Illness, Nashville, Tennessee, November 2017-February 2020

Characteristics	Emergency Department N=2,616	Inpatient N=1,491
Age, years—mean (SD)	4.6 (4.4)	3.4 (4.1)
Sex, male—no. (%)	1,405 (53.7)	873 (58.6)
Insurance type—no. (%)		
Public	2,093 (80.0)	968 (64.9)
Private	219 (8.4)	395 (26.5)
Both	13 (0.5)	27 (1.8)
None/Self Pay	262 (10.0)	80 (5.4)
Unknown/Missing	29 (1.1)	21 (1.4)
Number of household members—mean (SD)	4.6 (1.6)	4.7 (2.7)
Daycare/School attendance ^a	1,419 (54.2)	677 (45.4)
Time of Illness—no. (%)		
Respiratory season ^b	2,002 (76.5)	1,148 (77.0)
Clinical Symptoms—no. (%)		
Fever, >100.2 F	1,997 (76.3)	1,069 (71.7)
Maximum temperature, °F (mean [SD])	101.3 ^c (2.1)	101.3 ^d (2.2)
Cough	2,146 (82.0)	1,267 (85.0)
Nasal Congestion/Runny nose	2,100 (80.3)	1,182 (79.3)
Lethargy	1,643 (62.8)	1,124 (75.4)
Earache	663 (25.3)	202 (13.5)
Sore throat	1,107 (42.3)	377 (25.3)
Myalgia	608 (23.2)	224 (15.0)
Wheezing	1,15 (42.6)	943 (63.2)
Shortness of Breath	1,219 (46.6)	1,139 (76.4)
Illness duration, days (mean [SD])	2.8 ^e (2.3)	3.3 ^f (2.6)
Vital Signs at presentation—mean (SD)		
Heart rate, bpm	135.6 ^g (28.5)	150.3 ^e (27.2)
Respiratory rate, bpm	28.5 ^h (9.2)	38.5 ^e (13.7)
Oxygen Saturation, capillary	98.4 ⁱ (1.9)	95.5 (5.3)
Physical assessment—no. (%)		
Wheezing	278 (10.6)	539 (36.2)
Retractions	232 (8.9)	767 (51.4)
Underlying medical conditions—no. (%)		
≥1 Underlying medical condition	869 (33.2)	765 (51.3)
Respiratory, including asthma/RAD	471 (18.0)	406 (27.2)
Cardiovascular	52 (2.0)	127 (8.5)
Hematologic/Oncologic/Immunosuppressive		
Neurological/Neuromuscular	120 (4.6)	220 (14.8)
Other ^j	236 (9.0)	357 (23.9)

Footnote:

^areported attending daycare/school ≥4 times/week; ^bRespiratory season, October-April; ^cno. missing=136;

^dno. missing=46; ^eno. missing=1; ^fno. missing=2; ^gno. missing=13; ^hno. missing=12; ⁱno. missing=11;

^jOther includes renal, gastrointestinal, endocrine, and other underlying medical conditions

Appendix Table C5. Viral ARI Diagnostic Model Characteristics and Performance Measures, by Setting

Model(s)	Characteristic(s)	Emergency Department	Inpatient
Model 1, Laboratory+ICD- 10 Discharge Diagnoses ^a	Prevalence of outcome (Viral, only), %	1888/2616=72.3	1039/1491=69.7
	EPV %, candidate predictors	1888/27=69.9	1039/27=38.5
	EPV %, final model	1888/10=189	1039/10=104
	Discrimination, c-index	0.74 (95% CI: 0.72, 0.76)	0.71 (95% CI: 0.68, 0.74)
	Discrimination: optimism-corrected c-index	0.74 (95%CI: 0.72, 0.76)	0.70 (95% CI: 0.67, 0.73)
	Brier score	0.172	0.186
	Calibration, slope	0.9728	0.9429
	Calibration, intercept	0.0181	0.0330
	Heuristic shrinkage factor	0.9708	0.9445
Model 2, Laboratory+ICD- 10 Discharge Diagnoses ^b	Prevalence of outcome (Viral, only), %	1281/2009=64%	663/1115=59
	EPV %, candidate predictors	1281/27=47.4	663/21=31.6
	EPV %, final model	1281/12=106.8	663/6=110.5
	Discrimination: c-index	0.76 (95% CI: 0.74, 0.78)	0.71 (95% CI: 0.68, 0.74)
	Discrimination: optimism-corrected c-index	0.75 (95% CI: 0.73, 0.78)	0.71 (95% CI: 0.68, 0.74)
	Brier score	0.186	0.209
	Calibration, slope	0.9630	0.9629
	Calibration, intercept	0.0187	0.0153

Footnote:

^aModel 1, determines viral ARI based on research laboratory results (virus-positive) or a tier 3 ICD-10 discharge diagnosis; other ARI is based on bacterial cultures, rapid *Streptococcus* antigen, or a tier 1 or 2 ICD-10 discharge diagnosis.

^bModel 2, excludes children who had a tier 3 ICD-10 discharge diagnosis, but did not have a respiratory virus detected from a research laboratory result or any other ARI (i.e., bacterial) suspicion based on clinical laboratory results and ICD-10 discharge diagnoses.

Appendix Table C6. Sensitivity Analysis of Final Viral, only ARI Prediction Model Results^a in the Emergency Department from Bootstrapped Backwards Selection^b after Multiple Imputation for Missing Values^c

Emergency Department N=2,009			
Characteristic(s)	Bootstrap Inclusion Frequency (%)	Coefficient	Standard Error
Intercept	100.0	0.0665	0.2834
Cough (yes/no)	100.0	0.9537	0.1563
Ear pain (yes/no)	100.0	-1.5453	0.1148
Illness duration	99.8	-0.0956	0.0236
Nasal congestion/rhinorrhea (yes/no)	99.8	0.7178	0.1472
Age, years (RCS,5 knots)	99.4	-0.1324	0.2384
Age, years (RCS,5 knots)'	99.4	1.0139	9.5993
Age, years (RCS,5 knots)''	99.4	-2.2718	15.7537
Age, years (RCS,5 knots)'''	99.4	2.1511	7.2362
Respiratory season ^b (yes/no)	98.6	0.4785	0.1312
Sore throat (yes/no)	92.0	-0.3382	0.1162
Myalgia (yes/no)	90.2	0.3307	0.1286
Wheeze, physical exam (yes/no)	89.0	0.6649	0.2110
Total people in household	50.0	--	--
Respiratory rate, bpm	49.0	--	--
Heart rate, bpm	38.0	--	--
Neurological underlying condition (yes/no)	31.0	--	--
Respiratory underlying condition (yes/no)	30.2	--	--
Cardiovascular underlying condition (yes/no)	24.4	--	--
Maximum temperature, °F	24.0	--	--
Insurance		--	--
Private	23.2	--	--
Both, Public & Private	23.2	--	--
None/Self-pay	23.2	--	--
Hematologic/oncologic/immunosuppressive underlying condition (yes/no)	21.0	--	--
Other underlying condition ^c (yes/no)	19.6	--	--
Oxygen saturation, %	17.6	--	--
Fatigue	15.2	--	--
Inpatient N=1,115			
Intercept	100.0	18.5516	3.4153
Age, years	100.0	-0.216	0.0206
Maximum temperature, °F	100.0	-0.1798	0.330
Ear pain (yes/no)	100.0	-1.0534	0.1872
Cough, (yes/no)	99.6	1.1948	0.2323
Wheeze, physical exam (yes/no)	99.6	0.6143	0.1512
Respiratory rate, bmp	94.4	-0.0160	0.0058
Insurance			
Private	81.8	-0.3358	0.1509
Both, Public & Private	81.8	-1.0193	0.5162
None/Self-pay	81.8	0.1777	0.3113
Respiratory season ^b (yes/no)	79.0	--	--
Neurological underlying condition (yes/no)	78.6	--	--
Illness duration, days	74.6	--	--
Total people in household	44.4	--	--
Nasal congestion/rhinorrhea (yes/no)	43.2	--	--
Oxygen saturation, %	41.2	--	--

Other underlying condition ^c (yes/no)	36.0	--	--
Sore throat (yes/no)	33.2	--	--
Respiratory underlying condition (yes/no)	24.2	--	--
Heart rate, bpm	22.0	--	--
Fatigue	21.2	--	--
Myalgia (yes/no)	20.4	--	--
Cardiovascular underlying condition (yes/no)	18.2	--	--
Hematologic/oncologic/immunosuppressive underlying condition (yes/no)	18.0	--	--

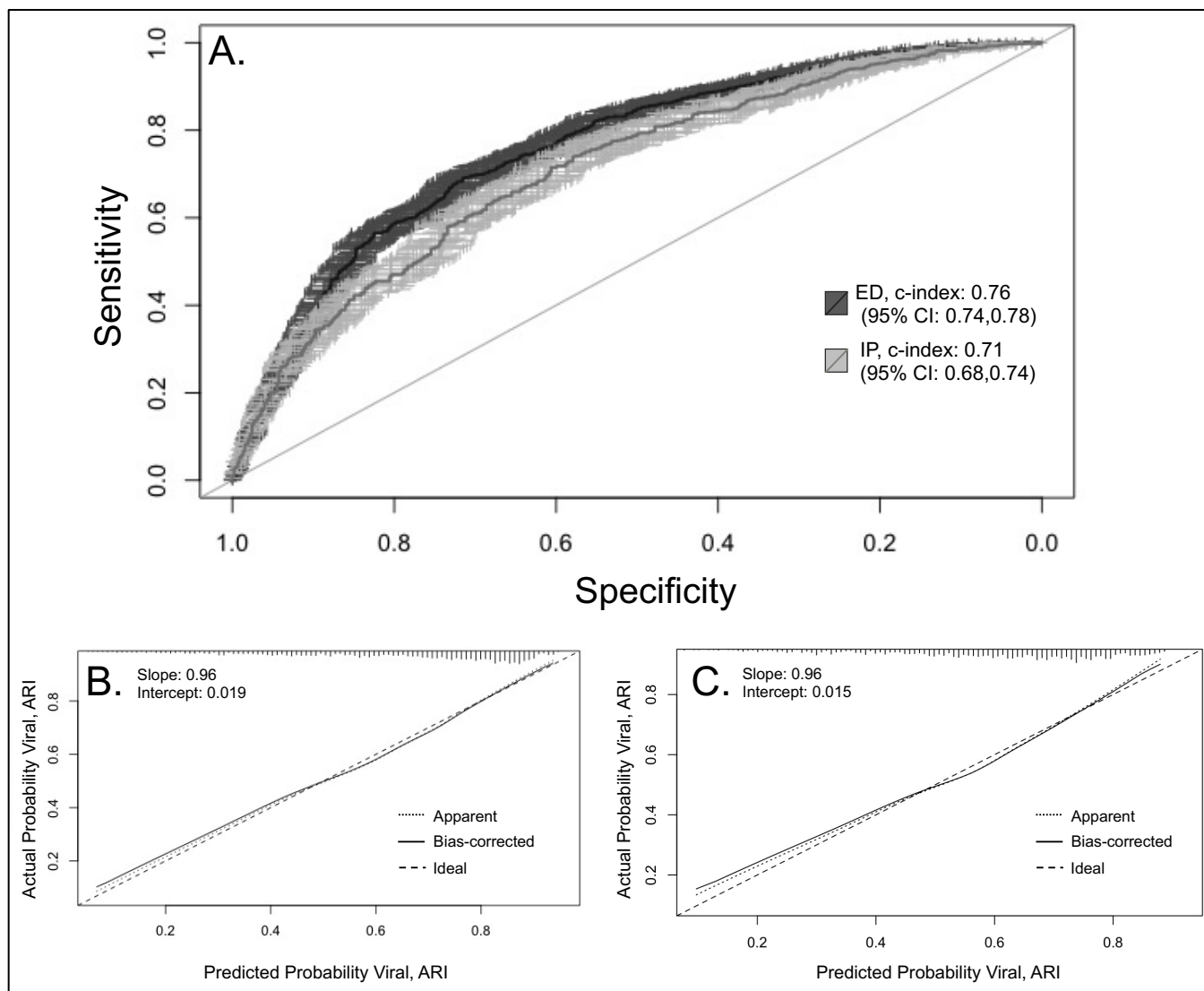
Footnote:

^aFinal model is based on 80% inclusion frequency in the bootstrapped backwards selection.

^bBootstrapped backwards selection included 500 repetitions.

^c2,919 complete cases; 205 children missing ≥ 1 covariate (ED: 154; inpatient: 51)

Appendix Figure C1. Sensitivity Analysis of Viral Acute Respiratory Infection Prediction Model 2 Characteristics Depicting Model Discrimination with a Receiver Operating Characteristic Curve (A) and Calibration Plot of Observed and Predicted Outcome Probabilities in the Emergency Department (B) and Inpatient Setting (C), Excluding Tier 3 Diagnoses from the Viral Outcome Category



Appendix Table C7. Sociodemographic Characteristics of External Validation Data Sources

Characteristic(s)	Outpatient ^a , December 2019-February 2020 N=174	Inpatient, Jordan ^b January- February 2020 N=363
Age, years—mean (SD)	0.6 (0.3)	0.5 (0.4)
Sex, male—no. (%)	87 (50.0)	196 (54.0)
Race—no. (%)		
White, Non-Hispanic	66 (37.9)	--
Black, Non-Hispanic	57 (32.8)	--
Other Non-Hispanic	16 (9.2)	--
Hispanic	34 (19.5)	--
Unknown	1 (0.6)	--
Insurance type—no. (%)		
Public	85 (48.9)	--
Private	83 (47.7)	--
None/Self Pay	4 (3.4)	--
Number of household members—mean (SD)	3.0 (1.3)	5.5 (2.0)
<i>Clinical Symptoms—no. (%)</i>		
Fever, >100.2 F	111 (63.8)	150 (41.3)
Maximum temperature, °F (mean [SD])	100.5 ^c (1.7)	99.7 ^d (1.5)
Cough	151 (86.8)	340 (93.7)
Nasal Congestion/Runny nose	164 (94.3)	324 (89.3)
Lethargy	67 (38.5)	211 (58.1)
Earache	59 (33.9)	64 (17.6)
Sore throat	20 (11.5)	--
Myalgia	9 (5.2)	--
Shortness of Breath	63 (36.2)	258 (71.1)
Illness duration, days (mean [SD])	3.6 (2.7)	3.7 (2.2)
<i>Physical assessment—no. (%)</i>		
Wheezing	18 (10.3)	132 (36.5)
Respiratory rate	--	45.1 (14.4)
<i>Underlying medical conditions—no. (%)</i>		
≥1 Underlying medical condition	41 (23.6)	57 (15.7)

Footnote:

^a reported attending daycare/school ≥4 hours/week; ^c no. missing=6; ^d no. missing=53; ^e no. missing=10

--, denotes data not collected or not applicable to study population (i.e., race/insurance)

Appendix Table D1. Evaluation of the Emergency Department Study Population Repeated Visits Included in Analysis by Enrollment Count, Nashville, Tennessee, November 2017-February 2020

Characteristic(s)	1-enrollment N=2,341	2 enrollments N=241		≥3 enrollments N=34		
	1 st enrollment (n=2,341)	1 st enrollment (n=114)	2 nd enrollment (n=127)	1 st enrollment (n=11)	2 nd enrollment (n=12)	3 rd enrollment (n=10)
Age, years—median (IQR)	3.1 (1.1, 7.2)	1.9 (0.6, 4.8)	2.7 (1.3, 5.2)	0.7 (0.5, 2.8)	1.9 (1.0, 2.9)	2.7 (1.9, 3.5)
Sex, male—no. (%)	1,244 (53.1)	67 (58.8)	76 (59.8)	5 (45.5)	6 (50.0)	6 (60.0)
Race—no. (%)						
White, Non-Hispanic	334 (14.3)	8 (7.0)	10 (7.9)	--	1 (8.3)	--
Black, Non-Hispanic	967 (41.3)	67 (58.8)	68 (53.5)	3 (27.3)	5 (41.7)	5 (50.0)
Other Non-Hispanic	168 (7.2)	5 (4.4)	8 (6.3)	1 (9.1)	--	--
Hispanic	848 (36.2)	33 (28.9)	40 (31.5)	7 (63.6)	6 (50.0)	5 (50.0)
Unknown	24 (1.0)	1 (0.9)	1 (0.8)	--	--	--
Insurance type—no. (%)						
Public	1,854 (79.2)	96 (84.2)	110 (86.6)	11 (100)	12 (100)	9 (90.0)
Private	203 (8.7)	7 (6.1)	8 (6.3)	--	--	1 (10.0)
Both	13 (0.6)	--	--	--	--	--
None/Self Pay	243 (10.4)	10 (8.8)	9 (7.1)	--	--	--
Unknown	28 (1.2)	1 (0.9)	--	--	--	--
Days since prior enrollment— median (IQR)	--	--	297 (182, 428)	--	181 (115, 265)	261 (220, 369)
Time of Illness ^a —no. (%)						
Respiratory season	1,804 (77.1)	90 (78.9)	86 (67.7)	8 (72.7)	7 (58.3)	7 (70.0)
Daycare exposure—no. (%)	1,301 (55.6)	44 (38.6)	62 (48.8)	4 (36.4)	4 (33.3)	4 (40.0)
Underlying medical conditions— no. (%)						
≥1 Underlying medical condition	703 (30.0)	41 (36.0)	54 (42.5)	4 (36.4)	5 (41.7)	4 (40.0)
Respiratory	403 (17.2)	29 (25.4)	34 (26.8)	1 (9.1)	2 (16.7)	2 (20.0)
Asthma/RAD, only	375 (16.0)	25 (21.9)	28 (22.0)	1 (9.1)	2 (16.7)	2 (20.0)
Cardiovascular	45 (1.9)	3 (2.6)	4 (3.1)	--	--	--
Neurological/Neuromuscular	108 (4.6)	3 (2.6)	9 (7.1)	--	--	--
Oncologic/Immunosuppressive	283 (12.1)	8 (7.0)	21 (16.5)	1 (9.1)	2 (16.7)	3 (30.0)
Renal	--	2 (1.8)	2 (1.6)	--	--	--
Gastrointestinal/Hepatic	44 (1.9)	7 (6.1)	11 (8.7)	1 (9.1)	1 (8.3)	--
Endocrine	8 (0.3)	--	1 (0.8)	--	--	--
Other	65 (2.8)	4 (3.5)	4 (3.1)	2 (18.2)	1 (8.3)	--
Prematurity, <37 weeks ^a —no. (%)	87 (3.7)	5 (4.4)	13 (10.2)	--	2 (16.7)	2 (20.0)
Primary Discharge Diagnoses at visit—no. (%)						
Acute upper respiratory infection	293 (12.5)	14 (12.3)	14 (11.0)	2 (18.2)	1 (8.3)	1 (10.0)
Asthma	125 (5.3)	11 (9.6)	14 (11.0)	2 (18.2)	--	1 (10.0)
Bronchiolitis	153 (6.5)	8 (7.0)	7 (5.5)	3 (27.3)	1 (8.3)	--
Fever, unspecified	201 (8.6)	10 (8.8)	12 (9.4)	1 (9.1)	2 (16.7)	2 (20.0)
Influenza	381 (16.3)	19 (16.7)	21 (16.5)	2 (18.2)	1 (8.3)	2 (20.0)
Viral infection, unspecified	171 (7.3)	6 (5.3)	8 (6.3)	--	1 (8.3)	2 (20.0)

Footnote: ^a Respiratory season, October-April; ^b reported attending daycare/school ≥4 times/week; ^c History of prematurity was reported for children aged <2 yrs

Appendix Table D2. Evaluation of the Hospitalized Study Population Repeated Visits Included in Analysis by Enrollment Count, Nashville, Tennessee, November 2017-February 2020

Characteristic(s)	1-enrollment N=1,311	2 enrollments N=149		≥3 enrollments N=31		
	1 st enrollment (n=1,311)	1 st enrollment (n=81)	2 nd enrollment (n=68)	1 st enrollment (n=10)	2 nd enrollment (n=9)	3 rd enrollment (n=11)
Age, years—median (IQR)	3.3 (4.0)	1.5 (0.4, 5.4)	3.2 (1.4, 7.3)	2.6 (1.4, 7.8)	3.7 (1.7, 9.9)	4.0 (2.0, 9.1)
Sex, male—no. (%)	781 (59.6)	47 (58.0)	38 (55.9)	3 (30.0)	2 (22.2)	2 (18.2)
Race, no. (%)						
White, Non-Hispanic	609 (46.5)	28 (34.6)	29 (42.6)	3 (30.0)	3 (33.3)	4 (36.4)
Black, Non-Hispanic	307 (23.4)	19 (23.5)	18 (26.5)	4 (40.0)	3 (33.3)	3 (27.3)
Other Non-Hispanic	117 (8.9)	11 (13.6)	4 (5.9)	2 (20.0)	--	1 (9.1)
Hispanic	269 (20.5)	22 (27.2)	16 (23.5)	--	1 (11.1)	2 (18.2)
Unknown	8 (0.6)	1 (1.2)	1 (1.5)	1 (10.0)	2 (22.2)	1 (9.1)
Insurance type—no. (%)						
Public	835 (63.7)	60 (74.1)	53 (77.9)	7 (70.0)	5 (55.6)	8 (72.7)
Private	368 (28.1)	14 (17.3)	8 (11.8)	2 (20.0)	1 (11.1)	2 (18.2)
Both	18 (1.4)	2 (2.5)	4 (5.9)	1 (10.0)	2 (22.2)	--
None/Self Pay	70 (5.3)	4 (4.9)	3 (4.4)	--	1 (11.1)	1 (9.1)
Unknown	20 (1.5)	1 (1.2)	--	--	--	--
Days since prior enrollment— median (IQR)	--	--	291 (164, 404)	--	204 (121, 275)	188 (112, 207)
Time of illness ^a —no. (%)						
Respiratory season	1,020 (77.8)	63 (77.8)	46 (67.6)	6 (60.0)	6 (66.7)	7 (63.6)
Daycare/school exposure ^b —no. (%)	606 (46.2)	32 (39.5)	25 (36.8)	4 (40.0)	3 (33.3)	6 (54.5)
Underlying medical conditions— no. (%)						
≥1 Underlying medical condition	559 (42.6)	58 (71.6)	60 (88.2)	10 (100)	9 (100)	9 (81.8)
Respiratory	307 (23.4)	33 (40.7)	46 (67.6)	6 (60.0)	6 (66.7)	7 (63.6)
Asthma/RAD, only	230 (17.5)	17 (21.0)	32 (47.1)	4 (40.0)	5 (55.6)	3 (27.3)
Cardiovascular	93 (7.1)	13 (16.0)	14 (20.6)	1 (10.0)	3 (33.3)	6 (54.5)
Neurological/Neuromuscular	152 (11.6)	27 (33.3)	25 (36.8)	5 (50.0)	5 (55.6)	2 (18.2)
Oncologic/Immunosuppressive	214 (16.3)	20 (24.7)	26 (38.2)	3 (30.0)	2 (22.2)	2 (18.2)
Renal	11 (0.8)	3 (3.7)	1 (1.5)	--	--	--
Gastrointestinal/Hepatic	102 (7.8)	15 (18.5)	25 (36.8)	3 (30.0)	4 (44.4)	7 (63.6)
Endocrine	25 (1.9)	5 (6.2)	7 (10.3)	--	1 (11.1)	--
Other	70 (5.3)	11 (13.6)	3 (4.4)	2 (20.0)	--	2 (18.2)
Prematurity, <37 weeks ^c —no. (%)	122 (9.3)	7 (8.6)	12 (17.6)	--	1 (11.1)	2 (18.2)
Primary Admission Diagnoses at visit—no. (%)						
Asthma	154 (11.7)	8 (9.9)	13 (19.1)	2 (20.0)	2 (22.2)	1 (9.1)
Bronchiolitis	286 (21.8)	19 (23.5)	4 (5.9)	--	--	--
Fever, unspecified	110 (8.4)	8 (9.9)	4 (5.9)	2 (20.0)	--	1 (9.1)
Hypoxemia	50 (3.8)	6 (7.4)	6 (8.8)	2 (20.0)	1 (11.1)	1 (9.1)
Pneumonia	112 (8.5)	7 (8.6)	6 (8.8)	--	1 (11.1)	--
Acute respiratory distress	27 (2.1)	--	9 (13.2)	--	1 (11.1)	--

Footnote:

^a Respiratory season, October-April; ^b reported attending daycare/school ≥4 times/week; ^c History of prematurity was reported for children aged <2 yrs