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REVIEW

State of the art of research in pediatric pulmonology

Susanna A. **McColley** *

* **Correspondence to:**
mccolleysusanna@gmail.com. ORCID: https://orcid.org/0000-0003-0842-728X

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Feinberg School of Medicine, Northwestern University, Chicago, USA

ABSTRACT

Despite high global prevalence, morbidity, and economic impact, respiratory disease research has long had disproportionate investment compared to disease burden. This is especially true for pediatric respiratory diseases that are leading causes of childhood morbidity and mortality. Nevertheless, advances in science, technology and research study design have increased opportunities for efficiency, effectiveness and global representation in research. This review presents evolving research approaches and technologies, emphasizing strategies to improve accessibility, inclusion, generalizability, rigor, and reproducibility.

IMPACT STATEMENT: This review can impact the design and implementation of childhood respiratory disease research through enhancing knowledge of new study designs and technologies, increasing access to and generalizability of studies.

KEY WORDS
Cinical research; clinical trials; study design; digital technology; pediatric respiratory disease.

INTRODUCTION

Respiratory disorders are major contributors to childhood morbidity and mortality worldwide (1). These include high-prevalence diseases such as viral, bacterial and mycobacterial infections, asthma, and obstructive sleep apnea; rare genetic disorders such as cystic fibrosis and diffuse lung diseases; and respiratory complications of neuromuscular, hematological, oncological and rheumatological disorders. There is ongoing, disproportionately low investment in respiratory disease research (2), compounded by low investment in pediatric research (3), even in high income countries. There are also many barriers to the conduct of clinical research across fields. Nevertheless, international collaborations, new approaches to clinical study design, and new technologies are increasingly being applied to improve understanding of and advance therapeutics for pediatric respiratory disorders.

Many conferences and journals include ‘best of’ or ‘year in review’ presentations or papers in a given calendar year. This review will instead focus on new and evolving research approaches and technologies, highlighting recent articles of interest to the pediatric respiratory research community. Throughout, there will also be a focus on inequities in opportunity to participate in and benefit from research advances.

INTERNATIONAL COLLABORATIONS, NETWORKS, AND METHODOLOGIES ADVANCE UNDERSTANDING AND GLOBAL REPRESENTATION

As of July 2024, an estimated 5.4 billion people have internet access, representing just over 67% of the world's population (4). Expanded connectivity and advances in computing have allowed increased collaboration, crossing borders and time zones, and application of sophisticated methods in quantitative sciences, including biostatistics and epidemiology. This presents opportunities for international collaborations, data harmonization and methodological standardization that enhance transparency, generalizability, rigor and reproducibility of research findings.

A 2024 study of the global burden of respiratory syncytial virus (RSV) in preterm infants and young children exemplifies use of international collaborations and advances in technology and analysis (5). This sophisticated systematic review and meta-analysis of aggregated and individual participant data, registered in PROSPERO, the International prospective register of systematic reviews (6), included investigators from two global networks and was written by an author team from China, the United Kingdom, Europe, Africa and the United States. Combined aggregated data from studies published between January 1995 and December 2021 and individual participant data from the Respiratory Virus Global Epidemiology Network on respiratory infectious diseases were included. Methods, including meta-regression and two-stage metanalysis, allowed sophisticated estimates of global RSV acute lower respiratory infection morbidity, mortality and risk factors for hospitalization. Among important findings are that, in 2019, an estimated 1,650,000 (uncertainty range [UR] 1,350,000-1,990,000) children under 2 years of age were diagnosed with RSV; 533,000 (UR, 385,000-730,000) were hospitalized, and 26,760 (UR, 11,190-46,240) with preterm birth died. One in 4 hospitalized infants were preterm, and early preterm infants and children had higher hospitalization rates. In-hospital mortality was not different between infants born preterm compared to those born at any gestational age. Risk factors for RSV acute lower respiratory infection were mostly perinatal and sociodemographic, and risk factors for severe outcomes were mostly underlying medical conditions.

While this study confirms many previously identified risk factors for RSV hospitalization and death, the description of the contemporary global magnitude, severity and risk factors is both novel and timely. Recent advances in RSV prevention, including RSV vaccines for pregnant people (7) and monoclonal antibody administration to infants <8 months of age (8), have potential to markedly reduce infant and early childhood morbidity and mortality from acute lower respiratory infections. How quickly these advances will reduce the heavy toll of RSV disease is, however, dependent on an adequate supply, global distribution, and ability of public health and health care systems to deliver these preventive therapies at the right time. Implementation of RSV prophylaxis using the monoclonal antibody, nirsevimab, in the US was hampered by shortages in 2023. Furthermore, disparities in availability and acceptance were evident across pediatric practices in the state of Massachusetts (9), whose child health system performance is among the highest in the nation (10). The availability of data on worldwide incidence, morbidity and mortality is essential for industry leaders, governments and health care systems to create pathways to access to apply these scientific advances to benefit children across geographies.

ADVANCES IN CLINICAL STUDY DESIGN TO PROMOTE EFFICIENCY, ACCESS AND GENERALIZABILITY

Delays from scientific discovery to new treatments (11), and from efficacy trials to effective implementation (12), are well described, and include specific challenges for pediatric trials (**Table 1**). Participants in clinical trials often do not reflect the general population of people with, or at risk for, diseases, including children, people from minoritized groups, and people who live in remote or rural regions (13). There are evidence-based approaches to enhancing representative study recruitment (14) for both observational and interventional research. New study designs (**Table 2**), approaches, and technologies can overcome longstanding barriers to efficiency, access and inclusion, accelerating research processes, reducing study participant burden, and aiding generalizability of findings by using data from large, geographically distributed populations.

Table 1. *Barriers to conduct of pediatric clinical trials.*

Barrier	Example(s)
Caregiver consent and child assent	Caregiver concerns about safety Caregiver and child aversion to study procedures (e.g., phlebotomy)
Ethical and regulatory considerations for vulnerable population	More protections increase time needed for regulatory and ethics committee approvals
Eligibility criteria	Strict inclusion and exclusion criteria limit availability of participants and generalizability
Awareness	Caregivers and may not be aware of clinical trials or why they are needed
Accessibility	Trial sites are often in large urban areas that are difficult for many families to access
Communication	Study materials and consent/ assent documents may be difficult for caregivers and children to understand Study staff and investigators may have difficulty communicating in plain language
Language	Materials and consent/assent may not be available in all languages spoken by potential participants
Logistics	Caregiver responsibilities and child school attendance can make traveling to study sites infeasible
Incentives and reimbursement	Financial constraints and ethical considerations may make incentives and reimbursements in adequate to account for time and lost income for caregivers

Table 2. *Advances in study design and enabling technologies.*

New study designs	Benefits	Caveats and risks
Real-World Evidence	Uses data from existing records/registries Clinical characteristics and treatment responses from in larger, more heterogenous populations	Data may not include representative populations
Decentralized studies	Study procedures performed at home increase recruitment and retention	Internet service and device availability vary geographically and by household resources
Adaptive trial designs	Trial parameters can be adjusted based on interim results without compromising study integrity	Increased complexity May introduce bias if not carefully designed
Participant-centric trial design	Involving participants and their families in study design can improve acceptability of the ultimate protocol, enhancing recruitment	Requires time and resources Patient and family preferences may not align with regulatory requirements
Enabling technologies		
Artificial Intelligence and Machine Learning	Supports identification of eligible study participants, identification of physiologic and laboratory predictors of disease/disease severity, and analysis of large datasets	Bias in data sources, data entry or algorithms may reduce performance and/or result in inequitable disease or disease severity prediction
Digital tools	Portals and applications provide secure, easily accessible platforms for informed consent, interactions with study staff, and entry of participant/ caregiver reported outcomes	Internet access and digital literacy vary between and within regions

REAL-WORLD EVIDENCE

Real-world evidence (RWE) studies are being increasingly used to characterize disease and effectiveness of treatment in children (14). Rather than collecting data prospectively, RWE studies electronic health records, registries, and other data collected without specific attention to hypotheses or observing natural history. Study designs using RWE include observa-

tional studies to describe phenotypes, single-arm trials that use RWE as a proxy for a control group, as in studies of therapies for very rare diseases that extend new therapies to children based on adult clinical trial data, or when controlled, randomized efficacy trials are limited in size.

An outstanding 2024 study of children with asthma represents the power of RWE in disease phenotyping. Nearly 30,000 children from in a Danish nationwide database were studied to explore how routinely collected clinical data could be used for clinical phenotyping and risk assessment (15). Elevated blood eosinophils and elevated total- or specific-IgE were associated with asthma exacerbations and higher asthma severity, respectively. Children with both these laboratory findings, in utero tobacco exposure, and severe viral infections were at the highest risk of any adverse asthma outcome. These findings can be applied to clinical practice and can also aid in developing therapeutic clinical trials by guiding inclusion criteria and/or risk stratification.

An important caveat in interpreting RWE studies is understanding how the population from whom data were derived are similar, or different, from a population that may benefit from study findings, whether for clinical care or design of clinical trials. Ancestry, environment, rates of child poverty, access to and quality of health care vary by country, region, and demographics influence incidence and prevalence of disease and contribute to disease severity. While race and ethnicity are sociopolitical constructs, children of minoritized race or ethnicity have worse outcomes across acute and chronic diseases in the US and other countries. For example, there is clear evidence that poorer quality in health care delivery is a major contributor to adverse outcomes in minoritized US children (16). Even the mandatory and highly comprehensive Danish National Child Health Register used for the above-referenced study has missing data, to which ethnic background or socio-economic disparities may contribute (17). Although RWE study protocols can be replicated in any region where electronic health data are available, the proportion of children with a disease who have data, and how data are entered and analyzed can limit generalizability of findings (18). Thus, RWE studies, while efficient, useful and relatively inexpensive, should be interpreted in the context of these limitations.

DECENTRALIZED STUDY DESIGNS

Clinical research is hampered by accessibility to study sites posed by distance, costs of transport, and other factors such as missed school for children and missed work for parents. Studies that are decentralized, either wholly or in part, are an important solution to enhance enrollment and representative participation. During restrictions imposed to reduce COVID-19 exposure, many trials originally designed to have study procedures at health care or research facilities made rapid adaptations to offsite procedures and remote study visits, conducted by telephone or videoconference (telehealth visits) (19). One such clinical trial is especially memorable to the author. The extension trial of elexacaftor/tezacaftor/ivacaftor for children with cystic fibrosis (CF), homozygous or heterozygous for the F508del CFTR variant, and 6-11 years old was rapidly decentralized during the COVID-19 pandemic (20). Study medication was delivered to the homes of enrolled children, clinical samples were collected in homes or local laboratories, and some clinical assessments (*e.g.*, sweat chloride) were missed. Despite these challenges, most participants remained enrolled, the trial was completed, and the medication has become available in countries whose health care systems have adequate resources.

An important paper describing incidence and symptoms of long COVID was published in 2024, demonstrating how a large prospectively enrolled cohort from a single center can be retained in a low burden, partly decentralized, longitudinal study (21). The investigators recruited a cohort of children, up to age 13, who had been seen at the hospital Emergency Department, admitted to the hospital, or seen by an external pediatrician over the course of ~4 years. Baseline, 3- and 6-month assessments were conducted in person, and those who had returned to pre-COVID health were subsequently assessed by telephone. Among 1319 children referred, 98.6% received follow-up at 3 months, 97.9% at 6 months, and 85.6% at 12 months, and 82.2% at 24 months. Even at 36 months, when the majority had recovered, retention was 66.2%. This allowed thorough evaluation of diagnosis of long COVID incidence, using published definitions, and clinical course of those who met diagnostic criteria. Findings were important for both health care practitioners and

public health leaders. These include a high prevalence of persistent symptoms and long COVID, present in ~23% of children at 3 months and continuing at 36 months in some, demographic and clinical predictors of long COVID, variation in long COVID associated with specific variants, emergent autoimmune disorders, and the protective effects of vaccination.

It is unlikely that this study will be fully replicated in other regions, given expansion of COVID-19 vaccines to younger children and ongoing variant shifts. The implications of the study are critically important for primary care physicians and pediatric subspecialists, providing insights into natural history and setting a stage for clinical trials to prevent or alleviate long COVID. Furthermore, this example of a rapidly designed and implemented prospective study, with low participant burden, can be replicated or applied to other emerging diseases.

ADAPTIVE CLINICAL TRIAL DESIGNS

Adaptive clinical trials (22) allow modifications of trial parameters, such as drug dose, participant selection, or measurements based on prespecified interim results. This allows trial adjustments without compromising study integrity. To date, adaptive trial designs have not been widely used in pediatric respiratory disease. For example, a recent systematic review of adaptive trial designs in pediatric critical care reported that only 3% of reported trials conducted between 1986 and 2021 used an adaptive design (23). However, adaptive trial designs are in progress or planned for studies of childhood respiratory disorders. These include the Precision Medicine in Severe Asthma study (24), which has enrolled adolescents and adults and uses an adaptive design to test novel interventions in biomarker-defined subgroups of severe asthma. Another trial in progress is the Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) study (25). In addition to generating important new knowledge, these studies may serve as examples for future adaptive trials of pediatric respiratory disorders.

PATIENT-CENTRIC TRIAL DESIGNS

Nearly 1 in 5 pediatric clinical trials fail to enroll enough participants. A potential solution to this persistent problem is to involve children and their caregivers in the design of study protocols. A 2023 report described lessons learned and recommendations from a collaboration between two European Innovative Medicines Initiative Innovative Health Initiative projects, conect4children and European Patient-CEntric ClinicAl TRial Platforms (26). The groups conducted advice meetings that included experts in relevant scientific disciplines and clinical study design. Children (referred to as patients in this report) and caregivers affected by relevant diseases advised on scientific feasibility and acceptability of the proposed study design, or acceptability alone. Patients and caregivers gave feedback in groups or in interviews. Positive outcomes included synergy between investigators and patients/caregivers that generated unique inputs and insights, balancing scientific feasibility with acceptability, and generating culturally relevant information by engaging patients/caregivers from different countries. Social benefits were derived from participation in groups, but not interviews. Limitations included that some topics are less suitable for discussion, that patients/caregivers may be afraid to speak up in the presence of experts, and that patient/caregiver input may not be fully considered. Study protocol changes included changes in eligibility criteria and including patient reported outcome measures in composite study endpoints.

ENABLING TECHNOLOGIES

Artificial intelligence and machine learning

Artificial intelligence (AI) and machine learning are technologies that allow computers to perform tasks that otherwise require human intelligence. Artificial intelligence is a broad term to describe use of machine-based learning and algorithms, while machine learning describes automated changes in programs or algorithms based on exposure to data to improve performance over time (27). These technologies are applied in many industries for customer service, targeted advertising, process automation, analytics, and other business functions. In medicine, AI and machine learning are being increasingly used for diagnostic and prognostic prediction, monitoring and medication management (27). Data may be derived from electronic health records, medical devices, or applications

for non-medical devices, as applied to detect atrial fibrillation from a widely available 'smart watch' (28).

A 2023 article demonstrated applications of machine-learning trained devices to aid diagnosis of pediatric lung disease (29). Electronic stethoscope recordings were recorded during routine clinical care by pediatric pulmonologists and labeled as normal, crackles, or wheezing, based on the examiner's findings. Models were trained to differentiate normal *vs*. abnormal, crackles *vs*. wheezing, normal *vs*. crackles, and crackles *vs*. wheezing. A prospective validation showed that the machine learning breath sound classification model performance was high, was lower than pediatric specialist performance, but was better than non-pediatric physician performance, except for practice. This technology could potentially be deployed for more rapid assessment of children with respiratory symptoms during viral respiratory outbreaks.

A 2024 article described development of a mechano-acoustic sensor for accurate cough detection in children with cystic fibrosis (30). This study adapted technology from a previously described sensor (31) and studied children with CF who had brief, protocolized study visits in which they coughed, talked, ate, drank, and moved; in clinic during visits, including pulmonary function testing; and for longer periods while stable and during pulmonary exacerbations. Machine learning algorithms accurately detected cough and vital signs, and quantified reduction in cough with resolution of pulmonary exacerbation. Such technology could be deployed to monitor children with CF at home, or as a clinical trial endpoint.

Another 2024 article described development of a machine-learning strategy to diagnose obstructive sleep apnea syndrome (OSAS) in children (32). Children with symptoms of OSAS had clinical evaluations, standardized questionnaires, and physical assessments, including neck, waist and hip circumference. A machine learning algorithm was trained based on clinical evaluation and polysomnography findings. Machine learning selected 47 clinical features associated with apnea-hypopnea index (AHI)>5 and 31 features associated with AHI>10. Linear discriminant analysis using these features had sensitivity of 44% and specificity of 90% for detecting OSAS, performing better than the questionnaire alone.

Digital tools to facilitate communication and collect study data

Digital tools, including applications for portable devices and participant portals, are increasingly used for communication with research participants (or their proxies) and to collect participant-reported information, including participant (*i.e.*, patient) reported outcome measures. A 2021 paper described how the Asthma Research in Children and Adolescents (ARCA) cohort was developed (33). Children aged 6-16 who had persistent asthma were eligible for enrollment. Parents/proxy, children, and adolescents submitted information related to asthma control on a smartphone application. Data was sent to pediatricians through a portal that displayed color-coded in the familiar 'traffic light' system of green, yellow and red to indicate asthma control. High usability scores were found across age groups. The smartphone application was subsequently used in a prospective observational study that assessed longitudinal associations between inhaler adherence and technique and asthma control (34). This study demonstrated the associations between adherence, symptom control and health-related quality of life, and associations between inhaler technique and health-related quality of life.

SUMMARY AND CONCLUSIONS

Advances in connectivity, study design, and technologies have great potential to increase and enhance research in childhood respiratory disorders. Improving access to technology, including child and caregiver perspectives in study designs, and increasing awareness and accessibility of clinical research are essential to advance health and health equity in respiratory and other childhood diseases. Researchers should consider new study designs, technologies and approaches that increase collaboration between investigators, awareness of research opportunities by caregivers and health care providers, and reduced burden to participants and caregivers.

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COMPLIANCE WITH ETHICAL STANDARDS

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Author contributions

SAM wrote the article.

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Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

The Author declares no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real. The development of this manuscript was aided by ChatGPT through the Chat Smith application. All language is original and attributable to the author.

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