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Children's Health and the impact of COVID-19

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Children's Health

Clinicians who take care of children understand that there are many factors—some beyond their control—that can impact a child's health and well-being, including access to health care. In this issue of WMJ, *authors explore several issues related to caring for kids, both with and without the influence of the COVID-19 pandemic.*

Cover design by Kendi Neff-Parvin

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EDITORIAL

ORIGINAL RESEARCH

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Children's Health in Wisconsin

Sarina Schrager, MD, MS, *WMJ* Editor-in-Chief

Children's health encompasses physical, social, and psychological components. For a child to be healthy, they need to have access to food, shelter, and loving relationships. Clinicians who take care of children understand that there are many factors (some out of our control) that can impact a child's health and well-being—including access to health care.

Children without health insurance are less likely to get routine screenings and preventive interventions. Data from 2019 show that 3.8% of children in Wisconsin do not have health insurance, ranking the state 17th out of 51 (including the District of Columbia).[1] And while Wisconsin ranks highly (12/51) for the overall health of children based on high-quality public education and low rates of uninsured children,[2] these numbers are lower for children of color.[3] Both African American and LatinX children have higher rates of being uninsured.[1] Further, data regarding the mental health of children in Wisconsin is less favorable. Based on 2016 data, Wisconsin ranked 42nd for youth mental health.[2] This ranking included high depression rates among children and low levels of treatment for this population. Over 20% of Wisconsin children have been diagnosed with anxiety, depression, behavioral issues, attention deficit hyperactivity disorder, or other mental health disorders.[2] Objectively, those are very high numbers and mean that 1 in 5 kids in the state has been diagnosed with a mental health condition.

Alcohol use among youth in Wisconsin is also at epidemic proportions and exceeds the national average at several age levels.[4] In 9th grade, half of all Wisconsin youth have tried alcohol compared to 43% on average in the rest of the US.[4] This number increases up to two-thirds by the time these kids reach 12th grade.

Further exacerbating these issues is the impact of the COVID-19 pandemic. We know that the pandemic has affected the educational progress of many children due to school closings and inconsistent access or lack of support for virtual schooling options. Many children in Wisconsin do not have access to reliable high-speed internet and do not have adults at home who can help them complete schoolwork, which has led to many children falling behind academically. The lack of social interaction, as well as the isolation of being at home and not at school, have contributed to the worsened mental health of both children and adolescents.[5]

Indeed, the pandemic has affected several different aspects of mental health. Admissions for eating disorders among adolescents increased significantly during the first year of the pandemic.[6] Overdoses are at an epidemic proportion, with over 100,000 people dying of overdoses in 2021 alone.[7] It is unclear how the pandemic has affected youth's use of alcohol and other substances.[5] However, over the last year, Wisconsin youth are above the national average for misuse of opioids and other pain medications.[8]

> The last two years have been difficult to navigate for all, not just children. But for children in particular, the consequences of the pandemic are far reaching. As clinicians, it is imperative that we focus on optimizing the health of Wisconsin children moving forward.

Several papers in this issue of the *WMJ* discuss issues around caring for children—in general, and during this pandemic. Falk et al evaluated a widespread COVID-19 testing campaign in a secondary school in Southeastern Wisconsin during the early part of the pandemic. They found challenges in completing the testing in a low-prevalence, high mask-wearing area and suggest instead focusing efforts on COVID vaccination and other preventive strategies.[9] Liljestrom and colleagues looked at hospitalization rates for asthma, bronchiolitis, and bacterial pneumonia before and during the pandemic. Not surprisingly,

they found significantly decreased hospitalization rates for these conditions during the pandemic compared to previous years.[10] This study provides more evidence that isolating and mask-wearing decrease transmission of all respiratory illnesses. Lehrer et al report on disparities in childhood immunization rates exacerbated by the pandemic;[11] and in a commentary calling for increased COVID vaccinations of children, Soung discusses the incidence of multisystem inflammatory syndrome in children after a COVID-19 infection.[12] Even though this is an uncommon condition, it is potentially life-threatening, providing evidence to support universal vaccination of children.

In another paper, Chelimski et al evaluated unconscious bias among a cohort of pediatricians in an academic department in Milwaukee.[13] The clinicians were asked to complete a survey that measured their biases and then given some sample clinical vignettes to see if their decision-making was affected by a child's race or ethnicity. The survey found that there were some unconscious biases present but that the decision-making (based on the vignette) was not significantly affected. This is a small study but underscores the importance of self-reflection on how we treat patients differently.

Other topics included in this issue related to the health of children include nutritional infantile failure to thrive (Marten et al),[14] return rates in pediatric patients treated for croup (Udoh et al),[15] and current practice and rationale for prescribing dexamethasone for pediatric patients hospitalized for asthma (Nelipovich et al).[16]

The last two years have been difficult to navigate for all, not just children. But for children, in particular, the consequences of the pandemic are far-reaching. As clinicians, it is imperative that we focus on optimizing the health of Wisconsin children moving forward.

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Multisystem Inflammatory Syndrome in Children: A Call for Improving Pediatric COVID-19 Vaccination Rates

Paula Soung, MD

The COVID-19 pandemic continues to loom over the medical community while the visibility of vaccine campaigns is waning. As the peaks and waves of COVID-19 and its variants have hit the American population hard, pediatrics has fared well overall. Children under 18 years account for 0.1% of US deaths related to COVID-19.[1] For the most part, children have experienced relatively milder disease than adults, and arguments in favor of vaccination have been disregarded by many, with societal concerns about safety peaking as approval rolled out for pediatric age groups.[2-4] In Wisconsin, only 60% of children ages 12 to 17 and 26% of children ages 5 to 11 have received at least 1 dose of COVID-19 vaccine.[3] Meanwhile, in addition to protection from acute COVID-19 disease itself, data are emerging about the protection COVID-19 vaccines may provide to children from multisystem inflammatory syndrome in children (MIS-C).

MIS-C is a condition presenting with fever, inflammation, and multisystem organ involvement, typically occurring within 4 weeks of a SARS-CoV-2 infection or exposure.[5] This postinfectious syndrome has set SARS-CoV-2 apart from the viral milieu we are accustomed to in pediatrics. While children with immunocompromised states or comorbidities have been at greatest risk for requiring hospitalization with acute COVID-19 infections, there is a growing body of data demonstrating COVID-19 vaccination is associated with lower MIS-C incidence among adolescents.[8-10] A study in France evaluating the effects of COVID-19 mRNA vaccine on MIS-C outcomes in adolescents 12 years and older admitted to French pediatric intensive care units showed most adolescents with MIS-C had not been vaccinated.[8] To account for the increasing vaccination rate in adolescents over time, hazard ratios (HR) of unvaccinated vs vaccinated adolescents with at least 1 dose of vaccine were estimated using Cox proportional hazard models. Among 38 vaccine-eligible adolescents hospitalized with MIS-C, no patients had been fully vaccinated and 7 had received a single dose with median time between vaccination and onset of MIS-C of 25 days. The hazard ratio for MIS-C was 0.09 (95% CI, 0.04-0.21; $P < .001$).[8] By the end of the study period, eligible adolescent vaccination rates reached 72% fully vaccinated with Pfizer (>95%), Moderna (<5%), and other COVID-19 vaccines (<1%) used. Despite these vaccination rates, most adolescents with MIS-C had not been

> While considered a rare condition associated with COVID-19 and most patients having overall good outcomes, MIS-C still poses a significant risk and morbidity to the pediatric population.

MIS-C has been dragging on the tails of the variant peaks, waiting for mostly healthy children to present. Often, affected children have had asymptomatic or mild acute COVID-19, providing no warning of the sequalae to come. The Centers for Disease Control and Prevention has confirmed over 6,800 cases of pediatric MIS-C and 60 deaths.[1] Data trends show that more than 50% of patients present with hypotension or shock requiring intensive care admission, and cardiac dysfunction is common with more than 30% of patients having pericardial effusion, myocarditis, or coronary artery dilatation or aneurysms.[6] While considered a rare condition associated with COVID-19 and most patients having overall good outcomes, MIS-C still poses a significant risk and morbidity to the pediatric population.[7]

As Wisconsin reports its first MIS-C death,

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vaccinated, suggesting COVID-19 mRNA vaccination was associated with a lower incidence of MIS-C.[8]

An additional case-control design study within a multistate US hospital network demonstrated that receipt of 2 doses of the Pfizer-BioNTech vaccine was associated with a high level of protection against MIS-C in patients aged 12 to 18 years.[9] Among 102 MIS-C case patients and 181 hospitalized controls, estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% (95% CI, 78%-97%).[9] All of the MIS-C patients requiring life support were unvaccinated. Most patients (95%) aged 12 to 18 years hospitalized with MIS-C were unvaccinated. While there are several limitations to the study, it supports evidence that vaccination of children and adolescents is protective against COVID-19 and MIS-C, highlighting the importance of vaccination for all eligible children.[9]

Further data analysis is needed to evaluate the impact of immunization status on younger age groups and additional factors associated with MIS-C. Age ranges for MIS-C have included infants to adolescents, with peak ages 5 to 11 years (> 45%). (Notably, children ages 5 to 11 years old have been able to receive the Pfizer-BioNTech vaccine only since November 2021.[1]) Furthermore, the majority of MIS-C patients have been of Hispanic/Latino or non-Hispanic Black race/ethnicity (59%).[1,11] The same populations are also disproportionately affected by COVID-19, having lower vaccination rates than White, non-Hispanic ethnicities.[1] Further studies of MIS-C are needed to identify why certain racial or ethnic groups may be affected at higher rates and whether this relates to vaccination inequities or other risk factors.[1,11]

While COVID-19 vaccinations are the most effective strategy we have to prevent the serious consequences of COVID-19 in pediatrics, including MIS-C, hospitalizations, and death, pediatric immunization rates are low. Utilizing system improvement to increase opportunities for COVID-19 vaccination, including during planned and unplanned health care visits, may be a step forward to improve pediatric vaccination rates and health inequities.[12,13] With increasing data demonstrating the many benefits of COVID-19 vaccination, hopefully future vaccination campaigns and immunization discussions with patients and families will be bolstered as the waves of this pandemic continue.

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Systems Thinking Is Vital to Long-Term Equitable COVID-19 Response and Recovery in Wisconsin

Sarah Davis, JD, MPA; Eunice Y. Park, MS; Maria Morgen, BS; Baila Khan, BS; Kylie Donovan, BS; Manpreet Kaur, BS; Margaret B. Hackett, BA

For some, COVID-19 served as yet another crisis to illuminate the deep structural inequities in our society. Black, Indigenous, People of Color (BIPOC) individuals, those in rural communities, and people experiencing homelessness experienced disproportionate harm—including death—from COVID-19. Deep analyses exist to guide experts who focus on specific communities. Here we champion tools that can be applied in times of calm and crisis to name longstanding structural deficiencies and intervene on root causes. The issue of equity in COVID-19 response and recovery involves multiple, interconnected systems, each with their own rules, histories, and invested stakeholders. The public health system does not stand isolated from health, economic, and civil systems, as emphasized by colleagues naming the triple threat of health, civic engagement, and economic opportunities faced by BIPOC individuals.[1] Many communities and individuals experience intersectional disparities and find themselves at a disadvantage for COVID-19 response and recovery due to multiple factors. This complexity often can get lost in attempts to make sense of problems and select effective solutions. We undertook a systems analysis to learn from the response and recovery in Wisconsin and share takeaways in this commentary.

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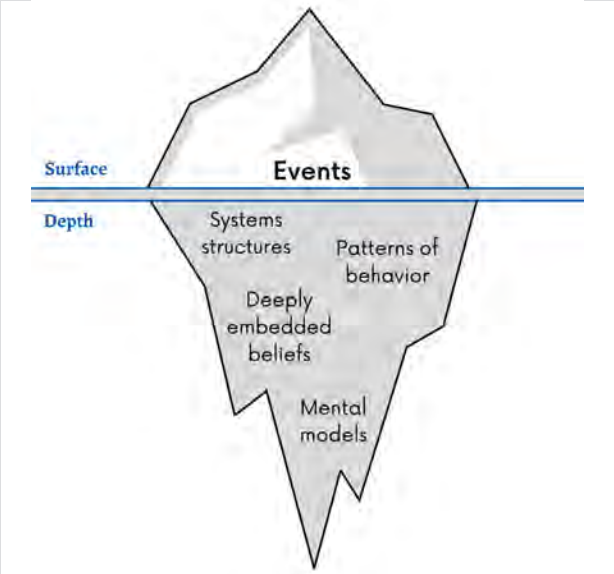
A SYSTEMS THINKING APPROACH

Systems thinking takes into account structures, patterns of interaction, events, and organizational dynamics. Such an approach helps actors—be they individuals, institutions, or communities—to anticipate rather than react to events and better prepare for emerging challenges.[2] It emphasizes looking at a whole rather than parts, stressing the role of interconnectedness.[3,4] Systems thinking provides public health professionals with a "toolbox" that equips them with the understanding of how to first prevent and then tackle these issues.[5] Diagnostic tools include the Iceberg Model, which can be used to examine the role of deeply embedded beliefs or mental models, systems structures, and patterns of behavior that live below the surface of events. Feedback loops are also extremely useful to name patterns that must be broken. An example of a pervasive feedback loop (Figure 1) is "Success to the Successful," in which powerful and vocal groups of stakeholders have more and more influence over decision-makers, further supporting their privileged status and continuing to diminish the status of others.[6] Responsive tools include ABLe Change[7] and the Water of Systems Change.[8] We will apply the latter, which highlights three different levels of the conditions holding a problem in place: structural, relational, and transformational, and the various conditions at play, including policies, practices, relationships, and mental models. Some tools are both diagnostic and responsive. Process mapping, which allows public health professionals to comprehend, examine, and enhance processes in complex systems, has been shown to considerably improve the function of health systems in the event of a public health emergency.[9]

> "The world as we know it is built on a story. To be a change agent is, first, to disrupt the existing story...and second, to tell a new story so that people have a place to go."

Figure 1. Pervasive Feedback Loop

Figure 2. Iceberg Model



APPLYING SYSTEMS THINKING TO EMERGENCIES

Public health emergencies are "wicked problems" with no simple solution and include many actors who interact and depend on one another to respond effectively. Preexisting relationships, collaboration, and communication plans make emergency response more effective. Systems thinking tools, such as the Iceberg Model (Figure 2), have been used successfully to illuminate the systemic barriers that are the root causes of events, seen repeatedly during different crises. Diagnosing complex mental models that influence policies and practices ensures that lessons gleaned from cross-sectoral collaboration, information sharing, and capacity building are implemented during responses.[5] In other words, all the collaborating in the world is insufficient without a comprehensive understanding of structural causes. Studies have shown the benefits of systems approach in enhancing preparedness for natural disasters like floods,[10] tsunamis,[11] and earthquakes.[12] We join others in the belief that such an approach can also be applied to crises like the COVID-19 pandemic.[4,13,14]

WHAT SYSTEMS THINKING REVEALS

In the wake of the COVID-19 pandemic, many state and local municipalities struggled with the challenges of mass vaccination across populations. Whether partisan vaccine hesitancy, barriers to communication across diverse communities, or technological advancement implementation, one may view vaccination as a logistical challenge in which the seemingly vast differences in particular populations are insurmountable.[15] However, a common theme connects the challenges these populations face posed by this vital task of vaccination: systematic disinvestment in health care-dependent infrastructure.[16]

Let's take technology as an example. Many public health leaders and agencies turned to technology as the answer to the logistical challenges a mass vaccination rollout poses for messaging and vaccine appointment scheduling.[17] The reliance on technology served as a barrier to those experiencing the most burden of the disease—socioeconomically or geographically underserved communities.[18] We can see this in rural communities in particular, which have the added barrier of limited access to broadband internet and public health infrastructure based on years of limited funding to small and local health care providers.[19] The unhoused also represent a microcosm of the worst effects the pandemic can have on an underserved population, as these people face the added hurdle of being disconnected from typical means of communication and access to care.[20] When health care is viewed as a commodity, not a collective right, it is easy to see how divestment results.

These disparities are even further pronounced among racial minorities who have suffered disproportionately throughout the pandemic in morbidity and mortality.[21] The impact of the pandemic on Black and Brown communities extends far beyond COVID-19, resurfacing wounds caused by centuries-long exploitation, mistreatment, or disregard by the medical community.[22] From historic medical experimentation on Black people to current socioeconomic policies and barriers that perpetuate lack of public health and medical investment in these communities and mistrust in medical institutions, these factors result in a reinforcing feedback loop.[23] Longstanding disinvestment serves as proof that the government either is actively harming or does not care enough about BIPOC communities.[24]

AN EQUITABLE RESPONSE IN CONTEXT

The COVID-19 pandemic spurred the rapid development of vaccines—a momentous and unprecedented accomplishment resulting from significant financial investment and urgency. When vaccine distribution began, COVID-19 had already had a disproportionate impact on the health of BIPOC individuals, with increased amounts of deaths and hospitalizations com-

pared to White individuals.[25] Within Wisconsin, as we write in September 2021, over 6 million vaccine doses have been administered thus far, with Black and Indigenous individuals receiving the vaccine at significantly lower rates.[26,27]

Vaccine Hesitancy

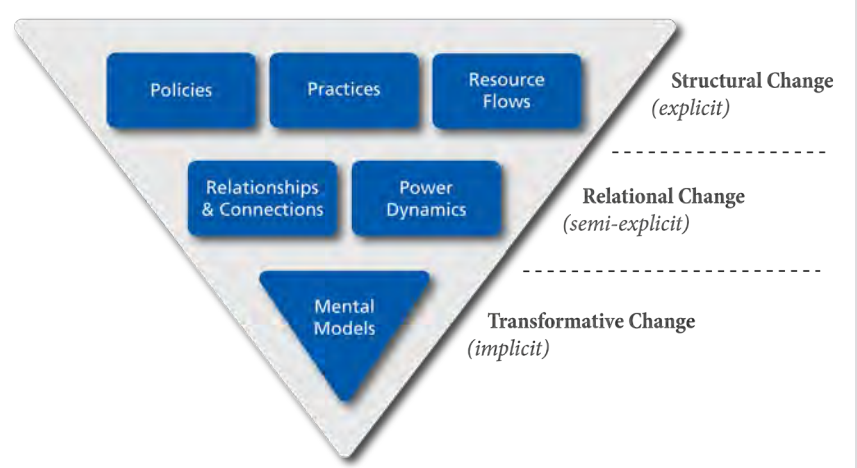
Despite their effectiveness and safety, many people remain skeptical and hesitant to receive COVID-19 vaccines in the United States. Systemic contributions to hesitancy include "inequitable distribution of doses, failure to place clinics in sites accessible to BIPOC communities, and underinvestment in health care providers and services in BIPOC communities."[24] Learning from the "Three Cs" framework,[28] vaccine hesitancy results from a decision-making process involving a constellation of factors: complacency, convenience, and confidence. For this pandemic, lack of confidence was amplified due to longstanding distrust within BIPOC communities, as described above. Black people are understandably wary of whether vaccines are truly safe or if the history of being used as the subjects of experiments is repeating itself, since contemporary experiences of politics and medical care do not allay such fears.[29]

Convenience also played a role in COVID-19 vaccination efforts and importantly served to reinforce existing distrust. Early on, vaccine distribution focused on exigency—using major drug stores and grocery chains that offered maximum reach and assured access to infrastructure for proper storage of vaccines. It was well-documented that these locations were not as accessible for many BIPOC communities, due to food and pharmacy deserts.[30] The combination of lack of convenience and confidence results in a feedback loop, exacerbating distrust within communities and further perpetuating inequity.

Early Distribution Priorities

COVID-19 vaccine distribution was further complicated by the diverse priorities, goals, and needs of the stakeholders involved. The classic "Tragedy of the Commons" paradigm emerged as stakeholders with different goals and priorities competed for a limited resource.[6] Decision-makers who decide where the vaccine goes, how much vaccine is allocated, and who is eligible are influenced by a variety of factors. Influence from advocacy groups and corporate interests further complicated these decisions. The pervasive Success to the Successful feedback loop emerges, as more powerful and vocal groups of stakeholders have more influence over decision-makers, further supporting their privileged status.[6] The lack of an existing clear plan for vaccine prioritization and eligibility, as well as poor communication, created public confusion and slowed vaccine distribution in the state early on.[31] By summer 2021, however, systems thinking approaches that emphasize trust and accessibility resulted in increased uptake, a step in the right direction to address inequities in vaccination rates.[32]

Figure 3. Six Conditions of Systems Change[8]



RECOMMENDATIONS

"The world as we know it is built on a story. To be a change agent is, first, to disrupt the existing story…and second, to tell a new story so that people have a place to go."[33]

A systems thinking approach to improve health equity in COVID-19 response and recovery offers the opportunity for lasting, transformative change—change that is essential for the endemic phase of COVID-19, and to prepare for the next public health emergency. We offer recommendations using the "Six Conditions of Systems Change" (Figure 3) framework considering the impact of interventions on structural, relational, and transformative levels.[8]

Structural Change

Reinvesting in the economy and infrastructure in communities creates lasting structural change that fosters health equity. For example, the Reconnecting Communities Act[34] includes funding (albeit insufficient) to remove highways that cut through Black and economically disadvantaged areas. Literal physical barriers to connectedness impede easy access to anchor institutions that can offer vaccinations, such as local schools, churches, or community centers.

Broadband infrastructure will offer a different sense of community and connectedness. Funding is included in both federal and Wisconsin budgets to ensure home internet access.[35] The federal legislation endeavors to end "digital redlining" and create a permanent program to help more low-income households access the internet.[36] While the internet can be used to access false information, which has exploded online, it can also be used for telemedicine, education, connecting with one's familial and social network, and signing up for vaccination appointments.

Relational and Transformative Change

Relational and transformative change are deeply intertwined. Transformational change happens when the stories we tell ourselves and our community change. Whether one believes the new stories or not is driven by relationships. Lasting change is possible when we undo the implicit mental models that drive behavior; in

other words, discrediting the current story and telling a new one. One such ingrained story is individual responsibility—especially with health issues; we collectively as Americans believe that a person is at fault if they get sick, and the flipside of prioritizing patient autonomy over community consciousness.[37] This story is perpetuated in data reports and media coverage.[38] Telling the story that personal health care is a privilege makes public health impossible to sell.

Additionally, the story of vaccination is politicized, and our historic and deep-seated distrust in government has been weaponized, making vaccine hesitancy and refusal prominent mental models and badges of honor for some. The sociologist Brooke Harrington reminds us that the most prominent relevant systems at play are the informal economy of an individual's social capital.[39] In other words, our "reference groups" are those we listen to, those who can lend us money, those who have our back and step in to help with everyday tasks, and those who share our values. It has been recommended that messaging should focus on autonomy and personal freedom.[40,41] For example, the message could be framed to get vaccinated so you can attend a concert or an indoor sports event. Such an approach will no doubt work in the short run, but it perpetuates the story that we should act for ourselves. In the long run, we need a story of collective concern.

FINAL THOUGHTS

A noted truism is that systems are designed to achieve the results they get. If we want equity in COVID-19 response and recovery, we need to design systems to achieve equity. System thinking tools help us imagine lasting change and commit to continuously implement policies and procedures to achieve that change. While it is extremely challenging to change the story that undergirds the American psyche, an equitable future depends on it.

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COVID-19 Surveillance Testing in Secondary Schools: Findings and Barriers to Implementation

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ABSTRACT

Problem Considered: K-12 schools have shown minimal spread of COVID-19 when mitigation measures are employed. This study sought to determine baseline asymptomatic COVID-19 rates in secondary schools as students returned to full-time in-person learning with universal masking in place and to evaluate the logistical obstacles of implementing surveillance testing.

Methods: An observational cohort study lasting 11 weeks during spring 2021 included 2,288 students and staff in Wood County, Wisconsin. SARS-CoV-2 nasal polymerase chain reaction testing was done on consenting students and staff to determine baseline disease burden. Teacher surveys collected data on student masking compliance and classroom distancing. Information about percent positivity, secondary transmission, quarantine and distancing policies, screening participation, costs, and volunteer hour requirements were obtained. Modified quarantine for fully masked in-classroom exposures was evaluated.

Results: Percent positivity averaged 3.0% (0%-16.2% weekly) among students and 1.72% (0%-6.9% weekly) among staff. Two cases of secondary transmission were suspected out of 163 individuals quarantined. An average of 15.6% of the school population consented to participate each week. Minimum classroom distance between students ranged from 2.7 to 5.5 feet. Student masking compliance was greater than 87%. The cost of the program was $106,400 and required approximately 300 volunteer hours. The modified quarantine policy, where students were allowed to continue to attend in-person school after exposure to a case of COVID-19 if the infected and exposed parties were masking, did not result in additional transmission.

Discussion: In the setting of relatively high student masking compliance and limited distance between students, weekly secondary school screening of students and staff in an area of high community disease spread was found to be low yield, costly, and burdensome for the school district. Surveillance participation was low. A modified quarantine policy was not associated with increased in-school transmission. School funding may be better spent on targeted testing or other school expenses, especially with increasing vaccination rates.

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INTRODUCTION

COVID-19 has greatly disrupted in-person learning, and strategies regarding safe modes of instruction have varied. Some school districts in the United States maintained a fully virtual learning environment due to concern for disease spread within schools. As the 2021-2022 school year continues, an understanding of school COVID-19 transmission in varying settings is essential.

Limited COVID-19 spread among 17 K-12 schools in Wood County, Wisconsin, in the setting of universal masking has been documented during a time of high community transmission.[1] One limitation was that surveillance testing was not performed to screen for asymptomatic infections among students and staff. Subsequent studies have suggested asymptomatic transmission is low.[2,3] It is currently not known how much asymptomatic transmission may be occurring among secondary school students seated less than 6 feet apart.

This investigation aimed to determine the rate of asymptomatic cases and in-school transmission rates through a school-based SARS-CoV-2 surveillance program among secondary students in a public school district in Wood County where masking was required. Nasal polymerase chain reaction (PCR) testing was performed on consenting students and staff over an 11-week study period from February 22 through May 7, 2021. Percent positivity ranged from 0% to 13.2%, with an average of 2.7%, despite 1 week with increased asymptomatic detection. Students were reintegrated into in-person learning 5 days per week and were seated 3 feet apart, if possible, with a modified quarantine

policy in the classroom setting only. A secondary aim was to report the logistics of surveillance testing, costs, and work hours required.

METHODS

Nearly 2,300 students and staff (n=2,288) attending school in person were eligible for the study; 867 students and 126 staff at the middle school and 1,124 students and 171 staff at the high school. COVID-19 vaccinations were not yet approved for children under 16. Vaccination rates for staff and older students were not available. The school district requested consent from parents and teachers to perform nasal PCR testing to assess the burden of asymptomatic SARS-CoV-2 infection in schools. Those with a history of positive COVID-19 PCR or antigen test were excluded. Additionally, only students and staff without reported symptoms of COVID-19 underwent surveillance testing. Any individuals with symptoms were sent for PCR testing, with results tabulated as "symptomatic" individuals. The percentage of students and staff consenting to testing varied during the study period, ranging from 15.9% to 24.9% of the student body and 26.9% to 32.3% of staff. The school district purchased testing kits from Aspirus Laboratories, utilizing grant funding from the Legacy Foundation of Central Wisconsin. The reverse transcriptase–polymerase chain reaction had a limit of detection of 50 copies/mL. Results were returned to the schools within 24 hours.

Consenting students and staff were tested once weekly. The testing schedule varied during the study period: initially, testing was performed 4 days per week for students and 1 day per week for staff. During the last 8 weeks, testing was done twice per week for students and once per week for staff, generally in the mornings. An average of 64 students were tested per week, with a range of 34 to 145. An average of 16 staff were tested each week, with a range of 12 to 23. Participants initially were selected using an Excel randomize feature, but as the consented number decreased, participants were divided into 2 groups to be tested every other week. Tests were administered by school staff or volunteers who were trained by county public health officials on swabbing technique. They utilized full personal protective equipment. Students and staff with a positive PCR test result during the study period were excluded from further surveillance testing.

Surveillance testing was initiated during a hybrid model of 2 in-person days per week in order to establish a baseline. At week 4 of the study, students returned to 4 days a week in person, and by week 10, students attended in person 5 days a week. Students were able to maintain a distance of nearly 6 feet in the classroom with the hybrid model, but as additional students were added at week 4, the minimum distance between students decreased. A goal of keeping a distance of 3 feet was recommended in the classroom when possible.

Masking was mandatory for students and staff when inside the school. Current guidelines from the Centers for Disease Control and Prevention[4] recommend quarantining at home after exposure within 6 feet for 15 minutes, regardless of mask compliance. In this study, a modified quarantine policy was used where students and staff were allowed to continue attending school in-person if they were fully masked (wore a mask covering mouth and nose) during their exposure to a positive case in the classroom (who was also fully masked), even when within 6 feet of the positive case for 15 minutes or more.[5] This modified quarantine policy applied only to classroom exposures. Due to students being unmasked while eating, close lunch contacts underwent standard at-home quarantine. Standard at-home quarantine also was employed if the contact was within 6 feet for greater than 15 minutes during any extracurricular or sporting activity. Hallway passing time was thought to be too brief for transmission and did not result in quarantine.

Contact tracing was performed by parents, school staff, and public health officials. If there were positive cases in the classroom setting, the school made note of those considered close contacts. Those individuals were instructed to carefully monitor for symptoms but remained in the classroom if they had been properly masked. The Wood County COVID-19 dashboard[6] was utilized to capture weekly data on community COVID-19 data. Using descriptive statistics, trends were evaluated regarding school-related COVID-19 cases, asymptomatic positives found on school-based screening, and any changes in community COVID-19 levels.

Twice weekly, middle and high school teachers were asked to complete a Google Forms survey, administered by the research team. Information was collected regarding masking compliance and approximate minimum and average distancing between students in the classroom. Staff were asked to differentiate between proper masking with nose and mouth covered from students with nose chronically showing and students who were not masked at all.

This study received institutional review board approval through Aspirus Wausau Hospital Investigational Review, IRB # 21.01.586

RESULTS

Surveillance testing was done for 10 weeks. Of the total student population, 19.9% were entirely virtual for the 2020-2021 school year. On average, consents were obtained from 15.6% of the student and staff population (Figure 1). A total of 1,578 surveillance PCR tests were performed during this timeframe, and 35 students and 5 staff tested positive. Percent positivity of students who were tested ranged from 0% to 16.24% weekly, with an average of 3.01%. Staff percent positivity ranged from 0% to 6.9% weekly, with an average of 1.72% positivity. Together, percent positivity of students and staff averaged 2.7% weekly.

No in-school surveillance testing was done during spring break, which was week 6 of the study (March 29-April 2). On March 31, 2021, the Wisconsin statewide masking mandate was withdrawn, though the school district maintained a separate indoor masking mandate. During week 7, there was a more than 12% increase in positive results via surveillance PCR testing; 19 cases, all in students, were detected. Nine were from middle school and

10 from high school. No students reported traveling outside Wisconsin. Students and/or staff who were in the classroom and fully masked with these individuals were allowed to continue with in-person attendance via the modified quarantine policy. No cases linked solely to in-classroom contact were found through contact tracing in subsequent weeks. There was no evidence of transmission to staff by close classroom contact with an asymptomatic positive student. Throughout the subsequent weeks, surveillance percent positivity returned to 0% to 3.3%.

At the middle school, 9 students tested positive on surveillance testing during week 7. Two students subsequently tested positive while undergoing standard at-home quarantine as a result of unmasked exposures. One student was a lunchroom contact of an asymptomatic positive individual. Another student was in class with an asymptomatic positive individual but also had a positive close contact outside of school. No secondary cases were found to result from the 10 positive asymptomatic cases from the high school.

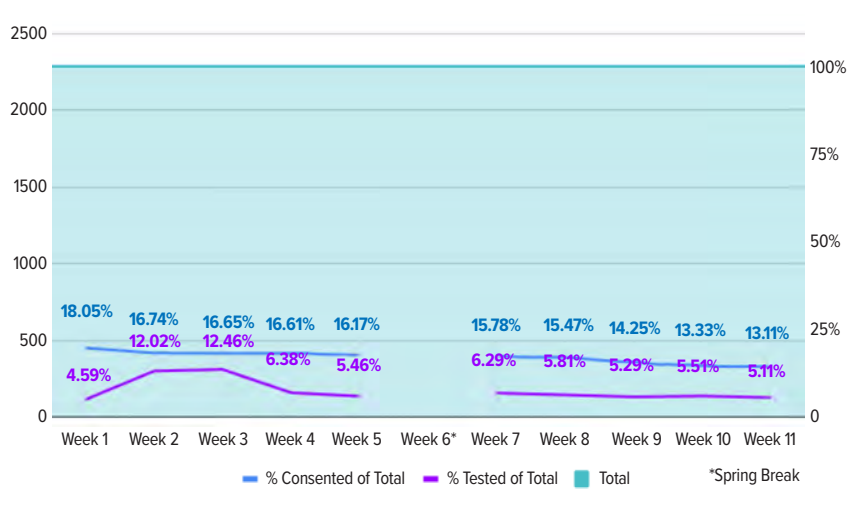
The number of symptomatic COVID-19 cases during the study period ranged from 0 to 4 new cases per week, even during and after the increase in asymptomatic cases seen in week 7 of surveillance testing (Figure 2).

During the study period, the Wood County COVID-19 case rates had an upward trend, ranging from 21.76 new cases/100,000 persons per week (the week of March 15, 2021) to 116.9 cases/100,000 per week (the week of May 3, 2021). During week 2 of the study period, the public health department performed an audit of its records and found 5 cases incorrectly counted as positive from prior months, accounting for the apparent decrease in county cases that week. Percent positivity in the county ranged from 2.5% to 14.18% (Figure 3).

The teacher survey was sent to a total of 208 educators twice weekly. Survey response rate was 52%. Regarding distancing in the classroom, while in hybrid mode with half of the students attending in person at a time, the middle school reported an average distance of 4.74 feet between students (with average minimum distance of 3.72 feet), and the high school reported an average distance of 6.07 feet (with average minimum distance of 5.5 feet). When all students returned during week 4 for full-time in-person learning, the middle school reported an average distance of 3.52 feet between students (with average minimum distance of 2.74 feet), and the high school reported an average distance of 4.59 feet (with average minimum distance of 3.69 feet) (Figure 4).

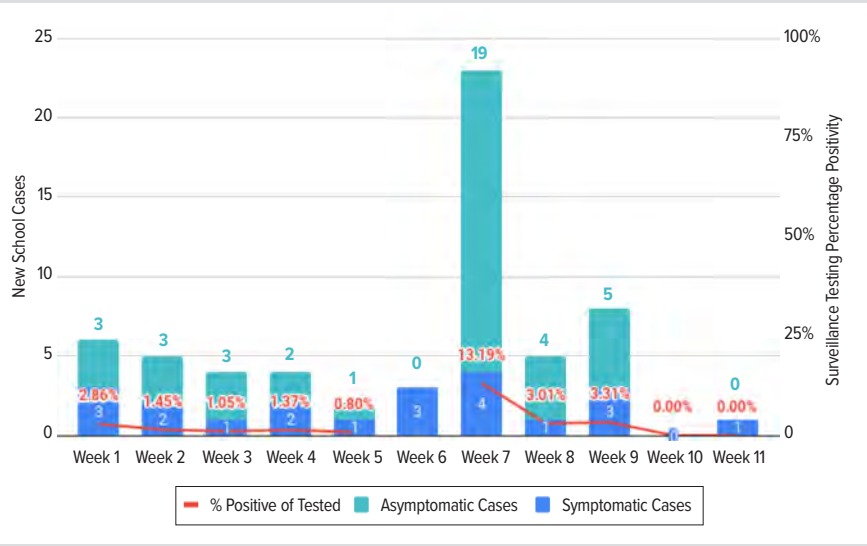
Student masking compliance remained high. At least 87.13% of middle and high school students were reported to have mouth and nose covered at all times.

Figure 1. Percentage of Asymptomatic Students and Staff Consented and Tested for COVID-19, Wood County, Wisconsin, Feb 22-May 7, 2021



Total student and staff population: N=2288.

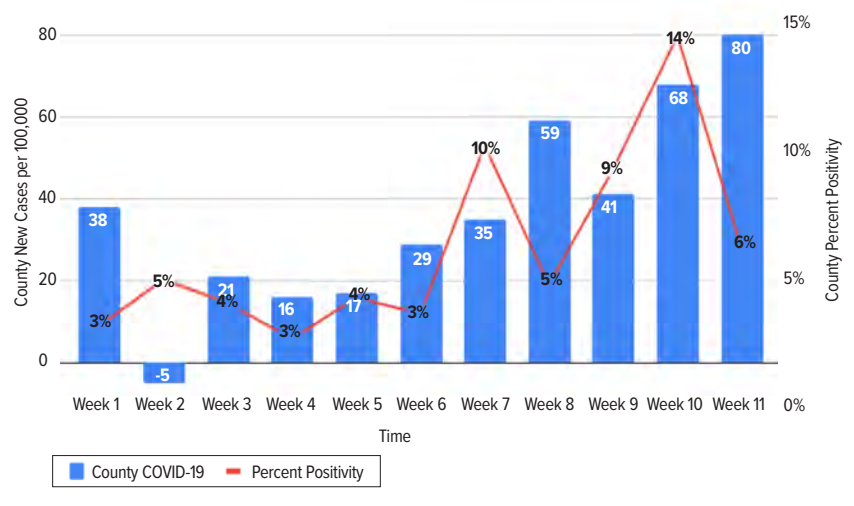
Figure 2. Symptomatic vs Asymptomatic School COVID-19 Cases, Wood County, Wisconsin, Feb 22-May 7, 2021



DISCUSSION

Surveillance testing of asymptomatic middle and high school students in rural central Wisconsin provided reassurance while rein-

Figure 3. Community COVID-19 Cases per 100,000 and County Percent Positivity, Wood County, Wisconsin, Feb 22-May 7, 2021



During week 2 of the study period, the public health department performed an audit of its records and found 5 cases incorrectly counted as positive from prior months, accounting for the apparent decrease in county cases that week.

Figure 4. Classroom Distancing By Feet at Middle and High Schools, Wood County, Wisconsin, Feb 22-May 7, 2021

troducing the entire student body to full-time, in-person learning. In the setting of mandatory masking, the baseline asymptomatic infection rate was low. There was no appreciable change from baseline in asymptomatic case rates found on surveillance or on reported symptomatic case rates as the number of students in the building increased. During week 7 of the study, following spring break, asymptomatic percent positivity increased dramatically to 13.24% at the middle school and 13.16% at the high school.

Our surveillance testing program found asymptomatic spread within the school to be minimal to nonexistent. No asymptomatic transmission to staff was identified despite 40 cases being identified during the study period and over a 24-hour delay before test results were returned. Two middle school students tested positive while quarantining at home; however, 1 student had close contact during lunch and the other had contact both in the classroom (while masked) and socially outside of school (while unmasked).

While distance within the classrooms was maximized, due to class density, more than 6 feet of distance between students was not possible, and students were in some classes less than 3 feet apart. Student masking compliance, with correct masking of mouth and nose was reported to be high (87%) in these classrooms. No outbreaks were identified related to minimal distancing, and in-school transmission was also found to be rare. There was insufficient statistical power to determine the impact of masking or classroom distancing on disease spread with 2 potential cases spread within the school. Modified classroom quarantining policy did not result in any identification of in-school transmission, and over 2,000 days of quarantine were avoided with the implementation of this policy.

There were many barriers to school surveillance testing implementation. First, less than one-fifth of students and staff consented to being part of the surveillance pool. That percentage continued to decline as surveillance testing progressed over the 10-week study period. This was in spite of school board support, administration encouragement, and medical liaison promotion. The low number of those consenting limited the ability to test a random sample of the population and, thus, reduced the generalizability of the results.

Second, there are many logistical issues for school administration and school nurses in developing an infrastructure for surveillance testing. Testing was not able to be secured through the state of Wisconsin, so it was contracted through a local health system with a 24-hour wait for a result. School administration organized testing lists, made labels, handled results, organized volunteer schedules to perform testing, and performed contact tracing. It is estimated that initially, at least 20 hours of staff time were required per week. Once established, school nursing staff devoted an aver-

age of 1 to 2 hours per week, and school administration spent 6 hours per week. This was in addition to their usual and COVID-19 pandemic-related workload. Additionally, 8 volunteers were recruited, and each spent 1 to 2 hours 1 to 3 times a week testing—or approximately 300 hours in total—which defrayed the burden on school nurses. Not all school districts may have access to school nurses or volunteers able to assist in this way. Third, the cost of implementing surveillance testing was $106,400 for the study period. Nasal PCR kits were $70 per test, and a total of 1,578 tests were performed. Grant funding through the Legacy Foundation of Central Wisconsin covered the cost of testing.

There are several limitations to this study. First, given that students and staff opted into testing, there is potential selection bias that might not represent true asymptomatic disease burden in the secondary school population. Second, student masking compliance and distancing data relied on voluntary teacher survey completion. Third, no information was collected on other mitigation measures the schools might have employed to reduce infection burden, such as staff vaccination, disinfection policies, and ventilatory practices. Fourth, no racial or socioeconomic information is available regarding the study population, possibly reducing generalizability. Finally, it remains unknown what the role of surveillance testing might be in a more highly vaccinated and/or mask-optional school setting. "Test to Stay" programs, which test exposed students even in unmasked exposures, may allow more students to remain in the classroom at lower cost and school district burden than surveillance testing.[7]

With 40 positive cases over the study period, only 2 potential cases of secondary spread were identified and none among staff, despite relaxing distancing and quarantining guidelines. However, mandatory masking indoors at school was required, with a reported student masking compliance of 87%. This was consistent with what was found in 20 elementary schools in Salt Lake City, Utah.[3] Their study also was able to rule out a number of cases of suspected in-school transmission with genomic testing, which was not conducted in our study. This type of surveillance testing required substantial funding in addition to volunteer hours and, while it provided reassurance, the detected in-school spread was minimal—even without at-home quarantine of students after masked classroom exposures. We found surveillance testing to have limited utility and substantial cost in our secondary school environment.

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Does Unconscious Bias Affect How Pediatricians Manage Their Patients?

Gisela Chelimsky, MD; Pippa Simpson, PhD; Mingen Feng, MS; Earnestine Willis, MD

ABSTRACT

Background: Both implicit bias—referred to as unconscious bias—and explicit bias affect how clinicians manage patients. The Implicit Association Test (IAT) has incremental predictive validity relative to self-reports of unconscious bias. Few studies have uniquely specified the impact of unconscious bias in pediatric practices.

Objective: We aimed to assess the influence of unconscious bias on decision-making in the faculty in a pediatric academic center using the IAT, in addition to and separately applying clinical vignettes with racial and socioeconomic class associations in both tools as it relates to clinicians' race, gender, years in practice, education achieved by the clinician's parents, and language spoken.

Methods: We conducted a prospective quality control evaluation of faculty in an academic center's pediatrics department. An anonymous online tool was used to gather IAT responses, clinical vignette responses, demographics, and explicit bias questions.

Results: Of 295 faculty members (73% females), 230 completed the questionnaire, at least in part. On the explicit bias questions, faculty reported neutral feelings when comparing the demands of educated vs noneducated patients, African American vs European American patients, and patients in the upper vs lower socioeconomic class. Of the approximately two-thirds who answered the IAT, faculty showed preference for European American and upper socioeconomic class. However, the clinical vignettes revealed no differences in how faculty responded to patients based on race or socioeconomic status when stratified by factors listed above, except physicians who favor upper socioeconomic class over lower socioeconomic class were more likely to give a detailed explanation of options if the patient's parent was upper socioeconomic class ($P = 0.022$).

Conclusions: Pediatricians exhibit racial and socioeconomic unconscious bias that minimally affects decision-making, at least based on vignette responses.

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BACKGROUND

According to the Institute of Medicine's (IOM) Unequal Treatment report, health systems offer unequal quality of care, affecting some racial/ethnic groups.[1] Medical practitioners may have unconscious biases that influence their practice of medicine, although most will not demonstrate overt prejudice against certain groups of patients.[1] The IOM in 2002 described many disparities in medical care, underscoring the need to understand how clinicians' bias, stereotyping, and prejudices contribute to health care disparities.[2] Unconscious bias may be more significant when clinicians are tired, overloaded with information, and have limited time to spend with patients.[3,4] Clinicians in these circumstances may be more likely to make assumptions based on previous experiences and stereotypes.[5-7]

Self-reporting of biases is unreliable, mainly because of the desire for social acceptance and difficulties with introspection.[8] Few tools are available for measuring unconscious bias. The most frequently used tool is the Implicit Association Test (IAT). Other methods are available but are either experimental[9] or difficult to implement in large cohorts, such as the priming method.[8]

IAT is a priming method that evaluates the automatic associations between an object, race, socioeconomic class, and an attribute (good, bad, dangerous, safe). The IAT was developed to assess unconscious bias, with 2 types of objects being associated. One is

an attitude object, like ugly and beautiful; the other is a target object of bias, such as race or socioeconomic class. In the target set, there may be a picture of a European American or African American face. Depending on the speed of clicking the keyboard—the association between the attitude set and the target set—a value is obtained, which is used to derive the IAT D score. People tend to respond faster to items they like when paired with positive attitude and items they dislike when paired with negative attitude.[10] The validity of the IAT has been assessed in many populations, including race, sex, and nationality.[10] Based on the speed of response, a score is generated.[11] IAT scores are reported based on a Cohen *d* score, which normalizes by comparing means and dividing by the standard deviation.[12] The higher the score, the higher the unconscious bias. However, there are some concerns around IAT. Participants can develop strategies to pair the 2 sets of items or attempt to slow down the association of an attitude object with a pleasant attribute. Despite these concerns, the IAT is currently the tool of choice to assess unconscious bias.[8] Cunningham et al demonstrated that the IAT is consistent across time and measures.[13]

In the United States, biases against patients of color are significant. Physicians having different racial/ethnic backgrounds are more verbally dominant with African American patients than with European American patients and engage less in communication with patients of color.[14] Clinicians are positively biased towards European American patients and negatively towards young women[5] and often are biased against African American and Hispanic patients.[15-18] This bias against African American patients is similar for any ages, including children,[19] and has been found at all levels of pediatric faculty, from leadership to people involved in recruitment.[20] Sadly, unconscious bias against African American patients affects outcomes.[5] For example, when pediatric patients are seen in the emergency department (ED) for abdominal pain, African American patients are less likely to receive analgesics.[21] Interestingly, unconscious bias affecting patient management was not observed when caring for obese children.[22]

Our study was conducted in a medical center in Milwaukee, Wisconsin. In 2006, the city of Milwaukee ranked as worst in health outcomes compared to all 72 Wisconsin counties.[23] In 2019, Milwaukee was described as one of the most impoverished and racially segregated urban centers in the nation.[24] In Milwaukee, the ZIP codes with the lowest socioeconomic class (LC) had a > 2.0 increased risk ratio when compared to the upper socioeconomic class (UC) in sexually transmitted diseases, no health insurance, lack of health care, smoking during pregnancy, and physical inactivity. Ten of approximately 26 ZIP codes in the city of Milwaukee meet the criteria for LC.[23] Given the significant poverty and racial issues in Milwaukee, the aim of this quality improvement project was to understand the racial and socioeconomic bias of pediatricians and determine if this bias affected how they managed their patients. This topic has been explored minimally, with only 2 studies looking at unconscious biases toward race[25,26] and, to the best of our knowledge, none looking at unconscious biases regarding socioeconomic class. If we want to make changes, it is critical that we understand the problem and have baseline information prior to implementing potential interventions. With this in mind, we developed a proposal to obtain baseline information regarding a potential problem in the pediatrics department of an academic center in Wisconsin. We postulated that pediatric faculty are biased against LC African American patients, but that this bias would not affect patient management. We also hypothesized that female faculty and faculty with a diverse background, measured by speaking more than 1 language or being born outside the US, would be less biased than male faculty, faculty born in the US, and/or only English-speaking faculty.

METHODS

We designed a survey to prospectively understand implicit bias in our faculty on a deidentified basis. Since this was considered a quality improvement project, our institutional review board (IRB) determined that it did not qualify as research or human subject research and, therefore, did not require an IRB submission. The evaluation was performed in the pediatrics department in November and December, 2018, prior to starting an intervention training to raise awareness about unconscious bias.

With an online tool providing anonymity, unconscious bias was assessed by the racial and socioeconomic associations in IAT, and clinical judgement was assessed through 2 possible sets of clinical vignettes that differed only by the description of the socioeconomic condition or a picture of a pediatric European American or African American. This methodology was modified and adapted for pediatrics from Haider et al.[27] Answers to the vignettes were scored as acceptable, neutral, and unacceptable. The questions and answers were developed by the authors, who agreed which answers were acceptable, neutral, and unacceptable. The questions addressed informed consent, trust, and reliability. We also included questions assessing gender; race; continent of birth, if not born in the US; language spoken; education achieved by parents of professionals to assess cross-generational impact; income; ZIP codes where the faculty reside; and questions regarding explicit bias. Explicit bias was assessed by asking the faculty how they felt towards statements regarding different groups of patients (Tables 1 and 2). They would rate their reaction from 0 to 10, with 0 being cold, 5 being neutral, and 10 being warm. The vignettes described a clinical scenario and had either a picture of a European American patient or a patient of color. Other questions described the same scenario in a family of upper socioeconomic class and in a family of lower socioeconomic class, with the same answer, hoping to determine if there was bias toward one group or the other regarding patient management or credibility.

Table 1. Ratings for Explicit Bias to Statements

Please rate how cold or warm you feel in relation to the following statements (0 = coldest; 5 = neutral; 10 = warmest): Median (IQR)	Total (N=213)
Educated patients are more demanding than less educated patients	5 (5-6)
Less educated patients are more demanding than educated patients	5 (3-5)
Caucasian patients are more demanding than African-American patients	5 (5-5)
African-American patients are more demanding than Caucasian patients	5 (3-5)
Poor patients require much more attention than wealthy patients	5 (3-5)
Wealthy patients require much more attention than poor patients	5 (3-5)
Wealthy patients are more demanding than poor patients	5 (5-6)
Poor patients are more demanding than wealthy patients	5 (3-5)
Missing	N = 17

Abbreviation: IQR, interquartile range.

Table 2. Ratings for Explicit Bias of Patients by Socioeconomic Factors

Please rate how cold or warm you feel in relation to the following patients (0=coldest; 5=neutral; 10=warmest): Median (IQR)	Total (N=213)
Hispanic non-Caucasian patients	5 (5-8)
Caucasian patients	5 (5-7)
Poor patients	5 (5-8)
Uneducated patients	5 (5-8)
Educated patients	5 (5-8)
Wealthy patients	5 (5-7)
Missing	N = 17

Abbreviation: IQR, interquartile range.

All pediatric department faculty received via email an online link with a brief explanation of the goal of this instrument:

> As part of the DOP (Department of Pediatrics) Diversity and Inclusion Assessment, I would ask you to complete as best as you can these questions, vignettes and the association of items at the end. This is completely anonymous and will be administered via third party (Project Implicit at Harvard University). We will only have access to aggregate data and will not know your individual answers, therefore no identifiers will be shared with DOP officials. I really appreciate your help in this Assessment.

The decision to administer this tool though a third party (Project Implicit, Harvard University) was secondary to faculty expressing concerns about potential consequences if their data would be known to department leadership. We divided the IAT D score into 3 categories due to sample size:[27] (1) ≥ -2 and ≤ -0.15 are equal to "any preference for African American over European American" or "any association for LC with Approach and UC with Avoid;" (2) > -0.15 and <0.15 are equal to "little to no preference between European American and African American" or "little to no association between UC and LC with Approach and Avoid;" (3) ≥ 0.15 and ≤ 2 are equal to "any preference for European American over African American" or "any association for UC with Approach and LC with Avoid." Explicit bias was assessed by asking about cold/warm ratings as described in Tables 1 and 2 as well as how they felt towards Hispanic, European American, poor, uneducated, educated, and wealthy patients.

Statistical analysis was performed utilizing SAS 9.4 and SPSS 24.0. Chi-square or Fisher exact tests were used for comparing categorical variables (ie, categories of IAT D scores), and results were reported as number (%). Cochran-Armitage trend test was used to compare the trend of proportions between categorical variables (ie, survey A vs B) as the levels of ordinal variable increases (ie, vignette answers from "unacceptable" to "neutral" to "acceptable"). Nonparametric Kruskal-Wallis and Mann-Whitney U tests were used to compare continuous variables (ie, IAT D score), and results were reported as median (interquartile range). Spearman correlation summarized the relationship between continuous variable (ie, IAT D score) and ordinal variables (0-10 Likert scale conscious bias ratings). We compared proportions of IAT scores ≥ 0.15 to 50% using a 1-sample test of proportions, and results were reported as percentages (95% CI). Missing data patterns were examined by comparing responses for those who answered and those who did not and, where they may not be missing at random, are described. An unadjusted *P* value <0.05 is reported as statistically significant.

RESULTS

Demographics

Of 295 total department faculty members, 230 (166 females [73%], 61 males [27%], 3 unidentified) completed part or all of the questionnaire, IAT, and vignettes (Table 3). Most of the respondents had a medical or doctoral degree (n = 173 [76%]), 52 (23%) had a master's degree, and 3 (1%) were advanced nurses or physician assistants. Only 10 (4%) reported themselves as Hispanic. Eighty percent (n = 184) reported being married, 19 (8%) single, 15 (7%) living with a partner, and 11 (5%) divorced/separated. Most respondents reported themselves as White/Caucasian (n = 183 [83%]), followed by Asian (n = 26 [12%]), and most were born in the US (n = 187 [83%]) or Asia (n = 23 [10%]). The majority had lived in the US for ≥ 20 years (n = 214 [94%]), with 220 (96%) being US citizens, 4 (2%) having permanent residence, and 4 (2%) having a temporary visa. Approximately one third of respondents had been practicing for >19 years (n = 72 [31%]) while one fourth had been practicing 0 to 4 years (n = 55 [24%]). Sixty-seven percent (n = 155) only spoke English at home, and 75 (33%) spoke other languages. Most respondents' parents had an advanced degree (n=120 [53%]) or undergraduate degree (n = 54 [24%]); 39 (17%) of the respondents' parents had a high school diploma and 13 (6%) had an associate degree. Five (2%) respondents lived in ZIP codes designated as LC.

Explicit Bias

In relation to explicit bias, median ratings reported by faculty were neutral when comparing the demands of educated to less-educated

patients, African American to European American patients, and LC to UC patients (Tables 1 and 2).

Vignettes

For the vignettes, we did not find any differences in how faculty responded to an African American or European American picture in relation to informed consent ($P = 0.22$) and patient trust ($P = 0.11$). Neither did the faculty show a difference in how they responded to social class vignettes that were assessed for patient reliability ($P = 0.51$), informed consent ($P = 0.18$), and patient trust ($P = 0.91$).

Responses to Vignettes By Those Who Did vs Did Not Complete IAT

Twelve faculty did not respond to the clinical vignettes. Of the remaining 218 respondents, only 146 (67%) completed the racial IAT, and 165 (76%) completed the socioeconomic IAT. We compared answers to the clinical vignettes for those who completed the IAT and those who did not. There were no significant differences in response to the clinical vignettes, except by the Cochran-Armitage trend test (not the chi square or Fisher exact test). Those who did not complete the racial IAT had a nonsignificant response between both sets of clinical vignettes ($P = 0.75$), whereas those who did complete the racial IAT had a borderline significant result (Cochran-Armitage trend $P = 0.047$) when comparing the proportions of vignette answers regarding patient trust. Faculty who completed the racial IAT were more likely to believe the patient's story behind cause of injury if the patient was African American and less likely if the patient was European American.

The IAT D score for racial bias had a median of 0.319 (95% CI, 0.064-0.590); for socioeconomic bias, the median was 0.609 (95% CI, 0.334-0.820). Of the 146 faculty who completed the IAT for racial bias, 100 (68%) had an IAT D score ≥0.15, while 29 (20%) were neutral (IAT D score > -0.15 and < 0.15, Table 4). Similarly, of the 165 faculty who completed the IAT for socioeconomic bias, 139 (84%) had an IAT D score ≥ 0.15, while only 18 (11%) had a neutral feeling. The proportions of racial IAT D score ≥ 0.15 (68% [60%-76%], $P < 0.0001$) and socioeconomic IAT D score ≥ 0.15 (84% [78%-89%], $P < 0.0001$) were significantly higher than by chance (50%). Thus, on the IAT, more than half of the respondents showed a preference for European Americans vs African Americans, as well as a preference for UC over LC.

Comparison of IAT D Scores and Vignettes

When we compared the vignette responses in relation to informed consent, patient trust, and patient reliability with the IAT for race and socioeconomic class, we did not find any association in 4 of the 5 vignettes (Figures 1 and 2). In the vignette regarding informed consent, if a patient's parent is UC, physicians who favor UC over LC (socioeconomic IAT ≥ 0.15) are more likely to give a more detailed explanation of options, but those who favor LC

Table 3. Demographics of Department of Pediatrics Faculty

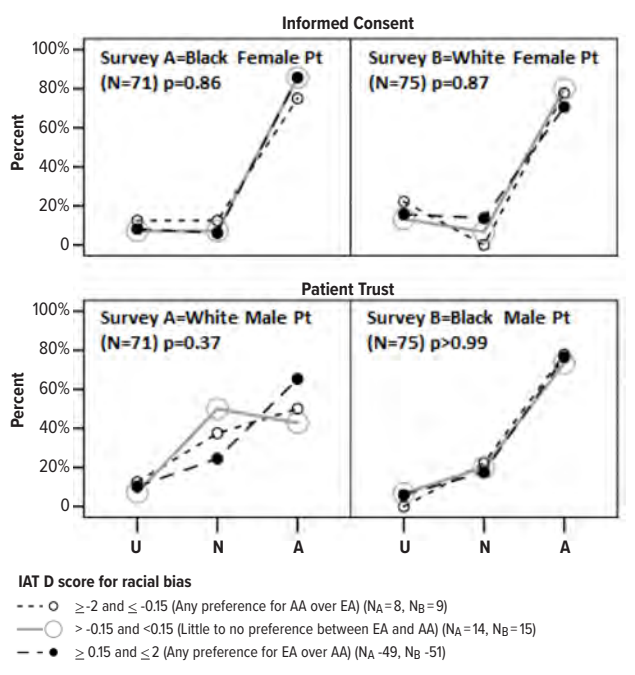
Demographics	Total (N = 230)
Gender: N (%)	
Female	166 (73.13)
Male	61 (26.87)
Missing	3
Highest educational attainment: N (%)	
Doctoral degree (DO/MD/PhD)	173 (75.88)
Master's degree	52 (22.81)
Advanced nurse/physician assistant	3 (1.32)
Missing	2
Marital status: N (%)	
Married	184 (80.00)
Single	19 (8.26)
Living with a partner	15 (6.52)
Widow/widower	1 (0.43)
Divorced/separated	11 (4.78)
Ethnicity: N (%)	
Non-Hispanic	220 (95.65)
Hispanic Caucasian	8 (3.48)
Hispanic non-Caucasian	2 (0.87)
Race: N (%)	
African American	3 (1.36)
Asian	26 (11.76)
Caucasian	183 (82.81)
Pacific Islander	3 (1.36)
African American and Caucasian	1 (0.45)
Caucasia and Native American	5 (2.26)
Missing	9
Region/continent of birth: N (%)	
United States	187 (82.74)
Africa	1 (0.44)
Asia	23 (10.18)
Central America	2 (0.88)
Europe	10 (4.42)
Other North American country	1 (0.44)
Pacific Islands	1 (0.44)
South America	1 (0.44)
Missing	4
Years lived in the United States: N (%)	
< 5 years	2 (0.88)
5-9 years	5 (2.19)
10-14 years	2 (0.88)
15-19 years	5 (2.19)
20 years or more	214 (93.86)
Missing	2
Citizenship status: N (%)	
US citizen	220 (96.49)
Permanent resident	4 (1.75)
Temporary visa	4 (1.75)
Missing	2
Other languages: N (%)	
Yes	75 (32.61)
No	155 (67.39)
Years in practice: N (%)	
0-4 years	55 (24.02)
5-9 years	44 (19.21)
10-14 years	30 (13.10)
15-19 years	28 (12.23)
> 19 years	72 (31.44)
Missing	1
Parent's highest degree: N (%)	
High school diploma	39 (17.26)
Associate degree	13 (5.75)
Undergraduate degree	54 (23.89)
Advanced degree	120 (53.10)
Missing	4

Table 4. Categories of Unconscious Racial and Socioeconomic Bias by Pediatric Faculty

Demographics	Total (N=230)
IAT D score for racial bias: N (%)	
≥-2 and ≤-0.15 (Any preference for AA over EA)	17 (11.64)
>-0.15 and <0.15 (Little to no preference between EA and AA)	29 (19.86)
≥0.15 and ≤2 (Any preference for EA over AA)	100 (68.49)
Missing	84
IAT D score for socioeconomic bias: N (%)	
≥-2 and ≤-0.15 (Any association for LC with Approach and UC with Avoid)	8 (4.85)
>-0.15 and <0.15 (Little to no association between UC and LC with Approach and Avoid)	18 (10.91)
≥0.15 and ≤2 (Any association for UC with Approach and LC with Avoid)	139 (84.24)
Missing	65

Abbreviations: IAT, Implicit Association Test; AA, African Americans; EA, European Americans; LC, lower class; UC, upper class.

Figure 1. Responses to Clinical Vignette by IAT D Score for Racial Bias



Abbreviations: IAT, Implicit Association Test; Pt, patient; U, unacceptable; N, neutral; A, acceptable; AA, African Americans; EA, European Americans; N_A, sample size for Survey A; N_B, sample size for Survey B.

P values, calculated using Fisher exact test, examined association between vignette answers with categories of IAT D score for racial bias.

(IAT ≤ -0.15) or have no preference (-0.15 < IAT < 0.15) are less likely to give a more detailed explanation ($P = 0.022$).

Comparison of IAT D Scores and Demographics

We did not find any association between IAT D score for socioeconomic bias and speaking other languages ($P = 0.29$), IAT D score for socioeconomic bias and parents of faculty's education achievement ($P = 0.49$), and faculty gender and IAT D score for racial bias ($P = 0.75$). The race of faculty also had no association with the IAT D scores for racial bias ($P = 0.43$). There was no difference for racial ($P = 0.61$) and socioeconomic ($P = 0.68$) IAT D scores based on years in practice (<5, 5-9, 10-14, 15-19, and >19), and after regrouping years in practice as <10 and ≥10, we still did not find any difference for racial ($P = 0.40$) and socioeconomic D score ($P = 0.38$). Due to the small sample size, we divided place of birth into 4 categories: US, Asia, Europe, and other (Africa, Central America, other North American country, Pacific Islands, and South America). Again, there was no significant difference in the racial ($P = 0.65$) and socioeconomic IAT D score ($P = 0.22$).

Comparison of IAT D Scores and Explicit Bias Ratings

Unconscious bias evaluated through the IAT (race and socioeconomic class) also was not related to the explicit bias reported by the faculty (data not shown).

DISCUSSION

Our study revealed significant findings: (1) pediatric faculty in this study were highly biased in favor of UC and European American individuals; (2) their unconscious bias was not related to faculty gender, race, number of languages spoken, place of birth, years in practice, and education of the faculty member's parents; (3) there was little evidence that unconscious bias affected how faculty managed patients evaluated by clinical vignettes, except faculty who favor UC were more likely to give detailed explanations of options if a patient's parent is UC than faculty who favor LC or have no preference; (4) unconscious bias did not relate to explicit bias; (5) answers to clinical vignettes did not vary between faculty who did and did not complete the IAT, except faculty who completed the racial IAT were more likely to believe the patient's story behind cause of injury if the patient was African American and less likely if European American.

Prejudice involves an attitude or prejudgment towards a group. This usually originates from previous experiences.[28] In our study, we used the IAT to assess racial and socioeconomic bias among pediatric faculty. Given that individuals' unconscious bias was probably developing since early childhood, our initial hypothesis was that faculty with more international background would have less unconscious bias. We also hypothesized that females would be less biased. Thus, we were surprised that none of these factors affected unconscious bias.

Clinical vignettes are accepted as a reliable measurement to assess clinical practice decisions.[29,30] Although the faculty showed racial and socioeconomic bias, this bias was not translated into how they managed patients. This finding was also reported in an extensive review of the literature by Maina et al,[31] who reported on 12 studies using vignettes. Out of the 12 studies, 8 found no association between the unconscious bias and how respondents

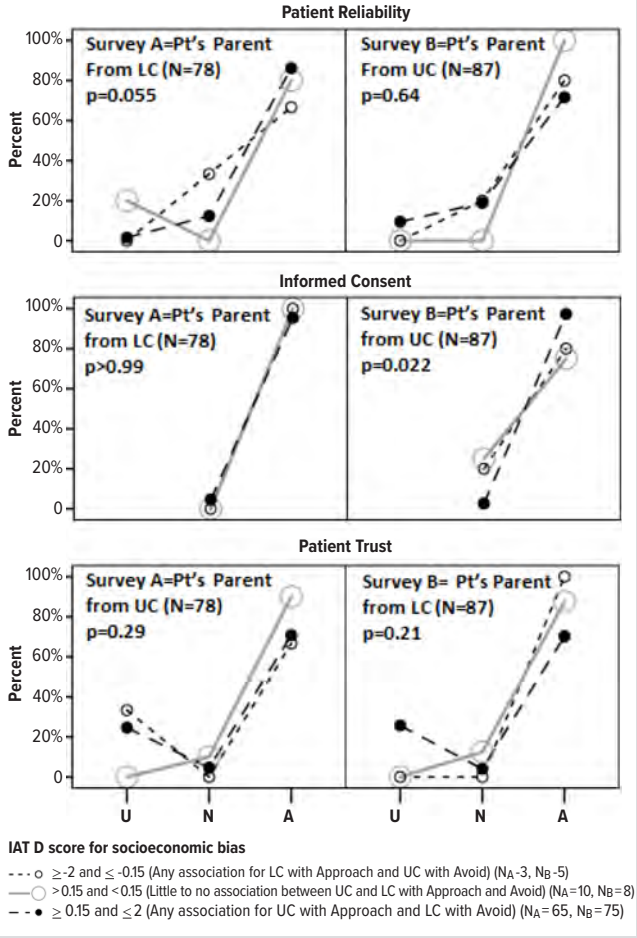
managed patients.[31] One of the studies showing that unconscious bias affected patient care was a pediatric study by Sabin and Greenwald, who found that pediatricians' unconscious bias affected how they managed pain.[32] This seems to be the exception. In the few other pediatric studies reported, clinicians' bias was seldom reflected in patient management. A study of pediatricians in an urban academic center evaluating the treatment recommendations through clinical vignettes divided by patient's race for pain control, urinary tract infection (UTI), attention deficit hyperactivity disorder, and asthma control, found that the median IAT D racial score was 0.18 (95% CI, -0.26 to 0.62).[25] In our study, the racial bias (0.32 [95% CI, 0.06-0.59]) was slightly higher than that found in the previous referenced study, which differed from ours in that both faculty (41%) and resident/fellows (59%) were included, while we only included faculty. The study demonstrated a difference in the management of UTIs between European American and African American patients. European American patients were more often admitted to the hospital for treatment (unnecessary hospitalization). The authors did not find other significant differences in the management of the other disorders.[25]

Another study by Puumala et al performed in 5 EDs in urban and rural areas serving Native American Indian (NAI) children that utilized clinical vignettes and race IAT with pictures of NAI and European American children and adults found an unconscious bias preference for European American patients (average IAT score = 0.54, 95% CI, 0.47-0.62).[33] Furthermore, when the authors compared the pictures of children to those of adults, the mean IAT score for the child picture IAT was higher than that of adults. In this study, most clinicians were family practitioners, but nurses and advance practice providers were also included. Interestingly, older providers (≥ 50 years) had lower unconscious bias than those who were middle aged (30–49 years) ($P = 0.01$). In relation to the correlation between clinical vignettes and race, the authors did not find any difference in the faculty regarding asthma treatment and pain control. Nurses were biased in declining to offer a work note to European American patients.

In contrast, in our study we did not find any difference regarding years in practice for unconscious bias. Furthermore, we only included advance practice providers who had faculty appointments. We did not look at age in relation to unconscious bias, but we did assess years in practice, which presumably would be related strongly to age. We also did not find any correlation between years in practice and unconscious bias. We are unclear why there is this difference between the Puumala et al study and ours. As individuals get older, racial biases may increase, perhaps due to failure to self-regulate.[34] This was obviously not the finding in either study.[33]

Unlike pediatrician studies, those involving adult medicine clinicians have shown that unconscious bias affects how they manage their patients. An extensive literature review described 17 studies that used the IAT tool, with at least 9 showing that unconscious bias against African Americans and in favor of European Americans was also reflected in the patient interaction.[5]

Figure 2. Vignette Responses by IAT D Score for Socioeconomic Bias



Abbreviations: IAT, Implicit Association Test; Pt, patient; LC, lower class; UC, upper class; U, unacceptable; N, neutral; A, acceptable; N_A, sample size for Survey A; N_B, sample size for Survey B.

P values, calculated using Fisher exact test, examined association between vignette answers with categories of IAT D score for socioeconomic bias.

Our study and the literature review show that although pediatricians are biased in favor of European American patients, they are less likely to allow their biases to affect how they manage patients. In Milwaukee specifically, despite the fact that most of the faculty who provided their ZIP codes live in areas associated with UC (data not shown), and despite their bias against LC and African American people, their bias was minimally reflected in how they managed patients. Interestingly, we received a few emails from faculty complaining that the IAT was offensive, and several faculty members did not complete the IAT. We can speculate that, given the emails we received and some personal communications, some faculty would be uncomfortable answering the IAT. This is reflected in the difference we found between those who

did and did not completed the IAT. Faculty who completed the racial IAT were more likely to believe the patient's story behind cause of injury if the patient was African American and less likely if European American, perhaps showing less bias against African American patients.

Questions arise from these findings: (1) why are pediatricians different from adult care providers? and (2) can unconscious bias be changed through training? For the first question, we could postulate that pediatricians tend to be more acculturated to demonstrate compassion and empathy for the targeted population, although there are no data published that support this hypothesis. Further research is needed to answer this question.

In relation to changing unconscious bias, a study from the University of Wisconsin-Madison demonstrated that unconscious bias in psychology students can be changed though interventions.[35] Investigators based their intervention on the premise that to improve, persons must be aware of their bias and also need to be concerned about the consequences that bias produces. The authors evaluated unconscious bias utilizing the race IAT at baseline and 4 and 8 weeks post intervention. During a training session, the investigators gave the subjects 5 strategies for recognizing their biases. The intervention group showed a decrease in the IAT score at 4 and 8 weeks post intervention.[35] Another study in an ED utilized the IAT and some discussion to increase awareness of unconscious bias and how it affects patient care without repeating the IAT after the intervention.[7]

To change unconscious bias in medical institutions, the change has to be at the organizational and personal levels.[36] The organization has to recruit a significant number of underrepresented individuals and provide the needed support and environment for those individuals to thrive. The change in recruitment has to involve the medical school admissions, as well as the faculty and staff. To achieve this, women, minorities, junior faculty, and students need to participate in the admission committees.[36] Furthermore, there is a need to decrease the emphasis on the Medical College Admission Test and grade point average and be blind to those scores during the interview process and focus more on a holistic assessment of the candidates.[37] This can only be accomplished with a change in the structure and culture of leadership. The institution needs to assess frequently how the training of unconscious bias and cultural humility is changing the sense of belonging, mainly among underrepresented groups. At an individual level, individuals need to self-reflect and recognize their biases to decrease their effect in admission interviews, patient care, and interaction with colleagues.[36] There are preliminary data on the results of incorporating a skill-based curriculum for medical students through role-playing to address unconscious bias when they perceive it in the learning space.[38]

Our pediatrics department has now developed training in unconscious bias with the goal of reassessing the same variables after most of the faculty undergo the training. Furthermore, we plan to repeat the same evaluation 2 and 4 years later to see if the changes are sustained. Our belief is that to change unconscious bias, clinicians will need to undergo frequent training and self-reflection, understand microaggressions and micro-affirmations, have discussions on White fragility, reflect on examples of bias or lack of inclusion in the workplace, and promote empathy for people who look different from us to produce a deep and permanent change. To achieve a change, automatic responses have to change. This requires habituation through repetition of controlled interventions.[39] As reported in the literature, we postulate that a "one shot" intervention will not affect unconscious bias.[39] An article in *Harvard Business Review* concludes that unconscious bias training to increase bias awareness does not change behaviors.[40] Some people would even argue that unconscious bias training may even produce the opposite effect, produce more discrimination. To produce a change, companies need a firm and long-term commitment to the changes in bias and behaviors and not just a "check-the-box" obligation. To produce positive results, unconscious bias training needs to provide specific tools to change behavior. Furthermore, the institution needs to monitor the changes and act on those areas where there is no improvement.[40] It is very important that the training send the message that we can change our biases, provide a safe environment for discussion, and never include shaming or activities that may create a defensive response.[41]

Study Limitations

Our study has several limitations. First, although vignettes are thought to represent how professionals treat patients, the stress and time constraints of the medical system are not present when answering clinical vignettes. In "real life," unconscious bias may play a bigger role than demonstrated in our model. A future study may require direct observation rather than vignettes. Second, the faculty was aware that these questions were related to a diversity and inclusion initiative within the department, which may have influenced how they answered the vignettes and the explicit bias. A third of the 230 faculty did not complete the racial IAT, and 65 respondents (28%) did not complete the social IAT. The lack of answering any part of the IAT could also be related to bias. Our analysis excluded missing data, which could bias our results, especially if the data are not missing completely at random. Third, there may have been some bias in that not every faculty member participated, allowing for the possibility that the most biased individuals may have opted not to complete the instrument.

CONCLUSIONS

Unconscious bias is present in our pediatric faculty, but based on clinical vignettes, it minimally affects patient care decisions. Unconscious bias is not significantly different between genders, country of birth, and is not associated with years in practice or parental education.

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Retrospective Evaluation of Return Rates in Pediatric Patients Treated With Inhaled Racemic Epinephrine for Croup

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ABSTRACT

Background: Croup (viral laryngotracheitis) is a respiratory illness that often affects infants and young children.

Objectives: To determine if the length of observation (< 2 hours vs ≥ 2 hours) following treatment of croup with inhaled racemic epinephrine in the emergency department (ED) is associated with return rates (within 48 hours after treatment) in pediatric patients.

Methods: We conducted a retrospective review of patients' medical records from February 2010 through June 2018 for pediatric patients (male and female, ≤ 12 years of age) diagnosed with croup in the ED, treated with racemic epinephrine, and discharged from the ED.

Results: We evaluated patients observed for less than 1 hour, 1 to 2 hours, and greater than 2 hours to determine difference in return rates within 48 hours. For patients with mild croup symptoms, 2% observed for less than 1 hour returned; 5% observed for 1 to 2 hours returned, and 3% observed for greater than 2 hours returned. Of the patients with moderate croup symptoms, 29% observed for less than 1 hour returned, 20% observed for 1 to 2 hours returned, and 20% observed for greater than 2 hours returned. A majority who returned for follow-up were not retreated with racemic epinephrine.

Conclusion: Based on our study results, we can conclude that observing patients following treatment of croup with inhaled racemic epinephrine in the ED for less than 2 hours did not increase their risk of deterioration or need to return. Our data did not show that a longer observation time resulted in lower return rates within 48 hours.

INTRODUCTION

Croup (viral laryngotracheitis) is a respiratory illness that often affects infants and young children. It is characterized by inspiratory stridor, barking cough, and hoarseness. These symptoms occur due to inflammation in the larynx and subglottic airway.[1] In addition to inspiratory stridor, cough, and hoarseness, other common symptoms include those seen in any respiratory viral illness, such as nasal congestion and fever. Croup occurs most frequently between the ages of 6 months and 3 years, with most cases occurring during the second year of life.[2] Parainfluenza virus type 1 is the most common cause of acute laryngotracheitis.[3] Other less common causes of croup are respiratory syncytial virus, influenza, rhinovirus, and other respiratory viruses. Most cases of croup occur in the fall and early winter.

Although viruses cause most cases of croup, bacterial causes exist, and secondary bacterial infection also may occur.[4] Infection with croup is self-limiting in a majority of cases, and respiratory failure is uncommon, with fewer than 2% of cases requiring hospitalization.[2] In rare cases, significant respiratory distress and pulmonary complications may occur. Treatment for croup usually includes a single dose of steroid and the addition of racemic epinephrine in selected cases. Corticosteroids—specifically dexamethasone—are recommended.[1] Corticosteroids are particularly important, as they can shorten the duration of croup-related symptoms.[2]

Several randomized controlled trials and meta-analyses have demonstrated the benefit of racemic epinephrine in reducing croup symptoms in children treated in the emergency department (ED). Racemic epinephrine has been shown to improve inspiratory stridor, retractions, and air entry when used in croup treatment.[5] However, there is no consistent evidence published to guide physicians on how long to observe patients in the ED before dis-

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charge after receiving racemic epinephrine for those patients who require it. Traditionally, physicians are taught to observe patients for at least 2 hours after treating with inhaled racemic epinephrine for croup before discharge. This practice might have been derived because the effects of racemic epinephrine last 90 to 120 minutes and usually dissipate after 2 hours; therefore, observing patients for 2 hours or more would allow physicians to identify patients who might have a return of stridor and retractions. Despite this consensus, little is known about the optimal observation time.

In this study, looking specifically at patients who were treated with racemic epinephrine, we set out to determine whether the length of observation (< 2 hours vs ≥ 2 hours) following treatment of croup with inhaled racemic epinephrine in the ED is associated with return rates within 48 hours after treatment in pediatric patients. The results of this study may help inform future guidelines for observation time following inhaled racemic epinephrine treatment for croup.

METHODS

This study is an 8-year retrospective analysis of patients diagnosed with croup who received treatment with racemic epinephrine at 3 regional EDs in central Wisconsin. The EDs were Marshfield Medical Center-Marshfield, Marshfield Medical Center-Eau Claire, and Marshfield Medical Center-Rice Lake; all are similar in practice. This study focused only on patients who received racemic epinephrine. The use of racemic epinephrine was not standardized and was determined by the treating clinician. It was our intent not to determine who should get racemic epinephrine; however, if a clinician gave it, we looked at whether it was safe to discharge prior to 2 hours.

Electronic medical records for pediatric patients (male and female, ≤ 12 years of age) who were diagnosed with croup (International Classification of Diseases, Ninth Revision [ICD-9] code 464.4) in the ED and discharged from the ED from February 2010 through June 2018 were reviewed for analysis. Records for patients who were diagnosed at the same time with asthma, bronchiolitis, and/or pneumonia were excluded from the analysis. The principal investigator and study assistant manually cross referenced the corresponding admission/discharge records for date and time of admission to the ED for croup to link clinical data with ED event information.

Information abstracted included observational data from clinician notes to calculate croup severity score, croup treatment (ie, whether steroid was administered and, if so, steroid type), time of inhaled racemic epinephrine treatment, observation time, date and time of discharge from the ED, and returns for croup within 48 hours after treatment. Our study focused on a 48-hour return rate, because historically that was the recommended time frame. It does seem that if patients are going to return with persistent croup symptoms, they are more likely to return within the first 48 hours. In our institutions, the dose of racemic epinephrine used is 11.25 mg solution nebulizer. We defined observation time as the time from administration of first dose of racemic epinephrine until the time of discharge by clinician and identified any patient diagnosed with croup in the ED who returned to care with persistent symptoms within 48 hours from discharge. We also identified whether returned patients were retreated with steroid or another dose of racemic epinephrine. This included patients who returned to either the ED or were seen in the clinic or urgent care departments. Croup severity score was calculated using the Wesley Croup[6] scoring system based on patient's initial presenting symptoms as documented in the clinician's note.

Table 1. Description of Study Sample

Number of visits	294
Number of patients	276
Average age, years	2.8 (2.1)
Average length of observation, hours	1.3 (0.7)
Maximum length of observation, hours	4.6
Observation length group	
<1 hour	45%
1-2 hours	42%
>2 hours	13%
Male	65%
Steroid treatment	93%
Westley croup score[a]	
Mild	93%
Moderate	7%
Time of day racemic epinephrine was administered	
Day (6:00-17:59)	27%
Night (18:00-5:59)	73%
Multiple doses of racemic epinephrine were administered	2%

Mean (SD) shown for numeric variables.
[a]Westley et al, 1978.[6]

Data were compiled in an Excel spreadsheet and validated by the principal investigator and study assistant before delivery to the biostatistician. Our primary outcome was to compare the return rate within 48 hours between patients observed for less than 2 hours with those observed for 2 hours or more. Visits were grouped as having observation less than 1 hour, 1 to 2 hours, and greater than 2 hours after treatment with racemic epinephrine. Subdividing visits into these groups provided a more granular understanding of return rates. Visit characteristics were described using means and SD for continuous variables and counts and percentages for categorical variables. Comparisons of visit characteristics across observation time groups were made using analysis of variance (ANOVA) for continuous variables, and chi-square tests for categorical variables. Return rates by observation time groups were further compared using chi-square tests after stratifying for croup severity. Retreatment among patients who returned within 48 hours of discharge also were tabulated. All statistical analyses were performed in SAS version 9.4. The Figure was generated using the ggplot2 package in R version 3.6.0.

RESULTS

Over the 8-year period, 294 individual visits for 276 pediatric patients met inclusion criteria. The 294 visits were individual visits within the 8-year period and not repeat visits within the 48

Table 2. Patient and Clinical Characteristics by Observation Length Group

Characteristic	Observed <1 hour N=32	Observed 1-2 hours N=123	Observed >2 hours N=39	*P* value
Age, years	2.7 (2.1)	3.0 (2.2)	2.8 (2.2)	0.680
Male	64%	67%	62%	0.801
Steroid treatment	87%	98%	100%	0.001
Westley croup score[a]				
Mild	95%	96%	74%	<0.001
Moderate	5%	4%	26%	
Time of day RE was administered				
Day (6:00-17:59)	30%	24%	26%	0.639
Night (18:00-5:59)	70%	76%	74%	
Multiple doses of RE administered	1%	2%	8%	0.044

Abbreviation: RE, racemic epinephrine.
Mean (SD) shown for numeric variables.
P values are derived from ANOVA for continuous variables and chi-square test for categorical variables.
[a]Westley et al, 1978.[6]

hours' time for 1 episode of croup. Table 1 highlights the demographic and clinical information for the sampled ED visits. The average age of our patients was 2.8 years, and 65% of the patients were male, for a male to female ratio of 1.9:1.

The average length of observation in our patient population was 1.3 hours, with 45% observed for less than 1 hour; 42% observed for 1 to 2 hours; and only 13% observed for greater than 2 hours. The maximum length of observation was 4.6 hours in our study sample. The majority of patients (93%) had mild croup symptoms, while 7% had moderate croup symptoms. No patients in our study sample had severe croup symptoms. A majority of our patients (93%) received steroids—specifically dexamethasone 0.6 mg/kg—as part of their treatment. It is not clear from the medical records why the other 7% did not receive steroids.

Preliminary evaluation of clinical characteristic by observation time did not reveal a statistically significant difference in patient ages among the different observation periods (Table 2). In the less than 1 hour observation group, 95% had mild symptoms, while 5% had moderate symptoms. In the 1 to 2 hours observation group, 96% had mild symptoms, and 4% had moderate symptoms. In the greater than 2 hours observation group, 74% had mild symptoms, while 26% had moderate symptoms. Regarding steroid treatment, 100% of patients observed for greater than 2 hours were treated with steroid, compared to 87% of patients in the less than 1 hour group and 98% of the 1- to 2-hour group. Given these data, a greater percentage of those observed for less than 1 hour had milder symptoms compared to those observed for greater than 2 hours. In addition, of those who received more than 1 dose of racemic epinephrine, 8% were in the greater than 2 hours observation (Table 2).

Further cohort analysis was performed to determine whether return rates were associated with initial observation time. The return rates within 48 hours were compared between the different observation times (Table 3, Figure). In the greater than 1 hour observation group, only 5 patients with croup symptoms returned for additional care within 48 hours. Of these 5 patients, 3 had initial mild symptoms, while 2 had moderate symptoms. None of the patients who returned were retreated with racemic epinephrine, though 2 of them received steroids. The age of these patients ranged from 20 months to 3 years, and a majority (4 out of 5) were male.

In the 1- to 2-hour observation group, 7 patients returned to care within 48 hours with persistent croup symptoms. Only 1 of these patients was retreated with racemic epinephrine, and this was a patient with initial moderate symptoms by croup score. Three out of the 7 patients received steroids. In the greater than 2 hours observation group, only 3 patients returned, and 1 was admitted to the hospital for further treatment. Only 1 out of the 3 patients received steroids. When comparing the total return rate based on observation times in our study population, we found no significant association.

DISCUSSION

Croup is a common pediatric illness often encountered by ED physicians. Although much is known regarding the treatment of croup, the appropriate observation time after administration of racemic epinephrine is not well established. The current recommendation is to observe patients for at least 2 hours prior to discharge, though this practice was not adapted from well-conducted studies. Several studies have attempted to define an appropriate length of observation in this population. A small observational study conducted at a children's hospital in Atlanta, Georgia suggested that selected patients with croup can be safely discharged after observation for 2 hours following racemic epinephrine administration.[7]

Our study aimed to compare patients observed for less than 2 hours versus those observed for 2 hours or more to see if there is an association in return rates within 48 hours. Croup symptoms are mild in most cases and, as such, the return rate in croup cases is low. When we compared return rates based on observation time, there was no association between return rates and observation time ($P=0.538$) among mild cases. Similarly, when looking at return rates among moderate cases, there was no statistically significant difference in return rates based on observation time ($P=0.905$); however, there were too few cases to detect small differences in readmission rate. In those patients who did return within 48 hours, the majority were not retreated with racemic epinephrine. The majority of our patients were male. This sampling result corresponds to observations in the general population, where there is slight male predominance with croup, with a male to female ratio of approximately 1.4:1.[4] Consistent with a typical presentation of croup—which generally occurs during the night/early morning

hours due to resting secretions and edema building without clearing during sleep—in our patient population, a majority of cases presented to the ED at night (73%).[8]

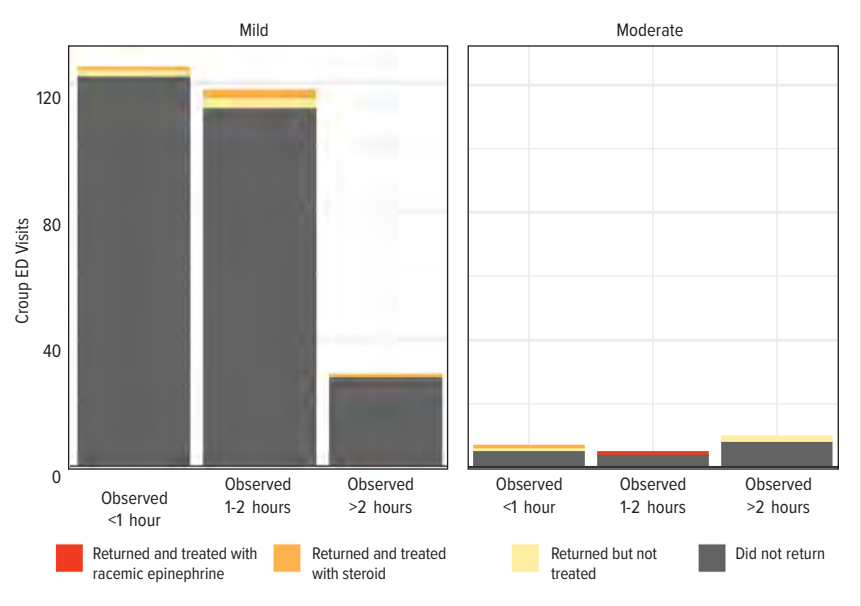
Limitations

There are several limitations to our study, including that it is a retrospective study dependent on chart review from different clinicians at different EDs. In addition, we only included charts from 3 institutions in Wisconsin, which might limit the generalization of our study results to other populations. Another limitation is that the croup severity score was not assigned/standardized prior to treatment. We had to extrapolate/calculate croup severity score based on patients' presenting symptoms from the charts. Furthermore, there were only a few cases of patients who returned with croup symptoms after receiving racemic epinephrine. To account for these differences, there is a need for a larger prospective study with standardized croup severity scoring prior to treatment with racemic epinephrine to determine appropriate observation times after its administration. Another limitation in our study is that we had very few cases with moderate croup symptoms; and although it does not appear that observing these group of patients for less than 2 hours leads to an increase in return rate within 48 hours, we recognize that there were too few cases to detect small differences in return rate.

Table 3. Rate of Return Within 48 Hours by Observation Length Group

	Observed <1 hour	Observed 1-2 hours	Observed >2 hours	*P* value
Total (N = 294)				
Did not return within 48 hours	127 (96%)	116 (94%)	36 (92%)	
Returned within 48 hours	5 (4%)	7 (6%)	3 (8%)	
Mild cases (N = 272)				
Did not return within 48 hours	122 (98%)	112 (95%)	28 (97%)	0.538
Returned within 48 hours	3 (2%)	6 (5%)	1 (3%)	
Moderate cases (N = 22)				
Did not return within 48 hours	5 (71%)	4 (80%)	8 (80%)	0.905
Returned within 48 hours	2 (29%)	1 (20%)	2 (20%)	

Figure. Comparison of Return Rates Within 48 Hours Between the Different Observation Times



CONCLUSION

From our study results, we can conclude that observing patients with mild croup symptoms for less than 2 hours did not increase their risk of deterioration or need to return. In patients with moderate croup symptoms, there was no statistically significant difference in return rates based on observation time; however, there were too few cases to detect small differences in return rate. Our data did not show that a longer observation time in patients with mild and moderate croup symptoms results in lower return rates within 48 hours. Despite the recommendations to observe patients for greater than 2 hours, it seems that clinicians are safely discharging patients after observing for less than 2 hours, and this is not leading to worse outcomes.

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Current Practice and Rationale of Prescribing Dexamethasone for Pediatric Patients Hospitalized for Asthma

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ABSTRACT

Objective: Dexamethasone use for pediatric asthma exacerbations in the emergency department is supported in literature as a beneficial alternative to prednisone; however, there is limited data in the hospital setting. This study assesses factors that influence pediatric hospital providers' steroid choice for patients hospitalized for status asthmaticus.

Methods: A survey was developed to assess factors influencing steroid prescribing practices. It was completed by our institution's pediatric hospitalists and advance practice providers in June 2019 and April 2021. Responses were summarized using descriptive statistics, interrater agreement was analyzed with Cohen's kappa statistic, and bivariate comparisons were analyzed with chi-square tests.

Results: Thirty-six of 39 providers completed the survey in 2019; 31 of 43 completed it in 2021. They reported wide disagreement with the use of dexamethasone in both surveys (2019 vs 2021: 34% vs 55% in favor, 43% vs 35% neutral, 23% vs 9% opposing, $P=0.191$). There was a self-reported increase in prescribing frequency of dexamethasone from 2019 to 2021 ($P=0.007$). There was moderate agreement with prescribing dexamethasone for patients with poor oral tolerance or medication noncompliance (2019: $\kappa=0.485$, $P=0.002$; 2021: $\kappa=0.281$, $P=0.048$). There was moderate agreement with prescribing prednisone for patients with higher severity of baseline asthma or current exacerbation (2019: $\kappa=0.537$, $P<0.001$; 2021: $\kappa=0.500$, $P<0.001$). Length of the dexamethasone course did not influence prescribing practices ($P>0.05$).

Conclusions: In our inpatient setting, prednisone is preferred for severe asthma cases, while dexamethasone is preferred for patients with poor oral tolerance or medication noncompliance. The length of the dexamethasone course did not influence providers' steroid choice.

INTRODUCTION

Asthma is the most common chronic medical condition among children worldwide.[1] In the United States, the prevalence of asthma among children is 8.5% and as high as 18% for children living in poverty.[1] It is the second most common cause of pediatric hospitalizations.[2] Over the span of 4 years, 16.7% of children with asthma had emergency department (ED) visits, and 4.7% were hospitalized for asthma, with the highest rates among children aged 0 to 4 years.[3,4]

Steroids are an essential component for status asthmaticus treatment. The standard of care in children has been a 5-day course of prednisone, with daily dosing because of its relatively short half-life.[5] However, the length of the course, taste, and associated nausea and vomiting side effects of prednisone can lead to noncompliance.[6] Dexamethasone, on the other hand, is relatively long-acting and can be administered as a 2-dose course, with the second dose administered 36 to 48 hours after the first.[5] Dexamethasone is also considered more tolerable than prednisone but may be less commonly available than prednisone at community pharmacies. Both steroids are usually covered by private insurance and Medicaid. Additionally, dexamethasone is associated with a shorter length of hospital stay and lower health care costs.[5]

Over the past decade, there has been substantive research comparing the use of a 2-dose course of dexamethasone with

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the use of prednisone in emergency care-based settings. Two randomized controlled trials found that dexamethasone had similar rates of unscheduled visits to medical facilities for worsening symptoms and similar hospitalization rates from the ED, improved compliance, and fewer side effects when compared to a 5-day prednisone course prescribed in ED settings for patients who were discharged from the ED.[6-9] Additionally, a meta-analysis showed that there was no difference between the 2 steroid courses in ED reutilization or hospital readmission rates up to 30 days after the initial ED visit.[10] In 2016, Children's Wisconsin ED implemented these findings into a new asthma protocol, in which dexamethasone is frequently ordered as a 2-dose course, with the assumption that the patient would be discharged and take the first dose in the ED and the second dose 36 hours later at home. If the patient is hospitalized instead of discharged from the ED, the caregiver sometimes has the second dose of dexamethasone that was provided in the ED.

While there has been extensive research evaluating the efficacy of prednisone and dexamethasone in the ED setting and demonstrating increased compliance with dexamethasone, there is limited evidence regarding the use of dexamethasone in the inpatient setting, where the acuity and severity of disease is often higher. As a result, there is wide variability in hospitalists' prescribing practices for pediatric patients hospitalized for status asthmaticus.[5,11] Currently, only a single small study has explored the factors influencing providers' prescribing practices and contributing to this variability.[11] Our study aims to further investigate the patient- and provider-related factors that influence the medical decision-making process of prescribing dexamethasone versus prednisone in pediatric patients hospitalized for status asthmaticus.

METHODS

We obtained institutional review board approval for our survey. Survey questions and design were informed by a comprehensive review of existing literature and focused group discussions with 6 physicians in the Pediatric Hospital Medicine Section at Children's Wisconsin, from which a list of factors was identified that may contribute to a provider's choice of prescribing prednisone or dexamethasone for a pediatric patient with status asthmaticus.[6,7,12] A pilot survey was conducted to test the instrument, after which the survey was finalized for distribution.

The anonymous electronic survey was sent to 39 hospitalists in the Pediatric Hospital Medicine section in June 2019 and to 43 hospitalists in April 2021, as a result of provider turnover and new hires. The survey was limited to pediatric hospitalists and advanced practice providers. It did not include pediatric pulmonologists, as patients with status asthmaticus are primarily cared for by hospitalists; patients hospitalized on the primary pulmonology team for asthma typically have other comorbidities—such as cystic fibrosis—resulting in different, individualized treatment plans. The survey also did not include allergists/immunologists, as they act as consultants at our institution.

The survey assessed the following: providers' years in practice (1-5 years, 6-10 years, more than 10 years), opinions on prescribing dexamethasone, frequency of prescribing dexamethasone, and steroid preference based on patient and institutional factors. Patient factors included smoke exposure in the home, severity of baseline asthma, poor asthma control, history of medication noncompliance, severity of current exacerbation, and poor tolerance of oral medications. Institutional factors included prednisone being the standard of care, the limited evidence level of dexamethasone for inpatient asthma, the availability of dexamethasone at the in-house outpatient pharmacy, whether the caregiver already has a second dose of dexamethasone in their physical possession from the ED, and the length of course of dexamethasone. Some questions were formatted using a Likert scale. Other questions presented respondents with a particular patient factor and offered the choices of "prednisone," "dexamethasone," or "does not influence" their decision.

Survey responses were summarized using descriptive statistics, Cohen's kappa statistic was used to analyze interrater agreement, and bivariate comparisons were analyzed with chi-square tests. Cohen's kappa coefficient was interpreted as follows: slight ≤ 0.20, fair 0.21-0.40, moderate 0.41-0.60, substantial 0.61-0.80, and almost perfect 0.81-1.00. Differences in responses between the 2019 and 2021 surveys were analyzed with a chi-square test. In the instance that a respondent did not complete a question, they were excluded from the analysis of that question. Statistical significance was defined as $P \leq 0.05$, and all analyses were performed using SPSS 27.0 (IBM Corp, Armonk, NY).

RESULTS

Thirty-six out of the 39 providers completed the survey sent in June 2019, with a total of 32 hospitalist attendings and 4 advanced practice providers. Thirty-one out of 43 providers completed the survey in April 2021, with a total of 26 attendings and 5 advanced practice providers.

Providers' Opinions on Dexamethasone

Providers' years of practice across the 2019 and 2021 survey respondents are shown in Figure 1. In the 2019 survey, providers reported wide variability regarding the use of dexamethasone, with 34% in favor, 43% neutral, and 23% opposing (Figure 2). This variability was consistent in 2021, with 55% in favor, 35% neutral, and 10% opposing (Figure 2). There was not a significant difference in this variability between years ($P = 0.191$). Additionally, the provider's years of practice did not affect their opinions regarding the use of dexamethasone (2019: $P = 0.887$; 2021: $P = 0.065$). There was a significant increase in reported prescribing frequency of dexamethasone from 2019 to 2021 ($P = 0.007$).

In the 2019 survey, most respondents agreed that the current status of prednisone as the standard of care influences their deci-

Figure 1. Hospital Medicine Providers' Years of Practice Across the 2019 and 2021 Surveys

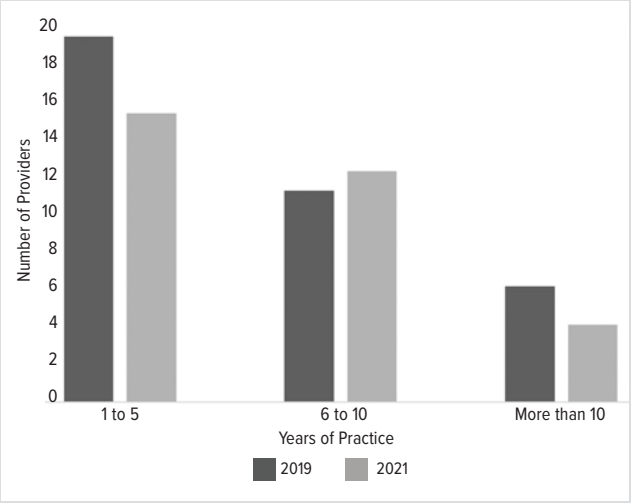
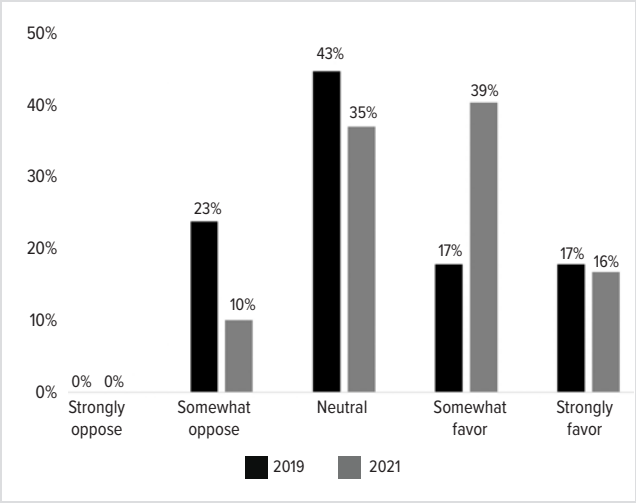
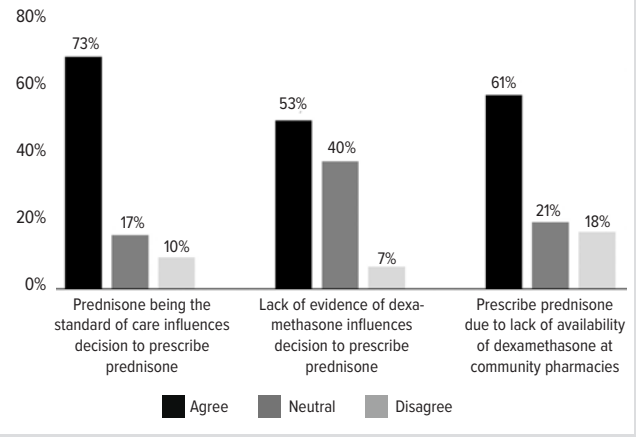


Figure 2. Pediatric Providers' Opinions on the Prescribing of Dexamethasone for Patients With Status Asthmaticus in 2019 and 2021



There was no significant difference in opinions across years ($P = 0.191$).

Figure 3. Providers' Level of Agreement With Institutional Factors' Influence on Steroid Choice in 2019 Survey



sion to prescribe prednisone. Seventy-three percent agreed with this statement, 17% were neutral, and 10% disagreed (Figure 3). Similarly, the lack of evidence of dexamethasone for inpatient use influenced the majority's decision to prescribe prednisone, with 53% in agreement, 40% neutral, and 7% opposing (Figure 3). When asked whether they will prescribe prednisone if the resident physician prefers it, 60% agreed, 37% were neutral, and 3% disagreed. When asked whether they will prescribe dexamethasone if the resident physician prefers it, 43% agreed, 33% were neutral, and 24% disagreed. There were no significant differences in the responses to these questions on the 2021 survey ($P > 0.05$).

Patient Factors

Smoke exposure in the home was not an influential factor, with over 90% of respondents in both surveys indicating it had no impact on their decision-making. For patients with poor asthma control, there was an increasing preference for dexamethasone in 2021 compared to 2019 (0% vs 19% preferred dexamethasone, respectively; $P = 0.019$). Fair-to-moderate agreement between providers was found regarding the decision to prescribe dexamethasone for patients with poor oral tolerance or a history of medication noncompliance (2019: $\kappa = 0.485$, $P = 0.002$; 2021: $\kappa = 0.281$, $P = 0.048$). There was also moderate agreement regarding the decision to prescribe prednisone for patients with a more severe baseline asthma classification or with a more severe current exacerbation (2019: $\kappa = 0.537$, $P < 0.001$; 2021: $\kappa = 0.500$, $P < 0.001$) (Figure 4).

Institutional Factors

Providers were more likely to agree with the use of prednisone due to lack of availability of dexamethasone at community pharmacies, with 61% in agreement, 21% neutral, and 18% in disagreement in 2019 (Figure 3). There was no difference in the responses in 2021 ($P = 0.618$). Similarly, providers in 2019 reported that the availability of dexamethasone at the in-house outpatient pharmacy affected their decisions to prescribe dexamethasone, with 39% in agreement, 39% neutral, and 22% in disagreement. Over the last 2 years, there has been significantly increased influence of in-house outpatient pharmacy availability of dexamethasone on prescribing practices, with 72% of providers in 2021 agreeing that this influenced their prescribing decisions ($P = 0.028$).

The ED having already provided the patient with a second dose of dexamethasone and the length of the 2-day course of dexamethasone did not significantly influence prescribing practices (2019: $\kappa = 0.147$, $P = 0.191$; 2021: $\kappa = 0.0.066$, $P = 0.384$), and there were no significant changes in these factors over the 2 years ($P > 0.05$).

DISCUSSION

Without specific patient context, pediatric hospitalist providers' general opinions about the use of dexamethasone demonstrates

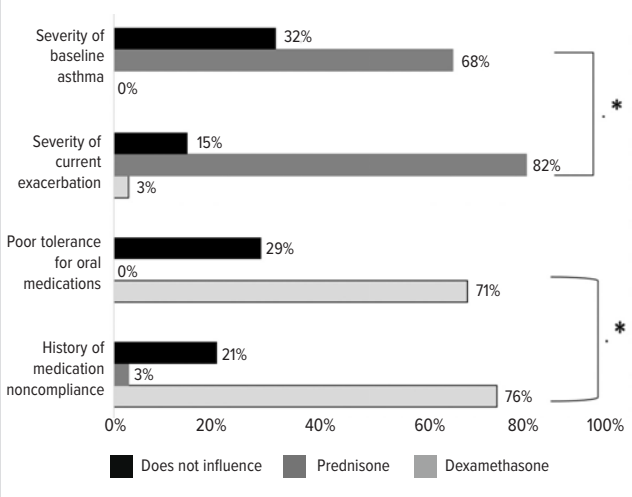
wide variability, which likely results in inconsistency in patient care. Despite this variability, we have found a significant increase in self-reported prescribing frequency of dexamethasone over the last 2 years. This may be due to increased provider comfort and familiarity with prescribing dexamethasone over time, as well as increased discussions of steroid choice at section meetings and resident teaching conferences as a result of this study. There were no substantial changes in local acute care practice guidelines or available comparative evidence for steroid prescribing practices for pediatric patients with status asthmaticus during this timeframe.

While there was a reported increase in dexamethasone use, prednisone was still preferred for patients with more severe asthma, suggesting that providers are less likely to deviate from the standard treatment for those with a higher severity of illness. Furthermore, hospitalists were more likely to disagree with a resident physician's choice of dexamethasone when compared to prednisone. Survey responses suggest these findings may be due to key reported factors that influence providers' decisions. For example, a hospitalist may disagree with a resident choosing dexamethasone for a patient with severe asthma because they feel prednisone is the standard of care. Similarly, they may disagree with a resident's choice of dexamethasone for a patient with mild persistent asthma because they believe a patient's family may have difficulty accessing dexamethasone at a community pharmacy.

The length of the dexamethasone course was not identified as an influential factor; however, a history of poor oral medication tolerance or medication noncompliance significantly affected the decision to prescribe dexamethasone. This suggests that the providers at our institution are not prescribing dexamethasone specifically because of the shorter duration. It is mainly prescribed as an alternative to prednisone when there are patient factors that conflict with the use of prednisone, such as noncompliance and poor oral tolerance. This correlates with a previous study which showed that children treated with dexamethasone were less likely to vomit in the ED and at home.[5]

Furthermore, institutional factors also played a role in prescribing practices. Dexamethasone had not historically been readily available at many community pharmacies, particularly in pediatric-friendly formulations, which likely influenced the providers' decision to prescribe prednisone. Over the past 2 years, there has been a significant increase in the self-reported frequency of prescribing dexamethasone and the influence of the availability of dexamethasone at the outpatient pharmacy within our hospital, despite no significant changes in dexamethasone availability. This may be due to increased discussions about dexamethasone amongst providers leading to increased comfort and, thus, more usage of the institution's outpatient pharmacy. Additionally, the lack of agreement regarding the continuation of the ED's second dose of dexamethasone demonstrates that there is not a consensus

Figure 4. Patient Factors' Influence on Provider Corticosteroid Preferences for Patient With Status Asthmaticus in 2019



* Represents $P < 0.05$.

on whether the evidence supporting the use of dexamethasone in ED settings can be extrapolated to the inpatient setting. This has remained consistent over the past 2 years and is congruent with previous studies that have acknowledged there is limited evidence for the use of dexamethasone for patients hospitalized with status asthmaticus.[13]

To our knowledge, there is only one other study that investigates factors influencing providers' prescribing practices in pediatric patients hospitalized for asthma. Both our survey and a survey by Cotter et al[11] found wide variability in prescribing practices and found that the severity of current exacerbation, history of severe asthma, and limited data of dexamethasone in the inpatient setting affected providers' decisions to prescribe prednisone. Dr Cotter and colleagues' survey did not identify medication tolerability as an influential factor. Our findings, however, demonstrated that in addition to these factors, a patient's history of noncompliance or poor oral tolerance influence providers' decisions to prescribe dexamethasone. This difference may be attributable to the population of respondents, which included hospitalists, pulmonologists, and advanced practice providers. In Cotter et al's study, pulmonologists were less likely to agree with the use of dexamethasone in the inpatient setting, which may account for medication tolerability not being considered an influential factor. Overall, the similar findings of both surveys demonstrate that the variability in prescribing practices for pediatric patients with status asthmaticus is a widespread trend rather than isolated to a single institution.

The wide variability observed in both this study and the previous survey are representative of the significantly limited body of research regarding the use of dexamethasone compared to prednisone in the inpatient setting. Existing literature

has focused primarily on differences in outcomes of patients given dexamethasone versus prednisone in the ED setting, with a small number of studies focusing on the inpatient setting. A systematic review and meta-analysis that included 6 randomized controlled trials and 1 quasi-randomized control trial—all in the ED setting—compared relapse rates with oral dexamethasone versus prednisone.[14] The study concluded that there was no difference in relapse rates between patients prescribed dexamethasone and prednisone. However, the power of this meta-analysis was limited by the small sample size of 3 of the included studies.[14] Additionally, there has been only 1 multicenter retrospective cohort study that investigated the effectiveness of dexamethasone versus prednisone in pediatric patients hospitalized with asthma.[5,11] This study demonstrated that patients who received dexamethasone had a shorter length of stay and a lower cost of admission, with no significant differences in intensive care unit or readmission rates compared to patients who received prednisone. However, this study is limited in that it is an observational study and severity of illness was not included.[5]

Given the results of our survey study and the previously published survey,[11] severity of baseline asthma and current exacerbation are significant factors that affect provider decision-making and prescribing practices. Our study adds to the growing body of literature by demonstrating that not only does a patient's baseline asthma severity and severity of exacerbation influence provider steroid choice, but a patient's history of noncompliance or poor oral tolerance does as well. Additionally, the lack of availability of dexamethasone at community and in-house pharmacies was influential. We also demonstrate an increase in self-reported dexamethasone prescribing practices, which may be due to increased discussions of the topic and, consequently, increased usage of our hospital's outpatient pharmacy. These results demonstrate factors that further contribute to the variability in steroid choice for patients hospitalized with asthma, despite a lack of substantial evidence demonstrating comparative effectiveness.

While this study highlights the practices at our single institution, the matter of steroid choice has become a subject of variability throughout many hospitals across the United States.[5,11] Both the patient and institutional factors that this survey identified can influence patient outcomes, which are subject to this variability. For example, patients with a history of noncompliance may not complete their prednisone course, leading to readmission. Likewise, patients with a history of severe asthma may have a readmission after being prescribed dexamethasone. Further studies are needed to examine the subsequent impact of these steroid prescribing practices on outcomes, such as length of hospital stay, ED reutilizations, and hospital readmissions, in order to bring better consensus and standardization of steroid prescribing for hospitalized patients with status asthmaticus.

Study Limitations

Limitations of this study include variability in the interpretation of survey questions among respondents, response bias, and conflicting patient factors influencing responses to specific survey questions. For example, providers may consider a patient who has both severe asthma and noncompliance when completing the survey, which may contribute to more variability when deciding between prednisone and dexamethasone. Additionally, while the majority of survey respondents were the same between 2019 and 2021, a few were unique to either survey and responses were not paired due to technological limitations in the first survey. Hospitalist meetings were held in-person in 2019, allowing for promotion of completing the survey. Due to the conversion of nonessential hospital work to virtual in response to COVID-19, promotion to complete the survey was held virtually in 2021, potentially leading to the decreased response rate. This can limit the ability to draw conclusions regarding the change in opinions over time. The results of this survey may not be generalizable as the cohort of respondents are from the Pediatric Hospital Medicine section of a single institution, and there may be variability with patient placement, availability of dexamethasone, and other institutional factors that influence prescribing practices at other institutions.

CONCLUSION

This study demonstrates that there is wide variability in steroid prescribing practices for inpatient management of status asthmaticus in pediatric patients within 1 institution. Although this variability has remained consistent over the past 2 years, there has been an overall increase in self-reported dexamethasone prescribing frequency. The limited evidence supporting dexamethasone use contributes to this variability, as do a variety of influential patient and institutional factors. These factors include the severity of current exacerbation, severity of baseline asthma, history of medication noncompliance, history of poor oral tolerance, and availability of dexamethasone at community pharmacies.

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Idiopathic Congenital Talipes Equinovarus in Wisconsin Newborns: Incidence and Associated Risk Factors

Brooke J. Olson, BS; Scott Van Valin, MD; Xue-Cheng Liu, MD, PhD

ABSTRACT

Introduction: Clubfoot, also known as idiopathic congenital talipes equinovarus, is one of the most common pediatric deformities affecting 1 to 2 in every 1,000 live births. We sought to provide the first known analysis of incidence of clubfoot diagnoses in the most populous region of Wisconsin as well as risk factors associated with the deformity.

Methods: We conducted a retrospective study on children treated for clubfoot at Children's Wisconsin from January 1, 2004, through December 31, 2018. To examine trends, we performed a linear trend of annual clubfoot births for each county covered as well as the southeastern region of Wisconsin. We also analyzed common risk factors associated with clubfoot.

Results: The study population included 760 patients diagnosed with clubfoot: 497 males and 263 females. Most patients were non-Hispanic/Latino (76.8%) and White (72.2%). A total of 414 patients (54.4%) had no family history of clubfoot, 130 patients (17.1%) had a positive family history of clubfoot, and family history was unknown for 216 patients (28.4%). The southeastern region of Wisconsin contained the largest patient population (n = 523) and, among counties studied, Milwaukee County had the largest patient population (n = 269). Linear trends for Milwaukee County and the southeastern region of Wisconsin showed a statistically significant increase in clubfoot births from 2004 through 2017 ($P < 0.001$).

Conclusions: In this study of children diagnosed with clubfoot, high population areas showed a statistically significant increase in the number of children affected over time, with a low evidence of family history. This study provides further insight into the possible etiology of clubfoot being influenced by an exogenous, environmental factor.

INTRODUCTION

Idiopathic congenital talipes equinovarus, also known as clubfoot, is one of the most common pediatric deformities, affecting 1 to 2 newborns in every 1,000 live births.[1] While an effective treatment method has been established, the prevalence of clubfoot in the newborn population has given rise to concerns regarding the possible etiologies of the deformity. Multiple theories have been proposed, including aspects of genetics, maternal demographics, and some environmental factors, with no single hypothesis predominating in literature.

Myriad risk factors have been associated with clubfoot, including male sex, family history, maternal smoking, and amniocentesis. Studies exploring the role of population density in the development of clubfoot are relatively rare in the literature. While changes in incidence of clubfoot births may not be related entirely to population density, as there may be multiple factors of influence, it is valuable to look at this trend to assess if changes have occurred. Whether they are demographic, environmental, or unknown, any factor affecting the diagnosis and development of clubfoot is worth noting.

The objective of this study is to provide the first known analysis of incidence of clubfoot diagnoses over a defined time period in the most populous region of Wisconsin. We hypothesize that if there are no exogenous factors of influence, incidence of clubfoot births over time should remain relatively unchanged. This study also provides an analysis of certain risk factors associated with clubfoot diagnosis, comparing our findings to current published literature.

METHODS

This study was a retrospective analysis utilizing electronic medical records (Epic Systems, Verona, Wisconsin) to collect infor mation

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on all clubfoot diagnoses encountered at Children's Wisconsin from January 1, 2004, through December 31, 2018. This includes diagnoses made at the institution's MAIN campus in Milwaukee, Wisconsin, as well as Children's Wisconsin-affiliated locations throughout Wisconsin. A clubfoot diagnosis code was utilized to search for charts of interest. Risk factor data were collected via the patient's medical record. Data collection was limited by availability of variables within a patient's record. To evaluate the incidence of clubfoot births, annual birth rates were collected via the Wisconsin Department of Health Services for the years 2004 through 2017 per county and region. (Population data were available only through 2017, despite data collection through 2018). The institutional review board approved this study and waived the parental consent requirement since the study analyzed previously collected data.

Study Population

To be eligible for inclusion in this study, patients had to be born in Wisconsin with a documented diagnosis of idiopathic congenital talipes equinovarus. Subjects were required to have at least 1 encounter at one of the Children's Wisconsin locations between January 1, 2004, and December 31, 2018. Medical records of more than 1,300 children were reviewed. A total of 760 patients fit the required population criteria and were included in this study.

Variables Collected

To evaluate incidence of clubfoot births by county/region, patients' addresses at birth—including ZIP code and county—were collected. Demographic data collected from chart review included date of birth, sex, ethnicity/race, address, laterality, preterm vs term delivery, birth weight (kg), and family history of clubfoot. Ethnicity was reported as non-Hispanic/Latino or Hispanic/Latino, and race was reported as White, Black, Asian, American Indian/Alaskan Native, American Indian, and other. Laterality of clubfoot was reported as bilateral or unilateral. Preterm delivery was defined as delivery before 32 weeks gestation. Less than 32 weeks gestation was chosen to define prematurity, as this is considered very preterm and is associated with higher rates of death and disability. Researchers wanted to ensure that subjects born before 32 weeks gestation could have a diagnosis more reliably accountable to their pre-term delivery. Family history was reported as yes (positive family history of clubfoot), no (negative family history of clubfoot), or unknown.

Statistical Analysis

Simple linear regression analyses were used to examine linear trends in annual rates of clubfoot births over the 14-year data collection time period. Linear trends were estimated for the entire southeastern region of Wisconsin as well as each county within the region. Observed annual rates were plotted with mean and 95% confidence intervals. Demographic data were summarized by frequencies, and birth weight was further characterized by boxplot. Statistical significance was determined at P value < 0.05.

Table 1. Clubfoot Encounters at Children's Wisconsin per County, 2004-2018

Counties	No. of Clubfoot Births
Brown	47
Clark	1
Columbia	2
Dane	3
Dodge	11
Door	5
Fond Du Lac	25
Grant	1
Green Lake	8
Jefferson [a]	13
Kenosha [a]	27
Kewaunee	4
Manitowoc	24
Marathon	2
Marinette	9
Milwaukee [a]	269
Oconto	7
Outagamie	27
Ozaukee [a]	24
Racine [a]	42
Rock	6
Shawano	4
Sheboygan	20
Vilas	1
Walworth [a]	18
Washington [a]	31
Waukesha [a]	92
Waupaca	3
Waushara	3
Winnebago	30
Wood	1

[a] Counties within the southeastern region of Wisconsin.

RESULTS

Location Data

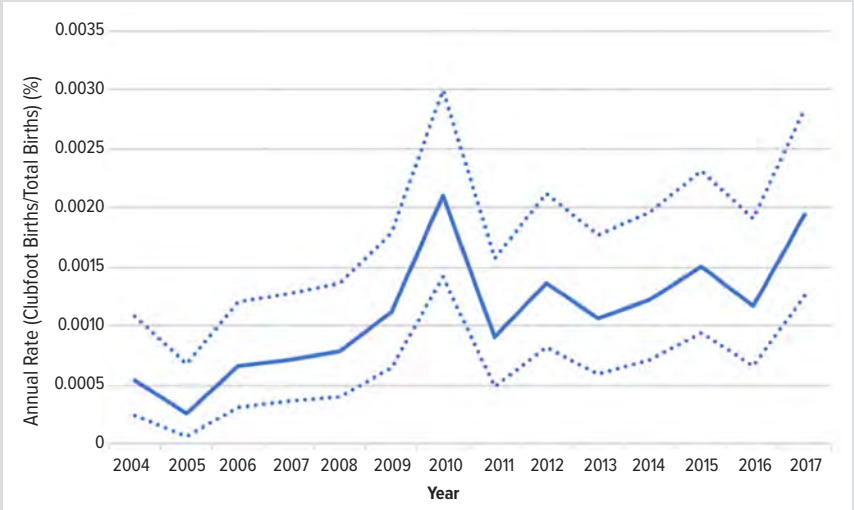
Out of Wisconsin's 72 counties, final population data reached 31 of these counties with coverage of all 5 regions. The majority of clubfoot births (n=523) were recorded in the southeastern region of Wisconsin, with most (n=236) occurring in Milwaukee County (Table 1).

Incidence of Clubfoot Births

Linear trends were plotted for each county in the southeastern region of Wisconsin. Milwaukee County was found to have a statistically significant increase in the incidence of annual clubfoot birth rates from 2004 through 2017 (P for trend < 0.001, $R^2 = 0.5185$) (Figure 1). The linear regression model shows that the annual rate of clubfoot among all births increased by approximately 0.0004 every year. In 2004, approximately 1 in every 2,000 births in Milwaukee County was diagnosed with clubfoot. In 2017, the incidence increased to 4 in every 2,000 births. Overall, there was a 245% increase in the rate of clubfoot births in Milwaukee County from 2004 through 2017.

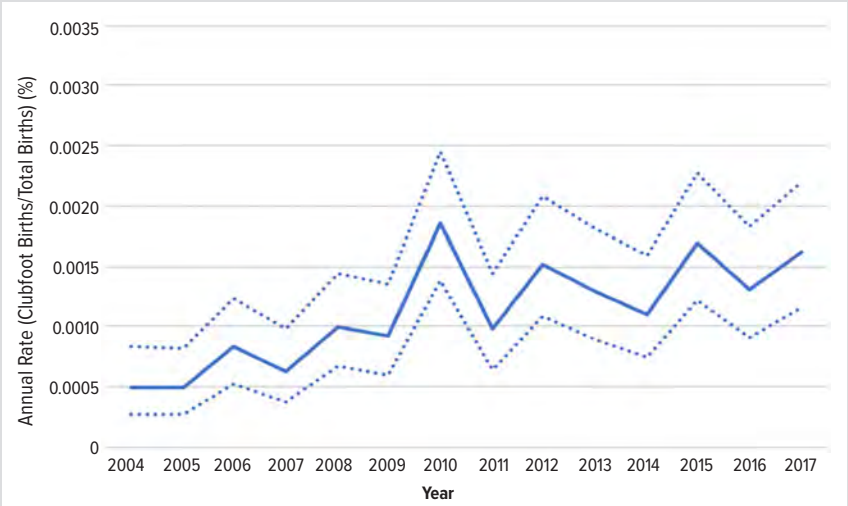
The southeastern region of Wisconsin also experienced a statisti-

Figure 1. Significantly Increased Incidence of Clubfoot Births in Milwaukee County, 2004-2017



Solid line: mean value; dotted lines: 95% CI; *P* value < 0.001

Figure 2. Significantly Increased Incidence of Clubfoot Births in the Southeastern Region of Wisconsin, 2004-2017



Solid line: mean value; dotted lines: 95% CI; *P* value < 0.001

cally significant increase in the incidence of annual clubfoot births over this time period (*P* for trend < 0.001, $R^2 = 0.5958$) (Figure 2). In 2004, approximately 1 in every 2,000 births in the southeastern region of Wisconsin was diagnosed with clubfoot, a rate similar to that of Milwaukee County. In 2017, the incidence rose to 3 in every 2,000 births. Overall, there was a 224% increase in the rate of clubfoot births in the region from 2004 through 2017.

Population Demographics

This study included a population of 760 patients with clubfoot: 497 males (65.4%) and 263 females (34.6%). The majority of patients were non-Hispanic/Latino (76.8%) and White (72.2%). Most (81.1%) were born at term, and unilateral vs bilateral clubfoot birth rates were nearly equal. Average birthweight was 3.068 kg (median 3.180 kg) (Figure 3). A total of 414 patients (54.4%) had no family history of clubfoot, 130 patients (17.1%) had a positive family history of clubfoot, and family history was unknown for 216 patients (28.4%). Populations demographics are shown in Table 2 and Figure 3.

DISCUSSION

This retrospective study showed a significantly increasing annual rate of clubfoot births over a 14-year period, specifically in the most populous areas in Wisconsin. The data do not support the hypothesis that clubfoot birth rates remained stable in Wisconsin from 2004 through 2017. We hypothesized that if clubfoot is a purely genetic phenomenon with no exogenous, environmental factors of influence, then the annual clubfoot birth rate should not change significantly over time. Moreover, a majority of our population reported no family history of the deformity.

Interestingly, a recent report analyzing trends of the most common birth defects in the United States found that the prevalence of clubfoot remained relatively stable from 2010 through 2014.[2] However, Wisconsin data were not included in this study, and one must consider if the southeastern region of Wisconsin has been subject to factors that impact the diagnosis and development of clubfoot.

In a comprehensive 2018 meta-analysis and systematic review on the etiology of clubfoot, family history was noted as the strongest predictor of clubfoot diagnosis.[1] Studies have reported that 24% to 50% of all patients with isolated clubfoot report a positive family history.[3] Our study, while limited by the unknown percentage (28.4%), reports a positive family history in 17.1% of our population (Table 2). Yet even if the unknown percentage of family history were considered, most of the study population still reports a negative family history of clubfoot. Family history points toward clubfoot being dependent on genetic predisposition. While genetics have been studied in reference to clubfoot development, only associations have been made; no sole genetic cause of clubfoot has been identified.[4] Genetics certainly may play a role in the pathogenesis of clubfoot,

but our analysis suggests that the etiology may be multifactorial.

Our study is not the first to suggest that exogenous factors impact clubfoot pathogenesis. Maternal smoking, maternal selective serotonin reuptake inhibitor (SSRI) use, and regional and seasonal variation have been linked to clubfoot development. Chen et al noted that maternal smoking has been shown to have a strong gene-environment association, having a significant association with clubfoot.[1] Multiple studies support this finding.[5-13] Prescription drug use also has been explored as a possible risk factor for clubfoot development. One of the most common complications during pregnancy is the development of depression, with up to 70% of women reporting symptoms of depression during pregnancy.[14] SSRIs are the most commonly prescribed antidepressant in pregnant women and have been found to have an association with clubfoot.[1,15-17] It is hypothesized that this may be due to the vasoconstrictive effects of serotonin compromising uterine blood flow.[18]

Literature on possible environmental factors associated with clubfoot is limited. A similar study conducted in Denmark by Krogsgaard et al reported an incidence of clubfoot that was significantly correlated with population density.[19] This is consistent with findings reported in our study. Milwaukee County is the most populous county in Wisconsin and the city of Milwaukee is the 31st most populous in the United States.[20] It is well known that areas of higher population density are more exposed to environmental stressors, such as pollution, viral illness, noise, crowding, and air quality. Generally, areas of higher population density also are associated with increased use of alcohol, tobacco, and illicit drugs. Galiatsatos et al concluded that tobacco store density and neighborhood socioeconomic factors were associated with the prevalence of maternal smoking while pregnant, a well-known risk factor correlated with clubfoot.[21] Higher population density areas are also associated with increased stress of daily living and higher rates of mental illness.[22] Specifically, living in areas characterized by ethnic segregation has been associated with greater risks of depression and anxiety,[23] and based on 2013-2017 data, Milwaukee is the most segregated city in the nation.[24] Increased rates of anxiety and depression come with increased use of SSRIs as a treatment method—another risk factor significantly associated with clubfoot.

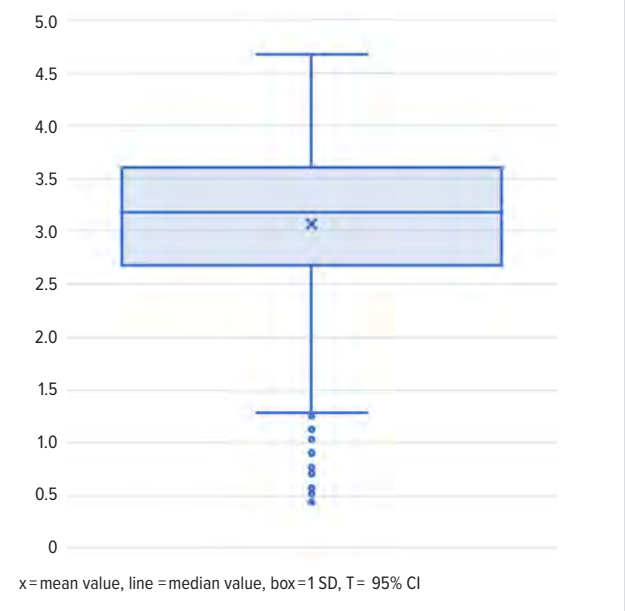
Our study's demographic data show a male-to-female ratio of 1.89:1. Male preponderance with a male-to-female ratio near 2:1 in the diagnosis of clubfoot is a well-known finding that has been reported consistently in literature.[4,5,8] Our study also found a nearly 50:50 ratio on unilateral vs bilaterally affected clubfeet—another common finding that has been reported consistently in literature.[25] Preterm birth was not a predominant finding in our study. Our population's mean and median birthweight values were considered normal and healthy. Additionally, while the literature does not consistently report a specific ethnicity/race as a predisposing risk factor, a majority of our population was non-Hispanic/Latino and White.

Given that this is an observational study, the scope of our findings is limited as we cannot demonstrate definitive causality. The increase in incidence of clubfoot diagnoses could be explained by myriad factors not mentioned in our study. Our study was also limited by the inability to gather information on the mothers of our subjects, which would have provided more data and helped us to better understand our population's exposures. In the future, a prospective study with a survey of mothers would be needed to

Table 2. Risk Factor and Laterality Data

Sex	**n=760, n (%)**
Male	497 (65.4%)
Female	263 (34.6%)
Laterality	**n=760, n (%)**
Unilateral	384 (50.5%)
Bilateral	376 (49.5%)
Term vs Preterm	**n=718, n (%)**
Term	582 (81.1%)
Preterm	136 (18.9%)
Race	**n=760, n (%)**
White	549 (72.2%)
African American	120 (15.8%)
Unknown	51 (6.7%)
Asian	19 (2.5%)
White/African American	12 (1.6%)
American Indian/Alaskan Native	4 (0.5%)
Other	3 (0.4%)
Asian/African American	1 (0.1%)
White/American Indian	1 (0.1%)
Ethnicity	**n=760, n (%)**
Non-Hispanic/Latino	584 (76.8%)
Hispanic/Latino	89 (11.7%)
Unknown	87 (11.4%)
Family History	**n=760, n (%)**
No	414 (54.4%)
Yes	130 (17.1%)
Unknown	216 (28.4%)

Figure 3. Boxplot of Clubfoot Births (kg), n = 483



gather this information. We were also limited in our ability to collect data from hospitals not affiliated with Children's Wisconsin. While Children's Wisconsin has multiple locations throughout the state, it cannot be assumed that all diagnoses of clubfoot were treated at a Children's Wisconsin institution. This would have provided us with a larger, more comprehensive patient population.

CONCLUSION

This study found a significantly increasing rate of clubfoot births in the most populous areas of Wisconsin, with a negative family history in the majority of patients. Notably, other regions of the country reported a stable prevalence of clubfoot during a portion of our study's timeframe. Our investigation provides further insight into the possible etiology of clubfoot relating to exogenous, environmental factors. These possible exogenous determinants are not known at this time but could be related to myriad factors, including population density, changes in the prevalence of maternal smoking or SSRI use, and age of conception. This is speculative and further research is needed to investigate what these possible factors of influence may be.

This study also provides an analysis of commonly studied risk factors associated with the diagnosis of clubfoot, including support for male preponderance. Future research should provide additional analyses of clubfoot birth rates in other highly populous cities, along with further geographical characterization to pinpoint highly affected areas. Future research is also needed to further explore possible exogenous factors of influence in the development of clubfoot, which could account for the significantly increasing incidence found in our study.

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Telehealth in Genetics: The Genetic Counselor Perspective on the Utility of Telehealth in Response to the COVID-19 Pandemic in Wisconsin

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ABSTRACT

Background: Due to the COVID-19 pandemic, many genetics clinics across the country were prompted to integrate telephone visits and videoconferencing into their practice to promote the safety of patients and clinic staff members. Our study examined providers' perspectives on the utility and effectiveness of these telehealth-based clinic visits in response to the COVID-19 pandemic in Wisconsin.

Methods: An anonymous Qualtrics survey was distributed via email in October 2020 to all members of the Wisconsin Genetic Systems Integration Hub and the Wisconsin Genetic Counselor Association. Current clinical genetic providers were eligible to participate in the survey. The survey assessed providers' experiences and perceptions toward utilizing telehealth in delivering clinical genetic services to their patients during the pandemic.

Results: Forty-seven currently practicing clinical genetic counselors in Wisconsin either partially or fully completed the survey. Nearly all respondents somewhat (23%) or strongly (75%) wanted to incorporate telehealth in the future, primarily because of perceived improvements in clinic functioning. Patients with suboptimal telecommunications capacities were considered the most challenging aspect of telehealth, and better technology support was the most frequently cited strategy for addressing current telehealth limitations.

Conclusion: Clinical genetic counselors in Wisconsin generally reported positive experiences integrating telehealth into their patient care during the COVID-19 pandemic. Many counselors see telehealth as a way to increase access to genetic services and, with better technology support from their institutions, would support utilizing telehealth in their clinical practice.

BACKGROUND

Due to the COVID-19 pandemic, many outpatient clinics across the country and globally were prompted to integrate telehealth delivery modalities into their clinical practice, either by telephone, videoconferencing, or a combination of both to promote the safety of patients and clinic staff members. From their experiences during the pandemic, several medical clinics noted the feasibility of utilizing telehealth in various specialties and commented that telehealth may have a significant effect in reshaping and advancing health care in the future.[1-3] The experiences were similar in clinical genetics, where telehealth genetic counseling was viewed to be a viable alternative model to in-person counseling and allowed uninterrupted access to genetic services during the pandemic.[4-6]

Providing patient care via telehealth is not new in clinical genetics. As the demand for genetic services has continued to rise, telehealth has been increasingly utilized by genetic professionals in efforts to improve patient access and mitigate health disparities in underserved communities.[7-10] In addressing the issue of workforce shortage of clinical genetic professionals, telehealth has proven successful in increasing clinic appointment availability and patient volume and decreasing patient wait times.[11] However, many states across the country, including Wisconsin, continue to face the supply and demand imbalance of clinical genetic providers in meeting patient referral needs.[12,13] In fact, a 2020 study confirmed a workforce shortage of direct patient care genetic

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counselors in Wisconsin that resulted in long patient wait times and an inequitable distribution of services throughout the state.[13] As it is expected that telehealth will continue to be utilized by genetic providers to meet patient needs in Wisconsin and likely other regions, it is important to learn providers' perspectives of telehealth—especially now that many have experience providing patient care via telehealth during the COVID-19 pandemic.

Prior to the pandemic, past studies have reported high provider and patient satisfaction towards clinical genetic services being delivered via telehealth.[8-10,14] Many genetic providers showed strong interests in learning and implementing innovative service delivery models like telehealth to improve access and efficiency in their clinical care.[15-17] However, the pandemic affected genetics clinics differently as providers had to quickly transition and adapt to using telehealth in their clinical practice with no other option. Our study aimed to examine providers' perspectives on the utility and effectiveness of telehealth in response to the COVID-19 pandemic in Wisconsin.

METHODS

Recruitment and Eligibility

Study participants were recruited from the Wisconsin Genetic Systems Integration (GSI) Hub and the Wisconsin Genetic Counselor Association (WIGCA) electronic mailing lists. All members—including genetic counselors, geneticists, researchers, and other genetic professionals—were invited to complete an anonymous online survey via email. Participants provided their consent by reviewing the initial consent page and then continuing with the survey. Eligibility was limited to clinical genetic providers who were currently providing clinical care to patients in Wisconsin. To determine the participant's eligibility, the first survey question asked if they currently provided clinical genetic services for patients living in Wisconsin. Only those who answered yes were allowed to complete the rest of the survey. The initial study invitation email was distributed in early October 2020, followed by a reminder email 2 weeks later. A final reminder email was sent 2 weeks after the first follow-up email. The survey stayed open until the end of November 2020. The Education and Social/Behavioral Science Institutional Review Board at the University of Wisconsin-Madison determined that the study met criteria for exemption (IRB#2020-1253).

Survey Instrumentation

A 39-item survey that included multiple choice, dropdown, slider, Likert scale, and open-ended response questions was developed, designed, and analyzed using Qualtrics, University of Wisconsin-Madison version (Qualtrics 2019). Survey items were designed by manuscript authors (SHC, MNS, CAR, MSM, and EMP) to explore genetic providers' experiences providing clinical genetic services to their patients via telehealth during the COVID-19 pandemic. The survey was then pretested by genetic counseling and medical students, as well as a clinical genetic counselor. For ease and equity of analysis, a timeline for the spread of COVID-19 was established. We defined the beginning of the pandemic as March 1, 2020, the early spread as between March 1, 2020 and July 1, 2020, and the current spread as between July 1, 2020 and the current date in which the participant completed the survey in October 2020 through November 2020. With the established timeline, the survey included questions on: (1) basic demographics, (2) providers' telehealth experiences prior to the spread of COVID-19, (3) providers' telehealth experiences during the early spread of COVID-19, (4) providers' telehealth experiences during the current spread of COVID-19, and (5) providers' perspectives on the effectiveness and utility of telehealth.

Data Analysis

Characteristics of the close-ended questions were summarized using basic descriptive statistical analysis (frequencies and percentages), and an inductive thematic analysis was used for analyzing the open-ended questions following the 5 analysis phases: familiarizing with data, generating initial codes, reviewing themes, defining and naming themes, and producing the report.[18] First, the corresponding author (SHC) read through the open responses and generated initial codes and themes. Then a second author (LER) helped define the themes and subthemes. To establish intercoder reliability, the 2 authors separately coded the responses and later discussed to reach a consensus on any discrepant items. The intercoder percent agreement between the 2 coders before reaching a consensus on any discrepant item was approximately 94%.

Two specific subgroups—those with any experience in cancer genetics (yes/no) and those whose primary work was in a university or academic setting (yes/no)—were identified to determine whether survey responses were associated with these subgroups. Survey responses concerning their opinions about telehealth on important elements were ordinal in nature (eg, ranging from strong disagreement [-2 points], through neutral [0 points], up to strong agreement [+2 points], or from "not at all" [0 points] to "extremely" [4 points], and were compared between subgroups using the Wilcoxon rank-sum test. Changes in opinion between early and current COVID-19 time periods were assessed using the signed-rank test to understand whether any shift had occurred over time; tests for differences between subgroups (yes vs no) with respect to these changes in opinion over time were again compared using the rank-sum test. Analyses were done using R (version 4.0.4).[19] No adjustment for multiple testing was done for this exploratory hypothesis-generating research and *P* values are provided solely for descriptive purposes.

RESULTS

Demographics of Survey Respondents

A total of 57 individuals either partially or fully completed the survey. Seven individuals were excluded from analysis as they did

not indicate as clinical genetic providers on the eligibility screening question. Of the 50 individuals who indicated as clinical genetic providers, 47 (94%) were genetic counselors, and the remaining 3 (6%) were MD/DO clinical geneticists. Because of the smaller sample size of MD/DO clinical geneticists and differences in scope of practice between genetic counselors and geneticists, further analysis was restricted to those 47 genetic counselors who provided clinical genetic services for patients living in Wisconsin. As all survey questions were optional, N varied by each question.

In 2020, there were approximately 110 genetic counselors who self-reported their clinical work or were members of the WIGCA in Wisconsin, according to the WIGCA. With this information, we estimated a response rate of 43% (47/110). Among the 47 genetic counselors who responded to the survey, 22 (47%) listed exactly 1 type of specialty and 25 (53%) listed involvement with 1 or more specialties. Demographic results are described in Table 1.

Table 1. Demographics of Survey Respondents

	n	(%)
Specialty (may choose more than 1) (N=47)		
Cancer	25	(53)
Prenatal	25	(53)
General genetics	24	(51)
Other clinical specialty	14	(30)
Other nonclinical specialty	2	(4)
Primary work setting affiliated with academic health center (N=40)		
Yes	23	(58)
No	17	(43)
Region of Wisconsin where majority of patients are seen (N=46)		
Southeastern	19	(41)
Southern	13	(28)
Western	6	(13)
Northeastern	5	(11)
Northern	3	(7)
Prior telehealth experience before COVID-19 (N=45)		
Yes	12	(27)
No	33	(73)

Changes in Perspectives Between Current and Early COVID-19 Spread

Participants were asked to rate from strongly disagree to neutral to strongly agree on questions about having sufficient training, comfort of use, sufficient technical support, and ability to bill for services with telehealth during the early and current spread of COVID-19 (Appendix). Differences in scores between the 2 time periods are shown in Table 2. Scores tended to improve over time by an average of 0.3 to 0.7 points, though the degree of change did not differ between genetic counselors who practiced in cancer specialty and those who did not ($P > 0.15$). Likewise, the degree of change did not differ between those who worked in an academic health center and those who did not. In looking at the frequency distributions and after discounting the large number of changes equal to zero, there still remains a strong asymmetry, with an excess of positive change scores relative to negative changes for all 4 items ($P < 0.001 \sim 0.002$).

Table 2. Change in Scores Between Current and Early Spread of COVID-19

Current—Early	N	*P* value[a]	Mean Change
I've received sufficient training in telehealth prior to utilizing it	35	<0.001	0.514
I am comfortable using the mode of telehealth utilized in my clinic	36	0.002	0.306
I had sufficient and readily available technical support when needed	36	0.002	0.417
I was able to bill for telehealth services	32	0.001	0.688

[a]*P* value of change in scores over time between current and early spread of COVID-19.

Effectiveness of Telehealth

Summarized in Figure 1, most genetic counselors viewed telehealth as moderately to extremely effective when assessing various components of a genetic counseling session. Collecting family history via telehealth had the highest number of responses (92%) reporting as very or extremely effective. On the other hand, about 60% of respondents reported that using visual aids via telehealth was either slightly effective or not effective at all. "Not applicable" responses were excluded from these calculations.

Current Perception of Telehealth

The majority of genetic counselors who responded to the survey had a positive perception towards telehealth after experiencing it during the pandemic. As shown in Figure 2, almost all respondents agreed that telehealth is an efficient way to provide care to their patients. They were also interested in incorporating telehealth in the future. All respondents believed that they could provide good care to their patients via telehealth and that their patients can benefit from telehealth visits. No one reported disagreement to these statements.

Open Response Themes

The most common aspect of telehealth that went well for the counselors included improvement in clinic functioning (42%, n = 47/113) that was most often related to increased access for patients (eg, people who live far away or cannot travel due to health complications) (32%, n = 15/47). Many counselors found it difficult to counsel patients who had communication barriers (34%, n = 23/68) via telehealth. Specifically, they had challenges providing quality care to patients with low health literacy or learning difficulties (35%, n = 8/23), as well as those who were not proficient in English and required interpreter services (30%, n = 7/23). When asked about ways to improve the current mode of telehealth utilized in their clinical practice, 70% (n = 31/44) of the responses were related to better technology support from their institutions. Twenty-nine percent (n=9/31) of these responses

Figure 1. Genetic Counselors' Views on the Effectiveness of Telehealth

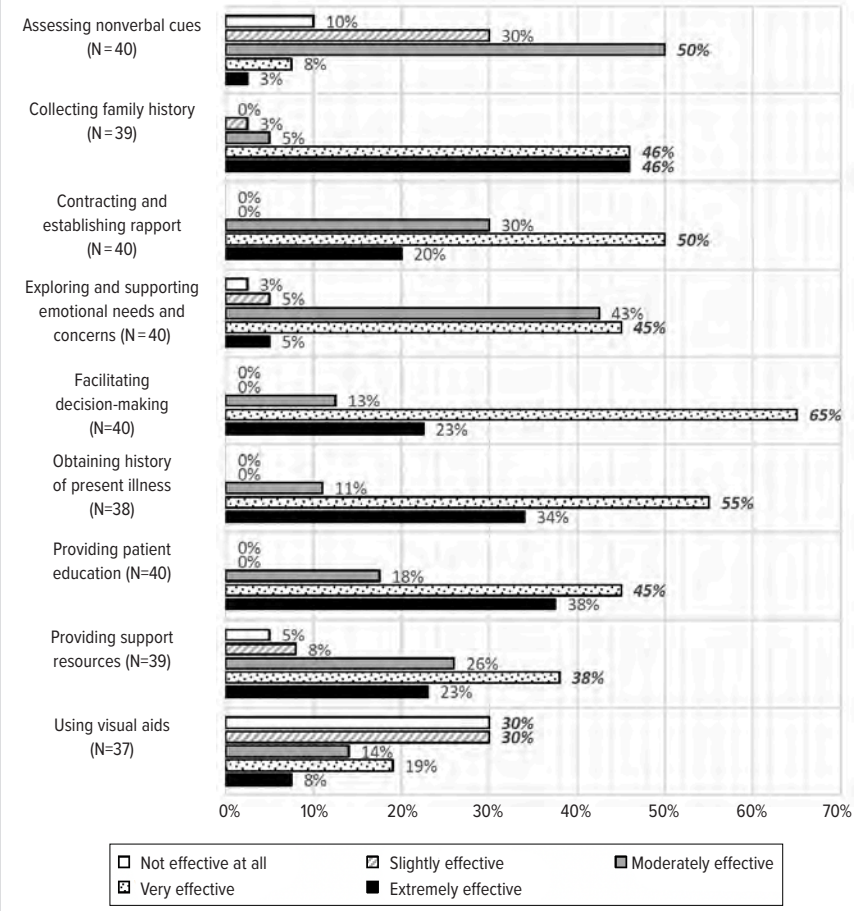
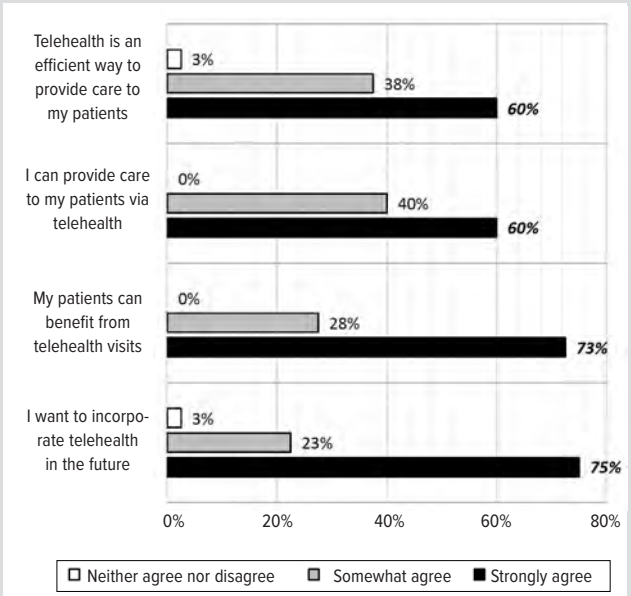


Figure 2. Genetic Counselors' Views on the Utility of Telehealth (N=40)



None of the survey respondents selected somewhat disagree or strongly disagree.

commented specifically on better equipment and device support that have video capabilities. Main themes and representative quotes are shown in Table 3A-C. All themes and subthemes are represented in the Appendix.

DISCUSSION

Telehealth has increasingly become an essential tool utilized in clinical genetics as providers try to balance the supply and demand of clinical genetic providers, as well as provide safe clinical services during a pandemic.[12,13,15,16] While previous studies have proven telehealth to be a viable alternative delivery model in clinical genetics, the COVID-19 pandemic prompted nearly all providers to quickly transition into integrating telehealth delivery models. Hence, the experiences of genetic providers with telehealth may differ prior to and during the pandemic. Better understanding of provider perspectives on the utility of telehealth is needed to identify effective ways to optimize clinical genetic services for both patients and providers, not only in Wisconsin but also across the country.

Overall, the majority of genetic counselors who participated in this study had a positive experience providing clinical genetic services via telehealth during the pandemic. Collecting family history, contracting, facilitating decision-making, obtaining history of present illness, providing patient education, and providing support resources were most commonly reported as very or extremely effective. Assessing nonverbal cues, exploring and supporting emotional needs and concerns, and using visual aids were not rated as highly as effective, but it is possible that this is due to the lack of video and/or screen sharing capabilities, which was a common theme in the open responses. Interestingly, some open responses mention that telehealth was more effective in assessing nonverbal cues because personal protective equipment such as masks were not required on video, whereas masks and face shields were required for in-person visits during the pandemic.

As there have been past studies evaluating telehealth in cancer genetic counseling, the survey looked to assess possible differences in providers' experiences between those who worked in cancer specialty and those who did not.[14,20] The survey also looked for potential differences between whether the genetic counselor worked in an academic health center, as support resources may vary depending on the type of institution. Our study data did

not reveal any differences in these groups. However, scores generally improved from the early spread to the current spread of COVID-19 when assessing the provider's experience with training, level of comfort, technical support, and billing for telehealth services, which suggests that genetic counselors had a positive experience with telehealth as the pandemic progressed. While there was some suggestion (P = 0.05) that counselors in an academic setting tended to gain a greater sense of comfort using telehealth over time compared to those in a nonacademic setting, the sample size was too small to make a strong statistical argument.

Additionally, genetic counselors in our study had strong interests in telehealth to improve patient access and efficiency in their clinical care, similar to what has been shown in a few past studies.[15-17] Ninety-eight percent of counselors wanted to incorporate telehealth in the future and agreed that telehealth is an efficient way to provide care to their patients. One individual had neutral views, which shows that none were in disagreement. Importantly, all of the counselors indicated that they could provide good care to their patients via telehealth and that their patients would benefit from telehealth visits. This demonstrates great confidence in the provider and the care that they are providing to their patients via telehealth.

Improvement in clinic functioning was the most common theme reported when providers were asked to state the aspects that went well with telehealth during the pandemic. Increasing access for patients and fewer no-shows were the 2 common subthemes identified in improvement in clinic functioning. This was consistent with other genetic clinics implementing telehealth during the pandemic where there was a decrease in patient no-show rates.[6,21] Although our study did not directly capture the patient perception of telehealth visits, many genetic counselors reported increased patient satisfaction, which may be viewed as a positive indication for continuing telehealth services in genetics clinics.

Table 3. Open Response Main Themes (More Than 1 Response Allowed)

Theme	n (%)	Representative Quotes
A. List at least 3 aspects of telehealth that have been working well for you. (N = 37)		
Improvement in clinic functioning	47 (42)	*Increasing access to patient care because it reaches throughout the state without travel restriction.*
		The no show rate for patients has dropped significantly so more patients are being seen.
Increased patient satisfaction	20 (18)	*Patients state that they love not needing a babysitter or can just take a break at work rather than having to drive into the clinic.*
		Patient satisfier due to expanded access to genetics services.
Ability to provide comparable care to in-person visits	19 (17)	*Rapport–I was concerned about this but patients seem very at ease and open when we meet.*
Improvement in provider work/life balance	15 (13)	*Being able to work from home (reducing commuting times).*
Minimized exposure to COVID-19 for staff and patients	7 (6)	*Safer for the patient (who usually is pregnant and therefore in a high-risk COVID group) and safer for me to not be in a room alone with them.*
Other	5 (4)	*Can have more resources available during the session.*
B. What types of patients do you find most challenging to provide optimal clinical care through your current use of telehealth (video, phone, or other virtual means)? (N = 37)		
Patients who have communication barriers	23 (34)	*Patients with intellectual disability (ID) or developmental disability (DD). It is harder to engage on a video screen especially when hands on aids would be appropriate.*
		Deaf or patients that speak another language other than English where an interpreter is needed.
Patients who are distracted by their surroundings	14 (21)	*Because patients are doing the appointments from home, some are very distracted by their surroundings.*
		Those who try to do an appt at work/driving–not treat ing as formal appointment.
Patients who are required to be seen in clinic	13 (19)	*Patients where physical exam is critical for determining test/evaluation recommendations.*
Patients who have issues with technology	9 (13)	*I see their forehead or no part of them, certainly not their face, making connection more challenging.*
Patients who are difficult to engage in conversation	4 (6)	*Patients with a flat affect, it's even more difficult to assess their emotional state.*
Other	3 (4)	*Family visits where an adult child accompanies Medicare-aged proband.*
C. How would you improve the current mode of telehealth utilized in your clinical practice? (N=32)		
Better tech support	31 (70)	*Support for video telehealth.*
		Better explanation of telehealth process (login, launch, setup, etc) to minimize delays in starting appointments due to patient technical issues.
		I would like the telehealth session to be integrated with Epic like Zoom for health care.
		Be able to more easily send files to the patient. Find some way for a patient to make an e-signature on a visit.
Ability to bill/get reimbursement	7 (16)	*ALLOW GENETIC COUNSELORS TO BILL FOR TELEHEALTH SERVICES!*
Sample handling for genetic testing	2 (5)	*More training of nurses and lab professionals in my institution on the genetic testing kit preparation as this was the reason I was told I had to return to in-person visits almost 100% of the time.*
Telehealth is going smoothly	2 (5)	*It is as good as it could be currently.*

When providers were asked to list the most challenging types of patients to provide optimal clinical care via telehealth, about a third of the responses referred to patients who have communication barriers that included subthemes of patients with low health literacy and those who are not proficient in English. It is possible that many counselors either did not have interpreter services available to communicate with their patients or faced challenges in incorporating interpreter services with the current mode of telehealth being utilized in their clinic. Genetic counselors also had difficulty counseling patients who were distracted by their surroundings, which was observed in earlier studies prior to the pandemic.[20,22]

To improve the overall delivery of clinical genetic services via telehealth, the majority of genetic counselors who responded to the survey desired better technology support. It was apparent that many of them lacked tech support from their institutions, as several commented about not having the appropriate equipment and device. They specifically wanted better equipment with live video and audio, which they thought would help in providing high-quality patient care. Genetic counselors also suggested implementing training and education materials for patients in preparation of their telehealth visit and advocated for the ability to bill and receive reimbursement for telehealth genetic counseling. Until there is a policy change that includes new billing and coverage models, it seems difficult for genetic counselors to be granted the support they need in order to provide optimal genetic services to their patients.[15,16]

Study Limitations

It is important to note that our study had a small sample size of genetic providers from a single state, Wisconsin. Some questions had a smaller sample size due to participants not answering every survey question. It is possible that those who responded to the survey might have had a more favorable view of telehealth. While there were participants who had experience with telehealth prior to the COVID-19 pandemic, completing a full longitudinal analysis of the different time periods was unreasonable because of the small and inconsistent sample size. Additionally, our predefined dates of different phases during the pandemic may not hold any significance in thinking about the early or current spread of COVID-19.

Another important consideration is that the open responses were analyzed by 2 authors and no formal qualitative analysis was completed. Hence, while the most common theme for improving telehealth services was better technology support, it is difficult to distinguish in some responses whether the response referred to better support for the provider or for the patient. Lastly, the study data do not directly compare the effectiveness between telehealth and in-person visits but rather evaluates the genetic provider experiences with telehealth visits during the pandemic.

Future Directions

As much as it is significant to learn about the provider perspective of telehealth, it is imperative that we explore the patient perspective to consider creative methods to improve access to genetic services. A larger study exploring both provider and patient telehealth experiences during the pandemic would offer a more complete assessment, especially comparing the experiences between communities that have adequate access to genetic services and those that are underserved. As we restricted our study analysis only on genetic counselors; it would be meaningful to evaluate the perspectives of other genetic providers, including MD/DO geneticists, nurse practitioners, physician assistants, and other genetic providers who provide clinical genetic services. Additionally, as several study participants suggested in their open responses, implementing a hybrid model of both in-person and telehealth visits in genetics clinics would be beneficial and effective for patients and providers.

CONCLUSION

Clinical genetic counselors in Wisconsin generally had a positive experience integrating telehealth into their patient care during the COVID-19 pandemic. Their experiences improved as the pandemic progressed. Almost all of them reported that they would like to incorporate telehealth in the future, as many believed it to be effective in providing optimal genetic services to their patients. One silver lining of the COVID-19 pandemic for clinical genetics is that virtually all genetic counselors have now had experience with telehealth, which may be an asset for ongoing delivery of timely genetic counseling services. While in-person visits will certainly need to be available for patients who are required to be seen in clinic, with better technology support from their institutions, many genetic counselors seemed interested in utilizing telehealth in their clinical practice—especially as a way to increase access to genetic services for patients.

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Hereditary Angioedema: A Review

Heidi Zafra, MD

ABSTRACT

Hereditary angioedema (HAE) is a rare and disabling disorder wherein there is excessive bradykinin production, with subsequent increased vascular permeability in the superficial tissues and gastrointestinal and respiratory mucosa. This article serves as a review of the pathogenesis of the disease, as well as an update of the evidence-based new treatment recommendations to help clinicians with the diagnosis and management of HAE.

CLINICAL CASE

A 13-year-old White female presented to the emergency department with swelling and pain of the right arm. There was cyanosis of her right distal arm and hand. She underwent emergency fasciotomy because of compartment syndrome. On postoperative day 2, her right arm continued to improve; however, she began to develop edema of the left hand. Her past medical history included recurrent leg swelling and abdominal pain. Family history was significant for the father's diagnosis of hereditary angioedema (HAE). Pertinent laboratory tests showed a complement C4 level that was undetectable (< 6 mg/dL; reference range, 13-44 mg/dL), quantitative C1 inhibitor (C1-INH) 7 mg/dL (reference range, 21-39 mg/L), functional C1 inhibitor 47% (reference range, > 67%). All other labs for infection, allergic, and autoimmune diseases were normal.

The patient was diagnosed with HAE type 1. Early inpatient treatment was started with intravenous (IV) C1 inhibitor 2000 units, and she was discharged with a scheduled 1500 units IV infusion twice weekly and icatibant 30 mg subcutaneous (SQ) injections as a rescue medication.[1] An IV port was placed for C1 inhibitor infusions at home. Over the next couple of years, she underwent several port revisions and replacements due to poor flow and port clotting issues. Despite access difficulties, she remained on C1 inhibitor IV treatments with good control of her symptoms until she had the opportunity to enroll in a clinical trial for lanadelumab. She entered a clinical trial of lanadelumab 300 mg SQ every 2 weeks and continued on this medication when the drug was available commercially. She subsequently entered the clinical trial of berotralstat 150 mg orally and is currently on the commercially available product. She is tolerating this drug well, with minimal breakthrough attacks.

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DEFINITION

Hereditary angioedema (HAE) is a rare disorder caused mainly by the lack of, or diminished function of an enzyme, C1 inhibitor (C1-INH). The end result is the overproduction of bradykinin, which increases localized permeability of blood vessels, resulting in tissue swelling. It is characterized by recurrent facial, abdominal, or extremity swelling—typically without urticaria or pruritus.[2,3]

C1-INH is a member of the serpin (serine protease inhibitor) superfamily, with significant homology to α1-antitrypsin. The gene, named SERPING1, is located on chromosome 11 (p11.2-q13). It is a suicide inhibitor, forming a complex with the target protease, followed by clearance of the entire complex.[2-5]

C1-INH inhibits steps in the classical and lectin complement pathways, intrinsic coagulation pathway (contact system), fibrinolytic pathway, and kinin-generating pathways (most directly related to the pathogenesis of HAE) (Figures 1 and 2).[2,5,6]

Clinical Characteristics

Patients with HAE will complain of episodic, nonpruritic swelling

of skin and submucosal tissues (extremities, abdomen, genitourinary tract, face, oropharynx, larynx). It is usually associated with pain, nausea, vomiting, diarrhea, and possibly life-threatening airway obstruction. A prodromal serpiginous erythematous rash is sometimes seen, but HAE should not have a pruritic urticarial rash. Thus, usually urticaria with pruritus makes the diagnosis of HAE unlikely. The age of onset is variable and may present under 1 year of age. Laryngeal attacks are uncommon before age 3 years and tend to occur later than other symptoms. Angioedema events often worsen with hormonal changes like puberty, the use of estrogen-containing birth control pills, or hormone replacement. Other triggers for HAE attacks include stress, fatigue, infection, mechanical trauma (ie, intubation), and angiotensin-converting enzyme (ACE) inhibitor usage.[3]

Classification

The prevalence of HAE in North America and Europe is about 1.1 and 1.6 per 50,000, respectively.[3] There are different forms of HAE currently recognized: HAE type 1, HAE type 2, and HAE with normal C-INH.

HAE type 1, due to low quantitative and functional C1-INH levels, is an autosomal-dominant disease and occurs in 85% of cases. However, patients do not always have a positive family history. Approximately 25% of the patients with HAE have a de novo mutation in the C1-INH gene (SERPING1). During episodes of angioedema in patients with HAE, plasma bradykinin levels have been shown to be 7-fold higher than normal.[2-4]

HAE type 2 is also autosomal dominant and occurs in 15% of cases. It is characterized by normal quantitative and low functional C1-INH levels. These patients have the same clinical features as HAE type 1.[3]

The primary mediator of swelling in HAE type 1 and 2 is bradykinin, which is generated when plasma kallikrein cleaves high-molecular-weight kininogen. It is metabolized by endogenous metalloproteases like ACE. Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII. Both plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor.[2,3,5]

HAE with normal C1-INH shares the same clinical features of HAE types 1 and 2, but with normal quantitative and functional C1-INH levels. It has been associated with different genetic mutations. One mutation is in the factor XII gene. There have been reports of 2 new mutations in angiopoietin-1 and plasminogen. However, in most patients with HAE with normal C1-INH, no gene mutation can be found and the exact pathogenesis is unknown. There is some evidence that bradykinin may play a role in some types of HAE with normal C1-INH, primarily in patients with a FXII mutation.[2,5]

Figure 1. Kinin Activated Pathway

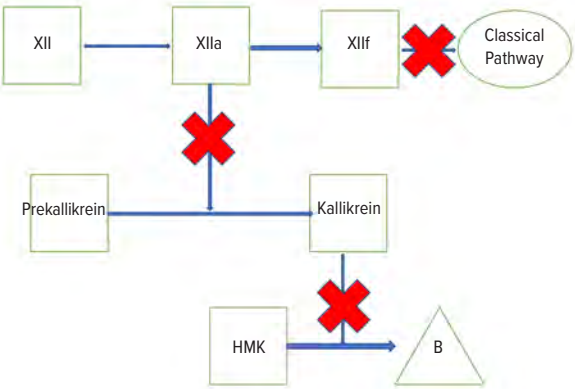
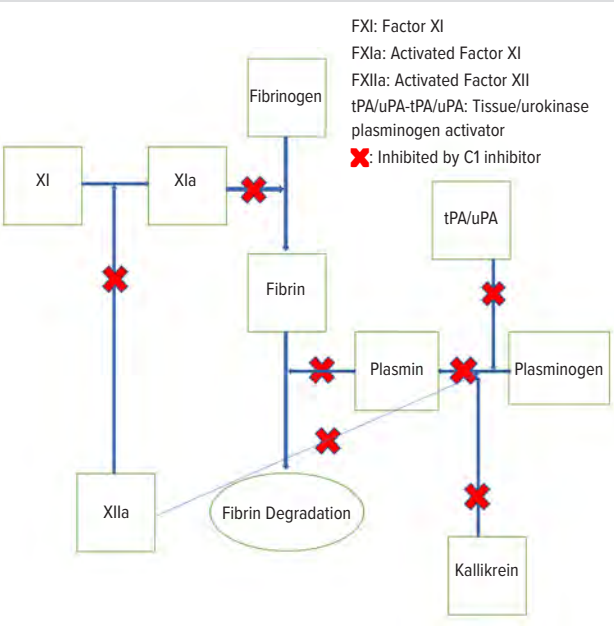


Figure 2. Coagulathion and Fibrinolysis Pathway



Differential Diagnosis

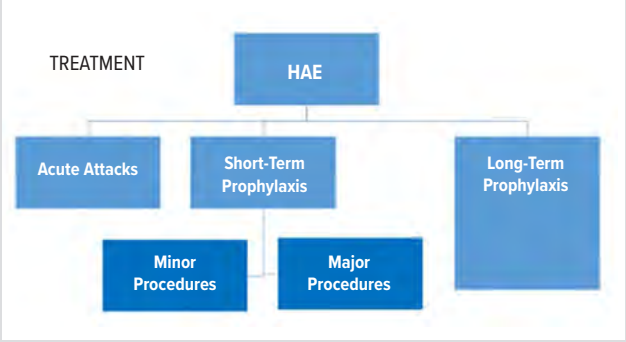
ACE Inhibitor Angioedema: ACE inhibitor angioedema is associated primarily with ACE inhibitor use. It is a bradykinin-induced angioedema that results from medications that increase production or decrease degradation of bradykinin. Other medications implicated in this category include blockers of the renin-angiotensin-aldosterone system like angiotensin receptor blockers (ARB), dipeptidyl peptidase 4 inhibitors, and neprilysin inhibitors. Incidence is about 0.1% to 0.7% of patients on an ACE inhibitor.[7,8] Symptoms prominently involve the face and tongue. Higher

Table. Laboratory Value of the Different Types of Angiodema

	C1-INH Level	C1-INH Function	C4	C3	C1Q
HAE type 1	Low	Low	Low	Normal	Normal
HAE type 2	Normal-High	Low	Low	Normal	Normal
HAE-nC1-INH	Normal	Norman	Normal	Normal	Normal
Acq-AE	Low	Low	Low	Low-Normal	Low
ACEi-AE	Normal	Normal	Normal	Normal	Normal
IAE	Normal	Normal	Normal	Normal	Normal

Abbreviations: CI-INH, C1 inhibitor; HAE, hereditary angioedema; HAE-nC1-INH, HAE with normal C1-INH; Acq-AE, acquired angioedema; ACEi-AE, ACE inhibitor angioedema; IAE, idiopathic angioedema.

Figure 3. Management of Heritary Angioedema (HAE)



risk is shown in African Americans. Other risk factors for ACE inhibitor angioedema include smoking, increasing age, and female sex. Laboratory findings for patients with ACE inhibitor angioedema include a normal C4, normal C1-INH, and normal C1Q. Treatment includes discontinuation of ACE inhibitor angioedema/ARB. Efficacy of icatibant/fresh frozen plasma has been described but has not been reproduced in phase 3 trials and, therefore, is not approved by the US Food and Drug Administration (FDA) for this indication.[9,10]

Acquired Angioedema: Acquired angioedema is angioedema usually associated with lymphoproliferative diseases (lymphoma and autoimmune disorders like systemic lupus erythematosus). Laboratory workup will show a low C4, low C-INH (quantitative and functional), and low C1Q. Acquired angioedema may be associated with C1-INH autoantibodies. Androgens and antifibrinolytics have been used for long-term prophylaxis. Ecallantide and icatibant treatment has been reported to be effective as on-demand therapy for attacks.[11]

Idiopathic Angioedema: Idiopathic angioedema is a diagnosis of recurrent angioedema after having ruled out all other angioedema diagnoses. Idiopathic histaminergic angioedema is the most common form of angioedema observed in clinical practice. Laboratory workup will show a normal C4, normal C1-INH, normal C1Q, and normal tryptase. Since it is mostly histaminergic in nature, initial treatment would include continuous administration of a 4-fold antihistamine dose. After failure of antihistamines, omalizumab, an anti-IgE monoclonal antibody, is suggested for 6 months. Failure of omalizumab suggests an idiopathic, nonhistaminergic angioedema[12] (Table).

TREATMENT

Treatment of HAE type 1 and type 2 consists of on-demand therapy, short-term prophylaxis, and long-term prophylaxis. (See Figures 3 and 4.)

On-demand Therapy: On-demand therapy is given during acute attacks, especially attacks involving the upper airway. Attacks of the airway can be life-threatening and need attention and on-demand treatment immediately. Abdominal attacks could cause extreme pain. Extremity attacks of the hands and feet could be debilitating. Therefore, acute attacks—especially those affecting the airway—should be treated immediately. It is recommended that all patients have sufficient medication for on-demand treatment of 2 attacks and carry on-demand medication at all times.[2,3]

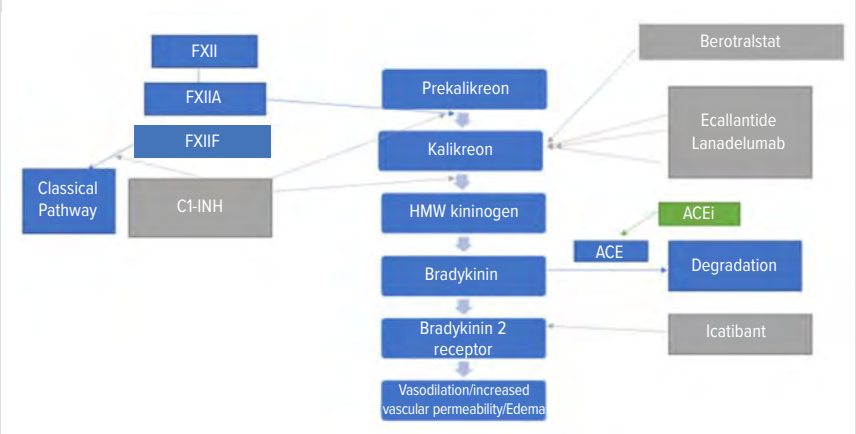
Bradykinin-Receptor Antagonist: Icatibant (Firazyr; Shire) is an antagonist of the bradykinin B2 receptor and prevents binding of bradykinin. When bradykinin binds to the bradykinin B2 receptor, there is subsequent vasodilation and increased capillary permeability. Icatibant is a self-administered on-demand treatment for HAE attacks in adults and children (>2 years) with a plasma half-life of 1 to 2 hours. Allergic reactions have not been reported, but there are reports of transient local injection site reactions (erythema, wheal, pruritus, and burning sensation).[10] Adult dosing for icatibant is 30 mg SQ, which may be repeated every 6 hours for a maximum dose of 90 mg/day. Pediatric dosing for children older than 2 years is 0.4 mg/kg once SQ, with a maximum dose of 30 mg/dose.

C1-Inhibitor Concentrate: Plasma derived C1-INH concentrate or recombinant C1-INH concentrate replaces the deficient/dysfunctional protein in HAE type 1 and type 2 patients. Exogenous C1-INH concentrate acts on the same targets as endogenous C1-INH. Treatment results in an increase of the plasma levels of C1-INH and helps to regulate all cascade systems involved in the production of bradykinin during attacks. One unit of C1-INH concentrate corresponds to the mean quantity of C1-INH present in 1 mL fresh normal plasma. Plasma-derived C1-INH concentrate is obtained by separating C1-INH from cryodepleted human plasma by adsorption and precipitation, purification, pasteurization, and virus filtration. Currently 2 plasma-derived C1-INH concentrates are available for on-demand treatment of HAE type 1 and type 2: Berinert (CSL Behring) and Cinryze (Shire).[13,14] Berinert dosing for on-demand therapy in children older than 5

years and adults is 20 units/kg IV; Cinryze dosing for children older than 6 years and adults is 1000 units IV, which may be repeated in 1 hour if needed.

Recombinant C1-INH: The only currently available recombinant human C1-INH is Ruconest (Pharming). There is a similar mode of action to plasma-derived C1-INH. It is indicated for on-demand treatment for HAE attacks in adults and adolescents older than 13 years. It is derived from the milk of transgenic rabbits, thus contraindicated in patients with a suspected or known rabbit allergy. The plasma half-life is approximately 3 hours. Transmission of human viruses is not a concern.[13,14] Dosing for on-demand therapy is 50 units/kg (max dose of 4200 units as a single dose) for < 84 kg and 4200 units as a single dose for ≥ 84 kg.

Figure 4. Targeted New Treatments for Hereditary Angioedema



Abbreviations: FXII, factor XII; C1-INH, C1 inhibitor; HMW, high molecular weight kinninogen; ACE, angiotensin converter enzyme; ACEi, ACE inihibitor.

Kallikrein Inhibitor: Ecallantide is a kallikrein inhibitor (Kalbitor; Shire) currently indicated for the on-demand treatment of HAE attacks in patients aged 12 years and older. Inhibition of kallikrein activity inhibits the cleavage of high-molecular-weight kininogen to bradykinin, as well as the further activation of activated factor XII. Ecallantide is a protein produced in the yeast *Pichia pastoris.* It has a plasma half-life of 2 hours. The main safety concern is potentially serious hypersensitivity reactions, including anaphylaxis, which was reported in 3% to 4% of treated patients. Thus, ecallantide has a black box warning for anaphylaxis and should be administered in a health care setting with appropriate medical support to manage anaphylaxis.[15] Dosing for HAE attacks in children older than 12 years and adults is 30 mg SQ (in three 10 mg injections); if attacks persist, another 30 mg may be repeated within 24 hours.

Short-Term Preprocedural Prophylaxis: Patients with HAE may have episodes of swelling near the site of intervention during procedures such as surgical trauma, dental surgery, endotracheal intubation, bronchoscopy, or esophagogastroduodenoscopy. Swellings associated with these procedures usually occur within 48 hours. Therefore, preprocedural prophylaxis with C1-INH concentrate is recommended as close as possible to the start of the procedure, 1000 units or a dose of 20 units/kg of plasma-derived C1-INH. Fresh frozen plasma may be used for short-term prophylaxis and on-demand therapy but is not as safe as C1-INH concentrate and is a second-line agent because of the greater risk of bloodborne disease transmission and allosensitization.[2,16]

Anabolic Androgens (17α-alkylated Androgens): Attenuated androgens danazol (2.5-10 mg/kg/d, max 600 mg) and stanazol (4-6 mg/d) can be used for preprocedural prophylaxis as an alternative to C1-INH concentrates. For scheduled preprocedural prophylaxis, androgens are started for 5 days before and 2 to 3 days after procedure. Short courses of androgen are even considered safe for children.[2,16]

With all preprocedural prophylactic treatments, breakthrough attacks can occur, so patients should remain under observation, and on-demand treatment needs to be available.[2,16]

Long-Term Prophylaxis (LTP): In patients with confirmed HAE type 1 and type 2 with frequent attacks, scheduled or regular use of medication is considered to reduce the burden of the disease. Individualized treatment plans should be considered, taking into account the activity of the disease, frequency of attacks, patient's quality of life, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy. The patient's preferences should be taken into consideration because successful long-term prophylaxis requires a high degree of compliance. All patients with HAE should be evaluated for long-term prophylaxis at every visit, at least once a year. Patients with ongoing long-term prophylaxis should be assessed regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response. Breakthrough symptoms like upper airway edema and other attacks may occur, despite the use of long-term prophylaxis. Therefore, all patients using long-term prophylaxis should also have on-demand medication (eg, icatibant, C1-INH concentrate, or ecallantide) readily available.[2]

Plasma-Derived C1-INH: Plasma-derived C1-INH is a safe and effective long-term prophylaxis for the prevention of HAE attacks. Dosing should be at least twice a week based upon its half-life. Dose and/or frequency may need adjustment for optimum efficacy, typically at 40 U/kg or 60 U/kg body weight to pro-

vide satisfactory dose-dependent preventive effects. The SQ route (Haegarda, CSL Behring) may provide more convenient administration and maintain improved steady-state plasma concentrations of C1-INH.[6,14]

For patients who are on plasma-derived C1-INH, there is a rare occurrence of thromboembolic events that may occur in patients with underlying thromboembolic risk factors (eg, implanted central venous catheters). Vaccination for hepatitis A and B also should be considered in patients requiring repeated administration of human plasma-derived products due to the concern of transmission of blood-borne viruses.[12,17]

Lanadelumab: Lanadelumab (Takshyro, Shire Pharmaceuticals) was approved by the FDA in 2018. It is a recombinant, fully human immunoglobulin monoclonal antibody inhibitor of kallikrein produced in Chinese hamster ovary cells. Dosing is 300 mg SQ every 2 weeks; spacing out to every 4 weeks may be considered in some patients. This medication may be self-administered at home. A phase 3, randomized, double-blind, parallel-group, placebo-controlled trial, 26-week treatment with SQ lanadelumab 150 mg every 4 weeks (n = 28), 300 mg every 4 weeks (n = 29), 300 mg every 2 weeks (n = 27), or placebo (n = 41), showed that treatment with SQ lanadelumab for 26 weeks significantly reduced the attack rate compared with placebo. The most common adverse drug reactions in patients are injection site reactions, upper respiratory infections, headache, rash, muscle pain, dizziness, and diarrhea.[17]

Berotralstat: Berotralstat (Orladeyo, Biocryst) is an oral, once-daily tablet, inhibitor of plasma kallikrein. Dosing is 110-150 mg daily with meals for adults and children older than 12 years. In a double-blind, parallel-group study that randomized 120 patients to receive once-daily berotralstat in a dose of 110 mg, 150 mg, or placebo, berotralstat demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks per month; $P = .024$) and 150 mg (1.31 attacks per month; $P < .001$) relative to placebo (2.35 attacks per month). The most frequent reported adverse events with berotralstat were abdominal pain, vomiting, diarrhea, and back pain. Doses >150 mg have been associated with QT prolongation.[18]

Androgens: Androgen derivatives have long been used for long-term prophylaxis in HAE type 1 and type 2. Oral administration makes these medications easy to use; however, there are major concerns about their androgenic and anabolic adverse effects, especially in women. Androgens can cause virilization, menstrual disorders, and even amenorrhea. They can also cause weight gain, headache, myalgia, depression, and acne. Androgens are contraindicated during pregnancy, as they can cause virilization of the fetus. In children and adolescents, therapy with androgens may interfere with growth and maturation. Androgens also cause numerous drug interactions (as with statins). Patients on androgens should routinely have liver panel and urine tests and an annual ultrasound of the liver.[2,16]

The dose of androgens needed to control HAE attacks is from 100 mg every other day to 200 mg of danazol 3 times a day. The minimal effective dose should be used. Dosages above 200 mg of danazol daily for extended periods of time are not recommended because of side effects. The dosage should be adjusted according to clinical response and not adjusted based on C4 and C1-INH results.[2,16]

Antifibrinolytics: Epsilon aminocaproic acid and tranexamic acid (20-50 mg/kg/d) are oral antifibrinolytics widely used in Europe (not available in the US). These medications are not licensed for long-term prophylaxis although often are used for this indication. The mechanism of action for control of HAE is not completely understood. Common adverse reactions include nausea, diarrhea, vertigo, postural hypertension, fatigue, and muscle cramps/weakness from increased muscle enzyme concentrations. A major concern with use of this drug is enhanced thrombosis.[16]

Avoidance of Triggers: Triggers of HAE attacks include accidental trauma, surgical procedures, estrogen-containing oral contraceptive agents, and hormone replacement. Antihypertensive agents containing ACE inhibitors also may precipitate HAE swelling. Other triggers include stress, fatigue, infections, and the menstrual cycle. Mindful awareness and avoidance of triggers as much as possible can minimize precipitation of attacks; however, many attacks are unpredictable. Physicians should recommend judicious avoidance of suspected triggers and encourage a normal quality of life.[2]

CONCLUSIONS

HAE patients are encouraged to find a health care provider with expertise in the disease and a health care facility that can manage and provide emergency treatment for severe attacks. Family members of HAE type 1 and type 2 patients should be screened for C1-INH function, C1-INH protein, and C4 plasma levels. Delayed diagnosis could lead to increased morbidity with life-threatening consequences. A comprehensive and tailored therapeutic strategy to include avoidance of triggers and pharmacotherapy options can effectively mitigate morbidity and mortality and improve quality of life for patients with HAE.

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Pediatric Respiratory Illness Hospitalizations Prior to COVID-19 and During the First Year of the COVID-19 Pandemic in Southeast Wisconsin

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ABSTRACT

Background: Public health measures combatting the COVID-19 pandemic also led to a decrease in other pediatric respiratory illnesses. We describe the local pattern of pediatric respiratory hospitalizations in southeast Wisconsin prior to COVID-19 and during the first year of the pandemic.

Methods: We performed a cross-sectional examination of hospitalizations for asthma, bronchiolitis, and bacterial pneumonia at a single tertiary children's hospital prior to COVID-19 through the first year of the COVID-19 pandemic.

Results: We found a significant decrease in the average monthly hospitalization rates prior to and during COVID-19 for asthma, bronchiolitis, and bacterial pneumonia ($P < 0.001$), with average percent decrease of hospitalizations per month of 48%, 78%, and 47.7%, respectively.

Discussion: The decrease in hospitalizations is likely multifactorial and related to public health measures, behavior changes, and other epidemiological factors.

INTRODUCTION

The coronavirus 19 (COVID-19) pandemic led to dramatic changes in the behavior of populations worldwide to limit the spread of severe acute respiratory syndrome coronavirus 2 (SARCoV-2). Early public health measures taken against COVID-19 included masking, physical distancing, limiting the size of gatherings, restricting travel, and moving businesses and schools to virtual environments.[1] These measures affected the incidence of other infectious illnesses. Early in the pandemic, there was a significant decrease in the prevalence of other respiratory viruses, including respiratory syncytial virus (RSV) and influenza, and associated diseases like asthma and bronchiolitis.[2,3] Asthma, bronchiolitis, and bacterial pneumonia are among the most common respiratory diagnoses leading to the hospitalization of children.[4] These respiratory illnesses have a seasonality to their presentations: asthma prevalence increases in the fall with a peak in September and October, while bronchiolitis and bacterial pneumonia increase in the winter with peaks in December and January.[5,6] The annual respiratory season typically spans September through April.

Public health measures against COVID-19 began in Wisconsin with a declaration of a public health emergency on March 12, 2020. All schools closed the following day and remained closed through the end of the school year.[7] The Safer at Home Order was enacted on March 24, 2020, which limited movement outside the home to essential functions and closed nonessential businesses, although it was later overturned by the Wisconsin Supreme Court on May 13, 2020. The first statewide mask mandate was issued on July 30, 2020.[8] In the fall, school districts in southeast Wisconsin remained primarily virtual, with some districts offering opt-in plans for in-person education or hybrid models. Throughout the school year, more schools began to return in-person, and most schools were back to in-person education by March 2021 with mask requirements. The effect of these local public health measures in southeastern Wisconsin on pediatric respiratory illnesses over a full respiratory season has not been described.

Our objective is to describe the incidence of hospitalization for 3 common pediatric respiratory illnesses–asthma, bronchiolitis, and bacterial pneumonia—in southeast Wisconsin and com-

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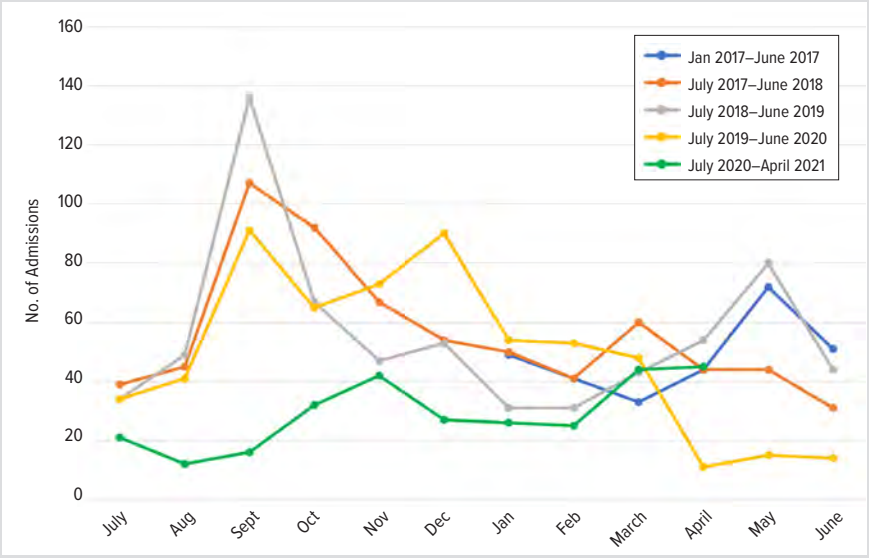
pare pre-COVID-19 respiratory seasons during 2017-2019 with the 2020-2021 intra-COVID-19 respiratory season corresponding to the first full respiratory season of the COVID-19 pandemic. Earlier literature describing the trend towards a decrease in pediatric respiratory illnesses during the pandemic did not capture a full respiratory season and was limited to the earlier months of the pandemic when public health measures were most robust. In this study, we include the first full respiratory season in the northern hemisphere since the declaration of the COVID-19 pandemic.

Figure 1. Number of Asthma Hospitalizations Per Month



METHODS

This is a retrospective examination of hospitalizations at a single center in Milwaukee, Wisconsin from September 1, 2017, through April 30, 2021. Our hospital is a 306-bed tertiary care, academic, standalone children's hospital and admits over 16,000 patients per year, on average, prior to the COVID-19 pandemic. Our primary catchment area is the southeast region of Wisconsin, representing an approximate population of 2,260,000.[9] Our site Institutional Review Board deemed this study exempt.

We identified all patients hospitalized in the acute and intensive care units with encounter diagnoses of asthma, bronchiolitis, and bacterial pneumonia using ICD-10 codes (*International Statistical Classification of Diseases, Tenth Revision*) (Appendix 1). Results included patients hospitalized under observation and inpatient status and were analyzed by month. Patients aged 0-24 months with bronchiolitis and 0-18 years with asthma or bacterial pneumonia were included.

The pre-COVID-19 period was defined as January 2017 through February 2020; the intra-COVID-19 period was defined as March 2020 through April 2021. The pre-COVID hospitalization mean by calendar month was calculated using each corresponding month's hospitalizations during 2017-2019. The month with the highest mean hospitalizations was defined as the peak month. The percent reduction in hospitalizations was calculated using pre-COVID peak month means and the intra-COVID hospitalizations for that corresponding month. The mean monthly hospitalization rate during the respiratory season (September-April) was calculated for each diagnosis pre- and intra-COVID. Two-tailed *t* test assuming unequal variances was applied to determine significant difference between the mean monthly hospitalizations pre- and intra-COVID. All calculations were done in Microsoft Excel for Microsoft 365 MSO version 16.0.

RESULTS

Asthma

Pre-COVID-19, asthma admissions showed a seasonal increase in the fall, winter, and spring months, with peaks in September and May (Figure 1). Admissions sharply declined in April 2020 and remained low without a typical peak during the fall. The pre-COVID peak month was September with 111.3 hospitalizations, while intra-COVID September had 16 hospitalizations—an 85.6% decrease in peak month hospitalizations. The pre-COVID mean monthly hospitalization rate was 60.9 (SD ± 24.6, range 31-136) and intra-COVID mean was 31.6 (SD ± 12.1, range 11-48), significantly lower ($P < 0.001$) than the pre-COVID average and corresponding to a 48% decrease.

Bronchiolitis

Pre-COVID bronchiolitis hospitalizations increased in the fall, peaking around December and January and decreasing in the spring (Figure 2). Intra-COVID-19, there was a sharp decrease in hospitalizations starting in April 2020 and lack of the typical seasonal increase in the fall and winter. The pre-COVID peak month for hospitalizations was December, with a mean hospitalization of 215.3. The intra-COVID December had 14 hospitalizations, a 93.5% decrease. The mean number of admissions per month during the pre-COVID respiratory season was 108.5 (SD ± 72.1, range 23-283). During the intra-COVID respiratory season, the monthly hospitalization mean was 23.8 (SD ± 34.6, range 3-126), significantly lower than the pre-COVID monthly mean ($P < 0.001$) and representing a 78% decrease.

Bacterial Pneumonia

Pre-COVID-19 admissions showed a seasonal peak in December and January (Figure 3). Bacterial pneumonia admissions declined

Figure 2. Number of Bronchiolitis Hospitalizations Per Month

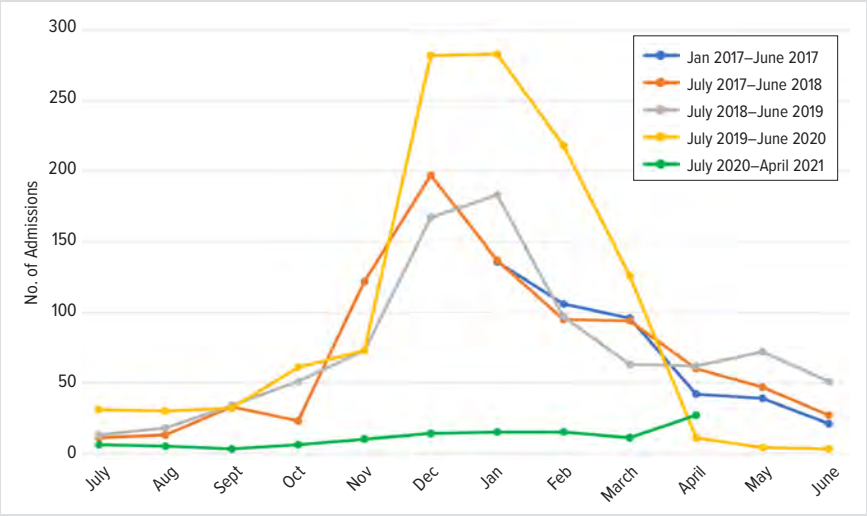
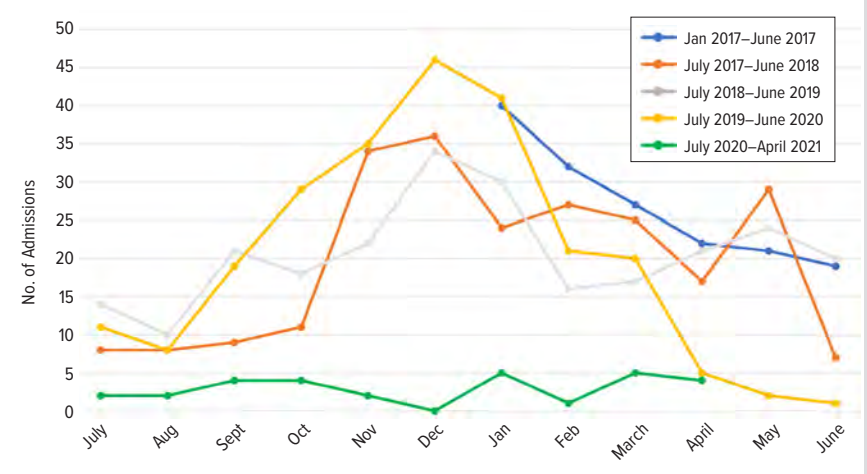


Figure 3. Number of Bacterial Pneumonia Hospitalizations Per Month



in April 2020 and remained low. December was the peak month for pre-COVID hospitalizations, with an average of 39 versus zero during the intra-COVID December—a 100% decrease. The mean monthly hospitalization rate during the pre-COVID respiratory seasons was 60.4 (SD ± 24.6, range 31-136). The intra-COVID mean monthly hospitalization rate was significantly lower ($P < 0.001$) at 31.6 (SD ± 12.1, range 11-48), representing a 47.7% decrease from pre-COVID.

DISCUSSION

Pediatric hospitalization rates for bronchiolitis, asthma, and bacterial pneumonia decreased significantly during the first year of the COVID-19 pandemic in southeastern Wisconsin. Our findings are consistent with previous literature describing the seasonality of pediatric respiratory illnesses prior to the pandemic[5,6] and the decrease in pediatric respiratory illnesses after implementation of public health measures to combat the pandemic.[2,3,10] In contrast to previous work, our data spans an entire respiratory season and show that both observational and inpatient hospitalizations remained low in southeastern Wisconsin during the COVID-19 pandemic, despite fluctuations in public health measures throughout the year.

We chose to examine the hospitalization rates of bronchiolitis, asthma, and bacterial pneumonia, as they are common pediatric lower respiratory tract diseases with seasonal presentations but differing underlying etiologies. Despite different etiologies, all 3 diseases showed a marked decrease in incidence during the COVID-19 pandemic response and blunting of prior seasonality.

The decrease in pediatric hospitalizations for respiratory illness is likely multifactorial and related to public health measures and behavior changes occurring as a response to the pandemic. Pre-COVID-19, handwashing and physical distancing were shown to decrease viral respiratory illnesses in children.[11,12] We saw the largest percent decrease pre- to intra-COVID-19 admissions in bronchiolitis—the diagnosis most closely tied to viral transmission—with significant but smaller percent decreases in asthma and bacterial pneumonia. The smaller decreases in asthma and bacterial pneumonia may relate to nonviral drivers of seasonality such as allergens.[13] Results also may reflect patients being less likely to seek care for respiratory illnesses, although the longer time frame of our study makes this less likely as restrictions on movement and businesses were eased. As public health measures continue to be eased, a resurgence of respiratory illnesses may be seen. The overall lack of immunity to typical respiratory viruses given the lack of exposure over the past year may also lead to an increased incidence of respiratory hospitalizations during the next winter season.[14] Our data may suggest that sustainable public health measures aimed at reducing viral transmission (ie, masking, handwashing) might ease pediatric hospitalizations without the need for the more invasive measures such as lockdowns taken earlier in the pandemic.

Our study has several limitations, including being a single center study. While our hospital is the only tertiary pediatric hospital in the southeastern Wisconsin region, patients may have been seen in other regions or states. Because this is an observational study,

causation for the decrease in hospitalizations for respiratory illnesses cannot be established, although it is reasonable to suspect that public health measures likely had an impact on hospitalizations. Identifying hospitalizations by diagnoses codes is limited by errors in coding and hospitalizations with multiple diagnoses. Further, we were unable to determine individual exposures such as daycare use and sick contacts, which may have provided insight into other epidemiological factors and their impact on hospitalization rates during the COVID-19 pandemic.

Our study confirms locally the decrease in hospitalizations for respiratory illnesses in pediatric patients during the first year of the COVID-19 pandemic. Continued surveillance of respiratory hospitalizations is warranted given changing public health measures and increasing in-person interactions, and it remains to be seen how further developments with the COVID-19 pandemic may continue to affect pediatric hospitalizations. Likewise, further research is needed to elucidate the optimal balance between public health measures targeting the general spread of infectious respiratory illnesses and their impact on society.

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Appendix: Available at www.wmjonline.org.

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COVID-19 Pandemic Exacerbates Childhood Immunization Disparities

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ABSTRACT

Background: The objective of this study was to measure the recovery of routine pediatric immunizations after a period of reduced vaccine administrations in the early weeks of the COVID-19 pandemic.

Methods: We recorded data on vaccines administered in Children's Wisconsin primary care or urgent care clinics from January 2019 through December 2020 and aggregated data by date and insurance type.

Results: During the gradual reopening period after week 21 in 2020, vaccine administration returned to prepandemic levels for children with commercial insurance but remained below baseline rates until the end of 2020 for children with Medicaid insurance.

Discussion: The decline in pediatric vaccination in 2020 disproportionately affected children with Medicaid insurance.

INTRODUCTION

Preventive measures implemented to minimize spread of coronavirus disease 2019 (COVID-19) caused a national decline in pediatric vaccine administration.[1,2] Decreased vaccine coverage persisted with initial reopening in 2020.[3,4] Prior to the COVID-19 pandemic, health insurance status correlated with vaccination coverage, with lower vaccine coverage in children with Medicaid or no health insurance compared to children with commercial insurance.[5] We evaluated changes in routine immunizations after health care clinics reopened in southeastern Wisconsin in May 2020 and identified disparities in catch-up vaccination by insurance type.

METHODS

We analyzed vaccination data from Children's Wisconsin, a health care system including 24 general pediatric and 7 urgent care clinics. The Institutional Review Board was aware of the project and determined it was a quality improvement activity. We recorded vaccines administered to patients aged 0 to 18 years, with commercial or Medicaid insurance, during primary pediatric or urgent care visits from 2019 week 1 through 2020 week 52, using epidemiologic weeks defined by the Centers for Disease Control and Prevention. Exclusions included seasonal influenza vaccine administration, vaccines administered to uninsured patients, and vaccines administered in other locations. Data were categorized by vaccine type, week administered, and insurance type.

We calculated the number of vaccines administered for active patient population size, defined as the number of patients who had a visit in the previous 3 years by insurance type. Periods in 2020 were categorized as "prepandemic" (weeks 1-11), "shutdowns" (weeks 12-20), and "gradual reopening" (weeks 21-53). The difference in vaccines administered in 2020 compared to 2019 was calculated as vaccines administered per 1000 patients per 4-week period in 2020 minus those administered in 2019 for each payer type, termed "commercial difference" and "Medicaid difference." The commercial difference minus the Medicaid difference defined the "Medicaid deficit." Data were analyzed using GraphPad Prism 8 (La Jolla, California), and statistical significance of differences was identified by Wilcoxon matched-pairs signed rank test.

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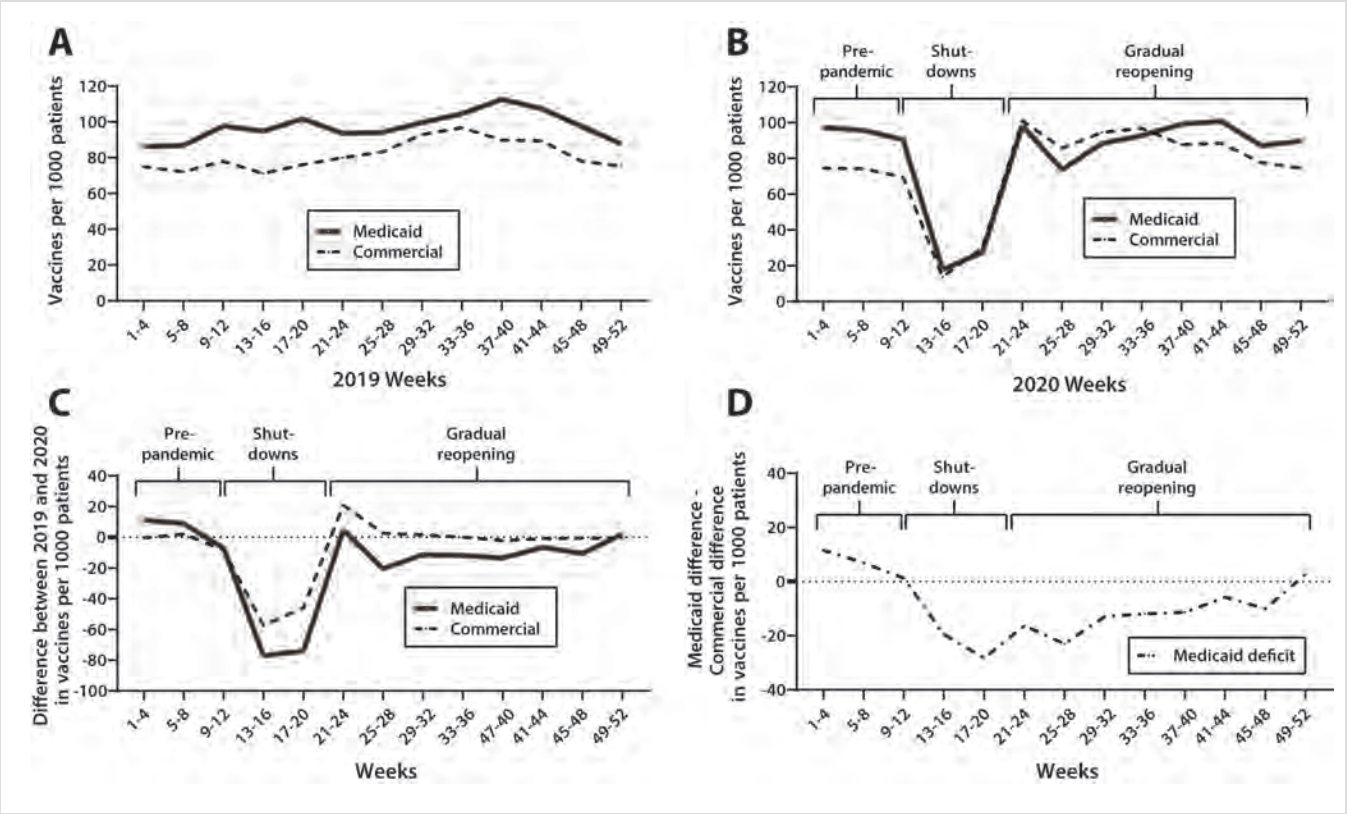
Figure. Vaccine Administrations by Insurance Type, 2019 and 2020



A and B. Vaccinations in each 4-week period per 1000 patients with the indicated insurance type in 2019 (A) and 2020 (B).

C. Difference in vaccinations between 2019 and 2020 by insurance type.

D. Deficit in vaccinations in Medicaid-insured patients over the course of 2020 vs commercial-insured patients over the same period.

RESULTS

In 2019, the average 4-week vaccine administration rate per 1,000 patients was 16% higher for 51,000 Medicaid-insured patients compared to 96,000 commercially insured patients (Figure 1A, $P<0.005$). During shutdowns, all patients had a sharp decline in vaccines administered (Figure 1B), but Medicaid-insured patients had a larger decline than commercially insured patients (Figure 1C). During the period of gradual reopening, the vaccination rates for commercially insured patients rebounded to 2019 levels, resulting in no difference between 2019 and 2020 vaccines per 1,000 commercially insured patients (Figure 1C). However, vaccination rates for Medicaid enrollees stayed below 2019 levels until weeks 49 to 53, with 11 fewer vaccines administered per 1,000 Medicaid patients per 4 weeks in 2020 compared to 2019

Table. Vaccines Administered, Excluding Influenza, 2019 and 2020

Vaccine	Commercial 2019	Commercial 2020	Commercial Difference in 2020 vs 2019 (%)	Medicaid 2019	Medicaid 2020	Medicaid Difference in 2020 vs 2019 (%)	Medicaid Deficit[a]
All vaccines	1058	969	-89 (-8)	1265	1059	-206 (-16)	117
Hepatitis B	123	115	-8 (-7)	170	143	-27 (-16)	19
Rotavirus	114	108	-6 (-5)	140	116	-24 (-17)	18
DTaP	206	192	-14 (-7)	270	226	-44 (-16)	30
HIB	118	113	-5 (-4)	159	138	-21 (-13)	16
Pneumococcal	160	152	-8 (-5)	210	183	-27 (-13)	19
IPV	165	154	-11 (-7)	222	184	-38 (-17)	27
Hepatitis A	88	76	-12 (-14)	112	86	-26 (-23)	14
MMR	91	80	-11 (-12)	114	92	-22 (-19)	11
Varicella	91	80	-11 (-12)	116	93	-23 (-20)	12
HPV	84	70	-14 (-17)	73	58	-15 (-21)	1
Meningococcal	99	95	-4 (-4)	71	62	-9 (-13)	5

Abbreviations: DTaP, diphtheria, tetanus, and pertussis; HIB, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; MMR, measles, mumps, and rubella; HPV, human papillomavirus.

All vaccine numbers are per 1000 active patients in each payer type.

[a]The difference between the Medicaid and commercial differences in 2020 vs 2019.

(Figure 1C, $P = 0.03$). The magnitude of the year-over-year vaccine deficit in patients with Medicaid compared to commercial insurance was as great as 28 per 1,000 patients in weeks 17 to 20 but recovered slowly and reached parity by the end of 2020 (Figure 1D).

Both commercial- and Medicaid-insured patients received fewer vaccine doses in 2020 than 2019 (8% and 16% fewer, respectively) (Table). Approximately 8,700 and 10,900 vaccines were missed in 2020 for 97,600 commercial- and 53,000 Medicaid-insured children, respectively. Vaccines primarily administered to young infants, such as *Haemophilus influenzae* type B (HIB), were relatively preserved in the commercial population, showing a 4% decline in 2020 compared to 2019, while the Medicaid population had a 13% decline in 2020 compared to 2019 (Table).

DISCUSSION

A dramatic decline in routine vaccinations was an unintended consequence of shutdowns in early 2020.[1,2] Our data show that commercially insured children in Southeastern Wisconsin initially received more vaccines during gradual reopening compared to the prior year, with a partial but incomplete catch-up in missed doses. In contrast, Medicaid-insured children continued receiving fewer vaccinations compared to 2019, prolonging the pandemic's effect on vaccination status in that group. This difference could be from delays in reopening of clinics with a high proportion of Medicaid patients, difficulty contacting families to reschedule canceled appointments, lack of transportation, or other complexities of daily living disproportionately affecting the Medicaid-insured patients.

By using data from this project externally to lobby for governmental support of outreach programs and grouping aligned health disparity projects internally for greater momentum, our health system aims to improve capacity to target vaccine-vulnerable populations. The availability of statistically robust data to uncover disparities and drive efforts to identify root causes of disparities is important in the quest for health equity. Once root causes are identified specific to the disparity, appropriate interventions can be implemented and the data mining tools can again be used to confirm improvement. Accurate data ensure that our efforts are efficient and effective.

Project limitations are inclusion of a single health care system, exclusion of vaccinations outside of primary care encounters, and no measurement of barriers to vaccination. The disparity we identified in Southeastern Wisconsin may be exacerbated by the highly segregated status of our most populous city, Milwaukee.

CONCLUSION

This study identified a prolonged lapse in routine pediatric vaccinations during the COVID-19 pandemic, primarily in Medicaid-insured patients. Our data suggest that the Medicaid population may be vulnerable to a resurgence of vaccine-preventable diseases.[6]

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Transaminase Elevation in Nutritional Infantile Failure to Thrive

Kristen A. Marten, DO; Nicole E. St. Clair, MD; Daniel M. O'Connell, MD; Daniel J. Sklansky, MD

ABSTRACT

Introduction: Laboratory investigations pursued for infants with failure to thrive (FTT) often show mild transaminase elevations, the incidence and significance of which are unknown.

Methods: This retrospective chart review included infants diagnosed with simple nutritional FTT at a single academic tertiary care system. Comparisons of diagnostic studies and outcomes between children with and without transaminase elevation were performed using chi-square and Wilcoxon rank sum tests.

Results: None of the infants with abnormal transaminases required additional follow-up or developed alternative diagnoses in the following year.

Discussion: Transaminase elevation may be common in infants with FTT and may not warrant further investigation if the history indicates an isolated etiology of insufficient nutrition.

BACKGROUND

Failure to thrive (FTT) is a common diagnosis made in otherwise healthy infants and can be a consequence of factors intrinsic to the infant and/or the environment.[1] Whether undernutrition is secondary to inadequate caloric intake, excessive caloric requirement, or malabsorption, the pathways lead to the same clinical phenomenon. Of infants diagnosed with FTT, 60% to 90% have laboratory or imaging studies performed in an attempt to delineate a possible etiology, including genetic, metabolic, and renal disease, among others.[2,3] FTT secondary to suboptimal caloric intake in otherwise healthy children accounts for the majority of infantile FTT cases, compared to a minority that are secondary to increased metabolic need or caloric losses.[4] In most infants with intrinsic causes of FTT, including genetic or metabolic conditions, the diagnosis is made with history or physical examination. Screening tests may provide reassurance but are unlikely to uncover an underlying disorder.[3-6] Some otherwise well infants diagnosed with FTT have mild transaminase elevations, which may compel clinicians to obtain further diagnostic testing. To date, no existing studies report the incidence of transaminase elevation in infants presenting with FTT, although the phenomenon has been well described in other populations experiencing starvation states.[7,8] It is also unknown how the finding of elevated transaminases may influence further diagnostic testing or predict diagnoses other than inadequate nutrition. The objective of this retrospective study was to determine the frequency and significance of transaminase elevation in infants diagnosed with FTT.

METHODS

Charts were identified for infants less than 1 year of age admitted to the hospitalist service or seen at the outpatient gastroenterology clinic at a single academic tertiary care system between July 1, 2012 and March 31, 2017 with FTT-associated International Classification of Diseases 9 and 10 diagnosis codes 783.41, 779.34, R62.51, and P96.2. Infants with Z scores for weight for age less than or equal to -1.64 were included in the study, consistent with a weight for age less than the 5th percentile.[4] Exclusion criteria included premature gestation less than 35 weeks; prior diagnosis of

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Table 1. Demographic Data for Infants Presenting to Pediatric Gastroenterology Clinic or for Admission to Hospital Medicine Service With Failure to Thrive Who Underwent Laboratory Studies

Patient Demographics	Elevated Transaminases (%) N=11	Normal Transaminases (%) N=28
Gender		
Male	4 (36)	14 (50)
Female	7 (64)	14 (50)
Race		
African American	0	2 (7)
White	9 (82)	17 (61)
Other	0	2 (7)
Unknown	2 (18)	7 (25)
Location		
Inpatient	6 (55)	21 (75)
Outpatient	5 (45)	7 (25)
Nutrition		
Breastfeeding	3 (27)	5 (18)
Formula	5 (45)	19 (68)
Both	3 (27)	4 (14)
Gestational age		
Term	11 (100)	23 (82)
Late preterm (35-36w7d)	0	5 (18)
Median age (months)	3 months (3 weeks-8 months)	4 months (3 weeks-10 months)

Abbreviations: w, weeks; d, days.

There were no statistically significant differences between the group who presented to the pediatric gastroenterology clinic or for admission to the hospital medicine service.

Table 2. Comparing Additional Studies Performed and Diagnostic Outcomes for Infants Presenting to Pediatric Gastroenterology Clinic or for Admission to Hospital Medicine Service With Failure to Thrive Based on Transaminase Status

Patient Evaluation	Abnormal Transaminases (%) N=11	Normal Transaminases (%) N=28	Odds Ratio (95% CI)
AST (mean, SD)[a]	70.2 +/- 15.5	39.8 +/- 12.4	NA
ALT (mean, SD)[a]	65.9 +/- 38.6	34.7 +/- 16.8	NA
Number of lab draws	2 +/- 1	1.5 +/- 1.8	1.17 (0.78-1.75)
Exclusive breastfeeding at discharge	4 (36)	3 (11)	4.76 (0.85-26.5)
Speech consult	6 (55)	11 (41)	1.75 (0.43-7.17)
Nutrition consult	10 (91)	27 (96)	0.37 (0.02-6.5)
Ultrasound (abdomen)	5 (45)	11 (39)	1.29 (0.32-5.27)
Upper GI study	5 (45)	13 (46)	0.96 (0.24-3.9)
Diagnosis leading to FTT	0 (0)	5 (18)	NA

Abbreviations: FTT, failture to thrive; AST, aspartate aminotransferase; ALT, alanine aminotransferase; upper GI study, water soluble oral contrast with a series of radiographs.

[a]Normal AST defined as 20-67 U/L and ALT 0-55 U/L..

genetic, cardiac, or metabolic diseases; and admission for illnesses other than FTT. Charts were abstracted for demographic data and diagnostic and therapeutic outcomes from the initial encounter through the subsequent year. Comparisons of diagnostic studies and outcomes between children with and without transaminase elevation were performed using chi-square and Wilcoxon rank sum tests. This study was considered exempt by the University of Wisconsin School of Medicine and Public Health's institutional review board.

RESULTS

A total of 670 patients were identified in the study period, with 95 meeting inclusion criteria. The majority were excluded due to age greater than 1 year, prematurity, or underlying illness contributing to FTT. The majority of patients were White, born at term, and formula fed at time of admission. There were no statistically significant differences between infants who did and did not undergo laboratory testing. Of the 39 (41%) infants undergoing laboratory testing, 11 (27%) had elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (ALT 23-138 U/L, AST 46-101 U/L). Infants with and without transaminase elevation did not have significant differences in demographic or presenting characteristics (Table 1). There was a trend toward additional investigations in infants with transaminase elevation, although this did not reach statistical significance (odds ratio [OR] 1.17; 95% CI, 0.78-1.75). None of the infants with abnormal transaminases required further clinic or hospital encounters for relapsing FTT or developed alternative diagnoses associated with FTT, and the transaminase elevation normalized within the following year (Table 2).

DISCUSSION

Approximately one quarter of infants with FTT who underwent laboratory testing were found to have elevated transaminases, and those patients were not found to have different exposures or outcomes compared to infants with normal transaminase levels. No infant with abnormal transaminases received a diagnosis explaining their FTT other than poor nutritional intake.

Transaminase elevation has been seen in other populations with suboptimal nutrition, with several proposed metabolic etiologies. In a study involving adolescents with anorexia nervosa, approximately one third of patients had transaminase elevation on admission, which resolved with refeeding and did not have long-term sequelae. Investigators have posited that this transaminase elevation was secondary to ischemic hepatitis from hepatic hypoperfusion, or to hepatic autophagy in the context of a catabolic starvation response.[7-10] Another proposed etiology for this phenomenon is that upregulation of transaminase production may occur in response to the increased need for uptake of amino acids to facilitate gluconeogenesis in the starvation state. Regardless of the etiology, patients in several studies show-

ing transaminase elevation during the starvation state showed laboratory normalization with nutrition and had no long-term sequelae.[7,8]

Over the last 40 years, evidence continues to show that laboratory and imaging studies are not necessary in the initial evaluation of FTT.[3-6] In several recent studies, only 1% to 3% of laboratory investigations revealed an underlying diagnosis, most of which were from genetic testing performed based on physical examination. Laboratory and imaging studies result in financial and emotional burden on families. A minority of infants may have an underlying medical diagnosis, but a focused history and physical exam with a period of observation prior to a more extensive evaluation is a reasonable first step.[2]

Our study is limited by its retrospective design, small sample size, single institution population, lack of ethnic diversity, and reliance on accurate coding of encounter diagnoses for chart identification. Additionally, the majority of patients were formula fed at the time of the study. Although patients were followed for 1 year, some may have received diagnoses outside of our system that were not imported to our electronic health record or could have received diagnoses after the follow-up period. Future work should verify our findings across multiple centers and in a larger and more diverse population.

Transaminase elevation associated with infantile FTT may be a common and insignificant finding that should not direct risk assessment or further diagnostic testing. Diagnosis and treatment of FTT should focus on optimization of nutrition rather than laboratory and imaging studies.

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Pilot Study of Feeding Tube Education Using a Graphic-Based Course

Lauren Johnson, MD; Theresa Maatman, MD

ABSTRACT

Background: Residents receive little formal education about feeding tubes; however, patients experience fewer complications if a formal feeding tube curriculum is implemented.

Objective: The aim of this study was to evaluate a graphics-based course for internal medicine residents.

Methods: Internal medicine residents participated in a new course on feeding tube placement and management. Surveys administered before and after the course assessed resident comfort level with the material.

Results: Based on a 10-point Likert scale, mean improvement in comfort level for 4 scenarios was 1.69, 2.13, 2.44, and 3.07 points ($P<0.001$ for all). Ninety-four percent of participants reported the graphics were helpful.

Conclusion: The new course significantly improved resident comfort level regarding feeding tube placement and management. The use of graphics played a role in increasing residents' understanding.

INTRODUCTION

Feeding tubes—consisting of nasogastric (NG) tubes, nasojejunal (NJ) tubes, and percutaneous endoscopic gastrostomy (PEG) tubes, are present in over 3% of hospitalized patients.[1] There have been reports of mishandling of feeding tubes by residents and medical students, leading to adverse outcomes or even untimely patient deaths, as well as multiple incidents reported to the National Patient Safety Agency.[2,3] These poor outcomes are likely tied to limited physician education, as data show that patients who rely on feeding tubes at home have fewer complications if their primary caregiver received education about tube complications.[4]

One might assume that every resident receives formal education regarding feeding tubes; however, reports show that only 76.1% of programs provide training on this topic, and confidence in feeding tube management among residents is only 50%.[5] This topic may be overlooked in graduate medical education because maintenance and basic troubleshooting of feeding tube complications are often handled by nursing staff and because radiographic confirmation of correct placement can be deferred to a radiologist. Not only is the topic of feeding tube placement and management missing from the curriculum of many residency programs, but there are no studies on the most effective ways to teach this topic.

One promising approach for feeding tube education might be the use of comics or graphics, which have been shown to be effective in teaching medical trainees about patient safety and hepatitis B.[6,7] In fact, educational tools with cartoons have been shown to be noninferior to traditional-style tools, and they had higher completion rates.[8]

Our hypothesis is that a formal teaching curriculum regarding feeding tubes and their complications will increase resident physician knowledge and comfort level, leading to improvements in patient care. As such, we created a pilot study for such a curriculum that incorporates the use of medical graphics.

METHODS

Setting and Participants

In 2019, internal medicine residents from the Medical College of

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Wisconsin—designated as post graduate year (PGY) 1 through 4 depending on the number of years since graduating from medical school—participated in a pilot study for a new curriculum and assessment. Course participation was optional.

Institutional review board approval was granted by the Department of Veterans Affairs, Milwaukee VA Medical Center. Written informed consent was waived in lieu of an informational letter.

Interventions

Educational lectures were presented to participants in a scenario-based format that included medical graphics (See Figure 1). Participants had no prior formal training on the topic. Scenarios included how to confirm placement of a NG or NJ feeding tube radiographically, how to troubleshoot common complications of PEG tubes, and what to do if a PEG tube is unintentionally removed.

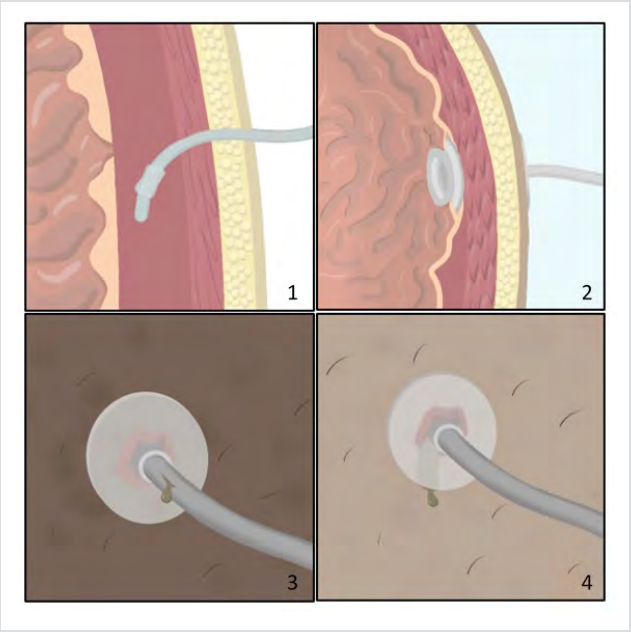
A 1-hour session for PGY1 residents and a separate 1-hour session for PGY2 residents and up were incorporated into existing protected academic time and taught by one of the senior residents. Educational content was approved by a staff gastroenterologist beforehand.

Outcomes Measured

Participants were asked to complete pre- and post-intervention surveys identifying their comfort level in 4 areas using a 10-point Likert scale (1 = very uncomfortable and 10 = very comfortable). The areas were (1) confirming placement of a NG feeding tube, (2) confirming placement of a NJ feeding tube, (3) knowing which medications can and cannot be administered through feeding tubes, and (4) troubleshooting complications that arise with PEG tubes. The post-intervention survey also asked whether participants thought the use of graphics enhanced their learning, based on a 4-point Likert scale from "not helpful at all" to "very helpful."

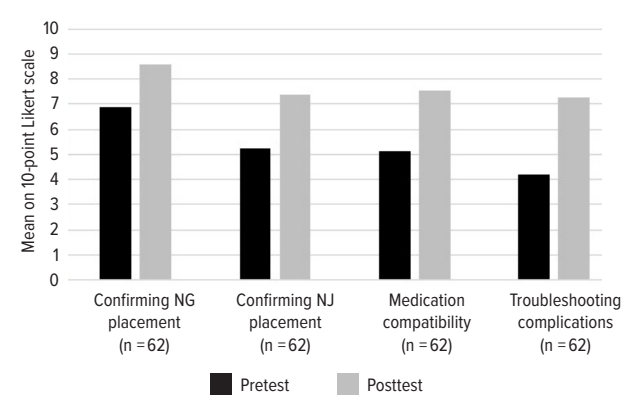
Data was analyzed using a 2-tailed paired Student *t* test and a Cohen's d_s test.

Figure 1. Medical Graphics Used During Educational Intervention, Representing (1) Replacement Peritonitis, (2) Buried Bumper Syndrome, (3) PEG Tube Leakage, and (4) PEG Tube Seepage



Abbreviation: PEG, percutaneous endoscopic gastrostomy.

Figure 2. Mean Scores From Resident Self-Assessments Regarding Their Comfort Level in 4 Areas of Content From Feeding Tube Curriculum



Abbreviations: NG, nasogastric; NJ, nasojejunal.

RESULTS

Sixty-two out of 122 residents (50.8%) participated in the study. This is consistent with the typical attendance at the residency program's weekly academic half day—the teaching venue—given that many residents on any given day are on call, postcall, or have a scheduled day off. Every resident who was in attendance that week volunteered to participate. There were 23 PGY-1 residents, 18 PGY-2 residents, 20 PGY-3 residents, and 1 PGY-4 resident.

Scenario #1—confirming placement of a NG feeding tube—had a mean preintervention rating of 6.89 and a mean postintervention rating of 8.58 (Cohen's $d_s = 0.92$) ($P < 0.001$). Scenario #2—confirming placement of a NJ feeding tube—had a mean preintervention rating of 5.23 and a mean postintervention rating of 7.35 (Cohen's $d_s = 1.01$) ($P < 0.001$). Scenario #3—understanding which medications should and should not be administered through feeding tubes—had a mean pre-intervention rating of 5.1 and a mean postintervention rating of 7.53 (Cohen's $d_s = 1.10$) ($P < 0.001$). Scenario #4—troubleshooting complications that arise with PEG tubes—had a mean preintervention rating of 4.19 and a mean postintervention rating of 7.25 (Cohen's $d_s = 1.45$) ($P < 0.001$). These data are shown in Figure 2.

Additionally, 58 out of 62 (94%) residents stated that including medical graphics illustrating possible complications was either helpful or very helpful for enhancing their learning.

DISCUSSION

Our pilot study created a large and significant improvement in resident physician comfort level with 4 areas of medical knowledge regarding feeding tube placement and management. A large majority of the residents felt that their understanding was enhanced by the inclusion of graphics.

These findings are promising for improvement in resident understanding of feeding tube complication management. They also provide more support for the inclusion of graphics in medical education to increase participation and enhance understanding. While a limited intervention such as this has low likelihood of showing a change in hospital-reported outcomes given the many confounding factors, it is possible that there have been downstream benefits wherein patients might have fewer adverse events from complications. These could be better elucidated through a longitudinal follow-up of our curriculum, by testing participants for retention and complete understanding of the content the year after they learned the material. Other future directions could include using a control group without medical graphics to better determine the role those graphics play in education. The residents in this study subjectively reported that the graphics enhanced their learning, however, it is possible that text-only or verbal-only instruction may have been sufficient in the setting of limited training prior to this intervention.

A potential limitation to the external validity of this study is the fact that the curriculum has been administered only to internal medicine residents in 1 residency program. Implementation of such a curriculum in the future may benefit not only internal medicine residents but also residents in other specialties, such as surgery or pediatrics, as not all programs have formal training on this topic. Further study will be needed to determine whether benefit is added across multiple types of residency programs and whether medical graphics may be a superior way to provide this education.

CONCLUSIONS

This pilot study demonstrated that a case-based curriculum with medical graphics significantly improved resident physician comfort level with 4 areas regarding feeding tube placement and management.

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Joseph E. Kerschner, MD

MCW's New Cancer Research Building Will Stimulate Collaborations in Science Aimed at Decreasing the Region's Cancer Burden

Joseph E. Kerschner, MD

The American Cancer Society estimates that in 2022, approximately 37,300 Wisconsin residents will be diagnosed with cancer and nearly 11,600 will die from the disease.[1] Unfortunately, our state is above the national average for rates of cancer incidence and mortality, with persisting disparities in geographic areas, as well as among racial and ethnic minority populations.[2]

In particular, a 2015 study by researchers at the Medical College of Wisconsin (MCW) on breast and colorectal cancer survival disparities in the 8-county region in southeastern Wisconsin – including the city of Milwaukee – revealed significant cancer survival disparities by race, ethnicity, sex, and geography in southeastern Wisconsin. Such disparities are a top public health priority.[3]

Accelerating discoveries that will eradicate the cancer burden in Wisconsin is a priority for MCW. In particular, focusing on eliminating disparities in cancer care and survival is a primary emphasis of this priority. To that end, the overarching mission of the MCW Cancer Center is to work through an equity lens to reduce the cancer burden in Wisconsin through transformational cancer research, exceptional education and training, multidisciplinary quality patient care, statewide cancer prevention programs, and progressive public policy implementation.

We have been moving quickly to execute effectively on this mission. In 2019, Governor Tony Evers and the Wisconsin State Legislature committed a $10 million Wisconsin State Building Commission grant within the 2019-2021 biennial state budget toward a cancer research building for MCW. When complete, the building will be Milwaukee's only cancer-dedicated research facility and will support our scientists and physicians to advance research that addresses the unique cancer burden of southeastern Wisconsin and beyond – ultimately improving clinical outcomes for all patients.

Accelerating discoveries that will eradicate the cancer burden in Wisconsin is a priority for MCW. In particular, focusing on eliminating disparities in cancer care and survival is a primary emphasis of this priority.

Currently in its design phase, this state-of-the-art facility features a building design with tremendous promise for accelerating research and community impact. Community impact continues to be at the forefront of the planning process, not only within this new research building but the entire MCW Cancer Center program. In particular, Melinda Stolley, PhD, Associate Director of Population Science Research at the MCW Cancer Center and the Ann E. Heil Professor in the MCW Department of Medicine is engaging members of the community in the building's design, as well as formally launching an investigative research project on the impact of the Cancer Research Building for the communities we serve and its role in advancing health equity.

On the research front, the new Cancer Research Building will serve many important purposes. It will increase capacity for wet and dry lab space, enabling our researchers – and those we collaborate with across the state – to accelerate their work toward discoveries that will lead to life-saving new treatments. The space will be used to stimulate new partnerships in science aimed at decreasing the region's cancer burden through research, education, and outreach in the causes, prevention, early detection, and development of cancer treatments. Among the cutting-edge enhancements expected to be included in the new building are CryoEM (a version of electron microscopy that enable high-resolution, 3-dimensional data collection on samples that

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could not be used with other techniques in the past) and cellular therapy labs for chimeric antigen receptor (CAR) T-cell therapy, which has been the subject of numerous MCW clinical trials in the past several years.[4]

Additionally, the 130,000 to 150,000 square-foot Cancer Research Building will maximize state-of-the-art and progressive research practices across the entire spectrum of disciplines including basic, translational, clinical, population science, and policy. Further, by leveraging the Cancer Center's team science approach, the new building will provide tremendous opportunities to enhance efficiencies and collaboration within scientific neighborhoods that address the MCW Cancer Center's strategic priorities. The Cancer Center's "Integrated Disease-Oriented Teams" (iDOT) – comprising basic, translational, and clinical cancer researchers/physicians who are involved in improving care delivery – will benefit from expanded collaborative space to develop research from the bench to the bedside to the community – and back.

The development of the Cancer Research Building underscores MCW's commitment to diagnosing and treating rare cancers, which affect fewer than 40,000 individuals annually in the US – although as a group, they comprise slightly more than 25% of all cancers. And because rates in children are very low, all children's cancers as considered "rare." Rare cancers cause about a quarter of all cancer deaths each year.[5] The new building will leverage key scientific investments to accelerate discoveries in metabolomics, structural biology, immuno-oncology, precision oncology, and rare cancers, and cancer disparities – for the eradication of cancer for all.

Groundbreaking for MCW's new Cancer Research Building is expected in summer 2022. I anticipate sharing progress on the new Cancer Research Building in future Dean's columns.

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