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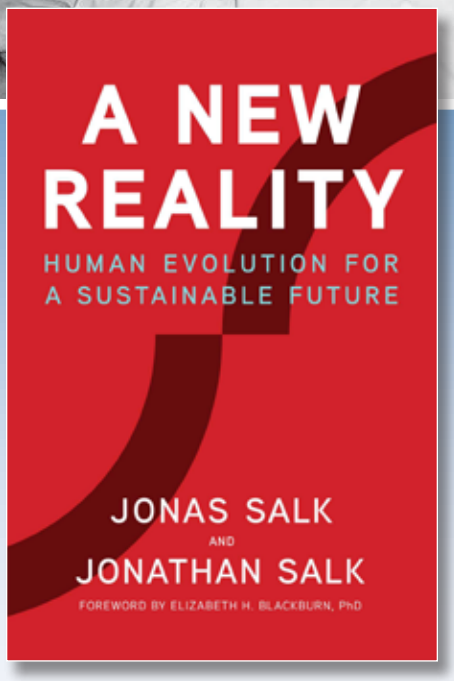

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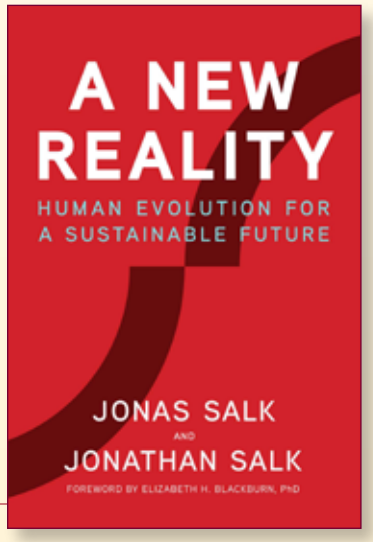

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From Concerts to COVID: Transforming the RI Convention Center into an Alternate Hospital Site in under a Month

SONYA NAGANATHAN, MD; KELLY MEEHAN-COUSSEE, MD; SCOTT PASICHOW, MD, MPH; HEATHER RYBASACK-SMITH, MD; WILLIAM BINDER, MD; FRANCESCA BEAUDOIN, MD, PhD; ANDREW N. MUSITS, MD, MS; ELIZABETH SUTTON, MD; GIANNA PETRONE, DO; ADAM C. LEVINE, MD, MPH; SELIM SUNER, MD, MS

ABSTRACT

Field hospitals have long been used to extend health care capabilities in times of crisis. In response to the pandemic and an anticipated surge in patients, Rhode Island Gov. Gina Raimondo announced a plan to create three field hospitals, or "alternate hospital sites" (AHS), totaling 1,000 beds, in order to expand the state's hospital capacity. Following China's Fangcang shelter hospital model, the Lifespan AHS (LAHS) planning group attempted to identify existing public venues that could support rapid conversion to a site for large numbers of patients at a reasonable cost. After discussions with many stakeholders – pharmacy, laboratory, healthcare providers, security, emergency medical services, and infection control – design and equipment recommendations were given to the architects during daily teleconferencing and site visits.

Specific patient criteria for the LAHS were established, staffing was prioritized, and clinical protocols were designed to facilitate care. Simulations using 4 different scenarios were practiced in order to assure proper patient care and flow, pharmacy utilization, and staffing.

KEYWORDS: disaster preparedness, COVID-19, EMS, operations, surge

BACKGROUND

Field hospitals have long been used to extend health care capabilities in times of crisis. In the American Civil War, field hospitals were used to provide solace and comfort, as well as limited care to (often mortally) wounded soldiers. During the 1918-1919 influenza pandemic, field hospitals played an important role in extending care beyond the limited capacity of the nation's hospitals. As the city of Providence braced for a surge of patients, Rhode Island Hospital added 75 beds, Saint Joseph's Hospital added 25 beds, and the former Hope Hospital, a specialty surgical facility, provided its nurses' home and billiard room for emergency care.[1] Emergency hospitals opened in Pawtucket, Woonsocket, Westerly, and Warwick.[2]

In December 2019, the first case of the novel coronavirus, SARS-CoV-2, known as COVID-19, was detected in Wuhan, China. Soon after, on Jan. 19, 2020, the first case of COVID-19 was reported in the United States in Snohomish County, Washington.[3] By the first week of March, there were nearly 110,000 cases of COVID-19 globally and nearly 600 cases in the United States.[4] At that time, there were still no documented cases of COVID-19 in Rhode Island (RI).[5] In response to the pandemic and an anticipated surge in patients, RI Gov. Gina Raimondo announced a plan to create three field hospitals, or "alternate hospital sites" (AHS), totaling 1,000 beds, in order to expand the state's hospital capacity.

On March 9, 2020, Gov. Raimondo signed Executive Order 20-02 directing the Rhode Island Emergency Management Agency (RIEMA) to activate the state emergency operations center, establish mobile support units, and deploy disaster teams.[6] One month later, Executive Order 20-21 was signed mandating the expansion of hospital capacity including "constructing and operating alternative hospital sites." The Rhode Island Convention Center (RICC) was identified as the Lifespan site, while the former Citizens Bank operations center in Cranston and the former Lowe's store in North Kingstown were utilized by the Care New England Health System.[7] Lifespan, the state's largest health care system, was given the task of creating a 600-bed AHS on March 28.

Erecting an AHS is no small feat, requiring the assistance and input of many. This article seeks to highlight components of the planning and execution involved in transforming the RICC into an AHS offering COVID-19 specific, hospital level care.

IDENTIFYING A SITE

Alternate hospitals have been created in all settings including fields, gymnasiums and conference rooms, but the challenge of needing to house up to 600 patients for an extended period made the more traditional field hospital approaches (i.e. tents and cots) less than ideal. The issue of where to establish such a facility without breaking ground on a brand-new structure presented a unique challenge in a small state. China's Fangcang shelter hospitals, created in response to the COVID-19 pandemic, were temporary hospitals converted from existing public venues to care for patients with mild to moderate disease. Following the Fangcang shelter hospital model, the Lifespan AHS (LAHS) planning group attempted to identify existing public venues that could support rapid conversion to a site for large numbers of patients at a reasonable cost.[8] Factors such as water and sewer capacity in

addition to the ability to deliver an oxygen supply to each bed were unique considerations in site identification.

The final determination of the LAHS was decided by the Governor's office with input from RIEMA, the RI Air National Guard (RIANG), and various consulting groups. Considering the state's largest hospital, Rhode Island Hospital, has only 719 beds, the decision to create 600 additional beds at an alternative site would require a significant amount of space. Identifying an existing venue that would allow for such capacity quickly narrowed down the options. The RICC was selected for its central location, size, easy access and egress, proximity to two acute care hospitals with ICU and surgical capacity, as well as an established relationship with local public safety agencies.

CONSTRUCTION

Design was the first step. By decree of the Governor, RIANG was tasked with overseeing the construction of the facility and providing logistical support. The state contracted with an infrastructure firm, which, in turn, sub-contracted the architectural and construction work. Many RI companies were used as subcontractors during the building process, providing jobs at a time where unemployment in the state was at a record high.

After discussions with many stakeholders, including pharmacy, laboratory, healthcare providers, security, emergency medical services, and infection control, design recommendations were given to the architects during daily teleconferencing and site visits (which were limited in space and time to respect social distancing measures). Ingress and egress, modifications to registration rooms, ward patient bays, and resuscitation pod designs were created after these feedback sessions. Actual construction took 13 days. While the RICC had excellent infrastructure, certain modifications needed to be made. Three industrial fans were installed on the roof and connected to large ducts in the facility to engineer a negative pressure environment in the clinical care area (**Figure 1**). Plumbing was installed to existing conduits for sinks. The loading docks were segregated into hot and cold zones for infection prevention; donning and doffing zones were created at entrance points to the clinical care areas, and pharmacy and lab services were isolated in the cold zones with a transition zone for handoff of materials. Bathrooms were modified to include showers.

INFECTION CONTROL

Emergency response to hazardous events dictate the division of areas based upon potential for exposure; these are

Figure 1. Clinical care area [PHOTOS: SELIM SUNER, MD]

Figure 2a. Handwashing stations

Figure 2b. Resuscitation room

commonly termed as "hot" (area with highest concern for exposure), "warm" (transition area), and "cold" (clean and without potential for contamination).[9] Since this AHS would house large numbers of infectious patients, zones with these distinctions were established to aid in the determination of medical personnel exposure risk. Any area where a patient would be while receiving care in the facility or where a patient would be entering or exiting the facility was designated as hot. This area was continuous and was surrounded by warm zones. Three large access points to the hot zone were chosen for the donning and doffing of personal protective equipment. This was based upon the need for larger numbers of staff to enter and exit together during change of shift. There was also a donning and doffing station placed just before staff bathrooms that was accessible from the hot zone, and a small station where ambulance patients would be leaving the hot zone. While ideal planning would have allowed for full decontamination on site (e.g. staff showers), facility limitations prevented this from being established. It was also determined that the risk to providers from incidental contact with the pathogen was low enough that offsite decontamination was reasonable. Changing areas were provided to allow for removal of clothing worn in the hot zone, and ample hand sanitation stations were available for additional hygiene measures (**Figure 2a**). The process of providing patient nutrition was also evaluated. Food for both patients and providers were prepared in the same cold zone, and then transported to different areas, with staff eating in a cold zone cafeteria, and patient food being transferred to the hot zone via a warm zone created by a two-layered door. Similarly, pharmacy developed hand-off procedures. Most medication preparation was to occur in a cold pharmacy and handed through a double-closed passage into the hot zone, creating a warm zone in between. Time sensitive medications needed in the event of resuscitation were kept in an Omnicell in the resuscitation room in the hot zone. (**Figure 2b**).

DEFINING THE PATIENT POPULATION

Globally, some of the alternative hospital sites were designed to provide additional intensive care unit (ICU) level facilities for the increased number of mechanically ventilated patients or designed to manage non-COVID-19 patient populations. However, the LAHS was designed to extend inpatient capacity for patients with COVID-19; the primary objective was to move floor-level patients from inpatient units, allowing the ICUs to expand into medical floors, rather than staffing and equipping a standalone ICU at the AHS. This, in turn, made regular floor space in the hospitals a premium. The LAHS was designed with the intent to not make this a fully functioning hospital, rather, to extend inpatient capacity in the disaster setting. For this reason, inclusion criteria was limited to patients that were between the ages of 18 and 65, had a laboratory confirmed or clinical diagnosis of COVID-19, were experiencing continued shortness of breath but had a pulse oximetry reading >92%, had a non-dynamic or non-ischemic appearing electrocardiogram, and were

exhibiting signs and symptoms meeting criteria for observation or inpatient hospital level of care. As the site was not fully capable of providing all hospital services such as imaging and escalation to ICU level of care, the very young, pregnant, those requiring more frequent evaluation, and those experiencing significant respiratory distress would be excluded from admission to the AHS.

Patients requiring imaging (plain X-ray or computerized tomography) or specialty services could be transported to a Lifespan hospital and returned to the AHS or be admitted to a Lifespan hospital if their condition required inpatient care. Patients could be directly admitted from local emergency departments or be transferred from Lifespan hospitals and other community facilities as long as they met LAHS admission criteria. Provisions were made to serve the diversity of our local population with availability of translator services, social services, and discharge instructions in the most commonly spoken languages.

STAFFING

A 2017 Prehospital and Disaster Medicine article found that healthcare providers may not be fully prepared for disasters.[10] With this knowledge in mind, along with an anticipated shortage of extra acute care providers (emergency medicine and critical care) due to their "home hospital" commitments, the decision was made to create a hybrid staff of acute care providers along with others from specialties whose practices were closed or operating at a minimal capacity. Acute care physicians were deployed as facility leaders available for the acutely decompensating or complex patients, while providers volunteered from many other specialties around the state and within Lifespan to staff the LAHS. While 600 beds were created at the LAHS, approximately 25 separate pods of 24 patients each were to be staffed by 1 attending physician or advanced practice provider and 2 nurses. A separate 12-bed area was created as a transition zone affording a higher level of care for patients requiring transfer to a hospital.

Nursing staff were recruited with the express goal of finding experienced nurses specializing in emergency or critical care medicine, while not straining staffing resources already committed to local hospitals. Emergency medical technicians were recruited to assist in monitoring staff members for symptoms prior to entering the facility as well as to respond to emergencies within the facility. Paramedics were deployed to evaluate patients transferring into the facility and to treat those patients needing a higher level of care in the resuscitation area, alongside the acute care physician. Fourth-year medical students were awarded early graduation and volunteered to work in the LAHS as newly minted doctors.

CLINICAL PROTOCOL DEVELOPMENT

Clinical protocols were developed for (1) COVID-19 general management; (2) emergency management of decompensating patients; (3) evaluation of new symptoms (e.g., chest pain); and (4) management in the event of a staff member illness. Protocols were adapted from current standard care in the parent hospital system (Lifespan) and were based on expert consensus, recommendations from the Centers for Disease Control and Prevention, and professional society guidelines. In addition, protocols were aimed at creating simple, easy-to-follow guides for the rapid identification and initial management of life- or limb-threatening emergencies by non-emergency trained providers until the patient could be moved to the resuscitation area for care by an acute care physician. Procedures for rapid specialty consultation (e.g., cardiology, infectious disease) were also developed, should the need arise. Protocols ultimately were a hybrid of in-hospital and pre-hospital emergency medical services (EMS) style algorithms. Examples may be seen in **Figure 3**.

Figure 3. Protocol examples

Acute Change in Neuro Status (including seizures)

1. Ensure airway protection; position in left lateral recumbent position as needed
2. If concern for acute psychiatric illness, ensure staff, patient and bystander safety.
3. Check glucose
4. Consider a trial of naloxone if there is respiratory depression AND concern for opioid overdose
5. Perform brief neurological exam to evaluate for focal deficit
6. Obtain 12-lead EKG

Hypoglycemia

1. Encourage PO and recheck glucose after 5 minutes
2. If unable to tolerate PO, administer D10 wide open until mental status improves
3. Once mental staus improves, encourage PO intake
4. Recheck q15 minutes glucose x 3 after resolution of symptoms to ensure stability

Intractable Nausea/Vomiting

1. Administer 4mg PO ondansetron ODT (if no h/o prolonged QTc)
2. Consider administration of additional 4mg of IV ondansetron PRN
3. If no response to ondansetron, consider alternatives (prochlorperazine, metoclopramide)
4. Evaluate for other causes of N/V including MI, bowel obstruction, etc.
5. IVF bolus for persistent symptoms

EQUIPMENT & INVENTORY

Medical equipment, supplies, and medication needed for the facility were determined by the planning group with the help of pharmacists, physicians, and nurses from key specialties. The final list reflected medications required for the stabilization of critical and acutely decompensating

patients prior to transfer to the hospital. Some of the determinations made in this planning process included keeping the minimum necessary equipment for stabilization prior to transfer to a standard emergency department (ED) without overwhelming staff with infrequently used items. The focus was on having equipment available to treat immediately life-threatening conditions and performing stabilizing procedures rather than definitive management. For example, it was determined that thoracostomy tubes would likely not be needed since a tension pneumothorax would be a rare event in this population, and rapid interventions such as needle decompression or finger thoracostomy could replace the need for this time- and equipment-intensive procedure.

A handheld point-of-care ultrasound machine was also obtained for use by the acute care physicians in the resuscitation area in place of typical ED and ICU portable (X-ray) and nonportable (computed tomography) imaging equipment. A complete inventory list was assembled and reviewed by members of the team and procured with state assistance.

USE OF SIMULATION TO TRIAL PROTOCOLS

A systems-based evaluation leveraged high-fidelity simulations of common patient-care scenarios and high-risk, low-frequency events. These onsite simulations were facilitated by the Lifespan Medical Simulation Center during a four-hour session. Following each scenario, a debriefing session was held to solicit feedback and potential modifications in clinical protocols or equipment needed. More than 30 individuals representing various stakeholder groups were present. Two notable changes that came from this session included: a change in the medication stored in the resuscitation room (from intubation-focused to resuscitation-focused), and the addition of an extra donning and doffing station adjacent to the ambulance egress from the hot zone in the event a LAHS staff member required transfer to a hospital.

COMMUNITY COLLABORATION, SECURITY, AND EMERGENCY MEDICAL SERVICES

As the LAHS was not meant to function as a full hospital, plans for transfer to local hospitals were of the utmost importance. In collaboration with multiple RI EMS agencies including LifePact Critical Care Transport and the Providence Fire Department, plans were established for transfer of patients into the LAHS, transfers to higher level care, and discharge from the LAHS. Communication was established with EMS agencies, acute care hospitals, and urgent care centers regarding inclusion and exclusion criteria for patients cared for in the LAHS and transfer protocols. The Lifespan Communications Center and ExpressCare (an inter-hospital emergency care referral center) played an integral role in the coordination of patient transfers in and out of the LAHS.

Fire safety and security were an important concern as historically, field hospitals have been targets of violence. Since the September 11, 2001 terrorist attacks, hospitals have been thought of as ideal, soft targets for terrorist threats – both organized and "lone wolf" type attacks.[11,12, 13]

In order to ensure safe operations at the LAHS, this massive undertaking required the cooperation of multiple agencies including the RIANG, State Police, Providence Police Department, Providence Fire Department, State Fire Marshal's Office, and Lifespan Hospital Security. RIANG facilitated tabletop exercises in order to identify risk and hazards and possible mitigation measures.

CONCLUSION

The decision to expand the state hospital-bed capacity by construction of alternate sites was based on predictive models which signaled a deficit of beds during the height of the pandemic. By use of public health measures such as distancing, isolation, closure of schools and non-essential businesses, increased testing, contact tracing, and isolation of individuals who test positive for SARS CoV-2, the surge was blunted significantly in Rhode Island. Though the LAHS has yet to care for patients, the additional time allowed for more planning and fine-tuning of protocols. This issue is not unique to RI, however. Multiple field hospitals throughout the nation have been built and remained empty or minimally used, including several facilities in New York, Colorado, Illinois, Wisconsin, and Michigan.[14] The LAHS will remain intact through 2020. As many hospitals throughout the state reached 90% capacity during the spring and with community spread still a threat, the state stands prepared for an expected "second wave."

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Stereotype Threat: Racial Microaggression Undermines Performance of Black Health Professionals

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A CLASSIC STUDY: *Black and white college students take a difficult test. Half are informed that the test measures intelligence; the other half are told that the test is not related to intellectual ability.*

RESULT: *Blacks scored worse than whites if the task was described as an intelligence test, but performed as well as whites when told the test is not a measure of intelligence.*[1,2]

What's happening here?

In their landmark 1995 study, Steele and Aronson explored underperformance on a test or problem-solving exercise manipulated by stereotyped racial distinctions. Less obvious than the widespread, overt prejudice in American society are subtle, often unconscious acts or microaggressions directed against a stigmatized, marginalized group that can facilitate impaired self-reflection and behavior. This damaging state occurs when actual or perceived cues in specific situations facilitate negative self-stereotypes connected to an individual's group (such as women, elderly, disabled or Black medical students). These threats can trigger impaired cognitive, physiologic, psychologic and emotional responses, which may interfere with academic or other task performance, diminished self-worth and a sense of belonging.[3,4] Stereotype threats are perceived whether or not others actually hold biased racial, gender- or age-based stereotypes. Rather, a threat is activated by the target's belief in a specific pejorative stereotype attached to their group. A perpetrator may be unaware of such microaggressions.

Our focus in this reflection will be an underrepresented minority group in medical school – Black students for whom the risk and reality of this phenomenon is particularly high.[5] Black medical students experience racism and discrimination which increase stress and challenge opportunities and aspirations associated with learning and socialization in what they frequently perceive to be a prejudiced and hostile environment.

Stereotypes are oversimplified beliefs which may mischaracterize and homogenize all persons in a group, typically an underrepresented, stigmatized minority. These rigid beliefs minimize or ignore the reality of a world of diverse, unique individuals. A common result is a biased, frequently negative perception of an individual or group. There is a pervasive under-appreciation of the consequences of these biases, termed stereotype threats or social identity threats.

This threat is commonly, but not always, associated with systemic racism and negative perception (believed or actual) held by a dominant group (e.g., whites, men), toward the targets – Blacks or women, for example. When minority students perceive a stereotype threat and then act in patterns in accord with the stereotypes, they tend to reinforce and enhance the threat's impact.

Am I treated as an individual or as a one-size-fits-all member of a group?

Racism facilitates practices which negatively influence beliefs and values (**Table 1**) for common detrimental contexts or cues that minority medical students confront that trigger threats.

The consequences of this damaging reality are diverse. (**Table 2**)

Racial distancing

Data indicates that racial distancing and intergroup avoidance are common and can be unrelated to explicit interracial bias.[6] Racial prejudice and racial distancing are not the same. Less frequent and open interactions with members of dominant groups harm everyone. Frantz and co-workers reported that stereotype threat impaired whites in settings where whites could assess their behavior as inadvertently supporting the stereotype that whites are racist.[7] Thus, the threat of being outed as racist may induce some whites to distance themselves socially from Blacks. Social distancing can blunt the contributions of minorities including survival skills honed in difficult neighborhoods, a tight, supportive intergenerational ethos and commitment to family and community.

What do Black med students say?

In focus groups, Black medical students decry what they perceive as too frequent misinformation and limited understanding by whites of affirmative action, medical school admission guidelines, scholarships and financial aid.[5,8] Students also targeted administrators who frequently did not seem to understand the importance of embracing diversity or advancing a culture of inclusion. Group participants also stated that their ethnic majority classmates

Table 1. Common contexts facilitating stereotype threats in Black medical students

Mistaken for housekeepers, orderlies, other med students
Social/numerical isolation, loneliness, low social status
Inadequate same race, gender, ethnic role models
Financial limitations impairing socialization
Institutional discrimination, racism, perceived slights
Tokenism exacerbating self-doubt
Mass media portrayal in subordinate or unflattering roles
Self-pressure to represent their race rather than be an individual
Effects most likely in tasks pushing upper limits of ability
Absence of a shared identity with mainstream groups

Table 2. Stereotype threats, consequences

Impaired self-esteem, self-identity, sense of belonging
Decreased performance/aspirations/expectations
Reduced sense of personal accomplishment/competency
Disengagement: avoidance of settings perceived as threatening
Deidentification: withdrawal, loss of interest in settings triggering stereotypes
Code switching: alteration of speech, clothing, behavior, mannerisms when with non-minority groups to appear "less" Black
Racial distancing; miscommunication with mainstream groups
Discounted/devalued contributions
Increased risk of burnout, depression, suicidality, impostor syndrome
Conforming bias: more likely to stifle creativity, go along with the crowd, leads to loss to group problem-solving by self-censoring to confer inclusion, acceptance
Decreased interest for leadership positions
Fear of confirming stereotypes resulting in underperformance

lacked confidence in Blacks' skills. Participants also noted a "minority tax" related to a disproportionate burden placed on underrepresented students and faculty to participate in recruitment of candidates and diversity-associated service and committee assignments. Fear of tokenism exists.

COVID, racial violence and stereotypes

Mass media portrayal of Blacks as violent protesters or in subordinate roles accentuates negative stereotypes. Blacks complain that they are overrepresented as criminals and underrepresented as victims compared to real-world crime statistics. Media accentuation of intergroup differences and boundaries can impair empathy with marginalized groups, such as Black medical students. Misinformation about disproportionately higher COVID-related mortality in Blacks can target minorities as less fit, healthy, health-conscious, inferior or "different."

Social identity threats also attack privileged, mainstream groups. Some data indicates that whites underperform on motor skill tasks if described as testing athletic ability.[9] Another finding is that white men may underachieve on math exams when told that their scores would be compared with those of Asian men.[10] Importantly, whites threatened by the Asian math stereotype underperform only if they were very identified with math as integral to their self-identity. In one study, women under stereotype threat had lower leadership aspirations than women who did not experience that threat.[11]

Do stereotype threats explain real-world performance?

Some scholars debunk the validity of stereotype threat effects, believing that they arise mainly from manipulated experimental study conditions, not actual performance impairment.[2] This view posits that stereotype threat effects do not contribute to actual gaps in performance between Blacks and whites, or women and men. This alternate analysis claims that self-identity threats exist primarily as laboratory phenomena, where investigators artificially manipulate study parameters to ensure stereotypes are especially salient. Adding to this debate is the fragmentation in the literature, which is fraught with major, incompatible differences in study design, populations and environments and an absence of clear, uniform guidelines for investigation. Thus, generalizability may be compromised.

Conclusion

Co-author CH writes:

> *"As a Black woman and the first in my family to attend medical school, I must express how stereotype threat can negatively impact my medical school experience. Imagine transitioning from a historically Black college to a medical school where I can almost count the number of Blacks on one hand. Being a woman adds to the social identity threats. It is exhausting to see too few people who look like me. I am frustrated, as wonderful non-Blacks who genuinely want to help may not understand my struggles. Imagine not having same race, same gender, same ethnicity mentors in my specialty choice. All medical students confront huge stresses. But, most of my peers do not confront the added burden of decompressing from such heightened micro-aggression and fear of underperforming or being falsely perceived as "dumb." After summoning the mental reserves to avoid drowning in my daily challenges and wondering how I can look better the next day, I refocus to start studying."*

The sad reality is that talented, competent Black people may become "deskilled" and underachieve compared to their underlying ability. Social identity threats can interfere with performance, self-identity, motivation and effective engagement in triggering environments.

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Making Medical Student Documentation Count in 2020

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ABSTRACT

The recent changes to expand the permissible scope of medical student documentation draw ample parallels to historical efforts to increase the clinical role of medical learners. While the expanded role of medical student documentation holds the potential for increased community preceptorship and enhanced medical student participation in patient care, it also comes with possible consequences for preceptors, students, and patients. The authors posit that while the rule changes represent important steps forward, further guidance around how these rules are to be implemented will be necessary before the healthcare system can reap their full benefit.

KEYWORDS: undergraduate medical education, documentation, preceptorship, practice patterns, physicians, medical students

As of January 1, 2020, the Centers for Medicare and Medicaid Services (CMS) formally expanded the range of services eligible for documentation by medical students, physician assistant (PA) students, and advanced practice registered nursing (APRN) students.[1] The 2020 Medicare Physician Fee Schedule (MPFS) will build upon the foundation laid in February 2018 with Transmittal 3971, which states, "Students may document services in the medical record…The teaching physician must personally perform (or re-perform) the physical exam and medical decision-making activities of the E/M [Evaluation and Management] service being billed but may verify any student documentation…rather than re-documenting this work."[1] In addition to E/M services, students will also be able to document procedures and diagnostic tests. Furthermore, any preceptor (MD, PA, or APRN) may attest to the documentation provided by a student of any training specialty; a PA preceptor, for example, is not limited to attesting to only PA student documentation, but can also attest to MD or APRN student documentation.

This change in CMS policy, advocated by the American Association of Medical Colleges (AAMC) and the Society of Teachers for Family Medicine (STFM), was proposed to positively impact medical student preceptors by alleviating documentation burden.[3] This is particularly true for community-based preceptors who carry large patient panels in addition to teaching.[4] In fact, a survey of community preceptors conducted by the STFM found overwhelming support for expanding medical student documentation capabilities. Preceptors estimated the use of medical student documentation for billing purposes would save them up to one hour per half day of precepting.[5]

The 2020 MPFS changes are in line with CMS' "Patients Over Paper-work" initiative.

The 2020 MPFS changes are in line with CMS' "Patients Over Paperwork" initiative. The broad flexibility in the 2020 MPFS student documentation regulations aim, first and foremost, to reduce a widely recognized "note bloat" that is present in the Electronic Health Record (EHR). By allowing the attestation of student notes, duplicative documentation is reduced, allowing for a less cluttered and easier to use EHR, and in theory, increasing precepting time, rather than rewriting student notes. These two outcomes ultimately benefit both patients and providers who are working to provide high quality care.

Until the introduction of the aforementioned changes, medical student documentation use for billing purposes was limited to social history, family history, and the review of systems. This limitation resulted in teaching physicians rewriting all of the notes written by medical students to personally document the billable components of an E/M service, including the history of the present illness, the physical exam, and the medical decision making. Merging the expanded documentation afforded by medical students with their advanced roles in the healthcare system appears to be a win for all. This transmittal appropriately recognizes the value that medical students bring to health care while incentivizing teaching physicians to take on student learners.

Documentation in medical education over the years

The inclusion of the rule change in the finalized 2020 MPFS is critically important to its implementation. To fully understand why official codification was a crucial development, it is important to understand the more distant history of documentation in medical education, specifically with regard to resident physicians. Throughout its history, CMS has been ambivalent as to the value learners bring to the health care system. Despite Medicare funding Graduate Medical Education (GME) since 1965, regulation of the integration of resident education into patient care was largely ignored in the first three decades of Medicare's existence. A 1986 report from the United States General Accounting Office (GAO) called on the Health Care Financing Administration (HCFA; CMS' predecessor) to clarify the vague regulatory criteria undergirding teaching physician documentation for the billable components of the E/M encounter because they "[did] not spell out what documentation [was] considered appropriate to substantiate entitlement to Medicare fee-for-service reimbursement."[6]

In answering the call for clarity, CMS issued the *Medicare Physician Fee Schedule* (MPFS). First released in 1996, the MPFS annually updates regulations that govern which services are reimbursable under Medicare. It was not until the 1996 MPFS that CMS addressed, for the first time, how attending physicians engaged in the teaching of residents could bill for their work. The 1996 MPFS stated that, in order to bill for services rendered and documented by residents, the teaching physician had to be physically present for the key components of the encounter and that their presence had to be adequately documented. Perhaps more tellingly, the preamble to the 1996 MPFS stated there was no medical student contribution to documentation that could be used for billing.

Students were not mentioned by CMS again until 2002, when Transmittal 1780 was issued. Transmittal 1780 officially defined what a "medical student" was and what their limited contribution to E/M services documentation could be – documenting the review of systems, family history and social history. The teaching physician still had to re-document the rest of the patient encounter. There was hope, however, that the ambivalence of CMS towards medical student teaching abated in 2018 with Transmittal 3971 which provides for the expanded use of medical student notes for documentation and billing purposes. While the changes to medical student documentation are welcomed by many, some concerns remain with regard to their implementation.

The codification of the 2018 transmittal in the 2020 MPFS presents important opportunities for increased community preceptor participation in academic medicine, more meaningful student contributions to patient care, and decreased note bloat. However, there are important potential unintended consequences. Preceptors may be tempted to use medical students as they would residents or even advanced practice clinicians with respect to the workload students are expected to take on. This presents both the opportunity for students to flourish in a more demanding clinical atmosphere, and also the opportunity for increased student burnout as they become the principle documentarians of patient encounters. Another possibility is that students may be treated more as medical scribes than as learners. The roles of medical student, medical scribe, and employee have the potential to blur in ways that could be detrimental to both learner and patient wellbeing.[7]

Additionally, while maximum flexibility is widely desired with respect to documentation, particularly in team-based, ambulatory settings, not requiring a teaching physician to write a note might compromise patient care and documentation accuracy. In response to these concerns, CMS stated explicitly that they believe it is most in line with the goals of the regulation to allow maximum flexibility in documentation and, ultimately, it is the responsibility of the preceptor, regardless of their credentials, to ensure that documentation is accurate and that patient care is not compromised.

Further clarification needed

In a similar fashion to the confusion around resident documentation in the 1980s and 1990s, the question of the teaching physician's physical presence is a potential limiting factor in the applicability of the upcoming 2020 MPFS rule change. If, in fact, a preceptor needs to be physically present while a medical student takes a history, this would not alleviate the burden on teaching physicians. Instead, it would perpetuate the burden and may serve as a disincentive for teaching physicians to precept medical students. Clarification, published in the final 2020 MPFS response to public comments, confirm that a teaching physician's presence for all billable services is required for reimbursement. It remains unclear whether medical students presenting to the teaching physician with the patient present would meet the standard of "physical presence." Further clarification has also been requested with respect to how this rule change could be implemented when students work with residents.

Allowing medical student documentation to count within

the medical record is a welcome step forward in acknowledging the value of students within the healthcare system. In order for the potential of the final 2020 MPFS rule change to be fulfilled, further consideration from CMS is needed with regard to the requirement that a physician be present for all billable services. Additional concerns arise with respect to the potential unintended consequences for both students and patients. This will require close monitoring. Until such time, the authors remain cautiously optimistic that the final 2020 MPFS represents a movement forward in the context of the "Patients Over Paperwork" initiative.

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EMTALA: Testing the Good Faith Admission Requirement

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ABSTRACT

The Fourth Circuit Court of Appeals' March 13, 2020 decision in *Williams v. Dimension Health Corporation* reintroduced scrutiny on the lesser-known mandate of The Emergency Medical Treatment and Active Labor Act (EMTALA) concerning good faith admission to the hospital. EMTALA was enacted by Congress in 1986 to prevent patient dumping by prohibiting hospitals with emergency departments from refusing to provide emergency medical treatment to patients unable to pay for treatment, and prohibiting the transfer of those patients before their emergency medical conditions are stabilized. The reach of EMTALA ends when a patient is admitted and consequently becomes an inpatient, because then the hospital believes the patient would benefit from admission, and discharge and transfer would not occur as outlined in EMTALA. This paper examines the analysis of this mandate in *Williams v. Dimension Health Corporation*, and closely investigates one particular aspect of it: that admission must be made in good faith; otherwise, application of EMTALA's screening and stabilization requirements has not yet terminated, and hospitals can still be found culpable.

KEYWORDS: EMTALA, Emergency Medicine, Admission, Legal Liability

The Emergency Medical Treatment and Active Labor Act (EMTALA) is colloquially seen as the stipulation of emergency departments to treat all patients with emergency conditions, irrespective of the patient's ability to pay. However, a recent decision of the Fourth Circuit Court of Appeals, *Williams v. Dimension Health Corporation,* rekindled scrutiny under EMTALA, principally reviewing if there was culpability under EMTALA that extended beyond a categorical obligation of treating a patient with emergency medical conditions.[1] The case specifically analyzed the authority of good faith admissions under EMTALA, and discerned the boundaries of what was required to both constitute and prove an admission was not made in good faith, which is a conscious admission of a patient with the intent of providing the patient with subpar care. The application of EMTALA terminates when a patient is admitted for care and becomes an inpatient; however, this litigation highlights that not only does a patient need to be admitted, but that admission must also be made in good faith and not for the purpose of avoiding liability under EMTALA.[1]

In 1986, Congress enacted EMTALA to preclude hospitals with emergency departments from rejecting patients with emergency medical conditions due to their inability to pay. This unfunded mandate empowered Congress to delineate two irrefutable responsibilities of hospitals with emergency departments. One obligation is adequate medical screening, within the capacities of the emergency department and available ancillary services, to determine if a patient has an emergency medical condition.[2] An emergency medical condition is defined as a medical condition presenting with acute symptoms of sufficient severity, such that absence of immediate medical care would place an individual's health in serious jeopardy, serious impairment to bodily function, or serious dysfunctions of any bodily organ.[2] The other responsibility of hospitals with emergency departments is the stabilization of an individual's emergency medical condition before transferring the patient to another facility. Notably, EMTALA does not require treating a patient's emergency medical condition in full.[3] The legislation specifically states if any individual, whether or not eligible for benefits, comes to a hospital and the hospital determines that the individual has an emergency medical condition, the hospital must provide either further medical examination and treatment required to stabilize the medical condition, within the facilities available at the hospital, or transfer the individual to another facility.[4] The statute underscores an aim of ensuring medical treatment necessary to assure, within reasonable medical probability,

that no material deterioration of the condition is likely to result from or occur during the transfer of the individual.[5]

In *Williams v. Dimensions Health Corporation*, Williams was involved in a single-vehicle accident, where his vehicle rolled over, in 2014.[1] He was transported to George's Hospital Center, a Level II trauma center in Maryland, where he presented with severe hypovolemic shock, massive bleeding from arteries and extremities, massive soft-tissue injury, vascular injury to the left extremity, multiple open fractures, and pulseless extremities.[1] He was intubated and had a right antecubital cut-down performed by the on-call trauma surgeon within twenty minutes.[1] Throughout the night, Williams received CT scans on his head, chest, and spine, received X-rays, underwent his first surgery after the accident and was formally admitted.[1] Over the next eleven days, Williams underwent more surgeries and interventions, until he was transferred to the University of Maryland Medical Center.[1] Ultimately, William's injuries to the lower body necessitated a double-leg amputation. Williams later sued George's Hospital Center, claiming he received improper screening and that they did not satisfy the EMTALA stabilization requirement. These claims were argued and decided in favor of the hospital in 2018, by the District Court for the District of Maryland.[6] In 2020, Williams appealed the District Court decision to the Fourth Circuit Court of Appeals, and the crux of his argument on appeal was that his admission was not made in good faith, thereby allowing the application of EMTALA to the care he received during his inpatient stay.

The good faith admission requirement is not contained within the EMTALA statute itself, but rather was imposed under regulations promulgated under EMTALA by the Congressional authority of the Centers for Medicare and Medicaid Services (CMS), as part of the Department of Health and Human Services. CMS's regulations, passed in 2003, provide:

"If a hospital has screened an individual and found the individual to have an emergency medical condition, and admits that individual as an inpatient in good faith in order to stabilize the emergency medical condition, the hospital has satisfied its special responsibilities under this section with respect to that individual."[7]

Under the regulation, an emergency department cannot escape liability under EMTALA by admitting a patient it has no intention of treating and transferring the patient without satisfying the stabilization threshold.[8] This is because if a hospital believes that a patient would benefit from being admitted as an inpatient, then a transfer or discharge would not occur, so the hospital would not have to satisfy the stabilization threshold under EMTALA. The ruling in *Bryan v. Rectors and Visitors of University of Virginia* similarly reinforces that EMTALA's obligations terminate when the patient is admitted; however, that admission must be made in good faith.[9] If a party can prove that a hospital did not admit the patient in "good faith," then the hospital is liable under EMTALA. This is to discourage hospitals from using inpatient admission to avoid liability under EMTALA.[8]

In the *Williams* case, Williams specifically argues that the hospital did not admit him in good faith because the hospital did not involve a sufficient number of on-call physicians, the on-call trauma surgeon refused to perform surgery, and that the hospital was focused on reaping his premium insurance benefits. The judge relied on the 2003 CMS regulations' interpretation of good faith admission to identify whether there was a tenable defense to the liability under EMTALA in this litigation, and ruled that the hospital did admit Williams in good faith.[1,8] The Fourth Circuit specifically held in this case that:

> "[A] party claiming an admission was not in good faith must present evidence that the hospital admitted the patient solely to satisfy its EMTALA standards with no intent to treat the patient once admitted and then immediately transferred the patient. In other words, the standard requires evidence that the admission was a subterfuge or a ruse. The standard is not satisfied by simply alleging or showing deficiencies in treatment following admission.[1]"

Because he could not meet this burden of proof, Williams was denied the appeal, and the District Court's judgment was affirmed.[1] However, this ruling reinforced the claimant's responsibility to prove an admission was not made in good faith, with substantial evidence and not merely unfavorable health outcomes. The judge noted that Williams was provided treatment for eleven days after his admission, which encompassed resuscitation, surgeries, and several diagnoses.[1] This dispels the claim that Williams was admitted as a subterfuge because it exemplifies the level of care that Williams received. Williams's claim that the hospital admitted him in bad faith to collect his insurance benefits was also dismissed because the court believed it contradicted what the hospital would have done if there was a genuine desire to collect insurance benefits, which is admit him because of his exceptional insurance coverage and profit off that insurance coverage.[1]

Williams's inability to provide substantial evidence that his admission was not made in good faith and the documentation of the interventions he received over eleven days allowed the court to rule that the hospital was not liable under EMTALA.[1]

Another lesson from this case is the demarcation of appropriate screening. A violation of appropriate screening occurs when a patient does not receive screening or if a patient receives screening that is disparate from screening provided to other patients.[9] Therefore, to dismiss claims under EMTALA for improper screening, a court must verify the hospital abided uniformly by its own screening policies. Williams claimed the maximum acceptable response times for on-call trauma surgeons and specialty surgeons were 15 minutes and 30 minutes respectively, by state law.[1] Although the surgeons did not satisfy the time constraint, this is irrelevant to the ruling because state law does not affect EMTALA claims. EMTALA imposes a specific responsibility to abide by a hospital's own procedures, which was followed in this case. Additionally, this case exemplifies that subpar treatment alone does not prove an admission was not made in good faith.[1]

It is important to note that EMTALA does not serve as a conduit for claims that are intrinsically malpractice claims. In *Power v. Arlington Hospital Association* and *Brooks v. Maryland General Hospital Inc*, the judges stated EMTALA is not intended to guarantee proper diagnosis or provide a federal remedy for medical negligence.[10-11] EMTALA does not enforce a standard of treatment that must be upheld; rather it imposes an obligation of hospitals with emergency departments to provide treatment that is not disparate or inadequate. This litigation accentuates the significance of the lesser-known EMTALA good faith admission requirement because it could expand EMTALA's protections to the inpatient care setting, which can result in increased liability for physicians and hospitals. EMTALA extends beyond solely ensuring that patients are not rejected on their inability to pay for medical treatment; it standardizes a practice of ensuring admissions are made in good faith, patients receive uniform treatment in accordance to hospital policies, and conscientious attempts have been made to stabilize emergency medical conditions. ❖

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SARS-CoV-2 Complicated by Sinusitis and Co-Infection with Human Metapneumovirus

ABDULRAHMAN ALHARTHY, MD; FAHAD FAQIHI, MD; DIMITRIOS KARAKITSOS, MD, PhD

ABSTRACT

A previously healthy 25-year-old Asian male was admitted with acute respiratory failure due to COVID-19 pneumonia to our intensive care unit. He received empiric therapy and higher level of respiratory support via a high flow nasal cannula. Notably, human metapneumovirus was detected from the nasopharyngeal swab by RT-PCR. Six days post-ICU admission, sinusitis was clinically and sonographically detected. SARS-CoV-2 was detected in the fluid aspirated from the antrum. The patient has made an uneventful recovery. Further studies are required to investigate co-infections with SARS-CoV-2 and other viruses.

KEYWORDS: COVID-19, human metapneumovirus, high flow nasal cannula, sinusitis

[**Editor's note:** The following letter/case report was submitted by senior author Dr. Dimitrios Karakitsos, who did surgical/clinical rotations at Brown-affiliated hospitals during the early 1990s as a visiting medical student on scholarship from Greece.]

Dear Editors:

We have read with interest the article by *Touzard-Romo et al* regarding the co-infection with SARS-CoV-2 and human metapneumovirus that was recently published in the Journal.[1] We present a patient with SARS-CoV-2 disease (COVID-19) and co-infection with human metapneumovirus (HMPV). Considerations regarding oxygen support therapies are also discussed.

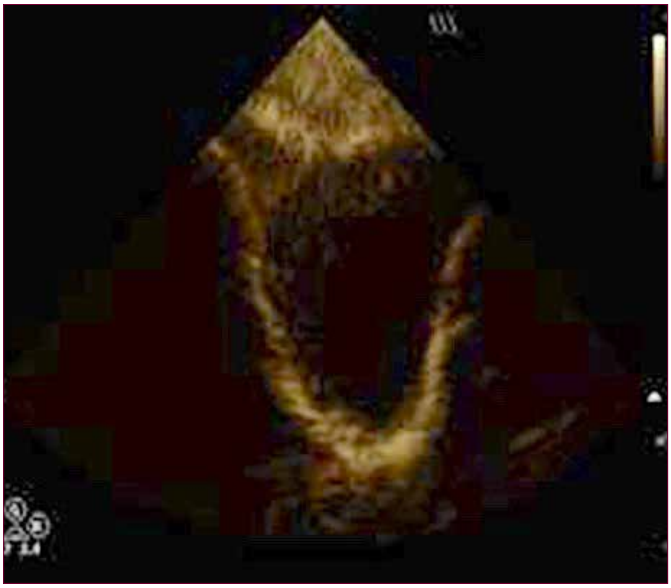
A previously healthy 25-year-old Asian male was admitted to the emergency room with three days fever (37.9° C; 100.22°F), dry cough, wheezing, and chest pain. His saturation of peripheral oxygen (SpO_2) was 75% on room air but he did not show any respiratory distress. He mentioned contact with his brother who has recently recovered from COVID-19 without sharing any further details. Physical examination revealed decreased breath sounds at the lung bases. Laboratory findings were within normal limits apart from lymphocytopenia (0.79×10^9/liter; normal: $1.1–3.2\times10^9$/L), and increased levels of C-reactive protein (656 mg/liter; normal: 0–5 mg/liter). Chest X-ray (**Figure 1**) revealed bilateral interstitial pneumonia. Nasopharyngeal swabs confirmed COVID-19 by Real-Time-Polymerase-Chain-Reaction (RT-PCR).

Figure 1. Chest X-ray depicting bilateral interstitial pneumonia.

The patient was admitted to our intensive care unit (ICU). He underwent a full diagnostic work-up for other viral, bacterial and systemic disorders. A higher level of respiratory support via a high flow nasal cannula (HFNC) was initiated (flow: 60 L/minute, fraction of inspired oxygen 40%) along with awake prone positioning (16 hours daily). The rate of oxygenation index [oxygen saturation / (fraction of inspired oxygen x respiratory rate)] was maintained over 6 for the upcoming 48 hours indicating successful oxygenation.[2] Empiric therapy with lopinavir/ritonavir, ribavirin and interferon beta-1b for 14-days, dexamethasone for 10 days, and prophylactic anticoagulation was administered.

Interestingly, RNA of HMPV was detected from nasopharyngeal specimens by RT-PCR after four days; however, no genotype was identified (types A and B) as phylogenetic analysis was not available. No treatment changes were made as ribavirin has shown some efficacy against HMPV.[3] Six days post-ICU admission, the patient developed new fever (38.9° C, 102.02° F). He complained of pain due to the application of HFNC. He had sensitivity over the right paranasal sinus. Ultrasound examination depicted a fluid collection

Figure 2. Ultrasound showing hypoechoic area in the right paranasal sinus (*"sinusogram"*) consistent with fluid collection.



(**Figure 2**).[4] Antral aspiration revealed clear fluid. RT-PCR performed on the fluid revealed SARS-CoV-2. Our patient has made an uneventful recovery. All work-up for systemic and other viral diseases was negative. He was discharged to home isolation after 22 days.

HMPV may cause lung infection in adults, especially elderly and immunocompromised patients as well as patients with underlying cardiopulmonary disorders. Diagnosis relies on RT-PCR, while treatment is mainly supportive. Co-infection with SARS-CoV-2 has only been recently reported.[1] Apart from the co-infection with HMPV, our patient has developed sinusitis while receiving oxygen via HFNC, which delivers high flow, warmed and humidified gas through the nasopharynx.[5] Whether this might facilitate recirculation and shedding of the viral particles in the upper airway is obscure. Further studies are required to investigate co-infections with SARS-CoV-2 and other viruses along with potential side effects of higher level oxygen therapies.

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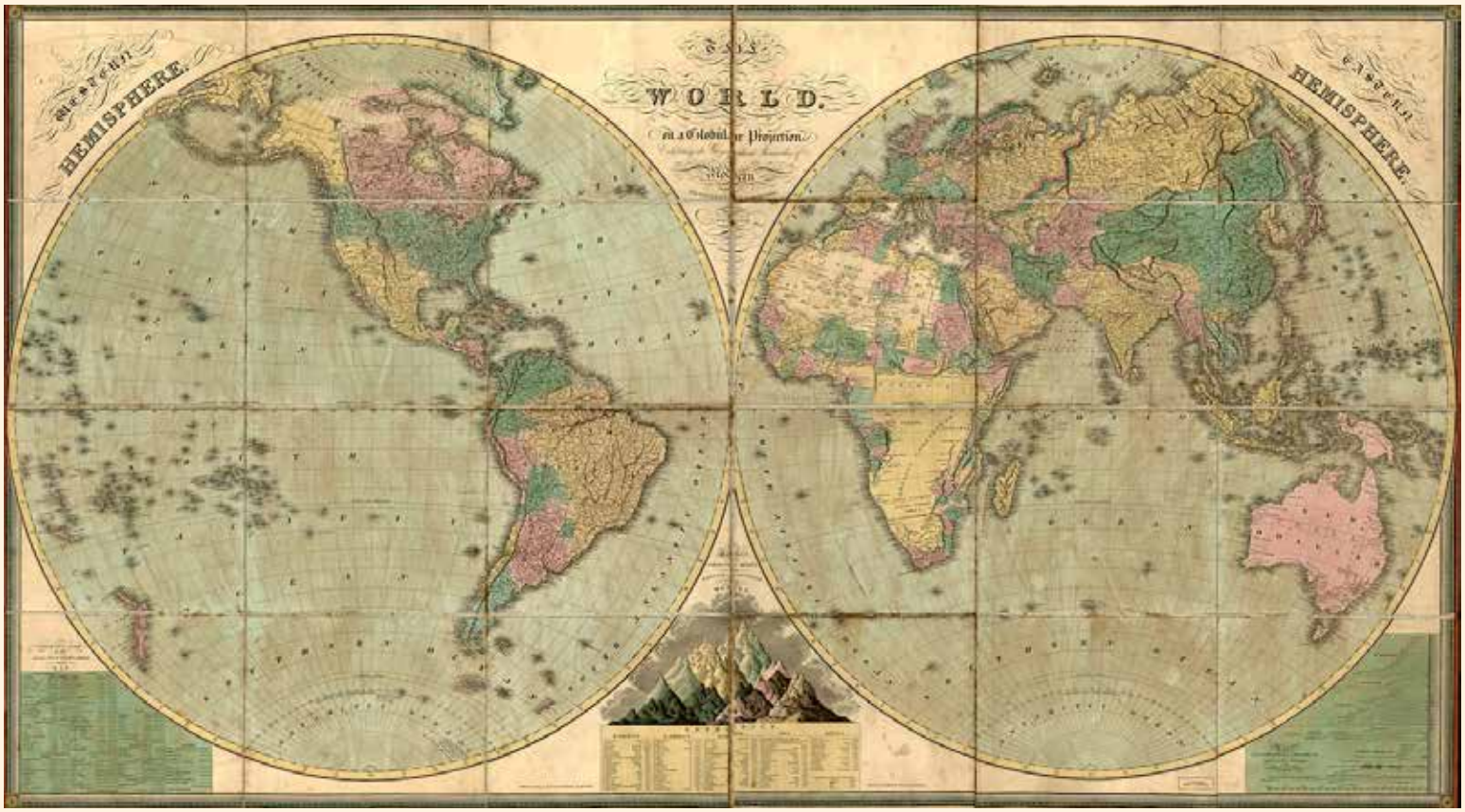
[Below] Vance, DH *The World, on a Globular Projection, Exhibiting the Geographical Researches of Modern Travellers & Navigators*. Philadelphia: Published by Anthony Finley, 1826. Map. Retrieved from the Library of Congress, www.loc.gov/item/2013591242



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A Review of Current Vaccine Recommendations, Schedules for Children, Adults

MARIA D. MILENO, MD
JENNIE E. JOHNSON, MD
GUEST EDITORS

At this unprecedented time of practicing medicine during the coronavirus pandemic, the focus on vaccines has never been more important.

Healthcare professionals of all backgrounds must remain up to date with the knowledge base regarding available vaccines and we must stay confident in our communications. We need to reach the ears, hearts and beliefs of our patient population – we are truly the ambassadors for the broad delivery of vaccines. We have the ability to protect our patients and ourselves from diseases that used to regularly sicken and even kill us!

Dr. Jennie Johnson and I and our colleagues working in the field of Infectious Diseases are delighted to create this special themed issue of the *Rhode Island Medical Journal* (RIMJ) to review the **latest vaccine updates** that can help all practitioners have a continuous dialogue about vaccine-preventable illness with our patients at every visit.

We review the **influenza vaccine** with tips on how to engage the patient. Practitioners get more push back on this vaccine than all of the others. It's of great importance that both primary care practitioners and specialists advocate for the flu vaccine. Cardiologists, for example, can present the standpoint that influenza is linked to an increased rate of myocardial infarction.

Adjustment and fine-tuning of the use of **pneumococcal pneumonia vaccines** was published in late 2019 due to a remarkable observation: vaccination of children with conjugate vaccines against the pneumococcus has dramatically reduced disease in older individuals.

All adults age 19 and older who have never had a dose of **Tdap** should get one as soon as possible, regardless of the interval since the last tetanus or diphtheria toxoid-containing vaccine. Pertussis, like influenza and pneumococcal pneumonia, may confuse the clinical evaluation of persons with coronavirus and can cause protracted respiratory symptoms that are now preventable. As students return to college campuses, two types of protection against **meningococcal meningitis** – also spread by respiratory droplets – is mandatory.

Prevention of shingles with the **recombinant varicella zoster vaccine** is now safer, more highly effective and longer lasting than the former live attenuated vaccine.

Broad recommendations for **hepatitis A and B vaccines** for US adults can help avoid infectious risks both during travel abroad as well as from increased local transmission.

Vaccine hesitancy clouds the mission of protection of the entire population. Educating, supporting and hopefully vaccinating individuals who may harbor selfish or unfounded fears may protect our vulnerable immunosuppressed individuals. A powerful opinion piece included here outlines the issues, including the increased number of US **measles** cases.

As guest editors we are perpetually optimistic that the world will heal and will desire to travel again – and that people take their flu shot and coronavirus shot, too! The latest Advisory Committee on Immunization Practices (ACIP) guidelines updated the recommendation to broaden use of the **Japanese encephalitis vaccine** for many travelers to Asia. We reviewed this vaccine as well as the **rabies vaccine.** In addition**,** the **Yellow Fever** vaccine shortage persists nationwide, yet remains available at our designated site at the Brown Medicine travel clinic.

The coronavirus pandemic, due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that originated in Wuhan china in late 2019 and has spread worldwide as of March 2020, has left us more isolated than ever.

We only wish we had a vaccine for this virus! This pandemic is the most significant current-day scourge the world is facing. We are excited that our Infectious Disease Division at Brown will be participating in research to develop safe and efficacious COVID vaccines.

The potentially strongly enthusiastic uptake of a coronavirus vaccine may pave the way for more individuals to adopt the other vaccines that have helped stem the past epidemics of polio, measles, mumps and many other processes, to keep those illnesses from resurfacing. We have to engage conversations empowered with up-to-date knowledge. It may help to use accounts of past outbreaks to illustrate how vaccines help us stamp out diseases before we need to deal with disease repercussions.

As practitioners we must convey a unified message. Vaccines do not cause autism. Vaccines help us go to school, help us travel to learn about other places and cultures and appreciate each other and help us see our grandparents. Vaccines help keep us together.

We can't emphasize this message strongly enough – it will take a shot in the arm!

Guest Editors

Maria D. Mileno, MD, Associate Professor of Medicine, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI; Consultant and Former Director of the Travel Medicine Service at The Miriam Hospital.

Jennie E. Johnson, MD, Assistant Professor of Medicine, Clinician Educator, Division of Infectious Diseases, Alpert Medical School of Brown University, Providence, RI.

Talking to Patients about the Influenza Vaccine

KATRINA M. BYRD, MD

ABSTRACT

Influenza is a significant cause of hospitalization and death in late fall and early spring, especially in our most vulnerable populations. Despite high mortality and morbidity of influenza infection, patients are still hesitant about getting the flu vaccine each year. This article offers advice on educating our patients to address misconceptions and help them embrace this important seasonal vaccination.

KEYWORDS: influenza, vaccine hesitancy, flu, cardiovascular risk, COVID

INTRODUCTION

Influenza is a common seasonal and often severe respiratory illness that affects humans and animals. It was first isolated in 1933 and has caused multiple pandemics since its discovery, with the most recent occurring in 2009 due to Influenza A/H1N1. Influenza is spread from person to person primarily through inhalation of infected droplets when a person coughs, sneezes, or speaks.[1] Individuals with influenza can shed the virus in the absence of symptoms. Once symptomatic, they are infectious up to 7 days after onset.[2] The most common symptoms on presentation include fever, cough, body aches and headache, yet most people recover without persistent sequelae.[3] However, through late fall and early spring it is a significant cause of hospitalization and even death, especially in our most vulnerable populations which include elderly, chronically ill individuals, pregnant women, and young children.[4,5] Annually, tens of millions worldwide are infected with influenza. According to the Centers for Disease Control and Prevention (CDC), in the 2018–2019 influenza season, ~35.5 million Americans were infected with influenza, which resulted in ~34,000 deaths.[6]

Despite high morbidity and mortality from influenza, patients are still hesitant about getting the influenza vaccine each year.[7] Most people recognize that vaccination is one of the most important public health interventions in the 21st century. Elimination of smallpox worldwide and elimination of polio in most of the world are two major accomplishments attributed to vaccinations.[8] However, when it comes to influenza vaccine, it is more challenging to convince patients to get their influenza vaccine. Notably, only 49% of the US population received the influenza vaccine in the 2018–2019 influenza season according to the CDC.[6] Here is a summary of key points to use when speaking to your patients about the influenza vaccine.

1: Offer the influenza vaccine

The first step to talking to patients about vaccination is to actively offer the influenza vaccine in a positive manner. Provider recommendation is a strong factor in convincing patients to be vaccinated.[9,10] In general, patients have trust in the person who is providing medical care for them. This is especially true if the provider has been caring for them for an extended length of time. As medical providers, we have a unique role in educating our patients about different diseases. When we take advantage of the opportunity to educate our patients about the rationale behind influenza vaccination and address misconceptions, they are less likely to internalize false information from family, friends, co-workers, and social media. Considering the COVID-19 pandemic there is heightened awareness on prevention of other respiratory infections. After offering the influenza vaccination, we should go into more detail on why it is so important.

2: Explain the importance of Influenza vaccination

Vaccination against influenza reduces the risk of significant illness that requires evaluation by a medical professional or hospitalization by 40–60%.[11] It decreases influenza-related hospitalization, hospital death, and ICU admission associated with influenza.[3] The Benowitz, et al 2010 study showed the vaccination of pregnant women was over 90% preventive of hospitalization of their infants due to influenza in the first 6 months of life. Unfortunately, the efficacy of the influenza vaccine is about 40%.[4] While it may be true that it will not prevent all vaccinated persons from infection, it may ameliorate the clinical presentation to a less severe illness. Lastly, studies show that illness due to the flu is associated with secondary increases in heart attacks and stroke, which provides patients, especially persons with heart disease, a reason for influenza vaccination.[12]

3: Know your audience

As medical professionals, we can appreciate the benefits of influenza vaccinations and have likely taken care of patients

who have had complications from influenza. However, many patients have either never had it, was infected and do not remember having influenza, or had a mild case and fully recovered. Consequently, focusing on death rates from influenza will likely not mean much to your patient. Therefore, when speaking with patients, focus on explaining that influenza vaccination is our primary prevention strategy to combat severe illness from this infection and to prevent them from spreading influenza to more vulnerable persons. Reiterate that if your patient were to be infected with an influenza strain that was not included in the vaccine, it may ameliorate the disease so that he or she will be less sick from this infection than someone who did not get vaccinated. Stress that it may keep your patient out of the hospital if he or she does catch the flu. It may even prevent having a heart attack or stroke. At this point, your patient may bring up some questions/concerns about the influenza vaccines.

MOST COMMON QUESTIONS ABOUT INFLUENZA VACCINE

Why do we have to get the flu shot every year?

Influenza is encapsulated by an envelope that contains host-derived lipid membrane and viral proteins including hemagglutinin (HA), neuraminidase (NA), matrix 1 (M1), and matrix 2 (M2). Infection of host cells occur when HA binds to the host cell, which triggers endocytosis of the virus. Once inside, M1 and M2 are activated resulting in the release of viral RNA into the cytoplasm and through a complex series of steps, transportation in to the host nucleus. Viral RNA-dependent RNA polymerase transcribes and replicates influenza.[13] However, this polymerase activity is known to be error-prone. Therefore, inaccuracies in replication results in production of slightly different influenza strains, which explains the propensity for influenza to have antigenic drift. Antigenic drift occurs when an accumulation of mutations in the viral genome results in small changes. However, over time, these errors produce antigenically different influenza strains.[14] Since the influenza vaccines target antigens on the envelope, the influenza vaccine needs to change each year with the hopes of including protection against the most predominant strains that year.

The significant changes needed in the influenza vaccines from year to year are evident by **Figure 1**, which shows the viruses used for the egg-based quadrivalent influenza vaccine by year. Only 1 influenza strain (B/Phuket/3073/2013 (B/Yamagata lineage)-like virus used in the vaccine formulation remains the same between the 2019–2020 season and the 2020–2021 season.

The following analogy simplifies the above answer for patients. Think of the envelope of the influenza virus as a coat. The buttons on the coat represent antigens on the envelope. When the vaccine gets into the system, it is looking to target the buttons on the coat. However, the virus learns this and adapts by either changing the buttons on its coat or changing its coat completely. This is happening all of the time. Therefore, the initial vaccine given becomes ineffective because the virus has changed. This is why influenza vaccine changes yearly. It's trying to keep up with the fashion choices of the influenza virus.

I have an egg allergy. Can I get the flu shot?

Inactivated influenza vaccine (IIV) and live attenuated influenza vaccines (LAIV) are the two types of vaccines available in the US against influenza. Formulations of other influenza vaccines are found in the table below (**Table 1**). All available vaccines are egg-based with the exception of recombinant Influenza vaccine (RIV4), which is a good option for patients with severe egg allergies.[1] Contraindications for influenza vaccine include history of severe allergic reaction to any component of the influenza vaccine.

FluMist is an example of the live attenuated vaccine that is administered via nasal spray. It can be given to people ages 2–49 years old. It is a safe alternative for individuals with aversion to needles. However, the following are contraindications to the live-attenuated influenza vaccine:

- Children and adolescents on aspirin or salicylate containing therapy
- Children aged 2-4 years old with asthma or wheezing within the last 12 months prior to vaccination
- Any immunocompromised persons
- Close contacts and caregivers of severely immunocompromised persons
- Pregnancy
- Administration of influenza antiviral medications in the last 48 hours[1,15]

Figure 1. Egg-Based quadrivalent influenza viruses used for vaccine by season

2019–2020 season	2020–2021 season
A/Brisbane/02/2018 (H1N1)pdm09-like virus	A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus
A/Kansas/14/2017 (H3N2)-like virus	A/Hong Kong/2671/2019 (H3N2)-like virus;
B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage);	B/Washington/02/2019 (B/Victoria lineage)-like virus
B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)	B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Table 1. Influenza vaccines – United States, 2019–2020 influenza season*

Trade name (Manufacturer)	Presentation	Age indication	HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal) (µg/0.5mL)
IIV4—Standard Dose—Egg based†					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS§	6 through 35 mos	7.5 µg/0.25 mL§	IM¶	—
	0.5-mL PFS§	≥3 yrs	15 µg/0.5 mL§		—
	5.0-mL MDV§	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)			24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV	≥6 mos			<25
Fluzone Quadrivalent (Sanofi Pasteur)	0.25-mL PFS**	6 through 35 mos	7.5 µg/0.25 mL**	IM¶	—
	0.5-mL PFS**	≥6 mos	15 µg/0.5 mL**		—
	0.5-mL SDV**	≥6 mos			—
	5.0-mL MDV**	≥6 mos			25
IIV4—Standard Dose—Cell culture based (ccIIV4)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV	≥4 yrs			25
IIV3—High Dose—Egg based† (HD-IIV3)					
Fluzone High-Dose (Sanofi Pasteur)	0.5-mL PFS	≥65 yrs	60 µg/0.5 mL	IM¶	—
IIV3—Standard Dose—Egg based† with MF59 adjuvant (aIIV3)					
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
RIV4—Recombinant HA					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM¶	—
LAIV4—Egg based†					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	$10^{6.5–7.5}$ fluorescent focus units/0.2 mL	NAS	—

Abbreviations: ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration; HA = hemagglutinin; IIV3 = inactivated influenza vaccine, trivalent; IIV4 = inactivated influenza vaccine, quadrivalent, IM = intramuscular; LAIV4 = live attenuated influenza vaccine, quadrivalent; MDV = multidose vial; NAS = intranasal; PFS = prefilled syringe; RIV4 = recombinant influenza vaccine, quadrivalent; SDV = single-dose vial.

* Vaccination providers should consult FDA-approved prescribing information for 2019–20 influenza vaccines for the most complete and updated information, including (but not limited to) indications, contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at https://www.fda.gov/vaccines-blood-biologics/approved-products/vaccines-licensed-use-united-states. Availability of specific products and presentations might change and differ from what is described in this table and in the text of this report.

† Persons with a history of egg allergy may receive any licensed, recommended influenza vaccine that is otherwise appropriate for their age and health status. Those who report having had reactions to egg involving symptoms other than urticaria (e.g., angioedema or swelling, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention should be vaccinated in an inpatient or outpatient medical setting (including, but not necessarily limited to, hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions.

§ The dose volume for Afluria Quadrivalent is 0.25 mL for children aged 6 through 35 months and 0.5 mL for persons aged ≥3 years.

¶ Intramuscularly-administered influenza vaccines should be given by needle and syringe only, with the exception of the MDV presentation of Afluria Quadrivalent, which may alternatively be given by the PharmaJet Stratis jet injector for persons aged 18 through 64 years only. For adults and older children, the recommended site for IM influenza vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh. Additional guidance regarding site selection and needle length for intramuscular administration is available in the ACIP General Best Practice Guidelines for Immunization (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf).

** Fluzone Quadrivalent may be given to children aged 6 through 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive the 0.5-mL dose volume.

Who should get the flu shot?

Generally, all persons 6 months old and older should receive the influenza vaccine by the end of October. Vaccines for the 2020–2021 are available for pre-order by clinics and health-care facilities but they will not be available to the public until October 2020. Children between ages 6 months to 8 years old who are receiving the influenza vaccination for the first time require 2 doses separated by 4 weeks. The first dose should be given in children who require 2 doses as soon as possible so that the 2nd vaccination can be given by the end of October.[15]

The following people have the highest risk of medical complications from severe influenza infection according to the ACIP at CDC:

- All children aged 6 through 59 months;
- All persons aged ≥50 years;
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- Persons who are immunocompromised due to any cause (including but not limited to immunosuppression caused by medications or HIV infection);
- Women who are or will be pregnant during the influenza season;

- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin or salicylate-containing medications and who might be at risk for experiencing Reye's syndrome after influenza virus infection;
- Residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- Persons who are extremely obese (body mass index ≥40 for adults)

I am healthy and I never get the flu. Why should I be vaccinated?

In healthy individuals, influenza may present as a severe cold and that person fully recovers. In fact, that person may never present to the healthcare system for testing.[2] However, if they live with a vulnerable person such as pregnant women or children < 6 months old, they can unknowingly pass the virus to that vulnerable person or surrounding community which can result in severe disease in the compromised person and infection in persons within their community.[14] Explaining this to patients is important to get them to understand the risk they can place on other household members.

The flu shot gives you the flu

It is important to remind patients that they are not being injected with the influenza virus when they receive the influenza vaccine. Therefore, it is not possible for them to actually contract influenza from the influenza vaccine. Typically, symptoms include redness and soreness at the injection site. However, some people do feel ill after vaccinations and this can be attributed to the following reasons:

Exposure to another respiratory virus. There are many viruses that cause influenza-like symptoms, which include rhinovirus, adenovirus, coronavirus. The influenza vaccine does not provide protection against these so if someone was exposed to them, then they will fall ill.

Low-grade fever, headache, and muscle aches are less common adverse effects of the influenza vaccine but it does occur. These symptoms represent a healthy immune response to the vaccine. Usually, these symptoms resolve in 1–2 days post-vaccination. However, they are uncomfortable and can be mistaken for a case of the mild flu.

It takes about 2 weeks for the body to mount an immune response that is protective against influenza. However, if a patient is exposed to the virus a few days before vaccination or in the 2-week period after vaccination, they can come down with influenza because their body did not have protection against it.

Lastly, vaccine manufactures predict the 3–4 most predominant influenza strains and create a vaccine against them. However, patients can get influenza strains that are not covered by the influenza vaccination and subsequently become sick from influenza.

Taking the time to review above scenarios will help alleviate patient concerns about getting ill from the influenza vaccine.

CONCLUSION

Influenza infection continues to cause high morbidity and mortality among Americans yearly, affecting the most vulnerable people such as young children.[1,14] In an environment where there is more distrust about vaccines than in the past, talking to patients about influenza vaccination is challenging to providers. However, studies have shown that patients listen to medical providers about vaccines.[8] Additionally, changing in-office practices regarding vaccination including sending patient reminders about upcoming flu shot, posting facts about influenza in the waiting/exam room, and creating standing orders or order sets in the electronic medical record can make having this important conversation with patients much easier.[9]

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Recent Updates to the Advisory Committee On Immunization Practices Recommendations for Pneumococcal and Herpes Zoster Vaccination

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ABSTRACT

Pneumococcal and herpes zoster – shingles – vaccination prevent a great deal of morbidity, particularly in elderly and immunocompromised hosts. Vaccination of children with conjugate pneumococcal vaccine in recent years has greatly reduced illness in older individuals as well. This article will review the historical and current recommendations for pneumococcal and herpes zoster vaccination and the rationale for changes at the level of the CDC's Advisory Committee on Immunization Practices.

KEYWORDS: vaccination, immunization, conjugate pneumococcal vaccine, herpes zoster, shingles

PNEUMOCOCCAL VACCINATION

Background

S. pneumoniae is the most commonly identified pathogen in community-acquired pneumonia (CAP) worldwide and can cause serious illness, particularly among young children, the elderly, or those with immunocompromising conditions. Severe infection may lead to invasive pneumococcal disease (IPD), including pneumococcal bacteremia or meningitis, which can result in significant neurological sequelae and death. The financial burden of IPD to the US healthcare system is substantial and is estimated to increase by $2.5 billion annually in the coming decades with an aging population.[1]

Historical ACIP Recommendations for Pneumococcal Vaccination

There are currently two licensed vaccines approved for the prevention of pneumococcal disease in the US: the 23-valent pneumococcal polysaccharide vaccine (PPSV23, [Pneumovax 23, Merck and Co., Inc]), containing antigens from 23 common serotypes, and the 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Pfizer, Inc.]), containing antigens from 13 common serotypes. There is considerable overlap among the antigens contained within each vaccine; 12 of the 13 antigens in PCV13 are common to PPSV23 apart from serotype 6A.

Recommendations for pneumococcal vaccination have evolved over time based on shifts in the epidemiology of IPD and as new products have been introduced into market. PPSV23 was first licensed in 1983 and was subsequently introduced into the routine schedule for all adults ≥65 years and for those ≥2 years with certain underlying medical conditions.[2] In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine pediatric schedule for all children <5 years, and in 2010, the approval of PCV13 led to replacement of PCV7 with PCV13 in the pediatric schedule.[3] In 2012, indications for PCV13 were broadened to all individuals ≥19 years with immunocompromising conditions, administered in series with PPSV23 eight weeks later.[4] In 2014, results from the randomized placebo-controlled Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) demonstrated that 20–25% of IPD and 10% of CAP cases in adults ≥65 years were caused by PCV13 serotypes and were potentially preventable.[5] This prompted the 2014 ACIP recommendation for vaccination with both PCV13 followed by PPSV23 ≥ one year later in all immunocompetent adults at age 65.[6,7]

Updated ACIP Recommendations for Pneumococcal Vaccination

Historical vaccination efforts in the pediatric patient population have been essential to decreasing overall pneumococcal disease burden, morbidity, and mortality both directly and indirectly through reduction in carriage and transmission to adults.[8] In 2019, ACIP reviewed the evidence over the preceding three years to determine if there was a continued need for PCV13 vaccination in elderly immunocompetent adults in series with PPSV23 versus PPSV23 alone. A systematic review was conducted including twenty studies published from 2014–2018 to evaluate data on the safety, efficacy, and cost-effectiveness of pneumococcal vaccination in this patient population. Results demonstrated that from 2000-2014, widespread uptake of pediatric pneumococcal vaccination in the US led to a ninefold decrease in the incidence of PCV13-type IPD in adults ≥65 through reduced carriage and transmission. A similar effect was seen for those at increased risk due to age or chronic medical conditions. From 2014–2018, the incidence of PCV13-type IPD in adults ≥65 has remained stable (5 cases per 100,000), with 47% estimated vaccination coverage in immunocompetent adults ≥65 years. Based on these results, it was estimated that 26,000 adults would need to be vaccinated with PCV13

to prevent one case of IPD per year. Additionally, there were minimal indirect benefits to other patient populations, including those aged 19–64 years. Cost-effectiveness models estimated a very high cost ($200,000–500,000) per quality adjusted life years with continuation of the current recommendation versus a recommendation to administer PPSV23 alone. Limitations to the presented evidence included the limited follow-up time (only three years of data were analyzed) and low PCV13 vaccination uptake in immunocompetent adults. Furthermore, the analysis did not take into consideration vaccination hesitation, commonly known as the "anti-vax movement," a growing movement which may impact pneumococcal pediatric vaccination rates and pneumococcal burden in the coming years.

Updated pneumococcal vaccination recommendations are summarized in **Table 1**. Based on these findings, ACIP voted to remove PCV13 from the routine immunocompetent adult immunization schedule in November 2019. As some adults may still benefit, the decision to administer PCV13 vaccination should be based on shared clinical decision-making between patient and provider depending on the individual's risk for exposure and invasive disease. PCV13 is still routinely recommended as a one-time vaccination for adults ≥19 years with an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant.[8] Additionally, a single dose of PPSV23 is still routinely recommended for all adults at age 65.

Shared Decision-Making: Who Should Still Receive PCV13 At Age 65?

Some adults may be at higher risk for exposure to PCV13 serotypes or at higher risk for complications based on certain factors, such as local pediatric vaccination rates or underlying medical conditions. The CDC provides guidance for shared clinical decision-making based on an individual's risk.

The CDC recommends considering regularly offering PCV13 to the following individuals:

- Those residing in a nursing home or other long-term care facilities
- Those residing in settings with low pediatric PCV13 uptake
- Those traveling to settings with no pediatric PCV13 program
- Those with chronic heart, lung, or liver disease; diabetes; or more than one chronic medical condition
- Those with alcoholism or those who smoke cigarettes

Table 1. Updated ACIP Recommendations for Pneumococcal Vaccination in Individuals ≥19 years

Patient Population	Age Group		Total Number of doses of PCV13 or PPSV23
	19–64 years	≥65 years	
Immunocompetent individuals	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23: none	PPSV23 x 1 dose	PPSV23: 1
Immunocompetent individuals with alcoholism; chronic liver, heart, or lung disease; diabetes mellitus; or smoking cigarettes	PCV13: none	PCV13 based on shared clinical decision-making; if administered give PCV13 first and PPSV23 ≥1 year after PCV13	PCV13: 0 or 1 dose
	PPSV23 x 1 dose	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompetent individuals with cochlear implant(s) or cerebrospinal fluid leaks	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 1 dose, give ≥8 weeks after PCV13	PPSV23 x 1 dose, give ≥8 weeks after PCV13 and ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 2 doses
Immunocompromised individuals*	PCV13 x 1 dose	PCV13 x 1 dose if no previous PCV13 vaccination	PCV13: 1 dose
	PPSV23 x 2 doses, give first dose ≥8 weeks after PCV13, give second dose ≥5 years after initial PPSV23	PPSV23 x 1 dose, give ≥5 years after any previous PPSV23 prior to age 65	PPSV23: 3 doses

*Includes those with anatomic or functional asplenia, sickle cell disease/hemoglobinopathies, chronic renal failure or nephrotic syndrome, congenital or acquired immunodeficiencies, iatrogenic immunosuppression, generalized malignancy, Hodgkin disease, leukemia, lymphoma, multiple myeloma, HIV infection or solid organ transplant

HERPES ZOSTER VACCINATION

Background

Herpes Zoster (HZ) is another infection that affects elderly and immunocompromised patients due to decreased immune control of the virus. It is caused by reactivation of primary Varicella Zoster Virus (VZV) infection in the neuronal ganglia leading to a painful vesicular rash along one or more dermatomes. According to the CDC, there are approximately 1 million cases of HZ per year in the United States.[9] Many studies have shown that the incidence of HZ has increased over time.[10,11] Harpaz and colleagues found that incidence has continued to rise from the 1990s to the most recent decade. The incidence per 1,000 persons has increased from 2.5 in 1993 to 6.1 in 2006 to 7.2 in 2016.[10] HZ is a vaccine preventable illness that carries significant morbidity and cost implications for the healthcare system. The most well-known complication, post-herpetic neuralgia (PHN), can persist for years after initial infection and is often refractory to traditional analgesics. Furthermore, treatments such as tricyclic antidepressants and gabapentin carry significant risks of toxicity in the elderly patient population that is most susceptible to this condition. Other potential complications include bacterial superinfection of the skin, HZ opthalmicus, acute retinal necrosis, HZ oticus, and meningitis/encephalitis. It is estimated that the total cost of HZ is 5 billion dollars annually in the United States.[12]

Historical ACIP Recommendations for Herpes Zoster Vaccination

Zoster Vaccine Live (ZVL, [Zostavax, Merck and Co., Inc]) was licensed in 2006 as a single subcutaneous dose and was recommended by the ACIP for use in immunocompetent adults aged ≥60 years. FDA approval was based on the Shingles Prevention Study, which was a double-blinded, multi-centered, randomized controlled trial. The study followed subjects for three years and compared incidence of HZ infection and PHN in patients receiving ZVL or placebo. For patients between 60-69 years of age, there were statistically significant decreases in both conditions in those who received ZVL compared to placebo: 66% decrease in HZ and 66% decrease in PHN.[13] However, post-marketing studies have shown marked decreases in effectiveness against HZ over time, especially in older subjects (age > 60 years old).[13] The incidence of injection site reactions such as erythema and pain was 35.8% and 34.5%, respectively. Systemic adverse events were similar in the vaccine group compared to placebo (24.7% vs 23.7%).[13] Furthermore ZVL is a live vaccine and therefore contraindicated in many immunosuppressed populations, which are one of the highest risk groups for developing HZ.

Updated ACIP Recommendations for Herpes Zoster Vaccination

Recombinant Zoster Vaccine (RZV, [Shingrix, GlaxoSmithKline]) was approved in October of 2017 as a two-dose intramuscular injection administered at 0 and 2–6 months. This inactivated vaccine contains a new VZV glycoprotein E antigen combined with adjuvant $AS01_B$ to promote humoral immune response and has the potential to be used in immunocompromised populations. RZV quickly became the preferred HZ vaccine in the adult immunization schedule in January of 2018.[15] This change was driven primarily by the increased effectiveness in primary prevention of HZ as well as superior sustained protection post-vaccination. Two multi-national, randomized, placebo-controlled clinical trials led to approval of RZV. The ZOE-50 study showed overall efficacy rates of 97.2%.[16] Furthermore, in older subjects aged 60–69 years old, it maintained efficacy at 97.4%. No significant differences were seen in regards to age. ZOE-70 enrolled patients over the age of 70 and showed an 89.8% decrease in incidence of HZ.[17] Pooled data from these studies showed an overall 91.2% decrease in PHN in those in the active treatment arm. Data from these studies demonstrate that RZV vastly outperforms ZVL across all age groups. Long-term efficacy has yet to be established, as the published data only includes 36 months of follow-up. The ZOE-50 study plans to complete a total follow-up of 60 months, but this data has not been published at the time this article was written.

Although RZV has shown superior efficacy, there is a higher incidence of adverse drug reactions likely related to the increased immunogenicity of the adjuvant. For example, in ZOE-50, a total of 81.5% of participants in the RZV arm reported injection site reactions.[16] While most of these reports were mild to moderate in nature, 9.5% had grade 3 reactions. In terms of systemic reactions, incidence was 66.1% with myalgia (46.3%) and fatigue (45.9%) as the most common in RZV-vaccinated subjects. However, median duration of reactions was less than 4 days. Despite the higher incidence of adverse reactions when compared to ZVL, the remarkable efficacy of RZV in preventing HZ and PHN warrants its place as the preferred HZ vaccine.

In addition to increased rate of side effects, availability of the vaccine has been a barrier to vaccination. The supply of the vaccine has been sporadic, and it is frequently under allocation limits. This presents a challenge for patients who have received one dose but have not received the second dose in the series. If more than 6 months have elapsed after the initial dose, there is no need to restart the series. RZV is recommended for patients previously vaccinated with ZVL and can be given simultaneously at different anatomic sites with other vaccines.[15]

Of note, ACIP currently provides no recommendation on the use of RZV in patients with high levels of immunosuppression, including those on chronic steroids (≥20 mg of prednisone equivalent per day), those who have received a transplant, or persons living with HIV due to insufficient data in these populations.[15] A recent phase 3 clinical trial in patients with renal transplant has shown sufficient rates of immunogenicity and a similar adverse event profile.[18] As new data becomes available for immunocompromised patients, these recommendations may change.

CONCLUSION

ACIP's recommendations for pneumococcal and herpes zoster vaccination have recently been updated. For pneumococcal vaccination, ACIP now recommends shared clinical decision-making rather than routine administration of PCV13 in immunocompetent individuals ≥65 years. A single dose of PPSV23 is still routinely recommended for all adults at age 65, and a one-time dose of PCV13 should still be administered for adults ≥19 years with an immunocompromising condition, CSF leak, or cochlear implant.

For herpes zoster vaccination, the ACIP now recognizes RZV as the preferred zoster vaccine for all eligible patient populations. RZV is preferred over ZVL due to higher efficacy and sustained protection over time and can be administered to patients who have previously received ZVL.

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Tetanus Vaccination 2020 and Collateral Protections against Pertussis and Diphtheria

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ABSTRACT

Tetanus is a life-threatening but vaccine-preventable disease caused by the toxin of the bacterium *Clostridium tetan*i and is characterized by muscle spasms and autonomic nervous system dysfunction. It is prevented through vaccination with tetanus toxoid, but because the causative agent is widespread in the environment, eradication is impossible. Therefore, efforts to reduce incidence are aimed at reaching elimination, rather than eradication. This article reviews the pathogenesis, clinical manifestation and treatment of tetanus, and summarizes all recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) regarding prevention and control of tetanus in the United States.

KEYWORDS: tetanus, tetanus vaccine, tetanus prophylaxis, tetanus immunoglobulin

INTRODUCTION

Tetanus is a serious and often fatal infection that affects the nervous system. It is characterized by generalized painful muscle spasms particularly in unvaccinated or incompletely vaccinated people. The disease is caused by a toxin-producing gram-positive anaerobic bacteria, *Clostridium tetani*, which is widely present in the surrounding environment, particularly in soil, dirt, and dust.

Tetanus is still prevalent in many developing countries. The disease can be prevented through vaccination but because the *C. tetani* spores are ubiquitous, it can never be eradicated. Due to the success of the US tetanus immunization program diphtheria – a disease of the upper respiratory tract and sometimes skin due to toxigenic strains of Corynebacterium diphtheriae biotype mitis, gravis, intermedius or belfanti – is nearly unheard of in the US, although the disease continues to cause illness globally and there have been outbreaks reported in recent years.

PERTUSSIS

Pertussis – "whooping cough" due to Bordetella pertussis – can be a life-threatening disease in infants with small airways and is endemic worldwide, including the US and other countries, with high vaccination rates. Disease in adults presents as a protracted cough with paroxysms that may be followed by vomiting. Coughing paroxysms may eventually become less intense but may recur with subsequent respiratory infections. Childhood vaccinations given since the 1940s helped to reduce infant mortality but would wear off by adulthood.

ELIMINATION STRATEGIES

The primary strategy to control and prevent these diseases is through elimination instead of eradication. The vaccination schedule is based on the tetanus component.

Tetanus is a leading cause for neonatal death in the developing world.[1]

The tetanus toxoid (TT) vaccines were first introduced in the United States in the mid-1940s. After that, the incidence of reported tetanus declined by >98%, from 0.39 per 100,000 population in 1947, when national reporting began, to 0.01 per 100,000 population by 2016.[2] The CDC reported 264 cases of tetanus in the United States between 2009 and 2017, 23% were in patients ≥65 years of age and only 13% were individuals younger than 20 years. The majority of new cases of tetanus occur in resource-limited countries with an estimated 48,000 to 80,000 deaths occurring from tetanus worldwide in 2016.[3]

PATHOPHYSIOLOGY

Humans become infected through wound contamination with *C. tetani* spores, which are durable and can survive for prolonged periods and germinate under the right environment (i.e. less vascularized necrotic tissue) to toxin-producing bacteria. The toxin is extremely potent and even deadly in small amounts. Once tetanus toxin invades the nerve cell, it can no longer be neutralized by the toxoid. The toxin can then move via retrograde axonal transport into the spinal cord and brain, where it accumulates and prevents the release of inhibitory neurotransmitters, resulting in overexcitation of the nervous system. This clinically manifests as painful muscle spasm and rigidity, increased muscle tone, and widespread autonomic instability.

Tetanus is a non-communicable disease and it is safe to come in close contact with someone that is affected by tetanus.

Tetanus is commonly acquired through septic burn wounds, animal bites and scratches, fractures, contaminated surgical instruments, lacerations, eye injuries, gunshot wounds, piercings and other puncture wounds. All of the above mechanisms have common predisposing factors, which include devitalized and dead tissue, foreign bodies and localized ischemia.

Tetanus can also manifest through the same pathophysiology in neonates from infected umbilical stump, obstetric patients after septic abortions, post-surgical patients with bowel necrosis, infected diabetic foot ulcer patients, and IV drug users.

The incubation period of tetanus is approximately 8 days but ranges from 3 to 21 days.

The most common and severe clinical form of tetanus is generalized tetanus. Rarely, tetanus presents with tonic and spastic muscle contractions in one extremity or body region which is localized tetanus. Patients with injuries to the head or neck may present with cephalic tetanus, involving initially only cranial nerves. Neonatal tetanus occurs as a result of the failure to use aseptic techniques in managing the umbilical stump in offspring of mothers who are poorly immunized. Severity of disease can range from grade 1 (mild trismus and/or general spasticity), to grade 2 (moderate trismus and general spasticity, with dysphagia and respiratory embarrassment), to grade 3 (severe trismus, severe and prolonged spasms, respiratory difficulties and sympathetic overdrive).

MANAGEMENT

Unfortunately, little evidence exists to support any particular therapeutic intervention in tetanus. Management includes early wound debridement, halting the toxin production, neutralization of the unbound toxin through post-exposure vaccination, control of muscle spasms, and general supportive care including airway management. Antibiotics are universally recommended, although they may play a minor role, and it is of vital importance to emphasize that unless adequate wound debridement is performed, antimicrobial therapy may fail. Metronidazole is the preferred treatment and should be given for a total of 7 days but penicillin is a safe alternative. Multiple other agents can be used such as doxycycline, macrolides, clindamycin, vancomycin, and chloramphenicol; however, the data on these agents is based upon in vitro susceptibility. Since tetanus toxin is irreversibly bound to tissues, much emphasis is placed on neutralizing the toxin before it enters the nervous system. Human anti tetanus immunoglobulin (HTIg) is the treatment of choice. The CDC recommends a single dose of 500 units intramuscularly with part of the dose infiltrated around the wound. Many studies have explored the efficacy of intrathecal immunoglobulin, but the evidence for its benefit is not concrete. All patients with tetanus should receive active immunization with a full series given immediately upon diagnosis. The tetanus toxoid should be given at a separate site from immunoglobulin administration.

Benzodiazepines remain the backbone of treatment regimens for tetanus, and the standard therapy for controlling muscle spasms. Diazepam is the most popular and has been used widely but other benzodiazepines are as effective. The use of magnesium sulfate has also been established since the 1980s due to its effect on reducing autonomic instability and controlling muscle spasms. Several studies concluded the beneficial effects of high dose magnesium sulfate infusion in tetanus, but it may be inadequate as sole therapy in patients with severe disease. Several other drugs which have been reported to be useful are labetalol, clonidine, morphine sulfate, intrathecal baclofen, dantrolene, and vitamin C. Despite all these interventions, the reported fatality rate ranges from 12–53%

VACCINE SCHEDULES

In the US, diphtheria-tetanus-acellular pertussis (DTaP) vaccine is routinely administered to children at 2, 4, and 6 months, followed by boosters at 15–18 months and 4–6 years. Single booster dose of a vaccine containing tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) is recommended for 11- to 12-year-olds and every ten years after that. In 2020, ACIP released new recommendations allowing either Tdap or Td to be used as the booster or for wound management while previously only Td was recommended.[5]

Individuals who have not been previously vaccinated against tetanus should complete a series of three tetanus and diphtheria toxoid vaccines, which includes at least 1 Tdap dose. The preferred schedule is 1 dose of Tdap, followed by 1 dose of either Td or Tdap at least 4 weeks afterward, and 1 dose of either Td or Tdap 6–12 months later.

In 2011, when ACIP first considered administration of Tdap during pregnancy, safety data on women and their infants were limited. However, additional evidence continues to be reassuring for mother and child, with no reported increase in adverse events including major malformations, stillbirth, preterm birth, or small for gestational age. Pregnant women should get Tdap during the early part of the 3rd trimester of every pregnancy.

ACIP has recommended administering tetanus toxoid containing vaccine and tetanus immune globulin (TIG) when indicated as part of standard wound management to prevent tetanus. For patients who have received fewer than three doses or an unknown number of doses of a tetanus toxoid-containing vaccine, tetanus immunization should be administered. For patients with clean minor wounds who have completed 3-dose primary tetanus vaccination series, another dose should be given if the last dose was given 10 or more years ago. For patients with dirty wounds (such

as, but not limited to, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, or frostbite) who have completed 3-dose primary tetanus vaccination series, another dose should be given if the last dose was given five or more years ago. If there is any doubt about whether or not an adult completed the primary series, three doses of Td or Tdap (with Tdap given for at least one of the doses) should be administered; the first dose and second dose should be separated by four weeks and the third dose should be given 6 to 12 months later. The pertussis component may dwindle after 3-4 years as data show the vaccine fully protects 4 in 10 individuals 4 years after receiving Tdap. For travelers or during pertussis outbreak settings it is safe to administer Tdap as early as 2 years after the prior dose.

HUMAN TETANUS IMMUNE GLOBULIN

In addition to tetanus immunization, human tetanus immune globulin (250 units intramuscularly) is indicated in unvaccinated or incompletely vaccinated individuals who have sustained a wound that is more severe than a clean and minor wound (eg, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, or frostbite).

People with human immunodeficiency virus (HIV) infection regardless of their CD4 count or with severe immunodeficiency who have contaminated wounds should also receive human tetanus immune globulin, regardless of their immunization status.

Appropriate tetanus prophylaxis should be administered as soon as possible following a wound but should be given even to patients who present late for medical attention. This is because the variable incubation period which ranges from 3 to 21 days (median: 7 days), with extremes of 1 day to several months.

Tetanus toxoid is one of the most extensively used vaccines globally. Mild local reactions (i.e., redness, pain and tenderness, and mild swelling) are common while more systemic reactions, such as fever, malaise, lymphadenopathy are less common but might still occur. Although there is a slight increase in injection site events with decreasing interval since a previous immunization, Tdap can be safely administered at intervals of > or = 18 months since a previous TD/Td vaccine.[6] Severe reactions, including neurologic complications (e.g., peripheral neuropathy, particularly brachial plexus neuropathy, Guillain-Barré syndrome, and acute encephalopathy) and hypersensitivity reactions (anaphylaxis, and angioedema) are rare. Arthus reactions – severe local and sometimes generalized vasculitic reactions - are now only rarely reported with newer tetanus vaccine preparations. ACIP recommends that persons who have experienced an Arthus reaction following a dose of tetanus toxoid or diphtheria toxoid–containing vaccine should not receive a tetanus toxoid–containing vaccine more frequently than every 10 years, even for tetanus prophylaxis as part of wound management.

CONCLUSION

Tetanus is a lethal infection, but vaccine preventable. Tdap offers protection against diphtheria and pertussis not only to children but also adults. All healthcare workers must emphasize and raise awareness of the importance of immunization. Protection against tetanus by vaccination is vital because there is no natural immunity against tetanus and no effective treatments exist. Inter-professional collaboration of physicians, nurses other clinical practitioners and pharmacists together with public health officials can place particular emphasis on education regarding the importance of up-to-date vaccination and reduce the morbidity and mortality of tetanus worldwide.

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An Update on Meningococcal Vaccination

JOSEPH M. GARLAND, MD

ABSTRACT

Neisseria meningitidis bacterial infection can cause severe life-threatening meningitis. Individuals who survive may be left with profound sequelae. In epidemic regions such as the meningitis belt of Africa, the case rate is drastically higher than in nonepidemic regions and is due to distinct outbreak serogroups. Two highly effective conjugate meningococcal vaccine against serogroups A, C, W and Y are licensed and indicated for prevention in childhood vaccination schedules and for travelers to outbreak regions. In the US, meningococcus serogroup B is the main cause of outbreaks, in areas with crowding such as college dorms. It has taken over 40 years to develop a meningitis type B vaccine and now there are 2 brands available for children and teens. All college-bound individuals should complete schedules of both conjugate ACWY serotypes and meningitis B vaccine series. This paper reviews details on who to vaccinate and how to use the currently available meningococcal meningitis vaccines.

KEYWORDS: meningitis vaccine, *Neisseria meningitidis,* serogroups ACWY, meningitis serogroup B, conjugate meningococcal vaccination

Neisseria meningitidis causes a wide range of clinical presentations, from asymptomatic carriage to severe life-threatening meningitis. When it presents with clinical disease, *N meningitidis* causes meningitis in over 50% of cases; other presentations include pneumonia and bacteremia. Person-to-person transmission of bacteria occurs through close personal contact with respiratory secretions or saliva of infected persons. Colonization is common – at any given time 5–10% of the population may be carriers of the organism. In contrast, invasive disease is rare in non-epidemic areas, occurring at a rate of 0.5 to 10 cases per 100,000. However, in epidemic regions such as the meningitis belt of Africa, the case rate can be drastically higher, up to 1,000 cases per 100,000, particularly during peak season. There are six major serogroups associated with human disease: A, B, C, X, Y, and W-135. *N meningitidis* is found worldwide, with some regional differences in serogroup distribution and prevalence.[1,2,3]

Though prevalence of clinical disease is low in non-epidemic regions, the severity of meningococcal disease when present, and the high mortality associated with *N meningitidis* meningitis, have led to recommendations for vaccination of key populations. Two types of meningococcal vaccines are available in the U.S. currently, one type covering serogroups A, C, Y, and W-135, and the other covering serogroup B. (**Table 1**)

For serogroups A, C, Y, and W-135, two similar vaccines are available: MenACWY-D (Menactra) and MenACWY-CRM (Menveo). Both are conjugate vaccines. The previously available quadrivalent polysaccharide vaccine (MPSV4, or Menomune) was discontinued in August 2017. The conjugate A, C, Y, and W-135 vaccines are approved for age 9 months and older (MenACWY-D) or 2 years and older (MenACWY-CRM) through the age of 55 years, though most authorities advise off-label usage if otherwise indicated in individuals over

Table 1.

VACCINE	TRADE NAME	AGE OF VACCINE INITIATION	DOSE	ROUTE	INTERVAL SINCE FIRST DOSE	BOOSTER
Conjugate Meningococcal A,C,W and Y vaccine	Menveo	2 mo	0.5 mL	IM	0,2,4, 10 mo	If at continued risk
		7–23 mo	0.5 mL	IM	0, 3 mo (2nd dose administered in 2nd year of life)	
		≥ 2 y	0.5 mL	IM	1 dose if traveling, then 2 doses given 8 weeks apart	
	Menactra	9–23 mo	0.5 mL	IM	0, 3 mo	If at continued risk
		≥ 2 y	0.5 mL	IM	1 dose	
Meningitis B vaccine	Trumenba	10–25 y	0.5 mL	IM	0, 1–2, 6 mo or 0, 6 mo The 3-dose schedule is preferred for groups at increased risk where more rapid protection is desired	None
	Bexsero	10–25 y	0.5 mL	IM	0, ≥ 1 mo	None

the age of 55 as, with the withdrawal of MPSV4, there is no approved vaccine for this age group. In polysaccharide vaccines only the sugar part of the bacteria, the capsule, is included as the antigen to stimulate the immune response. In conjugate vaccines the sugar is joined to a carrier protein to trigger a stronger and more long-lasting response. With the quadrivalent conjugate vaccines, protective antibody levels against all four serogroups develop within 10–14 days after vaccination, and protection of 90–95% is estimated. The duration of protection is shorter in children younger than 5 years of age, but generally considered to be 5 years in adolescents and adults. Conjugate vaccines carry the advantage over the older polysaccharide vaccine of eliciting stronger immunologic memory (generally with recommended revaccination only every 5 years in adults), a reduction in nasopharyngeal carriage, and more effective interruption of transmission and establishment of population protection.[3,4]

Meningitis B vaccinations have been more recently developed, as vaccine development against this serogroup was so challenging that it took over 40 years. The serogroup B polysaccharide resembles a human neural cell adhesion molecule, which raised concern about inducing autoimmunity. Outer membrane vesicle vaccines were developed and effective in outbreak settings, but were limited against the diversity of worldwide B strains. The current approved meningitis B vaccines in the US are recombinant protein-based and were developed through "reverse vaccinology" to identify target preserved proteins, and are widely protective against most meningitis B strains. Both approved in 2015, MenB-4C (Bexsero) and MenB-FHbp (Trumenba) are recommended as equivalent by the ACIP. They are approved for usage in individuals ages 10 through 25.[4] Meningitis B accounts for 40% of the meningitis cases in the US, and 10 university campus outbreaks were associated with this serogroup between 2013 and 2018.[5]

The ACIP now recommends meningitis vaccination routinely to adolescents and meningitis ACWY vaccination routinely in children between the ages of 11 and 18. MenACWY vaccination is administered as a two-dose series, separated by a minimum of 8 weeks, starting at 11–12 years of age, with a booster at age 16. Meningitis B vaccination is recommended, based on shared clinical decision-making, between the ages of 16 and 23 years (preferred ages 16–18). MenB-4C is administered as a 2-dose series separated by at least 4 weeks; MenB-FHbp is administered as a two-dose series separated by at least 6 months (a third dose at least 4 months later is recommended if dose #2 is administered prematurely). Patients should complete the series with the same vaccine as the original dose. Common reactions include pain and redness at the injection site and mild fever for 1 to 2 days. [6,7,8,9]

Other populations are encouraged to pursue vaccination due to increased risk. Vaccination against MenACWY is recommended in patients with functional or anatomic asplenia, patients with HIV infection, persistent complement deficiency, or use of a complement inhibitor (e.g. celuizumab, ravulizumab). It is also recommended in first-year college students and military recruits who were not previously vaccinated. MenACWY vaccination is additionally recommended in travelers to countries with high risk of sporadic outbreaks, particularly the so-called "meningitis belt" across sub-Saharan Africa, which includes a number of countries as well as parts of other African nations. (**Table 2**) Further, all persons entering Saudi Arabia for the Hajj and Umrah **require** MenACWY due to outbreak risk related to crowding. MenB vaccination is recommended outside of the standard dose interval described above in the setting of anatomic or functional asplenia, complement deficiency, and use of complement inhibitors. [6,7,8,9] During outbreak settings, vaccination of affected populations is recommended. A number of outbreaks in men who have sex with men in the past 10 years have led municipalities to offer MenACWY vaccination to these populations as well. [10]

Table 2.

Countries in the "Meningitis Belt"	Other African nations with increased meningococcal outbreak risk
Senegal	Uganda
Gambia	Mauritania
Guinea-Bissau	Mali
Guinea	Burkina Faso
Sudan	Côte d'Ivoire
South Sudan	Ghana
Eritrea	Togo
Ethiopia	Benin
Northwest Kenya	Nigeria
	Niger
	Cameroon
	Chad
	Central African Republic,
	Democratic Republic of Congo

Adapted from CDC website: www.cdc.gov/meningococcal

Though a rare disease, meningococcal disease can be associated with high morbidity and mortality. With the availability of effective vaccinations against most serogroups, including effective vaccines for serogroup B added in 2015, we have a new ability to prevent outbreaks and individual infections. Clinicians should remember to offer these vaccinations to all adolescents, but also remember key higher risk populations, including travelers to sub-Saharan Africa, individuals embarking on the Hajj or Umrah, and immunocompromised patients including people living with HIV. Meningococcal disease prevalence in the US is decreasing, in part due to increased vaccination, but further progress can be made by remembering and counseling adolescents, their parents, and high-risk individuals.

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Hepatitis A and B Vaccination in the United States

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ABSTRACT

Use of hepatitis A vaccine is a main component of travel vaccination practices. In the United States, fluctuations in the number of annual hepatitis A infections have occurred recently due to large outbreaks related to imported foods and urban transmission among homeless individuals, warranting consideration for wider local use of hepatitis A vaccine.

Hepatitis B vaccine is indicated for all adults, and especially healthcare workers. Since 1992, it has been administered at birth. A new novel hepatitis B vaccine given in two doses one month apart is available and has increased efficacy in adults. This article reviews the complete administration of these hepatitis vaccines.

KEYWORDS: hepatitis A, hepatitis B, immunizations, healthcare workers, heplisav-B

HEPATITIS A

Hepatitis A virus (HAV) is a nonenveloped positive strand RNA virus, member of the Picornavirus family, that is mainly transmitted through fecal-oral route and exposure to contaminated food and water sources. It commonly causes a self-limited inflammatory response in the liver that is associated with generalized symptomatology, but in rare cases it may progress to fulminant hepatitis and liver failure.[1] Although the average number of annual HAV infections reported to the Centers for Disease Control (CDC) recently has declined substantially compared to the year 2000, fluctuations have occurred in the last 20 years because of large outbreaks related to imported foods, people who use drugs, experience homelessness and men who have sex with men.[2]

Vaccines

There are two licensed Hepatitis A antigen vaccines available in the Unites States for individual 12 months and older, HAVRIX® (manufactured by GlaxoSmithKline) and VAQTA® (manufactured by Merck & Co., Inc). The schedule for HAVRIX® is 0, 6–12 months and for VAQTA® 0, 6–18 months.[3] Both vaccines provide high immunogenicity-inducing protective antibody levels in 94%–100% of adults one month after the first dose, and 100% one month after the second dose. Similar rates of neutralizing antibodies are found in children and adolescents. Protective antibody levels appear to persist beyond 20 years in healthy individuals.[1]

Twinrix® (manufactured by GlaxoSmithKline), a combined hepatitis A and hepatitis B vaccine, was first licensed by the Food and Drug Administration (FDA) in 2001 on a 3-dose schedule (0, 1, and 6 months) for vaccination of persons aged ≥18 years.[4] The efficacy of Twinrix has been found to be comparable with existing single antigen hepatitis vaccines at 1 month after completion of series. At an alternate 4-dose schedule, Twinrix doses can be administered at 0, 7, and 21 to 30 days, followed by a dose at 12 months. This alternate dosing may be useful when vaccination with Twinrix has been initiated and travel or other potential exposure is anticipated before the second dose.[5]

Indications

In 1999 the Advisory Committee on Immunization Practices (ACIP) recommended vaccination against hepatitis A routinely to children at age 12 to 23 months living in communities with high rates of disease, which led to a 79% decline of cases in states with prior elevated rates in 2004 compared to 1996.[6] In 2006, ACIP extended the recommendation of routine hepatitis A vaccination to children nationwide.

Other groups advised for HAV vaccination due to increased risk of exposure include: men who have sex with men (MSM), users of injection and non-injection drugs, persons with clotting-factor disorders, persons with occupational risk of infection, persons with chronic liver disease, persons traveling to or working in countries that have high or intermediate hepatitis A endemicity.[1]

Preexposure prophylaxis with hepatitis A vaccine is also indicated for unvaccinated persons who are household members and other close personal contacts of adopted children newly arriving from countries with high or intermediate hepatitis A.[7] The first dose of the HAV vaccine should be given ideally 2 or more weeks before the arrival of the adoptee. For infants 6–11 months of age that are at increased risk for HepA exposure, a single dose of HAV vaccine may be given; this dosage will not be counted toward the routine 2-dose series.

Given the higher risk for HAV infection and severe infection-associated outcomes in persons experiencing homelessness, in October 2018 the ACIP advised that all persons aged 1 year and older in this group be routinely immunized

against HAV.[8] Immunity towards HAV in this population is expected to reduce the risk of large-scale, person-to-person outbreaks, but possible barriers to vaccination include limited access to care and insurance coverage among persons experiencing homelessness.

Post-exposure prophylaxis has been shown to be beneficial for persons exposed to HAV within a 2-week period; it is favored over the immunoglobulin due to induction of active immunity, longer duration of protection, ease of administration, and greater acceptability and availability.[9]

Adverse Effects

Pain at the injection site (56%–67%), headache (14%–16%), and malaise (7%) are the most common side effects reported in adults. No serious adverse events have been definitively related to the hepatitis A vaccine.[1]

Contraindications

Hepatitis A vaccine should be avoided in those with a history of severe allergic reaction such as anaphylaxis to any component of the vaccine.

Pregnancy

The risk to the fetus when the vaccine is given during pregnancy has not been determined; since the vaccine is inactivated, it is suspected to be low.[10]

Safety

The vaccine may be given to immunocompromised patients, since it is inactivated. In this population, efficacy may be lower depending on the degree of immunosuppression.

Hepatitis A Immunoglobulin

GamaSTAN S/D is available in the United States, with recommended dosing of 0.1 mL/kg for up to 1 month of planned travel duration and 0.2 mL/kg for up to 2 months has been shown to decrease HAV infection by 90%. It may be given, in conjunction to the HepA vaccine, at separate anatomic sites, within 2 weeks potential exposure to HAV for: adults aged >40 years, immunocompromised persons, those with chronic liver disease, or other chronic medical conditions. Persons may receive the hepatitis A immunoglobulin alone if they are <12 months of age, are allergic to a component of the vaccine or choose not to receive the vaccine.[11] Immunoglobulin cannot be administered simultaneously with MMR.

HEPATITIS B

Hepatitis B (HepB) is a DNA virus of the Hepadnavirus family that is an important cause of chronic liver disease worldwide, which may lead to liver cirrhosis and hepatocellular carcinoma. It is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. The liver is the main site of infection, causing asymptomatic and symptomatic disease. The primary infection is usually self-limited in immunocompetent adults, causing chronic infection in about 5% but it may be as high as 30–90% in children <5 years old. In the US, the rate of reported acute hepatitis B virus infections declined 88.5% since recommendations for HepB vaccination were first issued, from 9.6 cases per 100,000 population in 1982 to 1.1 cases per 100,000 population in 2015.[12,13]

Vaccines

Two single antigen vaccines against hepatitis B are available in the United States, Recombivax HB® (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Either should be administered at 0, 1, and 6 months, but alternate schedule of 0, 2 and 4 months or 0, 1 and 4 months will provide similar response. After the first dose, 30–50% of healthy adults will have protective antibody levels, 75% after the second dose and 90% after the third. An accelerated schedule may be given at 0, 7, and 21 days, followed by a booster at 12 months. The hepatitis B virus (HBV) vaccine after the completed vaccination series provides protection for about 20 years and possibly lifelong.

A combined inactivated hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available for those 18 years and older to be given 0, 1 and 6 months or an accelerated schedule at 0,7, 21–30 days with a booster at 12 months.

On February 2018, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant was recommended for the prevention of HBV in persons aged ≥18 years. This vaccine is administered as 2 doses, 1 month apart, and has improved immunogenicity with a similar safety profile to Engerix-B®.[14,15] Seroprotective antibody to hepatitis B surface antigen (anti-HBs) levels were achieved in 90.0%–100.0% of subjects receiving 2 doses of HepB-CpG, compared with 70.5%–90.2% of subjects receiving 3 dose series of Engerix-B.

The same vaccine formulation should be used to complete the series, although vaccination should not be deferred if same vaccine manufacturer is not available or unknown.[16]

Indications

HepB vaccination is universally indicated within 24 hours of birth for medically stable infants weighing ≥2,000 grams. In addition, routine vaccination is advised for unvaccinated children and adolescents aged <19 years, as well as adults at risk for HBV infection – all healthcare workers, sexual exposure to hepatitis B, history of current or recent injection drug use, risk for infection by percutaneous or mucosal exposure to blood, persons with chronic liver disease, persons with human immunodeficiency virus infection, incarcerated persons – and those requesting protection from HBV without acknowledgment of a specific risk factor.[17]

International travelers to countries with high or

intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%) should be vaccinated against HBV, particularly healthcare workers, disaster relief personnel, receipt of medical care, sexual activity, intravenous drug use, tattooing, among others.

Postvaccination serologic testing 1–2 months after the final dose of vaccine is recommended for certain persons following vaccination (e.g., hemodialysis patients, HIV-infected and other immunocompromised persons, healthcare personnel, and sex partners of HBsAg-positive persons). Revaccination may consist of administration of a second complete HBV vaccine series using any of the available vaccines. Administration of more than two complete HBV vaccine series is generally not recommended, except for hemodialysis patients.[17]

Adverse events

Most common reported side effects are pain at the injection site >10%. Other reactions such as low-grade fever, myalgia, and headaches are rare (<1%). Mild adverse event, serious adverse event, or cardiovascular event in subjects that received HepB-CpG were 45.6%, 5.4%, and 0.27% compared to subjects receiving Engerix-B, 45.7%, 6.3%, and 0.14%, respectively.[14]

Contraindications

Hepatitis B vaccine should not be administered to those with a history of severe allergic reaction such as anaphylaxis to yeast or any other component of the vaccine.

Pregnancy

The vaccine contains a noninfectious hepatitis B surface antigen and the risk to the fetus when the vaccine is given during pregnancy is low. There is limited human data of vaccine-associated risks on HepB-CpG administered to pregnant women.

Immunoglobulin

HepB immunoglobulin may be administered in conjunction with the hepatitis B vaccines in patients after high-risk exposure with infected blood or body fluids within 24 hours of exposure.

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It's Not Only Vaccine Hesitancy; It's Also Physician Hesitancy

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ABSTRACT

The danger of vaccine hesitancy is perhaps one of the most critical challenges we face as practitioners. This riveting narrative helps us find common ground and courage as it reaches into the hearts of those of us who have encountered parents who also want what's best for their child.

KEYWORDS: vaccine hesitancy, immunizations, measles, vaccine side effects, pediatrics

The patient is here. I've printed out the CDC Vaccine Information Statements.[1] I can recite the top reasons for vaccine hesitancy while in a deep sleep. I've been here before and know all the rebuttals.[2-4] I have 15 minutes to help this family see why it is so important to immunize their child. I knock and open the door. A smile crosses my face and I sit down next to the parents. We discuss football, the weather, child development, nutrition. "…and today the immunizations we will be giving…"

Their backs straighten and the seats subtly shift. A deep inspiration echoes throughout the room, as the rapport I had built dissipates with their next words. "We do not vaccinate our children. We do not believe in vaccines."

As a physician, I've prepared for this. I know the arguments in their arsenal. Religion? I'll tell them about how most religions have no restriction on immunizations.[5] Infringement on personal rights? I'll tell them it's their choice, but more importantly, their duty to protect their child. Vaccines have side effects, cause autism, have too many toxins? I'll counter with CDC recommendations, cite small percentages, show the large studies, and go through the ingredient list.[6-8] I will "science" my way to victory.

The points and counterpoints flow in a volley of dialogue. I know that I have made a rock-solid case. I now ask if we will be vaccinating today. The words of parental defiance are palpable as defeat paints my ears with each syllable. Reflexes kick in as I confront myself with the stages of grief.

I couldn't have just failed, I was right!

I should kick them out of my practice. Any parent who can't get over this nonsense shouldn't be allowed to put my other patients at risk or waste my time.

Maybe if I offer a delayed schedule they will listen. But I'm doing that anyway. It's not good medicine.

I should just give up. This is just too hard to do.

Maybe I need to change my approach. That couldn't be it. Maybe I was using the wrong words. No, I know I'm right. Where did I go wrong?

"The single biggest problem in communication is the illusion that it has taken place."[9]
(Attributed to George Bernard Shaw)

I was not listening. I was debating. I was making my point and not feeling what they felt. I used arguments that fell on deaf ears and ignored their fears because "I was right." I was the doctor, the pediatrician. What I was hearing was their reasoning, their thought processes. *I had the illusion that I was communicating.* What was really being said was, "We're scared."

Acknowledge parental fears

It is really easy to scare someone, but really hard to un-scare them. Only by acknowledging fears, can we begin to understand how they are generated and then hopefully begin discussing how to overcome them. The issue is not the science and the issue is not physician knowledge. The issue is not antivaccine misinformation which we cannot control. The issue isn't even that we as physicians lack the time and tools to successfully teach our patients why we are so passionate about immunizing every child.[3,10,11] Every position, including those of our patients and their parents, has an underlying basis. What is the basis for vaccine refusal?

Basis for vaccine refusal

Eighty-one percent of Americans cannot name a living scientist.[12] We view ourselves as scientists, but apparently our patients do not. There is a lack of scientific appreciation in our society and this affects scientific literacy or, in this case, medical literacy. A doctor's visit may be the only time a patient or a parent has the ability to speak directly with someone who knows the science behind vaccines. But tainting the doctor-patient relationship with scientific terminology is often an ineffective way to teach our patients. Many scientists (ie, physicians) do not teach nonscientists (ie, patients or parents) effectively. This is evident in the lack of understanding we as healthcare professionals see in our patients every day. If we cannot explain our thoughts in simple terms, then we can teach nothing.

But do simple explanations always work? Can our patients understand how vaccines work and still be hesitant? In short, yes. Knowledge may not be the only barrier. It's one that needs to be addressed, but this hurdle does not stand alone. Most parents can understand statistics if explained clearly enough. But if fear guides that parent, statistics will not provide solace. A parent may understand the risk of contracting a disease by not vaccinating, but that knowledge is overshadowed by the fear of negative effects attributed to vaccination. The parent reasons that by avoiding vaccines, they are avoiding negative effects of vaccines. However, what is discounted is the real cost of not vaccinating, which is exposure to a much larger risk of disease.[4,13]

Statistics don't assuage fears. In addition to knowledge and statistics, we need stories. We need stories because each individual child does not fit into a statistical model. Parents, however, can relate to a story. A 1% risk of an adverse effect means nothing to the parent of a child who knows a story of a child who has been negatively affected by vaccines. Stories are powerful. Stories from people familiar to us (or seem close to us, such as those strangers on the Internet), who believe they have been harmed by vaccines, are the most powerful of stories.

> *"Belief begins where science leaves off and ends where science begins."*[14] — Rudolph Virchow

Parents are influenced by these anecdotes and we must fill our armamentarium with factual tales of our own, tales based in science. For many, anecdotes supersede statistics. It is difficult to convey the absence of disease caused by immunizations. Immunizations have been so successful in eliminating serious disease that most patients and many physicians don't have the same intimacy with invasive infections as we did in the past.[15] We need to speak about our patient intubated in the ICU with influenza pneumonia. We need to show emotion when speaking about our fear that the child in front of us may contract measles and die. We need to show exactly and in no uncertain terms why we care about our patients and what we are afraid of if they do not get immunized. What are the stories you want to tell?

Instead of asking why they are not immunized, we need to ask about their fears. We cannot afford to be hesitant engaging in effective communication. Instead of regurgitating vaccine facts, we need to teach how vaccines work. Vaccine-hesitant parents aren't necessarily difficult. What's difficult is effective communication. What's difficult is building or continuing the doctor-patient relationship when "they're not listening." When we encounter a parent who just wants the best for their child, we need to say exactly why we also want what is best for the child and exactly what we are afraid of. It isn't only the parent who is hesitant; we as physicians must overcome our own hesitancy.

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Japanese Encephalitis Vaccine

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ABSTRACT

Travelers to 24 endemic countries in Asia may be at risk for Japanese encephalitis. The ACIP has recently expanded guidelines on the use of Ixiaro, the inactivated Japanese encephalitis vaccine. This article reviews the disease burden of Japanese encephalitis and the role of a travel clinic in guiding travelers to Asia regarding decision-making about the use of this highly protective vaccine.

KEYWORDS: Japanese encephalitis, Asia travel, Japanese encephalitis vaccine, flavivirus, pig farming

INTRODUCTION

Travelers may be at risk for Japanese encephalitis (JE) in 24 endemic countries in Asia. Japanese encephalitis is caused by a Flavivirus closely related to West Nile virus and is transmitted predominantly by *Culex* mosquitoes that feed from dusk to dawn.[1] The JE virus is maintained in nature by mosquitoes and animal hosts, mainly pigs and water birds. Infection risk is therefore highest in rural farming areas but is also present in urban and periurban areas in Asia.

JE is endemic in most of Asia and parts of the western Pacific region and is one of the most common causes of encephalitis in Asia. Transmission is seasonal in some areas – May to September in northern Asia and monsoon season-related in India and Southeast Asia – but can occur year-round in other geographic regions such as in Bali, where rice paddies, pig farms, birds and *Culex* mosquitoes are abundant.[1] JE has also been reported in the Torres Strait Islands in northern Queensland, Australia. Interestingly, the great demand for pork in Asia has led to relocation and establishment of pig farms closer to urban centers for ease of distribution.[2] This may allow for increasing evolution of movement of risk for JE virus. Travel clinic consultation can help individuals navigate the country-specific information taking into account transmission months that can be found in the CDC Yellow Book.[1] JE infection is uncommon in tourists, with an estimated risk of one in 200,000 per week of exposure, and <1% of infections result in symptomatic illness. However, symptomatic cases are associated with significant morbidity related to acute encephalitis and present with a wide range of neurological symptoms. Case fatality rate of symptomatic cases is up to 30%. Of those who survive, 30% to 50% report long-term neurological, psychological, and cognitive impairment including polio-like weakness and life-long seizure disorders:[1,2] severe cases are very severe. Travelers to JE-endemic areas should be advised to take precautions against mosquito bites, particularly from dusk to dawn. Vaccination should also be considered, and recommendations must take into account the risk of infection (country, urban vs. rural, farming areas, seasons, outdoor activities, trip duration, and repeated travel). The high risk of death and serious long-term sequelae from symptomatic infections and the cost of vaccines are other important considerations.

The Advisory Committee on Immunization Practices (ACIP) has modified their guidelines.[3] As a general rule, it recommends vaccination for travelers who plan to spend a total of one month in endemic areas during the transmission season. Given that some US cases occurred in short-term travelers – some with less than one week of unexpected exposure – duration may not be the best factor in decision-making about vaccination against JE for an individual traveler to Asia. This disease is rare but has significant consequences. We offer JE vaccine for persons traveling outside of major urban areas. Those who plan to return to Asia will benefit from vaccination against the cumulative risk. Those traveling for <1 month should consider choosing vaccination if spending time in rural areas; taking part in high-risk activities (e.g., farming, outdoor sporting activities); staying in accommodations without screens, bed nets, or air conditioning; or traveling to outbreak areas.[1] Vaccination is strongly recommended for expatriates planning to live in Asia for more than 6–12 months, even in urban areas, because they often travel extensively throughout the region for work and vacations.[3] The only JE vaccine available in the USA is an inactivated Vero cell culture vaccine, Ixiaro (Valneva). In 2009 it was licensed for use in those aged 17 years, and in May 2013 the license was extended to children aged 2 months. Primary immunization consists of two IM doses given on days 0 and 28, completed at least a week before departure. Each dose is 0.25 mL for children aged <3 years and 0.5 mL for those aged 3 years. For adults with ongoing exposure to JE a booster dose is recommended 1–2 years after the primary course. There is currently limited evidence about the need for boosters for those aged <18 years.

An accelerated schedule on day 0 and day 7 with a booster in 1 year has been shown to provide excellent protection and is approved for last minute travelers to risk regions who are ages 18 to 65, weighing seasonal risk and planned outdoor activity.[4]

Adverse reactions

Local reactions such as pain and swelling are reported in 1% of vaccine recipients. Systemic reactions include headache, myalgia, fatigue, and fever.

Contraindications

Ixiaro is contraindicated in persons who have had serious adverse reactions from any JE vaccines or any of the vaccine components (including protamine sulfate or formaldehyde). No preservatives, stabilizers, or antibiotics are added to the formulation. For the manufacturing process Ixiaro also contains bovine serum albumin (not more than 100 ng/mL), Vero host cell DNA (not more than 200 pg/mL), sodium metabisulfite (not more than 200 ppm), and host cell protein (not more than 100 ng/mL). Safety data in pregnant women are currently lacking. The risk of vaccination to mother and fetus really cannot be defined, so this is an undefined situation in terms of making a decision based on risk. Ixiaro use should generally be avoided during pregnancy or breastfeeding unless the high-risk travel cannot be avoided. Some pregnant women opt to have the vaccine after consideration of their travel needs and discussion of disease risk.

OTHER CONSIDERATIONS

- For travelers who have been vaccinated with the previously available mouse brain-derived JE vaccine (JE-Vax, Biken), there is currently insufficient evidence regarding the effectiveness and duration of protection from a single booster dose of Ixiaro. Until further data are available, these travelers should be given a primary two-dose course of Ixiaro.
- For adult travelers who do not have time to complete the two-dose primary course before departure, an accelerated course of two doses on days 0 and 7 may be considered.[4]
- In immunocompromised hosts the immune response to Ixiaro is not well documented.
- Vaccination is recommended for residents of the Torres Strait Islands in Australia, as well as those traveling to the area for a cumulative total of 30 days during the wet season (December to May). Very few international tourists travel to the Torres Strait Islands, which are situated between the northern tip of Queensland and Papua New Guinea.

There are some JE vaccines available outside the USA in case travelers find themselves with last-minute plans while abroad, although use is generally discouraged without consultation. A live attenuated recombinant Vero cell vaccine (Imojev, Sanofi Aventis) is available in Australia and some countries in Asia, including Thailand, Malaysia, Hong Kong, Singapore, and the Philippines.[5] The vaccine is licensed for use in those aged 9 months. A single dose of 0.5 mL subcutaneously provides long-term protection in adults, but a booster is recommended for those aged 9 months to 18 years. Imojev is a live attenuated vaccine and therefore contraindicated in pregnant women, breast-feeding mothers, and immunosuppressed hosts. In Australia and New Zealand, Ixiaro is marketed as JEspect. In some countries a mouse brain-derived vaccine, with a poorly understood and worrisome safety profile, and other live attenuated vaccines, are also in use.[5] Given high risk of allergic responses with this product – including late onset of anaphylaxis – travelers are urged to seek travel advice in the US a few months prior to embarking on a trip to Asia to consider the safe and effective Ixiaro product. Hopefully, a coronavirus vaccine will also soon be available to facilitate all world travel once again!

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Epidemiology of Rabies and Current US Vaccine Guidelines

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ABSTRACT

Rabies is an acute encephalitis that is caused by rabies virus (RABV) infection, which belongs to the Rhabdoviridae family of viruses. It causes about 59,000 human deaths per year (although this number may be under-reported) and is generally fatal, once signs and symptoms begin to appear. Rabies is still very prevalent and under-reported, particularly in low to middle-income countries such as Asia and Africa, where there is lack of access to healthcare and domestic dogs are not widely vaccinated. Although not commonplace in the USA, rabies is mostly transmitted by wild animals such as bats, raccoons, skunks and foxes. Domesticated cats and dogs are also at risk of acquiring rabies, if they have not been vaccinated. Larger carnivores, such as coyotes, bobcats, mountain lions, wolves, bears, woodchucks, and beavers, should also be considered rabid (unless proven otherwise) if they are involved in an unprovoked attack on a person. The rabies vaccine can prevent 99% of deaths if administered promptly after exposure. There are two main vaccination strategies for rabies prevention: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). This article reviews background and epidemiology of rabies and current guidelines for rabies PrEP and PEP regimens for the United States.

KEYWORDS: rabies, animal bites, dogs, rabies vaccine, rabies immunoglobulin

BACKGROUND

Rabies is an acute progressive encephalitis caused by the rabies virus (RABV), a single stranded RNA virus that's part of the family Rhabdoviridae, genus Lyssavirus. The virus is most commonly transmitted through the saliva of a rabid animal. It can also be transmitted through exposure to urine, sweat, and nervous tissues. RABV is not considered to be a bloodborne pathogen. When a human/animal is bitten by a rabid animal, the virus travels from the bite wound into the peripheral nervous system and then makes its way to the brain where the virus replicates and then disseminates back into various tissues, including the salivary glands, where the transmission cycle repeats itself. Human-to-human transmission has never been confirmed except in extremely rare case reports of transmission from infected tissue/organ transplantation.[1] The incubation period on average lasts 1–3 months, but has been documented to range from weeks up to more than a year. Clinical rabies rarely occurs after one year from exposure.[2] Signs and symptoms include pain/paresthesias at the wound site, fever, paralysis, delirium, convulsions, and hydrophobia. Death is almost always imminent within 7–10 days once the infection clinically manifests itself. The rabies vaccine and rabies immunoglobulin (RIG) are very effective in preventing rabies if administered during the incubation period. Rabies vaccines activate the immune system to produce rabies virus neutralizing antibodies (VNAs). Detectable antibodies take about 7–10 days to develop and generally last for several years.

Louis Pasteur and Emile Roux developed and tested the first live attenuated injectable rabies vaccine in 1885. It was made from rabbit nerve tissue. Since 1984, the WHO has recommended discontinuation of production and use of nerve tissue vaccines and replacing them with modern, concentrated, purified cell culture and embryonated egg-based rabies vaccines (CCEEVs). Nerve tissue vaccines can cause severe adverse events and are not as effective. However, they are still being used in some developing countries. Since the 1960s, CCEEVs have been widely distributed and used in the U.S.2 There are two types of CCEEVs licensed for use in the U.S: human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV). Both are formulated for intramuscular (IM) administration and can be used for pre- or post-exposure prophylaxis.[3] Intradermal injections are sometimes used off license in the USA, but are not approved by the FDA.

There are two human RIG, HyperRabTM S/D and Imogam® Rabies-HT, licensed for use in the U.S. for PEP. They are IgG preparations made from human donor plasma and formulated for IM administration only.[3] RIG provides passive immunity that is intended to protect the victim until active immunity produced by the administered vaccine kicks in.

EPIDEMIOLOGY

Rabies causes about 59,000 deaths globally per year and associated loss of 3.7 million disease associated life years (DALYs). The majority of deaths occur in Asia and Africa.[2]

Children under 15 years account for approximately 40% of deaths.[5] Children are more susceptible because of their curious nature and their shorter stature, making them more likely to sustain a wound in a higher-risk anatomical location such as the head.[1] Transmission by unvaccinated domestic dogs is responsible for the majority of human rabies cases globally. Mass vaccination of domestic dogs has been an effective strategy at decreasing the prevalence of rabies in many countries in Africa, Asia, Europe and the Americas. Dog-mediated rabies has been eliminated from the U.S. (i.e. no cases of dog-mediated rabies in the last 2 years).[2] Rabies in the U.S. is rare and is now primarily transmitted through wild animal vectors such as bats, foxes, raccoons, and skunks. Since 1980, there has been an average of 2 deaths per year in the U.S. Between 2000 and 2007, 20 of 25 cases of human rabies reported in the United States were acquired domestically. Among those 20 cases, 17 were associated with bat rabies virus variants.[4] The rate of rabies exposures is about 16 to 200 per 100,000 travelers.[1] Approximately 16,000 to 39,000 patients are exposed to rabies and receive PEP annually in the U.S. Since routine use of cell culture vaccines and HRIG, no PEP failures have been reported in the United States.

PREEXPOSURE PROPHYLAXIS (PREP)

PrEP should be offered to high-risk populations, such as travelers who will spend a long time in a rabies endemic country, veterinarians and their staff, animal handlers, rabies researchers, certain laboratory workers, and those with frequent exposures to rabid animals (i.e. cavers, animal control officers).

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends a series of three 1-mL IM injections in the deltoid. Immunizations should be administered on days 0, 7, 21 or 28. If exposed to rabies, PrEP does not eliminate the need to seek out PEP; however, it reduces the number of vaccine injections post-exposure and eliminates the need for RIG. A few studies have demonstrated that a two-dose regimen given over the course of a week is just as effective as three doses, and more cost-effective.

Rabies occurs most often in resource limited settings. A clinical trial of 500 healthy volunteers showed that an intradermal 2-dose regimen given on days 0 and 7 did not elicit less of an immune response compared with a 3-dose regimen given over the course of a month.[6] The WHO recommends a 2-dose vaccination regimen in resource limited settings given on days 0 and 7 given either IM or ID.

SEROLOGIC TESTING

Rabies virus researchers or those who work in vaccine production are at highest risk for rabies and should get virus neutralizing antibody titer testing every 6 months. Those in the frequent exposure risk category (i.e. cavers, veterinarians, wildlife workers in areas where rabies is enzootic) require antibody titer testing every 2 years. If titers fall under the acceptable level of complete neutralization at a serum dilution of 1:5, a single IM booster vaccine should be administered. Routine antibody testing for travelers in the infrequent risk exposure category is not recommended.

POSTEXPOSURE PROPHYLAXIS (PEP)

All persons exposed to rabies should start by thoroughly washing and cleaning out the wound with soap and water or a virucidal agent. This should be followed immediately by passive rabies immunization with RIG in unvaccinated patients and vaccination with a cell culture rabies vaccine. HRIG is made from the plasma of hyperimmunized healthy volunteers and is not easily accessible in some resource poor settings. Equine rabies immunoglobulin may also be used as an alternative if HRIG is not available.

After a Rabies Workgroup met in 2008 to review current literature and expert opinion, the ACIP published revised guidelines in favor of reducing PEP vaccination from 5 doses to 4 doses.[5] Unvaccinated individuals should receive four 1-mL dose vaccines and RIG promptly after being exposed to the rabies virus. For adults and older children, the only acceptable area to administer the vaccine is in the deltoid area. In younger children, the outer thigh can be used as well. Vaccine should never be administered in the gluteal area because efficacy is decreased.

The first dose of the vaccine should be administered as soon as possible after the exposure on what is considered day 0. It can also be started weeks to months after exposure within the incubation period if signs and symptoms of rabies have not yet appeared. The next 3 doses should then be administered on days 3, 7, and 14 after the first vaccination. Serum antibody titer testing is not recommended for healthy patients as the vaccine has been shown to consistently produce adequate VNAs.

For immunosuppressed persons, rabies PEP should be administered by using the 5-dose vaccine regimen (ie, 1 dose of vaccine on days 0, 3, 7, 14, and 28). Immunosuppressed patients should undergo rabies serum antibody testing 1 to 2 weeks after the fifth dose of vaccine. The WHO specified minimum serum antibody concentration of 0.5 IU/mL is widely used as a measure of adequate seroconversion after vaccination.[2]

RIG should only be administered once on day 0 to exposed humans who have never previously received a complete vaccination regimen (pre- or post-exposure). If RIG administration is delayed, it can be administered at any time up to day 7.2 HRIG is intended to provide passive rabies VNAs while the active antibody production is occurring. After day 7, we presume that antibodies have already been produced from vaccine administration. The recommended dose for patients of all ages is 20 IU/kg of body weight. RIG should be

infiltrated around the wound(s) as much as possible and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. RIG should be administered in a different syringe than the vaccine. No more than the recommended dose should be given because it may suppress active immunity production.[3]

Persons who have previously received complete vaccination regimens (pre-exposure or postexposure) with a rabies vaccine and have a documented rabies virus neutralizing antibody titer should receive only 2 vaccine injections 3 days apart (i.e. days 0 and 3). RIG should not be administered.

If an individual has a repeat exposure within 3 months, RIG and vaccine are not indicated. However, if the repeat exposure occurs >3 months, then the protocol for postexposure prophylaxis in a person who has been previously vaccinated should be followed (i.e. IM injection of vaccine on days 0 and 3).[2]

Minor deviations from the schedule by a few days are inconsequential. The schedule should be resumed with the same intervals between doses. For more substantial deviations from the schedule, antibody titers should be checked 1–2 weeks after the final dose of the vaccine is administered, as effects have not been properly studied.

Post exposure prophylaxis can be discontinued if the appropriate diagnostic laboratory testing (i.e., the direct fluorescent antibody test) concludes that the animal in question was not rabid.

ADVERSE EFFECTS AND SPECIAL CONSIDERATIONS

Serious hypersensitivity, neurological, and fatal adverse events following immunization are extremely rare. Considering the risk of death from rabies, there are no contraindications to rabies vaccination. Local symptoms of erythema, pain and swelling at the site of injection commonly occur. Mild systemic symptoms such as transient fever, headache, dizziness, nausea, and abdominal pain can present in about 5–15% of people after receiving the vaccine.[2] Prophylaxis should not be discontinued or interrupted because of minor or local adverse events.

Rabies vaccines and RIG should be administered normally to infants and children. Limited data suggests that rabies vaccines are safe in pregnancy and is not associated with abortion, premature births, or fetal abnormalities.[7]

Some studies suggest that antimalarial prophylaxis with chloroquine may blunt the immune response to rabies vaccine. According to the WHO, the effect of antimalarial agents on antibody production is unlikely to be clinically significant. They previously recommended IM over ID administration in persons taking antimalarial prophylaxis but removed this statement from their 2018 position paper.[2]

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Acute Vision Loss in a Patient with COVID-19

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ABSTRACT

To date, there have been reports of neurologic manifestations in COVID-19 patients including ischemic strokes, Guillain-Barre Syndrome and anosmia. In this case report, we describe a patient who presented with dysosmia, dysgeusia, along with monocular peripheral vision loss after being diagnosed with COVID-19.

KEYWORDS: vision loss, SARS-CoV-2, COVID-19, neurologic, ophthalmology

INTRODUCTION

As of June 6, 2020, there are more than 6,500,000 cases of SARS-CoV-2 worldwide.[1] To date, there have been several reports of neurologic manifestations in these patients including ischemic strokes, Guillain-Barre Syndrome and anosmia.[2-4] Wu et al described a case series involving 38 patients with COVID-19, where 12 patients had ocular signs of epiphora, conjunctival congestion and chemosis.[5] We report a patient who presented with dysosmia, dysgeusia along with monocular peripheral vision loss after being diagnosed with COVID-19.

CASE PRESENTATION

A woman in her 50s with a history of hypertension, hyperlipidemia, and headaches presented to the hospital with fever, chills, and cough one week after she tested positive for SARS-CoV-2. She reported acute, painless right eye monocular visual disturbance, described as a white cloud and blurriness involving most of her right eye, sparing the superior nasal aspect. She denied any left eye visual disturbances. She denied any other ocular symptoms such as flashers, floaters, or diplopia. She denied any jaw claudication, scalp tenderness, unintentional weight loss. Other neurological symptoms included dysgeusia, dysosmia, right ear hypoascusis, and subjective right hemiparesis. She was not taking any medications at home.

On the day of admission, her neurological exam was remarkable for severe right eye vision loss. She was unable to visualize or count fingers in the right temporal field and inferior nasal field. The left eye exam was normal. Relative afferent pupillary defect was absent. There was no tenderness to the palpation of the temporal area. The following day, she reported fifty percent improvement in her vision. Her vision in the far periphery of the right eye was blurry but she was able to count fingers in all fields. Visual acuity was 20/70. The dilated fundoscopic exam was normal. Ocular pressures were normal. There was no evidence of optic disc edema, Hollenhorst plaque, retinal whitening. or hemorrhages.

Her laboratory values were normal including CBC, BMP and ESR. Her CRP was 7, and d dimer was 206 ng/ml. LDL was elevated at 131. Initial MRI of the brain without gadolinium did not reveal any intraparenchymal or cranial nerve abnormalities, though it was notable for a partially empty sella turcica. MRI of the orbits, face, and neck with and without gadolinium revealed no area of abnormal enhancement. The optic nerves, chiasm, and optic tracts appeared normal. CT angiography showed no significant carotid disease. Her vision spontaneously improved during her hospitalization, and she was discharged home on aspirin and atorvastatin. She was advised to follow up in the Ophthalmology clinic in one month.

DISCUSSION

The clinical spectrum of illness due to COVID-19 continues to evolve. Acute vision loss is a medical emergency and can occur over a few seconds or minutes to a few days. Vision may become blurry, cloudy, entirely or partially absent, or affected by flashes or floaters. Acute vision loss is usually painless but may also be associated with ocular pain, redness and headache. Most cases of visual loss can be diagnosed by history and physical examination alone.

Common causes of acute vision loss include Central Retinal Artery Occlusion, Central Retinal Vein Occlusion (CRVO), Retinal Detachment, Optic Neuropathy, and Inflammatory conditions such as Giant Cell Arteritis (GCA). CRVO was unlikely due to the absence of retinal hemorrhages and cotton wool spots on the fundoscopic exam. Given the history of peripheral monocular vision loss, transient Branch Retinal Artery Occlusion (BRAO) was considered a possibility, although there was no evidence of retinal whitening or edema.

Given her normal ophthalmologic exam, Posterior Ischemic Optic Neuropathy (PION) was considered to be more likely. There are three different types of PION: arteritic,

non-arteritic, and surgical. The capillary plexuses supplying the posterior part of the optic nerve are vulnerable to hypoperfusion and ischemia. Vision typically recovers if circulation is restored before axonal death, as observed in our case. Arteritic PION is usually due to GCA, which was unlikely given normal ESR, CRP, and the absence of classic symptoms such as jaw claudication and scalp tenderness. Our patient likely had non-arteritic PION due to small vessel disease that is usually linked to systemic illness. Given the MRI evidence of a partially empty sella, idiopathic intracranial hypertension, or pseudotumor cerebri, was also considered a possibility for transient visual loss. She did not undergo a lumbar puncture to measure intrathecal pressure as her ocular symptoms had improved and she denied any headache symptoms.

Previous strains of coronavirus seem to invade the CNS mostly through the hematogenous route but also can invade through the cribriform plate and the conjunctiva.[5,6] The pathophysiology in our case is unclear. One of the mechanisms could involve inflammation associated with COVID-19 itself, although her CRP and ESR were normal.[7] Another mechanism could be related to the thromboembolic phenomenon and occlusion of small capillaries feeding the optic nerve, although our patient's d dimer was normal. Magro et al showed that there might be a microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state that may also be at play in these patients.[8]

Our patient's symptoms were early in the course of her illness and could be useful in triaging patients. A thorough neurologic exam is essential in all patients diagnosed with COVID-19. This case illuminates a broader spectrum of COVID-19-related symptomatology and emphasizes the need for clinicians to be aware of the various clinical manifestations associated with this infection.

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Short-Term Dexamethasone in Sars-CoV-2 Patients

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ABSTRACT

BACKGROUND: Dexamethasone, a synthetic glucocorticoid, has anti-inflammatory and immunosuppressive properties. There is a hyperinflammatory response involved in the clinical course of patients with pneumonia due to SARS-CoV-2. To date, there has been no definite therapy for COVID-19. We reviewed the charts of SARS-CoV-2 patients with pneumonia and moderate to severely elevated CRP and worsening hypoxemia who were treated with early, short-term dexamethasone.

METHODS: We describe a series of 21 patients who tested positive for SARS-CoV-2 and were admitted to The Miriam Hospital in Providence, RI, and were treated with a short course of dexamethasone, either alone or in addition to current investigative therapies.

RESULTS: CRP levels decreased significantly following the start of dexamethasone from mean initial levels of 129.52 to 40.73 mg/L at time of discharge. 71% percent of the patients were discharged home with a mean length of stay of 7.8 days. None of the patients had escalation of care, leading to mechanical ventilation. Two patients were transferred to inpatient hospice facilities on account of persistent hypoxemia, in line with their documented goals of care.

CONCLUSIONS: A short course of systemic corticosteroids among inpatients with SARS-CoV-2 with hypoxic respiratory failure was well tolerated, and most patients had improved outcomes. This limited case series may not offer concrete evidence towards the benefit of corticosteroids in COVID-19. However, patients' positive response to short-term corticosteroids demonstrates that they may help blunt the severity of inflammation and prevent a severe hyperinflammatory phase, in turn reducing the length of stay, ICU admissions, and healthcare costs.

KEYWORDS: CRP (C- reactive protein), corticosteroids, SARS-CoV-2, COVID-19, dexamethasone

BACKGROUND

In December 2019, the novel coronavirus that causes Severe Acute Respiratory Syndrome was discovered in Wuhan, China. The previous epidemics caused by SARS-CoV (10% mortality) and MERS-CoV (37% mortality) caused more than 10,000 cases in two decades.[1,2] As of June 18, 2020, there are more than 2,132,000 cases of SARS-CoV-2 in the United States.[3] The clinical spectrum of disease due to SARS-CoV-2 continues to evolve and remains a challenge for physicians.

Most patients with mild illness tend to do well. However, patients with moderate or severe disease tend to be older, have obesity, have comorbid conditions such as diabetes mellitus, hypertension, and are more prone for hypoxic respiratory failure needing ICU level of care.[4,5] The median time from onset of symptoms to hospital admission was five to seven days, and nine to ten days for ARDS and hypoxic respiratory failure.[6,7] The pathophysiology involves an initial viral response phase where patients mostly have mild constitutional symptoms, followed by a pulmonary and then a hyperinflammatory phase where patients have shortness of breath, hypoxemia, abnormal chest imaging and elevated inflammatory markers.[8]

Current treatment for patients with SARS-CoV-2 infection mainly involves supplemental oxygen, prone positioning along with supportive care. There are trials involving antiviral agents such as Remdesivir, hydroxychloroquine, and the use of convalescent plasma. However, a number of these trials mostly enroll patients in the early stage of the disease. Patients in the later stage (8 to 12 days) are often ineligible, leaving providers with few options to manage patients with worsening clinical and respiratory status.

A recent preliminary and as yet unpublished study from the UK showed that dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in COVID-19 patients that were on oxygen only.[9] We postulate that early treatment with corticosteroids in patients with rising CRP and worsening hypoxemia may help prevent or attenuate the hyperinflammatory response associated with this condition. We report the clinical characteristics, early outcomes, and levels of C-reactive protein (CRP) in a limited set of patients with moderate or severe disease and who received a short course of dexamethasone using our clinical management protocol.

METHODS

This case series involves 21 patients with confirmed SARS-CoV-2 who were seen by the Hospitalist team at The Miriam Hospital, Providence, RI, USA, between April 16 and May 16, 2020. A confirmed case was defined as a positive PCR assay for SARS-CoV-2 in a nasopharyngeal sample tested by the laboratory at Miriam Hospital or the Rhode Island Department of Health. The Institutional Review Board of the Hospital approved the study.

Patients were risk-stratified based on the severity of clinical illness, CRP levels, and oxygen requirements. Patients with mild disease had a minimal elevation of CRP (<50 mg/L), needed less than 2L/min oxygen, or only had GI symptoms. Moderate disease included patients with moderate elevation of CRP (50-200 mg/L) and 2-6L/min oxygen requirement. Patients with severe disease included patients with CRP greater than 200 mg/L and needed more than 6L oxygen requirement. Prone positioning was instituted in all patients with moderate to severe disease if they were able to tolerate it. Patients in the severe disease category were transferred to the Intermediate Care Unit (Step down Care Unit) for closer monitoring. They were also started on High Flow Nasal Cannula with or without Non-Invasive Ventilation. In addition, all the patients were provided with an incentive spirometer, antitussives, and bronchodilators as needed.

Patients were offered short courses of dexamethasone at the discretion of their providers based on the following criteria and the KODA clinical management protocol (the acronym KODA was coined after one of the clinicians at the hospital):

1. Moderate disease with at least a 30% increase in CRP within 36 hours of admission, and increasing oxygen requirements.
2. All patients with severe disease with evidence of escalating oxygen requirements.
3. The presence of secondary bacterial infections as a probable cause of increasing CRP levels was excluded in all the selected patients.
4. Pulmonary embolism and cardiac dysfunction were excluded as probable causes of worsening hypoxia in all the selected patients.

Patients with the following set of criteria were excluded from the study:

1. All patients that showed significant clinical improvement and decrease in CRP levels and/or oxygen requirements on investigative modalities such as Remdesivir or convalescent plasma.
2. Patient with associated COPD exacerbation who were primarily managed with systemic steroids.
3. Patients with Diabetic ketoacidosis, hyperglycemic hyperosmolar state, active concurrent bacterial infections.
4. Patients with a history of steroid-induced mania or psychosis.

Selected patients per the above criteria were administered dexamethasone 4mg three times daily for two days, followed by 4mg twice daily for two days and then 4mg once daily for two days.

The Infectious Disease service at Miriam Hospital followed these patients while they were admitted. Those who were eligible and were already enrolled in clinical trials for Remdesivir or convalescent plasma continued with their therapy. Hydroxychloroquine with or without azithromycin was given to patients who did not meet the criteria for the above trials and who were showing signs of clinical deterioration and had no contraindications to the use of both medications. If the patient was observed to have a subsequent rise in CRP after initiating dexamethasone, the provider actively searched for secondary infection and promptly initiated broad-spectrum antibiotics. Corticosteroids were discontinued if there was no overt clinical benefit after 72 hours or clinical worsening after initiation.

End Points

Our primary endpoints were escalation of care to the Intensive Care Unit (ICU) from General or Intermediate Care Level Unit, progression of respiratory failure needing mechanical ventilation and mortality. Secondary endpoints included change in CRP levels and Length of Stay (LOS).

Data Collection

Data were obtained from the EPIC Electronic Medical Record system and recorded in a standardized case report form. Demographic data, Laboratory findings, Oxygen requirements in Liters Per Minute (LPM), Length of Stay, CRP levels, and Comorbid conditions were ascertained.

RESULTS

We followed a total of 21 SARS-CoV-2 positive patients. 61.9% of the patients were male, their mean age was 60 ± 15.77 years, mean BMI was 28.68 ± 9.46 kg/m^2, and the most common comorbidities were Diabetes Mellitus and Hypertension (**Table 1**). The mean number of days after onset of symptoms to hospital admission was eight days. The mean maximum oxygen requirement was noted to be 15 LPM.

The mean CRP levels at the time of admission were 129.52 ± 72.05 mg/L. Peak levels were 185.09 ± 76.34 mg/L. At the time of discharge, mean levels were 40.73 ± 49.28 mg/L (**Table 2**). There was 77.98% reduction in peak CRP levels after the initiation of dexamethasone. Dexamethasone was discontinued early in one patient due to hyperglycemia. None of the patients were transferred to the ICU or had progression of respiratory failure needing mechanical ventilation. All the patients required days of management in the Intermediate Level of Care Unit for their hypoxic respiratory failure using High Flow Nasal Cannula with or without Non-Invasive Ventilation.

Table 1. Baseline Demographics of SARS-CoV2 Positive Patients

Variables	Values
Age (in years)	
30–49	28.57% (6)
50–64	52.38% (11)
>65	19.04% (4)
Sex (Males)	61.9% (13)
Race	
White	38.09% (8)
African American	19.04% (4)
Hispanic	28.57% (6)
Other	14.28% (3)
Mean Onset of Symptoms (in days)	8 ± 3.63
Mean BMI (kg/m²)	28.68 ± 9.46
Comorbidities	
Diabetes Mellitus	38.09% (8)
Hypertension	61.9% (13)
Coronary Artery Disease/Congestive Heart Failure	14.29% (3)
Chronic Lung Disease	14.29% (3)

Table 2. Laboratory Values and Hospital Course of SARS-CoV-2 Positive Patients

Mean CRP Levels on Admission (mg/L)	129.52 ± 72.05
Mean Peak CRP Levels (mg/L)	185.09 ± 76.34
Mean CRP Levels on Discharge (mg/L)	40.73 ± 49.28
Mean Length of Stay (in days)	7.8 ± 3.82
Mean Maximum Oxygen Requirement (Liters per minute)	15 ± 9.16
Antibiotic Use	47.61% (10)
Concurrent Use of Investigational Therapies	
Remdesivir	42.86% (9)
Hydroxychloroquine +/– Azithromycin	23.80% (5)
Convalescent Plasma	66.67% (14)
Patients Discharged Home	71.42% (15)

Of the 21 patients that were admitted to the hospital, 71.42% were discharged home with a mean LOS of 7.8 days. Four patients were discharged to Skilled Nursing or Acute Rehabilitation Facilities. Two patients were transferred to inpatient hospice facilities on account of persistent hypoxemia, in line with their documented goals of care.

DISCUSSION

In this limited case series, patients with rising CRP and worsening hypoxemia that received a short course of dexamethasone had a significant reduction in CRP levels and did not need to be transferred to the ICU or be mechanically ventilated. This may be a useful and low-cost tool that may help reduce critical care services utilization and free hospital beds, especially if there is a surge in inpatient volume.

SARS-CoV-2 attaches to ACE2 receptors that are primarily located on type II pneumocytes. After infection, these cells release inflammatory signals that recruit macrophages, which in turn causes a "cytokine storm" that causes vasodilation, increased capillary permeability, and leucocyte migration. There is a release of Reactive Oxygen Species along with loss of surfactant, which causes the destruction of pneumocytes and the collapse of alveoli.[10,11] This, in turn, leads to Severe Inflammatory Response Syndrome and further progression to Severe Acute Respiratory Syndrome in severe cases.

Early studies from China reported elevation of inflammatory markers including CRP, LDH, and IL-6 in patients with SARS-CoV-2.[12] CRP is a systemic marker of acute phase response in inflammation, tissue damage and infection.[13] Elevated levels of CRP were associated with higher mortality, higher risk of clinical deterioration and progression of respiratory failure.[14]

Corticosteroids cause decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Glucocorticoids inhibit neutrophil apoptosis and demargination. They also inhibit NF-Kappa B, inflammatory transcription factors, and also promote anti-inflammatory genes like interleukin-10. They are known to inhibit the production of other mediators, including arachidonic acid metabolites such as cytokines, interleukins, adhesion molecules, and enzymes such as collagenase.[15,16]

Dexamethasone is a synthetic adrenal corticosteroid that has both anti-inflammatory as well as immunosuppressive properties. It is 20–30 times more potent than hydrocortisone and 4–5 times that of prednisone. Dexamethasone was chosen to reduce the need for diuretics to address fluid and sodium retention, which would have confounded interpretation of the results. In addition, dexamethasone has a longer half-life compared to other corticosteroids and will auto taper when discontinued.

Corticosteroids have always been controversial in the management of patients with Acute Respiratory Distress Syndrome (ARDS) and are not routinely used unless there is an alternate indication. Current guidance by the World Health Organization (WHO) recommends against the routine use of corticosteroids in patients with SARS-CoV-2. Lee et al. showed that early steroid use in SARS-CoV1 patients resulted in prolonged detection of viral RNA and also did not benefit patients that received steroids later in their hospital course.[17] On the contrary, Fang et al. showed that low dose corticosteroid administration did not effect viral RNA clearance.[18] This can be explained by differences in the timing of initiation of therapy as well as patient heterogeneity. Numerous studies from China have reported routine use of corticosteroids in patients with SARS-CoV-2; however, the risks and benefits are unclear.[6,19] Two recent observational studies showed good outcomes in SARS-CoV-2 positive

patients with one study, even showing a mortality benefit.[20,21] The trial by Villar et al. evaluated the use of dexamethasone in 277 patients with ARDS and demonstrated accelerated liberation from ventilation along with reduced mortality.[22] Preliminary results from the RECOVERY trial showed that dexamethasone use prevented one death by treatment of around eight mechanically ventilated patients or approximately 25 patients requiring oxygen only. The trial studied the use of 6mg dexamethasone for ten days in contrast to our clinical management protocol that only used it for six days.[9]

A majority of our patients presented in the 7- to 12-day time period with rapid clinical deterioration, consistent with progression to the hyperinflammation phase. The present study supports the use of corticosteroids during an optimal time window to help attenuate the severity of the inflammation and prevent a severe hyperinflammation phase. Two patients that received steroids much later in the course of their hospitalization did not significantly improve and were transitioned to inpatient hospice in line with their goals of care. Our study has many limitations. Being a case series, there is only a small number of patients that were followed. The study design has inherent biases along with patient selection. In addition, it is difficult to delineate the role played by other therapies administered concurrently along with corticosteroids. There is, however, evidence that comparable patients who were enrolled in other therapies but did not receive the short course of dexamethasone ended up with a longer length of hospital stay.[21]

In conclusion, timely initiation of short-course dexamethasone, a low-cost and relatively low-risk intervention may help prevent the progression of hypoxic respiratory failure in moderate to severely ill patients and help accelerate recovery. Further large-scale studies are urgently needed to study the role of early use of corticosteroids in SARS-CoV-2 positive patients, especially those at high risk of clinical deterioration. Additional studies about the immune response associated with SARS-CoV-2 infections, the use of velocity of CRP in disease monitoring, and the utility of dexamethasone with or without other therapeutic options are needed.

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Disclosures

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Angioedema and Epinephrine Causing a Stress-Induced Cardiomyopathy

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ABSTRACT

Presentations of angioedema range from mild edema to immediate life-threatening airway involvement. Management is typically straightforward and dependent on the degree of presentation. In our case, a 61-year-old female presented with angioedema requiring immediate intubation. Before admission to the intensive care unit, a screening ECG was obtained that revealed ST segment elevations which redirected our patient to the cardiac catherization lab. Our patient was ultimately diagnosed with a stress-induced cardiomyopathy after initially presenting with ACE-inhibitor induced angioedema.

KEYWORDS: angioedema, stress-induced cardiomyopathy, epinephrine, STEMI, Takotsubo cardiomyopathy

CASE REPORT

A 61-year-old woman presented to our urban academic emergency department with facial edema, diffuse urticarial rash and dyspnea with wheeze that began acutely ten minutes prior while driving to work. She denied chest pain. There was no clear precipitant. Her medical history included non-insulin dependent diabetes and hypertension for which she was prescribed lisinopril. She reported taking lisinopril for the past 2 years. She denied a history of angioedema or anaphylaxis, and had previously been well.

Initial vital signs revealed a pulse of 110 BPM, respiratory rate of 25, blood pressure 140/70 mm Hg, and a room air oxygen saturation of 98%. She was afebrile. On initial physical examination, the patient was in moderate distress with mild uvular, peri-orbital, facial, and lip edema, along with scattered wheezes. An urticarial rash was noted on her chest and upper back. Intramuscular epinephrine, along with intravenous methyl-prednisolone, diphehydramine, and famotidine, were administered.

Within minutes our patient reported increasing dyspnea. Her oropharyngeal edema worsened and she developed notable voice muffling. Given impending airway compromise, she was successfully orotracheally intubated with a video laryngoscope using etomidate and succinylcholine to facilitate rapid-sequence intubation.

A screening ECG was obtained after appropriate sedation (**Figure 1**). ST segment elevations, meeting STEMI criteria were noted in the anterior-lateral distribution. No prior ECGs were available for comparison. Given clear ST elevations on ECG, lack of ability to obtain further history and recent epinephrine administration, interventional cardiology was consulted.

Our patient was transferred to the cardiac catheterization lab for suspected STEMI secondary to epinephrine. Kounis syndrome, known as allergic acute coronary syndrome, was also considered and has been reported in similar clinical scenarios.[4] On catheterization her cardiac vessels were unremarkable. There was no evidence of vasospasm or coronary vessel dissection. Despite normal vessels, the ejection fraction was globally reduced, and estimated at 30% with apical ballooning (**Figures 2, 3).** She was admitted to the medical intensive care unit with a diagnosis of Takotsubo cardiomyopathy.

During the subsequent 24 hours her angioedema resolved, and the patient was extubated on hospital day two. Complement pathways were within normal range, suggesting that hereditary angioedema was not the cause of her symptoms. Angioedema was concluded to be ACE-inhibitor mediated, and lisinopril was discontinued. She was initiated on an alternative anti-hypertensive, and successfully discharged

Figure 1. Initial ECG with ST segment elevation in leads V2-6. ST elevation also present in I & aVL.

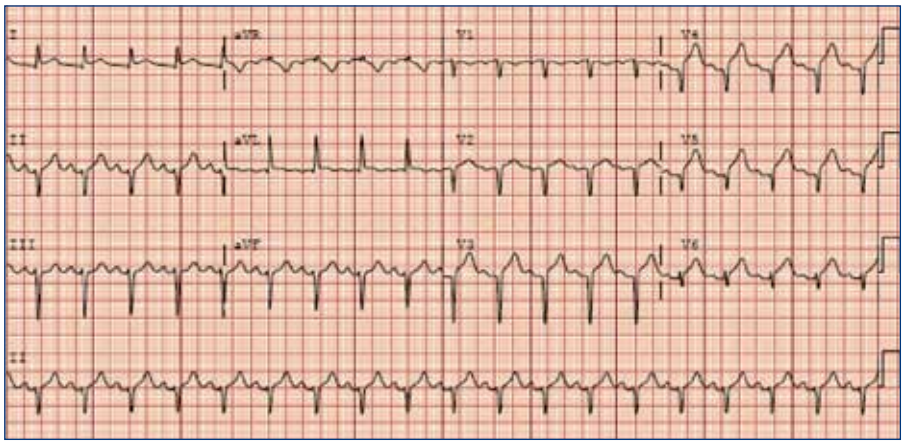

Figure 2. Catheterization revealing normal coronary vessels.

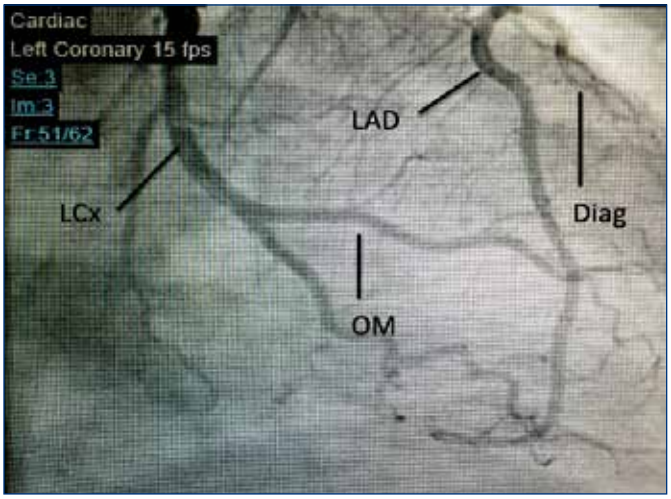

Figure 3. Apical ballooning on cardiac echocardiography.

home. A follow- up echocardiogram was normal a few months after her hospitalization, at which time the patient was well.

DISCUSSION

In patients who present acutely to the emergency department with angioedema, the cause is often uncertain. Our patient met criteria for anaphylaxis, and thus warranted epinephrine [**Table 1**].[1,12] Epinephrine is the cornerstone of treatment for anaphylaxis, although its use in patients with ACE-I angioedema has limited evidence.[1,6] However, it is generally considered safe when given at standard doses and route.[2,3,5] Adverse cardiovascular effects can occur following epinephrine administration, ranging from inconsequential transient tachycardia to myocardial infarction. Stress-induced cardiomyopathy is also a potential iatrogenic complication of epinephrine administration. A recent systematic review found 41 cases of epinephrine-triggered stress-induced cardiomyopathy.[7] A recent case report describes the development of Takotsubo cardiomyopathy in an acute angioedema presentation of a patient who also received epinephrine.[8] Our patient had normal coronary arteries on cardiac catheterization (**Figure 2**) and displayed characteristic apical ballooning and left ventricular dysfunction on echocardiography found in stress-induced cardiomyopathy (**Figure 3**). She returned to baseline physiologic function several weeks after her admission, a finding frequently noted in Takotsubo cardiomyopathy.[9]

Table 1. NIAID/FAAN clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Sudden onset of an illness (minutes to several hours) with skin, mucosal, or both involved and at least one of the following: a. Dyspnea, bronchospasm, stridor, decrease in PEF, and hypoxia b. Drop in blood pressure or symptoms of end-organ dysfunction (eg, decreased tone, syncope, loss of bladder/bowel control)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Skin or mucosal tissue involvement (eg, widely distributed urticarial, pruritus, flush, swelling of the lips-tongue-uvula) b. Dyspnea, bronchospasm, stridor, decrease in PEF, and hypoxia c. Drop in blood pressure or symptoms of end-organ dysfunction (eg, decreased tone, syncope, loss of bladder/bowel control) d. Gastrointestinal symptoms (abdominal pain, emesis)
3. Drop in blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low age-specific systolic blood pressure or more than a 30% decrement in systolic blood pressure b. Adults: systolic blood pressure lower than 90 mm Hg or more than a 30% decrement from that person's baseline

FAAN, Food Allergy and Anaphylaxis Network; NIAID

We are presenting this case of Takotsubo cardiomyopathy in the setting of acute angioedema and epinephrine administration. A similar case has been reported.[10] Although the exact mechanism of this disease pathology remains unclear, exogenous epinephrine is a theoretical culprit. Alternatively, it is possible that the cardiomyopathy was induced by endogenous catecholamine response incited by her angioedema. Despite lack of clarity regarding the pathogenesis of Takotsubo cardiomyopathy, this case provides additional evidence that a stress-induced cardiomyopathy is a possible adverse consequence of epinephrine use.

Angioedema is not an uncommon presentation in the emergency department, and accounts for 80,000 to 112,000 Emergency Department visits per year.[11] While initially thought to be straightforward, our case followed an atypical and unusual course. This case illustrates the nuanced complexity of the practice of medicine, especially within the bounds of the emergency department, and illustrates a rare adverse reaction to epinephrine. It is important for physicians treating angioedema in an emergency setting to recognize that administration of epinephrine can lead to significant cardiac complications.

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Cerebral and *Plasmodium ovale* Malaria in Rhode Island

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ABSTRACT

We report two cases of malaria diagnosed in Rhode Island. First, a 21-year-old female who presented with 5 days of fevers, chills, headache, and myalgias after returning from a trip to Liberia, found to have uncomplicated malaria due to *P. ovale* which was treated successfully with atovaquone/proguanil and primaquine. Second, a chronically ill 55-year-old male presented with 3 days of headache followed by altered mental status, fever, and new-onset seizures after a recent visit to Sierra Leone, found to have *P. falciparum* malaria requiring ICU admission and IV artesunate treatment. The diagnosis and management of malaria in the United States (US), as well as its rare association with subdural hemorrhage are subsequently reviewed.

KEYWORDS: malaria, cerebral malaria, artesunate, plasmodium

INTRODUCTION

Malaria remains a significant international health concern with over 200 million cases and 400,000 deaths annually.[1] Malaria is the result of infection by intracellular parasites of the *Plasmodium* genus transmitted by the female *Anopheles* mosquitos during blood meals. Due to the life cycle of the *Anopheles* mosquito, the disease is endemic in many tropical and subtropical climates. Over half the world's population is at risk of transmission, particularly those in sub-Saharan Africa (>90%) and Southeast Asia (~5%), where the majority of cases originate.[2] Despite its prevalence abroad, malaria has become a relatively uncommon diagnosis in the United States, with around 1,700 cases reported annually.[2] Malaria was once endemic in the Tennessee River valley and southeastern states, with 200–350 cases per 100,000 between 1920–1935. The disease was successfully addressed by the efforts of the National Malaria Eradication Program and by 1949 malaria was no longer considered a significant public health concern in the US.[2] Consequently, modern US clinicians may have less experience diagnosing and treating malaria, potentially resulting in a missed or delayed diagnosis with significant associated morbidity and mortality. While the CDC currently reports a stable incidence of malaria in the US, climate change is predicted to affect disease dynamics, and it remains unclear how the US incidence will be affected by climate change in the future.[2,3]

Given the potentially fatal consequences of a missed diagnosis of malaria and the relative inexperience of US clinicians with the disease, we review two cases of malaria recently diagnosed in Rhode Island that are representative of the spectrum of the disease one could expect to encounter in the US. The first is a classic, uncomplicated presentation of malaria in a 21-year-old female and the second is an example of severe malaria in a chronically ill 55-year-old male.

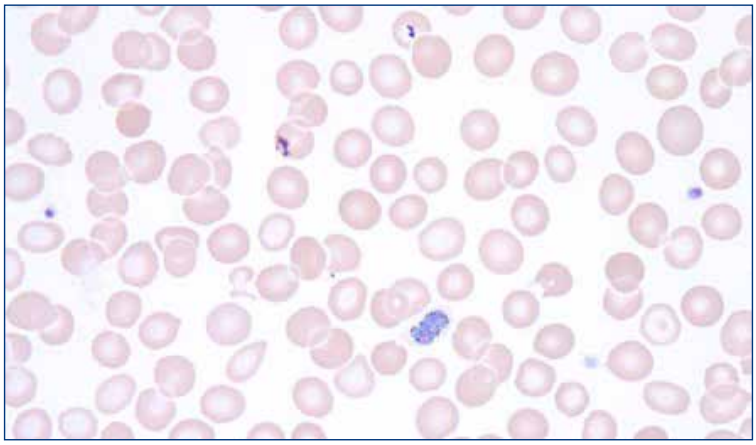
CASE 1

A 21-year-old female with a history of iron-deficiency anemia presented with 5 days of daily fevers, chills, headache, and myalgias after returning from a trip to Liberia during which she took no medications for malaria prophylaxis. She denied any other associated symptoms, sick contacts, or known exposures.

The patient's vital signs were notable for temperature 105°F, pulse 99 beats per minute, blood pressure 95/66 mmHg, respirations 18 breaths per min, SpO2 98% on room air. The physical exam was notable for an ill appearance but was otherwise normal.

Initial work-up was pertinent for hemoglobin of 8.7 g/dL, white blood cell count of 3.4 x 10^9/L, platelets 77 x 10^9/L,

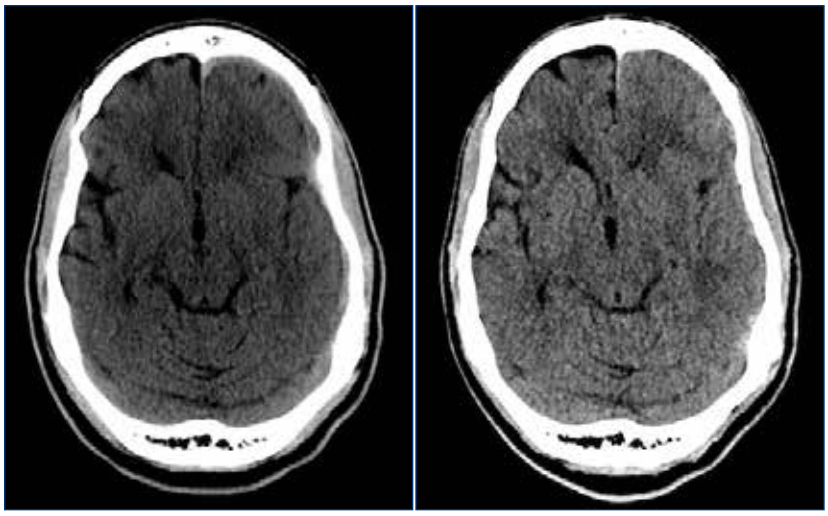
Figure 1. Peripheral blood smear from case 1 demonstrating *P Ovale*.



sodium 132 mEq/L, potassium 3.4 mEq/L, and normal urine studies. Blood parasite smear was notable for *Plasmodium* species, non-falciparum and a parasite burden of 0.07% infected erythrocytes. On further review, the hematopathologist suspected *P. ovale* due to the presence of enlarged, elongated red blood cells with polar fimbria. Molecular testing by the CDC later confirmed *P. ovale* as the culprit species (**Figure 1**).

Empiric treatment of non-falciparum *Plasmodium* infection was initiated in the emergency department with atovaquone/proguanil. After three days of inpatient therapy with atovaquone/proguanil, the patient was discharged and successfully completed a 14-day outpatient course of primaquine to cover any potential *P. ovale* hypnozoites.

Figure 2. Non-contrast head CT of patient in case 2 during initial hospitalization (left) and re-presentation with altered mental status (right).



CASE 2

A 55-year-old male with an extensive past medical history (Hodgkin lymphoma status post remote treatment; coronary artery disease status post bypass; heart failure with reduced ejection fraction and biventricular ICD placement; mechanical aortic valve replacement on warfarin; hypertension; hyperlipidemia; and diabetes mellitus) presented to the emergency department with 3 days of severe headache followed by altered mental status and fever. Nine days prior to this presentation, he had been hospitalized for an atraumatic subdural hemorrhage.

During his initial hospitalization, the patient reported 5 days of intermittent headache with photophobia as well as a transient episode of right-sided extremity weakness and heaviness. There were no infectious symptoms at that time, nor any history of trauma. However, he did endorse a recent trip to Sierra Leone (2 weeks prior) at which time he may have inadvertently taken an excess of enoxaparin (was bridging from warfarin) and was not on any form of malaria chemoprophylaxis. His workup revealed a new thrombocytopenia and an acute left-sided subdural hemorrhage. During the hospitalization, his neurologic exam remained stable, and he underwent cerebral angiography which revealed no evidence of causative vascular malformation. His coagulation status was optimized, and he was discharged home on warfarin.

The patient initially did well after discharge, but then developed three days of a severe headache with nausea and vomiting. His wife noted progressive somnolence and confusion, which prompted the return visit to the emergency department. There was no new travel, trauma, or exposures in the interim.

His vital signs were notable for a fever of 101.3 °F, pulse 107/min, blood pressure 158/83 mmHg, respirations 16 breaths per minute, and SpO_2 95% on room air. He was ill appearing, spoke nonsensical words, and was unable to follow simple commands. There was no nuchal rigidity. He could spontaneously move all extremities, albeit with constant agitation, while tossing and turning in the stretcher.

Further evaluation revealed platelets 108 x 10^9/L, INR 4.0, sodium 124 mEq/L, glucose 321 mg/dL, and a stable subdural hematoma on repeat CT (**Figure 2**). Peripheral blood smear demonstrated *P. falciparum* with a parasite burden of 2.48% infected erythrocytes. Parasites were not detected during his initial hospitalization. Due to recent subdural hematoma and elevated INR, lumbar puncture was deferred.

The patient was empirically treated with vancomycin, cefepime, and ampicillin for suspected meningitis. Atovaquone/proguanil was added following identification of *P. falciparum* on blood smear. Given the severity of his presentation and associated comorbidities, the patient was admitted to the ICU where, in conjunction with the CDC, his antimalarial therapy was escalated to IV artesunate for presumed cerebral malaria. Empiric treatment for meningitis was discontinued due to low clinical suspicion and an alternate etiology.

Although the patient demonstrated clinical improvement and resolution of parasitemia after completion of artesunate and atovaquone/proguanil therapy, he had a protracted hospital course complicated by seizures. After an extensive evaluation, the seizures were attributed to both the subdural hematoma and the cerebral malaria infection. Ultimately, the patient was discharged home on multiple antiepileptic medications. On outpatient follow-up he was doing well without further seizure activity and a return to his normal mental status.

DISCUSSION

While uncommon, malaria remains a diagnosis that should remain within the minds of US clinicians. The above cases illustrate the spectrum of disease in malaria: from classic, uncomplicated disease to a more severe presentation with cerebral involvement. Moreover, the latter case may represent a rare case of malaria presenting with subdural hematoma. Given its nonspecific and sometimes subtle presentation, malaria should be considered in any patient presenting with otherwise-unexplained infectious or flu-like symptoms and a history of recent travel to an endemic region.

If there is clinical concern for malaria, work-up should include a thorough travel history (destination, duration of stay, type of travel, activities performed, and prophylactics used), complete blood count, a comprehensive metabolic panel, and a broad infectious work-up as clinically indicated. Most importantly, a peripheral blood smear for parasites should be performed, as this remains the gold standard for diagnosis of malaria.[2,4]

Treatment and disposition are dependent upon the clinical status of the patient, the infecting Plasmodium species, the region of infection acquisition, and any previous antimalarial use. Due to evolving resistance patterns, it is appropriate to reference the most recent CDC guidelines or consult with local infectious disease experts prior to treatment. In all cases, admission should be considered to monitor for response to therapy and potential decompensation. [2,4,5]

Severe disease is most commonly caused by *P. falciparum* and is broadly characterized by evidence of organ dysfunction, high degree of parasitemia (greater than 5%), and inability to tolerate enteral therapy. Specific complications include severe anemia, hemolysis, hypotension, renal failure, and, in the case of cerebral malaria, alterations in mental status, seizure, and coma.[5,6] The treatment of choice for severe disease, regardless of pathogen, is intravenous artesunate. In the US, this medication can only be obtained through the CDC. As the disease can rapidly progress, interim therapy with artemether/lumefantrine or atovaquone/proguanil should be started while awaiting the arrival of artesunate.[2,5]

Special consideration should be given to cases of uncomplicated malaria caused by *P falciparum.* Patients who are non-immune (i.e. do not live in endemic regions) are at very high risk of rapid progression to severe disease and should always be admitted to the hospital for monitoring. Patients with *P knowlesi* infection should also be admitted as co-infection with *P falciparum* is highly possible.[4] In both cases, repeat blood smears for parasite burden should be performed every 12-24 hours until clinical improvement is seen.[2,4] Lastly, patients diagnosed with *P vivax* and *P ovale* malaria will require treatment with either primaquine or tafenoquine to eradicate hypnozoites and prevent relapse once the acute phase of infection has been managed.[2]

The latter case is of particular interest due to the subdural hemorrhage which may represent a rare complication of malaria. Although this patient had increased risk of subdural hemorrhage due to his coagulation status, he denied a history of trauma and had normal cerebral angiography. While the association between malaria and subdural hemorrhage is poorly understood, multiple cases have been reported in patients without any other clear cause for hemorrhage.[7-12] Past cases have been documented in association with *P. falciparum* and more rarely *P. vivax*.[12] It is hypothesized that infected, misshapen erythrocytes cause microvascular injury in small cerebral vessels which subsequently leads to hemorrhage that is further perpetuated by thrombocytopenia and coagulopathy.[9-11] Tumor necrosis factor-α (TNF-α) may also play a role in compromising endothelial integrity.[13] While, there is no way to confirm that this was the cause for the patient presented above, it is plausible given his risk factors and otherwise normal cerebral imaging.

CONCLUSION

Although malaria remains endemic in many equatorial countries, it has become an uncommon diagnosis in the US. With its sometimes-nonspecific presenting signs/symptoms and its potential morbidity, malaria requires US clinicians to maintain a high index of suspicion in patients who present with infectious symptoms after recent travel to endemic areas. Peripheral blood smear followed by molecular studies can confirm the diagnosis. In severe cases, intravenous artesuntate is treatment of choice.

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Outpatient Opioid Use After Cesarean Delivery

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ABSTRACT

OBJECTIVES: With a goal of informing opioid prescribing after cesarean delivery, we compared inpatient, prescribed, and outpatient Morphine Equivalent Doses (MED) and patient characteristics.

METHODS: Patients were enrolled after cesarean delivery and followed for 2–5 weeks with demographic, opioid use, and clinical characteristics collected from participants and the medical record. T-test, ANOVA, linear regression, and Pearson correlation coefficients were used in analyses.

RESULTS: Among 76 women, 21% used all opioids prescribed and 20% used none. History of psychiatric comorbidities was associated with higher outpatient opiate use (172 MED vs 103 MED; $p = 0.046$). There was no difference in opiates consumed inpatient and amount prescribed at discharge ($p = 0.502$). However, low, medium, and high inpatient consumers used 53 (SD 76), 111 (SD 96), and 195 (SD 132) MEDs outpatient, respectively ($p < 0.001$).

CONCLUSIONS: Outpatient opioid prescribing based on inpatient needs may facilitate judicious opioid use after cesarean delivery.

SIGNIFICANCE

What Is Already Known: Opioid abuse is a growing problem in this country, and excess prescribing contributes to the availability of opioids. Limited data exist regarding the amount of opioids patients need after cesarean delivery, or what factors are predictive of an individual patient's opioid needs.

What This Study Adds: This study further supports the growing literature demonstrating that providers frequently over-prescribe opioids following cesarean delivery. It uniquely adds associations of patient-specific factors and outpatient opioid needs.

KEYWORDS: Cesarean delivery, opioid pain medication, outpatient pain control, postoperative pain management, pregnancy

OBJECTIVES

Opioid misuse is a public health crisis, which is at least partially attributed to a ten-fold increase in opioid prescriptions over the past decade.[1] Because of this, judicious prescribing of opioid medications has received increased political, research, and media attention.[2] Opioid medications are a mainstay for the treatment of pain after major surgery, and cesarean delivery is the most common major surgery performed in the United States.[3, 4] Most women are prescribed opioids for outpatient pain control after cesarean delivery and recent studies have shown that most patients consume only a fraction of the opioid medication prescribed.[5,6,7] Opioid over-prescribing contributes to the national opioid epidemic; unused pills become available for misuse and diversion.

Despite the fact that women experience different levels of pain and require different amounts of opioids in the hospital prior to discharge, there has been limited variability in the amount of opioids prescribed at hospital discharge; Badreldin et al. (2018) found that among women who had cesarean delivery, 71.9% were prescribed identical quantities of opioids. "One-size-fits-all" approaches likely result in some women receiving too much (and thus having left-over pills) and other women too little (and may result in poor pain control).[7] To reduce the excess of prescription opioids, multiple professional organizations have recommended personalizing prescriptions to the individual patient's anticipated pain management needs.[3] However, in order to tailor prescriptions to individual patients, physicians and policy-makers need data describing the factors associated with the amount of opioids individual patients consume. We performed a prospective cohort study of women who had a cesarean delivery to generate pilot data both on opioid use after hospital discharge and patient factors associated with the amount of opioids women consumed. Our study objectives were to determine how much opioid medication patients consumed after hospital discharge post-cesarean delivery, and to assess which patient factors were related to outpatient opioid consumption. We hypothesized that greater opioid use in the final 24 hours of hospitalization following cesarean delivery would be associated with higher opioid consumption after hospital discharge.

METHODS

We conducted a prospective observational cohort study of women who had a cesarean delivery at our institution between January 1, 2016 and May 31, 2016. Women were eligible to participate in the study if they delivered a live infant at 24 weeks' gestation or greater, were age 18 years or older at the time of delivery, could speak and read English, and could provide informed consent. Women were ineligible to participate if prenatal records were not available or they planned to move out of the geographic area within the follow-up timeframe. We excluded women who were hospitalized for greater than 8 days following delivery. Women were also excluded from follow-up analyses if they were currently using opioids for medication assisted treatment (MAT) for opioid use disorder, because this population has unique needs related to outpatient pain control and opioid use and it was anticipated this population would be too small for subgroup analyses. Potentially eligible women were recruited by the study team during their post-partum hospitalization and within 4 days of delivery. As this was a pilot study to generate data on opioid prescribing, opioid consumption, and factors associated with amounts prescribed and consumed, we selected a targeted enrollment of n=100. The Women & Infants Hospital Institutional Review Board approved the study protocol (IRB number 14-0097).

Enrolled participants completed a questionnaire about medical and prenatal history and demographic characteristics. Participants were given a pill count diary to record their pain medication use for two weeks following hospital discharge. Two weeks after hospital discharge, patients were contacted by telephone and asked to refer to their pill count diary to determine the number of opiate pills they consumed since leaving the hospital, the use of non-opiate pain medications, and average pain scores since hospital discharge. If a participant did not maintain the diary, she was asked to count the number of opiate-containing tablets remaining in her pill bottle. Pain scores were obtained using patient report of their average pain score on the Numeric Pain Rating Scale (0–10) since hospital discharge. Phone call attempts were continued up to 5 weeks following hospital discharge, at which point participants were considered lost to follow-up if contact was not made. At the time patients were contacted, they were asked to report on their opiate use and pain levels only for the first 2 weeks after hospital discharge. For participants who reported no opiate usage following hospital discharge, we reviewed the electronic medical record external pharmacy linkage data to verify that no prescription had been filled. This allowed us to determine the number of unused dispensed opioid tablets for these participants (zero if a prescription was not filled, full number prescribed if prescription was filled and patient reported that none was used).

Maternal health and demographic information were abstracted from the medical record. Data collected included the total cumulative dose of opiate medications dispensed to the participant and standardized Numeric Pain Rating Scale scores (it is institutional protocol for nursing staff to collect and document at regular intervals) in the final 24 hours of hospitalization, as well as the type and quantity of opiates prescribed to the participant upon hospital discharge. During the study period, no attempt was made to alter providers' individual inpatient and outpatient opiate prescribing practices. Additionally, participant medical data such as method of delivery, antenatal complications, use of tobacco, alcohol and drugs, breastfeeding plans and several other factors were collected (**Table 1**).

We used descriptive statistics to evaluate the number of opiate tablets prescribed to and consumed by the study population. The main dependent variable was patient-reported opiate use in the two weeks following hospital discharge. Opiate use (inpatient and outpatient) was converted to Morphine Equivalent Doses (MED), which standardizes opioid pills of varying strengths (**Table 2**). T-tests, chi-square, and Fisher's exact tests were used to compare the baseline demographic characteristics between those patients who completed follow up and those who did not. Linear regression, t-test and ANOVA tests were used to describe inpatient and outpatient opiate use by subject characteristics. Lastly, we used ANOVA and Pearson correlation analyses to examine if there was an association between the amounts of opiate pain medication consumed inpatient and the amount consumed after hospital discharge. Tertiles of inpatient MED use (low <40 MED, medium 41–70 MED, and high >70 MED) were utilized to explore potential non-linear associations and for a more clinically useful comparison of average outpatient MED use among groups of patients with similar inpatient MED use.

RESULTS

Between January and May of 2016, 252 postpartum women were identified as potentially eligible and screened for enrollment in the study. One hundred forty-one women were approached by study personnel and offered enrollment, and 101 patients agreed to participate. Of the 101 women initially enrolled, one was excluded due to prolonged postpartum hospitalization (20 days). Seventy-six completed the telephone survey. Of those 76 women, one was excluded from data analysis due to ongoing MAT for opioid use disorder.

The mean age of study participants was 30.3 years [standard deviation (SD) 5.5], with a mean parity of 1.0 [SD 1.1] (**Table 1**). All but two patients included in the study had a low transverse hysterectomy; the remaining two had classical uterine incisions. Most study participants (63%) identified as Caucasian, with 79% self-identifying as non-Hispanic. There was a nearly equal division of study participants with public (49%) versus private (47%) health insurance.

Table 1. Baseline characteristics of study sample, overall and by completion of post-discharge telephone follow-up. Mean [SD] for continuous variables (with p-value for t-test comparing follow-up and no follow-up) and N (%) for categorical variables (with p-value for chi-square or Fisher's exact test comparing follow-up and no follow-up).

Variable	All Enrolled Participants (n=100) n (%)[a]	No Follow-up (n=24) n (%)[a]	Completed Telephone Follow-up (n=76) n (%)[a]	P-value for difference
Maternal age	30.3 ± 5.5	30.4 ± 5.7	30.3 ± 5.4	0.939
Parity (mean)	1.0 ± 1.1	1.1 ± 1.2	0.9 ± 1.1	0.458
Race (n = 99)				0.122[b]
Caucasian	62 (62.6)	17 (70.8)	45 (60.0)	
Black	5 (5.1)	0 (0.0)	5 (6.7)	
Asian	1 (1.0)	0 (0.0)	1 (1.3)	
Other	20 (20.2)	2 (8.3)	18 (24.0)	
Unknown	11 (11.1)	5 (20.8)	6 (8.0)	
Ethnicity (n = 99)				0.223[b]
Hispanic	19 (19.2)	2 (8.3)	17 (22.7)	
Not Hispanic	78 (78.8)	22 (91.7)	56 (74.7)	
Unknown	2 (2.0)	0 (0.0)	2 (2.7)	
Education				0.247
High school or less	28 (28.0)	9 (37.5)	19 (25.0)	
Some post HS training	33 (33.0)	9 (37.5)	24 (31.5)	
Bachelor's degree or higher	39 (39.0)	6 (25.0)	33 (43.4)	
Insurance (n = 99)				0.180[b]
Public	49 (49.5)	10 (41.7)	39 (52.0)	
Private	47 (47.5)	12 (50.0)	35 (46.7)	
Unknown	3 (3.0)	2 (8.3)	1 (1.3)	
History of drug use/abuse	5 (5.0)	2 (8.3)	3 (4.0)	0.591[b]
History of buprenorphine or methadone use	3 (3.0)	2 (8.3)	1 (1.3)	0.142[b]
Smoker	11 (11.0)	2 (8.3)	9 (11.8)	1.000[b]
Psychiatric comorbidity[c]	36 (36.0)	10 (41.7)	26 (34.2)	0.507
Repeat cesarean	49 (49.0)	14 (58.3)	35 (46.1)	0.294
Cesarean status				0.781[b]
Planned	59 (59.0)	16 (66.7)	43 (56.6)	
Unplanned, but pre-labor	5 (5.0)	1 (4.2)	4 (5.3)	
Unplanned, after labor	36 (36.0)	7 (29.2)	29 (38.2)	
Surgical complications[d]	16 (16.0)	4 (16.7)	12 (15.8)	1.000[b]
Chorioamnionitis	13 (13.0)	2 (8.3)	11 (14.5)	0.728[b]
Breastfeeding in hospital				0.435
No	20 (20.0)	7 (29.2)	14 (18.4)	
Yes	75 (75.0)	16 (66.7)	58 (76.3)	
Unknown	5 (5.0)	1 (4.2)	4 (5.3)	
Day postpartum discharged home				0.243[b]
2	4 (4.0)	1 (4.2)	3 (4.0)	
3	37 (37.0)	12 (50.0)	25 (32.9)	
4	59 (59.0)	11 (45.8)	48 (63.2)	

[a] Not all values total to n=100, n=24 or n=76 due to missing data on the variable of interest

[b] Fisher's exact test used

[c] Includes self-reported history of any one of the following: anxiety, depression, bipolar disorder, schizophrenia, eating disorder, or other psychiatric disorder

[d] Surgical complications include hemorrhage, cystoscopy, rupture of endometrioma, lysis of adhesions, or bowel injury. There were no cases of bladder or ureteral injury or intraoperative surgical consult.

Table 2. Morphine Equivalent Dosing Table

Medication	MED conversion factor	Total MED
Morphine 10 mg	1.0	10 MED
Oxycodone 10 mg	1.5	15 MED
Hydrocodone 10 mg	1.0	10 MED
Hydromorphone 10 mg	4.0	40 MED
Oxymorphone 10 mg	3.0	30 MED
Codeine 10 mg	0.15	1.5 MED

Table 3. Postoperative pain and management during inpatient stay, at discharge, and at follow-up survey post-discharge (n=100)

Characteristic	Value ± SD, range
Inpatient	
MED, final 24 hours of hospitalization, range	59 ± 43, 0-380
Average pain score inpatient, range	3.5 ± 1.0, 1.7-6.0
At discharge	
MED prescribed at discharge, range	258 ± 57, 0-450
Types of opiate pills prescribed at discharge, N(%) of participants	
Acetaminophen/oxycodone	88 (88.0)
Oxycodone	4 (4.0)
Acetaminophen/hydrocodone	3 (3.0)
Acetaminophen with codeine	2 (2.0)
Acetaminophen/oxycodone and acetaminophen/hydrocodone	2 (2.0)
None	1 (1.0)
At follow-up survey post-discharge (2-5 weeks)	
MED, outpatient in 2 weeks post-discharge, range (N=75)[a]	126 ± 123, 0.0-525
Average pain score, overall in 2 weeks post discharge, range (N=75)[a]	3.4 ± 1.8, 0.0-9.0

[a] N=75 who completed 2 week phone call (n=76) and were not discharged on maintenance opioids for addiction treatment (n=1)

Table 4. Morphine equivalent dose usage in final 24 hours inpatient hospitalization (n=100) and as an outpatient (n=75), by subject characteristics.

Subject Characteristic	Inpatient MED[a]			Outpatient MED		
	n[b]	Mean ± SD	P-value[c]	n[b]	Mean ± SD	P-value[c]
Overall	100	59 ± 43	—	75	126 ± 123	—
Maternal age	100	β=-0.41	0.611	75	β=-0.34	0.898
Psychiatric comorbidities			0.024			0.046
Yes	36	75 ± 58		25	172 ± 152	
No	64	50 ± 30		50	103 ± 100	
Cesarean Type			0.345			0.355
Primary	51	55 ± 26		41	113 ± 103	
Repeat	49	63 ± 56		34	141 ± 43	
Cesarean status			0.878			0.468
Planned	59	60 ± 51		42	116 ± 133	
Unplanned, pre-labor	5	63 ± 25		4	195 ± 141	
Unplanned, after labor	36	56 ± 29		29	130 ± 104	
History of buprenorphine or methadone			0.250			—
Yes	3	202 ± 159		—	—	
No	97	55 ± 27		—	—	
Smoker			0.316			0.156
Yes	11	88 ± 101		8	221 ± 188	
No	89	56 ± 29		67	114 ± 109	
Breastfeeding in hospital			0.279			0.214
No	20	72 ± 77		12	182 ± 151	
Yes	75	55 ± 28		59	117 ± 118	
Unknown	5	66 ± 19		4	94 ± 69	
Race (n = 99)			0.618			0.033
Caucasian	62	63 ± 49		44	99 ± 100	
Black	5	60 ± 28		5	222 ± 96	
Asian	1	75 --		1	323 --	
Other	20	46 ± 34		18	135 ± 154	
Unknown	11	60 ± 31		6	203 ± 122	
Ethnicity (n = 99)			0.658			0.465
Hispanic	19	53 ± 32		17	138 ± 132	
Non-Hispanic	78	61 ± 46		55	121 ± 121	
Unknown	2	78 ± 18		2	225 ± 106	
Insurance status (n = 99)			0.212			0.058
Public	49	67 ± 55		38	154 ± 135	
Private	47	52 ± 27		35	95 ± 101	
Unknown	3	48 ± 24		1	270 —	

[a] Inpatient MED use reported as cumulative MED use in final 24 hours of hospitalization.
[b] Not all values total to n=100, n=99 or n=75 due to missing data on the variable of interest
[c] P-value for linear regression for maternal age; p-value for t-test or ANOVA for all other variables.

Forty-nine percent of participants had undergone a repeat (as opposed to primary) cesarean delivery. A history of smoking was documented in the medical record for 11% of women, drug use was reported for 5% of women, and 3% had documentation of ever using methadone or buprenorphine. Any history of a psychiatric comorbidity, defined as anxiety, depression, bipolar disorder, post-traumatic stress disorder, schizophrenia, eating disorder or "other psychiatric comorbidity," were self-reported in 36% of the study population. Seventy-five percent of women were documented by nursing or medical staff as breastfeeding while in the hospital. Four percent were discharged on postpartum day 2, 37% on postpartum day 3 and 59% on postpartum day 4. We compared the sample of participants who completed follow up (n=76) and those who did not (n=24) and found no differences in these characteristics between the two groups (**Table 1**).

In the final 24 hours of hospitalization, participants consumed an average of 59 MED [SD 43], with a range from

Table 5. MED amounts prescribed at discharge and used as an outpatient, by inpatient MED use tertiles.

Inpatient MED Use	Total MED prescribed at discharge (n=100)			Total MED used outpatient post-discharge (n=75)						
Tertile	n (%)	MED Mean ± SD	ANOVA p-value	n (%)	25th percentile	50th percentile	75th percentile	90th percentile	MED Mean ± SD	ANOVA p-value
<= 40 MED	34 (34.0)	255 ± 47	0.502	26 (34.7)	0	23	75	203	53 ± 76	<0.001
41–70 MED	25 (25.0)	251 ± 41		18 (24.0)	38	86	150	315	111 ± 96	
>70 MED	41 (41.0)	266 ± 71		31 (41.3)	53	225	300	323	195 ± 132	

0 to 380 MED (**Table 3**). For reference, 59 MED is equivalent to 40 mg of oxycodone or 60 mg of hydrocodone. For participants, the average inpatient pain score for the final 24 hours of hospitalization was 3.5 [SD 1.0]. At hospital discharge, an average of 258 MED [SD 57] were prescribed per patient, which is equivalent to approximately 170 mg of oxycodone. Most women were prescribed acetaminophen with oxycodone (n=88). For the 100 patients enrolled in the study, a total of 3,150 tabs of acetaminophen/oxycodone, 162 tabs of acetaminophen/hydrocodone and 139 tabs of oxycodone were prescribed.

For the 75 participants included in the analyses of outpatient opiate use, a mean of 126 MED [SD 123] was consumed in the first two weeks after discharge from the hospital, equivalent to 84 mg of oxycodone. Twenty percent of women used no opiate pain medications after hospital discharge, 39% used less than half of what they had been prescribed, 20% used more than half but not all of what they were prescribed and 21% used the entire prescription, with 5 of these participants receiving additional opiate pain medication prescriptions. In total, 47% of prescribed opiates were reported as consumed in the first 2 weeks after hospital discharge. After verifying which of the women who took no opiates had filled their opiate prescription, we calculated that for 75 women, a total of 1,538 tablets of dispensed opiates were not consumed.

At the time of telephone follow-up, two of the 75 study participants reported they were still taking prescription opiates; 34 of the participants reported taking over the counter pain medication only, and 39 of the participants reported no longer using any pain medication. Mean pain score per participant, reported by the participant as average overall pain since hospital discharge on a 0 to 10 scale, was 3.4 [SD 1.8].

Average inpatient and outpatient opiate use was compared across patient demographic and medical characteristics (**Table 4**). Participants with any self-reported psychiatric comorbidity consumed significantly more opiate medication in the final 24 hours inpatient than women without a reported psychiatric comorbidity (75 MED [SD 58] versus 50 MED [SD 30], p = 0.024). This relationship was also seen for outpatient opiate use post discharge (172 MED [SD 152] versus 103 MED [SD 100], p = 0.046. Women who weren't breastfeeding and women with public insurance had higher MED consumption as outpatients than their breastfeeding and private insurance counterparts, but these findings were not statistically significant (**Table 4**).

Mean MED use post-discharge did not differ based on ethnicity, primary versus repeat cesarean or cesarean status (planned, unplanned pre-labor, unplanned in labor). When inpatient MED in the final 24 hours of hospitalization was stratified into three tertiles, there was no difference between low, medium, and high opiate consumers inpatient in the quantity of opiates prescribed at discharge (p = 0.502; **Table 5).** However, the amount of opiates consumed as an inpatient was related to the amount consumed after discharge with low inpatient consumers using 53 MEDs (SD 76), medium consumers using 111 MEDs (SD 96), and high consumers using 195 MEDs (SD 132) post-discharge (p < 0.001, **Table 5**). Among women who used less than or equal to 40 MED in the last 24 hours inpatient, 50% used less than or equal to 23 MED (equivalent to 3 tabs of 5 mg oxycodone) in the 2 weeks following hospital discharge, and 90% used less than 203 MED (equivalent to 27 tabs of 5 mg oxycodone) (**Table 5**). Similarly, when opiate use was analyzed as a continuous variable, there was a positive association between the opiates consumed in the final 24 hours of hospitalization and opiate use after discharge (Pearson r = 0.492, p <0.001) (data not shown). A moderate correlation was also observed between the amount prescribed at discharge and outpatient use (Pearson r = 0.401, p < 0.001). No significant correlation was found between inpatient use and the amount prescribed at discharge (Pearson r = 0.021, p = 0.836).

CONCLUSIONS

Principal findings

In this single-institution study, we found that cesarean delivery patients were prescribed an average of 258 MED for outpatient use and that, at two weeks post-hospital discharge, fewer than half of the opiates prescribed had been consumed. Outpatient opiate consumption after cesarean delivery varied widely (0 to 525 MED) and was positively associated with inpatient opiate use in the 24 hours prior to discharge and self-reported history of any psychiatric comorbidity. The amount of opioids prescribed at discharge was not related to inpatient use, but outpatient opioid consumption was moderately related to the amount prescribed at discharge.

Strength of the study

Strengths of this study include the use of medical record data combined with patient-reported information before and

after hospital discharge. This enabled us to compare three different types of data: inpatient opioid use in the 24 hours before discharge, opioids prescribed at discharge, and opioids used after discharge. Furthermore, participants were provided detailed information about the data which would be requested by the research team at the 2-week follow-up, and were provided with a tool to enhance the accuracy of pill consumption reporting. As this was an observational study and not a clinical trial, there was no standardization of prescriptions and medication dosing provided. In fact, providers were informed that this study should not alter their usual prescribing practices. While prescriptions were often similar, there was enough variation to allow us to compare prescribed opioids with both inpatient use and outpatient use.

Limitations of the data

This study also has several limitations. First, the retrospective collection of patient pill counts could be affected by inaccurate recall and reporting. Participants were asked to report on their opiate use in only the 2 weeks after leaving the hospital, but some participants did not maintain a pill count diary to aid recall. We made every effort to obtain participant reported opiate use in only the first 2 weeks after hospital discharge. However, since attempts to contact participants were made up to 5 weeks following discharge, participants who relied on counting remaining pills at the time of the phone call (as opposed to their pill diary) may have led them to overestimate opiate use (and underestimate the proportion left over in the 2-week window of interest). Although a loss to follow-up of 24% of the sample was a limitation for this study, we found no difference in key characteristics between participants who did and did not complete follow-up, suggesting that selection bias was not a major issue. Additionally, this was a small pilot study that involved only 100 English-speaking patients at an urban academic medical center, and was likely underpowered to detect differences in several patient characteristics. Data from this study may not be generalizable to other patient populations or healthcare delivery settings. Additionally, although body mass index (BMI) may be a factor in pain medication usage, data on patient weight and height were not uniformly recorded in the antepartum or postpartum course, and the study team decided that pre-pregnancy BMI would not be a valid substitute. Thus, weight and BMI were not analyzed with respect to opiate consumption.

Interpretation

Multiple state and federal agencies such as the Washington Agency Medical Directors' Group and the CDC recommend clinicians "tailor" opioid prescriptions to the individual patient, but provide little specific guidance on how that can be accomplished.[3, 8] A better understanding of patient characteristics associated with amount of opioid consumption (and hypothetically, opioid need) after cesarean delivery can assist healthcare providers looking to tailor opioid prescribing for outpatient pain management needs.

Similar to other recently published studies, our study showed that patients prescribed opioids for outpatient pain control after surgery (in our case, cesarean delivery) consumed only a fraction of the pills prescribed, which at a population level translates to millions of opioid tables accessible and available for misuse and diversion. In a recently published multi-center study, Bateman et al. (2017) reported that women were prescribed a median of 40 opioid tablets (interquartile range 30-40), but consumed a median of 20 opioid tablets (interquartile range 8-30) after hospital discharge.[6] Bartels et al. (2016) reported that among 30 women who had a cesarean delivery, a mean of 268 MED were prescribed at discharge and 53% of these women took none or fewer than 5 pills total.[9] Badreldin et al. (2018) reported that women were prescribed a median of 300 MED (interquartile range 200-300) at discharge and 18.5% of women with an opioid prescription used no opioids on the final hospital day.[7] Together with our results, these data suggest that the amount of opioid medication prescribed after cesarean delivery exceeds many patients' pain control needs. However, the amount of opiates consumed after hospital discharge varied widely between individual patients, which suggest that the amount prescribed likely needs to be not only reduced on average, but also individualized.

Other studies have shown that individual patient factors, such as baseline pain impact scores (hysterectomy patients), behavioral and pain disorders (inpatient surgeries including hysterectomy), and mean amount of opioid pain medication used per hour during hospitalization (cesarean delivery patients) are associated with the amount of opioid pain medication consumed after hospital discharge.[10, 11, 12] Based on our findings, a patient's opioid use in the 24 hours prior to discharge is a factor that clinicians could consider when deciding how much opioid medication to prescribe at hospital discharge. A recent randomized controlled trial found that the intervention group who received a tailored discharge prescription based on inpatient opioid use used the same proportion of pills as the standard practice group, but in absolute numbers were prescribed fewer pills, used fewer pills, and had fewer pills left over.[12] Our studies and others have also shown that amount of opioid prescribed is associated with the amount consumed, further emphasizing the need to reduce opioid over-prescribing.[13] Other strategies have been suggested for reducing excess opioid prescriptions; one recent study showed that using a model of patient-physician shared decision making for outpatient opioid prescribing after cesarean delivery decreased the amount of opioids prescribed from 40 tablets (typical) to 20 (actual median) without increasing patient pain.[13] Other suggested strategies to decrease excess prescribing have included limiting the amount that can be prescribed to any one individual patient ("Pain Management"). Prabhu et al. (2017) combined

shared-decision making and setting prescribing limits in a quality improvement project and showed that decreasing the maximum number of opioid pills prescribed from 40 to 30 and then 30 to 25 over time led to a significant decrease in the number of pills prescribed with no change in refill rates.[13]

CONCLUSION

Our study highlights the association of patient-factors with the amount of opioid consumed after delivery and highlights opportunities to develop patient-focused strategies to reduce opioid prescribing while still adequately managing pain after cesarean delivery. Future research should address the development of models and mechanisms to inform clinical resources for personalized pain management and opioid prescribing after cesarean delivery. Research is also needed to determine the optimal prescriptions at discharge that minimize dispensed opioids without increasing pain, dissatisfaction, and hassle for patients. Given the prevalence of cesarean delivery, obstetricians and gynecologists can play a major role in fighting the opioid use epidemic as more judicious prescribers: providing sufficient medication for pain control while minimizing excess opiates which may be misused or diverted.

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Consolidation in the Electronic Health Record Market, 2009–2017

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ABSTRACT

BACKGROUND: To quantify changes to the electronic health record (EHR) market in Rhode Island and to assess the degree of EHR market consolidation between 2009 and 2017.

METHODS: The EHR market in Rhode Island is represented by three measures: the proportion of physicians who have adopted an EHR, the number of EHR vendors in use, and EHR market competitiveness, captured by the Herfindahl—Hirschman Index (HHI).

RESULTS: The EHR market became more consolidated overall between 2009 and 2017. Among outpatient physicians, the market has remained competitive, despite ongoing consolidation. In contrast, the EHR market among inpatient physicians crossed into the "highly concentrated" zone in 2015.

DISCUSSION: While consolidation in the EHR market may facilitate the exchange of data across health systems, potentially reducing duplicative testing and facilitating timely diagnosis, limiting competition may affect vendors' responsiveness to calls for improved usability and innovation.

KEYWORDS: electronic health records, competition, consolidation, health information technology

INTRODUCTION

Over the past decade, the federal government has incentivized hospitals and physician practices to adopt and meaningfully use electronic health records (EHRs). Policymakers anticipated that these incentives would stimulate investment in health information technology and transform the EHR marketplace through the creation of new vendors and increased competition.[1] According to economic theory, competition in the EHR vendor market would help to lower costs, improve quality, increase choice, and encourage innovation.[2,3] However, competition in the EHR vendor market may also limit interoperability and fragment patient care, as competing vendors may not readily exchange patient information.[4]

While there is evidence that the 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act successfully increased EHR adoption and prompted an initial surge of competition for vendors, less is known about the level of competition in the EHR vendor market today.[5,6,7] Health policy professionals have voiced concerns about the recent trend towards consolidation in other aspects of healthcare – hospitals, health insurers, and physicians' services – and the implications of this consolidation for patient care.[3,8] The objective of this research is to 1) quantify changes to the Rhode Island EHR vendor market between 2009 and 2017 and 2) assess the degree of EHR vendor competition and market consolidation over the same time period.

METHODS

The Rhode Island Department of Health (RIDOH) administers a health information technology survey to all licensed independent practitioners in the state. This survey is administered as part of a legislatively-mandated public reporting program, and the data are used to report clinician-level process measures relating to health information technology adoption and use. The survey was distributed electronically to physicians annually from 2009 to 2015, and biennially since 2015. This study uses data from survey years 2009 to 2015, as well as 2017. The survey response rate ranged from a high of 68.3% of physicians in 2014 (n=2,567) to a low of 42.7% of physicians in 2017 (n =1,792).

The survey population includes all licensed physicians in active practice in Rhode Island. Respondent age was obtained from RIDOH licensure files. Physician respondents provided their specialty, main practice setting (office/outpatient or hospital/inpatient), and practice size. In the survey, an EHR was defined as "an integrated electronic clinical information system that tracks patient health data and may include such functions as visit notes, prescriptions, lab orders, etc."

We used three measures to describe the EHR market for each year of the study period. For the first measure – the percentage of physicians using an EHR – physicians were asked if they used an EHR at their main practice. If their main practice did not have an EHR, they were asked to answer based on the practice with an EHR in which they spent the most time providing direct patient care. Respondents who reported using an EHR at their main or any secondary practice were considered to use an EHR.

For the second measure – the overall number of EHR vendors in use – each physician was asked to identify their EHR vendor from a single-select list with an open-ended "Other" option. If a physician wrote in two EHR vendors, we only included the first vendor listed. We counted the total number of vendors in use each year. EHR vendors were included independent of certification status. We used Crunchbase, a business information platform, to verify EHR vendor mergers and acquisitions throughout the study period.[9]

Finally, for the third measure, we calculated EHR vendor competition using the Herfindahl-Hirschman Index (HHI), a commonly accepted measure of market competitiveness.[10,11] The HHI is the sum of each vendor's squared market share. A higher HHI indicates a lower degree of competitiveness, and an increasing HHI over time suggests market consolidation. Economists consider a market with an HHI score less than 1500 to be "competitive," between 1500 and 2500 to be "moderately concentrated," and greater than 2500 to be "concentrated."[10,11] We excluded respondents from the HHI calculation if they did not use an EHR, did not know which EHR vendor their practice used, or did not specify a vendor. We stratified all three measures of the EHR market by physician practice setting.

RESULTS

Sample Description

Most physician respondents worked in an office or outpatient setting, at a practice with ten physicians or fewer, and had an MD degree (**Table 1**). The highest proportion of physician respondents listed internal medicine as their specialty, followed by pediatrics, psychiatry, family medicine, and surgery (including both general and subspecialty). For most survey years, about half of the respondents fell between the ages of 30 and 50. In 2017, the sample differed slightly from previous years, with a lower proportion of younger and outpatient physicians.

EHR market among all physicians

The proportion of physicians using EHRs increased between 2009 and 2017, with 91.1% of respondents indicating that they used an EHR in 2017, compared to 69.2% in 2009 (**Table 2**). Awareness of EHR vendors also increased throughout the study, as the proportion of EHR users who were able to identify their practice's EHR vendor by name increased from 58.3% in 2009 to 97.5% in 2017. In 2009, no one EHR vendor had more than 10% of the EHR market, whereas over a third (36.9%) of EHR users used an Epic Systems Corporation product in 2017. eClinicalWorks had the largest market share between 2009 and 2013 until Epic Systems Corporation surpassed it in 2014. Epic Systems Corporation's market share grew substantially between 2013 and 2017, from 0% of physician EHR users in 2013 to 36.9% in 2017. Together, Epic Systems Corporation and eClinicalWorks accounted for half of the EHR market in Rhode Island in 2017. Cerner Corporation had the third-largest market share in 2017 at 7.9% of EHR users. The number of EHR vendors in the market increased from 75 in 2011 to 104 in 2015 and then decreased to 82 by 2017. Based on the HHI calculations, the EHR market among all physician respondents was "competitive" between 2009 and 2015, before transitioning to a "moderately concentrated" market in 2017 (**Figure 1**).

EHR market among outpatient physicians

Among office/outpatient respondents, 59.8% reported using an EHR in 2009 compared to 88.3% in 2017 (**Table 2**). For most of the study period, eClinicalWorks was the dominant EHR vendor in the office/outpatient market, growing from a market share of 16.3% of outpatient EHR users in 2009 to 27.6% in 2014, before decreasing to 20.4% in 2017. Epic Systems Corporation surpassed eClinicalWorks as the most commonly used EHR vendor in 2017, with a 25.8% market share. Although the HHI increased between 2009 and 2017, the HHI never passed the "concentration" threshold and remained reflective of a highly competitive market (**Figure 1**).

EHR market among inpatient physicians

Similar to office/outpatient physicians, the proportion of hospital/inpatient respondents using an EHR grew over the study period, from 84.7% in 2009 to 96.9% in 2017 (**Table 2**). More than half of inpatient EHR users were unaware of their EHR vendor or did not specify their vendor in 2009. However, by 2017, only 1.8% of inpatient EHR users were unaware of their practice's vendor. Cerner Corporation had the highest market share among inpatient EHR users between 2009 and 2012; a homegrown EHR system (LifeLinks) overtook Cerner Corporation in 2013. By 2015, Epic Systems Corporation had the highest market share. In 2017, the majority of inpatient EHR users (58.1%) used Epic Systems Corporation, and together Epic Systems Corporation and Cerner Corporation accounted for more than 75% of the inpatient market. Between 2009 and 2012, the inpatient EHR market straddled the line between a "competitive" and a "moderately concentrated" market. After 2014, however, the market transitioned to "highly concentrated" (**Figure 1**). The market consolidation for inpatient EHRs coincided with the transition by a large health system from a homegrown EHR to Epic Systems Corporation in 2015.

DISCUSSION

We found EHR adoption increased substantially over the study period, among both inpatient and outpatient physicians, and we observed a "competitive" market at the start of the study period moving towards consolidation, especially among inpatient physicians.[4,5,6,7] Unlike previous studies on the EHR vendor market, we did not find an increase in the number of EHR vendors in the state's outpatient or inpatient

market between 2009 and 2012, immediately after the passage of the HITECH Act.[5,6,7] This difference is likely because prior studies considered only certified EHRs, while our study included all EHR vendors independent of certification status.

Before 2014, there were a small number of EHR vendors in Rhode Island that controlled a large share of either the inpatient market or the outpatient market, but no one vendor controlled more than 20% of the entire market. However, starting in 2014, Epic Systems Corporation became a leading vendor in both markets, accounting for more than a third of physician EHR users in Rhode Island by 2017. Consolidation among EHR vendors coincides with the growth of several large health systems in Rhode Island and

Table 1. Characteristics of physician respondents

Characteristics	2009 N=1,995 n (%)	2010 N=1,855 n (%)	2011 N=2,128 n (%)	2012 N=1,958 n (%)	2013 N=2,365 n (%)	2014 N=2,565 n (%)	2015 N=2,570 n (%)	2017 N=1,792 n (%)
Age, years								
30–50	–	974 (52.7%)	1,116 (52.6%)	982 (50.2%)	1,173 (49.7%)	1,174 (45.9%)	1,264 (49.4%)	756 (42.4%)
51–64	–	690 (37.3%)	794 (37.4%)	761 (38.9%)	910 (38.5%)	1,014 (39.7%)	948 (37.0%)	695 (39.0%)
65–90	–	185 (10.0%)	213 (10.0%)	212 (10.8%)	278 (11.8%)	372 (14.5%)	348 (13.6%)	330 (18.5%)
Practice setting								
Office/outpatient	1,245 (62.4%)	1,129 (60.9%)	1,308 (61.5%)	1,184 (60.5%)	1,389 (58.7%)	1,543 (60.2%)	1,659 (64.6%)	1,180 (65.8%)
Hospital/inpatient	750 (37.6%)	726 (39.1%)	820 (38.5%)	774 (39.5%)	976 (41.3%)	1,022 (39.8%)	913 (35.5%)	612 (34.2%)
Practice size								
<=10 clinicians	1,246 (62.9%)	1,096 (59.4%)	1,259 (59.5%)	1,113 (57.3%)	1,347 (57.3%)	1,484 (58.0%)	1,562 (61.2%)	–
10+ clinicians	736 (37.1%)	749 (40.6%)	858 (40.5%)	830 (42.7%)	1,005 (42.7%)	1,074 (42.0%)	990 (38.8%)	–
Specialty								
Emergency medicine	92 (4.6%)	102 (5.5%)	102 (4.8%)	108 (5.5%)	128 (5.4%)	141 (5.5%)	144 (5.6%)	82 (4.6%)
Family medicine	162 (8.2%)	169 (9.1%)	170 (8.0%)	147 (7.5%)	191 (8.1%)	204 (7.9%)	208 (8.1%)	141 (7.9%)
Internal medicine	296 (14.9%)	261 (14.0%)	322 (15.1%)	262 (13.4%)	332 (14.0%)	422 (16.5%)	352 (13.7%)	258 (14.4%)
OB/GYN	99 (5.0%)	83 (4.5%)	117 (5.5%)	101 (5.2%)	128 (5.4%)	119 (4.6%)	133 (5.2%)	97 (5.4%)
Pediatrics	177 (9.0%)	156 (8.4%)	219 (10.3%)	198 (10.1%)	236 (10.0%)	254 (9.9%)	228 (8.9%)	165 (9.2%)
Psychiatry	178 (8.9%)	161 (8.7%)	193 (9.1%)	190 (9.7%)	199 (8.4%)	230 (8.9%)	241 (8.0%)	174 (9.7%)
Surgery*	172 (8.7%)	163 (8.8%)	167 (7.8%)	152 (7.8%)	191 (8.1%)	199 (7.8%)	205 (8.0%)	162 (9.0%)
Other	810 (40.8%)	767 (41.2%)	838 (39.4%)	800 (40.8%)	960 (40.6%)	996 (38.8%)	1,059 (41.2%)	713 (39.8%)
Degree type								
MD	1,887 (94.6%)	1,770 (95.4%)	2,015 (94.7%)	1,852 (94.6%)	2,226 (94.1%)	2,405 (93.8%)	–	1,680 (93.8%)
DO	108 (5.4%)	85 (4.6%)	113 (5.3%)	106 (5.4%)	139 (5.9%)	160 (6.2%)	–	112 (6.3%)

Age was not obtained from licensure files in 2009, degree type was not collected in 2015, and the 2017 survey used different categories for practice size.
Missing data are not shown; fewer than 1% of observations were missing in any one demographic category.
*General surgery & subspecialty surgery

Table 2. Measures describing the electronic health record (EHR) market in Rhode Island, 2009–17

	2009 N=1,995	2010 N=1,855	2011 N=2,128	2012 N=1,958	2013 N=2,365	2014 N=2,565	2015 N=2,570	2017 N=1,792
All physicians								
% of physicians using an EHR	69.2%	74.8%	81.7%	86.8%	88.4%	87.3%	89.3%	91.1%
Number of EHR vendors	79	76	75	88	93	94	104	82
HHI	739	820	1143	1130	982	990	1384	1807
Office/Outpatient								
% of physicians using an EHR	59.8%	66.8%	74.0%	80.8%	83.3%	82.4%	85.5%	88.3%
Number of EHR vendors	73	67	70	78	82	86	93	74
HHI	789	999	1160	1219	1105	1219	1041	1299
Hospital/inpatient								
% of physicians using an EHR	84.7%	87.3%	94.0%	95.0%	95.7%	94.8%	96.3%	96.9%
Number of EHR vendors	25	30	24	28	29	28	35	24
HHI	1649	1452	1561	1440	1763	1592	2994	3965

HHI = Herfindahl-Hirschman Index (HHI), a commonly accepted measure of market competitiveness. A higher HHI indicates a lower degree of competitiveness in the market.

Figure 1. Change in the Herfindahl-Hirschman Index (HHI) for the Rhode Island electronic health record market, 2009-17

an increased proportion of physicians employed by those health systems. Industry researchers anticipate that consolidation in the EHR market will continue, as major players acquire more market share and as healthcare systems consolidate themselves and seek to implement a common vendor across their practice sites.[12] Health system consolidation does not always lead to EHR vendor integration, but when it does, it intensifies EHR market consolidation.[13] Consolidation in the EHR market has important tradeoffs. The advantages of a less competitive EHR vendor market are primarily related to interoperability and efficiency.[14] The presence of fewer competing vendors, or one large monopolizing vendor, can contribute to common data and interface standards, data sharing, and research and development across different healthcare systems.[15] Despite recent trends in hospital and practice consolidation, patients still see multiple clinicians and are likely to interact with more than one EHR vendor. Between 2014 and 2016, only 4.5% of Medicare Part A and Part B expenditures were associated with patients who had their medical records in a single vendor, as compared to 20% of expenditures associated with patients with records spread across eight or more vendors.[4] Greater consolidation in the EHR market may mean that patients will have their health information spread across fewer vendors, but limiting competition can have important disadvantages related to costs and stifled innovation.[14,15]

The early competition in the EHR market post-HITECH occurred alongside EHR vendor business-model innovation, including repositioning to attract smaller office practices and adapting the EHR for e-prescribing.[6] There is lack of consensus whether the trend towards market concentration will encourage or discourage innovation. On one hand, consolidation in the EHR market could lead to more innovation, as vendors compete on the value and usability of their products.[16] On the other hand, consolidation to the point of a near monopoly has been associated with lower levels of innovation.[14,16] The large market share of a small number of vendors and the costly barriers to EHR market entry make it very difficult for disruptive innovation to occur.[15,16]

There have been recent efforts to achieve interoperability and encourage innovation through regulation. The 21st Century Cures Act was passed in 2016 with the goal of improving interoperability, data usability, and patient access to their health information.[17,18] The Office of the National Coordinator for Health Information Technology added a new interoperability rule to the 21st Century Cures Act in March 2020.[19] This rule attempts to limits patient information blocking and puts pressure on EHR vendors and other medical providers to make data available through standard interfaces within their operating systems.[19] These interfaces would allow for third-party apps and vendors to access the data and make it available to patients. This rule has the potential to

increase interoperability without sacrificing competition. The interface could also allow use of EHR data to drive clinical innovation from third-party vendors.[15] Future studies should explore the relationship between interoperability, innovation, and market competition.

LIMITATIONS

There are various limitations to this study. First, all data are self-reported. Physicians, particularly in the early years of the study period, may not have known their practice's EHR vendor or may have provided an incorrect EHR vendor. The relatively high proportion of physicians who did not know their EHR vendors early on may skew the HHI estimate if they disproportionally used one vendor. Second, the 2017 survey had a lower response rate than previous survey years. We suspect this dip in response rate is related to the 2015 transition from an annual to a biennial survey administration. Third, the survey was not conducted prior to 2009, so we are unable to describe how the market differed before the passage of HITECH. Finally, this survey was distributed electronically. Electronic distribution may bias the sample toward physicians more comfortable with technology and result in an overestimation of EHR use.

CONCLUSION

We found significant EHR vendor consolidation over the past decade among Rhode Island physicians practicing in the inpatient setting, while the EHR market has remained relatively competitive for outpatient physicians. Between 2015 and 2017, one existing EHR vendor gained significant market share in both the outpatient and inpatient settings. While a gain in market share may facilitate the exchange of data across health systems, potentially reducing duplicative testing and facilitating timely diagnosis, limiting competition may affect innovation in the EHR market.

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Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	JANUARY 2020	12 MONTHS ENDING WITH JANUARY 2020	
	Number	Number	Rates
Live Births	894	11,056	10.4*
Deaths	915	10,509	9.9*
Infant Deaths	3	63	5.7#
Neonatal Deaths	3	50	4.5#
Marriages	230	6,503	6.1*
Divorces	278	2,919	2.8*

* Rates per 1,000 estimated population
# Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	JULY 2019	12 MONTHS ENDING WITH JULY 2019		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	193	2,482	234.3	3,269.5
Malignant Neoplasms	191	2,264	213.7	5,089.5
Cerebrovascular Disease	44	468	44.2	390.0
Injuries (Accident/Suicide/Homicide)	79	923	87.1	12,581.5
COPD	35	484	45.7	490.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,056,298 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	FEBRUARY 2020	12 MONTHS ENDING WITH FEBRUARY 2020	
	Number	Number	Rates
Live Births	891	11,126	10.5*
Deaths	899	10,574	10.0*
Infant Deaths	5	64	5.8#
Neonatal Deaths	4	51	4.6#
Marriages	329	6,626	6.3*
Divorces	208	2,866	2.7*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	AUGUST 2019	12 MONTHS ENDING WITH AUGUST 2019		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	197	2,498	235.8	3,294.5
Malignant Neoplasms	199	2,258	213.1	5,017.0
Cerebrovascular Disease	33	471	44.5	407.5
Injuries (Accident/Suicide/Homicide)	72	928	87.6	12,848.5
COPD	47	501	47.3	565.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,056,298 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

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Friday, June 19, 2020

RIMS NOTES: NEWS YOU CAN USE

Welcome to the current issue of *RIMS Notes*, an exclusive member benefit. At this time, we are focusing our efforts on delivering timely information on COVID-19. Please check our website for up-to-the-hour updates, and your inbox for breaking news.

Volume 6 - Number 13

This issue sponsored by HUB

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A Message from RIMS President

MEDICAL SOCIETY STATEMENT ON DEATH OF GEORGE FLOYD Attached is a statement of the Rhode Island Medical Society regarding recent events.

Advocacy

June is Pride Month. Click here for a brief reflection on the significance for organized medicine.

GENERAL ASSEMBLY: Both chambers returned to the State House this week to pass a supplemental budget for the current state fiscal year that ends on June 30, and bills specific to certain cities and towns. The State House remained closed to the public. Leadership is targeting the week of July 13 to re-convene to finish crafting a new state budget for FY 22 and to deal with some of the large amount of proposed legislation that was left up in the air when the Governor declared the COVID-19 public health emergency in mid-March.

Physician Wellness and Stress

Physician Support Line for physicians and other healthcare workers:

- **Care New England/Lifespan Support Hotline for ANY healthcare worker: 401-606-6000**
- **National Physician Support Line: 888-408-0141 (9:00 AM to 3:00 AM next day EST)**
  https://www.physiciansupportline.com/

The Physician Support Line was created in March to provide confidential peer-to-peer support for MD's/DO's working on the frontlines of COVID-19. The Line is staffed by over 700 volunteer psychiatrists from across the country seven days per week.

What's New from the AMA

US Health and Human Services to distribute $15 billion to eligible Medicaid and CHIP physicians and organizations. Webcasts on 6/23 and 6/25 for interested physicians. Registration is required.

Q: Why is there a new Provider Relief Fund Payment Portal?
A: Portal will initially be used for new submissions from Medicaid and Children's Health Insurance Program (CHIP) providers seeking payments under the Provider Relief Fund starting Wednesday, June 10, 2020. At this time, this portal will serve as the point of entry for providers who have received Medicaid and CHIP payments in 2017, 2018, 2019 or 2020 and who have not already received any payments from the $50 billion Provider Relief Fund General Distribution.

What's New

Kathleen Boyd, MSW, LICSW, Director of RIMS' Physician Health Program, has been elected to the Board of Directors of the Federation of State Physician Health Programs (FSPHP). The FSPHP is an independent, non-profit, professional organization that supports education and research and promotes best practices to enhance the effectiveness of its 40 state physician health program members. Ms. Boyd also serves on the Performance Enhancement and Effectiveness Review (PEER) Committee of the FSPHP.

The biweekly e-newsletter exclusively for RIMS members.

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Contact Dulce Cosme if you've missed an issue, dcosme@rimed.org.

Working for You: RIMS advocacy activities

June 1, Monday

Meeting of RIMS Harm Reduction Effort Group

Health Professional Loan Repayment Program, Board of Directors, Steve DeToy, Member

RIMS Council: Christine Brousseau, MD, MPH, President; James McDonald, MD, MPH, Chief Administrative Officer, RI Department of Health, guest (via teleconference)

June 2, Tuesday

RIMS Physician Health Committee: Herbert Rakatansky, MD, Chair (via teleconference)

June 3, Wednesday

New England Delegation to the American Medical Association, Board of Trustees candidate interviews – Peter A. Hollmann, MD, Chair; Alyn Adrain, MD, Delegate; Sarah Fessler, MD, Alternate Delegate (via teleconference)

June 5, Friday

RIMS NOTES preparation

Conference call American College of Cardiology regarding membership; RIMS staff

June 9, Tuesday

Governor's Overdose Prevention and Intervention Task Force, Harm Reduction Work Group (via teleconference)

June 10, Wednesday

Board of Medical Licensure and Discipline (BMLD), RI Department of Health

Governor's Overdose Prevention and Intervention Task Force: Sarah Fessler, MD

Conference call regarding Office of the Health Insurance Commissioner; draft legislation on telemedicine

Workers Compensation Advisory Committee

Conference call with James McDonald, MD, MPH, Chief Administrative Officer, Board of Medical Licensure and Discipline regarding Continuing Medical Education; RIMS staff

June 12, Friday

Meeting with Emergency Medicine Political Action Committee

June 15, Monday

Conference call, RIMS Continuing Medical Education Committee regarding Board of Medical Licensure and Discipline (BMLD) and proposed CME requirement: Patrick Sweeney, PhD, MD, MPH, Chair; RIMS staff

June 16, Tuesday

Health Insurance Advisory Committee (HIAC), Office of the Health Insurance Commissioner (OHIC)

June 17, Wednesday

Primary Care Physician Advisory Committee (PCPAC), Dept. of Health

Meeting with Neurology Society regarding residents' advocacy training

June 18, Thursday

Teleconference regarding potential legislation on Institutional Review Boards (IRBs): Catherine A. Cummings, MD, RIMS President-Elect, and staff

June 19, Friday

RIMS NOTES preparation

Press Conference with Secretary of State Gorbea regarding mail ballots: Sarah Fessler, MD, Past President

June 24, Wednesday

Blue Cross Blue Shield of Rhode Island (BCBSRI) provider relations teleconference

June 25, Thursday

American Association of Medical Society Executives, state CEOs meeting: Newell Warde, PhD

June 26, Friday

Call with RI Business Group on Health regarding potential telemedicine legislation

June 29, Monday

Teleconference with Neurology residents regarding advocacy

The Health Professional Loan Repayment Program, Board of Directors, Steve DeToy, Member

June 30, Tuesday

American Medical Association (AMA), Advocacy Resource Center (ARC) conference call regarding telemedicine legislation

July 1, Wednesday

American Medical Association (AMA) federal advocacy update (via conference)

July 7, Tuesday

RIMS Physician Health Committee: Herbert Rakatansky, MD, Chair (via teleconference)

RIMS hosted telemedicine advocacy call

July 8, Wednesday

Board of Medical Licensure and Discipline (BMLD), RI Dept. of Health

Governor's Overdose Prevention and Intervention Task Force, Harm Reduction Work Group; Sarah Fessler, MD (via teleconference)

Centers for Medicare and Medicaid Services (CMS) Provider Relief Fund webcast

July 9, Thursday

RI Foundation/Racial Equity Institute; The Groundwater Approach (via teleconference)

RIMS hosted telemedicine advocacy update (via conference call)

July 13, Monday

The Health Professional Loan Repayment Program, Board of Directors, Steve DeToy, member

RIMS Board of Directors meeting with BCBSRI CEO Kim Keck and BCBSRI CMO and EVP Matthew Collins, MD, MBA

July 14, Tuesday

Governor's Overdose Task Force; Harm Reduction Work Group (via teleconference)

July 15, Wednesday

Department of Health Primary Care Physician Advisory Committee (PCPAC); Elizabeth Lange, MD, RIMS Vice President

July 17, Friday

RIMS NOTES preparation

July 21, Tuesday

AMA Advocacy Resource Center; Steve DeToy, Executive Committee member (via conference call)

Mental Health Association of RI Town Hall; Racism, Equity and Mental Illness

July 24, Friday

Conference call regarding FDA tobacco harm reduction update

July 28, Tuesday

AMA conference call on diabetes and COVID-19

July 29, Wednesday

RIMS Foundation Physician Health Program Governance Committee, Jerry Fingerut, MD, Chair

July 31, Friday

RIMS NOTES preparation

RIMS CORPORATE AFFILIATES

The Rhode Island Medical Society continues to drive forward into the future with the implementation of various new programs. As such, RIMS is expanded its Affinity Program to allow for more of our colleagues in healthcare and related business to work with our membership. RIMS thanks these participants for their support of our membership.

Contact Marc Bialek for more information: 401-331-3207 or mbialek@rimed.org

www.nhpri.org

Neighborhood Health Plan of Rhode Island is a non-profit HMO founded in 1993 in partnership with Rhode Island's Community Health Centers. Serving over 185,000 members, Neighborhood has doubled in membership, revenue and staff since November 2013. In January 2014, Neighborhood extended its service, benefits and value through the HealthSource RI health insurance exchange, serving 49% the RI exchange market. Neighborhood has been rated by National Committee for Quality Assurance (NCQA) as one of the Top 10 Medicaid health plans in America, every year since ratings began twelve years ago.

www.ripcpc.com

RIPCPC is an independent practice association (IPA) of primary care physicians located throughout the state of Rhode Island. The IPA, originally formed in 1994, represent 150 physicians from Family Practice, Internal Medicine and Pediatrics. RIPCPC also has an affiliation with over 200 specialty-care member physicians. Our PCP's act as primary care providers for over 340,000 patients throughout the state of Rhode Island. The IPA was formed to provide a venue for the smaller independent practices to work together with the ultimate goal of improving quality of care for our patients.

RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program

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Jonas Salk, Medical Sleuth and Scientist

STANLEY M. ARONSON, MD

When their first son was born on October 28, 1914, the Salks named him Jonas, a curious and rarely used spelling for the name of the minor prophet Jonah. The family, who lived in the Bronx, was poor. Jonas' parents, both immigrants from czarist Russia, worked in the garment industry in New York City, and the choice of Jonas' college was therefore narrowed to City College of New York, a tuition-free municipal institution in upper Manhattan. His original intention had been to prepare himself for a career in the law but exposure to the mysteries of biology led him to think, rather, of medicine.

Salk applied for and was accepted to the School of Medicine at New York University in Manhattan. Of the many aspects of human disease that Salk encountered as a medical student, the physiological intricacies of the immune response to pathogens fascinated him the most. His absorption in immunology was so intense that he was granted a year off solely to pursue research work in the chemistry of vaccines.

Upon graduation from medical school, Salk completed the customary internship training at Mount Sinai Hospital in New York City. He then left the arena of clinical medicine to join the University of Michigan Medical School basic sciences faculty, to conduct research on influenza vaccines. The influenza virus had recently been isolated, and working with Dr. Thomas Francis, Salk undertook the immense task of devising an influenza vaccine for the United States Army. Their efforts were successful and by 1947 Salk accepted a research professorship at the University of Pittsburgh, heading their virus research laboratory to further study vaccine programs.

The Foundation for Infantile Paralysis, more commonly known as the March of Dimes, through its director Basil O'Connor, expressed interest in Salk's theory that a vaccine composed of killed virus particles might be as effective as a vaccine of modified, virulent virus particles. It had been believed that any laboratory manipulation of viruses would so alter its capacity to elicit an immune response as to make it ineffective as a vaccine. Salk believed otherwise, and by minimally altering the poliomyelitis virus through exposure to formaldehyde, he believed that the resulting vaccine, devised from the killed virus, would prove to be both immunologically effective and clinically safe.

Dr. Jonas Salk, 1955 [NATIONAL LIBRARY OF MEDICINE]

The Foundation then chose to underwrite Salk's research protocol and for the next five years he labored to perfect a safe vaccine. Both he and the Foundation were under immense public pressure to hasten the development of this vaccine. In 1952, for example, 57,628 Americans, mainly children, were newly afflicted with paralytic poliomyelitis, making it the worst year on record for this dread disease. That same year, using a trial form of the vaccine, Salk inoculated a small group of volunteers, including his three sons, his wife and himself.

The results were encouraging and a massive inoculation campaign was then undertaken in 1954 with 1.83 million children receiving the Salk vaccine. In the following year his results were published in the *Journal of the American Medical Association*, and on April 12, 1955, a number of monitoring committees jointly declared the injectable vaccine to be both safe and effective.

Salk then endeared himself to a vast public when he refused to patent the vaccine and thus did not profit from his discoveries. ❖

[**Editor's Note:** This article, written by the late Stanley M. Aronson, MD, founding dean of Brown's medical school and a former editor-in-chief of the *Rhode Island Medical Journal*, appeared in *Medical Odysseys*, a book published by the Rhode Island Medical Society, in 2011.]

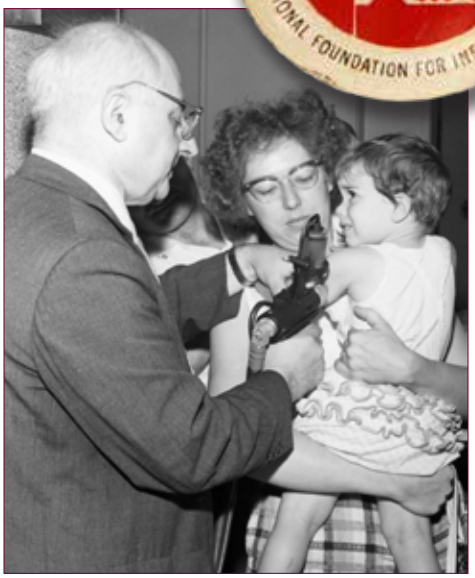
Polio Pioneers

In 1954, The March of Dimes organized testing of the Salk polio vaccine with 1.8 million schoolchildren who became known as "Polio Pioneers" and were part of the largest peacetime mobilization of volunteers in our history. In all, 1.3 children took part as vaccine recipients, placebo recipients, or observed controls. The vaccine was declared "safe, effective, and potent" against paralytic polio on April 12, 1955.

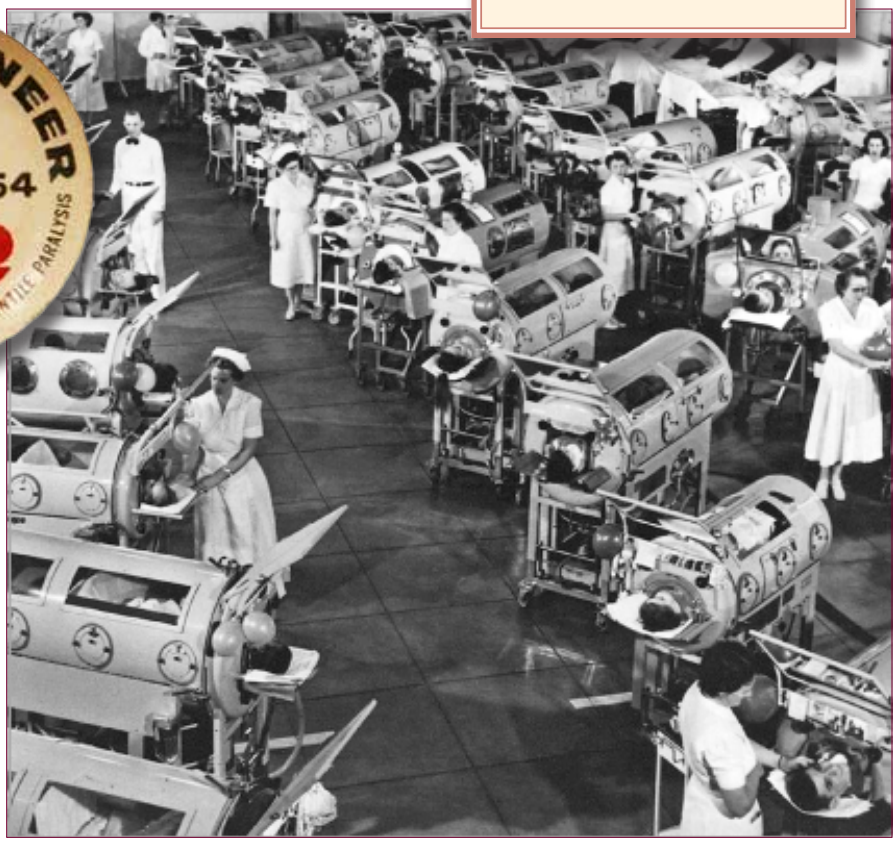
Peter Salk gets a polio shot from his father in the spring of 1953, as his mother looks on.
[MARCH OF DIMES, MARCHOFDIMES.ORG]

Children who participated in the 1954 U.S. trial of Jonas Salk's inactivated polio vaccine trial were dubbed "polio pioneers" and were given pins and cards to mark their status.
[PIN: THE HISTORICAL MEDICAL LIBRARY OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA]

> **"Hope lies in dreams, in imagination and in the courage of those who dare to make dreams into reality."**
> *— Jonas Salk, MD*



Child in Providence receives the vaccine at a polio clinic in 1962.
[RHODE ISLAND DIGITAL ARCHIVES, SECRETARY OF STATE'S OFFICE, DEPT. OF HEALTH PHOTOGRAPHS]



During devastating polio epidemics, the March of Dimes paid for and transported thousands of iron lungs in 1946.

Q & A with Jonathan Salk, MD

MARY KORR
RIMJ MANAGING EDITOR

JONATHAN SALK, MD, a psychiatrist and co-author with his late father, **JONAS SALK, MD**, of the 1981 book, "A New Reality," revised in 2018 and reviewed in this issue, answered queries from RIMJ editors on a range of topics – from his earliest memories of being vaccinated by his father, to the worldwide excitement that ensued with the formal announcement of the success of the polio vaccine, and finally to the present COVID-19 "new reality" the world is struggling with.

Figure 1. Jonathan Salk receiving polio vaccine from his father, Dr. Jonas Salk, in a photograph taken by a March of Dimes photographer. His mother, Donna Salk, is at left.
[PHOTO COURTESY OF JONATHAN SALK]

RIMJ: What are your memories of you and your brothers getting vaccinated by your father during the polio vaccine clinical trials in 1953–1954?

DR. SALK: I was around 3, so my memories are predominantly of my Dad giving us the shot or drawing our blood while we sat on the kitchen table. There was no sense of danger or risk of getting polio. He wasn't experimenting on us; he gave us the vaccine because he knew it worked, and he wanted us protected. There was, however, an element of fear and a kind of trauma in getting the shot from him. There is a photo of me getting one of my first injections that pretty much tells that whole story. (**Figure 1**)

RIMJ: What were the challenges and highlights of growing up the son of a famous father and then as a physician who was the son of a famed physician?

DR. SALK: There were many of both. One of the highlights was returning home to Pittsburgh from the University of Michigan where the vaccine's success was announced, and my father was vaulted, literally overnight, into worldwide fame. The results of the field trials were secret, even from my father, until the announcement on April 12, 1955. There was bedlam about it, with banner headlines, and church bells ringing. We had to stay an extra week there because of the crush of attention. We arrived home to a crowd of reporters and well-wishers, and to my delight as a 5-year-old, we had a police motorcycle escort home from the airport. We also went to the White House and met President Eisenhower. (**Figures 2 & 3**)

Other highlights were things I experienced in the beginnings of the Salk Institute in La Jolla, CA. I can recall, when I was around 11 or 12, Louis Kahn, the architect, and my father going over the plans and their visions for the building and the institution that they both saw as a place where scholars from both the sciences and the humanities could come together to address the basic problems of humankind. The building they worked on is considered to be one of the masterpieces of 20th-century architecture. And a few years later, there was a gathering of scientists at our home that included Francis Crick, who co-discovered the structure of DNA, and Leo Szilard, who conceived of the nuclear chain reaction. I didn't appreciate those things then, but as an adult, I see those moments as truly remarkable.

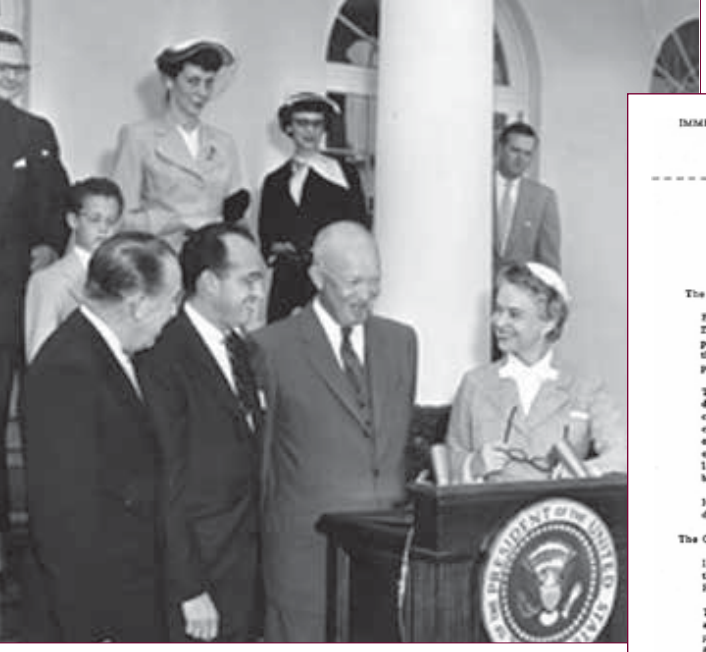
A persistent highlight was being around my father's extraordinary creativity – first with the vaccine, then with the Salk Institute and later, with his writings. He had the ability to have creative intuitions and actually make them come into reality.

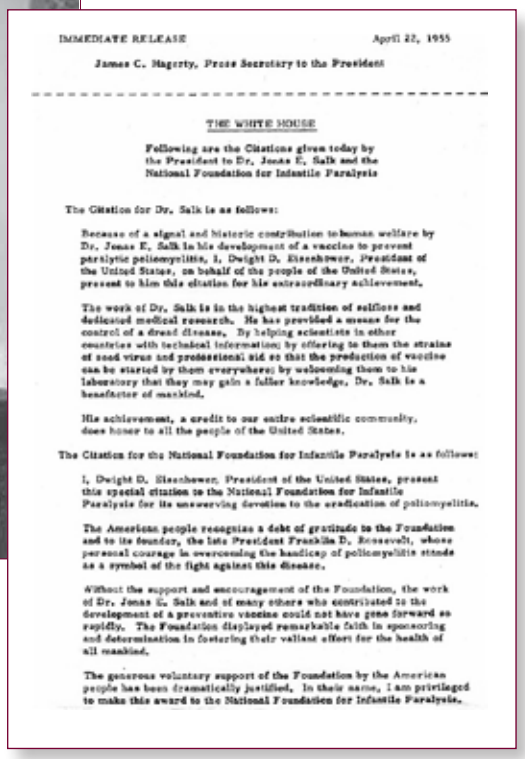
As for challenges, a big one was being frequently asked if I were related to him and dealing with people's responses. I was in my thirties before I made peace with that, understanding that it gave people a lot of joy to meet me.

As a physician in training it was mixed. On the one hand people joked with me about doing something great. But I found that patients felt remarkably confident and reassured being taken care of by a "Dr. Salk." As a practicing physician, I have, for the most part, felt secure in my identity as a psychiatrist and as a clinician.

RIMJ: What would be your father's approach to COVID-19 vaccine development in this time of global crisis?

DR. SALK: He would, of course, support a cooperative international effort to develop the vaccine. He would urge a balance between speed and caution, knowing the risks of putting out a vaccine that could potentially have harmful and adverse side effects. He would also point out that controlling and containing a viral epidemic is not only a scientific and technological





IMMEDIATE RELEASE April 22, 1955

James C. Hagerty, Press Secretary to the President

THE WHITE HOUSE

Following are the Citations given today by the President to Dr. Jonas E. Salk and the National Foundation for Infantile Paralysis

The Citation for Dr. Salk is as follows:

Because of a signal and historic contribution to human welfare by Dr. Jonas E. Salk in his development of a vaccine to prevent paralytic poliomyelitis, I, Dwight D. Eisenhower, President of the United States, on behalf of the people of the United States, present to him this citation for his extraordinary achievement.

The work of Dr. Salk is in the highest tradition of selfless and dedicated medical research. He has provided a means for the control of a dread disease. By helping scientists in other countries with technical information; by offering to them the strains of seed virus and professional aid so that the production of vaccine can be started by them everywhere; by welcoming them to his laboratory that they may gain a fuller knowledge, Dr. Salk is a benefactor of mankind.

His achievement, a credit to our entire scientific community, does honor to all the people of the United States.

The Citation for the National Foundation for Infantile Paralysis is as follows:

I, Dwight D. Eisenhower, President of the United States, present this special citation to the National Foundation for Infantile Paralysis for its unswerving devotion to the eradication of poliomyelitis.

The American people recognize a debt of gratitude to the Foundation and to its founder, the late President Franklin D. Roosevelt, whose personal courage in overcoming the handicap of poliomyelitis stands as a symbol of the fight against this disease.

Without the support and encouragement of the Foundation, the work of Dr. Jonas E. Salk and of many others who contributed to the development of a preventive vaccine could not have gone forward so rapidly. The Foundation displayed remarkable faith in sponsoring and determination in fostering their valiant effort for the health of all mankind.

The generous voluntary support of the Foundation by the American people has been dramatically justified. In their name, I am privileged to make this award to the National Foundation for Infantile Paralysis.

Figures 2 & 3. President **Dwight D. Eisenhower** presented citation to **Dr. Jonas Salk** recognizing his achievement in developing the first safe and effective polio vaccine on April 22, 1955, with the Salk family in background.
[THE EISENHOWER LIBRARY]

problem; it is also a social, economic and political one. He would insist that when developed, the vaccine would be available and distributed to everyone, worldwide, at an affordable cost.

RIMJ: What do you think about the vaccine deniers, and the anti-vaccination movement which challenges your father's landmark achievement and legacy?

DR. SALK: I don't think the movement really affects my father's legacy of humanitarian commitment combined with scientific achievement. That can't really be changed. I am very distressed that there is so much misinformation and vitriol and that the matter has become so polarized. Mostly, I am troubled by the threats to public health and the resulting unnecessary toll of illness and death. This would have pained my father deeply. He couldn't bear to see unnecessary human suffering in any form.

RIMJ: How do you think anti-vaccine parents should be approached?

DR. SALK: I think we have to start with an understanding and empathy for the parents' position and their concern for their children's well-being. Next we have to establish that neither they nor the physician is evil incarnate or ignorant. Once that is done, there can be room for discussion.

RIMJ: As a psychiatrist, can you speculate on the long-term behavioral sequelae of COVID-19 for the general population and for health professionals, as a result of the widespread, adverse individual/family, educational and societal disruptions?

DR. SALK: Among those most directly confronting suffering, loss, and death there will be PTSD and unresolved grief. Front-line medical personnel have already been severely affected, not only feeling overwhelmed and helpless in the face of the disease, but also confronting, in a new way for most, the danger and their own mortality. For those without financial and health security, this situation is devastating, creating chronic, severe stress in a large part of the population. The sequalae of children being sequestered for months at a time, and having reduced socialization, are unknown, and may well cause changes later in life. On the other hand, in some families, there has been enhanced family bonding, with potential positive effects.

Of interest to me will be the social, economic and political consequences as we adapt. While there is short-term uncertainty and chaos, in the long term I see some positives. We may learn that we can live with less demand for fossil fuels, accelerating a change to renewables. People are going to be working from home. There may be increased bonding with children and family members. We may adapt by forming novel forms of communities. Our economy may be forced to change to be based on human and planetary well-being instead of material growth and profit. This crisis is an opportunity to make significant individual and societal changes that will help us adapt to the approaching of planetary limits. This is one of the main messages of our book, "A New Reality."

RIMJ: What were the most profound insights your parents instilled in you and that you hope to pass on to the Millennials born in what the book, "A New Reality," terms Epoch B?

DR. SALK: What was instilled in me from the beginning was the importance and value of doing good for others and for the world as a whole. My mother was very active in civil rights, a social worker and a therapist herself, so I learned compassion and political activism from toddlerhood on. From my father, I learned that one can truly make a difference in people's lives and in society as a whole. For our family, that is a primary objective in life.

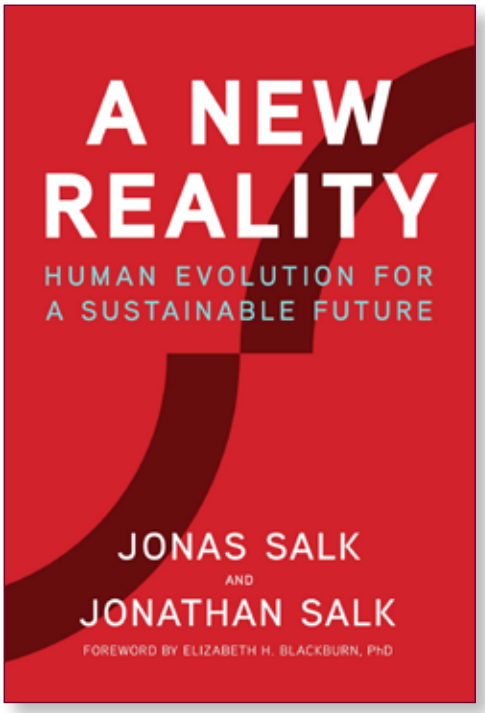
Epoch B represents a future in which we must adapt to limits and the resulting slowing of growth – a very different reality from what we have known for hundreds and thousands of years. In that new reality, the book maintains that those who are able to cooperate, who make decisions and plans for the long term and who are interdependent will be most successful and predominate. What I hope to pass on to coming generations is the possibility, despite the crises that plague us today, of a much better, more balanced and healthful world for all. ❖

Jonathan Salk, MD, updates "A New Reality," book he co-authored with his father, Jonas Salk

MARY KORR
RIMJ MANAGING EDITOR

In the mid- and latter stages of Dr. Jonas Salk's (1914–1995) career, he cultivated a scientific and creative approach of inquiry across the biological sciences, nature, as well as the arts and humanities, and explored and advanced these ideas in several books and at the Salk Institute for Biological Studies in La Jolla, CA., which opened in 1963.

According to the Institute's website (www.salk.edu): "In 1957, Jonas Salk, developer of the first safe and effective polio vaccine, began his quest to fulfill his second dream: create a collaborative environment where researchers could explore the basic principles of life and contemplate the wider implications of their discoveries for the future of humanity."



Website: anewrealitybook.com
A New Reality: Human Evolution for a Sustainable Future
By Jonas Salk and Jonathan Salk with David Dewane; foreword by Dr. Elizabeth Blackburn, 2018

He articulated his vision of a world he saw in transition, and at an inflection point, in "A New Reality: Human Evolution for a Sustainable Future," co-authored with his son, **JONATHAN SALK, MD**, which has been updated and re-released by the latter.

The beginning of the book states: "Jonas Salk's wish was that his ideas would continue to be disseminated so that, like a vaccine, they might have the most positive effect on the greatest number of people.…His wish was that these ideas would have the effect of giving people a scientific basis for hope and provide opportunities to enhance human wellbeing throughout the world."

The first edition in 1981 was a prescient call to action, examining the world through the lens of over-population. Today, the COVID-19 "new reality," as well as the effects of climate change, and political, social and economic upheavals, has exacerbated and reinforces the book's initial call for action to ensure the planet will evolve into a just, humane, cooperative, interdependent and sustainable world.

Salk & Salk present the population data in Sigmoid or S curves in Part One. Part Two examines World Population Trends; Part Three: A New Epoch; Part Four: Paradox and Conflict and Part Five: Resolution and Integration. The text is complemented by an elegant graphic design, compelling photographs, and illustrative figures that frame the narrative.

The book presents a world in transition, a naturally evolving process, from what is termed Epoch A (accelerated population growth) to Epoch B (decelerated growth and possible plateau). It describes a region of inflection where the two overlap. (**Figures 1 & 2**)

In a Zoom talk recently, Dr. Jonathan Salk elaborated on these concepts. "The Baby Boom generation was born in Epoch A. The sky was the limit," he said. "But then in the 1960s and '70s, we entered Epoch B. My children were born in Epoch B, with recycling, renewable energy, but also with the values of getting along with all types of people.

"…Change from A to B is not going to happen without conflict. We have polarity and division in the world today. Some people wish to adapt to climate change and others want to go back to fossil fuels. That is what is being played out on the national and world stage. In the short term things may look awful every morning when we get up, but if we take a look at the curve we see it as part of a natural and evolutionary process."

The book cautions it is up to us, individually and collectively, to fan these scientific and sustainable sparks for the

IMAGES COURTESY OF JONATHAN SALK, MD

Brief Bio: Jonathan Salk, MD

Stanford University, anthropology concentration

University of Southern California School of Medicine, MD, 1986

Post-graduate: Child, Adolescent, Adult Psychiatry, UCLA David Geffen School of Medicine

Current: In private practice, lectures, writes and teaches on the theory and practice of psychiatry

Assistant Clinical Professor of Psychiatry at the UCLA David Geffen School of Medicine.

Senior Fellow of the Design Futures Council

Member of the Advisory Board of the Population Media Center

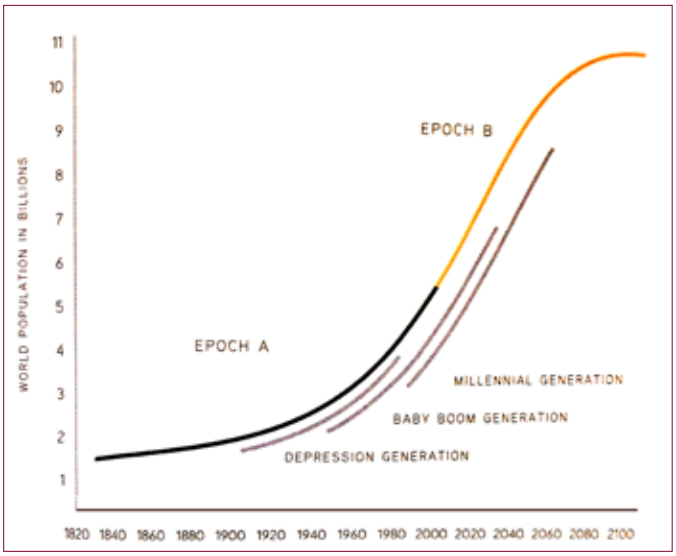


Figure 1 represents the time periods and generational labels of Epoch A and Epoch B, going from a period of accelerating population growth to a period of decelerating growth and possible plateau. The book describes the juncture of Epoch A and Epoch B as the point of inflection correlating to a shift in values and behaviors.

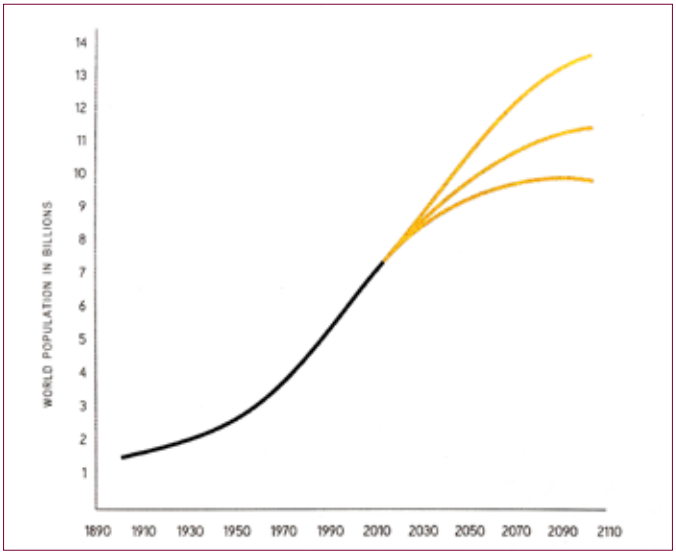


Figure 2. This curve shows the projected population growth from 2016–2100 as estimated by the Population Bureau of the UN; the lower estimate projects a plateau at a level of less than 10 billion people, whereas the higher one points to a 13.5 billion world population.

planet to survive in a world where its population, now 7.7 billion, could reach up to 13 billion or more by the end of this century. Actions taken now will have a great impact on what life will be like by 2100. Solutions and adaptations that are being undertaken are illustrated in the final chapter of the book. "The course of epochal change is not predetermined. It is subject to our influence," the authors conclude.

It takes a spark to ignite a fire to fan the flames of discovery, as Jonas Salk did notably in Epoch A, with the development of an effective polio vaccine. "A New Reality" is part of that intellectual legacy – not a blueprint but a palette, or a toolbox. In the new COVID-19 reality we are in, reading "A New Reality" resonates. ❖

Epilogue from "A New Reality"

"The future is simultaneously brighter and darker than it was when the first edition of this book was published. Gains have been made. At the same time, as in so many times in history, we are faced with dark forces of conflict, war, mass killing, and terrorism. Our strongest weapon against these is the promotion of health, hope and fulfillment for all human beings. As difficult and as daunting a task as that may seem, it is one that, if undertaken successfully, will result in a better world for all."

RI delegation announces $71.3M in CARES Act funds to five local hospitals

WASHINGTON, D.C. – U.S. Senators **JACK REED** and **SHELDON WHITEHOUSE**, along with Congressmen **JIM LANGEVIN** and **DAVID CICILLINE**, announced on July 22nd that $71.3 million in funding from the Coronavirus Aid, Relief, and Economic Security (CARES) Act has been distributed to five Rhode Island hospitals to offset the costs of caring for coronavirus patients. The funding was awarded by the U.S. Department of Health and Human Services (HHS).

According to HHS, the hospitals that received funding are:

- **Our Lady of Fatima Hospital, North Providence – $8,400,000**
- **Miriam Hospital, Providence – $24,000,000**
- **Rhode Island Hospital, Providence – $25,430,609**
- **Roger Williams Medical Center, Providence – $7,950,000**
- **Landmark Medical Center, Woonsocket – $5,550,000**

This round of funding was based on a formula for hospitals with over 161 COVID-19 admissions between January 1 and June 10, 2020, or that experienced a disproportionate intensity of COVID admissions, exceeding the average ratio of COVID admissions per bed.

"We set this funding aside in the CARES Act to help local hospitals and providers who are struggling with the fallout of this pandemic, but the Trump Administration's distribution has been slow and uneven. While I'm glad Rhode Island hospitals are finally receiving this additional infusion of CARES Act assistance, more needs to be done to help offset their COVID-19 related losses," said Senator Reed.

"Rhode Island hospitals have done excellent work under very challenging circumstances created by the pandemic, and I congratulate Lifespan in particular on receiving nearly $50 million in this distribution," said Senator Whitehouse, a member of the Senate Finance Committee. "This federal funding will help cover some of the costs hospitals already incurred caring for COVID patients, and help prepare our health care system for whatever may come in the months ahead. I'll keep working to assure all our hospitals get all the funding they deserve for their great work."

"For our state to recover from this unprecedented health crisis, Rhode Island hospitals need to continue receiving resources to provide quality care," said Congressman Langevin. "I'm encouraged by the way our healthcare system has weathered the pandemic, but serious risks remain, and we will continue to work to provide even more assistance as we negotiate a fifth COVID aid bill. These federal funds will help hospitals continue their invaluable work against COVID-19."

"This investment for Rhode Island hospitals will help, but it's clear that more will need to be done," Congressman Cicilline said. "Rhode Islanders have done an excellent job flattening the curve. We need to be prepared and help our hospitals be equipped for what comes next. I will continue fighting to ensure we get the resources we need." ❖

Thundermist Health Center receives $128K to expand telehealth capabilities

PROVIDENCE – U.S. Senators **JACK REED** and **SHELDON WHITEHOUSE** and Congressmen **JIM LANGEVIN** and **DAVID CICILLINE** recently announced that Thundermist Health Center has been awarded $128,347 from the Federal Communications Commission's (FCC) COVID-19 Telehealth Program to establish robust telehealth services during the ongoing pandemic.

Congress appropriated $200 million for the FCC's COVID-19 Telehealth Program under the Coronavirus Aid, Relief, and Economic Security (CARES) Act to help patients access health care from the safety of their homes during the COVID-19 pandemic.

The federal funding will allow Thundermist to adapt to the new reality of the COVID-19 pandemic by providing care through telephone or telemedicine intervention. The funds will support the purchase of a telehealth platform, telecommunications equipment upgrades, desktop and laptop computers, and videoconferencing equipment to implement telehealth solutions for medical, dental, and behavioral health care during the COVID-19 crisis.

By providing some services remotely, Thundermist can reduce the number of patients and staff members on-site and prevent patients with COVID-like symptoms from visiting a clinic in person. Continuing to provide high-quality health care for low-income, vulnerable populations in an outpatient setting is critical for reducing the burden on local hospitals during this crisis.

"Thundermist is grateful for the advocacy of Rhode Island's congressional delegation, and to the Federal Communications Commission for approving our award," said **JEANNE LACHANCE**, President/CEO of Thundermist Health Center. "This funding allows us to ensure seamless access to care for patients during the pandemic. Telehealth solutions are critical to keep both high-risk patients and providers safe while continuing to deliver the highest quality care for patients with chronic diseases such as diabetes, HIV, and opiate use disorder."

Thundermist provides community-based medical, dental, behavioral health, and social services for medically underserved and uninsured residents in Rhode Island. Thundermist served more than 48,000 patients at three clinical sites in Woonsocket, West Warwick, and South Kingstown in 2018. ❖

COVID-19 testing site opens at Convention Center

The Rhode Island Department of Health (RIDOH) opened a COVID-19 testing site on July 21st at the Rhode Island Convention Center with a capacity to do 1,500 tests a day.

Signage will direct people to the site in the parking garage. The site will operate Monday through Friday from 8 am to 5 pm, and Saturday through Sunday from 9 am to 3 pm. Tests are available by appointment only, for symptomatic people and certain asymptomatic people. People who are symptomatic can get a test scheduled for them by a healthcare provider. People who are asymptomatic can schedule a test if they work in a high-contact profession.

Examples of people who work in high-contact professions include barbers, child care workers, clergy, cosmetologists, first responders, gym and exercise trainers, healthcare professionals, personal care services (nail technicians, massage therapists, tattoo artists, estheticians, cosmeticians, manicurists, body piercers, and tanning facility staff), public transit drivers, and restaurant workers.

Asymptomatic Rhode Islanders who have recently traveled to a place with an elevated positivity rate can also be tested. ❖

Front-line physicians stressed and anxious at work and home

New study reports moderate to severe stress levels in ER doctors during the frenetic early phase of COVID-19 pandemic

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO – Amid the COVID-19 chaos in many hospitals, emergency medicine physicians in seven cities around the country experienced rising levels of anxiety and emotional exhaustion, regardless of the intensity of the local surge, according to a new analysis led by UC San Francisco.

In the first known study to assess stress levels of U.S. physicians during the coronavirus pandemic, doctors reported moderate to severe levels of anxiety at both work and home, including worry about exposing relatives and friends to the virus. Among the 426 emergency physicians surveyed, most reported changes in behavior toward family and friends, especially decreased signs of affection.

"Occupational exposure has changed the vast majority of physicians' behavior at both work and home," said lead author **ROBERT M. RODRIGUEZ, MD**, a professor of Emergency Medicine at UCSF. "At home, doctors are worried about exposing family members or roommates, possibly needing to self-quarantine, and the effects of excess social isolation because of their work on the front line."

The results, which appeared July 21, 2020, in *Academic Emergency Medicine*, found slight differences between men and women, with women reporting higher stress. Among male physicians, the median reported effect of the pandemic on both work and home stress levels was 5 on a scale of 1 to 7 (1=not at all, 4=somewhat, and 7=extremely). For women, the median was 6 in both areas. Both men and women also reported that levels of emotional exhaustion or burnout increased from a pre-pandemic median of 3 to a median of 4 after the pandemic started.

Lack of PPE was associated with the highest level of concern and was also the measure most often cited that would provide greatest relief. The doctors also voiced anxiety about inadequate rapid diagnostic testing, the risk of community spread by discharged patients, and the well-being of coworkers diagnosed with COVID-19.

But the survey also showed clear-cut ways of mitigating anxiety:

- Improve access to PPE;
- Increase availability of rapid turnaround testing;
- Clearly communicate COVID-19 protocol changes;
- Assure access to self-testing and personal leave for front-line providers.

The responses came from faculty (55 percent), fellows (4.5 percent), and residents (about 39 percent), with a median age of 35. Most physicians lived with a partner (72 percent), while some lived alone (nearly 15 percent) or with roommates (11 percent). Nearly 39 percent had a child under age 18.

The study involved healthcare providers at seven academic emergency departments and affiliated institutions in California, Louisiana and New Jersey. Researchers noted that the majority of study sites were in California, which at the time of the survey had not yet experienced the large surges of patients seen in other areas of the country. But the study found that median levels of anxiety in the California sites were similar to those in the New Orleans and Camden sites, which were experiencing surges at the time.

"This suggests that the impact of COVID-19 on anxiety levels is pervasive and that measures to mitigate stress should be enacted universally," Rodriguez said. "Some of our findings may be intuitive, but this research provides a critical early template for the design and implementation of interventions that will address the mental health needs of emergency physicians in the COVID-19 pandemic era."

The study is longitudinal, with this first phase focused on the early "acceleration" phase of the pandemic. Subsequent studies will address stressors that have arisen throughout the course of the pandemic, including childcare and homeschooling demands, the economic impact of fewer patients overall in the ER, and possible development of long-term post-traumatic stress.

Authors: From the University of California, co-authors are Anthony Medak, MD, of UC San Diego; Brian Chinnock, MD, of the UCSF-Fresno Medical Education Program; Remi Frazier, MS, of UCSF; and Richelle Cooper, MD, of UCLA.

RIDOH licenses state's first marijuana sampling and testing laboratory

As a part of the on-going process in Rhode Island to improve medical marijuana product safety and transparency, the Rhode Island Department of Health (RIDOH) has licensed Green Peaks Analytical as the State's first licensed marijuana sampling and testing laboratory.

To date, products sold at compassion centers in Rhode Island have been tested by cultivators or compassion centers with their own laboratory facilities, or by private, unlicensed laboratories. While some laboratories across the country are only licensed to test, Green Peaks Analytical will also collect samples directly from licensed cultivators and licensed compassion centers, to ensure that the sample's chain of custody is not broken.

"Like all other patients in Rhode Island, people who use medical marijuana deserve to have access to safe medication, and they deserve to have accurate information about that medication," said Director of Health **NICOLE ALEXANDER-SCOTT, MD, MPH**. "The increased oversight that RIDOH and DBR will be providing will help ensure that critical product safeguards are in place for medical marijuana patients."

Cannabinoids (e.g., tetrahydrocannabinol [THC], cannabidiol [CBD], tetrahydrocannabinolic acid [THCA], and cannabidiolic acid [CBDA]) are chemicals found within the cannabis plant. Cannabinoids affect users by binding to specific receptors in the central nervous system. Different cannabinoids produce different effects. For example, THC is associated with psychoactive effects while CBD is associated with anti-psychoactive or THC-moderating effects. This information helps users determine which products to use and how to use them safely.

Over a six-week period, the Rhode Island Department of Business Regulations' (DBR) Office of Cannabis Regulation will gather feedback from Green Peaks Analytical, cultivators, compassion centers, and the patient community about this process. With this information, DBR will establish a time frame by which all medical marijuana products will be required to have potency totals that have been verified by a licensed laboratory on their product labels.

RIDOH and DBR will work together with licensed laboratories, using a phased approach, to build capacity so that future certification can include testing for contaminants such as pesticides, metals, or solvents. ❖

FDA approves Tauvid for use in tau-PET imaging

Drug studied at Butler, RIH becomes first approved to use as imaging tool for early diagnosis of Alzheimer's

In May, The U.S. Food and Drug Administration (FDA) approved Tauvid (flortaucipir F18) for intravenous injection as the first drug used to help image a distinctive characteristic of Alzheimer's disease in the brain called tau pathology. The approval comes one month after publication of the results of the national A16 study, which showed that Positron Emission Tomography (PET) imaging used in combination with flortaucipir tracer was successful in confirming the presence of tau protein in the brain, helping to establish an Alzheimer's diagnosis in patients suspected of having the disease. Butler Hospital was one of 27 study sites across the U.S. to participate in the study, through a partnership between its Memory and Aging Program, which facilitated the study and Rhode Island Hospital, which conducted the imaging.

"We are so proud to have partnered with Rhode Island Hospital to be part of this major advance in the diagnosis and treatment of Alzheimer's disease and we're deeply appreciative of our courageous study participants who made this happen," said **DR. STEPHEN SALLOWAY**, Director of the Memory and Aging Program at Butler Hospital. Dr. Salloway was also one of the authors of the A16 study and a lead study clinician through all phases of the development of the flortaucipir tracer.

The A16 study was made possible by the selfless participation of terminally ill patients who agreed to donate their brains to science after death. Participants were all 50 years old or older with a diagnosed terminal illness and projected life expectancy of less than 6 months. All agreed to participate in PET imaging and to then donate their brain to science after their death for the purpose of postmortem examination. Changes in the brain found upon autopsy were compared to the results indicated by the scans.

Results showed that PET imaging with flortaucipir provides significant sensitivity and specificity for detecting tau protein in the brain. These results were confirmed by a second set of independent physician readers of the PET scans in a follow-up validation study. The study also showed that the use of flortaucipir was safe, with relatively few adverse effects among patients.

The study's authors concluded that in appropriate clinical cases of adults who have undergone adequate neurological assessment and have been evaluated for Alzheimer's disease or other causes of cognitive decline, PET imaging with flortaucipir may help in establishing a diagnosis of Alzheimer's, and that further research is required into the potential value of flortaucipir imaging in earlier stages of the disease.

Associate Director of the Alzheimer's Disease and Memory Disorders Center at Rhode Island Hospital, **DR. JONATHAN DRAKE**, said, "The announcement by the FDA regarding approval of tau-PET imaging for Alzheimer's disease in the clinic is a major advancement for the field. We know that tau protein buildup in the brain is one of the main drivers of Alzheimer's disease, which begins long before the first symptoms of memory loss occur. A longstanding goal of the field has been to develop techniques for detecting tau at its earliest stages and developing strategies for preventing disease progression, so this news is indeed very exciting." ❖

Aducanumab, an investigational drug for AZ, submitted to FDA for priority review

It was announced recently that aducanumab, an investigational drug for the treatment for Alzheimer's disease, has been submitted to the U.S. Food and Drug Administration (FDA) for approval with a request for Priority Review. Rhode Island contributed to the largest number of participants enrolled in the studies that led to the submission for approval, through study sites at the Memory and Aging Program at Butler Hospital and the Alzheimer's Disease and Memory Disorders Center at Rhode Island Hospital, both of which are affiliates of the Warren Alpert Medical School of Brown University.

If approved, aducanumab would become the first therapy to reduce the clinical decline of Alzheimer's disease and would also be the first therapy to demonstrate that removing amyloid beta from the brain resulted in better clinical outcomes.

The drug's makers, Biogen (Nasdaq: BIIB) and Eisai Co., Ltd. (Tokyo, Japan), completed the submission of the Biologics License Application (BLA) to the FDA. The submission includes clinical data from the Phase 3 EMERGE and ENGAGE studies, as well as the Phase 1b PRIME study. **STEPHEN SALLOWAY, MD, MS**, director of neurology and the Memory and Aging Program at Butler Hospital and the Martin M. Zucker professor of Psychiatry and Human Behavior and professor of neurology at the Warren Alpert Medical School of Brown University served as co-chair of the global investigator steering committee for the aducanumab Phase 3 studies.

"The submission of aducanumab for FDA approval represents a milestone in the fight against Alzheimer's disease and we are excited that so many Rhode Islanders contributed to making this happen," Dr. Salloway said. "For many people living with the early stages of Alzheimer's disease, maintaining independence for as long as possible is the ultimate goal. If we can help slow the progression from one stage to the next, this could preserve independence, which, in turn, could have truly meaningful benefits for people living with the disease and their loved ones. Aducanumab represents a potential breakthrough that we hope will provide a treatment foothold in the fight against Alzheimer's disease."

"Two clinical studies, ENGAGE and EMERGE, suggested that not only did aducanumab reduce amyloid plaques in patients with Alzheimer's disease but it also provided a meaningful reduction in worsening of clinical symptoms. The results of the EMERGE trial provide evidence that clinical trials in the disease can succeed, and that this breakthrough is a significant step toward conquering the disease over the long run. If approved by the FDA, aducanumab would be the long-awaited first therapy to slow the progression of Alzheimer's disease, and a significant achievement given that no new medication has been approved in the Alzheimer's disease field since 2003," said **DR. JONATHAN DRAKE**, associate director of the Alzheimer's disease and Memory Disorders Center at Rhode Island Hospital.

The aducanumab clinical development program included two Phase 3 trials, EMERGE and ENGAGE, in patients with early stage Alzheimer's disease (enrolled patients had mild cognitive impairment (MCI) due to Alzheimer's disease and mild Alzheimer's disease dementia with Mini-Mental State Examination (MMSE) scores of 24–30). In EMERGE, patients who received aducanumab experienced significant slowing of decline on measures of cognition and function such as memory, orientation and language. Patients also experienced slowing of decline on activities of daily living including conducting personal finances, performing household chores, such as cleaning, shopping and doing laundry, and independently traveling out of the home.

EMERGE (n=1,638) met its pre-specified primary endpoint, with patients treated with high dose aducanumab showing a statistically significant reduction of clinical decline from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores at 78 weeks (22% versus placebo, P=0.01). In EMERGE, patients treated with high dose aducanumab also showed a consistent reduction of clinical decline as measured by the pre-specified secondary endpoints: the Mini-Mental State Examination (MMSE; 18% versus placebo, P=0.05), the Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 Items (ADAS-Cog 13; 27% versus placebo, P=0.01) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version (ADCS-ADL-MCI; 40% versus placebo, P=0.001). Imaging of amyloid plaque deposition in EMERGE demonstrated that amyloid plaque burden was reduced with low and high dose aducanumab compared to placebo at 26 and 78 weeks (P<0.001). While ENGAGE (n=1,647) did not meet its primary endpoint, Biogen believes a subset of data from ENGAGE are supportive of the outcome in EMERGE.

The aducanumab clinical program also included the Phase 1b PRIME study and its long-term extension (LTE) in patients with early Alzheimer's disease (enrolled patients had prodromal Alzheimer's disease or mild Alzheimer's disease dementia with MMSE scores of 20–30). The results of this study indicated that aducanumab reduced amyloid beta plaque in a dose- and time-dependent fashion, and analyses of exploratory clinical endpoints showed a reduction of clinical decline (CDR-SB and MMSE, nominally statistically significant for the 10 mg/kg dose at 12 months), which continued out to 48 months in the LTE.

The completion of the BLA submission followed a planned pre-BLA meeting with the FDA. The FDA now has up to 60 days to decide whether to accept the application for review, at which point, if accepted, Biogen expects the FDA will also inform the Company whether the BLA has been granted Priority Review designation. The BLA will then be subject to review by the FDA to make a determination on the potential approval of aducanumab.

In addition to submitting the BLA to the FDA, Biogen has continued to engage in dialogue with regulatory authorities in other markets, including Europe and Japan, working diligently toward the goal of submitting applications in these markets. ❖

RIH to recruit individuals at known risk for developing Alzheimer's for new drug study

PROVIDENCE – Researchers at Rhode Island Hospital's Alzheimer's Disease and Memory Disorders Center are currently recruiting volunteer participants for the AHEAD 3-45 study, an innovative Phase III clinical trial of an anti-amyloid antibody, BAN2401, for individuals with normal memory function at risk for developing Alzheimer's disease. The purpose of the study is to investigate whether BAN2401, which works by selectively targeting abnormal build-up of amyloid-beta in the brain, can prevent the onset of Alzheimer's disease.

The AHEAD 3-45 study is, in fact, 2 trials for healthy individuals between the ages of 55 and 80 years, without current memory or thinking issues – the AHEAD-3 trial for those with intermediate levels of amyloid beta and the AHEAD-45 trial for individuals with higher levels of amyloid, as measured by a Positron Emission Technology (PET) brain scan. In this placebo-controlled study, either BAN 2401 or a placebo will be given intravenously 1–2 times a month, depending upon the level of brain amyloid measured by PET scan at the beginning of the study. Everyone participating must have a study partner who can come to some of the visits throughout the study, which lasts about 4 years.

"The AHEAD study will provide valuable information on a drug that shows real promise to be a key component of treatment to combat Alzheimer's disease," said Dr. Jonathan Drake, Associate Director of the Alzheimer's Disease and Memory Disorders Center and principal investigator for the AHEAD 3-45 study. "Many previous clinical trials of investigational agents that targeted reduction of brain amyloid have not succeeded; however, Biogen's recent decision to pursue FDA approval for aducanumab, another anti-amyloid antibody, has rekindled enthusiasm in this class of investigational drugs. As Biogen seeks regulatory approval for aducanumab, we feel a renewed hope that new treatments are within our reach. We invite individuals at known risk for Alzheimer's disease to consider participation in our research program. We value our Citizen Scientist® volunteers and the work they undertake with us as research partners. This research can't happen without them and their selfless desire to help find an end to this fatal disease." ❖

Clinical trial of treatment to prevent Alzheimer's symptoms begins at Butler Hospital

AHEAD 3-45, a new clinical study of a treatment aimed at preventing cognitive decline in people with preclinical Alzheimer's Disease (AD), has been launched in the United States. Butler Hospital's Memory and Aging Program is among the first U.S. study sites to begin screening potential participants.

AHEAD 3-45 is a Phase III, international, multicenter clinical trial with 100 study sites in the US, Japan, Canada, Australia, Singapore, and Europe. It will study the effectiveness of BAN-2401, an investigational drug that selectively binds to, neutralizes and eliminates the amyloid beta proteins in the brain that are thought to be a causative factor for AD. It is a double-blind, randomized study open to individuals ages 55 to 80 who are cognitively normal but have either elevated or intermediate levels of amyloid beta protein in the brain. A total of 1400 participants will be enrolled and treated with BAN2401 for 216 weeks.

The study is being conducted through a public-private partnership between Eisai Co., Ltd., a leading global research and development-based pharmaceutical company, and the Alzheimer's Clinical Trials Consortium (ACTC), a clinical trial network focused on accelerating and expanding studies of therapies for AD and related dementias which is funded by the National Institute on Aging, part of the National Institutes of Health. The ACTC has 35 primary clinical study sites across the U.S., including Butler Hospital, which is a founding member. The study will be led by academic principal investigators from three ACTC member sites: **DR. PAUL AISEN** from the University of Southern California, and **DR. REISA SPERLING** and **DR. KEITH JOHNSON** from Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School, in partnership with Eisai.

"The AHEAD-3-45 study is breaking new ground by testing a drug to remove amyloid plaques much earlier to prevent and delay memory loss," said **STEPHEN SALLOWAY, MD, MS**, director of neurology and the Memory and Aging Program at Butler Hospital, the Martin M. Zucker professor of Psychiatry and Human Behavior and professor of neurology at the Warren Alpert Medical School of Brown University, and a member of the ACTC Executive Committee.

"As a founding member of ACTC, we at the Butler Hospital Memory and Aging Program are excited to join with other Alzheimer's experts across the nation and locally to accelerate the development of effective treatments for Alzheimer's disease," Dr. Salloway said.

After a common screening period in AHEAD 3-45, participants will be enrolled into one of two randomized, double-blind, placebo controlled trials based on the level of amyloid in the brain: the A45 trial and the A3 trial. The A45 trial will enroll cognitively unimpaired participants who have elevated levels of amyloid in the brain, and aims to prevent cognitive decline and suppress the progression of brain AD pathology with BAN2401 administration. The A3 trial will enroll cognitively unimpaired participants who have an intermediate amount of amyloid in the brain, and who are at high risk for further amyloid beta accumulation.

Currently, BAN2401 is being studied in another pivotal Phase III clinical study called Clarity AD, also being conducted at Butler Hospital. The Clarity AD study is testing the effectiveness of BAN2401 in treating people who already have early Alzheimer's Disease. It is open to individuals ages 50–90 years old with a diagnosis of Mild Cognitive Impairment or mild Alzheimer's disease. ❖

RIDOH launches expanded serology testing effort for those in high-contact professions

The Rhode Island Department of Health (RIDOH) will be coordinating a second, expanded round of serology testing in the coming weeks to better understand the prevalence of coronavirus disease 2019 (COVID-19) among people in certain high-contact professions in Rhode Island. This effort is in collaboration with the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Health and Human Services. Rhode Island was one of three sites selected across the United States for participation in this serology testing effort, along with Detroit and New York City.

Starting July 17th, first responders (police, fire, and emergency medical services), Rhode Island National Guard members, RIDOH staff, correctional facility workers, and hospital and nursing home staff were able to schedule a test online. Testing will be voluntary. Results will be made available to participants approximately four days after they are tested.

"Serology testing is one part of a strategic, comprehensive approach to measuring the impact of COVID-19 in Rhode Island, and is critical to inform our efforts to prevent the spread of the virus," said **PHILIP CHAN, MD, MS**, the Consultant Medical Director of the RIDOH's Division of Preparedness, Response, Infectious Disease, and Emergency Medical Services. "Rhode Island is already a national leader in PCR-based diagnostic testing for COVID-19. Supplementing what we learn from diagnostic testing with antibody testing is important to understand how COVID-19 is spreading in the state and to support people and communities that are most vulnerable to COVID-19."

Most testing sites will be located at or near hospitals, nursing homes, correctional facilities, first responder facilities, and public safety agencies. People will get information about their testing site when they schedule a test.

In May, in an initial round of serology testing, 5,000 randomly selected Rhode Island households received invitations to be tested. A seroprevalence of 2.2% was found, meaning that 2.2% of people who were tested had been exposed to the virus that causes COVID-19. Higher seroprevalences were seen among Hispanic Rhode Islanders and African American Rhode Islanders.

To participate in this serology testing effort, someone must:

- Be currently working as a first responder (police, fire, or emergency medical services), Rhode Island National Guard member, RIDOH employee, correctional facility worker, or a hospital and nursing home staff member in Rhode Island. (Employee ID will be required to participate).
- Not have COVID-19 symptoms or a positive COVID-19 test within the last two weeks, and
- Have a valid mobile phone number or email address to receive test results. ❖

Brown Emergency Medicine launches telemedicine video visits

TeleCARE by Brown EM will provide timely diagnosis and treatment guidance to patients throughout the community

PROVIDENCE (JULY 15, 2020) – Brown Emergency Medicine has announced that *Telecare* is officially accepting virtual video-based appointments. This telehealth option was created in response to the COVID-19 pandemic and is available to all adult and pediatric patients throughout Rhode Island.

"We are pleased to offer this telehealth option to the community," said **JEREMIAH "JAY" SCHUUR, MD, MHS**, President of Brown Emergency Medicine. "*TeleCARE* makes it simple for patients to meet virtually with a Board-Certified Emergency Physician and Board-Certified Pediatric Emergency Physician at a time that fits their schedule. It's like having an emergency doctor on-call for you and your family."

TeleCARE treats a wide variety of medical problems and injuries including respiratory illnesses, fever, rash, sore throat, flu symptoms, urinary infections, allergies, headache, sports injuries, cough, earaches, minor falls, nausea/diarrhea, pink eye and sprains.

Adult and Pediatric appointments are currently available from 12 noon to 12 midnight, 7 days a week. To schedule a telehealth appointment, visitors access www.brownemtelecare.org, where they have the option to click on adult or pediatric appointments currently available. The video visit can occur through a phone, tablet, or computer with a video connection. ❖

Providence VA Groundbreaking for new mental health facility

From left to right, **Dr. Satish Sharma**, chief of staff for the VA Providence Healthcare System; **Matthiew Goulet**, associate director for patient care; **Ryan Lilly**, director of the VA New England Healthcare System; **Lawrence Connell**, director of the VA Providence HCS, and **Erin Clare Sears**, associate director for operations, break ground during a ceremony that was held privately due to social-distancing considerations July 14, 2020, for a project to build a new 14,000 square-foot mental health facility on the Providence VA Medical Center campus, located at 830 Chalkstone Ave. in Providence. The $14 million project will also make use of sloped land unsuitable for surface parking and allow for the retirement of outdated and inefficient modular buildings. [PROVIDENCE VA HEALTHCARE SYSTEM PHOTO BY WINFIELD DANIELSON]

Johnson & Wales University, University of Saint Joseph in Hartford partner to offer expedited pathway to PharmD degree

Eligible students can earn bachelor's degree, PharmD in six years

PROVIDENCE – Johnson & Wales University (JWU), in partnership with the University of Saint Joseph (USJ), has launched a new 3+3 program that creates a pathway for qualified JWU students to earn a bachelor's degree in biology and a Doctor of Pharmacy (PharmD) degree in six years. The program, which is now available to students, maximizes the time and investment of students by providing a path to complete their studies a year ahead of schedule, saving up to a year's tuition in the process.

As part of the articulation agreement between JWU and USJ, priority admission will be granted to eligible applicants from JWU to USJ's School of Pharmacy and Physician Assistant Studies' PharmD program located in Hartford, CT. Students who enroll in JWU's Biology program and meet admissions requirements will spend their first three years at JWU before matriculating directly into the USJ School of Pharmacy and Physician Assistant Studies to begin the PharmD program. Students who have completed their biology degree requirements will receive their bachelor's degree in biology from JWU during their first year enrolled in USJ's PharmD program.

"As JWU evolves into a more comprehensive university and continues to expand its footprint in the health arena, USJ became a natural partner in this endeavor," said **MICHAEL FEIN, PhD**, dean in the John Hazen White College of Arts & Sciences at Johnson & Wales University. "This accelerated pharmacy program provides students the best of both worlds: a strong academic foundation and a cost-effective, fast track to professional success. It also reaffirms JWU and USJ's commitment to the applied liberal arts. With this agreement, our Biology students now have another pathway to enter the health professions." ❖

Brown, Lifespan launch joint Center for Digital Health

PROVIDENCE – Brown University and Lifespan announced on July 28th the launch of the Brown-Lifespan Center for Digital Health. The Center for Digital Health's mission is to utilize the best of technology to seamlessly maximize health and eliminate health disparities for both individual patients and larger populations, extending from the local to global communities.

"Digital health technologies, from wearables to apps, are increasingly used by consumers to serve health care needs," says **MEGAN L. RANNEY, MD, MPH**, director of the center. "However, the development and widespread use of these technologies is limited by a lack of efficacy data, lack of implementation guidance, and, most of all, by lack of systematic collaboration among researchers, clinicians, patients, and other stakeholders."

The Center for Digital Health will serve as an incubator for research, fostering the development of practical digital health tools focused on solving the real needs of patients, health care providers, and populations. The center will train the next generation of digital health scientists and entrepreneurs by offering experiential education.

"We will help people from across our hospital and university campuses to go from 'idea-to-impact' quickly, efficiently, and ethically," Dr. Ranney says.

The ultimate goal is to be able to quickly scale up digital treatment modalities in order to have broad impact for both patients and populations.

To achieve these functions, the center will intersect with leading entrepreneurs, academicians, and clinicians across all Brown schools, the Lifespan health system, and the greater Providence area, as well as with national and international business and research leaders in the field.

The Center for Digital Health builds on the Emergency Digital Health Innovation program, which for more than six years successfully developed and studied digital applications in the field of emergency medicine, including text message programs to reduce injury among adolescents, machine learning-based mobile applications to provide support to adults with behavioral health diagnoses, and collaborations on novel social media monitoring programs. The Center will broaden its reach to encompass all aspects of health, with a focus on equity and vulnerable populations.

"We are excited to foster the Center for Digital Health's growth as part of the Brown Institute for Translational Science," says **JACK A. ELIAS, MD**, senior vice president for health affairs and dean of medicine and biological sciences at Brown University. "The faculty have a track record of successful clinical trials and industry partnerships to build on. This expertise presents a wonderful educational and research opportunity for Brown students."

"This outstanding partnership will enable us to further develop and apply digital health in the ever-changing practice of medicine," says **TIMOTHY J. BABINEAU, MD**, president and CEO of Lifespan. "Our clinicians and researchers are creative, innovative problem-solvers, and the Center for Digital Health further binds Lifespan and Brown together to support their individual efforts and fuse their energies into potentially life-changing technology for our patients and our providers."

Learn more about the Center for Digital Health, including video perspectives from our staff and trainees: digitalhealth.med.brown.edu/ ❖

Miriam named top RI hospital in *U.S. News & World Report*

PROVIDENCE – The Miriam Hospital has once again been named the top hospital in Rhode Island by *U.S. News & World Report* and for the second year in a row its adult urology program has been ranked among the top 50 in the nation.

U.S. News ranked The Miriam Hospital a Best Regional hospital – No. 1 among all Rhode Island hospitals as well as the top hospital in the Providence metro area. To be counted among this year's 563 Best Regional Hospitals, a hospital had to outperform in at least three of the procedures, conditions and specialties *U.S. News* evaluates. The Miriam Hospital wound up receiving a national "high performing" designation for eight programs and specialties:

- Colon cancer surgery
- Heart failure
- Hip replacement
- Knee replacement
- Geriatrics
- Nephrology
- Chronic obstructive pulmonary disease (COPD)
- Neurology and neurosurgery

The Miriam Hospital's Urology program was not among these because it actually ranked among the 50 best in the country – placing it among the top 3 percent in the nation. It is one of only three urology programs in New England to be ranked nationally and the only hospital specialty in Southern New England to achieve national ranking. It was the second consecutive year that The Miriam Hospital – home to the Minimally Invasive Urology Institute (MIUI) – was nationally ranked for urologic services for men and women, including kidney, prostate and bladder care. ❖

Appointments

Heather Smith, MD, named President-elect of AMA Foundation

The American Medical Association Foundation has announced the election of **HEATHER SMITH, MD, MPH**, as President-elect of its Board of Directors. Dr. Smith has a long history with the Foundation. She received an AMA Foundation Leadership award in 2001, was appointed to the AMA Foundation Board of Directors in 2013 and most recently served as Secretary of the Board from 2019–2020.

Dr. Smith is an assistant professor in the Department of Obstetrics & Gynecology at Women and Infants Hospital. She has been an active member of the AMA since 2002, serving as a delegate to the AMA House of Delegates since 2008, most recently representing the American College of Obstetricians and Gynecologists. She has previously served as the Vice Chair, as well as the Alternate Delegate for the Resident and Fellow Section. Additionally, Dr. Smith serves as a member on the Council on Legislation and has also served on the Council on Medical Services. Throughout her career and years of service, Dr. Smith has remained active in the Massachusetts Medical Society, the Connecticut State Medical Society, and now the Rhode Island Medical Society.

Dr. Smith completed a postdoctoral fellowship in health services research through the Robert Wood Johnson Foundation Clinical Scholars program at Yale University. There, she performed research in the field of health equity with a focus on disparities for women and adolescents, particularly from marginalized and underserved populations. Employing both quantitative and qualitative methods, she investigated the impact of local and federal policies on issues including access to care, access to information, and resource utilization.

Since her appointment to the AMA Foundation Board of Directors, Dr. Smith has been vital in expanding and strengthening communications activities for the organization. As Chair of the Ad-Hoc Communications Committee, she managed the implementation of updated branding materials and increased the Foundation's web presence, including the launch of a new Foundation website in 2019. Dedicated to fostering physician leaders of tomorrow, Dr. Smith has also served as a mentor to medical students through the Foundation's Leadership Development Institute since its inception. ❖

Kenneth E. Wood, DO, named Lifespan Executive Vice President of Physician Affairs and Chief Clinical Officer

After an extensive national search, **KENNETH E. WOOD, DO**, has been appointed Executive Vice President and Chief Clinical Officer for Lifespan, Rhode Island's largest health system.

Dr. Wood is a veteran health care administrator, educator and researcher with three decades of clinical experience across diverse settings ranging from community hospitals to large, integrated academic medical centers. Dr. Wood assumed his role on June 24, 2020, and succeeds John B. Murphy, MD, who is serving as the President of Rhode Island and Hasbro Children's Hospital.

Dr. Wood comes to Lifespan from the University of Maryland Medical Center (UMMC) where he was a Senior Vice President and Chief Clinical Officer, Associate Chief Medical Officer for the University of Maryland Medical System and Director of the University of Maryland Critical Care Network. Prior to these positions, Dr. Wood spent five years as the Chief Medical Officer at Geisinger Medical Center and was Director of the Center for Re-Engineering Healthcare for the Geisinger Health System in central Pennsylvania and previously spent 17 years at University of Wisconsin Hospital and Clinics where he held a number of leadership roles.

Dr. Wood holds a Bachelor of Arts degree from Lehigh University in Pennsylvania and a Doctor of Osteopathic Medicine degree from the Philadelphia College of Osteopathic Medicine. He completed an internship at Union Memorial Hospital in Union, N.J., a residency in Internal Medicine at Abington Memorial Hospital in Abington, PA and a fellowship in Critical Care Medicine at the University of Medicine and Dentistry of New Jersey's Robert Wood Johnson Medical School (now part of Rutgers University). Dr. Wood is board certified in internal medicine and critical care medicine. ❖

Appointments

Lawrence Connell named Director of Providence VA Medical Center

BEDFORD, MASSACHUSETTS – The De-partment of Veterans Affairs appointed **LAWRENCE CONNELL** as the new director of the Providence VA Medical Center, effective as of June 23rd of this year.

Connell will oversee a comprehensive health care system that provides care to over 35,000 Veterans from Rhode Island and southeastern Massachusetts, the Cape and Islands, with an operating budget of nearly $300 million.

"We are pleased to appoint Lawrence Connell as the new director of Providence VA Medical Center," said Ryan Lilly, network director for the VA New England Healthcare System. "His sound leadership qualities and proven experience will be valuable assets for the facility, the employees and volunteers, and for the Veterans we are honored to serve."

Connell previously served as the chief of staff for the Veterans Health Administration, Washington, DC. He is a retired U.S. Army colonel and served as the Deputy Chief of Operations, Joint Cyber Center, U.S. Pacific Command. Throughout his military career, he has held multiple leadership positions. He served more than 30 years as an Army medical service officer, including 15 years as a Medevac pilot. Additionally, Connell served as the Chief Operating Officer, Pacific Regional Medical Command, Honolulu, Hawaii; the Chief Executive Officer of Stuttgart U.S. Army Medical Health Clinic; the Commander of the 43rd Area Support Medical Battalion; and other medical-related staff positions.

Connell holds a Bachelor of Science in communications from the University of Rhode Island and a master's degree in international relations from Troy State University. He is a certified Lean Six Sigma Black Belt and a graduate of the Disney Institute for Health Care Excellence. Connell is the recipient of the Legion of Merit with Oak Leaf Cluster award and two Air Medals.

Providence VA Medical Center, part of VISN 1, is comprised of one main campus located in Providence and three community-based outpatient clinics (CBOCs) located in New Bedford, and Hyannis, Mass. and Middletown, R.I. VISN 1 is one of 18 Veterans Integrated Service Networks within the U.S. Department of Veterans Affairs. VISN 1 has 11 medical centers, 45 CBOCs, six community living centers and two domiciliaries. ❖

South County Health announces new providers to Cancer Center Team

The South County Health Cancer Center recently welcomed two new providers to its medical staff.

Hematologist/oncologist, **CHRISTOPHER W. SEIDLER, MD**, began seeing patients at the Cancer Center in May. Prior to joining the South County Health team, Dr. Seidler was the medical director at Harrington Hospital Cancer Center in Southbridge, MA. He received his medical degree from Rutgers Medical School and furthered his training in an internship and residencies in internal medicine at Brown University, Rhode Island Hospital. He then completed a fellowship in hematology/oncology at Dartmouth Medical School, Hanover, NH.

HANNAH WEINER, MSN, an advanced oncology certified nurse practitioner (AOCNP), also joined the Cancer Center team. Hannah attended Medical University of South Carolina where she earned a BSN before earning an MSN as an Adult Nurse Practitioner from Barnes Jewish College, Goldfarb School of Nursing, St. Louis, MO. She is ANCC board-certified and has provided care in primary care and cancer care environments.

The South County Health Cancer Center is located at South County Hospital. The Cancer Center, accredited by the Commission on Cancer, allows patients a continuum of care from diagnosis to treatment and rehabilitation within the Wakefield campus. ❖

Obituaries

RUTH APPLETON BELL, MD, widow of D. William J. Bell, MD, passed away on June 11th. She was the daughter of the late Paul Appleton, MD, Chief of Obstetrics at the former Providence Lying-In Hospital and Frances Ricker Appleton, RN.

Dr. Bell was a pediatrician in Providence and North Conway, New Hampshire. She retired to Great Falls, Montana, and moved to Williamsburg, Virginia, a few years ago. In 2019, she settled in Brandenburg, Kentucky. She was a 1939 graduate of the Lincoln School in Providence. In 1946, she earned her medical degree from the University of Michigan during World War II as one of four women out of 160 residents. Her class was accelerated into a three-year residency because of the wartime shortage of stateside doctors, and she was a member of Phi Kappa Phi and Alpha Omega Alpha. She was devoted to the university's medical school for the rest of her life.

She was a pioneer in pediatrics and a role model for aspiring female doctors. As a lifetime member of the American Board of Pediatrics, she presented at and attended the annual meetings up until her early 90s, co-authoring landmark findings on childhood diabetes in 2010. Dr. Bell was among the first group of pediatricians working with Dr. Sidney Farber to attain temporary remissions of acute lymphocytic leukemia, the most common cancer in children. She practiced in Providence from 1953–1984 and in North Conway from1984 until retiring to Montana.

Dr. Bell was an intrepid world traveler and her travels took her to all corners of the Earth, including an expedition to Antarctica when she was in her 80s. She spent many summers on Jekyll Island in Georgia, and her final trip was a walking tour of Scandinavia at 88 years of age.

Dr. Bell's volunteer work included working with Visiting Nurses in Warwick, sitting on the board of Warwick Libraries, and St. Mary's Home. She conducted dozens of free baby wellness checks for those in need in Providence, New Hampshire and Montana. She continued to take medical courses throughout her life to remain current with pediatrics. She loved animals, especially her beloved dogs.

She will be remembered by her countless patients and those who dearly loved her. ❖

CORNELIUS O. (SKIP) GRANAI, III, MD, died from cancer on June 28 at age 71 in his home in Ashaway, surrounded by the love of family.

Skip, the son of Ki and Loraine Granai, grew up in Barre, Vermont in a home across from the Lincoln School playground where there was always a ballgame to join. He graduated from Spaulding High School in the class of 1966 and graduated from the University of Vermont in the class of 1970. He had joined Army ROTC while in college and served before going back to school. Skip went on to earn a master's degree in cell biology from the University of Vermont in 1973 and his medical degree from the University of Vermont, College of Medicine in 1977. He served a residency in obstetrics and gynecology at Tufts University, School of Medicine and completed a fellowship in gynecological oncology at New England Medical Center.

Over the course of his professional life, he was on the faculties of Tufts, Harvard and Brown Universities and on the staffs of the New England Medical Center and Massachusetts General Hospital, ultimately ending up at Women & Infants Hospital in Providence, where he became the Director of Women's Oncology and Executive Chief of Oncology for Care New England. That innovative, patient-centered program emphasized the importance of the arts and the heart in equal parts with medical knowledge in the practice of medicine. He taught the many oncology fellows and residents he trained to keep "fighting the good fight." Central to this belief is advocating strongly for what they learn is right from being at a patient's bedside and by remembering the values and privilege that brought them to medicine in the first place. He became a sought-after speaker and spread his message throughout the world. Skip loved his work and would have done it unsung, but he was awarded many honors, among them the Arnold P. Gold Foundation Humanism in Medicine Award, a Lifetime Achievement Award from the American Cancer Society and the Kaali Award which he received in Hungary for his "invaluable and lasting contribution in gynecologic oncology and integrative care, for his motivational speeches worldwide, and for his passionate humanism."

Those who know Skip understand that he would be embarrassed by a listing of any professional achievements. (His family usually found out about them because someone in his office would send his parents a notice.) He would much rather talk about anything else, especially something that would have him at odds with many of the people in a room. His wit and barbs were quick and his humor was ever-present. His skill at arguing his point led to many extended family dinners where those in the younger generation could learn the fine art of defending their beliefs. His keen understanding of human nature and his caring heart showed clearly in the poetry he wrote and the music he loved. He found inspiration in the beauty of the farm on which he lived and the work he would do on it. His final speaking engagement entitled "Moo" blended the farm and his life-long message of the humanistic way of practicing medicine. Above all of the other things in his life, he cherished his children. He loved their spirits, perspectives, and most importantly, their hearts. He knew what they could do, and he did all he could to encourage the best in them to come out whether in

sports, arts, presentations or any other endeavor, and he taught them how to appreciate what new things life has to offer while respecting what and who came before. His support of the whole family will be sorely missed.

Skip is survived by Ann Kirby of Ashaway, his loving partner; his four children, Lieutenant Colonel Cornelius O. (Tad) Granai IV (wife Lindsey, children Hannah and Lilah) of East Greenwich, Rhode Island; Robert Granai (wife Audra, children Ava, Tyler and Ella) of Mapleville, Rhode Island and their mother Mary Manzi; Lily Granai and Kile Granai of Providence, and their mother Cheryl Granai; his sisters Susan Granai (husband David Van Slyke) of Yarmouth, Maine and Mary Corrigan (husband Ed) of Northfield Falls, Vermont; beloved nieces and nephews, caring aunts and cousins, faithful dog Jenna, and extended family in which he would include his many colleagues.

If so inclined, memorial contributions can be made to: The Skip Granai Endowed Lectureship "Humanism in Medicine: What Matters Matter" at https://foundation.womenandinfants.org/ (online designation: "Lectureship in Honor of Skip Granai") or payable to "Women & Infants Foundation" (memo: "Skip Granai Endowed Lectureship") addressed to WIH Philanthropy Department, 300 Richmond Street, Providence, RI 02903; The University of Vermont, Larner College of Medicine, Medical Alumni Association Scholarship Fund at http://www.med.uvm.edu/alumni/support (online designation: "Medical Alumni Association Scholarship") or call for more information at (802) 656-4014. A celebration of Skip's life will take place in the future. ❖

HAROLD M. HARGER, JR., MD, 87, passed away on May 30, 2020. He graduated from Tulane University Medical School and was a practicing radiologist in Rhode Island for many years before retirement. He was a veteran of the United States Air Force.

An avid boater for most of his life, Harold was a long-standing member of the Florida Coast Guard Auxiliary, serving in many capacities, including Flotilla Commander and IO Officer, during his tenure. He enjoyed building and flying model airplanes in his spare time and was a member of Aero Modeler Associations in both Rhode Island and Florida. He is survived by his wife of almost 42 years, Madelyn K. Harger, of Port St. Lucie, FL; sister, Muriel (Kit) Lipps and her husband Fred of Metairie, LA; daughter, Donna L. Harmon of Coventry, RI; grandchildren Trevor W. Harmon, Tyler J. Harmon, Tanner R. Wilkins and Sierra N. Wilkins; and several nieces and nephews. He was preceded in death by his daughter, Shirley E. Wilkins; son, H. Kevin Harger and his former wife, Janice H. Godbout. ❖

BANICE MORDECAI WEBBER, MD, 94, died on May 27th, 2020. He was born in Providence on June 26, 1925, the only son of Joseph and Sarah Olch Webber. He attended Brown University and graduated from Tufts Medical School in 1947. He trained as a surgeon, like his father, and later in his medical career went on to become a radiation oncologist, ultimately founding Radiation Oncology Associates in Providence.

He served his country, entering the Army in June 1943 prior to attending Tufts Medical School and was sent to Korea in 1952 as an Army surgeon. He was a Fellow in the Department of Radiation Oncology at Tufts New England Medical Center, an attending radiation oncologist at Rhode Island Hospital, and a member of the Brown University Medical School faculty. He was a Clinical Associate Professor Emeritus of Radiation Medicine at Brown University and an Associate Professor of Radiation Oncology at Tufts University School of Medicine. His long and distinguished medical career included stints as President, New England Cancer Society; President, New England Society of Radiation Oncology; President, Miriam Hospital Staff Association, a trustee of The Miriam Hospital; Chairman, Mediation Committee of the Rhode Island Medical Society, and member of the Board of Trustees of Home and Hospice Care of Rhode Island.

He retired in 2003 and in his later years tutored 4th and 5th grade children at the Paul Cuffee School, which he loved dearly. A lifelong sailing enthusiast, photographer, intrepid traveler and occasional musician among many other interests, Dr. Webber loved clams, oysters, mussels and chowder almost as much as he loved the summer. His many friends, colleagues and patients were all familiar with his deep intellect, endless curiosity, sharp wit and humor. He was a devoted son, brother, husband, parent, delighted grandparent and above all, a man of science, who honored the traditions but charted his own path.

He was married to Helen Ross Webber (1952–1962), Sherry Polan Webber (1963–1999), and Marie Clarke (2014–2016). He is survived by his two daughters, Rachel Webber Ryser of Brooklyn, NY, and Susan Webber Gatto of New York City and Park City, Utah; their spouses, Scott Ryser and James Gatto, and 4 grandchildren, Samuel Joel Ryser, Nina Sarah Ryser, Alexander Webber Gatto and Owen Edward Gatto. His two sons, Joel Benjamin Webber and Daniel Saul Webber, predeceased him.

World circumstances have forced postponement of a funeral/memorial service.

Eventually he will be buried in Providence, at Sons of Israel and David Cemetery. Donations will be gratefully accepted in his name at The American Cancer Society. ❖