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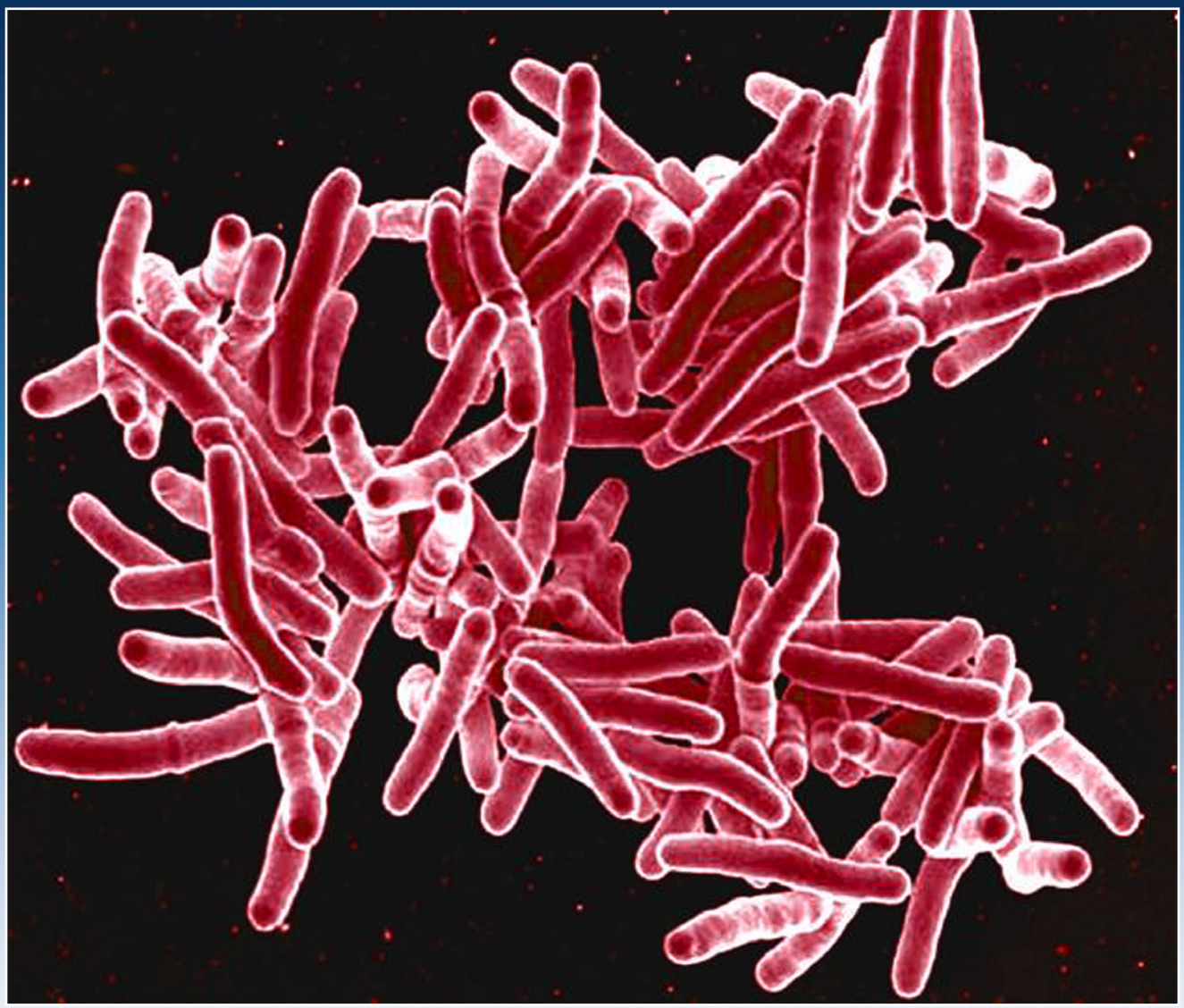

SPECIAL SECTION

INFECTIOUS DISEASES

GUEST EDITOR

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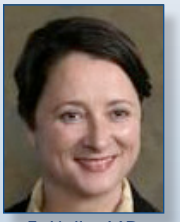
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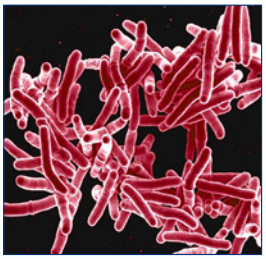
NIAID

Cover: Produced by the National Institute of Allergy and Infectious Diseases (NIAID), this digitally-colorized scanning electron micrograph (SEM) depicts a grouping of red-colored, rod-shaped *Mycobacterium tuberculosis* bacteria, which cause tuberculosis (TB) in human beings.

Public-private Partnerships, Programs Target Infectious Diseases in RI

BRIAN T. MONTAGUE, DO, MPH
GUEST EDITOR

Though morbidity and mortality from infectious diseases continues to decline in the United States, the recent epidemic of Ebola in West Africa highlights the ongoing importance of maintaining strong public health programs to address infectious diseases in the United States. Though epidemics may be infrequent, they consume considerable amounts of public resources and maintaining a strong public health approach to respond to these outbreaks is critical. In times of declining funding for public health programs, alternative strategies are needed to maintain the readiness of our health systems to respond to these crises. Dedicated public health treatment programs are increasingly transitioning into public-private partnership models in which community providers become the key care providers guided by public health programs. Targeted financial support addresses those aspects of control efforts not fundable through the existing public and private insurance systems. Both the increasing complexity of the system of care and the increasing emphasis on accountability in medical under the provisions of the Affordable Care Act, create a clear need to examine and monitor outcomes across the system of care. This issue highlights a number of programs in Rhode Island that address important issues in infectious diseases with implications for public health, including this public-private partnership model.

CONTRIBUTIONS

The article by Montague et al. highlights the opportunities and risks of public-private partnerships as an approach to sustaining tuberculosis (TB) control efforts in the context of declining incidence in Rhode Island and concomitant reductions in state and federal funding. The RI Department of Health has promoted a community-based testing and treatment model for latent tuberculosis infection focusing on the community health centers given their role as key sites for targeted testing for tuberculosis infection. The case study presented by Chow et al. highlights the need to consider tuberculosis as part of the differential diagnosis for persons from high-risk communities, even where specific exposure to persons with tuberculosis cannot be established.

Increasing attention is being given to a public health approach to HIV prevention using a treatment-as-prevention model, supported by the recent publication of the HPTN052 study, which showed near complete elimination of transmission within HIV serodiscordant couples when the infected partner is on suppressive antiretroviral therapy. In multiple settings strong inverse correlations are seen between the uptake to antiretroviral therapy and reductions in incident HIV in the community. Community viral load, assessed as the sum of detectable viral counts in the community, has been proposed as a potentially valuable index for risk of HIV transmission in the community. Touzard Romo et al. present clinic-based viral load data for the Miriam Hospital program, which may provide a useful baseline and framework for monitoring infection risk in the community going forward.

Recent epidemics of sexually transmitted diseases (STDs), particularly among men who have sex with men, have been described in many areas of the country. Chan et al. describe the recent observed increases in sexually transmitted diseases in RI as well as the working model of public-private STD testing and treatment clinic established at the Miriam Hospital. This clinic links STD testing with provision of pre-exposure and post-exposure prophylaxis for HIV and provides a unique source for this integrated care in RI.

Tick-borne illness is both a significant cause of morbidity in Rhode Island and an area of significant controversy. Reece et al. outline the current recommendations for diagnosis and treatment of tick-borne illnesses, particularly Lyme disease. They also discuss the important distinction between acute infection requiring antibiotic therapy and the post-Lyme inflammatory syndrome that likely accounts for a significant portion of persistent symptoms following treatment of the initial infection.

Increasing attention is being given to the management of persons receiving extended duration outpatient parenteral antibiotic therapy (OPAT). Touzard Romo et al. review the current guidelines for monitoring patients on these therapies and outline a program for monitoring these patients through an outpatient OPAT program.

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Tuberculosis Control in RI: Maintaining Control Efforts in the Context of Declining Incidence and Funding for Tuberculosis Programs

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INTRODUCTION

Tuberculosis (TB) infection is one of the most common infections in the world, affecting an estimated one-third of the world's population and accounting for 1.3 million deaths annually.[1] Incidence in the United States (US) peaked most recently in 1992 at 26,673 cases (10.4 cases per 100,000 persons), which was associated with the emergence of the HIV epidemic together with declines in funding for TB control in the 1980s.[2] Tuberculosis incidence has since declined, with only 9,945 cases reported in 2012 (3.2 per 100,000). Sixty-three percent of TB cases in 2012 occurred among foreign-born populations.[3] In Rhode Island (RI), highest rates are seen among persons from Guatemala (23%), Dominican Republic (15%), and Cambodia (15%). Multi-drug resistant tuberculosis, defined as resistance to isoniazid and rifampin, has been reported in 1% of US TB cases consistently. Though pulmonary TB is most common, disease can occur throughout the body with diverse manifestations.

Tuberculosis is spread by persons with pulmonary disease. Following initial infection within the lungs, the infection is usually contained and the mycobacteria remain quiescent within granulomas, a state termed latent tuberculosis infection (LTBI).[4] Ten percent of infected persons subsequently develop TB over the course of their life, with half of that risk occurring within the first 2 years after infection. For persons with HIV, the risk of reactivation is higher and may reach 10% per year. Though eradication of infection may be possible, this cannot be confirmed with current testing and the assumption is made that all those infected are at risk for reactivation disease. Predictive models have been developed to estimate the risk of TB and of treatment complications with risk calculators available online.[5,6]

Tuberculosis control involves the combination of active case finding for TB disease, assurance of adequate treatment for active disease with directly observed therapy (DOT), screening and treatment of TB infection among contacts to infectious cases, and targeted testing and treatment of LTBI among higher risk populations. This combined strategy has contributed to the substantial declines in reported TB.

Support for TB control has varied historically with increased support following times of higher incidence and declines when incidence diminishes. In 2000, the Institute of Medicine (IOM) report *Ending Neglect* highlighted the impact of declines in US categorical funding for TB on disease control and outlined key recommendations for improvements with the goal of TB elimination. It was estimated that 4 times the current funding of $528 million annually would be required to fully implement the IOM recommendations.[7] Despite this, federal funding for TB control has been level or declining when adjusted for inflation since 1994, with greater reductions in funding for lower-incidence states.

Given ongoing funding gaps, partnerships with other programs and primary care providers are needed to maintain TB control efforts. With increases in federal support for community health centers (CHC), these centers may be model partners in this work. In 2012, a framework was established in RI under the direction of the RI Department of Health (HEALTH) to promote community-based testing and LTBI treatment by starting with CHC primary care providers. In this article we review the elements of screening and treatment for LTBI, discuss challenges implementing these in a community-based setting, and provide recommendations for providers to support integration of LTBI treatment into community care programs.

Diagnosis of Latent TB Infection

The Centers for Disease Control (CDC) recommends targeted testing for persons at high risk for TB with the framework that a decision to test is a decision to treat.[8] Testing is recommended for persons who are at increased risk of exposure (e.g. persons from high-burden countries, contacts to persons with pulmonary TB) or persons at increased risk for reactivation disease (e.g. persons with HIV or on immunosuppressive medications). Given the role of the CHCs in serving immigrants, these sites and similar primary care practices are important for targeted testing.

Historically, the cornerstone of screening for TB infection has been the tuberculin skin test (TST). This test has been validated in large cohorts with long-term follow-up such that evidence-based recommendations for interpretation of results for most individuals can be provided. A key limitation of the TST has been the potential for false positives due to exposure to either BCG vaccine or non-tuberculous mycobacteria. This potential is highest among young persons with recent BCG administration.

Interferon Gamma Release Assays (IGRAs) were developed as more specific alternatives to TST, without cross-reactivity with BCG or common non-tuberculous mycobacteria.[9-11] Two forms of IGRA have been approved for use, the

QuantiFERON®-TB Gold, which is used most commonly, and the T-SPOT®.TB test. These assays have been validated with short-term follow-up of populations at high risk for disease with performances comparable to TST. False negatives and false positives, however, can occur. For persons tested with both TST and an IGRA, the interpretation of discordant results may not be clear.[12-14] CDC guidelines discourage the use of dual testing except in limited circumstances, principally:

1) When increased sensitivity for detection of TB infection is desired and treatment would be recommended based on positivity of either test.

2) When a confirmatory test is necessary to persuade a patient to take treatment due to skepticism regarding the interpretation of the TST.[8]

Given the potential for false positive TSTs for persons with a history of BCG, the recommendation is that IGRAs be used as the sole test.

Uncertainty exists with regard to the management of persons with a history of BCG or no clear exposures to TB who test positive by TST. The core recommendation is that testing be restricted to persons of sufficiently high risk that a positive test would be accepted as indication to treat. Though not endorsed by the guidelines, in practice IGRA testing has been used as a second test in low-risk individuals for whom false positive TST is likely. Because the sensitivity of the IGRA is not 100%, individuals with TB infection may be misclassified based on a negative IGRA and not offered treatment. IGRAs should not, therefore, be used as a second test in those at high risk for development of tuberculosis disease.

Diagnosis of LTBI requires exclusion of TB disease. Historically, about one-third of patients with active TB identified at the RISE TB Clinic were identified as part of initial evaluation for LTBI. Standard protocols include conducting a symptom screen and obtaining a chest x-ray. Symptom screens focus on the most common symptoms including fever, cough, unintentional weight loss, and drenching night sweats. These screens may miss extrapulmonary TB and so the initial evaluation needs to include review of other unexplained symptoms the patient may have that may be attributable to TB.

Treatment of Latent TB Infection

There are several approved regimens for the treatment of LTBI (see **table 1**). The oldest and best studied is therapy with isoniazid. The treatment course is 9 months and, if gaps occur, a total of 270 doses must be received within a period of 12 months. Liquid formulations are available but the sorbitol base limits tolerability at doses greater than 50mg. Isoniazid has the advantage that it has few drug interactions and serious toxicities are relatively rare.[15] The common side effects include inflammation of the liver, with the incidence of serious toxicity estimated to be as low as 0.1 to 0.6% of cases. Drug-induced neuropathic pains of the extremities can occur and are often preventable with vitamin B6 supplementation.

Shorter course treatment with rifampin has been both validated independently and tested compared to isoniazid.[16-18] Completion rates were better with rifampin and tolerance was higher. Hepatotoxicity can occur, though it is thought to be less frequent than with isoniazid. The relative risk of grade 3 or 4 hepatotoxicity was 0.12 for rifampin.[16] Hypersensitivity reactions and hematologic changes, principally thrombocytopenia and leukopenia can occur but are rare.

The third regimen is the combination of isoniazid and rifapentine dosed weekly as DOT for 12 weeks.[19,20] This regimen was validated for use in contacts to persons with pulmonary TB. Dosing for both agents is weight-based. This regimen is recommended for patients of age 12 or higher with high risk of disease based on recent exposure, documented conversion of TST or IGRA.

Whichever regimen is used, treatment monitoring and documentation of treatment outcome is a key component of therapy. Adherence assessment is necessary and where possible documentation of the number of doses received and the time period should be made. Persons who subsequently require immunosuppressive therapy may require retreatment if sufficient documentation of treatment adequacy is not available.

Latent Tuberculosis Infection in Rhode Island

RI is a low-incidence state for TB with 23 cases reported in 2012.[21] On average, more than 60% of cases occur among foreign populations. A National Health and Nutrition Examination Survey (NHANES) survey from 1999-2000 estimated the prevalence of LTBI at 4.2% nationwide with 18.7% prevalence among the foreign born.[22] The 4.2% overall prevalence would suggest that approximately 44,000 people in RI

Table 1. Treatment Regimens for Latent Tuberculosis Infection

Treatment	Dose	Duration	Minimum Doses
Isoniazid	10 mg/kg children, 5 mg/kg adults. Max dose 300 mg/day	9 months	Daily: 270 within 12 months Twice Weekly DOT: 76 within 12 months
Rifampin	10 mg/kg. Max dose 600 mg/day.	4 months	Daily: 120 within 6 months
Isoniazid + rifapentine	INH: 15mg/kg round up to nearest 50 or 100mg. Max dose: 900mg. RPT: 10.0-14.0 kg 300 mg 14.1-25.0 kg 450 mg 25.1-32.0 kg 600 mg 32.1-49.9 kg 750 mg ≥ 50.0 kg 900 mg	3 months	Weekly DOT: 11 or 12 within 16 weeks

are living with LTBI. Though LTBI has been reportable since 2010, it remains underreported and LTBI targeted testing expansion is needed to reach more high-risk individuals.

Funding for TB control in RI has decreased overall in the last 10 years, reaching its current nadir in 2012. Given these declines, the TB control program has prioritized:

1) Identification and medical treatment of active cases

2) Contact investigations and treatment of LTBI among contacts to actives

3) Evaluation and treatment of TB infection among persons at high risk of reactivation

4) Evaluation and treatment of TB infection among persons with no other access to services

The tuberculosis control program at HEALTH works in partnership with the Miriam Hospital RISE Clinic, which provides consultation and treatment services, and with Hasbro Children's Hospital for treatment of LTBI among children in RI. In 2013, there were 27 confirmed active TB cases in RI and the TB program identified 1,183 contacts to active cases and performed 5,056 DOT visits. During the same period, 413 LTBI cases were identified and managed at the Hasbro Children's Hospital and RISE TB Clinics. The overall completion rate for persons starting on LTBI treatment at RISE in 2013 was 67%.

The proposed framework to collaborate with CHCs for treatment of LTBI included CHCs consulting the RISE Clinic to conduct an initial evaluation to exclude active TB and set an LTBI treatment plan. Given the high risk of reactivation disease among persons with HIV, all persons without prior documented HIV testing and those with risk factors for recent HIV exposure would be screened as part of the initial Rise clinic evaluation. Low-risk LTBI patients who are able to receive treatment through the CHC would be referred back for the treatment and monitoring. In addition to contacts to persons with active TB, high risk or complex LTBI patients, particularly young children, persons with HIV, and those who are on or who are candidates for immunosuppressive therapy, would complete their treatment course at the RISE Clinic.

Several barriers were noted with the initial roll-out of this program. Medication costs and costs of associated monitoring for patients without insurance historically have been borne by the state and the Miriam Hospital. Patients referred back to CHCs without medication coverage were unlikely to receive the full treatment course in the absence of financial supports. Access to insurance under the Affordable Care Act has improved access to medications and diagnostics for some, though immigrants may be excluded and cost-share requirements continue to pose barriers. Without specific funding and mechanisms to support the costs of treatment for the uninsured, referral to the CHC would result in failure to treat.

Provider comfort with both medication management and clinical monitoring is equally a challenge. Many providers have rarely, if ever, prescribed TB medications and may be uncomfortable managing the side effects and toxicities. Though targeted education can address these concerns, a high level of commitment from CHCs is needed to maintain investment in the program over time.

The referral step before treatment creates the potential for loss to follow-up. This may be particularly a concern if there is inadequate tracking of referrals. If new symptoms develop during the period prior to follow-up for treatment, health center providers may be uncomfortable treating or providing the needed clinical reassessment. If treatment complications occur, explicit planning is needed to determine when referral to RISE Clinic is appropriate. Further solidification of this model is needed with the eventual goal of expanding to additional pediatric and adult primary care providers.

RECOMMENDATIONS

In order for a community-based treatment for LTBI to succeed there are several key areas that need to be addressed:

- Increased targeted testing is needed among high-risk groups.
- Use of IGRA per recommendations to minimize referrals due to false positive TSTs.
- Ongoing education of community providers is needed to improve knowledge of tuberculosis and the treatment of LTBI.
- Partnering primary care providers, starting with CHCs, need to develop internal processes for tracking prescriptions/adherence.
- Continued support for LTBI treatment at the Rise and Hasbro clinics is needed both for high-risk patients and to serve those without adequate coverage for treatment in the community.
- Treatment completion rates and complications need to be reviewed focusing on gaps or adverse outcomes resulting from the referral process.

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Disclosures

The authors have no financial disclosures to report.

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Tuberculous Meningitis in Child Born in the US to Immigrants from a Tuberculosis-Endemic Country

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ABSTRACT

This is a case of a child born in the US to immigrant parents from a tuberculosis (TB)-endemic area of Liberia who was diagnosed with TB meningitis after a greater than 1-month history of unremitting fever. This report aims to highlight the importance of early identification of TB in the pediatric population with risk factors for TB and considering TB as a diagnosis among US born children to immigrants from TB-endemic countries.

KEYWORDS: Tuberculous meningitis, refugee, pediatric, immigrant

INTRODUCTION

Tuberculosis (TB) continues to be the second most common infectious killer in the world among patients of all ages with approximately 1.3 million deaths worldwide attributable to the disease in 2012.[1] While many developing countries continue to struggle with TB control, widespread surveillance and appropriate treatment has allowed the US to maintain a low incidence of the disease. The Centers for Disease Control's (CDC) 2012 annual report noted a total of 9,945 new cases of TB, the lowest number ever of new TB cases in the US in a single year.[2] While the majority of these cases of TB occurred in foreign-born individuals, a significant percentage (37%) occurred in US-born persons.[3] Reaching the appropriate populations to test for TB continues to be key to controlling the transmission of TB.

Among refugee immigrant communities in the US, the risk of TB exposure is higher than the general population. Greater than 85% of refugees worldwide come from countries with a high prevalence of TB and many live in resource poor, crowded conditions prior to immigrating to their final destination.[4] In 2012, more than 58,000 refugees arrived in the US through the US Refugee Admissions Program (USRAP).[5] The state of Rhode Island (RI) has been an important site for refugee resettlement. From 1990–2008, a total of almost 4,800 refugees emigrated to the state of RI with 96% from Africa or Iraq.[6] Prior to relocation, refugees undergo screening by the US Department of State in countries of emigration. CDC screening standards since 2009 require immigrants older than 15 years of age in countries with WHO-estimated TB incidence rate $\geq$ 20 cases per 100,000 population to be screened by medical history, physical examination and chest radiograph. Only when individuals have symptoms or evidence suggestive of TB or HIV infection are sputum smears and cultures sent for TB.[7] Individuals with possible TB disease with negative smear and culture findings are not generally treated unless findings are highly suggestive of TB disease.[7] These screening exams are often completed months before departure, affording time for new exposure or reactivation. Although refugees are expected to be screened and receive treatment for active TB prior to arrival in the US, studies of refugee populations have found that when rescreened on arrival in the US, a significant percentage of refugees have active TB. A retrospective review of CDC data on refugees and immigrants arriving in the US from 1999-2005 found that 7.0% of those diagnosed with smear-negative tuberculosis and 1.6% of those with an overseas diagnosis of inactive TB (Liu et al described inactive TB as a chest radiograph with evidence of TB that was not clinically active including fibrosis, scarring, pleural thickening, diaphragmatic tenting or blunting of the costophrenic angles) were rediagnosed with active pulmonary TB.[8] This diagnosis was made on the results of chest radiography and sputum smears for those presenting for their follow-up evaluation upon arrival in the US. In the northeast, one study in Connecticut found that 4% of refugees with prior history of disease and presented for TB evaluation on arrival had active disease when reexamined in the US.[9] While the country of origin or emigration for refugees differ in each state, these data suggest that despite screening requirements, a significant number of individuals arrive in the US with active TB disease. Consequently, people who have regular close contact with the refugee community are at higher risk for TB exposure, including US-born children of refugees.

Here we describe a case of TB meningitis in a US-born child of refugee parents after a delay in diagnosis. We will highlight the importance of having a higher index of suspicion for TB in US-born children with TB symptoms and with immigrant parents from TB-endemic areas, especially in families with ongoing exposure to individuals from the immigrant community. Furthermore, we will demonstrate how a delay in diagnosis can increase the morbidity (and potentially mortality) of the disease in the pediatric population.

CASE REPORT

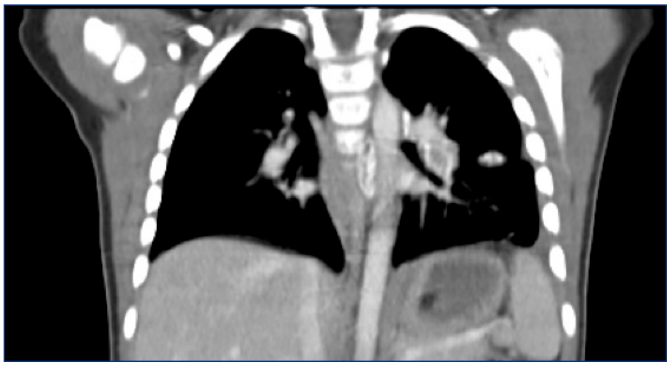
A 2-year-old girl initially presented to her outpatient primary care physician (PCP) after developing a fever to 102.3°F, ear pain and intermittent nonproductive cough. She was the US-born child of Liberian immigrant parents who had arrived in the US 20 years prior to her birth. Both parents were known to have positive PPDs (purified protein derivative) but negative chest x-rays (CXR), and the child had no history of travel outside of the US. Caregivers initially made a diagnosis of pneumonia and sent her home with a 5-day course of azithromycin. When symptoms did not improve, she was brought to the local emergency department (ED) where a further work-up for pneumonia was started. On CXR, she was noted to have a left pleural effusion. She was hospitalized for 7 days during which she underwent a video-assisted thorascopic surgery (VATS) with a left-sided chest tube and a course of ceftriaxone. Bacterial cultures, including acid-fast bacilli (AFB) used to detect TB, were performed and results returned as negative. Adenosine deaminase (ADA) levels and pleural biopsies that can be helpful in detecting TB pulmonary infections were not performed. After completing her course of antibiotics, the patient's fever persisted, and she was brought back to the PCP and ED for further evaluation. A subsequent CXR showed a resolution of the previous pleural effusion, and additional testing including a complete blood count, viral titers for infectious mononucleosis, lead levels and urinalysis were normal. Erythema was noted around the former chest tube site, and the patient was given cefdinir to treat cellulitis.

After an additional 3 weeks of fever, the patient's mother noted signs consistent with new left-sided neurological deficits, including left upper and lower extremity weakness. When the patient returned to the ED for work-up, she was afebrile and all vital signs were stable. On physical exam, she had an abnormal gait with repeated falling to her left side. She had no meningismus, and her lung, cardiovascular and abdominal exams were normal. Other than her gait, the neurological exam was documented to be normal, including no evidence of diminished strength in the upper or lower extremities. Labs showed that the patient had an elevated white blood count with no bandemia. The respiratory viral panel which included testing for respiratory syncytial virus, influenza A and B, metapneumovirus, rhinovirus, enterovirus, adenovirus, parainfluenza and coronavirus was negative. She had a computed tomography (CT) scan of the chest, abdomen and pelvis. Scans of the chest revealed multiple calcified lymph nodes consistent with a prior TB infection (**Figure 1**). The images were otherwise normal, and there was no evidence of active lung infection.

She was admitted for further work-up and evaluation. Overnight, she became increasingly lethargic and less responsive and was transferred to the pediatric intensive care unit (PICU). A CT scan of the head showed ventriculomegaly involving the lateral, third and fourth ventricles (**Figure 2**). A magnetic resonance image (MRI) of the brain revealed basilar meningeal enhancement as well as acute infarcts involving the corpus callosum and bilateral basal ganglia (**Figure 3**). Later that same day, her PPD was read as positive with a 15 mm induration. In the context of these findings, her imaging was highly suggestive of TB meningitis.

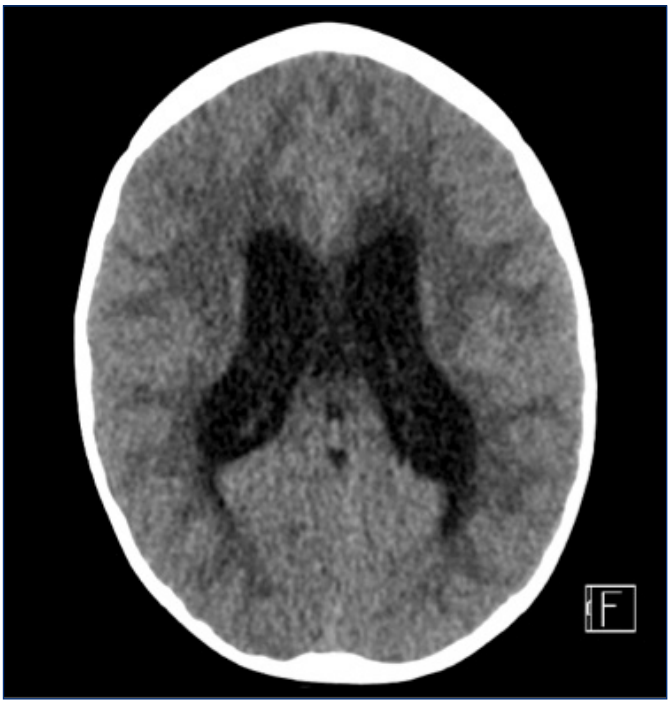
Lumbar puncture and cerebrospinal fluid (CSF) analysis showed an increased white cell count of 233 with a lymphocytic predominance, elevated protein to 103 mg/100mL (normal between 15-60 mg/100mL) and a decrease of glucose to 20 mg /100mL (normal between 50-80 mg/100mL). CSF polymerase chain reaction (PCR) was additionally performed for enterovirus and herpes simplex 1 and 2 that were all subsequently negative. Quantiferon gold blood test was

Figure 1. Calcified Lymph Nodes with Left Lung Focus on CT Chest



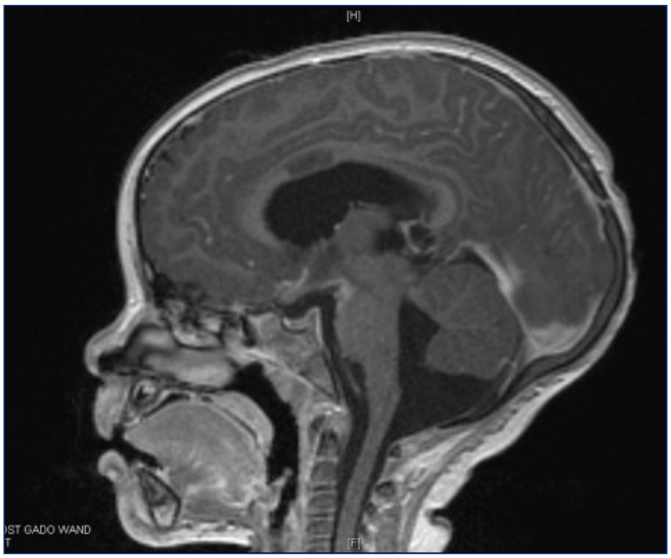
Computed tomography of the chest with IV contrast showing multiple calcified lymph nodes and left lung focus that is consistent with prior tuberculosis infection

Figure 2. Ventriculomegaly Seen on CT Head



CT head demonstrating moderate dilation of the ventricles

Figure 3. Meningeal Enhancement in the Sylvian Cisterns on MRI Brain



MRI showing patchy basilar meningeal enhancement extending to the sylvian cisterns, enhancement of the cranial nerves and acute infarcts along the genu of the corpus callosum and basal ganglia

sent as an additional test to support the diagnosis of TB and ultimately yielded a positive result. AFB cultures for blood, urine and CSF did not grow any bacteria.

Initially, the patient's diagnosis remained elusive because tuberculosis was not high on the care team's differential. Her fevers persisted through several trials of antibiotics prior to intiating her TB treatment. She had an extensive work-up for a broad range of viral and bacterial causes of her infection; all were negative except for mildly elevated Mycoplasma titers, thought to be an incidental finding. Given her pleural effusions, brain imaging findings, CSF analysis, PPD positivity and QuantiFERON-TB Gold test results, the patient's symptoms were attributed to TB meningitis. Her excellent response to treatment further supported the presumed diagnosis of TB meningitis.

She was started on a four-drug regimen of isoniazid, rifampin, ethambutol and pyrazinamide for a 12-month course of directly observed therapy (DOT). One year after discharge from the hospital, her symptoms have resolved and she has no neurological deficits. She has completed her treatment and has returned to her usual state of health. She was assessed to be a clinical case of tuberculosis based on evidence of exposure, a consistent clinical syndrome, and response to antituberculous therapy. To this day, the source case has not been identified.

DISCUSSION

This case of TB meningitis demonstrates the importance of increased suspicion for TB in patients living in immigrant and refugee communities in RI, regardless of whether the patient is US- or foreign-born. Delayed diagnosis can result in significant morbidity (and potentially mortaility), including further spread of TB. A recent study of US children younger than 5 with symptomatic TB infection found that it took a median of 52 days to initiate TB therapy.[10] Clearly, a higher degree of suspicion is needed. RI continues to welcome refugees who often live with multiple family members and have contact with close-knit communities from their countries of origin, allowing for the possibility of transmission despite efforts to screen and treat new immigrants.

The large majority of cases of active TB among pediatric patients in the US occur in children who are either foreign-born or in close contact with individuals from a TB-endemic country. In a study by Winston et. al. evaluating the demographics of pediatric TB cases in the US betweeen 2008–2010, the authors found that 69% of cases occurred in US-born children, but that 66% of these US-born children with active TB had at least one foreign-born parent.[11] Children younger than 5 represent a particuarly vulnerable population because they are more likely to progress to active disease and are more likely to develop severe manifestations of TB disease, such as TB meningitis. In an observational study by the Tuberculosis Epidemiologic Studies Consortium from 2005–2007, the majority (53%) of cases of active TB in young children younger than 5 in the US were reported among US-born children with at least one foreign-born parent. In contrast, foreign-born children represented only 17% of cases.[10] This study also examined the reasons for seeking healthcare that led to the diagnosis of active TB. Among US-born children younger than 5 with active TB, only 40% were evaluated and diagnosed due to contact investigations or known TB exposures. The remainder of the children were diagnosed either by routine screening (14%) or because they were symptomatic (46%). While young children should be prioritized during contact investigations of active TB cases, these data suggest that tracing of contacts alone is likely not sufficient to catch all active TB disease in young children in the US.

A child's parents' status as refugees or immigrants from TB-endemic countries should be added as additional risk factors when considering testing for TB in pediatric patients with TB-related symptoms. Despite TB screening policies in place before and upon entering the US, not all individuals with TB are appropriately identified or completely treated. A constant influx of new immigrants as well as contact with family members visiting from TB-endemic countries may also increase a patient's TB risk. Clinicians should have a higher index of suspicion for TB in US-born children living in refugee and immigrant communities from TB endemic countries.

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Conflicts of Interest

None of the authors have any conflicts of interest or financial disclosures to report.

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Monitored Viral Load: A Measure of HIV Treatment Outcomes in an Outpatient Setting in Rhode Island

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ABSTRACT

Community viral load measurements have been postulated to be a population-based biomarker of HIV disease. We propose the use of the monitored community viral load (mCVL) as an aggregate measure of viral load among persons receiving HIV care with available HIV-1 plasma viral loads and applied it to our clinic population from 2003-2010. We demonstrated a reduction in mCVL from 16,589 copies/ml to 11,992 copies/ml that correlated with a rising rate of antiretroviral use and HIV viral suppression; however, differences among risk populations were observed. The mCVL is a useful measure of HIV burden among patients in-care; it may reflect the HIV transmission risk in the community and help target preventive interventions.

KEYWORDS: Community viral load, HIV, Rhode Island, Antiretroviral therapy

INTRODUCTION

Antiretroviral therapy (ART) effectively suppresses HIV-1 RNA concentrations in blood and other body fluids, hence decreasing the risk of HIV infectivity.[1,2] Based on this principle, universal HIV testing and early antiretroviral therapy has been advocated as a strategy to lower HIV incidence. Clinical evidence and mathematical models support the use of ART to control HIV transmission risk at an individual and population level.[3, 4]

The concept of community viral load (CVL), defined as the mean or total HIV-1 plasma viral load (PVL) of infected individuals in a given geographic area or population, has been postulated as a useful population-based measure of the effect of treatment on HIV transmission and supported by ecological evidence.[5, 6-8] As a result, the Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention (CDC) has proposed the use of CVL as a tool to monitor the progress of the National HIV/AIDS Strategy goals and released guidelines to standardize definitions and calculations in 2011.[9, 10] Nonetheless, CVL measurements must include PVLs from all HIV-infected persons, including those who are not engaged in care, in order to accurately assess the population's aggregate viremia. We propose the use of the "monitored community viral load" (mCVL) instead, an estimate that includes patients in care with available PVLs, to examine HIV transmission drivers and quality of HIV care in a community-based outpatient practice.[10]

METHODS

This is a retrospective analysis of clinical and demographic data collected from a longitudinal electronic database of all HIV-infected individuals receiving care at the Miriam Hospital Immunology Center, the largest HIV care provider in RI, with approximately 1,500 active patients in 2012.[11, 12] We determined the proportion of patients on ART with undetectable HIV-1 plasma viral load (PVL), with CD4 cell counts below 200 and ≥ 350 cells/uL (based on the last available CD4 cell count each year), and the proportion retained in care between January 1, 2003 and December 31, 2010. ART use was defined as documentation of prescribed ART in at least one clinic visit in any given year. Given variability in the level of detection among viral load assays used over time, an undetectable PVL was defined as < 75 copies/ml. Patients who attended at least 1 clinic visit with a medical provider within each 6-month period in a given year separated by ≥ 60 days were considered retained in care.

Based on the CDC guidance, mean and median mCVLs were calculated using detectable and undetectable PVL values among patients in-care.[10] To be included in this analysis, patients must have had at least one PVL value recorded in a given year during the study period. Calculations were compared using three different PVL summary measures: 1) the mean of all available individual PVLs for each calendar year; 2) the aggregate mean of the annual mean PVL for each individual; and 3) the mean of the last available PVL for each individual per calendar year. The latter was used to assess changes in mCVL among patients stratified by HIV risk factor and to assess trends over time.

We summarized the demographics and clinical characteristics such as gender, age, race/ethnicity, HIV risk factor, proportion on ART, CD4 counts ≥ 350 cells/uL, retention in-care rates, and mCVL for the total sample from 2003 to 2010 using means (standard deviation) for continuous data and absolute numbers (percentages) for categorical variables. Ordinary Least Square linear regression models were used to assess time trends treating years as an independent variable. A regression coefficient estimated the changes over time; each series was analyzed independently. All data analysis was

conducted using Statistical Analysis Software (SAS) version 9.1 (Cary, NC), double sided p-values and a threshold for statistical significance set at < 0.05.

RESULTS

A total of 1959 unique HIV-infected patients received care at our center during the study period. As shown in Table 1, the number of active patients in-care increased from 922 in 2003 to 1,383 in 2010, particularly men who have sex with men (MSM) as reflected by the regression coefficient ($p < 0.01$). Over the time period, the clinic population was predominantly Caucasian, non-Hispanic males, between 25-64 years of age. MSM and heterosexual contact were the most common HIV risk factors recorded. Eighty-five to 95% of patients had at least one PVL in a given year from 2003 to 2010.

The proportion of patients receiving ART increased from 67% to 86% by the end of the study ($p < 0.01$). This finding correlates with a 22% increase in the proportion of patients with undetectable viral loads ($p < 0.01$) and a 12% rise in the proportion with CD4 counts ≥ 350 cells/uL ($p < 0.01$) over the 8-year period (Figure 1). The clinic population retention in-care rate remained stable, ranging from 61% to 68%, with similar trends observed across risk groups (Table 1).

We calculated the mCVL using the three calculation methods described and found there was a decrease in mCVL

Table 1. Demographic and Clinical Characteristics of Clinic Patients Over Time.

Year	2003	2004	2005	2006	2007	2008	2009	2010	R Coefficient (SD, P value)*
Total Active Patients, n	922	951	985	1064	1135	1204	1315	1383	
Patients entering care[1], n (%)	118 (12.7)	187 (19.6)	124 (12.5)	166 (15.6)	128 (11.2)	154 (12.7)	185 (14)	166 (12)	
New HIV diagnosis[2], n (%)	47 (5)	110 (11.5)	64 (6.5)	84 (7.9)	76 (6.7)	87 (7.2)	98 (7.4)	70 (5)	
Gender, n (%)									
Male	594 (64.4)	602 (63.3)	624 (63.4)	694 (65.2)	759 (66.9)	806 (66.9)	884 (67.2)	952 (68.8)	54 (4.1,< 0.01)
Female	325 (35.2)	348 (36.6)	360 (36.5)	370 (34.8)	376 (33.1)	398 (33.1)	431 (32.8)	430 (31.1)	15 (1.3,< 0.01)
Transgender	3 (0.3)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0	0	1 (0.1)	
Age, n (%)									
16–24 years	34 (3.7)	46 (4.8)	39 (3.9)	28 (2.6)	34 (3.0)	32 (2.7)	42 (3.2)	47 (3.4)	
25–44 years	539 (58.5)	567 (59.6)	503 (51.1)	526 (49.4)	536 (47.2)	545 (45.3)	557 (42.4)	555 (40.1)	---
45–64 years	343 (37.2)	336 (35.3)	437 (44.4)	502 (47.2)	549 (48.4)	601 (49.9)	683 (51.9)	741 (53.6)	
≥ 65 years	6 (0.7)	2 (0.2)	6 (0.6)	8 (0.8)	16 (1.4)	26 (2.2)	33 (2.5)	40 (2.9)	
Race, n (%)									
Caucasian	460 (49.9)	509 (53.5)	542 (55)	599 (56.3)	646 (56.9)	691 (57.4)	743 (56.5)	795 (57.5)	
AA	297 (32.2)	308 (32.4)	324 (32.9)	347 (32.6)	369 (32.5)	383 (31.8)	432 (32.9)	451 (32.6)	---
Others	165 (17.9)	134 (14.1)	119 (12.1)	118 (11.1)	120 (10.6)	130 (10.8)	140 (10.6)	137 (9.9)	
Ethnicity, n (%)									
Hispanic	182 (19.8)	183 (19.2)	197 (20)	214 (20.1)	235 (20.7)	261(21.7)	296 (22.5)	314 (22.7)	20 (1.8, <0.01)
Non- Hispanic	740 (80.2)	768 (80.8)	788 (80)	850 (79.9)	900 (79.3)	943 (78.3)	1019(77.5)	1069 (77.3)	49 (2.8, <0.01)
HIV Risk Factor[3], n (%)									
MSM	272 (29.5)	292 (30.7)	303 (30.8)	359 (33.7)	400 (35.2)	429 (35.6)	469 (35.7)	541 (39.1)	38 (2.7, <0.01)
Non-MSM	650 (70.5)	659(69.3)	682 (69.2)	705 (66.3)	735 (64.8)	775 (64.4)	846 (64.3)	842 (60.9)	31 (2.9, <0.01)
Retained in care[4], n (%)	575 (62)	580 (61)	663 (67)	731 (69)	767 (67)	809 (67)	867 (66)	937 (68)	53 (2.6, <0.01)
% on ART[5]	67	74	77	79	80	81	82	86	2 (0.32, <0.01)
% Undetectable PVL[6]	48	48	52	58	60	67	67	70	3.5 (0.3, <0.01)
% CD4 ≥ 350 cell/uL[7]	61.7	57.9	60.5	65.8	62.2	68.7	69.7	73.5	1.9 (0.4, <0.01)

[1] Includes all newly diagnosed registered to receive care in the clinic, patients transferring care from another provider, and patients who were reactivated into care.

[2] Includes patients who registered to received care in the clinic and were diagnosed with HIV within the previous 12 months.

[3] Based on patients self-reports during their intake interviews.

[4] Includes patients that attended to at least 2 medical visits with a medical provider separated by ≥ 60 days in a year.

[5] Documented prescribed ART in at least one clinic visit in any given year.

[6] < 75 copies/ml.

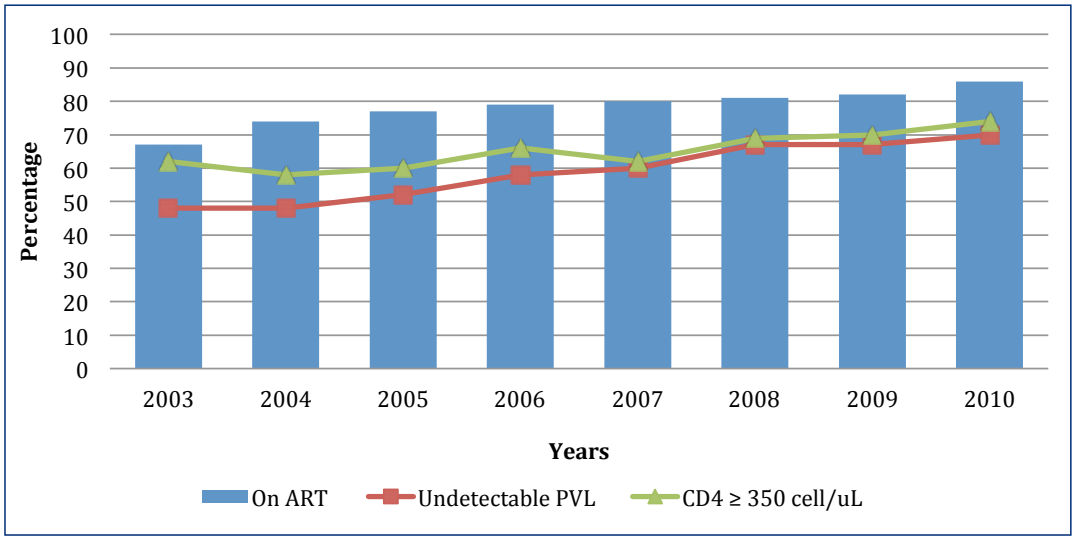
[7] Based on the last available CD4 cell count in each year.

* Regression coefficient, P value by ordinary linear regression

Abbreviations: AA, African American; SD, standard deviation, ART, antiretroviral therapy; PVL, HIV-1 RNA viral load

over time using each calculation method (Table 2). Using the aggregate mean of the last available PVL for each calendar year per individual, we observed decline in the mCVL from 16,589 copies/ml in 2003 to 11,992 copies/ml in 2010 ($p = 0.07$) as shown in Table 3. When looking at the mCVL among risk groups over the time period, there was a significant reduction in mCVL over the time period among MSM ($p = 0.035$) but not among other risk groups ($p = 0.14$).

Figure 1. Percentage of clinic patients on ART, with undetectable PVL and CD4 cell count ≥ 350 cells/uL over study period (2003-2010).



Abbreviations: ART, antiretroviral therapy; PVL, HIV-1 plasma viral load.

Table 2. Comparison of Monitored Community Viral Load Calculation Methods.

mCVL Calculation Methods	2003	2004	2005	2006	2007	2008	2009	2010	Mean (SD)*	R Coefficient (SD, P Value)**
Method #1[1]	24,244	27,195	22,483	24,166	20,986	18,031	15,510	16,012	21,078 (4,224)	-1578 (283.6, <0.01)
Method #2[2]	20,841	25,983	21,001	23,782	22,573	18,019	15,899	15,205	20,412 (3,795)	-1191 (404.6, 0.03)
Method #3[3]	16,589	20,511	16,508	17,493	20,923	14,163	11,254	11,992	16,179 (3,568)	-977 (441.1, 0.07)

[1] Mean of all available individual PVLs for each calendar year.
[2] Aggregate mean of the annual mean PVL for each individual.
[3] Mean of the last available PVL for each calendar year per individual.
* Across years.
** Regression coefficient, P value by ordinary linear regression.
Abbreviations: mCVL, Monitored community viral load; SD, standard deviation.

Table 3. Monitored Viral Load Over Time by HIV Risk Factor.

Year	2003	2004	2005	2006	2007	2008	2009	2010	RCoefficient* (SD, P value)
Mean mCVL[1]	16,589	20,511	16,508	17,493	20,923	14,163	11,254	11,992	- 977.0 (441.1, 0.07)
MSM (SD)	16,139 (51,766)	20,946 (61,058)	20,197 (63,342)	20,052 (70,941)	19,151 (73,021)	13,733 (53,485)	11,565 (40,001)	11,176 (67,742)	-1217 (450.6, 0.035)
Non-MSM (SD)	16,770 (55,658)	20,323 (60,806)	14,867 (54,846)	16,150 (59,687)	21,888 (182,023)	14,407 (59,016)	11,074 (51,844)	12,507 (94,389)	- 848.9 (503.6, 0.14)

[1] Using the last available PVL for each calendar year per individual.
[2] MSM – Non-MSM.
* Regression Coefficient, P value by ordinary linear regression.
Abbreviations: mCVL monitored community viral load; MSM, men who have sex with men; Non-MSM, all other risk factors.

DISCUSSION

The demographics and risk factor characteristics of our HIV population is comparable to the surveillance profile of RI's HIV/AIDS epidemic; the majority of cases occurring among white MSM with a decreasing proportion of IDU.[13] We detected a significant increase in ART use that correlated with improvement in HIV viral suppression rates and immune status among patients receiving care at our center between 2003 and 2010. Similar results have been reported in other large urban clinic settings nationwide.[14, 15] These findings likely reflect the effectiveness of widespread and earlier implementation of ART in response to national treatment guidelines.[16]

The increased proportion of patients on ART and those who achieved a suppressed HIV-1 viral load resulted in a concurrent downtrend of the mCVL over time. The decline of mCVL provides additional insight into the quality of our HIV care and implies a decrease in the HIV transmission potential of the clinic population and possibly at a broader community level.[17, 18] Several studies have shown an association between a decrease in the CVL and a reduction in new HIV infections in populations such as San Francisco and British Columbia.[6-8] Although our results are derived from a single center and are not necessarily generalizable to the entire state, there was a concurrent decline in the number of new HIV diagnoses reported to the RI Department of Health during this time period (178 new diagnoses in 2004 to 106 new diagnoses in 2010) raising the possibility that improved HIV viral control among our clinic population correlates with a reduction in new HIV diagnoses statewide.[13]

CVL has been used as a public health monitoring tool of the HIV epidemic.[5, 9] We believe the mCVL is particularly useful as a research and surveillance tool of community-level interventions that can be easily implemented in HIV care centers. It is methodologically feasible, reproducible, and is less affected by incomplete data. Nonetheless, we recognize that interpretation of the mCVL has several limitations as it excludes persons with undiagnosed HIV, those who are not engaged in care, and those who are engaged in care but do not have available PVL test results. As an ecological measure, population level observations can be mistakenly interpreted to reflect outcomes of individuals in that population.[18, 19] In addition, CVL calculations usually use one viral load value from each patient collected during a given calendar year but most patients in care will have several viral load measures and the selection of a single value could affect the accuracy of the result. For this reason, we compared three different mCVL calculation methods including multiple viral load values available for each patient per year and found a uniform decline of the mean mCVL over time using all three methods. It is evident that using the mean of the last available PVL for each calendar year per individual resulted in the lowest mCVL mean and standard deviation value and appears to be comparable to calculations used in other studies.[7, 8, 17]

While the downward trend of our mCVL reflects the remarkable impact of increased ART implementation and uptake in this urban HIV-infected population, there is a concern for persistent high disease burden among certain risk populations such as IDU, heterosexuals, and among persons classified as having "other" risk factors. HIV treatment as a prevention strategy can only be successful if all of the sequential steps of the HIV treatment cascade (HIV diagnosis, linkage to care, retention in care, ART receipt, and viral suppression) are optimized.[20, 21] Further research is needed to explore HIV treatment and retention in care among non-MSM persons in RI, given we did not observe a significant decline in mCVL over time among these risk groups. Despite MSM being the predominant risk factor among newly diagnosed HIV cases in RI, we observed a downtrend of the mCVL among MSM receiving care at our center.[13] A possible explanation for this discrepancy is that there could be a substantial population of undiagnosed HIV positive MSM in the community, or MSM who are aware of their HIV infection yet who are not engaged in care, who are contributing to ongoing HIV transmission in RI.

In summary, increased use of ART and the subsequent HIV viral suppression correlated with a decrease in the mCVL in our patient population. The mCVL is a useful indicator of clinical HIV care within a population engaged in treatment and may be helpful in estimating the infectiousness of a population receiving HIV care.

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Addressing the Increasing Burden of Sexually Transmitted Infections in Rhode Island

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ABSTRACT

The rates of sexually transmitted infections (STI) including chlamydia, gonorrhea, and syphilis, are increasing across the United States, including in Rhode Island (RI). These STIs affect many otherwise healthy adolescents and young adults, and represent a significant source of morbidity. The Centers for Disease Control and Prevention encourages states to develop strategies for addressing increasing STI rates in the setting of diminishing public health resources. The RI Department of Health (DOH) works with providers and funded community- based organizations to promote STI screening, expedited partner therapy, and partner services to reduce STI rates. The Miriam Hospital Immunology Center opened a public HIV/STI Clinic, which offers free and confidential testing for HIV, viral hepatitis, chlamydia, gonorrhea, and syphilis, as well as post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) services to prevent HIV. In collaboration with the RI DOH, the Clinic serves as a referral source across the state for complicated STI cases.

KEYWORDS: HIV, PREP, PEP, STI

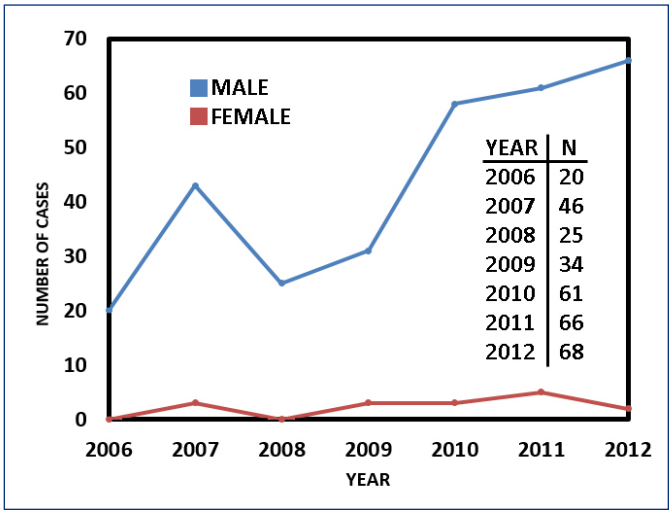
BACKGROUND

Sexually transmitted infections (STIs) are caused by a variety of pathogens that are acquired through sexual activity. Despite numerous public health interventions, the rates of STIs such as chlamydia, gonorrhea, and syphilis continue to increase across the United States (US). The most commonly reported STI is chlamydia. In 2012, there were 1.4 million cases reported to the Centers for Disease Control (CDC) which is the largest number of cases reported for any disease.[1] During the time period 2008-2012, there was a 25% and 11% increase in the chlamydia rate among men and women, respectively. Similarly, rates of gonorrhea have increased 9.6% since 2009. Gonorrhea and chlamydia are highest among individuals 15-24 years old. A resurgence in syphilis has also occurred in the last decade with an 11.1% increased rate from 2011 to 2012. These STIs account for $16 billion in medical costs in the US population.[2]

Chlamydia, gonorrhea, and syphilis infections have increased significantly in Rhode Island (RI) the past few years.[3] The majority of individuals who test positive for STIs reside in Providence County (78% of chlamydia, 87% of gonorrhea, 81% of syphilis). These STIs affect individuals across all age groups, genders, sexual orientations, and socioeconomic levels. However, certain groups of people are disproportionately affected by STIs. The two most common reportable STIs in RI are chlamydia and gonorrhea, caused by *Chlamydia trachomatis* and *Neisseria gonorrhea*, respectively. Both are transmitted through oral, vaginal, and anal sex with symptoms ranging from none to urethritis characterized by dysuria and penile/vaginal discharge. Serious complications include infertility, pelvic inflammatory disease, and ectopic pregnancy. Chlamydia is by far the most common STI in RI. In 2010, 3,840 cases of chlamydia were reported in RI. In 2012, there was a 12% increase with 4,313 new cases statewide. Just under three-fourths of new chlamydia cases were reported in females, likely due to higher STI screening rates in this group. Additionally, the majority of new chlamydia cases occur in younger individuals, aged 15-24 years old, highlighting the importance of early education and intervention during these years. The CDC recommends annual chlamydia screening for all females under the age of 26 years old. Similar to chlamydia, rates of gonorrhea have increased in RI over the last few years. In 2010 and 2012, 291 and 507 cases of gonorrhea were reported, respectively, representing a 57% increase. The majority of gonorrhea cases were in males (54%) and younger age groups 15-29 years old. In contrast to chlamydia, gonorrhea is more common among males and disproportionately impacts gay, bisexual, and men who have sex with men (MSM). In 2012, 32% of gonorrhea cases were diagnosed in MSM. In 2012, due to increasing resistance observed in *Neisseria gonorrhoeae* isolates,[4] the CDC recommended injectable ceftriaxone in combination with either azithromycin or doxycycline[5] to treat uncomplicated gonorrhea. Oral Cefixime or other single combination regimens are no longer recommended due to increasing resistance.

Syphilis is caused by the spirochete *Treponema Pallidum* and can lead to a diverse spectrum of symptoms including progressive neurological and cardiovascular disease. *Treponema Pallidum* remains highly sensitive to penicillin, the treatment of choice. In 2006, the CDC launched a highly ambitious national campaign to eliminate syphilis from the US. Unfortunately, rates of syphilis have risen drastically since that time. In 2012, the Rhode Island Department of Health (RIDOH) reported 68 cases of infectious syphilis, a

Figure 1. The number of infectious syphilis cases in Rhode Island, 2006–2012. The number of cases increased 300% over the time period. The majority of cases were among males.
(Source: Rhode Island Department of Health Surveillance)



300% increase from 2006 (20 cases, **Figure 1**).[3] This trend is observed across the country. In contrast to chlamydia and gonorrhea that affect both heterosexuals and MSM, syphilis tends to affect mainly MSM. Syphilis infection is classically divided into disease stages, including primary and secondary stages, considered "infectious," and the latent and tertiary stages. In 2012, the majority of infectious syphilis cases in RI were among males (97%), of which 94% were MSM. Of MSM with infectious syphilis, 52% were also HIV-positive. The high rate of syphilis and HIV coinfection likely results from behavioral practices including unprotected oral sex and "serosorting," or limiting sex to partners with the same HIV status. Due to the low risk of HIV transmission through oral sex, condoms are often not used for oral sex. Although the risk of HIV transmission from oral sex is low, transmission rates for syphilis may approach 30% per episode of oral sex.[6] Furthermore, serosorting to have unprotected sex in the MSM population likely leads to increased syphilis and other STIs. Although the total number of new HIV diagnoses has slightly decreased over the past five years, MSM populations continue to experience a disproportionately high burden of new HIV infections.[3]

For all STIs including HIV, gonorrhea, chlamydia, and syphilis, race and ethnicity is a key demographic factor in determining risk. Across the board, racial and ethnic minorities present with a higher incidence of STIs than their white counterparts. Complex social and structural factors contribute to the racial and ethnic STI disparities in in RI, including limited access to testing and treatment services and dense sexual networks. Perhaps most notably, the majority of new STIs are concentrated within a few select census tracts in Providence. These geographic and racial disparities suggest that greater efforts are needed to address heavily impacted communities in culturally competent ways.

PUBLIC HEALTH RESPONSE IN RHODE ISLAND

Federal and state funding for STI has decreased in RI and throughout the US due to diminishing public health resources while social media and geo-location apps promulgate more anonymous sexual encounters in high-risk populations such as MSM, adolescents, and young adults. Health departments are encouraged to implement strategies that focus on strengthening collaborative relationships in order to meet the increased STI demands stretching each jurisdiction's capacity. Within the Division of Infectious Diseases and Epidemiology at the RIDOH, the STI and HIV program have joined forces to integrate public health activities as the new combined Office of HIV/AIDS, Viral Hepatitis, STIs, and TB. To reflect the CDC priority for Program Collaboration and Service Integration (PCSI), community agencies in RI receive funding to provide comprehensive STI, HIV, and viral hepatitis testing and linkage to care for all patients. Partner services are strengthened through collaboration with clinical providers such as The Miriam Hospital HIV/STI Clinic and Planned Parenthood who service the most at-risk patients. In addition, academic detailing visits to primary care providers are used to promote STI prevention and care-specific messages such as syphilis screening among MSM, expedited partner therapy, and multidrug resistant gonorrhea.

THE MIRIAM HOSPITAL IMMUNOLOGY CENTER HIV/STI CLINIC

On June 30, 2011, Whitmarsh Clinic, the only public STI clinic in RI, closed due to state budget cuts. The clinic was located on the West side of Providence and had been offering accessible screening and treatment services for STIs. After Whitmarsh Clinic closed, there were no clinics in the state which provided safety net testing and treatment for STIs. To address this public health gap amid increasing rates of STIs, The Miriam Hospital Immunology Center opened a clinic in January 2012 offering free HIV and syphilis testing on a walk-in basis during Friday afternoons. The Clinic is under the direction of Dr. Philip A. Chan with support from the Division of Infectious Diseases. R. Bobby Ducharme, with over a decade of experience in HIV/STI prevention, manages the clinic.

The Clinic immediately became an important site for those in RI with undiagnosed and untreated syphilis. During the first year, the overall syphilis positivity rate was approximately 15%. With support from Dr. Kimberle Chapin (Department of Pathology), The Miriam Hospital agreed to provide financial coverage for STI testing at the Clinic, as a commitment to public health. As of January 1, 2013, the Clinic has expanded hours and is currently open Wednesday, Thursday, and Friday from 12:30–3:30 p.m. The Clinic currently works closely with the RIDOH as a referral center for partner notification and contact tracing services, and to provide education and support services to other clinics and medical providers in the state.

Figure 2. Services offered by The Miriam Hospital HIV/STI Clinic.

- Comprehensive testing and treatment for sexually transmitted infections including HIV, viral hepatitis, syphilis, gonorrhea, and chlamydia.
- Free services for individuals who are uninsured or underinsured.
- Walk-in hours, no appointments required.
- Personalized education and counseling services.
- Free condoms.
- Referral services for complicated cases of sexually transmitted infections.
- Expedited partner therapy.
- Partner notification through the Rhode Island Department of Health.
- Post-exposure prophylaxis (PEP) for sexual or other exposures to HIV.
- Pre-exposure prophylaxis (PrEP) for individuals at ongoing risk for HIV infection.

The Miriam Hospital Immunology Center HIV/STI Clinic provides free testing, treatment, and comprehensive counseling services for HIV, viral hepatitis, chlamydia, gonorrhea, and syphilis (**Figure 2**) to patients with or without health insurance. Clinic staff evaluate STIs such as herpes simplex virus, trichomoniasis, and others on a case-by-case basis. HIV and hepatitis C virus (HCV) testing are performed using rapid or serum antibody tests. For those with suspected acute HIV infection, viral loads are performed. Syphilis testing is performed via the standard CDC algorithm which involves nontreponemal testing (Rapid Plasma Reagin) followed by a confirmatory treponemal test (FTA-Abs). Gonorrhea and chlamydia are assessed by urine nucleic acid amplification testing (NAAT). For higher-risk individuals, pharyngeal and rectal NAAT testing is performed. Treatment and follow-up is arranged and provided for all patients.

BIOMEDICAL HIV PREVENTION INTERVENTIONS

Antiretrovirals (ARVs) are the cornerstone of HIV treatment. HIV -infected individuals who are diagnosed and treated early have a similar life expectancy to those who are HIV negative.[7] These medications have fewer side effects and are much simpler to take than previous regimens. Several single tablet regimens are now available. A landmark study demonstrated that HIV positive individuals who are on treatment and have an undetectable viral load are 96% less likely to transmit the virus to others.[8] This has led to increased efforts to diagnose and treat all those who are HIV positive. The Miriam Hospital Immunology Center has led aggressive retention and treatment programs for all individuals who are HIV positive.

ARVs are also now being used in HIV negative individuals to prevent HIV infection. Post-exposure prophylaxis (PEP) has long been used in the medical field after an occupational exposure to HIV.[9] Individuals with a non-occupational exposure (i.e. sex) can also take PEP within 72 hours of exposure to prevent HIV. The Clinic supports a PEP program to which individuals can be urgently referred to and seen same-day. The Clinic follows standard CDC guidelines for the administration and monitoring of PEP.[9] The US Food and Drug Administration also recently approved as the drug combination tenofovir/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP). PrEP is a single pill that HIV-negative individuals can take daily to prevent HIV infection.[10] TDF/FTC is safe and very effective when taken every day. PrEP is an option for individuals who are at-risk of HIV. Given the higher numbers of HIV among gay, bisexual, and other MSM in RI, this population should consider PrEP depending on other sexual risk factors (i.e. unprotected sex, multiple partners). The Clinic has an ongoing PrEP program, among the first in the country, to which any patient may be referred to for counseling and consideration of PrEP, and the RIDOH is using it as a model to build a network of providers throughout the state with the capacity to offer PrEP.

COMMUNITY PARTNERS

Contact tracing to offer testing and referral services to partners of STI patients is a crucial component of addressing STI rates and requires close collaborations with the RIDOH, The Miriam Hospital HIV/STI Clinic, and other key RI providers and organizations. HIV, viral hepatitis, syphilis, gonorrhea, and chlamydia require mandatory reporting to the RIDOH. Surveillance data collected through reporting helps guide ongoing outreach efforts and testing programs in the state, such as AIDS Care Ocean State (ACOS), Project Weber, and AIDS Project Rhode Island (APRI). Partnership and communication with DOH occur at various levels (i.e. patient-level, community-level, and policy/administration) in order to effectively coordinate STI prevention and treatment services with key stakeholders throughout the state.

The Rhode Island Public Health Institute (RIPHI), under the direction of Dr. Amy Nunn, also supports the Clinic and community health in general with efforts to eliminate health disparities in the state. The institute partners with Brown University and the RIDOH to develop innovative public health community initiatives, research health policy, and to train students as well as public health officials and practitioners. More specifically, RIPHI disseminates information about HIV and other STIs, and spreads awareness about free testing and treatment services (www.DoItRIght.org).

CONCLUSION

STIs have significantly increased in RI over the last few years. The Miriam Hospital HIV/STI Clinic fills a critical need in the state to provide testing and treatment for STIs. Partnerships and collaborations across multiple sectors

are needed to effectively address the epidemic and reverse the increasing trends. More specifically, adolescents and younger adolescents who are most at-risk of gonorrhea and chlamydia need improved education and access to resources, especially in Providence where the majority of these cases are diagnosed. Increased education and awareness is also needed among gay, bisexual, and other MSM about HIV and syphilis, including newer strategies to prevent HIV such as PrEP. Only through ongoing and multifaceted efforts can STIs be effectively addressed in the state.

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Tick-Borne Illness In Rhode Island – How Big a Problem Is It?

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ABSTRACT

Rhode Island is a state with a high incidence of tick-borne diseases, specifically Lyme disease. The *Ioxedes* tick which serves as vector for the three most common tick infections is endemic in both the New England and mid-Atlantic regions. However, differences in the density of infections exist within Rhode Island (RI), with the highest densities in the southern counties. Tick-borne diseases can have varying presentations, as well as varied response to appropriate treatment leading to many questions and confusion for patients, clinicians, and the public itself.

KEYWORDS: tick-borne illness, Lyme disease, TBDs, anaplasmosis, babesiosis

INTRODUCTION

In the United States, tick-borne diseases (TBDs), including borrelioses (Lyme), anaplasmosis, and babesiosis, are on the rise.[1] The three mentioned are significant causes of disease in the New England region including in RI. The reasons for this increase are multifactorial, including changes in the deer and mice population and the movements of humans into areas heavily populated by both host animals and the tick vectors.[2] All three of these TBDs are transmitted by the same vector in our region, the hard bodied *Ioxedes scapularis* tick, with infectivity concentrating in the summer months. Given the same vector for these infections, patients can be co-infected with more than one of these infections. Studies show an approximately 10% co-infection rate.[3,4] The clinical presentations of either of these diseases can vary among patients with many nonspecific acute symptoms such as fever, arthralgias, headache, and fatigue, to later presentations with arthritis, neurologic and other symptoms. Because of this, the diagnosis can be missed early on if TBDs are not considered. Of the three, Lyme disease is the most difficult to diagnose and treat appropriately given the different stages of presentation.

Early Lyme disease presents within the first 30 days from the tick bite and can be localized or disseminated. Localized presentation with the characteristic erythema migrans rash is the classic presentation. This is diagnosed clinically with supportive epidemiologic history as Lyme serology can be negative in this acute stage of infection. Early disseminated infection presents with objective findings of either arthritis, neurologic (e.g., cranial nerve palsy or meningitis), or carditis with heart block. These presentations are diagnosed by clinical findings, epidemiologic history and positive Lyme serology with two-tier testing of EIA and Western blot. Late Lyme disease most often presents with arthritis, or less common neurologic findings with encephalitis or neuropathy. This presentation occurs months to years after the tick bite. Diagnosis in this stage is most dependent on positive serology with both EIA and Western blot IgG. In terms of late neuroborreliosis, CSF analysis should be abnormal with a positive Lyme CSF index.[5] In addition to early and late Lyme stages, much debate has been around the post-Lyme disease syndrome or post-treatment Lyme disease syndrome (PTLDS). The clinical definition for post-Lyme disease syndrome is a clear objective history (i.e., positive serology) of prior Lyme infection and ongoing symptoms of joint pain, fatigue, or others after appropriate antibiotic treatment.[6] This can mimic many illnesses given its myriad of manifestations. Careful evaluation of the history of the illness, tick exposure, and consideration of concurrent disease is needed.

With the varying times and types of presentations for TBDs, diagnostic tests, specifically serology, are needed to aid in decision-making. However, the limitations of these tests can lead to varying interpretations of results by clinicians and to different treatment plans that, for the most part, are not strongly supported by evidence-based medicine. Research in the treatment of TBDs that do not fit the classic presentation is lacking, specifically in the late Lyme presentations. (**Table 1**) Without significant evidence-based

Table 1. Priorities for research on tick-borne disease

• Evaluation of current diagnostic tests
• Development of new diagnostic tests with better performance characteristics
• Evaluation of current treatment regimens for the different tick-borne diseases
• Characterization, diagnosis, and treatment of late Lyme disease
• Evaluation and treatment of post-treatment Lyme disease syndrome (PTLDS)
• Characterization of post-infectious inflammatory syndromes associated with Lyme disease
• Prevalence of novel or recently discovered tick-borne diseases (e.g. *borrelia miyamotoi)*

results, the guidelines for management of TBDs, particularly Lyme, are varied across different medical groups. This continues to add to the public's confusion of the management of Lyme disease and other TBDs and the frustration and suffering at the individual level of the patient. Adding to the many unknowns of TBDs and its higher prevalence in our region is the discovery of other infections being transmitted by these vectors. For example, in 2013 the first reported cases of *Borrelia miyamotoi* in the United States occurred in New England, including one case in RI, with presentation of relapsing fever and meningitis.[7,8]

Rhode Island and the Nation

Lyme disease (*Borrelia burgdorferi)* is the most common tick-borne infection reported in the US, with around 30,000 cases reported to the CDC annually. However, this is thought to be a significant underestimation of actual cases with the CDC reporting in August 2013 that the number of Lyme infection cases is approximately 300,000 nationwide.[9] This new estimation comes from the culmination of three ongoing studies that collects information from medical claims, clinical laboratories, and patient self-reporting, respectively. This ongoing effort to more accurately determine the burden of disease points to its importance among public health concerns.

Anaplasma (*Anaplasma phagocytophilum)* formerly known as *Ehrlichia phagocytophilum* is the second most common TBD reported in the US since its discovery in the 1990s. Over 10 years (2000 to 2010), the incidence rose from 1.4 cases per million to 6.1 cases per million. In 2010, a total of 1761 cases were reported.[10] The same hard bodied tick (*Ioxedes scapularis)* serves as the vector for anaplasma which explains the similar geographic distribution of anaplasma to Lyme. Babesia is less common with only 911 cases reported in 2012. Only 22 states conduct surveillance on babesia with the majority in the upper Midwest and the Northeast.[11] However, the majority of infected individuals have a brief febrile illness or nonspecific symptoms for which they do not seek medical attention, thus the true incidence of disease is unknown.

Regional Impact

The majority of Lyme disease cases are limited to the northeast and east coast of the US. In 2013, cases from New England made up 39% of the reported cases while the Mid-Atlantic comprised 34%. Rhode Island and its neighboring states continue to carry a significant burden of Lyme disease in the country. (**Table 2**) Within New England, the states reporting the highest number of Lyme disease cases in 2013 included Massachusetts (1319), Connecticut (840) and New Hampshire (396).[12] The incidence of Lyme disease in RI for 2012 was 12.1 (per 100,000), with higher incidence rates in nearby states: MA 51.1, CT 46.0, ME 66.6, and NH 75.9. There are 34 states that have an incidence of less than 2.0 for Lyme disease, highlighting the burden faced by this region of the country.[13] Anaplasmosis and babesiosis contribute to a number of TBD cases in the New England area as well. Nationwide, there were 1761 cases of anaplasma and 911 cases of babesia in 2012. Of the anaplasma cases, 90% occurred in six states: New York, Connecticut, New Jersey, Rhode Island, Minnesota, and Wisconsin. Similarly, babesia affected mostly New England states. The 911 cases reported in 2012 occurred in 14 states; however 96% of them occurred in seven states: NY, CT, NJ, RI, MN, WI, and MA. Given that babesia only recently became a notifiable disease in 2011, the total number of cases may be underreported in the New England region as well as other parts of the country. Both historical and current data show that a large number of cases of Lyme disease, anaplasmosis, and babesiosis were reported in New England, especially in Rhode Island's neighboring states. As such, Rhode Island has the potential for higher disease burden given its geographical location in the New England region.

Table 2. Incidence of Lyme disease by state and county in 2012.

	Incidence (per 100,000)
Connecticut	46.0
Maine	66.6
Massachusetts	51.1
New Hampshire	75.9
Rhode Island	12.1
Bristol County	*14.0*
Kent County	*16.9*
Newport County	*25.3*
Providence County	*13.7*
Washington County	*59.1*

Within RI

There is a high variation among the different counties in RI. (**Table 2**) So though overall, the state reports a higher incidence of Lyme, as well as other TBDs, certain counties have a higher density of infection that drives the statewide incidence above the national averages. Lyme infections are the most often reported TBD in RI, with 217 cases reported in 2012. This is an incidence of 20 per 100,000 people. The demographics of those infected show two age peaks among the population: ages 5 – 9 and ages 50+. There is a seasonality effect of overwhelming majority occurring in June and July, correlating with the summer months and increased activity of both tick vectors and people. The raw total number of cases shows Providence County to be most affected with 86 cases in 2012, followed by 75 cases in Washington, and 28 and 21 cases in Kent and Newport counties. However the incidence rates show a significantly higher density of Lyme disease in Washington County: 59.1 (per 100,000) compared to Providence County: 13.7. Newport and Kent counties also had higher incidence rates of 25.3 and 16.9 respectively.[14]

The findings for both anaplasma (ehrlichia) and babesia are similar with higher density of infection in the southern counties of Washington and Kent. The statewide incidence of anaplasma is reported at 10.2 per 100,000 for 2012 with a raw total number of 107 cases. However, on the county level Washington has an incidence of 30.7 and Kent with a rate of 20.5, while Providence County had a much lower incidence at 4.6.[15] Reported babesia cases per county follow the same trend, with a statewide incidence of 5.3 per 100,000 in 2012, and Providence County with a lower rate of 1.4. Washington, Kent, and Newport counties have incidence rates of 23.6, 6.0 and 6.0, respectively.[16]

Review of the surveillance data available for the years 2010-2012 shows that overall there has been a rise in reported Lyme and anaplasma cases statewide, though much more heavily concentrated in the aforementioned counties. Contrary to this, reported cases of babesia have declined in this same time period. However, similar to the national CDC data, these are likely underestimations of true burden of disease given that it is only through passive surveillance that these numbers are collected. The trends that are seen in terms of increasing cases and higher density of infections in southern counties can help to inform the medical and lay community on the burden of TBDs here in RI, but the true weight of that burden is likely unknown at this time.

CONCLUSION

As described above, RI has a higher burden of tick-borne infections compared to the majority of the United States, though not as severe as its neighboring states. It is important to be aware of the magnitude of the burden of TBDs faced in this region which is compounded by the many questions unanswered with Lyme disease and other TBDs. The difficulty in diagnosis particularly in late-presentation cases, the varied response to appropriate treatment, as well as the ongoing symptoms in select patients despite treatment are just a few of the questions faced by clinicians and patients. TBDs are an important public health concern given the gaps in the knowledge of these diseases and their outcomes, and the high prevalence among our community.

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Outpatient Parenteral Antibiotic Therapy in an Academic Practice in Rhode Island

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ABSTRACT

Outpatient parenteral antimicrobial therapy (OPAT) is an increasingly utilized treatment modality that has been proven to be safe and cost effective for treating infections that require prolonged antimicrobial treatment. Adequate patient selection, a structured OPAT team with an effective communication system, and routine clinical monitoring are key elements to establish a successful OPAT program. The Miriam Hospital Infectious Diseases Clinic offers a multidisciplinary OPAT model coordinated by infectious diseases specialists and serves as a major referral center in Rhode Island.

KEYWORDS: OPAT, antibiotics, infection, Rhode Island

INTRODUCTION

Outpatient parenteral antimicrobial therapy (OPAT) refers to the administration of intravenous antimicrobials to patients who suffer from chronic infections that warrant parenteral therapy but these patients are otherwise stable enough to receive this therapy in an outpatient setting. Since its introduction in the 1970s, OPAT has been shown to be a safe, practical and cost-effective treatment modality.[1] In the United States, it is estimated that more than 250,000 Americans receive OPAT services every year.[2] OPAT helps to reduce healthcare costs by reducing the length of inpatient hospitalizations and the success of OPAT has been facilitated by the development of antimicrobials with convenient dosing schedules and the development and utilization of convenient and safe long-term IV catheters.[3]

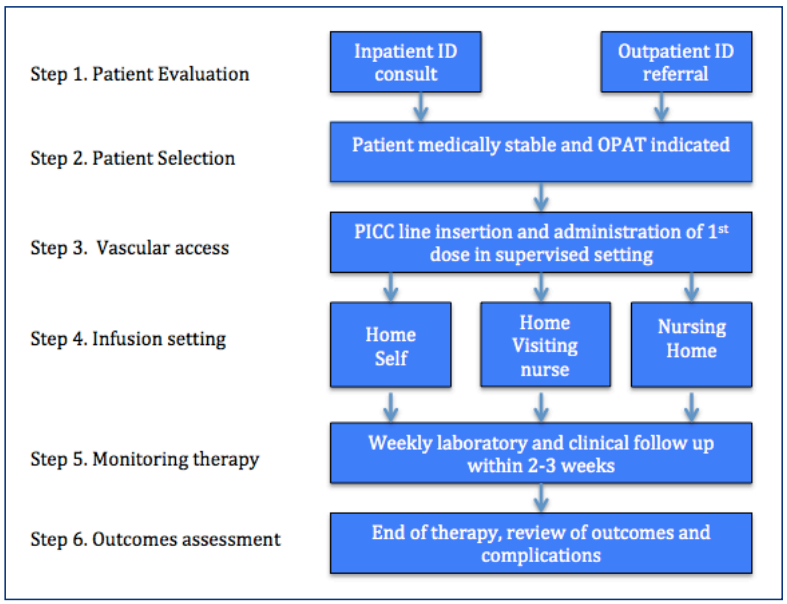
STRUCTURE OF THE OPAT PROGRAM

The Miriam Hospital Infectious Diseases Clinic, located at 1125 North Main Street in Providence, is the largest provider of outpatient infectious diseases treatment in Rhode Island. The clinic provides longitudinal OPAT for persons who have been discharged from the hospital with IV antimicrobials and serves as a specialty referral resource to community healthcare providers in New England. Every month, the clinic sees approximately 100 new patients, of whom 75% are patients who have been discharged from either Rhode Island Hospital or The Miriam Hospital on at least one IV antimicrobial treatment.

According to guidelines released by the Infectious Diseases Society of America, key elements of a successful OPAT program include: 1) A healthcare team comprised of infectious diseases specialists that work in collaboration with the primary care or referring physician, a nurse and pharmacist knowledgeable in antibiotic infusion therapy, and a case manager who can help coordinate care and manage reimbursements; 2) An accessible and rapid communication system between the patient and OPAT team members; 3) Established policies that outline the responsibilities of each team member, offer patient education materials, and help measure outcomes. [4]

As outlined in **Figure 1**, the Miriam Hospital OPAT program starts with the patient being seen by the infectious diseases consultation team inside of the hospital, or the patient is referred to the clinic by a community provider for infectious diseases evaluation. The OPAT physicians are responsible for ensuring the patient's suitability for OPAT, prescribing the intravenous antimicrobial regimen, formulating a treatment plan, and monitoring for adverse events or medical complications that may arise during the course of therapy.

Figure 1. Structure of OPAT Program.



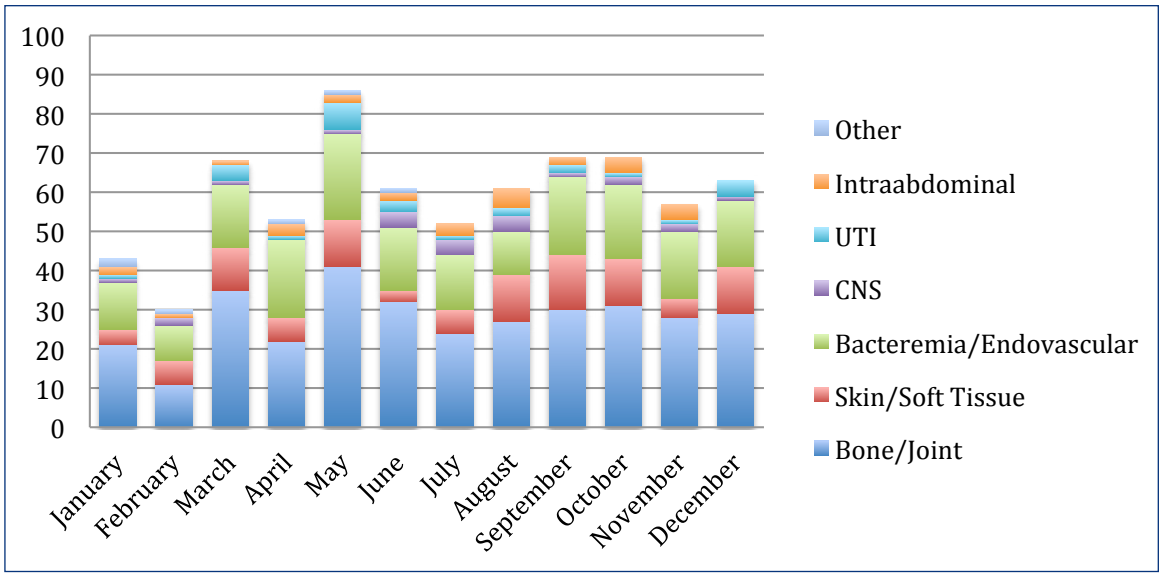


Figure 2. The Miriam Hospital Infectious Diseases Clinic: Infections treated with OPAT in 2013.

Once OPAT is considered appropriate, insertion of a long-term intravenous catheter for antimicrobial administration is arranged with interventional radiology or at an ambulatory infusion suite. A peripherally-inserted central catheter (PICC) is the most common type of catheter used for OPAT administration. PICC lines are inserted into the basilic or brachial veins and extend into the superior vena cava; position is confirmed with a chest x-ray. PICC lines can remain in place for over 90 days and seldom need to be exchanged.[5] Midline peripheral intravenous catheters, tunneled venous catheters or ports inserted for other purposes (i.e. parenteral nutrition, hemodialysis or chemotherapy) can also be used for OPAT.

Antimicrobials are infused either at a skilled nursing facility or at home. For home administration, the OPAT program partners with a community-based infusion company which provides dedicated pharmacists, arranges for home delivery of the antimicrobial, and provides nursing and educational support. OPAT inside of the patient's home often involves visiting nurses and the patient's own family members who can assist with infusions. A patient can even be taught to self-administer the antimicrobial safely, thus increasing the patient's independence and involvement with their own healthcare. Patients are typically seen by a visiting nurse at least once weekly to assess the IV catheter and to collect blood for routine laboratory testing as ordered by the prescribing physician. Constant communication and coordination between the patient and the OPAT team comprised of the pharmacist, visiting nurse, OPAT physician, and the referring physician has allowed us to successfully implement OPAT services to our patients. This process is greatly facilitated by a dedicated physician's assistant based within the Miriam Hospital Infectious Diseases Clinic who acts as liaison between patients and OPAT physicians, evaluates patients for routine follow-up visits, and who is responsible for monitoring safety labs and adverse reactions to treatment. Patients discharged from the hospital are seen at the Clinic within 2-3 weeks, and then at regular intervals throughout the course of treatment.

PATIENT SELECTION AND CLINICAL INDICATIONS

Candidates for OPAT therapy include clinically stable patients who can understand the risks and benefits of therapy, have a safe environment to support care, and can assume the costs of therapy through their health insurance provider. OPAT should be avoided in patients for whom oral antibiotic therapy is equally effective, continued hospitalization is warranted, or if a safe environment for OPAT cannot be established. Patients with active injection drug use often require continued antimicrobial administration in a monitored setting and are not appropriate for OPAT. OPAT is typically used to treat bacterial infections; however certain severe fungal, viral or even protozoal infections might require prolonged intravenous antimicrobials. The most common conditions treated with OPAT include skin and soft tissue infections, bone and joint infections, endocarditis, bloodstream infections, complicated urinary tract infections, meningitis, and respiratory infections. In 2013, the Miriam Hospital Infectious Diseases Clinic treated a total of 712 patients with OPAT. As displayed in **Figure 2**, bone and joint infections including osteomyelitis, discitis, septic arthritis, and prosthetic joint infections were the most common indications followed by bacteremia/endovascular infections and skin/soft tissue infections. The majority of these infections require a prolonged course of intravenous treatment (at least 4-6 weeks). Some infections including those that involved retained foreign bodies such as orthopedic hardware may require a longer course of therapy (months) sometimes followed by suppressive oral antibiotic therapy.

Table 1. Commonly Prescribed Antimicrobials, Dosing Schedules, Pathogens, and Types of Infections in the Adult OPAT Program
(Individual treatment decisions should be based on the antimicrobial susceptibility of pathogens and appropriate use of guidelines from the Infectious Diseases Society of America, www.idsociety.org)

Antimicrobial Class	Antimicrobial drug	Adult Dosing Schedule Assumes normal creatinine clearance (glomerular filtration rate > 50ml/min)	Pathogens	Common diagnoses treated
Penicillins	Penicillin G	3-4 MU every 4 hours or 18-24 MU via continuous infusion over 24 hours	Streptococci	Endocarditis
	Ampicillin	2 gm every 4-6 hours	Enterococcus Listeria monocytogenes	Endocarditis/bacteremia Meningitis
	Nafcillin	2 gm every 4 hours or 12 gm via continuous infusion over 24 hours	MSSA	Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections
	Ampicillin-Sulbactam	1.5-3 gm every 6 hours	Streptococci MSSA Gram-negatives* Anaerobes	Diabetic foot infections Aspiration pneumonia Intra-abdominal infections
	Piperacillin-Tazobactam	3.375-4.5 gm every 6 hours	Streptococci MSSA Gram-negatives β Anaerobes	Intra-abdominal infections Pleuro-pulmonary infections
Cephalosporins	Cefazolin	1-2 gm every 8 hours	MSSA	Septic arthritis Osteomyelitis Skin/soft tissue infections
	Ceftriaxone	1-2 gm every 24 hours (2gm every 12 hours for CNS dosing)	Streptococci MSSA Gram-negatives*	Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections
	Cefepime	1-2 gm every 8 hours	Streptococci MSSA Gram-negatives β	Intra-abdominal infections Pleuro-pulmonary infections Osteomyelitis CNS infections
Monobactam	Aztreonam	1-2 gm every 8 hours	Gram-negatives β	Intra-abdominal infections Pleuro-pulmonary infections Genitourinary tract infections
Glycopeptides	Vacnomycin	15mg/kg every 12 hours	Streptococci Enterococcus MSSA MRSA	Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections Pleuro-pulmonary infections
Aminoglycosides	Gentamicin	1mg/kg every 8 hours for synergy in combination with a beta-lactam antibiotic	Enterococcus MSSA MRSA	Endocarditis
Lipopeptide	Daptomycin	6mg/kg every 24 hours	MSSA MRSA Enterococcus	Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections
Carbapenems	Meropenem	1-2gm every 8 hours	Streptococci MSSA Gram-negatives β Anaerobes	Intra-abdominal infections Skin/soft tissue infections CNS infections
	Ertapenem	1 gm every 24 hours	Streptococci MSSA Gram-negatives* Anaerobes	Intra-abdominal infections Skin/soft tissue infections Osteomyelitis
Antivirals	Acyclovir	10 mg/kg every 8 hours	Herpes simplex virus Varicella zoster virus	CNS infections Disseminated infections
Antifungals	Amphoterocin B (liposomal preparations)	5mg/kg every 24 hours	Aspergillosis Zygomycetes Candidiasis Cryptococcosis	Invasive fungal infections CNS infections

ANTIMICROBIAL SELECTION AND ADMINISTRATION

The antimicrobial agent for OPAT should be selected based on the susceptibility testing of the infecting organism, pharmacokinetic and pharmacodynamics properties, safety profiles of the possible antimicrobials to be used, and the patient's drug allergy history. Ideally, the selected antimicrobial should be bactericidal, should reliably penetrate into the site of infection (including biofilms in the case of infections that involve retained foreign bodies), and can be administered at a convenient dosing schedule. The half-life of the drug determines the dosing, where as its temperature and pH stability defines mixture frequency and optimal storage. Antibiotics with time dependent-killing activity such as B-lactams require frequent dosing and may be best given through a continuous infusion, if preparation remains stable. Long half-life drugs that allow once daily dosing are preferred, such as ceftriaxone and ertapenem. Parenteral antibiotics commonly used in our practice include vancomycin, cephalosporins and daptomycin for gram-positive infections; ertapenem, third/fourth generation cephalosporins and aztreonam for gram-negative infections. Aminoglycosides are used in combination therapy for enterococcal endocarditis.

LABORATORY MONITORING AND COMPLICATIONS OF THERAPY

Adverse events and response to therapy are monitored at scheduled intervals through routine lab work and clinic visits according to the Infectious Diseases Society of America (IDSA) OPAT guidelines. Most antimicrobials require weekly complete blood count and renal function tests; some antimicrobials also require weekly liver function tests. Serum drug concentrations help monitor the potential for toxicity as well as predicted efficacy for certain antimicrobials including the aminoglycosides and vancomycin. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be useful surrogate markers of inflammation that can be helpful in monitoring response to therapy, particularly in hematogenous osteomyelitis.[6,7]

Adverse events encountered during OPAT therapy can be classified as either catheter-related or antimicrobial-related. Complications associated with indwelling intravascular devices include bloodstream infections, thrombosis, mechanical obstruction and chemical phlebitis.[8] Regular flushing of the catheter to ensure patency, use of local anticoagulants, and sutureless vascular devices can reduce the rate of these complications.[9] Most of our patients have routine catheter dressing changes by skilled nurses that help identify early catheter-related complications and arrange for a new vascular access if warranted. Possible complications associated with the antimicrobials themselves include: drug-related hypersensitivity reactions including rash or more severe cutaneous or systemic reactions (anaphylaxis); antibiotic-associated diarrhea; bone marrow suppression that may include leukopenia or thrombocytopenia; and secondary infections such as mucosal candidiasis.[10] Clostridium difficile infection (CDI) occurs in 15–25% of antibiotic-associated diarrhea cases and although fluorquinolones, clindamycin, and broad-spectrum B-lactams are most frequently implicated, it can potentially occur with any antibiotic exposure.[11,12] Co-administration of probiotics might reduce the risk of CDI, although evidence is inconclusive.[13] Certain antimicrobials are associated with higher risk of nephrotoxicity (i.e. aminoglycosides, vancomycin and amphotericin B). Patients who receive aminoglycosides are at risk of developing vestibular and oto-toxicity and routine clinical assessment is recommended to avoid permanent hearing loss and disequilibrium. The rate of hospital admissions due to OPAT related complications is approximately 9% in other academic institutions.[14] Clinicians prescribing OPAT are responsible for educating their patients on possible side effects related to their therapy and to provide education regarding monitoring for adverse events.

CONCLUSIONS

OPAT has become increasingly utilized for the treatment of infections that require a prolonged course of treatment. OPAT enables patients to return home and regain their independence and also helps to decrease healthcare costs. The Miriam Hospital Infectious Diseases Clinic has successfully implemented a multidisciplinary OPAT program. Our goal is to continue to safely deliver OPAT services, optimize the delivery of these services, and improve patient outcomes in RI for those who require prolonged antimicrobial treatment.

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