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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Childhood Diarrhea Varies Geographically Within Africa

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Each year, 30 million preschool-aged children still get sick with diarrhea and 330,000 die. Most diarrheal illness and death is concentrated in a few high-risk areas, including parts of Benin, Lesotho, Mali, Nigeria, and Sierra Leone. Targeting preventive and therapeutic interventions in areas of risk could markedly reduce morbidity and mortality.

SOURCE: Reiner RC Jr, Graetz N, Casey DC, et al. Variation in childhood diarrheal morbidity and mortality in Africa, 2000-2015. *N Engl J Med* 2018;379:1128-1138.

Childhood diarrheal illnesses often can be prevented through rotavirus vaccination, sanitation, and food and water hygiene. For children who become sick with diarrhea, appropriate use of oral rehydration and zinc supplementation can prevent death. Nonetheless, recent estimates suggest that 30 million cases of severe diarrhea occur each year and that 330,000 preschoolers die of diarrhea annually.

Even in Africa, there are variations in the incidences of diarrheal illness and diarrhea-related deaths from place to place. To provide geographically accurate data to identify high-risk areas (where interventions could be targeted), Reiner and his colleagues at the University of Washington performed a systematic analysis of local variations in the morbidity and mortality of diarrhea across Africa during the years of the Millennium Development Goals (2000-2015). They

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estimated the incidence of diarrhea and the frequency of diarrhea-associated deaths with detailed geographic accuracy (to 5 km^2 areas).

The distribution of the burden of diarrhea among young children was unequal. There were specific pockets or regions of frequent diarrhea in Nigeria, Ethiopia, and the Democratic Republic of the Congo. In some regions of Nigeria, 35-42% of children get diarrhea each year.

Diarrhea-related mortality decreased significantly during the first 15 years of this century in nearly all areas of Africa. In fact, case fatality rates dropped by 51% from 2000 to 2015. However, death rates due to diarrhea still vary geographically. The highest case fatality rates of diarrhea were in Lesotho (1.8 deaths per 1,000 children in 2015). Mali, Sierra Leone, Benin, and Nigeria had similarly high rates of death (1.6-1.7 per 1,000).

The median country-level case fatality rate was 0.5 per 1,000 preschool children per year. If all the countries with higher rates could reduce their rates to that median (a target already attained by half the countries of Africa), 137,000 deaths would be averted. More than half of those "saved" lives would be in Nigeria (and one-fourth of those lives "saved" in just three Nigerian states — Bauchi, Kano, and Jigawa).

There are some success stories. For instance, in Ethiopia, diarrhea case fatality rates declined by more than 60% during the first 15 years of the current millennium. This decline was linked to improved childhood nutrition and, it seems, enhanced use of oral rehydration therapy. Expanded use of rotavirus vaccination presumably could further decrease the risk of becoming ill with, and dying from, diarrhea.

■ COMMENTARY

Location, location, location is important not only for real estate but also for diarrhea. Frequent and fatal childhood diarrhea is becoming less common in children in Africa, but there still are some localized high-risk areas. Using a combination of disease surveys and mapping techniques, Reiner and his colleagues provided helpful new information. High risk for diarrhea is not only a national situation, but it also can be a local phenomenon.

It is encouraging that case fatality rates for diarrhea in children younger than 5 years of age have declined by more than 50% since the dawn of this century. Nonetheless, there are local areas, such as parts of Nigeria and the Democratic Republic of the Congo, where preventable gastroenteritis still is not prevented. In local areas, such as parts of Lesotho and Mali, treatable diarrheal illnesses still are not treated successfully. Some countries carry greater risk than others, and some parts of individual countries, such as Nigeria, carry excessive risk compared to other areas.

In some places, the successes in achieving lower rates of acute diarrheal illnesses serve as encouraging reminders to people living and working in other areas where diarrhea remains all too common. Sanitation and hygiene should continue to advance; indeed, the reduction of enteric infections in North America a century ago was linked more to indoor plumbing than to specific medical advances. However, medical advances still can help prevent diarrhea.

Rotavirus is thought to cause about 29% of all cases of childhood diarrhea,[1] and an effective vaccine now is available. The vaccine is effective in infants, but it is not administered uniformly in at-risk areas. It is estimated that the rotavirus vaccine prevented 28,000 deaths in 2016, but an additional 83,000 children's lives could have been saved if the vaccine was used uniformly.[1]

Once a child is sick with acute diarrhea, maintenance of hydration is vital. The use of oral rehydration for children who become dehydrated is referred to appropriately as "essential," "the most effective intervention to reduce mortality," and "the key intervention."[2] The new data from Reiner and his colleagues identified areas of excessively high case fatality rates for childhood diarrhea; efforts to increase the appropriate use of oral rehydration for dehydrated children probably would be effective in greatly reducing mortality.

In parts of sub-Saharan Africa where zinc deficiency is common, treating children who have acute gastroenteritis with zinc facilitates recovery and seems to reduce the future risk of diarrhea.[3] Prophylactic zinc supplementation for non-ill children also has some effectiveness.[3]

What about antibiotics? In resource-limited areas of the world, some childhood diarrhea is due to enterotoxigenic *Escherichia coli* infection. Aware of this bacterial cause of childhood diarrhea, some clinicians could be prompted toward the early use of antibiotics in ill children. However, researchers who conducted a study in India found that children who were treated with antibiotics when they had diarrhea were more likely to have a repeat bout of diarrhea sooner than their peers whose diarrhea was not treated with antibiotics.[4] Treating infantile diarrhea with antibiotics not only risks altered microbiomes that have implications for population health, but it also risks the personal health of the sick child.

Thus, we now know much of the "what" of diarrheal illness and some of the "how" for preventing diarrheal illness and death. Reiner's new data help with the "where" of diarrhea in Africa so policy-makers and program-implementers can target future interventions appropriately in the most life-saving and cost-effective ways. ■

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ABSTRACT & COMMENTARY

In Patients Who Self-catheterize, Antibiotic Prophylaxis Prevents UTIs but Increases Antibiotic Resistance

By Richard R. Watkins, MD, MS, FACP, FIDSA

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Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: A randomized, open-label, superiority trial found that daily antibiotic prophylaxis for patients who use clean, intermittent self-catheterization reduced symptomatic urinary tract infections by 48% over a 12-month period. Antibiotic resistance became prevalent in urinary isolates from the group receiving prophylaxis compared to controls.

SOURCE: Fisher H, Oluboyede Y, Chadwick T, et al. Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): A randomised, open-label trial. *Lancet Infect Dis* 2018;18:957-968.

Recurrent urinary tract infections (UTIs) in patients who practice clean, intermittent self-catheterization (CISC) are a frequent dilemma in clinical practice. Although meticulous technique is recommended, pragmatically this is difficult to maintain long term. Fisher and colleagues sought to determine whether daily antibiotic prophylaxis is an effective strategy to prevent UTIs in patients who self-catheterize.

The randomized, open-label, parallel group trial was conducted in the community in coordination with 51 organizations in the United Kingdom. Subjects were eligible for participation if they had either two or more symptomatic UTIs related to CISC within the preceding 12 months or at least one UTI that required hospitalization. Exclusion criteria included inability to tolerate the prescribed antibiotic prophylaxis, and women who intended to become pregnant, who were pregnant, or were breastfeeding. Patients who were taking an antibiotic for prophylaxis already were told to discontinue the medication for three months prior to randomization. Researchers allocated subjects

randomly in a 1:1 ratio to receive either antibiotic prophylaxis (experimental group) or no prophylaxis (control group). The antibiotics prescribed were nitrofurantoin 50 mg daily, trimethoprim 100 mg daily, or cephalexin 250 mg daily. Investigators assessed tolerability for the chosen antibiotic during a one-month review. If necessary, one of the alternative antibiotics was substituted. Subjects also submitted a perirectal swab at baseline, six months, and 12 months. Those who completed at least six months of follow-up were included in the analysis of the primary outcome, which was the incidence of symptomatic UTIs treated with antibiotics during the 12 months of participation in the study. The cost-effectiveness of antibiotic prophylaxis was expressed as the incremental cost per UTI avoided.

The experimental group included 203 subjects and the control group included 201 participants. The incidence of symptomatic UTIs treated with antibiotics in the experimental group was 1.3 cases per person year (95% confidence interval [CI], 1.1-1.6) and 2.6 cases (95% CI, 2.3-2.9) in the control group. The incidence rate ratio was 0.52 (95% CI, 0.44-0.66) in favor of prophylaxis. This rate indicated a 48% reduction in UTI incidence. However, the number of febrile UTIs was small in both groups: 15 cases in the experimental group and 22 cases in the control group. Also, the incidence of asymptomatic bacteriuria and hospital admission for a UTI did not differ between the groups. During the 12 months, the median number of symptomatic UTIs observed was one in the experimental group and two in the control group. The prophylaxis was well tolerated, with only 22 minor adverse events recorded. Most commonly, these were gastrointestinal symptoms and rashes.

At baseline, the frequency of antimicrobial resistance (AMR) of urinary isolates to eight antibiotics commonly prescribed for treating UTIs was similar in the two groups. However, during the trial, resistance became more common in the isolates from subjects in the experimental group. Indeed, there was no evidence of any change in AMR in the control group over the 12-month period. The level of resistance in *E. coli* cultured from perirectal swabs remained the same for both groups throughout the 12-month study period. Finally, the economic analysis showed a slight potential benefit for antibiotic prophylaxis, although the authors did not consider the potential cost of increasing AMR.

■ COMMENTARY

The study by Fisher and colleagues provides good evidence that antibiotic prophylaxis for patients who use CISC is effective in preventing UTIs. However, the difficulty is balancing this benefit vs. the high likelihood that prophylaxis will increase the spread of AMR. In light of the latter concern, a careful review of the study's design reveals some limitations that make the choice to use prophylaxis less straightforward. First, the treating physicians were aware of the patient's study group, which may have introduced bias into their treatment decisions. Second, the primary outcome was based on patient-reported symptoms, which are not always reliable in diagnosing UTIs in this patient population. Third, patients in the control group did not receive a placebo, and this could have led to an overestimation of their UTIs. Finally, the economic benefit of prophylaxis was modest and did not take into account the increase in spread of AMR at the societal level.

[Further research is needed to more clearly identify subgroups of CISC users for whom the benefits of antibiotic prophylaxis outweigh the risks.]

Should all patients who use CISC receive antibiotic prophylaxis? I believe the answer is no and that a more nuanced approach is necessary. For example, the researchers found that despite repeated UTIs, their effect on patient well-being was low. One approach might be to offer prophylaxis to patients with more severe symptoms, to those who experience more episodes than others, or to those with more frequent hospitalizations. Further research is needed to more clearly identify subgroups of CISC users for whom the benefits of antibiotic prophylaxis outweigh the risks.

An alternative to daily prophylaxis is self-start therapy, which involves providing patients with a supply of an antibiotic at home that they can start as soon as they begin to have UTI symptoms. This strategy also theoretically may promote AMR, but antibiotic cycling among two or three classes every year or two may reduce the risk. Cranberry extracts have proven to be ineffective in this population and should not be recommended. Finally, although the potential of methenamine hippurate is appealing, there currently is no strong evidence that this agent is beneficial in preventing UTIs in patients who use CISC. ■

ABSTRACT & COMMENTARY

Here Comes the Sun — And Here Comes Coccidioidomycosis

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Another occupational outbreak of coccidioidomycosis in solar farm workers in an endemic area points to the continued risk and the difficulty of preventing such occurrences.

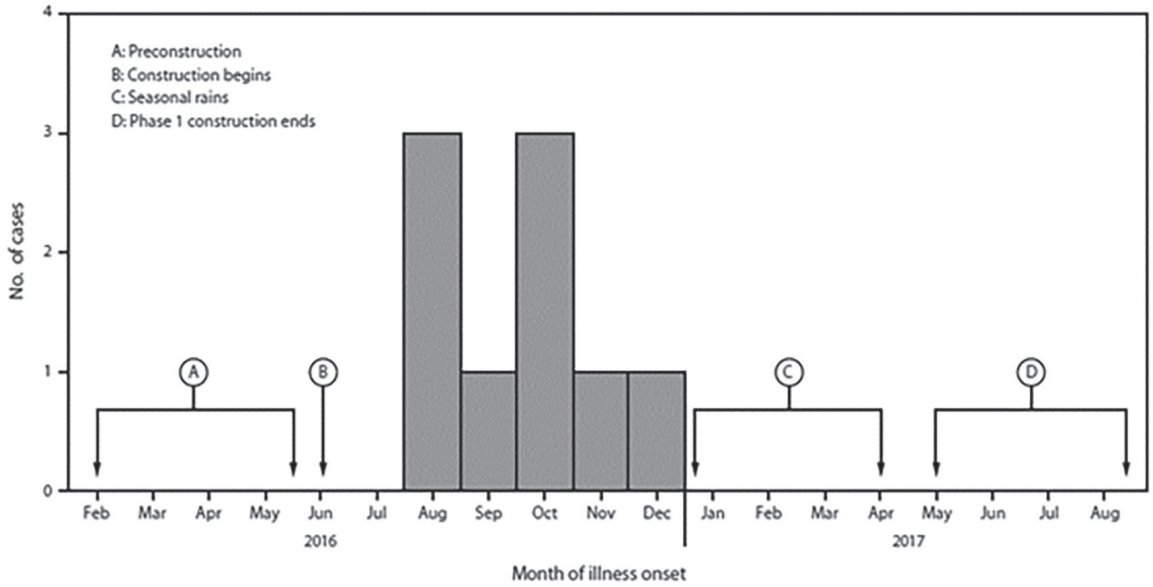
SOURCE: Laws RL, Cooksey GS, Jain S, et al. Coccidioidomycosis outbreak among workers constructing a solar power farm — Monterey County, California, 2016-2017. *MMWR Morb Mortal Wkly Rep* 2018;67:931-934.

The California Department of Public Health (CDPH) was notified in January 2017 of the occurrence of coccidioidomycosis in three workers involved in the construction of a solar power installation in southeastern Monterey County. The investigators ultimately identified nine cases among the 2,410 solar farm workers. The incidence among the workers was 1,095 per 100,000 persons/year, a rate that was 4.4-210.6 times higher than the background rate in the counties in which the cases resided (Fresno, Madera, Monterey, and San Luis Obispo). The incidence in the workers was 62.6 times higher than that in Monterey County.

Eight of the nine patients were available for interview. Six had received a diagnosis of pneumonia. Five patients had visited emergency departments one to five times, and one patient was hospitalized; none died. Seven of those interviewed had missed work as the result of the illness for a median of 14 days, but with a range of 1-320 days. The job titles of the patients included biologist, paleontologist, electrician, truck driver, iron worker, and general laborer.

The first patients became ill in August and the last in December, when seasonal rains controlled the dust, which the patients reported to be problematic. (*See Figure 1.*) Although attempts had been made to follow recommendations that emerged from previous outbreaks at California solar farms, the

Figure 1: Construction Schedule and Illness Onset of Coccidioidomycosis Among Workers Constructing a Solar Power Farm (N = 9) — Monterey County, California, 2016-2017



Source: Centers for Disease Control and Prevention

implementation proved inadequate, and CDPH has made further recommendations revolving around dust control, respiratory protection, and improved awareness of the risk and symptoms of coccidioidomycosis.

■ COMMENTARY

Outbreaks of coccidioidomycosis are a relatively common occurrence, with 47 involving 1,464 cases published between 1940 and 2015, with more than half caused by occupational exposures.[1] In addition to outbreaks involving solar farm workers, other recent occupational outbreaks of coccidioidomycosis in California have included highway workers, prisoners, and U.S. Navy SEALS undergoing training.

There undoubtedly will be more to come. On Sept. 10, 2018, California Gov. Jerry Brown signed legislation requiring that by 2030, 60% of electricity used in the state be generated from renewable sources and that this proportion will increase to 100% by 2045. A significant contribution to this switch to renewables in the fifth largest economy in the world is and will be solar energy.

Solar farms are built in rural areas (large areas of land are needed) and where the sun shines the most. In California, the Central Valley, including the San Joaquin Valley, fits the bill. Unfortunately, the construction of solar farms kicks up a lot of dust and, in such locations, that means the aerosolization of *Coccidioides immitis* arthroconidia. And there is more to come for other reasons, such as the current construction of California High-Speed Rail down the spine of the Central Valley. ■

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Plazomicin (Zemdri)

By Emily Mui, PharmD

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Dr. Mui reports no financial relationships relevant to this field of study.

Plazomicin is a next-generation aminoglycoside with potent in-vitro activity against Gram-negative aerobic organisms, including extended spectrum beta-lactamase (ESBL) and carbapenemase-producing *Enterobacteriaceae* and in-vitro activity against some Gram-positive organisms. On June 26, the Food and Drug Administration (FDA) approved plazomicin for treating complicated urinary tract infections, including pyelonephritis. In a Phase III trial, researchers compared plazomicin to meropenem (with the option to switch to oral levofloxacin) for the primary composite cure endpoint of microbiologic eradication and clinical cure at the end of therapy. In the non-inferiority trial, plazomicin achieved higher microbiological eradication at the test-of-cure visit.[1,2]

In a Phase III, open-label study consisting of a randomized, open-label cohort and a separate single-arm, observational cohort, investigators examined the efficacy and safety of plazomicin plus meropenem or tigecycline compared to colistin plus meropenem or tigecycline in patients who had serious infections caused by carbapenem-resistant *Enterobacteriaceae* (CREs), the primary endpoint of all-cause mortality and significant disease-related complications favored patients treated with plazomicin compared to colistin (23.5% vs. 50%; -26.5 (-51.2, 0.7). The secondary endpoint of all-cause mortality at day 28 was lower for the plazomicin group compared to colistin (11.8% vs. 40%; -28.2 (-52.5, -0.07).[3,4]

MICROBIOLOGY

Plazomicin exhibited in vitro activity that was more potent against most Gram-negative and Gram-positive pathogens than amikacin, gentamicin, and tobramycin. The FDA susceptibility breakpoint for plazomicin against *Enterobacteriaceae* is ≤ 2 mcg/mL, with isolates with an MIC of 4 mcg/mL considered intermediate and ≥ 8 mcg/mL considered resistant. Plazomicin's MIC50 and MIC90 values are comparable or lower than comparator aminoglycosides against *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter* spp., *Enterobacter* spp., and *Serratia* spp. (MIC90 values in the range of 0.5-2 mcg/mL). Plazomicin is less active against *Proteus mirabilis* and indole-positive *Proteus* spp. (MIC90 values of 4-8 mcg/mL).[5-14]

Plazomicin has less activity against nonfermentative bacteria (MIC90 values of 16-32 mcg/mL for *Pseudomonas aeruginosa* and 16 mcg/mL for *Acinetobacter* spp.) and is inactive against *Stenotrophomonas maltophilia* with MIC90 values > 64 mcg/mL.

The mechanisms of resistance to aminoglycosides in Gram-negative bacteria include: reduced drug penetration and/or increased efflux; production of aminoglycoside modifying enzymes (AMEs); and alteration of the ribosomal binding site. Resistance to the other aminoglycosides frequently is caused by AME production, and plazomicin resistance is mostly the result of ribosomal modification. As with other aminoglycoside medications, plazomicin is not active against bacterial isolates that produce 16S rRNA ribosomal methyltransferases.

PHARMACOKINETICS/PHARMACODYNAMICS

Oral absorption of plazomicin has not been studied, but is likely to be low since the bioavailability of aminoglycosides is low. In healthy adults, the mean volume of distribution of plazomicin is 17.9 (±4.8), and approximately 20% is bound to plasma protein. The Cmax and Cmin is approximately 73.7 (±19.7) mcg/mL and 0.3 (±0.2) mcg/mL, respectively. Plazomicin is not metabolized by the liver and is cleared by the kidneys primarily as unchanged drug in the urine. The average half-life of plazomicin is 3.5 hours in healthy adults with normal renal function (n = 54). The pharmacokinetic/pharmacodynamic parameter that best correlates with efficacy against *Enterobacteriaceae* is area under the plasma concentration-time curve to the minimum inhibitory concentration (AUC:MIC).[1]

Table: Dosing[1]

Estimated CrCL (mL/min)	Dosage
CrCL ≥ 90 mL/min	15 mg/kg IV Q24H
60-90 mL/min	15 mg/kg IV Q24H
30-60 mL/min	10 mg/kg Q24H
15-30 mL/min	10 mg/kg Q48H
Therapeutic drug monitoring is recommended in patients who have creatinine clearance between 15-90 mL/min. The goal plazomicin trough < 3 mcg/mL.	

ADVERSE EFFECTS/WARNINGS

For patients with known hypersensitivity to any aminoglycoside medication, plazomicin is contraindicated.[1]

Nephrotoxicity has been reported with plazomicin use. In trial 1 of the complicated UTI clinical trials, the incidence of renal function-associated adverse reactions was 3.6% in patients treated with plazomicin compared to 1.3% for patients treated with meropenem. Most increases in serum creatinine were ≤ 1 mg/dL above baseline and were reversible on discontinuation of the drug. In trial 1 and trial 2, the nephrotoxicity incidence was higher for patients with trough levels ≥ 3 mcg/mL (36%, 10/28) than for patients with plazomicin Cmin < 3 mcg/mL (5%, 11/215). Trough levels of ≥ 3 mcg/mL were associated with an increase in SCr of 0.5 mg/dL or more above baseline and occurred in 7% of patients treated with plazomicin compared to 4% in those treated with meropenem.[1]

Ototoxicity, including hearing loss, tinnitus, and vertigo, has been reported with plazomicin. The ototoxicity associated with aminoglycosides may not be reversible and may not be evident until after therapy is finished. In clinical trials, there was one case of reversible hearing impairment, one case of irreversible tinnitus, and one case of reversible vertigo. (Of note, one case of tinnitus occurred in the meropenem arm and one case of an abnormal audiogram occurred in a patient treated with levofloxacin).[1]

PREGNANCY AND LACTATION

Aminoglycoside antibiotics can cause harm to the fetus when administered to pregnant women. Reports of irreversible congenital deafness have been reported with streptomycin. Data are lacking regarding plazomicin in human milk, the effects on breastfed infants, or the effect of the drug on milk production. Approximately 2-4% of maternal plasma concentrations is detected in rat milk.[1]

CONCLUSION

Plazomicin is a new drug in the aminoglycoside class that is indicated for treatment of complicated UTIs, including pyelonephritis. Unlike other aminoglycosides, plazomicin is resistant to the effect of enzymatic inactivation by common AMEs and has potent activity against ESBL and CREs. Plazomicin also may have an adjunctive role in salvage therapy in serious CRE infections. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Tuberculosis Transmission From NAAT-negative Patients

SOURCE: Xie YL, Cronin WA, Proschan M, et al. Transmission of *Mycobacterium tuberculosis* from patients who are nucleic acid amplification test-negative. *Clin Infect Dis* 2018; doi: 10.1093/cid/ciy365. [Epub ahead of print].

One of the earlier uses of strain genotyping in a cohort of tuberculosis (TB) patients in San Francisco in the 1990s led to the recognition that AFB smear-negative/culture-positive patients resulted in at least 17% of TB transmission. More recently, rapid nucleic acid amplification (NAA)-based tests are used to evaluate patients with possible TB. NAA testing (either the Xpert MTB/RIF Version G4 or the Amplified Mycobacterium Tuberculosis Direct test [MTD]) is believed to be highly sensitive for the detection of TB in respiratory specimens, with a sensitivity somewhere between sputum smear and culture. The negative predictive value of NAAT on one or two respiratory specimens is comparable to three negative smears — and is used increasingly to remove patients more quickly from respiratory precautions or voluntary isolation. The TB transmission risk from NAAT-negative patients who ultimately have positive respiratory cultures has not been studied.

The authors retrospectively examined the risk of TB transmission in a cohort of 809 culture-positive cases in whom NAA testing was performed routinely between 2004-2009. Patients had at least one respiratory culture that was positive for MTB and also had smears performed on three or more respiratory specimens and NAA testing from one or more respiratory specimens. The primary outcome of the study was the transmission risk of a test-negative case, with smear and NAA testing examined separately. A secondary outcome was the minimum transmission risk combining smear and NAAT status.

Genotyping was available on 782 (97%) patients. Of these, 393 had no genotype matches, and the remaining 389 patients "clustered" into 158 groups. This left 83 clusters with 231 secondary cases within the study window. Forty-nine clusters had a recognized index case, which consisted of 47 NAAT-positive index cases, two NAAT-negative index cases, and 113 secondary cases. Based on this, the minimal TB transmission risk from a NAAT-negative case was 5.1% (95% confidence interval [CI], 0-11.4%); and the estimated TB transmission risk from a NAAT-positive case was 35.4% (95% CI, 26-43.2%).

The two NAAT-negative cases (one was known to be HIV negative, the other's HIV status was not known) were both smear negative, and the patients began TB treatment about one month after collection of their first culture-positive sputum. Importantly, of those 10 cases that were NAAT-negative on two or more respiratory specimens, the risk of TB transmission was zero.

Similarly, the minimum transmission risk from a smear-negative index case was 11.2%, and the estimated risk from a smear-positive case was 47.7%. Eighteen transmission events from 17 smear-negative cases accounted for 9.2% of TB transmission. Combining smear-negative/NAAT-negative cases, the minimum risk of TB transmission was 1.8% — still not zero.

[These data reinforce the need for prompt initiation of treatment when clinical suspicion is high, even when smears and/or NAA testing are negative.]

There are several reasons why patients with negative smears and/or NAA may transmit organism: the quality of the specimens tested, the time of day the specimen was obtained, and delays in treatment, during which a patient could develop worsening disease. Initiation of treatment often is delayed in such patients compared to those who are smear- or NAA-positive. These data reinforce the need for prompt initiation of treatment when clinical suspicion is high, even when smears and/or NAA testing are negative.

Recently, I saw such a case — a young man with a small RUL reticulonodular infiltrate, who was both smear (x3) and NAAT-negative. By the time I saw him in consultation in the office, he was clinically improved with a Z-pak, although the chest radiograph was unchanged. Four weeks later, sputum cultures were positive for TB. I believed the tests and not the case.

Worldwide Rabies Risk: Dogs

SOURCE: ProMED-mail post. Rabies (51): Asia (Viet Nam) Africa (Morocco) human, canine. Oct. 3, 2018. Available at: http://www.promedmail.org. Accessed Oct. 9, 2018.

Rabies remains a significant problem worldwide, especially in India, Southeast Asia, and Africa. The World Health Organization estimates that rabies results in ~59,000 deaths annually in 150 countries, although most of these deaths are concentrated in Asia and Africa. About half occur in children younger than 15 years of age. At least 20,000 deaths occur annually in India alone, generally from stray dog bites. In fact, it is estimated that 99% of global rabies deaths are dog-related.

Most of the time, in the comfort of the United States, we don't realize the global risk of rabies, until we are traveling and bitten by an animal. I've been involved with patients, friends, and family bitten by stray dogs in Belize, Thailand, India, and Turkey and by wild monkeys in Southeast Asia and Indonesia. One patient even was spit on by a camel in Egypt, and another was bitten by an angry pack mule on a trek. More than 15 million people receive post-dog-bite rabies vaccination every year, at an estimated cost of $1.5 billion.

Globally, there is a goal to eliminate human rabies from dog exposure by 2030. Efforts have focused on improved access to post-exposure prophylaxis as well as rabies vaccination of dogs. Rabies vaccine programs are being implemented in many countries, but in some countries the problem persists.

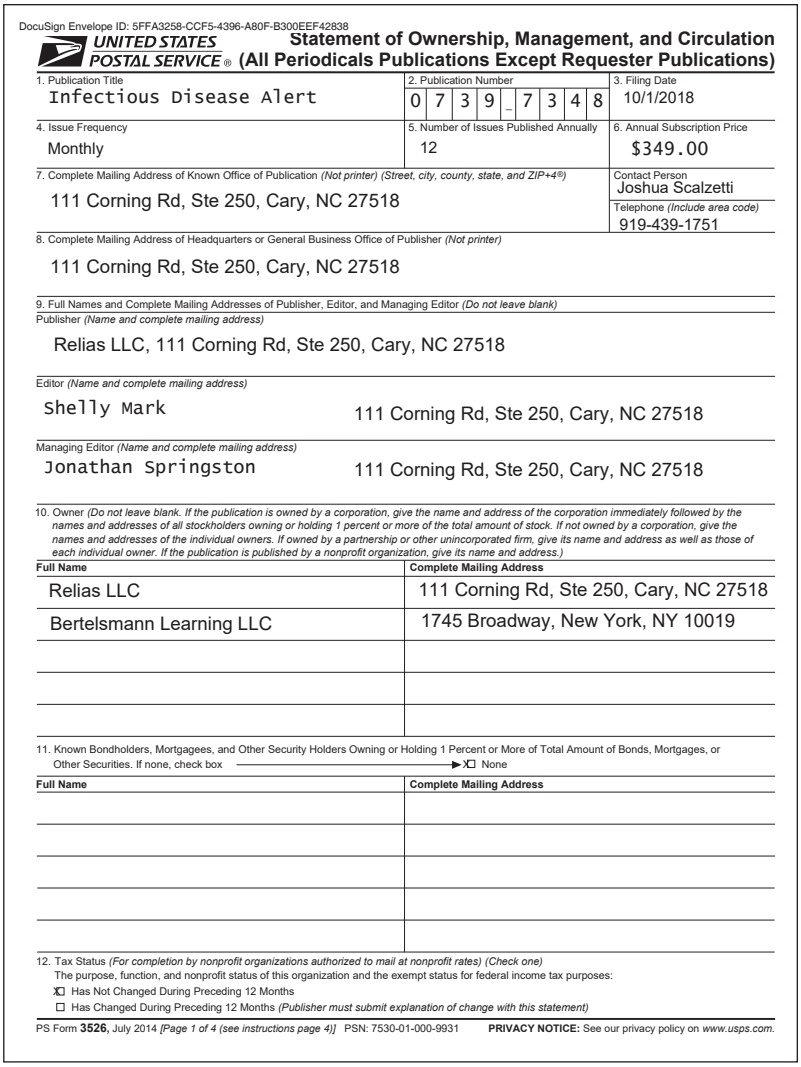
This ProMED mail alert highlights the problem in Morocco, where 65,000 people received post-exposure prophylaxis in 2017. Ninety percent of these individuals were bitten or scratched by a rabid dog. Four hundred cases of animal rabies are reported in Morocco every year. Although Morocco is doing a good job of providing post-exposure prophylaxis to those exposed, the country lacks an organized dog vaccine program, in part because of a lack of information on the number of strays.

The Association of Southeast Asian Nations (ASEAN) has implement a regional strategy to eliminate human rabies by 2020, and many

individual countries in this region have begun implementing programs to stamp out rabies. Recognizing a significant problem, Vietnam, for example, has implemented a well-funded nationwide program to eliminate all rabies by 2021.

But there is one area that remains a point of vulnerability, and that is the dog meat trade. Transporting, slaughtering, and butchering dogs and even ingesting infected meat remains an identifiable risk for rabies infection. Several reports document the risk of rabies from dog meat. The dog meat market in Asia remains quite active. For example, Vietnam estimates that 20,000 dogs are transported from south to north Vietnam every month for slaughter and use as food.

Unfortunately, some of the dogs captured and smuggled for slaughter in fact may be sick, sometimes with rabies. The authors of this article report that more than 80 animal rights organizations and charities have signed an open letter to global governments to take action to end the dog meat market, in part to end rabies virus transmission throughout Asia.



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Patients Need to Rethink the 'Quality' in Healthcare

SOURCE: Fenton JJ, Jerant AF, Bertakis KD, Franks P. The cost of satisfaction: A national study of patient satisfaction, health care utilization, expenditures, and mortality. *Arch Intern Med* 2012;172:405-411.

Patient satisfaction increasingly is an important and commonly used surrogate marker for healthcare quality. In addition, reimbursement to physicians may be based on patient satisfaction as a "quality" metric. But the evidence linking a patient's subjective sense of satisfaction and the actual delivery of quality care remains tenuous, at best. These authors conducted a prospective cohort study of 51,946 adults participating in the national Medical Expenditure Panel Survey from 2000-2007. The researchers compared patient satisfaction (based on five items from the Consumer Assessment of Health Plans Survey) at one year with healthcare expenditures (total cost, prescription drug cost) and healthcare utilization (ED visits, hospitalization) at two years, and mortality. Mortality figures were assessed at an average of 3.9 years of follow-up.

The data were adjusted for demographics, health status, chronic illness, insurance status, and socioeconomic status. In brief, the authors found that those with the highest level of satisfaction had the highest level of healthcare costs and the highest rates of mortality. Patients in the highest quartile for year 1 patient satisfaction had an adjusted 8.8% greater healthcare expenditure at year 2, and 9.1% higher prescription drug costs at year 2. They also exhibited a 12% greater risk of hospitalization (adjusted odds ratio, 1.12; $P = 0.02$) and a 26% greater risk of mortality (adjusted hazard ratio, 1.267; $P = 0.02$).

The risk of mortality remained significantly higher even when researchers eliminated patients with three or more diseases or the worst self-rated health scores from the analysis. Only the risk of going to the ED appeared lower in those more satisfied.

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How to make sense of this? My basic Midwestern way of thinking would like to suggest that the wrong questions are being asked. Perhaps we've trained patients to think about their healthcare in the wrong way. How many times have I heard patients complain that their surgeon wasn't warm? I've had to explain, you don't want your surgeon to be warm and fuzzy, you want him or her to do an excellent job at surgery.

Our large, multi-specialty clinic randomly contacts 10 of our patients per month with a lengthy questionnaire, detailing their satisfaction with their visit. This includes a few questions about their actual visit with the doctor (e.g., Did the doctor listen to your concerns?), but also questions such as "Were the chairs in the waiting room comfortable?" and "Was the parking adequate?" As best I can tell, all it takes is one in 10 patients who hated their experience, for whatever reason, to skew the results. Aside from the cost of generating all these data, how relevant is it? I don't know, but when I go to the movies and think about the movie, I don't think about the parking lot or fault the acting because the popcorn didn't have enough butter.

The most demanding patients may not be the most satisfied, unless of course they get everything they want, which simply cannot translate into the best healthcare. I have a patient who loves her plastic surgeon. He's good looking and so friendly, he gave her a discount for her last surgery, and she raves that the facility is so gorgeous, there are wait staff who take her drink orders; it's like going to the spa. Never mind the nasty infection she had for a routine tummy tuck. She still loves the guy.

My male partner has read that patients trust their male doctors more when their shoes are polished, they wear a nice watch, and their shirt is ironed, so he makes sure to polish his shoes every day he's on call, wears a conspicuous gold watch, and gets his shirts pressed. Patients believe male doctors should look like successful salesmen because they don't know what else to think.

Although access to parking is important, I am concerned we are training patients to rate their subjective "experience" as a measure of healthcare quality, rather than educating them on how to assess the actual appropriateness and quality of their care. We need to train patients to understand what is important for their healthcare. If you want quality, look at physicians' evaluations of each other, their referral base, and other hard indicators, like surgical outcomes and infection rates, not the color of the chairs in the waiting room. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **In geographical areas with high rates of diarrhea morbidity and mortality during childhood, helpful interventions currently include:**

   a. early use of antibiotics with each diarrheal illness.

   b. avoidance of zinc supplements.

   c. rotavirus vaccination.

   d. norovirus vaccination.

2. **Which of the following is correct regarding outbreaks of coccidioidomycosis in solar farm workers?**

   a. The major route of infection is skin inoculation of arthroconidia.

   b. The major route of infection is inhalation of spherules.

   c. The major route of infection is inhalation of endospores.

   d. The major route of infection is inhalation of arthroconidia.

3. **Which of the following is correct regarding plazomicin?**

   a. It is a novel siderophore cephalosporin.

   b. It is inactive in the presence of bacterial ribosomal methyltransferase.

   c. It has enhanced activity against non-fermenters relative to lactose fermenters such as *Escherichia coli*.

   d. Its mean serum half-life in healthy adult volunteers is 12 hours.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.