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E. coli, Europe, and Hemolytic Uremic Syndrome

ABSTRACT & COMMENTARY

By Megan M. Chock and Philip R. Fischer MD, DTM&H

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Ms. Chock and Dr. Fischer report no financial relationships to this field of study.

Synopsis: *In recent months,* Escherichia coli *O104:H4 has infected more than 4,000 people and caused 880 cases of hemolytic uremic syndrome (HUS) in Europe, with the majority of cases reported in Germany and with more recent outbreaks in France and Switzerland. Travelers should implement food hygiene precautions to prevent infection when visiting Europe.*

Sources: Frank C, et al; the HUS Investigation Team. Epidemic profile of shiga-toxin-producing *Escherichia coli* O104:H4 outbreak in Germany — Preliminary Report. *N Engl J Med* 2011 June 22; Epub ahead of print;

World Health Organization, Regional Office for Europe. Outbreaks of *E. coli* O104:H4 infection: Update 28, 01-07-2011. Available at: www.euro.who.int/en/what-we-do/health-topics/emergencies/international-health-regulations/news/news/2011/07/outbreaks-of-e.-coli-o104h4-infection-update-28. Accessed July 7, 2011;

Centers for Disease Control and Prevention. EHEC outbreak Update 27, 30 June 2011. Investigation Update: Outbreak of Shiga toxin-producing *E. coli* O104 (STEC O104:H4) Infections Associated with Travel to Germany. Available at: www.cdc.gov/ecoli/2011/ecoliO104/. Accessed July 7, 2011.

As of June 29, 2011, German authorities reported 3,189 cases of enterohemorrhagic *E. coli* (EHEC) infections, and 884 other cases have also been identified. Since May 2, 2011, Germany has reported 841 cases of hemolytic uremic syndrome (HUS) caused by the EHEC strain *E. coli* O104:H4. Most of the infections have been reported in northern Germany or in people who have traveled to this area. Cases of HUS and EHEC have been reported throughout 13 other European countries and the Centers for Disease Control and Prevention (CDC) has reported five confirmed and one probable case of *E. coli* O104:H4 infection in the United States. Of the six U.S. cases, five recently traveled to Germany. The cause of the outbreak has been traced to fresh sprouts produced by a farm in Lower Saxony, northern Germany. Current recommendations are to avoid eating raw sprouts regardless of their origin.

On June 24, 2011, France reported a new outbreak of *E. coli* and HUS in which *E. coli* O104:H4 was confirmed in four of the eight cases, and on June 28, 2011, Sweden reported an isolated case of O104:H4 infection. None of these patients had traveled to Germany, and first investigations indicate that locally grown sprouts may be the associated cause.

■ COMMENTARY

The outbreak of hemolytic uremic syndrome caused by Shiga toxin-producing *E. coli* (STEC) has been ongoing in Germany since May 2011 and peaked on May 21, 2011. Hemolytic uremic syndrome is a dangerous complication that can arise from STEC infection. HUS frequently includes acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia; the central nervous system is less frequently involved. Features of HUS usually begin 5-10 days after the onset of diarrhea. Most often, HUS is caused by infection with *E. coli* O157:H7; however, the STEC strain responsible for Germany's current outbreak is *E. coli* O104:H4.

The outbreak caused by *E. coli* O104:H4 is different than other outbreaks of STEC infection in several ways. First, HUS has complicated a higher proportion of infections with *E. coli* O104:H4 than other strains. Usually, HUS complicates 6%-9% of STEC infections in adults and 15% of STEC infections in children; however, HUS has been a complication in 25% of the *E. coli* O104:H4 infections. Second, while other STEC strains like *E. coli* O157:H7 tend to affect children more than adults, approximately 89% of HUS associated with the *E. coli* O104:H4 strain occurred in adults, and more than 65% of these cases were in females. Although the exact reasons for these age and gender risks are not known, the increased adult incidence of HUS in the current outbreak may be due to varied modes of transmission. *E. coli* O157:H7 maintains a wild reservoir in cattle, and humans are infected by ingesting fecal material or through direct human contact; perhaps children eat fewer bean sprouts and, thus, are at less risk of O104:H4 infection. In the active Europe outbreak, it appears that the O104:H4 may have stemmed from a genetic mutation of enteroaggregative *E .coli*, which normally causes watery diarrhea and does not have a zoonotic reservoir. The O104:H4 STEC strain contains genes from both enteroaggregative and Shiga-toxin Type 2 *E. coli*, which may be responsible for its altered virulence.

According to the Robert Koch Institute, which began investigating an outbreak of HUS in northern Germany on May 20, 2011, the outbreak began to grow on May 8 before peaking around May 21, 2011. The source of infection was attributed to cucumbers, tomatoes, and leafy vegetables before epidemiological studies indicated that raw sprouts from a farm in Lower Saxony were responsible for the current outbreak.

A person with symptoms of STEC or HUS who has recently traveled to Germany or has been in close contact with an ill person should get medical attention. STEC infection usually manifests itself clinically as acute bloody diarrhea and hemorrhagic colitis. Infected persons can then develop HUS, which sometimes leads to permanent renal and neurological problems. The diagnosis is usually made with Shiga toxin detection. In the O104:H4 outbreak, bloody diarrhea with abdominal cramps was the

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most common clinical sign in adults, and the median incubation period was 8 days. Treatment of hemolytic uremic syndrome is supportive; red cell and platelet transfusions are sometimes needed, and dialysis may be used for renal failure. Inhibition of complement complex formation holds promise of helping patients with severe HUS.[1]

Travelers should follow food safety precautions when visiting Europe to prevent infection. The CDC and German authorities' current recommendation to prevent further spread of *E. coli* O104:H4 is to avoid consumption of any raw bean or seed sprouts. People should only consume sprouts that have been cooked at a temperature of at least 70° C, which kills the *E. coli* bacteria.[2] The WHO also advises people to thoroughly wash their hands after touching seeds for planting or sprouting.[2] In addition, people should exercise general hygiene principles and wash their hands before and after handling or eating food items and after using the bathroom.

The current outbreak of *E. coli* O104:H4 infections should remind travelers that there are risks to seemingly safe European travel. In addition, measles infection is an active public health concern in Europe, with more than 7,000 cases reported in France alone from January to March 2011 and more than 11,000 cases in 38 other countries in Europe.[3] More than 75% of these cases occurred in people who had not been vaccinated. All travelers should be up to date on all of their vaccinations, even including full measles protection for European travel.[4] A recent publication details risks specific to travel in various parts of the world, even North America.[5] ■

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Interferon-γ Release Assays: Utility and Limitations

ABSTRACT & COMMENTARY

By Lin H. Chen MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School; Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA

Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex.

Synopsis: *Interferon-γ release assays are recommended in the screening for latent tuberculosis infection, but issues with discordance and reproducibility, lack of prognostic value, and low efficacy in children require further refinement to achieve proper interpretation.*

Source: Herrera V, et al. Clinical application and limitations of interferon-gamma release assays for the diagnosis of latent tuberculosis infection. *Clin Infect Dis* 2011;52:1031-1037.

Herrera and colleagues reviewed the use of interferon-γ release assays (IGRAs) for the diagnosis of latent tuberculosis infection (LTBI). Interferon-γ is released by CD4 cells when infected with *Mycobacterium tuberculosis* (MTB), and IGRAs measure interferon-γ response in blood. The FDA approved the first IGRA, QuantiFERON-TB test (QFT), in 2001, followed by QuantiFERON-TB Gold test (QFT-G) in 2005. More recently, the FDA approved QuantiFERON-TB Gold-In-Tube test (QFT-GIT) in 2007 and T-Spot in 2008.

QFT-G uses an enzyme-linked immunosorbent assay [ELISA] to measure the interferon-γ released when whole blood is incubated with MTB antigens. The GIT simplified the procedure by collecting blood directly into pre-coated tubes for incubation. T-Spot uses an enzyme-linked immunospot assay to count the cells that produce interferon-γ on pre-coated plates. The two newer tests, QFT-GIT and T-Spot, use specific MTB antigens (early-secreted antigen 6 [ESAT6] and culture filtrate protein 10 [CFP10]) that are not present in other strains of mycobacteria or the BCG vaccine strain; therefore, these tests have increased specificity compared to the tuberculin skin test (TST).

In the United States, TB screening primarily targets persons that may have been infected recently and persons with health conditions that increase their susceptibility for reactivation of LTBI. The ideal timing of screening test is considered to be 8-10 weeks after the possible ex-

posure, prior to which the test may be falsely negative.

Herrera et al note that the QFT-GIT, T-Spot, and TST vary in performance depending on the test population, study type, study definitions/parameters, and that there are very few direct comparisons. Nevertheless, the pooled sensitivity was 83%, 90%, and 89%, respectively, and pooled specificity was 99%, 88%, and 85%, respectively. The IGRAs are superior to TST in its specificity in BCG-vaccinated populations.

The limitations highlighted in this paper include:

- IGRAs are not sufficiently sensitive to detect a recent TB exposure
- IGRAs have shown discordance with TST
- A negative IGRA result does not rule out the diagnosis of LTBI
- The quantitative results from IGRAs have not yet demonstrated prognostic value regarding progression to active TB
- IGRAs cannot differentiate between active TB, LTBI, treated infection, or recent vs. remote infection
- Reproducibility of IGRAs has been variable and serial tests have found conversions and reversions in the range of 12%-50%
- Efficacy in children is low and a negative IGRA test does not exclude infection

The authors recommend some practical approaches to interpreting IGRA and TST results. First of all, conversion from a negative to a positive result could mean a false-positive test in a low-risk person, and possibly could be associated with concurrent illness, laboratory determinants, and nonspecific boosting of interferon-γ. Reversion from a positive to a negative result may be influenced by similar factors. Treatment can lead to reversion, or more likely to a decline in the quantitative result. Because delays in incubation and sample processing can lower interferon-γ responses, quantitative results aid in predicting reversion or conversion when the interferon-γ result is near the test cutoff point.

Regarding discordant IGRA and TST results in a low-risk person, a negative IGRA is more reliable than a positive TST in BCG-vaccinated individuals. On the other hand, a negative TST and a positive IGRA in a high-risk individual should not preclude further evaluation for TB.

■ COMMENTARY

A total of 11,181 TB cases were reported in the United States in 2010, corresponding to a rate of 3.6 cases per 100,000 population.[1] TB cases in foreign-born individuals comprised 60.5% of all cases in those with known country of origin, at a case rate of 18.1 cases per 100,000 population, and has remained in the range of 7,000-8,000 cases per year since 1993.[1] Foreign-born persons younger than 18 years of age also have a disproportionately high TB case rate, at 11.4 per 100,000 population or almost 20 times higher than that of their U.S.-born counterparts.[2] The burden of disease among foreign-born individuals suggests that screening these populations for LTBI should be a highly effective strategy for TB control and prevention in the United States.[3]

Similar to foreign-born persons, previous studies have also established that travel destinations determine the TB exposure risk and long-term travelers have risks that resemble the local incidence.[4,5] Additionally, health care work overseas was associated with increased risk, and travelers who are visiting friends and relatives (VFR) also have an increased risk.[4,6] For example, travelers who participate in health care work overseas had a TST conversion rate of 7.9 per 1,000 person-months of travel, whereas non-health care workers had a rate of 2.8 per 1,000 person-months.[4] Travelers whose trips include such activities should be prioritized for screening.

Since the FDA approval of IGRAs, the CDC has published guidelines for using these tests to detect MTB infection.[1] All indications focus on their use for TB screening, as an alternative or a complement to TST. Their major advantages over the long-standing TST are: 1) the convenience of a single visit; 2) the omission of trained staff to read and interpret the reaction; and 3) the higher specificity in BCG-vaccinated persons. However, a blood sample is required to perform IGRAs, and Herrera et al have pointed out some significant limitations.

In the U.S. population, IGRAs are more specific, but less sensitive, than TST for predicting future disease. Horsburgh recently summarized the sensitivity of IGRAs for predicting progression to active TB within several years after exposure to be 80%-90% with specificity of 56%-83%, or a positive predictive value of 4%-8%, and negative predictive value of 99%-100%.[3] At the same time, a positive TST of 5 mm has a sensitivity of 90%-100% to predict progression to active TB and a specificity of 29%-39%, or a positive predictive value of 2.7%-3.1%, and a negative predictive value of 99%-100%.[3]

An additional issue noted by Herrera and other authors is the establishment of cutoff points. Whereas TST conversion is defined as an increased induration of 10 mm or more, cutoffs for IGRA conversions are not fully defined.[3] Interestingly, screening guidelines using IGRAs vary among countries.[3,7] However, most experts agree that IGRAs are valuable when screening BCG-vaccinated individuals, and also better when there is high prevalence of recent TB infection, including recently arrived foreign-born individuals and likely international travelers.[1,3]

IGRAs can be especially useful in screening BCG-vaccinated travelers, VFR travelers, long-term travelers, and health care travelers. Travel medicine practitioners should be aware of the limitations articulated by Herrera

et al. Finally, we need more data to assess the efficacy of IGRAs in screening the specific population of travelers and to establish proper IGRA cutoff values and interpretation for this population. ■

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Strongyloidiasis in a Patient with HTLV-1 Infection

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD, and Peter Ackerman, MD

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Drs. Mileno and Ackerman report no financial relationships to this field of study.

Synopsis: *A timely piece by Eric Caumes, MD, and Jay S. Keystone, MD, emphasizes the risk of travelers acquiring acute strongyloidiasis while walking barefoot in tropical and subtropical areas in two cases published in the* Journal of Travel Medicine*. This review begins with the current case of an individual in Rhode Island with chronic strongyloidiasis — the "time bomb" — and acute T-cell leukemia associated with HTLV-1 infection who faces imminent chemotherapy.*

Sources: Caumes E, Keystone J. Acute strongyloidiasis: A rarity. Chronic strongyloidiasis: A time bomb! *J Travel Med* 2011;18:71-72;

Wang S, Ackerman P. Disseminated cryptococcosis in Liberian Female with new Diagnosis of HTLV-1 and Adult T-cell Leukemia. Submitted for presentation at the Annual meetings of the Infectious Disease Society of America. Boston, MA; October, 2011.

A 58-YEAR-OLD LIBERIAN-BORN WOMAN WAS IN EXCELlent general health, living and working in a large academic medical center in Rhode Island for more than 20 years when she developed nonspecific gastrointestinal symptoms and underwent endoscopy, which revealed *Strongyloides stercoralis* larvae on a duodenal biopsy in March 2010. Symptoms resolved with ivermectin therapy. No immunologic workup was performed.

In February 2011 the patient began to experience fevers, night sweats, non-productive cough, and shortness of breath. Her symptoms were refractory to outpatient management and she was briefly admitted to the hospital on two separate occasions in early March. Chest radiographs showed a persistent left upper lobe consolidation. She had mild neurologic complaints during those admissions, including headache and dizziness. She was discharged each time with a diagnosis of community-acquired pneumonia and treated with oral antibiotics.

Two days after her second hospital discharge she returned to the emergency room with meningismus. At that time a lumbar puncture showed an opening pressure of 30 cm H_2O and 23 white blood cells count with 56% neutrophils, 20% monocytes, and 14% lymphocytes. The cerebrospinal fluid (CSF) protein and glucose were within normal limits (42 mg/dL and 54 mg/dL, respectively). Routine Gram stain demonstrated many yeast forms and special staining showed encapsulated fungal elements consistent with *Cryptococcus* infection. Serum cryptococcal antigen was positive with a titer greater than 1:256. Ultimately, CSF, blood, and urine cultures grew *Cryptococcus neoformans*. The patient clinically improved during her 2-week course of induction therapy with liposomal amphotericin B (5 mg/kg IV daily) and flucytosine (25 mg/kg every 6 hours) followed by consolidation therapy with fluconazole 800 mg, daily, prior to her discharge. Epidemiologic investigation did not reveal any obvious cryptococcal exposure risk in this compromised host.

Rapid HIV and HIV-ELISA tests were negative. Analysis of the patient's peripheral blood smear showed a very small subset of small to medium sized lymphoid cells with irregularly lobulated nuclei resembling "flower-like

cells." Flow cytometry immunophenotype was most consistent with adult T-cell leukemia-lymphoma. Serologic and nucleic acid testing confirmed a new diagnosis of human T-cell lymphotropic virus-type 1 (HTLV-I).

Multiple sputum and urine samples were negative on staining for acid-fast organisms, and mycobacterial cultures showed no growth to date. Strongyloides serological testing and direct microscopy of stool for ova and parasites were negative. The patient's CD4 cell count was 203 cells/μL (11.3%) and she received prophylactic doses of trimethoprim-sulfamethoxazole. Given the grave prognosis for adult T-cell leukemia, the patient underwent a staging CT of the abdomen and pelvis, which showed extensive retroperitoneal lymphadenopathy. The hematology/oncology and infectious disease consultants have been justifiably concerned about potential *Strongyloides stercoralis* hyperinfection, if and when chemotherapy must be initiated for this immunocompromised patient.

■ COMMENTARY

Caumes and Keystone discuss the presentation of chronic strongyloidiasis as one that is usually asymptomatic or, as seen in our patient, with mild gastrointestinal symptoms and occasionally peptic ulcer-like symptoms. Disseminated infection resulting from decreased cell-mediated immunity is a clear possibility in our patient with HTLV-1 infection and profound depression of CD4 cell counts. The authors cite additional references that describe mortality rates ranging from 50% to 87% even with treatment. Our patient has presumably carried this infection for at least 20 years — since she moved to the United States from Liberia. This is made possible by the fascinating property of nematode persistence via autoinfection of the host. Although this disease has classically been associated with immigration, the recent Canadian data in the above editorial showed numerous cases of strongyloidiasis in tourists, including Italian tourists returning from southeast Asia.[1] Of 43 travelers with strongyloidiasis in Canada, the infection was associated with visiting friends and relatives in 37% of cases, tourism in 30%, and immigration in only 21%.

We had treated our patient with the recommended course of ivermectin of 200 μg/kg for 2 days in 2010. Although we cannot presently demonstrate larvae or serologic evidence of disease, we chose to presumptively repeat the regimen again in anticipation of potential life-threatening disseminated strongyloidiasis and hyperinfection syndrome.

Acute T-cell leukemia (ATL) is characterized by clonal proliferation of CD4+ T cells that may be identified on peripheral blood smear by their hyperlobulated nuclei (referred to as "flower cells"). There are actually four distinct clinical forms of ATL. The smoldering subtype, seen in this patient, is the least common and generally has a more favorable prognosis with median survival of more than 5 years. While there are no standard treatment recommendations for the management of HTLV-I disease, progressive adult T-cell leukemia-lymphoma is generally treated with conventional chemotherapeutic regimens such as cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP). Combination therapy with nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine (AZT), plus interferon-alpha may also be effective. The clonal CD 4+ T cells proliferating during this process are numerous, yet they are clearly ineffective against opportunistic pathogens.

For example, infections associated with *Cryptococcus neoformans* are typically seen in patients with compromised cell-mediated immunity such as those with advanced HIV infection or, much less commonly, HTLV-1 infections. The most common clinical manifestation of cryptococcal disease is meningitis, which can present with little or no meningeal signs.

HTLV-1 is a human retrovirus that infects an estimated 10-20 million people worldwide. Transfer of bodily fluids such as breast milk, blood, or genital secretions is the primary means of transmission. Endemic in parts of the South American, Asian, and African continents, it rarely causes clinical disease in infected individuals (~5% lifetime risk). Primary disease manifestations include HTLV-1-associated myelopathy (HAM) or adult T-cell leukemia-lymphoma. Its association with strongyloidiasis is well described and our case is presented both here and at the annual meetings of the Infectious Disease Society of America to illustrate the complexities involved in diagnosing and treating immunocompromised hosts, as well as the insidious nature of infection with *Strongyloides stercoralis*. How many other such time bombs are also out there? ■

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Polio Eradication 2011: A Work in Progress

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationships to this field of study.

Synopsis: *Efforts are ongoing in the attempts to achieve wild polio eradication worldwide, but challenges include adequate funding and political support, vaccine delivery logistics, the issue of vaccine-associated paralytic polio, and vaccine acceptance in resource-poor areas.*

Source: Centers for Disease Control and Prevention. Progress Toward Interruption of Wild Poliovirus Transmission — Worldwide, January 2010 — March 2011. *MMWR Morb Mortal Wkly Rep* 2011;60:582-586.

As of 2006, the ongoing transmission of indigenous wild poliovirus (WPV) was limited to only four countries — Afghanistan, Pakistan, India, and Nigeria. Subsequently, 39 countries that were previously certified as polio-free experienced new outbreaks and polio became re-established in Angola, Chad, Democratic Republic of the Congo (DRC), and Sudan. This *MMWR* report summarizes the progress toward polio eradication during 2010 and the first quarter (Jan-Mar) of 2011.

Globally 1,291 WPV cases were reported in 2010. This represented a 19% decline from 2009. WPV type 3 (WPV3) accounted for only 87 cases, whereas WPV type 1 (WPV1) accounted for 1,204 cases, a 145% increase from WPV1 numbers in 2009. The cases occurring within the four endemic countries (Afghanistan, Pakistan, India, and Nigeria) accounted for only 232 of the total cases, with 100 cases originating in Pakistan. Of the re-established transmission countries (Angola, Chad, and DRC), there were 159 cases with 100 cases from DRC. The big upswing came from countries affected by WPV1 outbreaks, the largest of those in Tajikistan (458 cases) and Republic of Congo (382 cases).

In the first quarter of 2011, there were 20 cases in Chad, 26 cases in Pakistan, and 36 cases in DRC, which represent a significant increase in cases compared to the first quarter of 2010. Now, as of July 6, 2011, Chad is taking the lead with 85 cases, DRC with 60 cases, and Pakistan with 58 cases of the total 252 cases year-to-date in 2011.[1]

The good news is that outbreaks in nine countries in 2010 have been halted (i.e., > 6 months since the last reported cases) and six other countries with outbreaks in late 2010 and early 2011 are on track to being stopped. The trouble spots to control will be Pakistan, Angola, DRC, and Chad if the Global Eradication Initiative (GPEI) is to achieve its strategic goals for 2012.

An Independent Monitoring Board (IMB) recently was formed to oversee progress toward wild polio eradication. Their recent report stresses that governments will need to react quickly with added resources and political will if the goal of WPV eradication is to keep on its timeline.

■ COMMENTARY

A decade ago, the number of polio cases worldwide had dropped from an estimated 350,000 in 1988 to fewer than 500 in 2001 due to the heroic efforts of the Global Eradication Initiative (GPEI). But during 2002, in India, and later during 2003 in Nigeria, resistance to vaccination led to increases in new polio cases, which then led to spread of these strains to other countries, many of which had been certified as polio-free.

In a recent article in *Nature*, Heidi J. Larson and Isaac Ghinai from the London School of Hygiene and Tropical Medicine examine the lessons learned from polio eradication efforts over the last 10 years.[2] From years of field research, they highlight the importance of community acceptance of vaccines and engagement strategies with local populations to eradicate polio. They cite the story of Nigeria in 2003 as the example of the importance of community support. At that time, five predominantly Muslim states in northern Nigeria boycotted polio vaccination when rumors spread that it was an American conspiracy to spread HIV and infertility. Around the same time, families in the Kano State in northern Nigeria were also suing Pfizer for allegedly unethical practices during the Trovan trial in 1996, so feelings of mistrust were strong. The boycott of oral polio vaccine (OPV) in Kano State lasted 11 months and polio cases in Nigeria went from a low of 56 in 2001 to 1,143 in 2006. From Nigeria poliovirus spread to 15 other sub-Saharan countries and as far as Indonesia, where 303 cases were all traced back to Nigeria.[3]

The experience in Nigeria, and similar vaccine refusals in India, made the GPEI redirect their strategies away from typical mass communication measures — posters, street banners, and radio messages — to work with local community members and local institutions to better deliver vaccine information and answer questions or concerns of families. The strategy has worked well. In Uttar Pradesh, India, after implementation of this approach, there has not been a case of polio for more than a year. The London School of Hygiene and Tropical Medicine has also established an early-warning system to detect and investigate public concerns or vaccine rumors before they snowball into larger problems *(see www.lshtm.ac.uk/eph/ide/research/vaccinetrust/)*.

In other areas, the increase in polio cases likely relates more to logistical barriers of vaccine delivery and distribution, coupled with lack of political will to invest both money and resources to polio eradication. This seems to be the case in southern Chad. Here, vaccine acceptance is not an issue, but rather adequate supplies of badly needed

vaccine hinder eradication efforts. In areas of Africa embroiled in conflict issues and political upheaval, health and vaccine programs are always in jeopardy.

Last, but certainly not least, is the issue of vaccine-associated paralytic polio (VAPP). OPV has the advantage of low cost, ease of administration, and induction of mucosal immunity. However, the attenuated variants in OPV can mutate and acquire neurovirulence; they can cause paralytic disease in vaccinees and contacts of vaccinated infants and children. Therefore, after mass OPV campaigns, the environment is abundant with a mix of excreted viruses, some of which have the virulence of wild polioviruses. Neal Nathanson in a recent *New England Journal of Medicine* commentary likens this to "fighting fire with fire."[4] Similarly, an epidemiologist involved in the early polio vaccine trials used the phrase "in like a lamb, out like a lion."[5]

In the United States and many industrialized countries, use of OPV was transitioned to inactivated polio vaccine (IPV) during and after 1998-2000. But the difference in cost between OPV and IPV is substantial. Although most experts see the way forward to eventually include cessation of the use of OPV, how and when that exactly will take place is unclear. Polio eradication will likely involve ongoing coordinated efforts and novel strategies, some of which might include use of IPV in certain geographic areas, bivalent and monovalent OPVs, new development of antiviral agents, and even possibly using fractionated intradermal doses of IPV,[6] which would make the product more affordable. Such a multi-faceted approach, coupled with vaccine programs supported and endorsed by local governments and communities, will hopefully end the long and successful reign of polioviruses. ■

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CME Questions

1. **The current outbreak of hemolytic uremic syndrome in Europe:**
   a. is unique in mostly affecting adults rather than children.
   b. has been linked to eating raw beef.
   c. involves the strain of *E. coli* that commonly causes HUS in children in the United States.
   d. demonstrates a low rate of progression from diarrheal disease to HUS.

2. **Interferon-γ release assays:**
   a. are more specific than tuberculin skin test.
   b. require skilled staff for reading of the assays.
   c. are based on the interferon-γ released by red blood cells.
   d. require multiple visits to the physician for proper interpretation.

3. **Which of the following statements concerning strongyloidiasis and its association with HTLV-1 infections is *true*?**
   a. Chronic HTLV-1 infection suppresses the expression of asymptomatic strongyloidiasis.
   b. Strongyloidiasis occurring during HTLV-1 infections causes severe myelopathy if left untreated.
   c. Treatment for strongyloidiasis is generally indicated if HTLV-1 infection is diagnosed, even if the patient is asymptomatic.
   d. Ivermectin is no longer effective in the treatment of strongyloidiasis when HTLV-1 infection becomes clinically apparent.

4. **All of the following issues play roles in the problems associated with polio eradication *except*:**
   a. vaccine acceptance by local communities.
   b. transmission of vaccine-associated polioviruses.
   c. adequate funding.
   d. persistent use of IPV.
   e. logistical barriers to vaccine delivery.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■