Extensively drug-resistant tuberculosis in a young child

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Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen?

The recent, rapid spread of Zika virus in South America and increasing reports of cases of congenital abnormalities spatiotemporally associated with Zika virus infections led WHO to declare a Public Health Emergency of International Concern on Feb 1. WHO also recently described measures that pregnant women should take to avoid infection.

This infection was a neglected tropical disease before 2015 and its natural history is still understudied. Male to female sexual transmission seems possible[1] and infectious virus was detected in semen from a patient with haematospermia during the 2013–14 French Polynesia outbreak.[2]

We describe the case of a 32-year-old man whose Zika virus infection was identified in January in the Toulouse University Hospital (Toulouse, France). He presented with clinical symptoms typical of an arbovirus infection 2 days after returning to France from Brazil and French Guyana. Molecular tools (RealStar Zika Virus RT-PCR Kit 1.0; Altona Diagnostics GmbH, Hamburg, Germany) were used to rapidly diagnose Zika virus infection, while finding no evidence of either chikungunya or dengue using an in-house RT-PCR system.

He completely recovered in a few days and further blood, urine, and semen samples were collected 2 weeks after diagnosis. Zika virus RNA loads were quantified with a commercial synthetic RNA transcript (Altona diagnostics GmbH, Hamburg, Germany). The RNA virus loads were 2·8 $\log_{10}$ copies per mL in plasma, 3·1 in urine, and 8·6 in semen. The viral load in the semen was roughly 100 000 times that of his blood or urine more than 2 weeks after symptom onset. The reason for this difference is unknown and needs investigation. Perhaps the virus can replicate specifically in the male genital tract, fill a specific genital reservoir, or both. Furthermore, we noted that Zika virus in semen could replicate in African green monkey cells—viral load increased by 4 $\log_{10}$ in culture fluid on days 3 and 8 after inoculation. This infectious viral load in semen possibly suggests that Zika virus is a sexually transmitted pathogen. The duration of excretion is unknown, but the virus might persist for many months. Ebola virus RNA has been detected in semen 7–9 months after disease onset.[3]

The presence of Zika virus in semen is a significant challenge, as is the possible teratogenicity of the virus. First, more than 80% of infected people are probably asymptomatic,[4] making them an enormous potential reservoir. Hence, pregnant women in areas where Zika virus is widespread should protect themselves not only from mosquitoes, but also from infectious virus in the semen of their partners—at least during pregnancy. Second, countries currently most affected by Zika virus have varying laws on womens' sexual and reproductive rights.[5] New efficient strategies to prevent unintended pregnancy and also the provision of easy access to contraception or medical abortions must be implemented quickly. But this emergency response to the outbreak proposed by WHO must be appropriate, accounting for the economic, ethical, educational, cultural, social, juridical, and religious factors dominant in affected regions.

Our findings confirm that infectious Zika virus is excreted into semen resulting in a high viral load that could lead to sexual transmission. Guidelines for women of reproductive age as well as women already pregnant must be widely implemented, understood, and put into practice. Furthermore, in many countries, especially those most affected by Zika virus, sexual transmission should lead to adaptation of current laws of womens' concern.

Lastly, the presence of Zika virus in semen (and potentially in a woman's follicular fluid) must be accounted for by reviewing all protocols used for gamete preservation or conservation.

We declare no competing interests. We would like to thank Isabelle Da Silva for technical contribution.

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1 Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis* 2011; **17:** 880–82.
2 Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis* 2015; **21:** 359–61.
3 Deen GF, Knust B, Broutet N, et al. Ebola RNA persistence in semen of Ebola virus disease survivors—preliminary report. *N Engl J Med* 2015; published online Oct 14. DOI:10.1056/NEJMoa1511410.
4 Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; **360:** 2536–43.
5 Roa M. Zika virus outbreak: reproductive health and rights in Latin America. *Lancet* 2016; published online Feb 12. http://dx.doi.org/10.1016/S0140-6736(16)00331-7.

Extensively drug-resistant tuberculosis in a young child

The Grand Round by Nicole Salazar-Austin and colleagues[1] presented a case of a 2-year-old child who had acquired extensively drug-resistant (XDR) tuberculosis after a 3 month visit to India.[1] After conducting different advanced clinical tests in the USA, a diagnosis of XDR tuberculosis was confirmed by drug-susceptibility testing of the isolates.

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The authors suggested the use of CT imaging as a biomarker to monitor treatment, because GeneXpert might not be sufficient to detect rifampicin-resistant strains. The child was immunised with the BCG vaccine, which is only partly protective against tuberculosis in India. Walter and colleagues[2] identified that 85% of all US immigrants who acquire tuberculosis do so after travelling to endemic countries. Reactivation rates of latent tuberculosis of 6–9% might lead to XDR tuberculosis and BCG failure. Also, the intracutaneous tuberculin test might produce false-positive results after BCG exposure and infection with non-tuberculous *Mycobacterium* spp. The Mantoux response to interleukin 1 polymorphism might also contribute to tuberculosis pathogenesis and interfere with sputum culture testing.

Because of the absence of an effective tuberculosis surveillance system, modelling exercises were used to quantify the cases reported in high-burden countries. Prolonged household contacts with sputum smear-positive sources might lead to the transmission of drug-susceptible organisms in children, which pave the way for the development of multidrug-resistant tuberculosis. Although the source of transmission was unclear, the young child might have previously been infected with *Mycobacterium tuberculosis* strains resistant to isoniazid and rifampicin by an individual with mixed infections. Due to appropriate laboratory monitoring and good tolerability of second-line antituberculous drugs, the child was treated successfully.

Reports of XDR tuberculosis are rare but might pose a risk for future tuberculosis epidemics. The Global Plan to Stop TB 2006–15 has taken major initiatives to decrease tuberculosis prevalence. Nevertheless, an improved understanding of molecular surveillance data is needed for enhanced control of the disease. Innovative diagnostic instruments are needed for more rapid detection of drug-resistant strains particularly in children. Novel T-cell assays are more specific than the traditional tuberculin skin test. Pilot studies testing these techniques in different areas of India that are endemic with tuberculosis might facilitate diagnosis. The failure of the BCG vaccine has emphasised the urgent need for an effective vaccine against all *M tuberculosis* strains. Additionally, an adjuvant delivered after vaccination might also be needed to boost immunity. Novel vaccines are ultimately needed to reduce the incidence of tuberculosis globally.

We declare no competing interests.

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1 Salazar-Austin N, Ordonez AA, Hsu AJ, et al. Extensively drug-resistant tuberculosis in a young child after travel to India. *Lancet Infect Dis* 2015; **15:** 1485–91.
2 Walter ND, Painter J, Parker M, et al. Persistent latent tuberculosis reactivation risk in United States immigrants. *Am J Respir Crit Care Med* 2014; **189:** 88–95.

How to minimise antibiotic resistance

The letter by Jung Hun Lee and colleagues[1] makes important additions to the comments of Glenn Tillotson on antimicrobial resistance.[2] The importance of "the development of fast and accurate diagnostic methods to detect antibiotic resistance genes (or pathogens) other than bla (or bla-harbouring Gram-negative pathogenic bacteria)" is well made. However, a practical issue remains that there is substantial variation in the ability to get an effective sample in cases of clinical infectious diseases in order to do any genomic testing in the first place. In certain situations, this can be in up to half of the cases of presumed infection.[3]

Diagnostic tests are crucial to the management of infectious diseases and combatting the rise in antimicrobial resistance.[4] However, reliance on genomic testing alone can be problematic. These tests should be done in conjunction with clinical examination and with diagnostic tests on clinical, physical, and biochemical and biomarker parameters associated with infectious diseases. Point-of-care (POC) biomarker tests are now being advocated by national governments, alongside antimicrobial stewardship, as a means of adding precision to diagnosis and management of infectious diseases in patients presenting to clinics in general.[5] In particular, C-reactive protein POC has been shown to reduce antibiotic prescribing for respiratory tract infections by 25%.[6–8]

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1 Lee JH, Park KS, Karim AM, Lee C-R, Lee SH. How to minimise antibiotic resistance. *Lancet Infect Dis* 2015; **16:** 17–18.
2 Tillotson G. Antimicrobial resistance: what's needed. *Lancet Infect Dis* 2015; **15:** 758–60.
3 Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). *Clin Infect Dis* 2013; **57:** e22–121.
4 O'Neill. Rapid diagnostics: Stopping unnecessary use of antibiotics. London: HM Government and Wellcome Trust, 2015.
5 Aabenhus R, Jensen Jens-Ulrik S, Jørgensen Karsten J, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014; **11:** CD010130.