

Interpretation of TORCH

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Abstract: Diseases in expectant mothers and newborns, like long-term disabilities, should be prevented by establishing an early diagnosis, evaluating and implementing adequate therapy. Some maternal infections, especially those during early gestation, can result in foetal loss or malformation because the ability of the foetus to resist infectious organisms is limited and the foetal immunological system is unable to prevent the dissemination of these organisms to the various tissues. One group of microbial agents generally known as TORCH can cause remarkably similar manifestations. The increasing need to diagnose these infections has fuelled and supported the rapid improvement in antigen and antibody tests. All seroassays are only surrogate markers of the disease. The presence any positive pathogen-specific IgM in the maternal serum should call for additional confirmatory testing in a reference laboratory before undertaking any intervention. Direct antigen testing or multiple testing would seem to be appropriate for confirmation. All these assays need to be correlated clinically to avoid misinterpretation of results and minimize the anxiety of patients, especially if termination of pregnancy is being considered.

Introduction

Maternal viral and protozoal infections *contribute enormously* to childhood morbidity. Primary TORCH infections include infections associated with *Toxoplasma*, Other organisms (Parvovirus, Human Immunodeficiency virus, Epstein Barr virus, Human Herpesvirus 6 and 8, Varicella, *T. pallidum*, enterovirus), rubella, cytomegalovirus (CMV) and herpes simplex virus (HSV) type 1. These infections in a pregnant woman can lead to severe foetal anomalies or even foetal loss. Highly sensitive and specific tests are available for the diagnosis of TORCH infections. Individual TORCH tests based on the clinical presentation and history of the patient may be useful. Because evidence of foetal infection on initial screening raises the spectre of complicated and dangerous foetal diagnosis (cordocentesis) or elective abortion, accurate testing and its proper interpretation are crucial to achieve a reduction in the number of foetuses who are unnecessarily injured by such techniques.

Toxoplasmosis

Toxoplasmosis is caused by *T. gondii*, a unicellular protozoan parasite found worldwide. Serological prevalence data indicate that toxoplasmosis is one of the common infections of humans throughout the world. The seroprevalence of *T. gondii* among various patient groups in India has been reported to be between 6% and 57%.^{1,2,3}

Maternal acute toxoplasmosis during pregnancy has been implicated in spontaneous abortion, stillbirth and premature births. Congenital toxoplasmosis occurs when a woman gets infected during pregnancy, or, more rarely, if she is

immunocompromised and a previously acquired infection is reactivated. The incidence of vertical transmission ranges from 11% in the first trimester to 90% in the late third trimester, with an overall transmission rate of approximately 50%.⁴ There may be no sequelae of congenital toxoplasmosis, or sequelae may develop or be evident after birth. The clinical features include chorioretinitis, strabismus, blindness, epilepsy, psychomotor or mental retardation, anaemia, jaundice, rash, encephalitis, microcephaly, intracranial calcification, hydrocephalus, diarrhoea, hypothermia and non specific illness.⁵ The isolation of *T. gondii*, detection of *T. gondii* antigen in tissues, blood, amniotic fluid, cerebrospinal fluid (CSF) and antibodies for *T. gondii* (IgG, IgM and IgA), and detection of *T. gondii* DNA by molecular assays may be used for the diagnosis of toxoplasmosis. When *Toxoplasma* infection is suspected during or before pregnancy, the diagnosis is primarily based on serology.

Interpretation of *Toxoplasma* serology in pregnancy

The diagnosis of acute *T. gondii* infection in most cases requires demonstration of a rise in the IgM or IgG antibody titres (OD values or IU/ml) in serial serum samples drawn 3 weeks apart tested in parallel (either seroconversion from a negative to a positive or its significant rise from a low to a higher value).⁵ Because the diagnosis is frequently considered relatively late in the course of the disease, the antibody levels might already have achieved their peak values at the time the first sample is obtained. It is, therefore, often difficult to discriminate between infections acquired recently (possibly during pregnancy) or in the distant past. Thus, the initial serum sample must be obtained as early as possible during gestation. An algorithm for the serodiagnosis of toxoplasmosis during pregnancy is shown in Fig 1.⁶

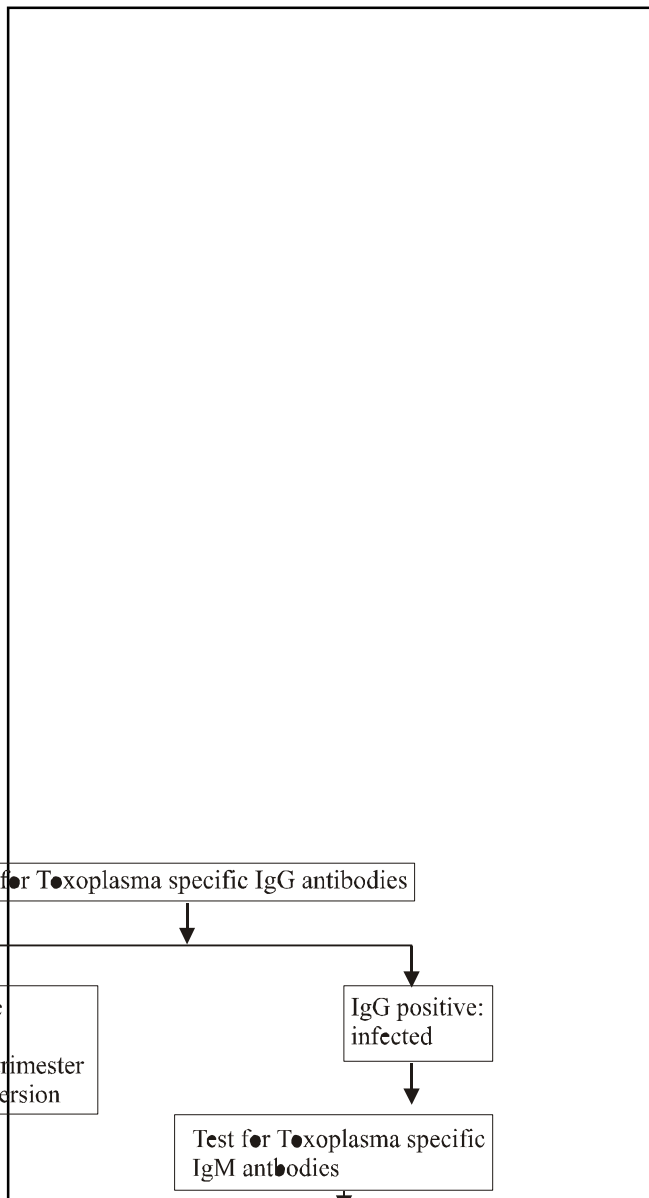


Fig. 1] Diagnostic algorithm for *Toxoplasma* serology in pregnant women.

Initial screening of maternal serum involves testing for IgG and IgM antibodies. A lack of both essentially excludes active infection, but identifies the patient as being at risk for first trimester acquisition of primary infection and hence, in need of instruction about primary prevention and retesting during each trimester to rule out seroconversion. The presence of IgG antibodies in the absence of IgM antibodies in the first two trimesters almost always indicates maternal exposure to infection with essentially no risk to the foetus (the exceptions are immunodeficient patients). In the third trimester, a negative IgM test is most likely to be consistent with a chronic maternal infection, but does not exclude the possibility of an acute infection acquired early in pregnancy. This is especially true in those patients who exhibit an rapid decline in their IgM titres during the acute phase of infection. In these cases, other serological tests (e.g. IgG avidity) may be used. Hence, if a

IgG positive
IgM negative
Infected for 1 year if tested in first trimester
If tested later, instruction about primary prevention and retesting during each trimester

IgG positive
IgM positive
Test for IgG avidity

High avidity
Past infection acquired early in pregnancy. This is especially true in those patients who exhibit an rapid decline in their IgM titres during the acute phase of infection. In these cases, other serological tests (e.g. IgG avidity) may be used. Hence, if a

Low avidity
Test for IgG avidity

Draw second sample 2-3 weeks later; send both the samples to a reference laboratory for confirmation of results

pregnant woman is tested in the second or third trimester rather than the first trimester and is found IgG positive but IgM negative, it is advisable to perform an IgG avidity test. High-avidity IgG indicates that the infection was acquired more than 4 months ago and low avidity may be indicative of recent infection. However, the avidity test is not confirmatory for recent infection.

A negative IgM essentially excludes recent infection, but a positive IgM result is difficult to interpret without fallacies because *Toxoplasma* specific IgM antibodies may be detected by ELISA as late as 6-12 months and rarely 18 months after acute infection.⁵ A major problem with *Toxoplasma*-specific IgM testing is the lack of specificity. Two situations are frequently seen. First, positive IgM but negative IgG, and second, both IgG and IgM positive in the serum. In the first case, a follow-up blood sample of the patient should be drawn 3 weeks after the initial collection and both samples tested simultaneously. In case of acute infection, the second specimen drawn 3 weeks later may have high positive IgG and IgM antibodies. If the IgG remains negative and IgM is positive in both the specimens with not much difference in values, the IgM result should be considered false-positive and the patient as not infected. In the second situation, avidity testing followed by prenatal molecular assays are recommended. In fact, all serology test results with equivocal IgG or IgM or positive IgM should be verified at a reference laboratory (e.g. *Toxoplasma* Reference Laboratory, Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi).⁶

Prenatal diagnosis for foetal infection is advised in a pregnant woman when a diagnosis of acute infection is suspected clinically. Acute infection is confirmed by the isolation of *T. gondii* or amplification of its DNA in the blood or body fluids. Polymerase chain reaction (PCR) performed on the amniotic fluid for the detection of *T. gondii*-specific DNA at 18 weeks of gestation is a sensitive, rapid and specific assay compared with conventional serodiagnostic procedures done on the foetal blood.⁷

The treatment of an acutely infected pregnant woman does not eliminate, but may decrease, the incidence of foetal infection. Spiramycin is the drug of choice and sulfadiazine can be used as an alternative with proper precautions at term. As spiramycin does not reliably cross the placenta, if foetal infection is documented, daily administration of sulfadiazine (4 g), pyrimethamine (25 g) and folinic acid (5-15 mg) is recommended as an alternative to the termination of pregnancy where abortion is illegal or when the woman wishes to continue the pregnancy.⁸

Cytomegalovirus infection

Cytomegalovirus infection in humans has a varied presentation, ranging from no disease in normal hosts; congenital CMV syndrome in neonates, which is frequently

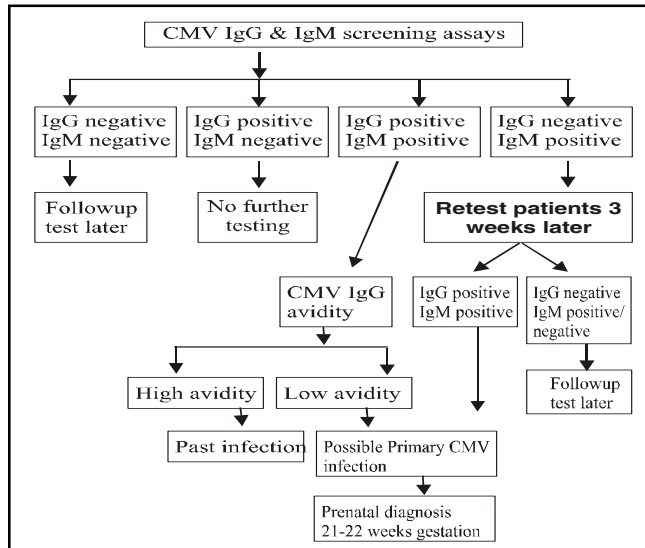


Fig. 2: Diagnostic algorithm for CMV serology in pregnant women

fatal; to the infectious mononucleosis syndrome in young adults. Primary infection is seen in seronegative patients who have never been infected with CMV. Secondary infection is the activation of latent infection or reinfection in a seropositive person. Intrauterine CMV infection has been detected in 0.2%-2.5% of cases and is the most commonly identified cause of congenital infection. Serological surveys indicate that in India, 20%-94% of pregnant women are seropositive for CMV.^{9,10} Most of them have no symptoms and very few have a disease resembling mononucleosis. It is the foetus that may be at risk of congenital CMV infection following primary CMV infection (40%). Intrauterine transmission of non primary CMV is rare (0.2%-1%). It is in this context that prenatal risk assessment of pregnancy at 21-22 weeks of gestation, potentially complicated by CMV, can be accurately estimated using molecular assays, e.g. nucleic acid sequence-based (NASBA) amplification assay.

Fewer than 5% of congenitally infected infants develop symptoms during the neonatal period. Possible manifestations range from severe disease with intrauterine growth retardation, jaundice, hepatosplenomegaly, petechiae, central nervous system (CNS) abnormalities and chorioretinitis, to a more limited involvement.

Interpretation of cytomegalovirus serology in pregnancy

Severe infections with CMV in pregnant women are generally asymptomatic or accompanied by symptoms non-specific for CMV, so serological testing for CMV antibodies is usually the first test ordered by the physician. The main challenge for diagnostic laboratories in screening pregnant women for CMV specific IgM during non-primary infections is latency of the virus or cross-reactivity of CMV (also known as human herpesvirus 5) with the herpes group of viruses. The approach to these problems requires a diagnostic algorithm based on screening pregnant women with a CMV-specific IgG assay and a sensitive IgM capture assay, followed by further testing of

CMV IgM-and IgG-positive specimens with a CMV IgG avidity assay (Fig. 2).

If the tests for CMV IgG and IgM antibodies are negative, it indicates that there is no active infection and the patient has to be tested later as she may be at risk for acquiring the infection in future. If IgG alone is positive, it suggest that the patient is immune and no further testing is required. If both IgG and IgM are positive, a CMV IgG avidity test may be done which measures the functional binding affinity of the IgG class of antibodies in response to infection. During the first few weeks of primary infection, IgG antibodies with a low avidity are produced whose avidity increases over time. This maturation of antibody avidity over time can be used at the diagnostic level to discriminate between primary and non-primary infections.¹¹ Detection of low avidity in specimens from pregnant women generally indicates that primary CMV infection has occurred within the past 18- 20 weeks, whereas detection of high-avidity CMV IgG excludes primary infection.¹² However, in as may as 35%-40% cases, low-avidity IgG response may also be seen in infections of more than 4 months duration.

Avidity tests can be performed only on IgG-and IgM-positive specimens, so the main problem occurs when only the CMV IgM result is positive. Since the rise of CMV IgM and IgG titres occurs almost simultaneously in response to primary CMV infection in immunocompetent individuals, it is recommended that another specimen be obtained within 3 weeks and test for CMV IgG and IgM antibodies. If the IgG test remains negative, the first CMV IgM result is taken as false-positive which can be due to viral cross-reactivity in CMV IgM assays.

If primary CMV infection in a pregnant woman is documented, further testing should be done to determine if actual transmission of the virus has occurred. As stated earlier, these antibody assays are surrogate markers of the disease and need to be proven further. Detection of viral DNA by molecular assays has now replaced cell culture as the 'gold standard' for the detection of CMV. Recent studies have shown that a high viral load determined by quantitative PCR in the amniotic fluid correlates with CMV disease in the foetus and newborn.¹³ Determination of CMV pp67 mRNA using NASBA has also been found to be useful in determining the reactivation of this disease¹⁴. There are limited treatment options for CMV infection in pregnancy. Current recommendations limit the use of ganciclovir in pregnancy to severe (life- or sight-threatening) maternal infections.

Rubella virus

Rubella (German measles) acquired in the first 12 weeks of pregnancy is associated with a 90% risk of congenital malformations. The seroprevalence of rubella in Indian pregnant woman has been reported to be between 74% and 95%.^{10,15} The typical features of congenital rubella syndrome are cataract, intrauterine growth retardation,

thrombocytopenia, purpura, patent ductus arteriosus, osteitis and hearing impairment. The only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, or a positive viral culture for rubella that remains the 'gold standard' for diagnosis. Although rubella infection is definitively diagnosed by isolation of the virus in tissue culture, viral cultures are labour-intensive, and therefore not carried out in many laboratories and the generally not used for routine diagnosis of rubella. Hence, serology is the most common method of confirming the diagnosis of rubella. Neonatal rubella infection can be diagnosed reliably by using a cord blood sample for IgM rubella assay.

Interpretation of rubella serology in pregnancy

The immune status of a pregnant woman is determined by routine antenatal screening for rubella-specific IgG antibody, and detection of levels >10 IU/ml implies immunity following vaccination or infection before pregnancy. The diagnosis of infection is usually made by the detection of rubella-specific IgM. Although commercial assays are available, they vary in format, sensitivity and specificity. Furthermore, rubella-specific IgM may be present a year or more after natural infection or vaccination and after subclinical reinfection.¹⁶ False-positive results may also be due to cross-reacting IgM antibodies or rheumatoid factor as in other IgM-based serologies, so the results of rubella IgM assays in pregnant women should always be confirmed in a reference laboratory and interpreted with caution. Any history of rash or contact, previous rubella immune status and history of vaccination should be taken into consideration. Also, measurement of rubella IgG avidity may help to determine the presence of primary infection, reinfection or approximate time of infection in an asymptomatic pregnant woman.¹⁷

Herpes simplex virus

Herpes simplex virus is a DNA virus belonging to the family *Herpesviridae*. Two biologically distinct serotypes have been identified - HSV-1 and HSV-2. The clinical manifestations of primary HSV-1 infection include gingivostomatitis, conjunctivitis, keratitis, herpetic whitlow and encephalitis. The classic presentation of primary HSV-2 infection is herpes genitalis, an infection characterized by the appearance of extensive, bilaterally distributed lesions in the genital area, by fever, inguinal lymphadenopathy and dysuria. Approximately 85% of cases of primary genital HSV are caused by HSV-2, with the remaining cases being caused by HSV-1. The acquisition of genital herpes during pregnancy has been associated with spontaneous abortion, prematurity, and congenital and neonatal herpes. The majority of neonatal infections occur during the peripartum period, but some also occur *in utero* or perinatally. Neonatal HSV infection is almost

invariably symptomatic and frequently fatal. Babies may present with localized disease of the skin, eyes and mouth, encephalitis with or without skin involvement or disseminated disease. It has been reported that the seroprevalence of HSV in Indian pregnant women is 70%.⁹

There is considerable difference of opinion regarding routine screening of pregnant women for HSV. An estimated 35%-80% of infants with neonatal herpes are born to women with no known history of genital herpes or physical signs of infection at delivery. Therefore, the screening of asymptomatic pregnant women has the potential of identifying unrecognized active HSV infections.¹⁸ To identify newly acquired infection in HSV-seronegative women, repeat testing in late pregnancy should be carried out. In those who are HSV-seropositive, a concern for transmission to the infant is likely to result in administration of antiviral drugs to the mother or in a caesarean section; the effectiveness of neither of which in controlling HSV transmission has been substantially demonstrated.¹⁹ Though serological testing for HSV in the latter half of pregnancy could identify susceptible women, so that serological testing of their partners and appropriate counselling as to the risk of acquiring genital herpes could be undertaken, the effectiveness of such counselling has not been demonstrated.

Risk and cost-benefit analysis are needed to assess HSV type specific serological screening of pregnant women. After one such evaluation, it was concluded that screening for maternal type-specific HSV antibodies is not beneficial in preventing neonatal herpes.²⁰ Therefore, routine serological screening for genital herpes in asymptomatic pregnant women remains debatable. Viral culture is the most sensitive method for the laboratory diagnosis of HSV. It also allows typing of the viral isolate whereas no single seroassay is available that can reliably differentiate between HSV-1 and 2. Moreover, the above and below the navel concept of HSV-1 and 2 is also not absolute. An equal number of infections with HSV-1 below the navel have been documented.

TORCH testing in HIV-infected women

This issue remains confusing, even more so than it is in non-HIV infected gravidae. Patients who are newly diagnosed as being HIV infected and referred for prenatal care should be tested for the TORCH group of infections and *T. gondii*-specific IgG antibodies. If positive, test for IgM antibodies to rule out acute *T. gondii* infection should be carried out. Patients who test negative do not require further testing until after the pregnancy unless they are severely immunocompromised or show signs and symptoms of toxoplasmosis. IgG antibodies to CMV should be obtained in or HIV-infected gravida who is at high risk of CMV infection, i.e. patients with CD4+ counts less than 100/c- mm. There is no value in routinely testing prenatally for evidence of HSV infection.²¹

Conclusion

There have been tremendous advances in direct antigen detections and the sensitivity and specificity of assays detecting TORCH antibodies. It is the interpretation of the results in individual cases that need to be made carefully. The relatively poor degree of reliability can lead to unnecessary obstetric interventions or elective termination of pregnancy. Any positive pathogen-specific IgM in the maternal serum should be subjected to additional confirmatory testing in a reputed research laboratory before any intervention is carried out. No termination of pregnancy should be recommended only on the basis of a single antibody test. Antenatal diagnosis must be attempted by way of virus isolation or its antigen detection using molecular assays. Limitations of IgM serology by way of false-positive and negative results cannot be undermined; however, cord blood samples are preferred for IgM serology. At the same time, undue importance cannot be given to low-avidity IgG antibodies. Seroassays cannot be viewed in isolation, therefore, the results need to be correlated clinically to avoid their misinterpretation and minimize the anxiety of patients, especially if termination of pregnancy is being considered.

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Literature Review

Compiled by Dr. DDS Kulpati

Inhibitory effect of Nicotine on Experimental Hypersensitivity Pneumonitis (HP) on Vivo and in Vitro. *Bianchet, Mr, Assayag E1 and Cormier Y. Am J Respir Crit Care Med* 2004;**169**:903-909.

The nicotine, which is a major component of cigarette smoke, has immunomodulatory and antifibrotic effects. In fact, it inhibits lymphocyte proliferation, interleukin (IL), IL-1, tumour necrosis factor (TNF) IL-6 and IL-12 production by macrophages and fibroblast proliferation. Interestingly certain inflammatory diseases, such as sarcoidosis and ulcerative colitis are less frequent in smokers than in non-smokers and cigarette smoking protects against radiation pneumonitis. When exposed to an environment that can cause hypersensitivity pneumonitis, smokers have lower level of specific antibodies to causative antigen. On the other hand when HP occurs in smokers, it promotes an insidious and more chronic form of the disease and worsens the clinical outcome.

In this study HP was induced mice that were treated with nicotine either intraperitoneally (IP) (0.5 to 2.0 mg/kg/day or intranasally (IN) (0.025 to 2.0 mg/kg/day) both IP & IN - treated animals had fever bronchoalveolar larvae total cells and lymphocytes and a decreased lung-tissue inflammation IFN- γ but not interleukin-10-m RNA expression was reduced in lung tissue of 2.0 mg/kg. IN - treated animals. To test the effect of nicotine on alveolar macrophages, AMJ2-C11 cells were treated with nicotine and stimulated with LPS or saccharopolyspora rectivigula (SR) a causative agent of HP.

Nicotine reduced TNF release & TNF, interleukin-10, & IFN- γ mRNA expression after stimulation and decreased CD-80 expression by 55% in LPS stimulated cells and by 41% in SR-stimulated cells. It was concluded that

nicotine could be at least impart, responsible for the protection observed in smokers against HP. The inhibitory effect of nicotine on alveolar - macrophages could be one of the mechanisms involved.

The Bactericidal activity of Moxifloxacin in patients with pulmonary tuberculosis. Gosline, RED, Viso, LO, San N E et al. *Am J Respir Crit Care Med*. 2003;**16**:1342-40

Fluoroquinolones, which inhibit DNA-gyrase, are highly active against Mycobacterium tuberculosis, including strains resistant to first line drugs. The minimum inhibitory conc. of moxifloxacin, is four fold lower than that of levofloxacin. It has the greatest sterilizing activity. The combination of rifampin, pyrazinamide, and moxifloxacin had substantially greater sterilizing activity compared with the standard regimen.

In this study, patients in whom acid-fast bacilli smear-positive tuberculosis was newly diagnosed, were randomized to receive 400mg moxifloxacin, 300mg isoniazid, or 600mg rifampicin daily for 5 days. Bactericidal activity was estimated by the time taken to kill 50% of viable bacilli (Vt50) and the fall in sputum viable count during first 2 days designated as the early bactericidal activity (EBA). The mean Vt50 of moxifloxacin was 0.88 days (95% confidence interval) and the EBA was 53 (95% CI). For the isoniazid group the (Vt50) was 0.40 days (95% CL) and the mean EBA was .77. For rifampin, the mean Vt50 was .71 days (85cl) and the mean EBA was .28 (5%CI). Using EBA method isoniazid was significantly more effective than rifampin (p<0.01) but not moxifloxacin. Using Vt50 method isoniazid was more effective than both rifampin and moxifloxacin.

Moxifloxacin has an activity similar to rifampin in human subjects with pulmonary tuberculosis, suggesting that it should undergo further assessment as a part of a short course regimen for the treatment of drug resistant tuberculosis