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â€œSearch on for 'Holy Grail' of TB controlâ€?

26 April 2013 | Interviews | By Rahul Koul Koul

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QIAGEN, a global leading provider of sample and assay technologies, has developed and market more than 500 sample and assay products as well as automated solutions for such consumables. QIAGEN's assay technologies include one of the broadest panels of molecular diagnostic tests available worldwide. This panel includes the digene HPV Test, which is regarded as a "gold standard" in testing for high-risk types of human papillomavirus (HPV), the primary cause of cervical cancer, as well as a broad suite of solutions for infectious disease testing and companion diagnostics. QIAGEN acquired Cellestis, a known medical diagnosis firm in 2011. This has broadened the horizons of the company in the TB control. As of now, the company employs nearly 3,900 people in over 35 locations worldwide.

Q: What made QIAGEN to acquire Cellestis?

The Cellestis, now a QIAGEN company, develops and markets QuantiFERON (QFT) technology products for medical diagnosis and scientific research. It was an important acquisition for QIAGEN in late 2011 because of accelerating growth of QFT, the global market and potential impact on TB control. Cellestis was also at a point of either growing bigger or get acquired. The acquisition was a perfect match..

Q: Tell us about the QuantiFERON (QTF) technology? What are the advantages?

QFT is a patented whole blood immunoassay for detecting cell mediated immune (CMI) responses of T cell lymphocytes using whole blood samples. If TB infection is present, the stimulation of effector T cells with highly-specific TB antigens or mitogen coating the assay tubes will result in the release of a cytokine or chemical messenger called interferon gamma. This cytokine is then identified and quantified from plasma by standard ELISA, a very familiar technology to laboratories.

Compared to the current tuberculin (or Mantoux) skin test which is a subjective clinic-based test, this technology provides more accuracy and sensitivity in detecting TB infection. The fact that it is a laboratory based test with a familiar platform means standard procedures, and high standards of quality. This should result in better clinical accuracy which should lead to better decision making!

QFT is a modern alternative to the 110 year old Mantoux test. As the modern alternative, studies have shown that QFT is more precise than TST in identifying people who are infected from recent TB exposure and who will progress to active TB disease. It is significantly more specific in contacts, by reducing the number of individuals needing evaluation while maintaining a very high negative predictive value. QFT is >99% specific and virtually eliminates false-positive readings caused by BCG.
The operational advantages of the laboratory-based QFT are numerous. It eliminates the staff and patient time needing to return to clinic for skin test reading, the recording of test results and unnecessary medical evaluation and treatment from falsely positive Mantoux readings. The Mantoux test is notoriously inaccurate in BCG vaccinated persons because of cross reacting antigens that commonly cause false positive results. QFT does not use any antigens that cross react with BCG and this is huge in a country like India where BCG vaccination is the policy for every newborn. .

Q: Why is QFT TB Gold a very popular test? What are its limitations?

There is growing interest in QFT- -TB Gold in India for both good and bad reasons. The "good" consists of interest caused by its excellent track record and higher sensitivity, accuracy and operational advantage compared to the century old skin test. It has great potential as a screening tool. The "bad" is that some providers may think it is a substitute for the banned serologic tests for TB diagnosis, which it absolutely is not! The mistaken allure of using a blood test instead of the correct evaluation of pulmonary tuberculosis with sputum collection is one that we have been fighting. There is no blood test that can be used as a stand-alone test for the diagnosis of active tuberculosis. Unlike the banned serodiagnostics tests, QFT is a well-studied, FDA approved test whose intended use is that of an aid to diagnosis to TB infection. TB infection can be either active or latent (dormant). When the individual is a "carrier" of latent TB, there are no symptoms and the person is neither ill nor contagious. Because there are no TB bacteria that can be cultured in this latent condition, IGRAs (including QFT) and the Mantoux are the only tests available for detection by measuring the cellular immune response to TB. However, that said, the limitation of IGRAs are the same as the Mantoux, it cannot distinguish between active and latent infection. Like all assays, results should always be interpreted in conjunction with other clinical information. Critical information for interpretation include a symptom review, a TB risk assessment, radiography and other medical and diagnostic evaluations if clinically indicated. Qualified and well trained doctors may be outnumbered by untrained providers who don't know. A clear need for education is needed and we are doing all we can.
Other limitations include its cost and the lack of knowledge of the importance TB screening of high risk populations and addressing latent TB through prevention. For example, QFT could impact the TB burden of India if the private sector used it as a tool to screen and prevent TB among diabetics, those on dialysis, and people being placed in high transmission settings such as teaching, public transport etc. QFT may be the best technology to reach the masses but due to its costs, as one provider told me recently, "It is the product for the classes and not the masses" The affordability is a huge issue in developing nations like India. We have been in talks with the government agencies about screening and treaten latent TB infection but due to budget contraints,their priority is justifiably on treating active TB and not the latent TB infections. Funding is a big challenge for public health programmes.

Q: Please tell us in brief about the current status of the TB situation globally?

India accounts for over 20% or 2 million out the 9.1 million cases globally. Although deaths from TB has been reduced substantially from nationwide treatment coverage, the number of cases has not changed over the past 5 years and the estimated Indian mortality from TB is 330,000 deaths due to TB each year. Over 1000 deaths occur per day and two deaths happening every 3 minutes. Another depressing fact is that the Indian prevalence of latent TB infection is 40% (~500m) infected with M. tuberculosis (with a 10% lifetime risk of TB disease in the absence of HIV or diabetes). This reservoir of infection is maintained by the transmission from fresh cases and lack of prevention of TB among those who are likely to break down or removal of cases that are in settings of high outbreak risk. Multi-drug resistant TB is another alarming issue that has been on the rise with half of the globes half a million MDR-TB cases in India and China alone.

Apart from that, the disease leads to loss of work hours and money in huge amount. The indirect costs to society is estimated to be $3 billion and direct costs to society is $300 million. The productive work days lost due to TB illness are 100 million. In addition, there are additional grave social implications such as the300,000 school drop-outs due to parental TB and 100,000 women rejected by families due to TB.
Q: How are the Interferon-Gamma Release Assays (IGRAs) different from banned sero-diagnostic test?
QFT is a whole blood, ELISA-based IGRA that can aid in diagnosing Mycobacterium tuberculosis infection and should not be

confused with banned serologic ELISA tests for TB. IGRAs measure the cellular immune response (CMI) to TB infection, which is key to controlling the disease. They detect gamma interferon, a chemical messenger that is easy to measure when TB is present. Serologic tests are unreliable because they measure antibodies from the humoral immune response that may or may not be detected during infection because of TB's tendency to hide inside of cells.

Unlike the banned tests, commercial IGRAs have been rigorously studied for regulatory approval in the US, Canada, Australia, Japan and European markets where they are currently licensed for use. There are over 1000 clinical studies to date on the commercial IGRAs with the vast majority on QuantiFERON TB-Gold (QFT Gold).

Q: How do you compare IGRA with TST? Which is better?

In my personal and programmatic experience of using QFT for nearly a decade in San Francisco, IGRAs are clearly superior. For one thing QFT is a laboratory based blood test while the TST is a skin test that results as a bump (if reactive) that is read in millimeters by clinic staff. Would you prefer a laboratory result or someone reading a bump on your arm? Further, formal TST training varies or may not exist at all, making subjectivity of the reading and inter-reader variability just a few out of many weaknesses of the test. As mentioned before, the antigens used in QFT are highly specific TB antigens, where as the antigens used in the TST are anan antigen soup of hundreds of proteins that cross-react with BCG and many environmental non-tuberculous mycobacteria (NTM). False positives from prior BCG and NTM colonization therefore occur frequently with the TST and are often not trusted by the patient or doctor. When switching from the TST to QFT in our immigrant clinic in San Francisco, the positive rate dropped by almost 50% and much larger in immigrant children. This made using the TST in BCG vaccinated persons like flipping a coin. The accuracy translates into savings from not having to do medical and radiographic evaluations from false positive results. QFT results are also obtained with one visit, so there is less patient drop out than the TST, which can be substantial. Unfortunately, the highest rate of noncompliance was in our HIV clinic, more than 50% would not return. The other advantages of using QFT is the automated lab results and elimination of manual documentation of the TST that would often be lost. This makes QFT an ideal surveillance and research tool. gives out automated results and is not affected by BCGIn the US, guidelines say that IGRAs can be used in all situations where the skin test is currently being used and are preferred in BCG vaccinated persons, and persons unlikely to return for TST reading.

Q: What are the latest technological trends as far as the TB control measures are concerned?

The big search is on for the bio markers that distinguish active and latent TB, and one that can predict active TB. This is the holy grail for TB screening that will bring immense benefits to mankind because it will enable programs to clearly focus on who needs prevention treatment. In the absence of this "ideal test", TB programs should focus on high risk groups. Targeted screening and prevention has been very successful in the in the US and other western nations, and resulted in crushing the HIV-TB epidemic and waves of increases caused by immigrants coming from TB endemic countries. Important risk groups for India to focus screening and prevention on are contacts to active TB, HIV, and the growing diabetes population which is likely contributing more TB cases than HIV in the Asia-Pacific region. Preventing TB among those with unacceptably high ndividual risk for TB should also be addressed as well. These include, individuals with latent infection that are being placed on immunosuppressive treatment, those undergoing organ transplant or being placed on biologic agents or steroids for autoimmune disease.

Q: Are the policy decisions getting hampered due to the various challenges?

I would say yes in case of Indiaand many developing countries. The country standards that are based on WHO standards of passive diagnosis by smear and not universal culture and drug susceptibility, is a bar that is set too low and impairs countries from obtaining funding for higher standards. In my opinion, these standards are partly to blame for rising MDR-TB and the stagnant burden in TB in India and the rest of the world. In order to have maximum impact quickly, the highest standards for care should exist where cases are highest and there must be a focus on preventing cases and finding cases before they spread. This would require a major shift in policy and funding. But if there is any country in the world that can do it, it is India, if she finds the will to do it. Getting there however, is the big question. There are challenges beyond TB health policy and strategies in India. Imbedding the health care infrastructure with policy and enforcement for quality and safety and accessibility to those who need it most is critical but is a long road. None of this should be a show stopper however, I do think that greater partnership with the private sector is the opportunity that can enhance case finding and prevention. New tools such as IGRAs and rapid molecular active TB diagnostics with collaborative guidelines and policies can be a way to engage them and provide them a role in TB control that could make a tremendous difference.