

PALEOPATHOLOGY IN CHAGAS DISEASE

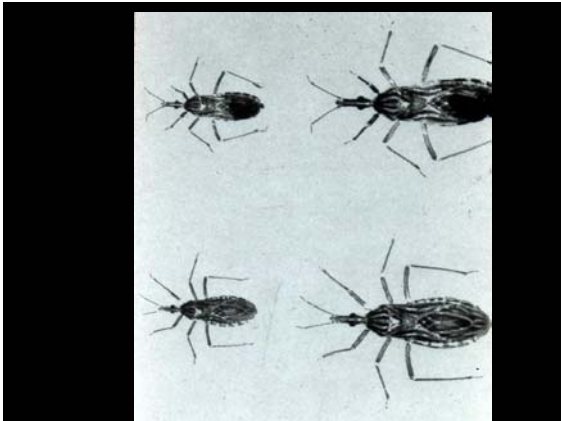
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REDUVIID (KISSING BUG- CHIRIMACHA)

THERE ARE MANY SPECIES OF TRIATOMINE BUGS AND NUMEROUS MAMMALIAN HOSTS FROM NORTHERN ARGENTINA AND CHILE TO NORTHERN CALIFORNIA. LOCALLY ACQUIRED INFECTIONS IN HUMANS ARE GENERALLY VERY LIMITED, AND ONLY PRODUCED BY BUGS THAT HAVE ADAPTED TO COLONIZING HUMAN DWELLINGS. THIS IS BASICALLY 5 SPECIES. THESE INSECTS DEPOSIT THEIR FECES CONTAINING THE T. CRUZI AND THEY ENTER THE BODY BY SCRATCHING THE BITE SITE OR VIA THE MOUTH OR THE EYES. THEY MAY ALSO BE TRANSMITTED BY BLOOD OR ORGAN TRANSPLANTS.



- 1885 BROUGHT TO PERU BY CHILEAN SOLDIERS IN WAR OF THE PACIFIC
- 1907 MINAS GERAIS, BRASIL DISCOVERY
- 1950 FOUND IN AREQUIPA/MOQUEGUA PERU
- 1990 BROUGHT TO JAEN, NORTHERN PERU BY INFECTED DOCTOR FROM AREQUIPA
- 2000 FOUND ALL OVER PERU

CARLOS CHAGAS 1879-1974

- GRADUATED MEDICAL SCHOOL , RIO, BRASIL 1903
- MALARIA CONTROL OFFICER , LASSANCE, 1907
- LOCAL INHABITANTS COMPLAIN THEY WERE BITTEN BY A BLOOD SUCKING BUG AT NIGHT.
- CHAGAS COLLECTED BUGS AND FOUND PROTOZOAN FLAGELLATES IN THEIR FECES.
- HE FOUND THE SAME CIRCULATING TRYPANOSOMES IN THE BLOOD OF CHILDREN WITH ACUTE FEBRILE ILLNESS.
- THIS IS THE FIRST TIME THE VECTOR OF A DISEASE WAS FOUND BEFORE THE DISEASE.



ACUTE PHASE CHAGAS DISEASE

USUALLY CHILDREN – FATALITY RATE 10%
 INCUBATION PERIOD - 2 WEEKS/SEVERAL MONTHS
 MAY BE ASYMPTOMATIC
 MAY BE LESION AT PORTAL OF ENTRY – CHAGOMA
 FEVER – EDEMA, RASH, VOMITING
 LYMPHADENOPATHY, HEPATOMEGALY
 INFANTS – MULTIPLE SKIN CHAGOMAS
 HEPATOMEGALY COMMON
 CONVULSIONS, TREMOR, WEAK REFLEXES

CHRONIC CHAGAS DISEASE

HEART – 30% OF SURVIVORS ABNORMAL ECG
 RIGHT BUNDLE BLOCK
 AV CONDUCTION ABNORMALITIES
 ARRHYTHMIA
 CHEST PAIN, EDEMA, DIZZINESS
 MEGACARDIA – EMBOLISM, SUDDEN DEATH
 GASTROINTESTINAL – VARIES IN GEOGRAPHIC LOCALS
 MEGAESOPHAGUS
 MEGACOLON
 INFLAMMATION OF MUSCULARIS LAYER
 LOSS OF NERVE CELLS FROM AUERBACH'S PLEXIS
 LOSS OF PERISTALSIS PRODUCES DEATH FROM FECAL IMPACTION

CHAGAS DISEASE

DOCTORAL THESIS – DR. URIEL GARCIA, 1951
 5 CASES IN CHILDREN IN MOQUEGUA, PERU.
 THEY HAD ROMANA'S SIGN OF ACUTE DISEASE
 STERILE CHIRIMACHAS BITE CHILDREN
 BUGS FECES HAD PROTOZOAN FLAGELLATES.

CULTURES

TIME BEFORE PRESENT

CHINCHORROS
ALTO RAMIREZ
CABUZA
TWANAKU
MAITAS/CHIRIBAYA
SAN MIGUEL
GENTILAR
INCA
COLONIAL

7000 YEARS
2500 YEARS
1650 YEARS
1600 YEARS
1000 YEARS
900 YEARS
600 YEARS
550 YEARS
450 YEARS



FORTY FIVE BODIES RECOVERED IN ILO, PERU, 600 BEFORE PRESENT ABOUT HALF WITH SOFT TISSUE

HARRIS LINES OF ARRESTED GROWTH :
NEGATIVE 17
POSITIVE 28

PNEUMONIA	5
GHON COMPLEX	2
RECENT DELIVERY	3
CHAGAS DISEASE	1
ARTIFICIAL MUMMIFIED	10
WOMEN	6
MEN	2
CHILDREN	2

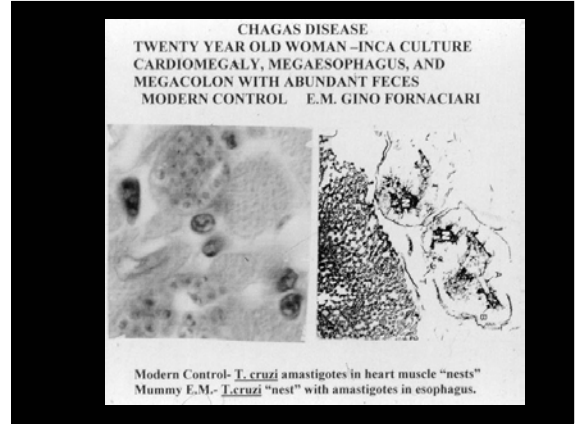


TARAPACA 22 AUTOPSIES- WANKARANI CULTURE-500BC

SEX	AGE	MEGACOLON	MEGAESOPHAGUS	CARDIOMEGALY
MALE	25 YEARS	POSITIVE	NEGATIVE	POSITIVE
MALE	25 YEARS	POSITIVE	POSITIVE	NEGATIVE
MALE	40 YEARS	POSITIVE	NEGATIVE	POSITIVE
MALE	45 YEARS	POSITIVE	NEGATIVE	NEGATIVE
MALE	45 YEARS	POSITIVE	NEGATIVE	NEGATIVE
MALE	45 YEARS	POSITIVE	NEGATIVE	NEGATIVE
FEMALE	12 YEARS	POSITIVE	NEGATIVE	NEGATIVE
FEMALE	35 YEARS	POSITIVE	NEGATIVE	NEGATIVE
FEMALE	35 YEARS	POSITIVE	NEGATIVE	NEGATIVE
FEMALE	40 YEARS	POSITIVE	NEGATIVE	NEGATIVE
FEMALE	40 YEARS	POSITIVE	NEGATIVE	NEGATIVE
		50%	9.0%+	4.5%+

MUMMIES WITH MEGACOLON HAD FECAL OBSTRUCTION WITH AS MUCH AS 3 KILOS OF DRIED FECES. FIVE HUNDRED MUMMIES FROM THE AZAPA VALLEY HAD ONLY ONE WITH MEGACOLON WITH FECES.





SEROLOGICAL SURVEYS IN LATIN AMERICA REVEALED:

- 18 MILLION CARRIED *T. CRUZI*
- 90 MILLION WERE EXPOSED TO INFECTION
- 500,000 ARE INFECTED IN USA

“Chagas disease and Tuberculosis: The past and the present”

Chagas Disease Today

Chagas disease is an infection caused by the flagellated protozoan parasite *Trypanosoma cruzi*. This disease is also referred to as American trypanosomiasis. Chagas disease, found only in the American Hemisphere, has a wide distribution in Central and South America. It is endemic in 21 countries. The overall prevalence of human *T. cruzi* infection is 16-18 million and 120 million, or 25% of the inhabitants of Latin America, are at risk of acquiring the infection. *T. cruzi* infection is naturally transmitted to humans by reduviid bugs, also known as kissing bugs, that live in cracks and holes of the substandard housing commonly found in South and Central America. Common triatomine vector species for trypanosomiasis belong to the genera *Triatoma*, *Rhodnius*, and *Panstrongylus*. This infection can also be transmitted by an unscreened blood transfusion. The percentage of infected blood in blood banks in selected cities of the South American continent is documented to be above 50%. In some, but unfortunately not all, countries in South and Central America, 100% of blood donors are screened. Between 1960 and 1989, the prevalence of infected blood in blood banks in selected cities of South America ranged from 1.7% in Sao Paulo, Brazil to 53.0% in Santa Cruz, Bolivia, a percentage far higher than that of hepatitis B and C or HIV contamination. As a consequence, infection rates among blood recipients vary from 0.1- 4.2% in Argentina, Brazil, Chile and Uruguay, to as high as 24.4% in Bolivia. The infectivity risk, defined as the likelihood of being infected when receiving an infected transfusion unit, has been estimated as 20%. Other methods of *T. cruzi* transmission include organ transplantation and congenital infection. However, information on the effects of *T. cruzi* infection on pregnancy is scarce despite the fact that in an endemic area, such infections affect 3 to 51% of pregnant women, of which 2 to 10% transmit the parasite to their fetuses. Chagas' disease was present in 17.22% of persons undergoing kidney transplantation in an Argentinian hospital. It has been also reported in cardiac transplant patients in the USA and other countries.

Chagas disease occurs in two stages. The first, acute stage appears shortly after the infection; however, acute symptoms only occur in about 1% of cases. Instead, the majority of infected persons are asymptomatic, with an indeterminate number eventually developing symptoms of the second, chronic stage after a silent period that may last several years. The lesions of the chronic phase irreversibly affect several internal organs, namely the heart, the oesophagus, and the colon; it may also affect the peripheral nervous system. After a several year asymptomatic period, 27% of those infected develop cardiac symptoms which may lead to sudden death; 6 % develop digestive damage, mainly megavisera; and 3% will present with peripheral nervous involvement. In humans, the acute phase of Chagas disease lasts for weeks to months and is typically either asymptomatic or associated with fever and other mild symptoms, one of those being the classic Romãlha's sign which is swelling of the eye on one side of the face, usually at the bite site where insect feces was rubbed into the eye. The other nonspecific symptoms seen in acute Chagas disease may include fatigue, fever, enlarged liver or

The most important achievements of the program include a 72% reduction in the incidence of human infection in children and young adults in the countries of the Initiative of the Southern Cone. In 1997, Uruguay was certified free of vectorial and transfusional transmission of Chagas disease. In 1999, Chile is certified free of vectorial and transfusional transmission of Chagas disease. In 2000, ten out of the twelve endemic states of Brazil were certified free of vectorial and transfusional transmission of Chagas disease.

Priorities and strategic emphases for WHO/TDR-supported research on Chagas disease.

While elimination of the disease as a public health problem (through interruption of transmission) is a reasonable goal, eradication is not, due to the zoonotic nature of the disease.

The major problems and challenges are:

Sustainability of vector control strategies and policies in the countries of the Southern Cone.

Implementation of specific disease transmission control strategies in those countries where, besides domiciliated vectors, sylvatic vectors also play an important role.

Implementation of suitable diagnosis/prognosis and treatment strategies and policies.

Definition of a long-term research agenda for the future, aiming at the development of new prevention and control tools, such as efficient vaccines and safer drugs.

Research activities needed

Precise epidemiological information about the magnitude of the morbidity and mortality associated with *T. cruzi*. Incidence of infection in young age groups.

Discovery and development of new chemotherapeutic and diagnostic tools (through creation of basic and clinical research networks and partnerships with the private sector).

Susceptibility and resistance to insecticides, and other issues relevant to vector control.

Sustainability of activities relevant for control of transmission based on blood transfusions.

Technical and policy frameworks, for getting research into action in elimination programmes in Central America and the Andean countries. Also getting research into

spleen, and swollen lymph glands. Sometimes, a rash, loss of appetite, diarrhea, and vomiting occur. In general, symptoms last for 4-8 weeks and then resolve, even without treatment. However, occasionally, life-threatening myocarditis or meningoencephalitis can occur during the acute phase, particularly in young children and immunocompromised persons. After years to decades of subclinical infection, 10-30% of infected persons develop chronic Chagas disease, which is characterized by potentially lethal cardiomyopathy or megasyndromes (i.e., megaesophagus and megaecolon). Even persons who remain asymptomatic probably are infected and infectious for life, with low levels of the parasite in their blood and other tissues. In persons who are immune compromised, including persons with HIV/AIDS, Chagas disease can be a fatal disease; meningoencephalitis occurs in 70% of the patients who present with unifocal or multifocal chagoma lesions which are often not responsive to drug treatment. Not everyone develops the chronic symptoms of Chagas disease.

In most cases treatment of symptoms is all that is possible. Currently available medications can reduce the duration and severity of an acute infection, but are only 50% effective, at best, in eliminating the organisms.

Cardiac disease is managed with pacemakers and medications. Esophageal complications require either endoscopic or surgical interventions to improve esophageal emptying, procedures similar to those used to treat the disorder known as achalasia. Constipation is treated by increasing fiber intake and the taking bulking laxatives, or by removal of diseased portions of the colon. Two drugs, nifurtimox and benznidazole, are capable of curing at least 50% of relatively recent infections, being active in the acute and short-term (up to a few years) chronic phase. Viotti (1995) showed that the treatment of Chagas disease in the indeterminate phase can prevent the development of the chronic disease. Fragata (1995) compared treatment with benznidazole versus observation of patients with either cardiac or asymptomatic disease and concluded that treatment is more effective in stopping or preventing disease progression (7% versus 14% in non-treated group, p<0.05).

Recently, several double-blind randomized trials showed that benznidazole may be useful for early stage disease in children under 12 years of age. Further studies with long-term follow-up will be necessary to determine the value of generalizing treatment to all patients with Chagas disease regardless of age and disease stage. Regardless, the ideal trypanocidal agent has yet to be found. Although attempts to immunize animals have not been complete failures, current results are not adequate to put forth hope of a vaccine for use in man within the foreseeable future.

The burden of chagas disease

The medical and social impact of Chagas disease is high. It is estimated that about 752,000 working years are lost annually due premature deaths caused by the disease in the seven countries of South American, a number that corresponds to 1,2billion US\$/year

action in the management of congenital and indeterminate Chagas disease, is needed, as are harmonized guidelines relative to case definition, management and treatment.

. Profound economic and social changes in the last four decades are stimulating rural-urban migration in most endemic areas, with more than 60% of the population presently settled in urban centers. It is estimated that, because of migration, about 300,000 infected individuals are living today in the city of São Paulo and more than 200,000 in Rio de Janeiro and in Buenos Aires. In addition, chagasic patients are migrating northward to the USA and even eastward to Europe: nowadays, around 100,000 infected individuals are living in the USA, most of them immigrated from Mexico and Central America. According to the UNDP Human Development Report the estimated average annual per-capita gross domestic product in Latin America, is US\$ 2,966. Thus, the economic loss for the Continent due to early mortality and disability by this disease occurs in the economically most productive young adults; this currently amounts to US\$ 8,156 million which is equivalent to 2.5 % of the external debt of the whole Continent in 1995. In Brazil, there are 6.3 million infected people. In 2000, there were an estimated 21,000 deaths and 200,000 new cases of Chagas disease (WHO, 2002) with a DALY of 649,000. About 10% of infected people develop severe cardiac or digestive chronic involvement. Treatment expenses for the consequences of chronic infection such as pacemaker implantation or corrective surgery (which has an average cost of US\$ 5,000 per patient) for the various disease presentations in Brazil was around US\$ 750 million per year (YASUDA,1998). The World Bank estimated the there was 2.7 million years of life lost in Latin America by due to this in 1993 (YASUDA, 1998).

Disease Control Activity

Initiative for Southern Cone Countries. In Brasilia, Brazil in June 1991, the Ministers of Health of Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay launched the **Initiative for the elimination of Chagas disease** with a goal target date by the end of the century. To facilitate the attainment of this goal, an **Intergovernmental Commission** (composed of technical representatives of each Ministry) was formed to implement and evaluate the control programs in each member country, and to administer funding arrangements. They meet annually to monitor progress in operations.

Initiative for Andean Countries. The first meeting of the interested parties of the **Andean Countries Initiative** for the vectorial elimination of Chagas disease, was held in Bogota, Colombia, in February 1997, and attended by representatives of Governments from Colombia, Ecuador, Peru and Venezuela, where a plan of action (including financial engagements from individual Governments) was agreed upon. It is expected that the interruption of vectorial and transfusional transmission will be achieved in 2010. A Technical Inter-governmental Commission was established to meet annually to assess progress in control operations.

Initiative for Central American Countries. The first meeting of the interested parties of the **Central America Initiative** for the elimination of Chagas disease was held in Tegucigalpa, Honduras, in October 1997. Delegates from the governments of Belize, Costa Rica, and El Salvador attended and declared that the control programmes of the above countries were a priority and that the goal of interruption of vectorial and transfusional transmission should be achieved in 2010.

Paleopathology of Tuberculosis

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Our Paleopathological studies on human Andean mummies began in 1971 at the Museum of Ica, Southern Perú and later in 1973 at the Museum of Arica, Northern Chile. Archaeological materials and mummies from vandalized cemeteries were recovered by nationally known archeologists. The mummies were radiographed and autopsied. Samples of organs were taken for C¹⁴ and pathological diagnoses. The tissues were rehydrated in Ruffer's solution, paraffin blocked and stained with the usual techniques performed in a modern Pathology Laboratory. Pathological features were found in the mummies of both geographic areas consistent with tuberculosis in soft and bone tissues. The soft tissues consisted of Ghon complex, cavitary pulmonary disease, miliary disease and in bones, Pott's disease. Many tissues had visible acid-fast mycobacteria. García Frías had reported several cases of tuberculosis with bacilli in Perú in 1940, published in "Actualidad Médica Peruana"¹ but at that time C¹⁴ was not available although acid-fast organisms were found in sections.

We reported the first case of tuberculosis in Pre-Columbian America in 1973 in the American Review of Respiratory Disease² with stained acid-fast organisms in tissues and dated the mummy with C¹⁴. The report was from a mummy bundle excavated with all of its burial goods from the province of Nazca, Perú. The mummy, an 8-year-old boy, was

found seated on an adobe seat with a thick cushion. Carbon¹⁴ dated the mummy around 700 A.D. The position of the legs is commonly seen in persons who are paralyzed in the lower limbs and unable to walk. The main findings in the gross examination were severe scoliosis in the lumbar area. Radiographs showed Pott's disease with a right psoas abscess. During the autopsy, small nodules were seen in the lungs, pleura, liver and kidneys. Tissue sections from the organs were rehydrated and stained. Ziehl-Nielsen stains confirmed the gross diagnosis revealing many clumps of acid-fast bacilli in these lesions; mainly in the lungs and kidneys. The disease process in this case can be reconstructed by an X-ray of the tibia, which revealed Harris lines starting at about 3 years of age. The boy developed a chronic stage of this disease with secondary Pott's disease. The terminal event was a re-infection with a hematogenous spread producing extensive miliary disease. In total, we reported 12 cases showing healed calcified Ghon complexes and primary active cases and reinfection cavitary disease of soft tissue and bone that had the pathological findings of tuberculosis. Acid-fast bacilli were found in only two of them.

The Medical College of Virginia (MCV), in Richmond, Virginia, had a 200-bed sanatorium that closed in 1967. Two important studies of tuberculosis were performed while the sanatorium was operating. The first one was comparing the outcome of patients from the MCV sanatorium who received anti-tuberculosis therapy, with another sanatorium in Farmville, VA, where the patients did not receive anti-tuberculosis therapy. Farmville had 2,421 patients treated between the years 1936 and 1945. The Medical College of Virginia sanatorium in Richmond had 2,205 patients treated between 1956 and

1967 with anti-tuberculosis drugs. The two Sanatoriums had similar clinical classifications of patients with tuberculosis as minimal, moderate and far advanced. The results showed that in the later years, the improvement rate of patients treated with antibiotics almost doubled. The gender incidence had little difference in both eras, but was slightly more common in males than females in the later years. The percentage of extra-pulmonary disease with pulmonary disease was reduced by half, (47% to 24%) in the anti-tuberculosis drug therapy group. It is interesting that in both groups the numbers of systems with extra-pulmonary disease per patient was the same, about 80%, 17% and 3% from one, two or three systems, respectively. The distribution of the systems in the two groups, however, was different. The patients who were untreated with antibiotics had extra pulmonary lesions more commonly in the larynx, gastro-intestinal tract and male reproductive system, but antibiotic treated patients had lesions more common in the urinary, central nervous and skeletal systems.

The second important study⁴ undertaken at the MCV sanatorium was related to the increased resistance of Mycobacterium tuberculosis to drug therapy seen shortly after the 3 drugs: Para-aminosalicylic acid, Isoniazid and Streptomycin were introduced in the treatment. Four hundred eighty two black, tuberculosis patients were followed after being admitted. Their organisms were tested for sensitivity to streptomycin, isoniazid and para-aminosalicylic acid. They were classified on the basis of their histories as new or old patients, depending on whether or not they had prior anti-tuberculosis therapy. Forty four percent of the new patients and 67% of the old patients had organisms resistant to one or more of the three antituberculosis agents used. The patient's rate of recovery decreased as

the resistance of the organisms increased. Tuberculous patients that previously received anti-tuberculosis therapy developed chronic disease or died of their tuberculosis 3½ times more frequently than new patients without any prior anti-tuberculosis therapy.

References:

1. Documentation of a Case of Tuberculosis in Pre-Columbian America. M.J. Allison, D. Mendoza, and A. Pezzia.
2. La Tuberculosis en los Antiguos Peruanos. J.E. García Frías. Actualidad Médica Peruana, Vol. 6, 1940, p. 1-19.
3. Increased Resistance of Mycobacterium Tuberculosis to Drug Therapy. E. Gerszten, D.L. Brummer, M.J. Allison, and M.E. Hench. The Journal of the American Medical Association, Vol. 85, 1963, p. 6-10.

Tuberculosis

New Facts about an Old Disease

Antonino Catanzaro, M.D.
Professor of Medicine
UC San Diego



Definition

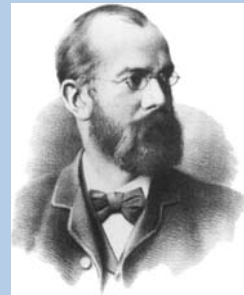
- Tuberculosis was known as a specific disease by ancient cultures
- The disease was called by names like
 - consumption
 - ptysis
- The name tuberculosis was introduced when tiny nodules or tubercles were noted on examination of diseased lungs

Robert Koch

- March 24, 1892 announced his discovery that TB is caused by an infection caused by a microorganism
- named the organism *Mycobacterium tuberculosis*
- developed tuberculin and injected it subcutaneously

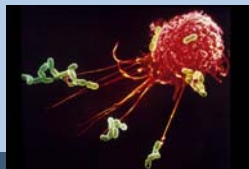
Robert Koch

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Pathogenesis of TB to Bug: *Mycobacterium tuberculosis*

- 1 or 2 *Mtb* enough to infect a normal person
- *Mtb* grow, on and off, over many years
- The cough of TB propels *Mtb* into the air
- New infections result from inhalation of infected residual of droplets



Pathogenesis of TB

Primary TB

- Healthy Host
 - Infection contained in the Lung and/or Lymph Nodes
 - Progressive Pulmonary Disease
 - Extrapulmonary TB

Latent TB Infection (LTBI)
90% remain well
10% reactivate

Factors
Hematologic malignancy
Steroids
Anti TNF
Ageing



Reactivation or Post-Primary TB

- Comorbidity avert or occult
 - Pulmonary in 85%
 - Extrapulmonary in 15%

Tuberculosis: global epidemiology



Stop TB
Department
WHO
Geneva



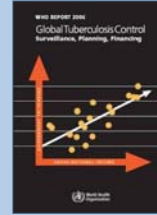
The burden of TB in 2006



250,000 deaths
due to TB/HIV

1.7 million deaths in 2004
– 98% of these in developing world

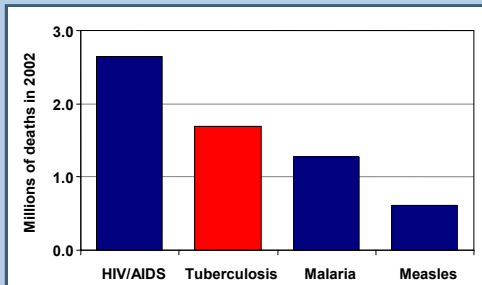
8.9 million new
cases in 2004 –
80% in 22 high-
burden countries



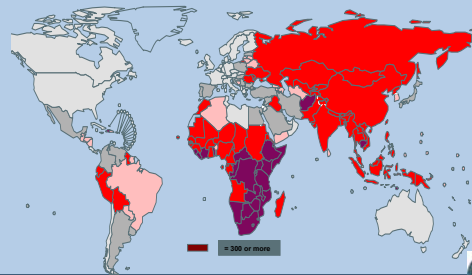
MDR-TB present
in 102 of 109
countries and
settings surveyed



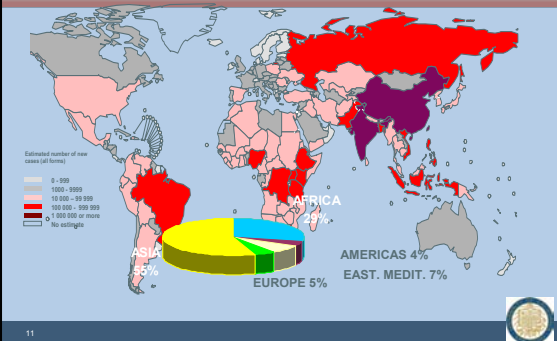
TB is the biggest cause of death from a curable or preventable infectious disease



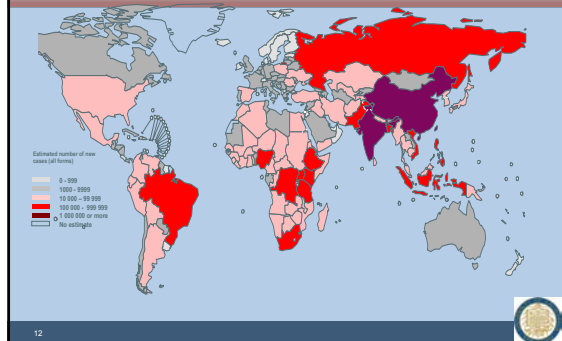
Highest incidence rates per capita in Africa...

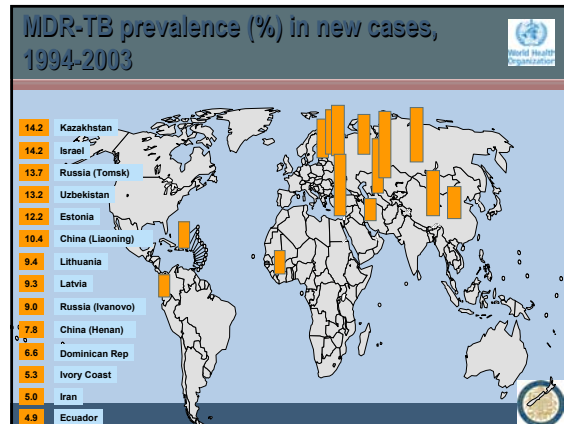
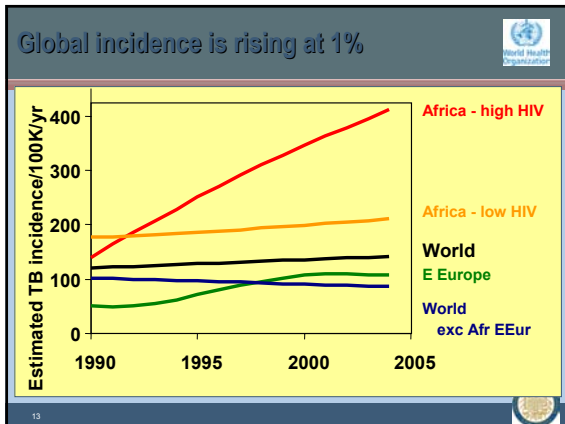


.....but the highest number of cases is in Asia



.....but still almost half a million cases a year in Europe, with peaks in the former USSR





XDR-TB – extensively and 'extreme' drug resistant TB

MMWR
Morbidity and Mortality Weekly Report

World TB Day – March 24, 2005

Emergence of Multidrug-Resistant Tuberculosis with Extensive Resistance to Second-Line Drugs - Worldwide, 2000-2004

XDR = MDR-TB plus resistance to any fluoroquinolone, and to at least 1 of 3 injectable second-line anti-TB drugs (capreomycin, kanamycin, amikacin)

Of 17,690 isolates during 2000-2004 20% were MDR and 2% were XDR

XDR found in:
USA: 4% of MDR
Latvia: 19% of MDR
S Korea: 15% of MDR

WHO recommended Stop TB Strategy to reach the 2015 MDGs

COMPONENTS OF THE STOP TB STRATEGY

- PURSUE HIGH-QUALITY DOTS EXPANSION AND ENHANCEMENT**
 - Public commitment with increased and sustained financing
 - Care initiation through quality-assured technology
 - Standardized treatment with supervision and patient support
 - An effective drug supply and management system
 - Provision of incentives, systems, and human resources
- ADDRESS TREATMENT, HIV-TB AND OTHER CHALLENGES**
 - Implement collaboration TB/HIV activities
 - Identify and control multidrug-resistant TB
 - Address prisoners, refugees and other high-risk groups and special situations
- CONTRIBUTE TO HEALTH SYSTEM STRENGTHENING**
 - Active participation in efforts to improve systems including human resources, financing, management, service delivery, and information systems
 - Share innovations that strengthen systems, including the Practical Approach to Lung Health (PALH)
 - Identify innovations from other fields
- ENGAGE ALL CARE PROVIDERS**
 - Public Health, and Public-Private Partnerships (PPP) approaches
 - International standards for TB Care (2002)
- EMPOWER PEOPLE WITH TB, AND COMMUNITIES**
 - Advocacy, communication and social mobilization
 - Community participation in TB care
 - Patient's Charter for Tuberculosis Care
- ENABLE AND PROMOTE RESEARCH**
 - Support basic operational research
 - Research to shorten time, diagnostics, drugs and vaccines

Structure of the Global Plan to Stop TB 2006-2015

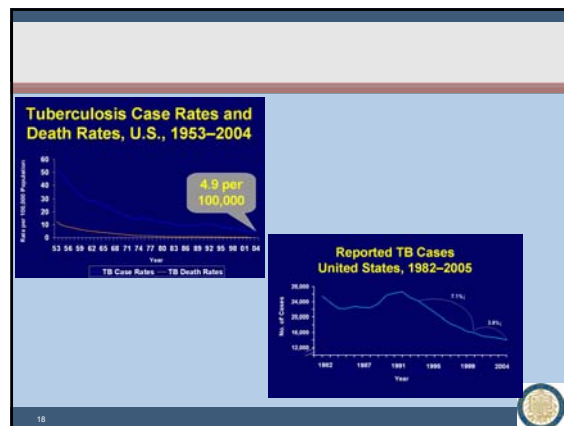
THE GLOBAL PLAN TO STOP TB 2006-2015

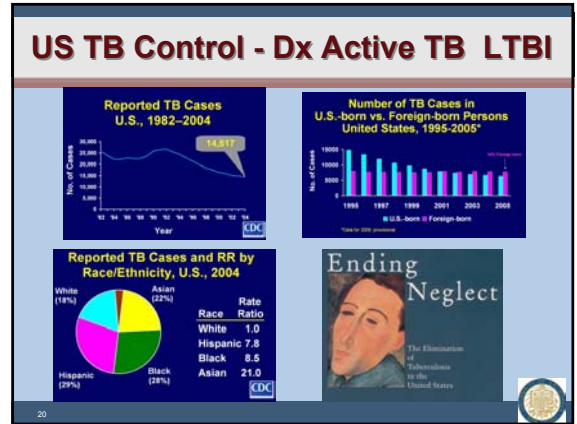
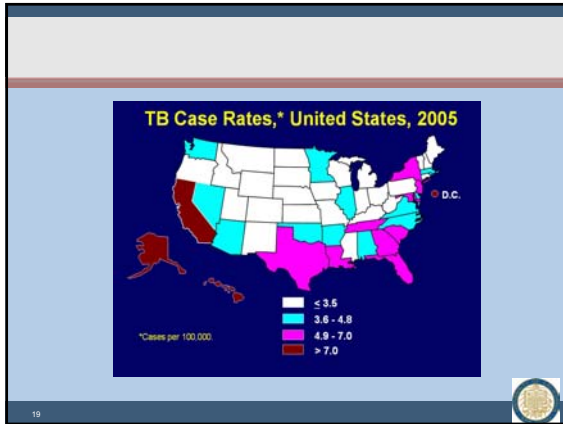
Actions for Life

"If 2005 was the year of commitment, then 2006 must be the year of delivery"
Gordon Brown
UK Finance Minister

"We're willing to triple our funding for tuberculosis, and we urge others to do the same"
Bill Gates,
Microsoft founder

"...call upon African governments to commit their share of the resources needed..."
Olusegun Obasanjo,
Nigerian President





The Journal of the American Medical Association

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Original Article

TUBERCULIN OF TUBERCULOSIS BY PIRQUET*

GRASER FOR PIRQUET, MD
CHICAGO, ILLINOIS

- Robert Koch
 - developed tuberculin and injected it subcutaneously
- Clemens Freiherr von Pirquet
 - first use of intradermal injection of tuberculin as a diagnostic tool
- First use of the term Latent TB Infection

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Treatment of LTBI

- In Rome Omodei Zorini was the first to demonstrate that in cattle the reactivation of TB could be prevented if the latent disease were treated with INH
- USPHS in a series of trials demonstrated the effectiveness of INH in human trials

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Testing for Latent TB Infection - LTBI

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False Negative /False Positive TST

False Negatives

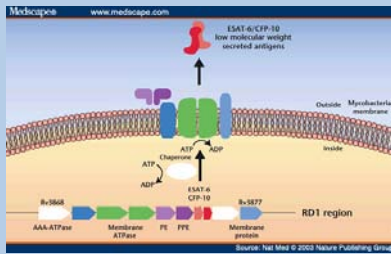
- Technical Factors
 - Application location
 - PPD improper storage
 - Reading experienced
- Biological Factors
 - Poor nutrition or infection
 - * viruses esp HIV, measles mumps chicken pox
 - Drugs
 - * esp steroids, and other immunosuppressives
 - Chronic Renal Failure
 - Malignancy
 - * esp lymphoma & leukemia
 - Stress
 - * esp burns, surgery
 - Age
 - * newborn, elderly(booster)

False Positives

- Infection with Mycobacteria other than TB
 - BCG
 - *M avium complex*
 - Other environmental mycobacteria

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A Benefit of the Genome Era ESAT-6/CFP-10 Complex



Pym et al, 2003

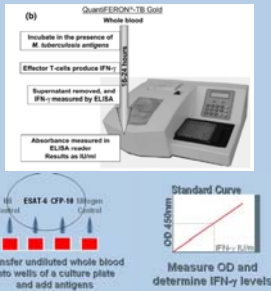
25

Species specificity of ESAT-6 and CFP-10

Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
M tuberculosis	+	+	M abscessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG substrain	-	-	M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M mageritense	-	-
montreal	-	-	M marinum	+	+
pasteur	-	-	M neoaurum	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M vaccae	-	-
			M xenopi	-	-

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Gamma Interferon release assays



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Specificity of QFT Gold

- **Johnson et al**,
 - 99 Low Risk subjects, Mean age 29 (18 to 59), 30% BCG vaccinated, 41% female, Specificity 98/99=99%
 - Clin Diag Lab Invest. 6:934-37 1999
- **Mori et al**,
 - 216 Healthy individuals, No identified risk factors for TB exposure, all vaccinated with BCG, Mean age 20 (18-33), 93% female, Specificity 212/216 = 98%
 - AJRCCM 170:59-64 April 2004
- **Mazurek**
 - 550 with no TB risk, Only 1 positive of the low risk subjects, Specificity 449/550 = 99.8%
 - Publication in preparation

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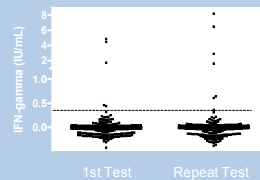
Sensitivity of QFT-Gold for active TB disease

- **Mori, et al**
 - 118 Culture-confirmed active TB Patients, 85% no-treatment (the rest < 7 days), Mantoux = 65.8% (5mm induration) Sensitivity 105/118 = 89%
 - AJRCCM 170, 59-64, 2004
- **Ravn et al**
 - 48 Culture confirmed active TB, 30 (71% - no treatment) 22 Male Age 19 to 80 years - mean 36.9 Sensitivity 41/48 = 85.4%
 - Clin Diag Lab Immunol. 12:491-6 2005
- **Kang et al**
 - 54 Culture -confirmed active TB Sensitivity of Mantoux 77.8 % (5mm) Sensitivity 44/54 = 81.5%
 - JAMA 293:2756-2761 2005
- **Mazurek**
 - 23 confirmed active TB 21/ 23 positive Sensitivity 21/23=91%
 - personal communications manuscript in preparation

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US Military Recruit Reproducibility

- TST placed after first QFT-Gold test
- Subjects re-tested 4 to 5 weeks later
- Reproducibility is 99.3% after TST (n=557)



-personal communications manuscript in preparation

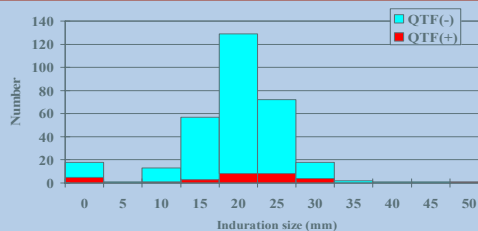
30

CDC Guidelines on the Use of QuantiFERON Gold

- “the antigens impart **greater specificity** than is possible with ..PPD”
- QFT-G is “**as sensitive** as TST in detecting infection” in untreated TB
- “QFT-G can be used in all circumstances in which TST is currently used”

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TST distribution and QFT Gold results



•TST positive @ 10 mm = 314/332 (94.6%)

•QFT-GOLD positive = 33/332 (9.9%)

Mori personal communication

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- Contact investigation in a Japanese University
- 220 close contacts
- 242 controls (limited or no contact)
- Nearly all (>90%) BCG vaccinated
- 11 contacts identified with active TB, 1 to 6 months after exposure

Funayama et al Kekkaku 2005

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Results for those that developed active TB

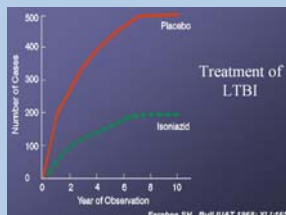
TB 1 month after QFT				
Code No.	E-N	C-N	Highest	Group
4010643	7.463	0.873	7.463	B
4010666	0.222	-0.002	0.222	B
4010758	13.861	0.307	13.861	C
4010645	6.481	-0.029	6.481	?
TB 3 months after QFT				
4010767	8.807	0.004	8.807	A
TB 6 months after QFT				
4010728	1.285	-0.002	1.285	A; friend
4010773	6.692	1.977	6.692	A
4010684	2.285	-0.022	2.285	A
4010604	0.003	0.19	0.19	B
4011095	2.471	0.009	2.471	A
4010984	0.532	1.281	1.281	D

9 of the 11 were QFT-Gold positive

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Key Items 2000 ATS-CDC LTBI Treatment Recommendations

- 9 mo. INH preferred (vs 6 mo.) for HIV-
- 9 mo. INH preferred (vs 12 mo.) for those with fibrotic CXR and HIV
- 2 mo. RZ for HIV+ and HIV- under very limited circumstances
- 4 mo. RIF for HIV+ and HIV- usually when source case is INH resistant
- Under study INH 900 mg & Rifapentine 900 mg once week x 12 weeks



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Baseline Medical Evaluation for Candidates for Treatment of Latent TB

- **Medical history**
 - History of TB or HIV treatment
 - TB exposure
 - Drug toxicity
- **Chest x-ray**
 - Rule out TB disease
- **Laboratory tests**
 - CBC and platelets and chemistry panel, if indicated
 - 3 sputum samples for smear, culture, and susceptibility testing if TB symptoms or findings on chest x-ray

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2000 ATS-CDC Recommendations Clinical and Chemical Monitoring

Selective use of blood tests

- Serum transaminase levels
 - HIV or HCV infection
 - liver disease
 - alcoholism
 - pregnancy
- **Emphasis on clinical monitoring for signs & symptoms of adverse effects (prompt evaluation and changes in Rx)**
 - **INH or Rm monthly**
 - **Rif/PZA weeks 2,4 & 8**

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Clinical Approach to the Diagnosis of Active TB

- **History**
 - **Epidemiology**
 - Contact with TB
 - Immune Status
 - Socio-economic Status
 - **Clinical Symptoms**
 - Major Symptoms
 - Fever, Chills, Night Sweats, Anorexia, Weight Loss, Hemoptysis
 - Chest pain
 - Dyspnea
 - Cardinal Symptoms
 - Any above esp cough > 3 weeks
 - No symptoms
- **Physical Exam**
 - **Fever**
 - **Cachexia**
 - **Local Organ Involvement**
 - Rales
 - Adenopathy
 - Swelling
 - Etc...



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Diagnosis of TB: Radiology

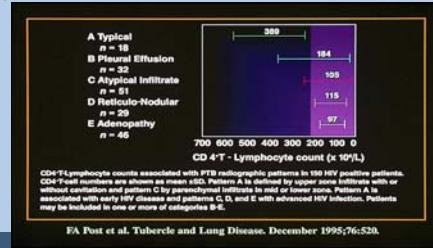
- **Radiology**
 - **Primary TB**
 - Lower Lobe Disease Dominates
 - Adenopathy Common
 - No Cavitation Unless Progressive
 - **Reactivation (Post Primary)**
 - Upper Lobe Disease Predominates
 - Cavitation Common in Later Stages
 - **Dissemination**
 - Miliary
 - Local Organ Involvement



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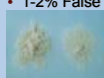
Radiology in HIV

- **Primary Disease Common**
- **Extrapulmonary Involvement Increases**
- **Atypical Presentations Predominate**



Laboratory Diagnosis of TB

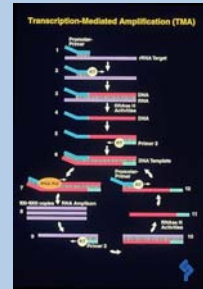
- **Microscopy**
 - 6,000 - 10,000 organisms per ml to see 3 AFB on slide
 - Acid Fast Stain
 - Auramine Fluorescent Stain
 - Repeat 3 Times
 - Sensitivity
 - 55% positive on average
 - Specificity
 - 5 - 50% May be Due to MOTT
- **Culture**
 - 100 organisms per ml to get 1 colony
 - Lowenstein Jensen Slant
 - Middlebrook 7H10
 - Liquid Medium
 - ACCUPROBE
 - Sensitivity
 - 80% of CDC Verified Cases
 - Specificity
 - 1-2% False Positive



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Rapid Diagnostic Tests Approved by FDA: Nucleic Acid Amplification (NAA) Tests

- **MTD**
 - approved for use in AFB positive or negative samples
 - Target
 - RNA, 1000 Copies Per Bug
 - Amplification procedure
 - TMA
- **Amplicor**
 - approved for use in AFB positive samples only
 - Target DNA
 - Amplification PCR



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Sensitivity and Specificity of MTD

Respiratory Specimen

	Sensitivity	Specificity
Catanzaro	83.7%	97%
Bergmann	90.9%	99.1%
Gamboa	94.7%	100%
O'Sullivan	97.8%	99.1%
Aleala	90.8%	93.2%
Chedore	100%	99.6%

Non Respiratory Specimen

	Sensitivity	Specificity
Gamboa	86.8	100
Woods	89.3%	100%
O'Sullivan	77.3%	98.5%
Akala	88.9%	92.1%
Chedore	93.8%	99.3%

J Clinical Micro Piersimoni Dec 2003

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TABLE 2. Diagnostic sensitivities of QFT-RD1, microscopy, and culture

Patient group (n ^a)	Positive responses with ^b									
	QFT-RD1		Microscopy			Culture			Microscopy, culture, and QFT-RD1	
	No. (%)	CI	No. (%)	CI	P value	No. (%)	CI	P value	No. (%)	CI
Pulmonary TB (35)	29/35 (83)	70-96	16/35 (46)	29-63	0.009	22/35 (63)	47-79	0.121	34/35 (97)	92-100
Extrapulmonary TB (13)	12/13 (92)	78-107	4/13 (31)	5-56	0.013	5/12 (42)	13-70	0.041	12/13 (92)	78-107
All TB patients (48)	41/48 (85)	75-96	20/48 (42)	27-56	0.001	27/48 (56)	44-71	0.009	46/48 (96)	90-100

^aSensitivity of the QFT-RD1 test, microscopy, or culture for *M. tuberculosis* or combined sensitivity of microscopy, culture, and the QFT-RD1 test. For each group the numbers and percentages of responders are shown together with the 95% confidence intervals. Differences in sensitivity between QFT-RD1 and other microscopy or culture were calculated using the McNemar test, and differences in proportion between the patient groups were calculated using a chi-square test; a P value of <0.05 was considered significant.

^bn, no. of patients.

^cThe extrapulmonary manifestations were distributed as meningitis (n = 1), lymphadenitis (n = 9), appendicitis (n = 1), osteomyelitis (n = 1), cystitis, prostatitis, and a strong clinical suspicion of TB (n = 1).

- Prospective eval of 82 TB suspects
- 48 TB, 25 non TB, 9 excluded
- Sens AFB+QFT-G=96%, Spec=60%

Ravn, P et al Clin Diag Lab Immunol, 491, April 2005

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UCSD Experience with NAA in Pulmonary TB

Ronelle Campbell, Phung Lam, Ed Barber, Joseph Caperna, Kolpana Chalasani, Adelita Greeley, Kathleen Moser, Alyssa Tugend, Antonino Catanzaro.

- Retrospective review of 515 TB suspects from 11/1/99-11/20/2003 (47 mos)
- TB suspects defined as having submitted NAA on one respiratory specimen and two or more sputa for AFB
 - N=60 smear + and NAA +
 - 58/60 (96.6%) culture positive TB
 - 2 false positives
 - N= 30 smear + and NAA -
 - 30/30 non TB (culture negative for TB)
 - N=15 smear - and NAA +
 - 11/15 (73.3%) culture positive TB
 - 4/15 false positives
 - N= 410 smear - and NAA -
 - 17/410 (4.1%) culture positive TB 13 pulm 4 extra pulm
 - 393/410 (95.8%) culture negative and TB excluded

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Standard Treatment

- Induction Phase - QD 2 Months Start DOT
 - Isoniazid 300mg/dose
 - Rifampin 600mg/dose
 - Ethambutol 15-25 mg/kg/dose
 - PZA 30 mg/kg/dose
- Evaluate Sensitivity of Patient's Isolate
- Consolidation Phase - QD to BIW for 4 Months
 - Isoniazid dose according to
 - Rifampin or Rifapentine frequency

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TK Culture Medium



- Solid culture system
- Color readout
- Sensitivity = LJ
- Time to detection
 - TK - 14 days
 - JL - 28 days

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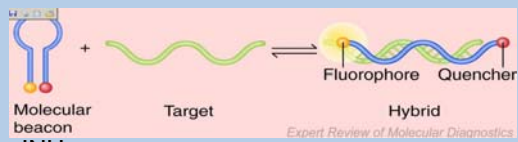
Diagnosis of MDR TB

Molecular Basis of antibiotic resistance

- INH 60-70%
 - katG
 - inhA
- RM 96%
 - rpoB
- EMB
 - embCAB operon genes
 - emb-1, emb-2, emb-3
- SM
 - rpsL
- PZA
 - pncA
 - gyrA

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Molecular beacon



- INH
 - Sensitivity 82.7% Specificity 100%
- RM
 - Sensitivity 97.5% Specificity 100%
 - Cal State TB Lab Ed Desmond

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What new drugs are of interest presently?

- Newer rifamycins
- Fluoroquinolones
- Oxazolidinones
- Nitroimidazopyrans
- Pyrrole derivatives
- Congeners of ethambutol
- Isocitrate lyase inhibitors
- Diarylquinolines (DARQ)
- Nitro-imadazo-oxazole derivatives
- Immunotherapies



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