U.O.C. Clinica Ginecologica ed Ostetrica
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Tubercolosi e gravidanza

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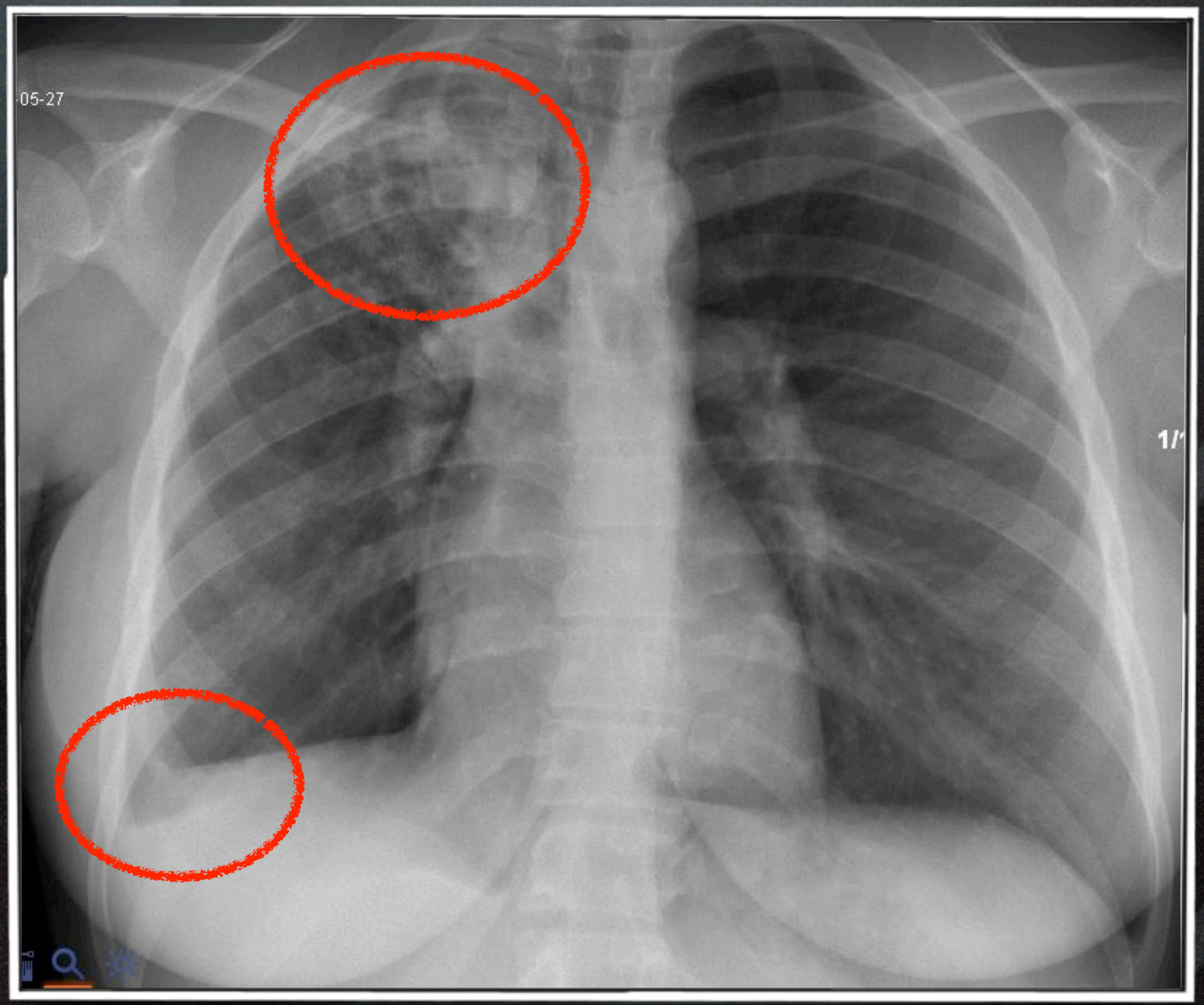
Caso clinico

- 26 aa, **Nigeriana**, in Italia da circa 1 aa, PARA 1001;
- **38 sg:** accesso in PS per **dolore toracico, tosse e febbre**: eco torace: addensamento apicale dx trattato con amoxicillina con modesto beneficio;
- **39+1 sg: TC** per pregresso TC in data 11.03.2013;
- ♀, 3510 gr, Apgar 9 e 10/10;
- **Puerperio caratterizzato da tosse non produttiva e febbricola** trattate con amoxicillina;
- Dopo 3 settimane dalla dimissione **accesso in PS per tosse produttiva, febbre (39.7°) e dolore toracico** ➪ addensamento apicale dx all'RX ➪ ricovero c/o Malattie Infettive

Caso clinico



Caso clinico

- Durante il ricovero riscontro di **crescita Mycobacterium tuberculosis** non rifampicina resistente su espettorato e di MT c.-DNA su broncoaspirato;

- Si instaura **multi-terapia per TBC attiva sulla madre** (HRZE) e **profilassi con isoniazide sulla neonata**;

- Inizialmente concesso allattamento, poi **isolamento della neonata** per ripetuta positività su espettorato materno.

- Dimesse madre e neonata dopo 40 gg, 4 escreati consecutivi negativi;

- Sospeso allattamento per richiesta materna;

- **Screening su oltre 40 contatti**.

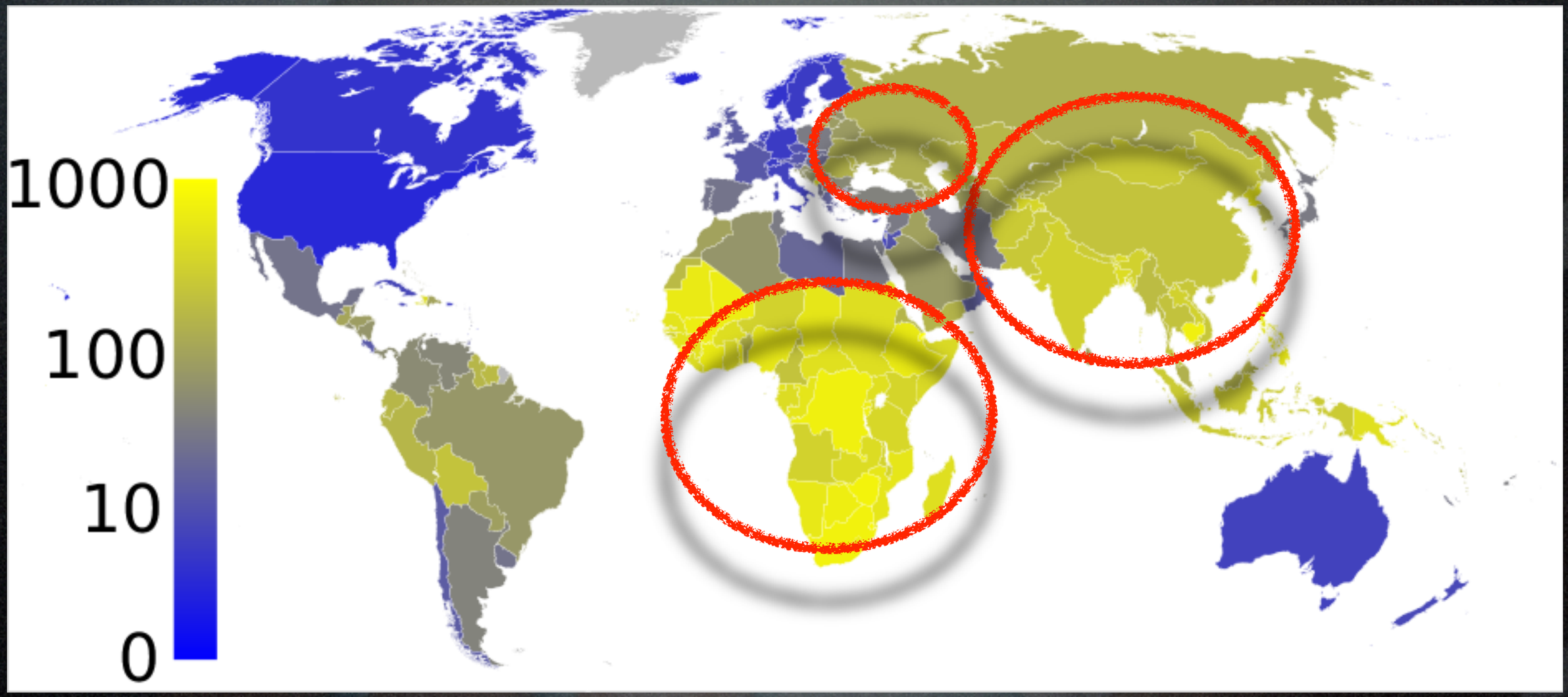
Tubercolosi

- Infezione da **Mycobacterium tubercolosis**;
- Trasmissione aerea;
- Polmonare ed extrapolmonare;
- 25% dei casi asintomatica;
- **10% progredisce a forma attiva** (> se meno di 4 aa);
- **50% mortalità se non trattata**.
- 2.000.000 di morti/anno

WHO, 2010

Epidemiologia

Prevalenza



WHO, 2010

Epidemiologia

Table 1. New Tuberculosis Cases Notified Among Women and Children for 22 High Tuberculosis Burden Countries, 2010.

Country	Total New Cases Notified, All Forms	Total New Cases Notified, All Forms, Among Children 0–14 y (%)	Total New Cases Notified, All Forms, Among Women 15–44[a] y (%)
Afghanistan	26 280	NR	NR
Bangladesh	150 903	4235 (2.8)	36 825 (24)
Brazil	70 979	2450 (3.5)	14 892 (21)
Cambodia	39 994	NR	NR
China	869 092	6710 (0.8)	150 212 (17)
Democratic Republic of the Congo	110 032	NR	NR
Ethiopia	152 030	NR	NR
India	1 227 667	NR	NR
Indonesia	296 272	28 312 (9.6)	71 914 (24)
Kenya	95 604	5721 (6)	27 044 (28)
Mozambique	42 126	NR	NR
Myanmar	127 134	NR	NR
Nigeria	81 454	NR	NR
Pakistan	255 329	24 474 (9.6)	101 294 (40)
Philippines	163 248	NR	NR
Russian Federation	102 823	831 (0.8)	20 662 (20)
South Africa	335 974	50 474 (15)	121 870 (36)
Thailand	64 512	NR	NR
Uganda	41 594	NR	NR
United Republic of Tanzania	59 668	5216 (8.7)	20 218 (34)
Vietnam	88 033	NR	NR
Zimbabwe	42 872	4371 (10.2)	14 642 (34)

Data shown are from the 22 countries with a high burden of tuberculosis, which accounted for 82% of the world's notified tuberculosis cases in 2010 [1].

Abbreviations: NR, not reported to the WHO, disaggregated by age and sex for all forms of tuberculosis (smear-positive pulmonary, smear-negative pulmonary, extrapulmonary); WHO, World Health Organization.

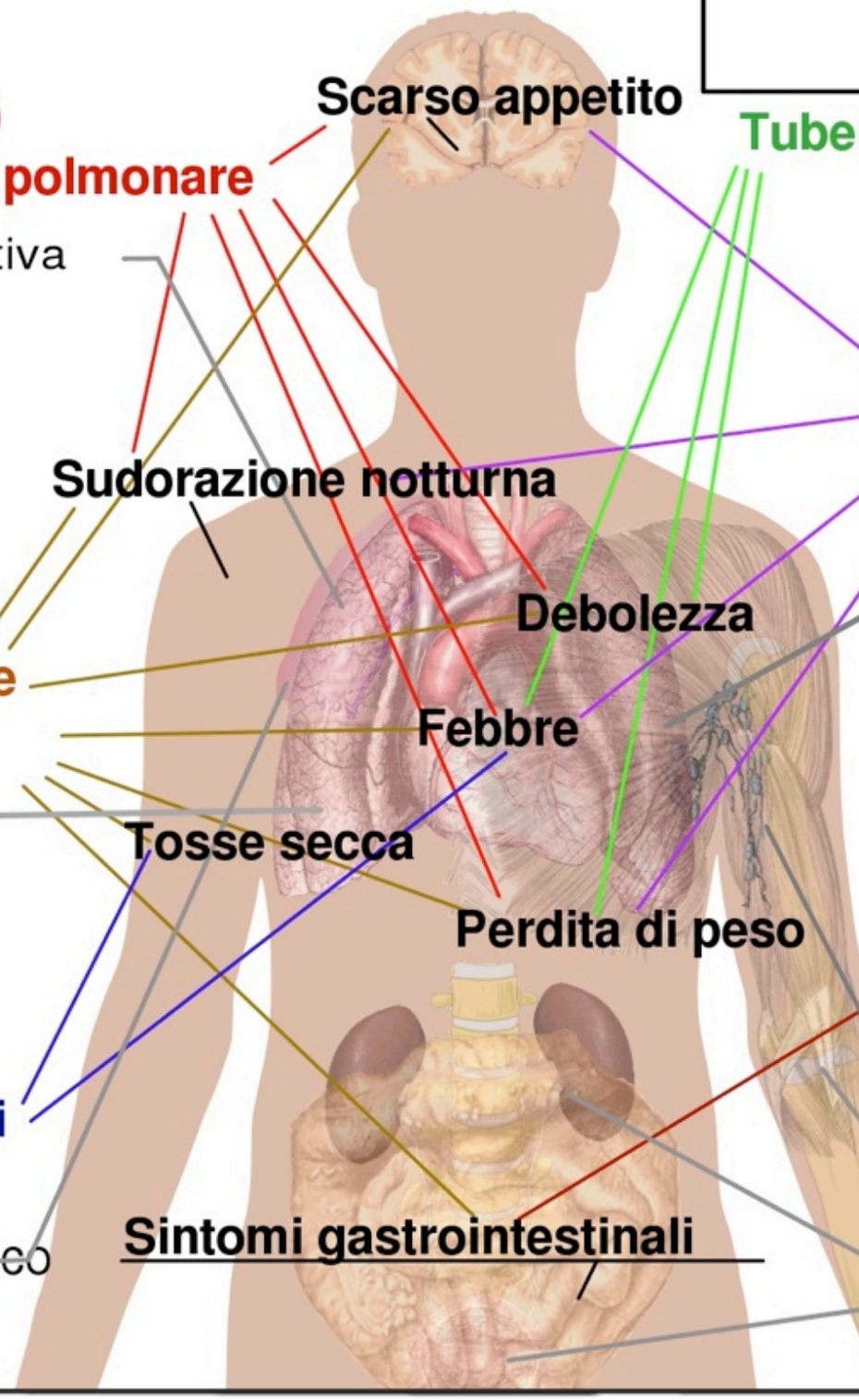
[a] Standard WHO reporting of notification data is done with 10-y bands (ie, 15–24, 25–34, 35–44, 45–54, 55–64, >65), so it is not possible to account for 15–49 y.

WHO, 2010

Sintomi della **Tuberculosi**

Linee grigie = più specifico

Linee colorate = sovrapposizioni



(Dimostrata) Tubercolosi polmonare

Tosse produttiva

Scarso appetito

Tubercolosi miliare

Ritorno della tubercolosi latente

Sudorazione notturna

Debolezza

Tosse con incremento di muco

Tosse con sangue

Polmonite primaria

Febbre

Anomalie strutturali

Tosse secca

Perdita di peso

Tubercolosi extrapolmonare

Siti comuni:

Meningi

Linfonodi

Ossa e articolazioni

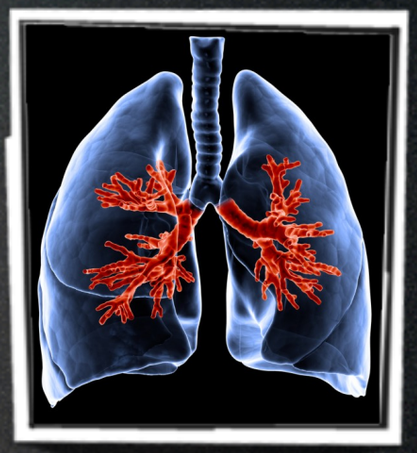
Tratto genitourinario

Tuberculosi pleurite

Dolore toracico

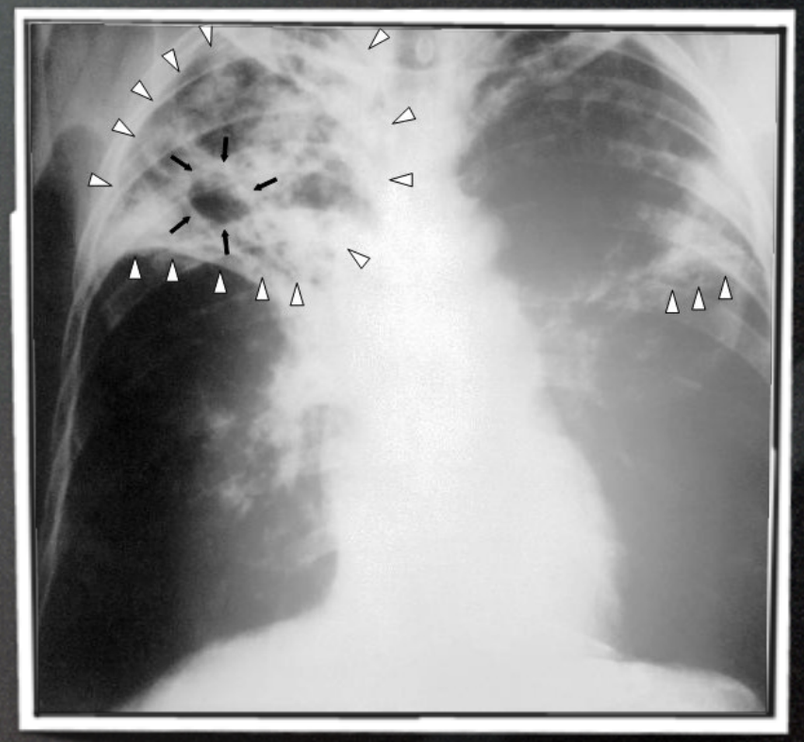
Sintomi gastrointestinali

Tubercolosi polmonare **primaria**



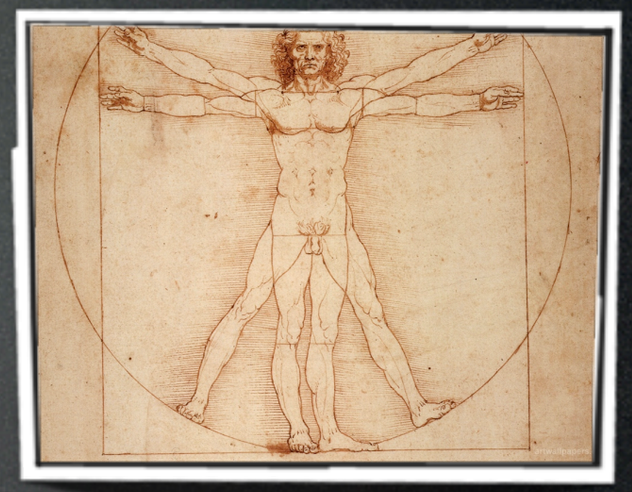
- Più frequente in **età pediatrica**;
- Possibile **guarigione spontanea** (lesione di Ghon);
- Possibile **evoluzione infausta** con complicanze locali anche da compressione vie aeree per linfoadenomegalia;
- Possibile **diffusione miliare**.

Tubercolosi polmonare **post-primaria**



- **Riattivazione** locale;
- **Cavitazioni**;
- Polmonite tubercolare;
- **Progressione cronica** (consumption);
- **ARDS**;
- Aneurisma di Rasmussen.

Tubercolosi **extra-polmonare**

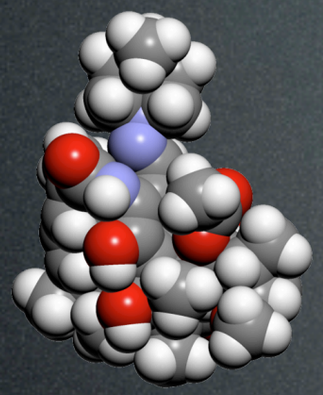


- **Linfoadenite tubercolare**;
- **Tubercolosi genitourinaria**;
- Tubercolosi scheletrica (malattia di Pott);
- Meningite tubercolare;
- Pericardite tubercolare;
- Tubercolosi gastrointestinale;
- Tubercolosi miliare.

Diagnosi

- **Analisi fattori di rischio**;
- **Sintomatologia**;
- **RX torace**;
- **Esame microbiologico** su espettorato o biopsia tissutale;
- **Test alla tubercolina** PPD;
- Saggio rilascio IFNγ **(QuantiFERON)**.

Terapia antibiotica



- **Isoniazide (H);**
- **Rifampicina (R);**
- **Pirazinamide (Z);**
- **Etambutolo (E);**
- **Streptomicina (S).**

TABLE 150-2 *Recommended Dosage for Initial Treatment of Tuberculosis in Adults*[a]

Drug	Dosage	
	Daily Dose	Thrice-Weekly Dose[b]
Isoniazid	5 mg/kg, max 300 mg	15 mg/kg, max 900 mg
Rifampin	10 mg/kg, max 600 mg	10 mg/kg, max 600 mg
Pyrazinamide	20–25 mg/kg, max 2 g	30–40 mg/kg, max 3 g
Ethambutol[c]	15–20 mg/kg	25–30 mg/kg

Dosages for children are similar, except that some authorities recommend higher doses of isoniazid (10–15 mg/kg daily; 20–30 mg/kg intermittent) and rifampin (10–20 mg/kg). Dosages for twice-weekly administration are the same for isoniazid and rifampin but are higher for pyrazinamide (50 mg/kg, with a maximum of 4 g/d) and ethambutol (40–50 mg/d).
In certain settings, streptomycin (15 mg/kg daily, with a maximum dose of 1 g; or 25–30 mg/kg thrice weekly, with a maximum dose of 1.5 g) can replace ethambutol in the initial phase of treatment. However, streptomycin is no longer considered a first-line drug by the ATS, the IDSA, or the CDC.

Terapia

TABLE 150-3 *Recommended Antituberculosis Treatment Regimens*

Indication	Initial Phase		Continuation Phase	
	Duration, Months	Drugs	Duration, Months	Drugs
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c,d]
New culture-negative cases	2	HRZE[a]	2	HR[a]
Pregnancy	2	HRE[e]	7	HR
Failure and relapse[f]	—	—	—	—
Resistance (or intolerance) to H	Throughout (6)	RZE[g]		
Resistance to H + R	Throughout (18–24)	ZEQ + S (or another injectable agent[h])		
Resistance to all first-line drugs	Throughout (24)	1 injectable agent[h] + 3 of these 4: ethionamide, cycloserine, Q, PAS		
Standardized re-treatment (susceptibility testing unavailable)	3	HRZES[i]	5	HRE
Drug intolerance to R	Throughout (12)[j]	HZE		
Drug intolerance to Z	2	HRE	7	HR

[a] All drugs can be given daily or intermittently (three times weekly throughout or twice weekly after 2 to 8 weeks of daily therapy during the initial phase).

[b] Streptomycin can be used in place of ethambutol but is no longer considered to be a first-line drug by ATS/IDSA/CDC.

[c] The continuation phase should be extended to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture–positive after the initial phase of treatment.

[d] HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase.

[e] The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

[f] Regimen is tailored according to the results of drug susceptibility tests.

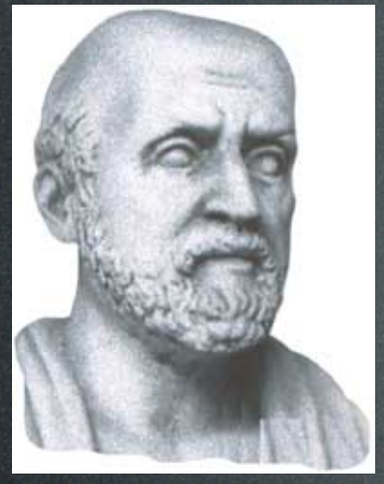
[g] A fluoroquinolone (Q) may strengthen the regimen for patients with extensive disease.

[h] Amikacin, kanamycin, or capreomycin. All these agents should be discontinued after 2 to 6 months, depending upon tolerance and response.

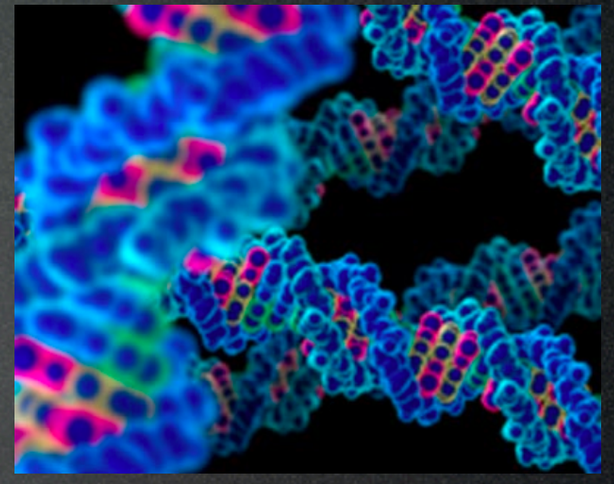
[i] Streptomycin should be discontinued after 2 months. This regimen is less effective for patients in whom treatment has failed, who have an increased probability of rifampin-resistant disease. In such cases, the re-treatment regimen might include second-line drugs chosen in light of the likely pattern of drug resistance.

[j] Streptomycin for the initial 2 months or a fluoroquinolone might strengthen the regimen for patients with extensive disease.

Note: H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol; S, streptomycin; Q, a quinolone antibiotic; PAS, para-aminosalicylic acid.



TBC e gravidanza
Storia



- Descritta da **Ippocrate** (IV-V sec. a.C.): si credeva che la gravidanza peggiorasse i sintomi per aumento della pressione intraddominale;

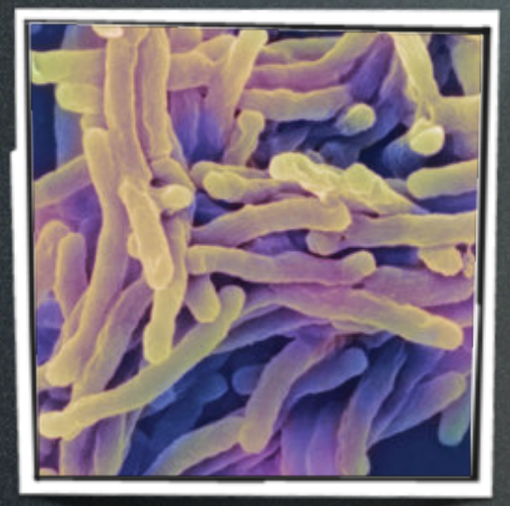
- **Germania XIV sec.**: gravidanza consigliata per alleviare i sintomi;

- **Primi ‘900**: consigliato aborto terapeutico;

- **Anni ’50-’70**: nessun effetto negativo;

- **E oggi?**

Olabisi, 2012; Mathad, 2012; Jana, 2012



TBC e gravidanza

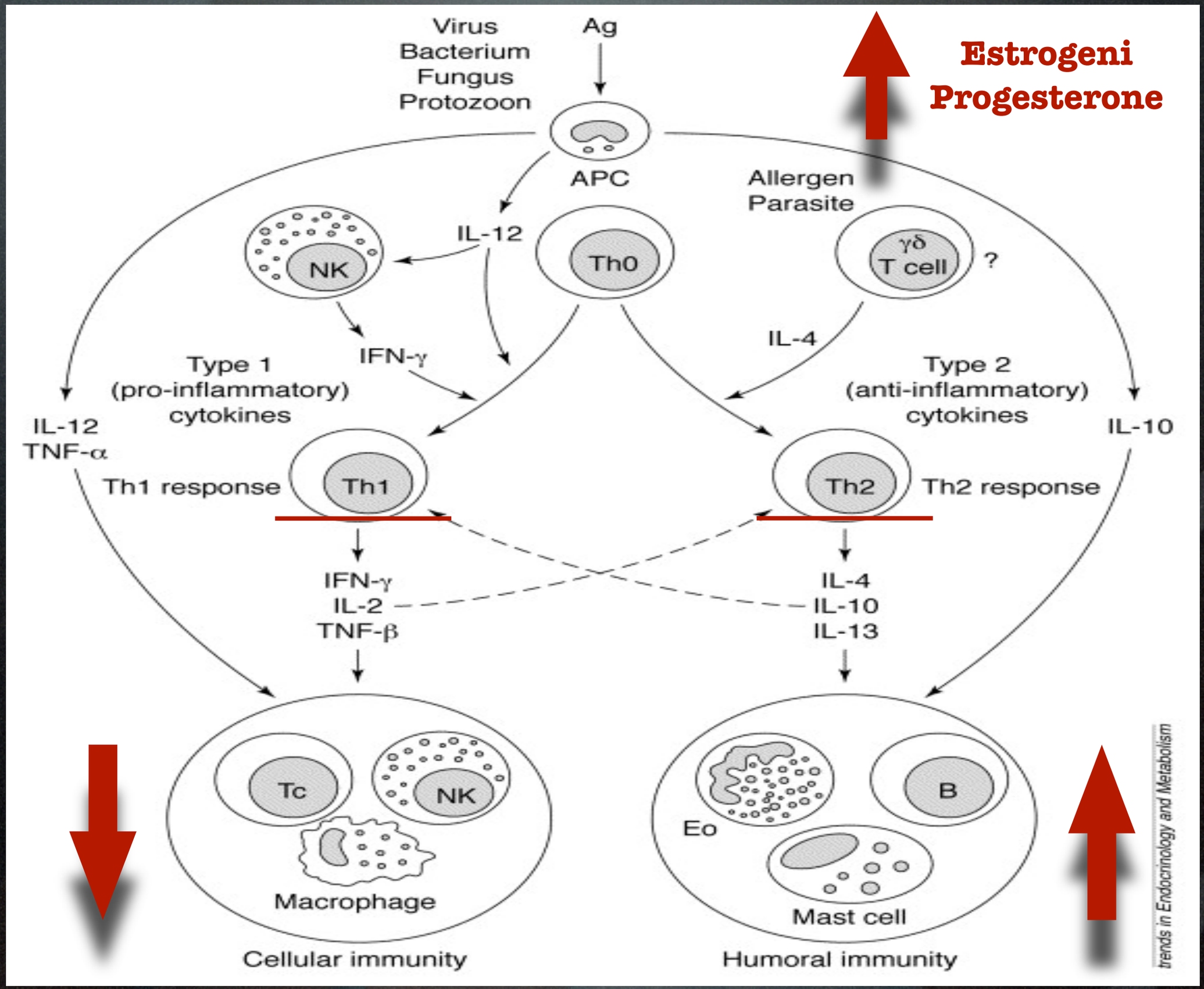
- **III causa di mortalità materna nel mondo;**
- Incidenza **18-80/100.000 gravidanze**;
- **Prevalenza?** 500.000 donne muoiono/anno;
- Stretta correlazione con **AIDS**;
- Diagnosi difficoltosa, **sintomi sfumati**, **ingiustificata reticenza all'esecuzione di RX torace in gravidanza**;

Olabisi, 2012; Mathad, 2012; Jana, 2012

TBC e gravidanza
Effetti sul decorso della patologia

- **Gravidanza → risposta Th2**;
- **Miglioramento dei sintomi;**
- **Maggior rischio di infezione (RR 2);**
- **Maggior rischio di riattivazioni**;
- Nel post-partum **peggioramento dei sintomi** per shift Th1;
- **Gravidanza sconsigliata** se remissione < 2 aa

Olabisi, 2012; Mathad, 2012; Jana, 2012



Olabisi, 2012; Mathad, 2012; Jana, 2012

TBC e gravidanza
Effetti sul decorso della patologia

- **Gravidanza → risposta Th2**;
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- Nel post-partum **peggioramento dei sintomi** per shift Th1;
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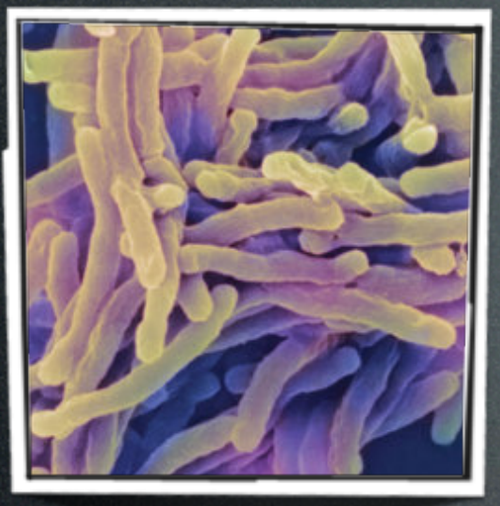
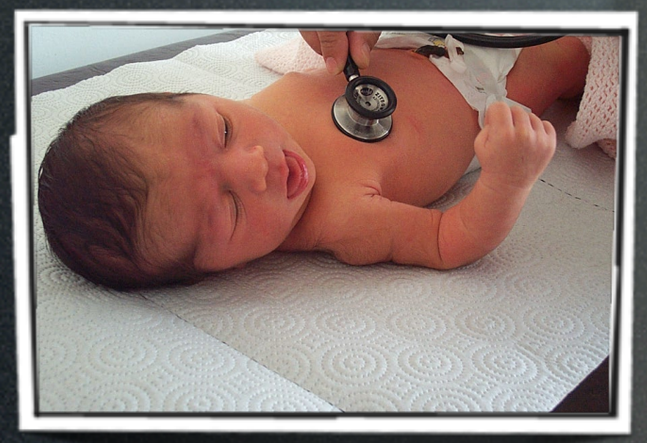
Wilsher, 1999; Piccinni, 2010; Mathad, 2012



TBC
Effetti per la gravidanza

- **Aborto spontaneo**;
- Aumentata **mortalità perinatale** (RR 5);
- **IUGR** (RR 2);
- **Parto pretermine** (RR 9);
- Defedamento materno grave.

Ormerod, 2001; Kishan, 2001; HPA, 2006; Olabisi, 2012; Mathad, 2012; Jana, 2012

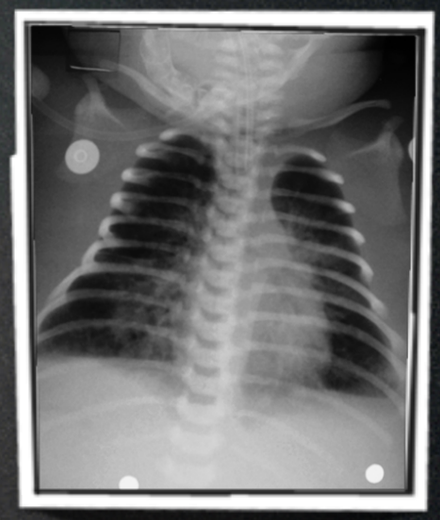


TBC perinatale
Forma neonatale

- Acquisita per **contatto sociale**;
- Localizzazione prevalentemente **polmonare**;
- Alto tasso di progressiona a **forma attiva**;
- Progressione sovrapponibile a **forma adulta**;
- Terapia come per **forma adulta**.

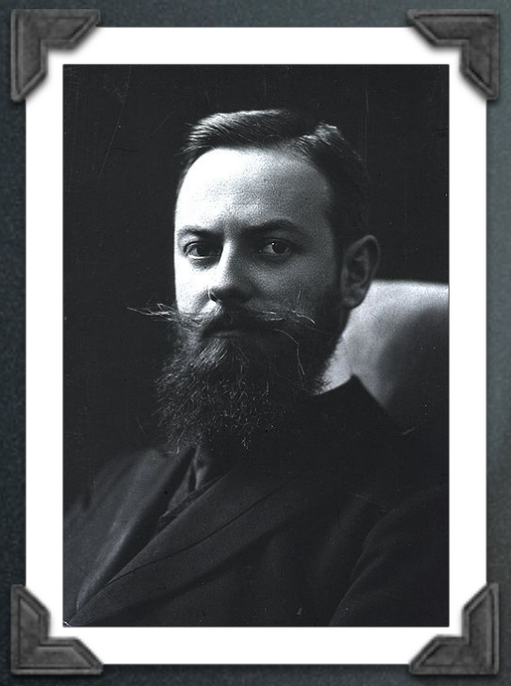
Connelly Smith, 2002; Coulter, 2011; Peng, 2011; Getahun, 2012

TBC perinatale
Forma congenita



- Ritenuta **rara** (descritti 500 casi);
- **Reale incidenza: 16% ???**;
- **Probabile sottostima** per ridotto accesso alle cure materno-fetali nelle zone maggiormente colpite;
- Diffusione ematogena **trans-placentare**, ingestione **LA infetto** o contatto al parto con **lesioni genitali materne**.

Connelly Smith, 2002; Coulter, 2011; Peng, 2011; Getahun, 2012



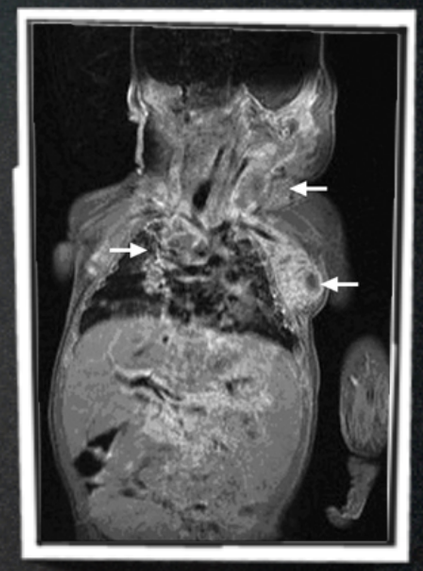
TBC perinatale
Forma congenita

Diagnostic criteria	Beitzke's criteria	Cantwell's criteria
Primary criteria	The infant have proved tuberculous lesions	The infant must have proved tuberculous lesions
Secondary criteria	(1) Lesions in the first few days of life (2) A primary hepatic complex (3) Exclusion of post-natal transmission by the separation of the infant at birth from the mother and other sources of infection	(1) Lesions in the first week of life (2) A primary hepatic complex or caseating hepatic granulomas (3) Tuberculous infection of the placenta or the maternal genital tract (4) Exclusion of the possibility of post-natal transmission by a thorough investigation of contacts, including the infant's hospital attendants, and by adherence to existing recommendations for treating infants exposed to tuberculosis

Congenital tuberculosis can be diagnosed by the primary criteria and at least one of secondary criteria.

Beitzke, 1935; Cantwell, 1994; Peng, 2011

TBC perinatale
Forma congenita

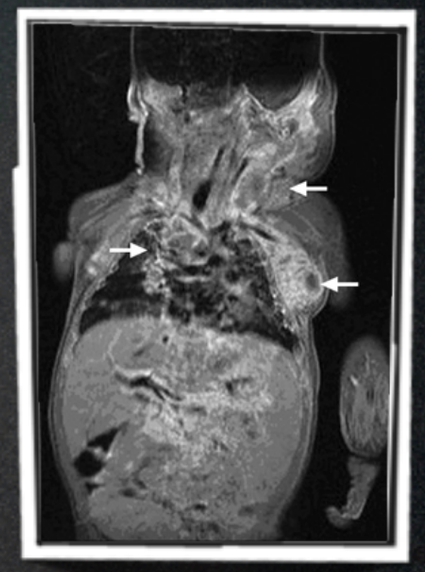


Symptom or sign	Frequency (%)
Hepatosplenomegaly	76
Respiratory distress	72
Fever	48
Lymphadenopathy	38
Abdominal distension	24
Lethargy or irritability	21
Ear discharge	17
Papular skin lesions	14
Vomiting, apnea, cyanosis, jaundice, seizures, petechiae	< 10 each

- Tipico **“pattern epatico”**;
- Mantoux e QuantiFERON **NEGATIVI**;
- Diagnosi: **PCR-DNA e reperto RX**;
- **Multi-terapia aggressiva ad alte dosi**.

Connelly Smith, 2002; Coulter, 2011; Peng, 2011; Getahun, 2012

TBC perinatale
Forma congenita

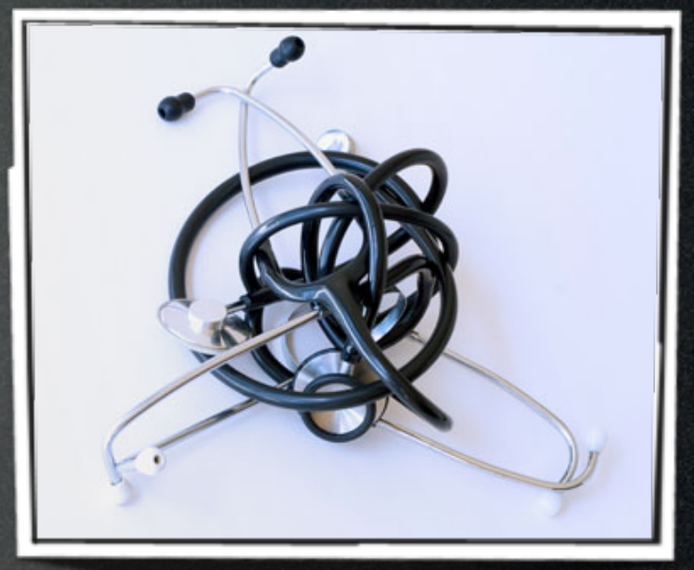


Factors	Mortality of exposure	Mortality of nonexposure	χ^2 value	*P*
Premature	30/70	38/99	0.341	0.559
Intracranial lesions	13/20	10/48	12.304	<0.001
Onset age				
≤1 week	12/30	45/115	0.008	0.993
≤2 weeks	25/59	32/86	0.391	0.532
≤3 weeks	45/94	12/51	8.212	0.004
≤4 weeks	50/101	7/44	14.500	<0.001
Leukocytes count $\geq 12 \times 10^9$	14/53	20/30	12.381	<0.001
Liver dysfunction	14/39	3/12	0.123	0.762
Specific image performance	38/83	17/58	3.894	0.048
Platelet count				
$>100 \times 10^9$	11/20	3/5		0.622[1]
$<50 \times 10^9$	8/12	6/13		0.302[1]
DIC	3/6	65/163	0.005	0.942[2]
Treatment	28/129	40/40	77.834	<0.001

50% di mortalità.

Connelly Smith, 2002; Coulter, 2011; Peng, 2011; Getahun, 2012

TBC e gravidanza
Diagnosi



- **Clinica**;
- **RX torace** da eseguire con schermatura;
- Test tubercolina: **alto tasso FP** per vaccino o **FN** in HIV;
- QuantiFERON: **FN in gravidanza** per shift Th2 (dati contrastanti in letteratura) rimane **GOLD STANARD**;
- **Ricerca DNA su espettorato** (Xpert MTB/RIF test), costoso (macchina: 17.000 $).

Worjoloh, 2011; Jonnalagadda, 2012; Lighter-Fisher, 2012; Minkoff, 2012; Getahun, 2012

TBC e gravidanza
Diagnosi

Performance of an Interferon-Gamma Release Assay to Diagnose Latent Tuberculosis Infection During Pregnancy

Jennifer Lighter-Fisher, MD, and Ann-Marie Surette, MD

OBJECTIVE: To evaluate an interferon (IFN)-gamma release assay in diagnosing latent tuberculosis infection in pregnant adolescents and women at risk for exposure to *Mycobacterium tuberculosis*.

METHODS: This was a prospective study of women and adolescents receiving health care at Bellevue Hospital Outpatient Clinics in New York City. Each patient was assessed for *M tuberculosis* risk factors, had a tuberculin skin test placed, and an IFN-gamma release assay performed. The concordance between the tuberculin skin test and the IFN-gamma release assay was calculated and the results analyzed according to the likelihood of exposure to *M tuberculosis*. Mean mitogen IFN-γ levels were used across groups to compare reliability between trimesters and assay performance in pregnant compared with nonpregnant females of childbearing age.

RESULTS: A total of 140 pregnant and 140 nonpregnant females were enrolled in the study. The IFN-gamma release assay was highly specific, and IFN-gamma release assay positivity was associated with a greater likelihood of exposure to *M tuberculosis*. The overall agreement between the tuberculin skin test and IFN-gamma release assay results was 88% for all pregnant patients, corresponding to a κ of 0.452 (confidence interval 0.26–0.64). Interferon-γ release from the mitogen did not appear to have any temporal association with pregnancy trimester in cross-sectional or longitudinal studies. The IFN-gamma release assay performed equally well in pregnant and nonpregnant females.

CONCLUSION: The IFN-gamma release assay performed equally well in each trimester of pregnancy with comparable results to nonpregnant females. Interferon-gamma release assays are much more specific, at least as sensitive, and may be a better predictor of disease progression than the tuberculin skin test.

(Obstet Gynecol 2012;119:1088–95)
DOI: 10.1097/AOG.0b013e3182546aff

LEVEL OF EVIDENCE: II

Mycobacterium tuberculosis infects one third of the world's population and causes death in approximately one million women yearly.[1] In the United States, tuberculosis (TB) incidence is low as a result of great effort devoted to identifying and treating latently infected individuals with 6–9 months of isoniazid.[2,3] In the United States, latent TB occurs in 4.2%

Lighter-Fisher, 2012; Minkoff, 2012

TBC **attiva** e gravidanza Management

- Schemi terapeutici **come nell'adulto (HRE per 2 mesi, Z se MDR, HE per altri 4-7 mesi)**;
- **Farmaci sicuri in gravidanza** passano BEP ma a basse concentrazioni;
- Se H: **supplementare piridossina (50 mg/die)** nella madre per rischio neuropatia periferica + **funzionalità epatica** per rischio epatotossicità;
- Se R: **vit. K (10 mg/die)** nelle ultime 4-8 s.g. ed al neonato per rischio emorragico alla nascita
- **Streptomicina teratogena**: neuro ed ototossica nel feto;
- **Parto vaginale** salvo lesioni granulomatose vagino-vulvari;
- **Allattamento possibile** salvo mastite tubercolare o forma attiva grave;
- **Nel neonato: H per 6 mesi e vaccinazione BCG**.

WHO, 2009; Getahun, 2012; Mathad, 2012 Olabisi 2012;

TBC **attiva** e gravidanza
Terapia

	Low-Burden Countries[b]	High-Burden Countries[c]
HIV-negative	Isoniazid 5 mg/kg/d × 9 mo	Isoniazid 5 mg/kg/d × 6 mo
	Rifampin 10 mg/kg/d × 9 mo	Rifampicin 10 mg/kg/d × 6 mo
	Ethambutol[d] × 2 mo	Ethambutol 15 mg/kg/d × 2 mo
	Pyridoxine 25 mg/d × 9 mo	Pyrazinamide 25 mg/kg/d × 2 mo
		Pyridoxine 10–25 mg/d × 6 mo
HIV-positive	Isoniazid 300 mg/d × 6 mo	Isoniazid 5 mg/kg/d × 6 mo
	Rifampin 600 mg/d × 6 mo	Rifampicin 10 mg/kg/d × 6 mo
	Ethambutol[d] × 2 mo	Ethambutol 15 mg/kg/d × 2 mo
	Pyrazinamide[e,f] × 2 mo	Pyrazinamide 25 mg/kg/d × 2 mo
	Pyridoxine 25 mg/d × 6 mo	Pyridoxine 10–25 mg/d × 6 mo

Abbreviation: HIV, human immunodeficiency virus.

[a] Treatment of extrapulmonary tuberculosis involves the same medications as pulmonary tuberculosis, but many experts recommend 9–12 mo of treatment for tuberculosis meningitis (plus steroids) or tuberculosis bone/joint infections [70, 71].

[b] Based on recommendations of the Centers for Disease Control and Prevention, American Thoracic Society, and Infectious Diseases Society of America [70].

[c] Based on recommendations of the World Health Organization and International Union Against Tuberculosis and Lung Disease [71].

[d] Ethambutol weight-based dosing: 800 mg/d for 40–55 kg, 1200 mg/d for 56–75 kg, 1600 mg/d for ≥76 kg.

[e] Pyrazinamide weight-based dosing: 1000 mg/d for 50–55 kg, 1500 mg/d for 56–75 kg, 2000 mg/d for ≥76 kg.

[f] Pyrazinamide is only recommended in HIV-positive women because the benefit of potent 4-drug therapy in HIV-positive women outweighs the potential risk of pyrazinamide use during pregnancy [70].

WHO, 2011; Mathad, 2012; CDC, 2012

TBC **latente** e gravidanza Management

- **Se asintomatica rimandare il trattamento a 2-3 mesi dopo il parto** salvo nuovi contatti o fattori di rischio;

- **Stratificazione del rischio**:

TABLE 150-1 Risk Factors for Active Tuberculosis among Persons Who Have Been Infected with Tubercle Bacilli

Factor	Relative Risk/Odds[a]
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidity	
HIV infection	100
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Diabetes	2–4
Intravenous drug use	10–30
Immunosuppressive treatment	10
Gastrectomy	2–5
Jejunoileal bypass	30–60
Posttransplantation period (renal, cardiac)	20–70
Malnutrition and severe underweight	2

- **Se 1 o più fattori di rischio profilassi con ISONIAZIDE + piridossina per 6 mesi**, salvo evoluzione a forma attiva, con monitoraggio AST/ALT (sospendere terapia se rialzo AST/ALT > 3v. in pz. sintomatico o > 5v. in pz. asintomatico).

Harrison, 2005; WHO, 2011; Mathad, 2012; Getahun 2012; CDC, 2012

TBC **latente** e gravidanza Management

Table 5. Preventive Tuberculosis Therapy in Pregnant Women

	Low-Burden Countries[a]	High-Burden Countries[b]
Regimen	Isoniazid 300 mg/d × 6–9 mo	Isoniazid 300 mg/d × 6 mo or 36 mo[c]
	Pyridoxine 25 mg/d × 6–9 mo	Pyridoxine 10–25 mg/d × 6 mo or 36 mo
	OR	
	Isoniazid 900 mg twice weekly × 9 mo	
	Pyridoxine 25 mg/d × 9 mo	
HIV-negative	Defer treatment for TST^+ or $IGRA^+$ until 2–3 mo postpartum unless recent known tuberculosis contact	No recommendations
HIV-positive	Immediate treatment for TST^+ or $IGRA^+$	Immediate treatment for all HIV- positive without active tuberculosis

Abbreviations: HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; TST, tuberculin skin test.

[a] Based on recommendations of the Centers for Disease Control and Prevention [96].

[b] Based on recommendations of the World Health Organization [51].

[c] Consider 36 months if in a setting with high tuberculosis prevalence and transmission.

WHO, 2011; Mathad, 2012; CDC, 2012

Vaccinazione

- Efficacia 80% per forma disseminata;
- **Efficacia 0-80%** per forma polmonare;
- **Controindicato in gravidanza**;
- **Controindicato in HIV**;
- **Somministrare dopo 6 mesi dal parto a neonati** di madri positive.

Linee guida TBC Regione Veneto, 2007; Mathad, 2012; CDC 2012

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