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Women and Tb: Impact of Gender

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Disclosures

- Grant Funding
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- Boards
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  - World Lung Foundation (NYC, NY)
- Committees
  - Advisory Panel -TB Modeling and Analysis Consortium
  - Global Fund- Committee on Tuberculosis
- Consulting
  - Consultant, Global TB Institute, New Jersey, USA
  - Consultant, JSI: Project – Linking Primary Care Sites to TB Control in Massachusetts
- No financial relationship with a commercial entity producing health-care related products and/or services as well as no tobacco related associations.

Talk Outline

- Epidemiology
- Gender Issues in TB Control
- Issues in Low Incidence, High Resource Countries (Focus on Canada and US)
  - Screening
  - Treatment

Epidemiology Global 2013

Global

- 9 million TB cases
- 3,697,499 TB cases notified
- 1.1 Million in PLWAs
- 1.5 Million people died

- 360,000 of deaths in patients with TB/HIV

Women

- 3.3 million
- 1,427,151 TB Cases notified

- 510,000 women died with TB
- 180,000 of deaths were in women with TB/HIV
- 550,000 children with TB
- 80,000 children without HIV died of their TB

WHO Global TB Report 2014

Sex differences in Infection

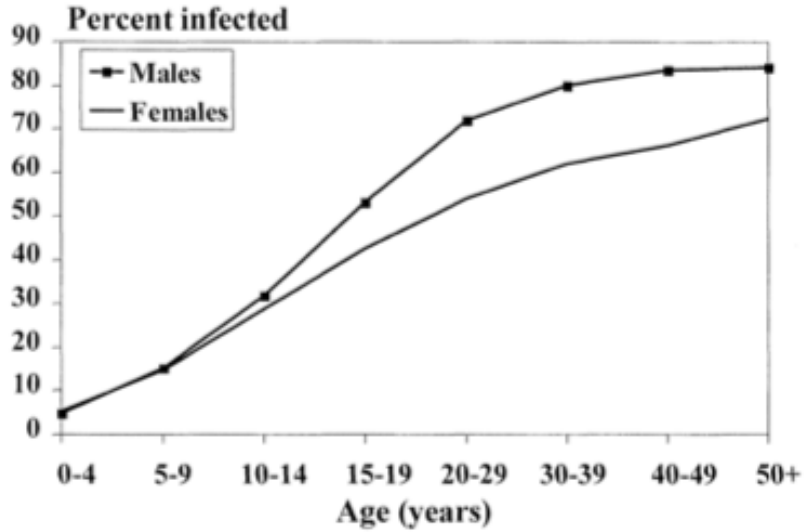


Figure 1 Prevalence of *M. tuberculosis* infection (%). Chingleput, India 1968–1970.

- Annual infection rates consistent across many studies in various sites
- M=F until about age 14 then M>F
- Hypothesis:
  - ? After 14 men have more external exposures then women
  - ? TST is less sensitive in women

Holmes et al. Int J TB Lung Dis 2 (2):96-104; 1998

Sex Differences in Notification rates Influences of country incidence

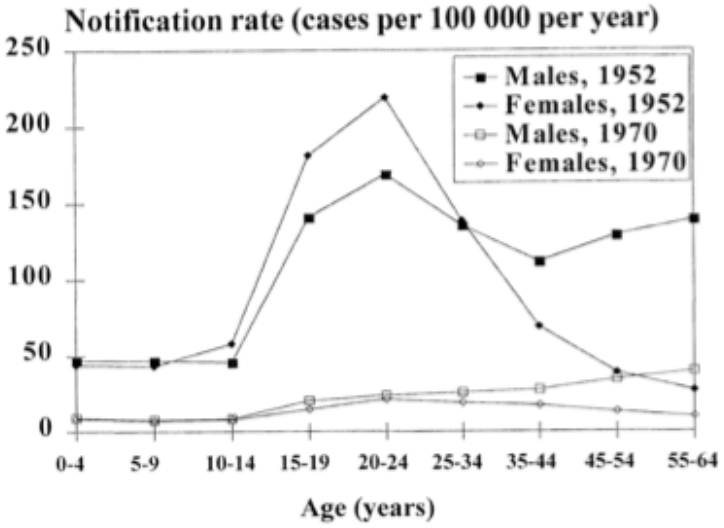


Figure 2 Shift in age and sex patterns of tuberculosis notification rates. England and Wales, 1952 and 1970.

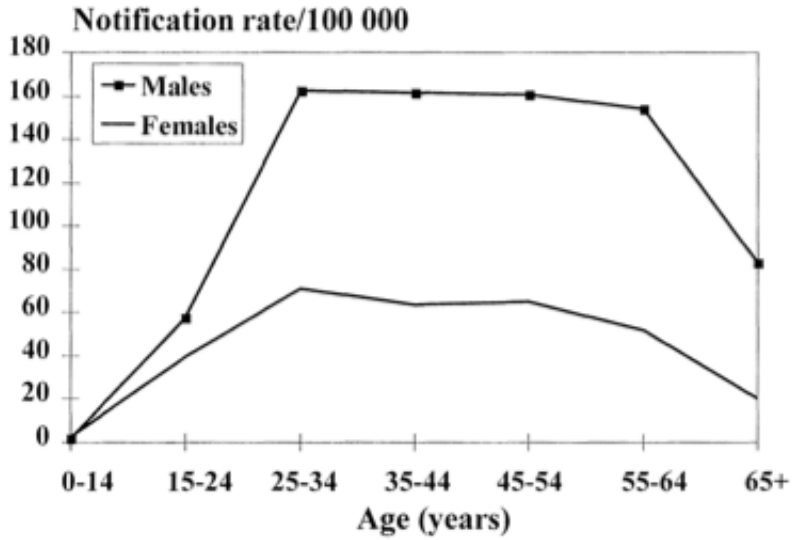


Figure 3 Tuberculosis notification rates for Tanzania (cases/100 000), 1989–1991.

Holmes et al. Int J TB Lung Dis 2 (2):96-104; 1998

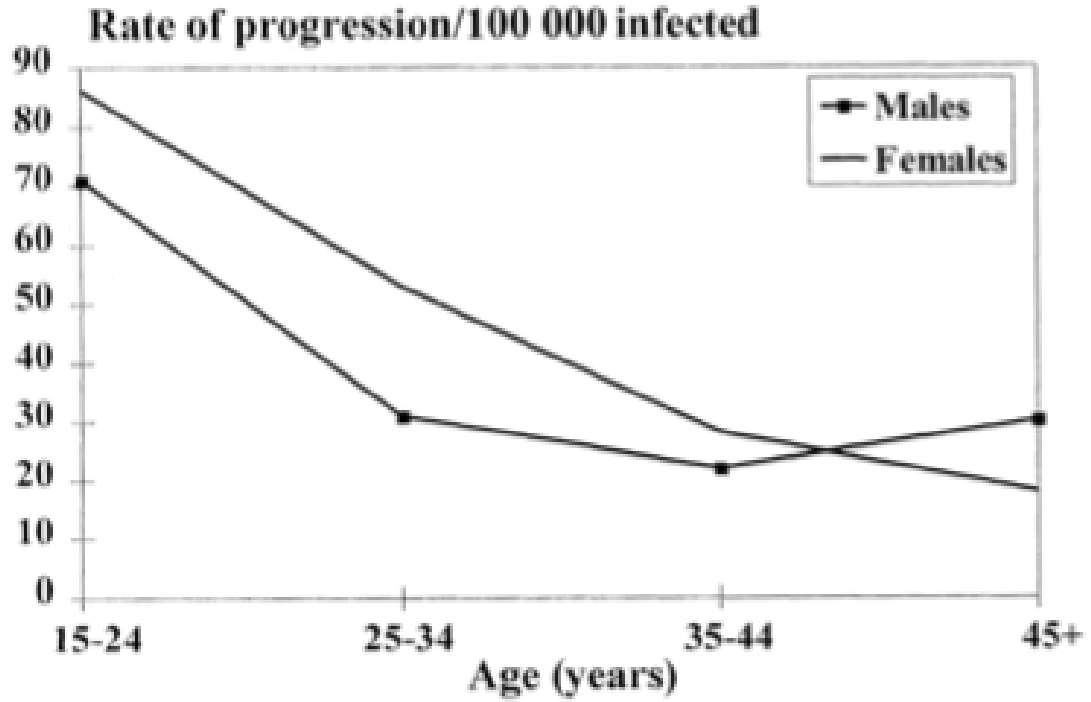


Figure 4 Rate of progression from tuberculosis infection to disease (cases/100 000). Denmark 1952–1956.

Do women of child bearing years have higher rates of progression to disease?

? Biology

? Recent exposure leading to progression

? Timing of interaction with the health care system

Holmes et al. Int J TB Lung Dis 2 (2):96-104; 1998

Male: Female Notifications 2013

Region	M:F ratio
Global	1.6
Africa	1.4
The Americas	1.7
Eastern Mediterranean	1
Europe	1.9
South East Asia	1.5
Western Pacific	2.2

The HIV epidemic is affecting the notification ratios as well.

In high HIV and TB incidence countries, the rates of F TB notification are increasing and approaching M notification rates (HIV and TB both are diseases of age 15-34 – reproductive years for F)

As a result, most research looking at gender differences appears to be focuses on LIC/MIC countries where HIV and TB have a high intersection

Tb in High burden areas

- Reduction of tuberculosis (TB) transmission, morbidity and mortality relies largely on intensified case finding, with consequent early initiation of adequate treatment
- Screening and diagnosis still remains a challenge in resource limited settings especially among women due to:
  - Pregnancy
  - Poverty and low women empowerment
  - Higher burden of HIV infection among women
    - In Kenya women have a higher (6.4%) prevalence of HIV compared to men (4.4%)

Gender Imbalance (in notification rates) caused by?

Socioeconomic

- Restricted access to Health care
- Traditional beliefs
- Greater reliance on less qualified (less expensive) health providers
- Stigmatization

Biologic

- Higher rates of contributing co-morbidities in men
  - Alcoholism
  - Cigarette Smoking
- Influence of pregnancy and child bearing in women
  - Biologic differences (change in symptoms?)
  - Health Care Access – for example radiography use

Evidence for biologic or non biologic basis?

- Rwanda – case control study
  - Women more likely to be HIV infected, more likely to be smear negative or have EPTB and more likely to die during treatment of smear positive disease (Int J TB Lung Dis 15 (6):776-781, 2011)
- Malawi-review of 2 years country register data
  - Women less likely to submit sputa and less likely to be smear positive (Int J TB Lung Dis 4 (9):882-4, 2000)

Most information has focused on Pregnancy and the Post Partum state

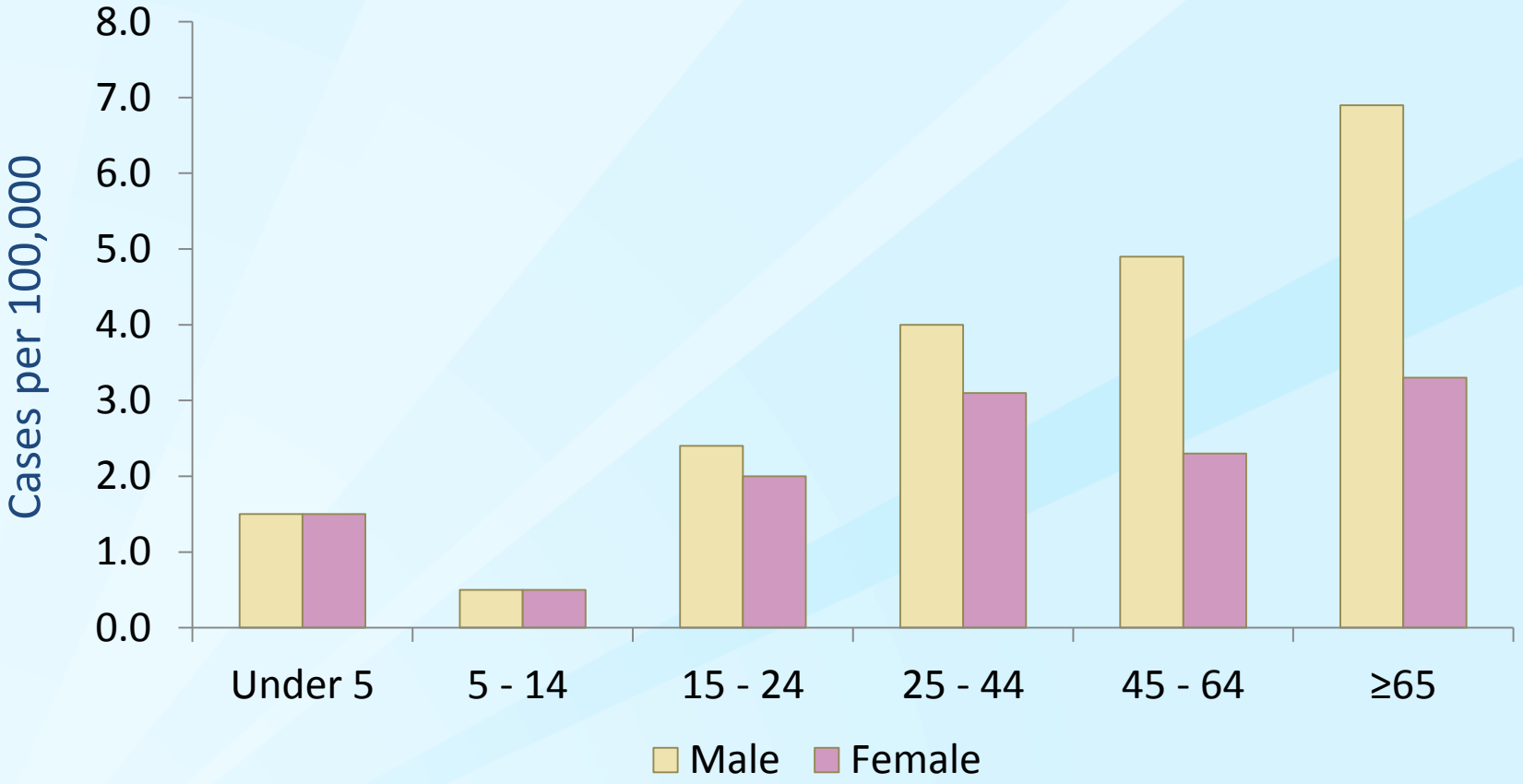
- ? Due to fact that women are in care at this time
  - Prenatal care
  - PMTC programs
- ? Biologic differences during pregnancy that influence care
  - Th1 proinflmmatory responses are suppressed in pregnancy = masking of symptoms, increased susceptibility of new infection or progression to disease
  - Postpartum Th1 suppression reverses (similar to IRIS) which may exacerbate sx

Risk of TB in Pregnancy

- Cohort series with case control
- All pregnancies in General Practitioner Data base in England over 12 years
- 192,801 women with a total of 264,136 pregnancies
- 177 TB events – 22 during pregnancy and 22 during 180 days postpartum
  - Incident rate ratios 1.29 pregnancy and 1.95 postpartum
  - Administrative, immunologic or medical factors

Zinner AJRCCM 185(7):779-784;2012

TB Case Rates by Age Group and Sex, United States, 2013



What are the pragmatic issues of concern?

- Screening
  - LTBI
  - TB Disease
- Treatment
  - Tolerability
  - Side Effects
- Breastfeeding
- Infant evaluation

- Recommended
- Disease RX always indicated
- Well tolerated
- Reasonable data
- Good data re Protection
- How extensive the evaluation should be is the ?.

Screening for LTBI In Pregnancy

- CDC, ACOG, Canadian Guidelines suggest screening for LTBI as targeted testing
  - Those at risk: FB, contact to active, HIV, co-morbid disease that predisposes to TB
- TST or IGRA – screening thresholds do not change
- CXR for those who are found to have LTBI or are symptomatic
- Barrier in low burden countries is awareness of term “those at risk”

LTBI Treatment in Pregnancy

- Risk factors for side effects appear to be elevated
  - Concomitant factors in and postpartum period
  - (An Aside- risk may be elevated in women outside of that time frame as well)
- Treatment should not be deferred until the post partum period if high risk (new conversion, HIV infected)
  - Interpretation of other high risk is left open ended

Liver and Pregnancy

TABLE 2. CHARACTERISTICS OF LIVER DISEASES IN PREGNANCY.*

DISEASE	SYMPTOMS	JAUNDICE	TRIMESTER	INCIDENCE IN PREGNANCY	LABORATORY VALUES†	ADVERSE EFFECTS
Hyperemesis gravidarum	Nausea, vomiting	Mild	1 or 2	0.3–1.0%	Bilirubin <4 mg/dl, ALT <200 U/liter	Low birth weight
Intrahepatic cholestasis of pregnancy	Pruritus	In 20–60%, 1–4 wk after pruritus starts	2 or 3	0.1–0.2% in U.S.	Bilirubin <6 mg/dl, ALT <300 U/liter, increased bile acids	Stillbirth, prematurity, bleeding, fetal mortality 3.5%
Biliary tract disease	Right-upper-quadrant pain, nausea, vomiting, fever	With CBD obstruction	Any	Unknown	If CBD stone, increased bilirubin and GGT	Unknown
Drug-induced hepatitis	None or nausea, vomiting, pruritus	Early (in cholestatic hepatitis)	Any	Unknown	Variable	Unknown
Acute fatty liver of pregnancy	Upper abdominal pain, nausea, vomiting, confusion late in disease	Common	3	0.008%	ALT <500 U/liter, low glucose, DIC in >75%, increased bilirubin and ammonia late in disease	Increased maternal mortality (≤20%) and fetal mortality (13–18%)
Preeclampsia and eclampsia	Upper abdominal pain, edema, hypertension, mental-status changes	Late, 5–14%	2 or 3	5–10%	ALT <500 U/liter (unless infarction), proteinuria, DIC in 7%	Increased maternal mortality (~1%)
HELLP syndrome	Upper abdominal pain, nausea, vomiting, malaise	Late, 5–14%	3	0.1% (4–12% of women with preeclampsia)	ALT <500 U/liter, platelets <100,000/mm³, hemolysis, increased LDH, DIC in 20–40%	Increased maternal mortality (1–3%) and fetal mortality (35%)
Viral hepatitis	Nausea, vomiting, fever	Common	Any	Same as general population	ALT greatly increased (>500 U/liter), increased bilirubin, DIC rare	Maternal mortality increased with hepatitis E

*ALT denotes alanine aminotransferase, CBD common bile duct, GGT γ-glutamyl transpeptidase, DIC disseminated intravascular coagulation, and LDH lactate dehydrogenase.

†To convert bilirubin values to micromoles per liter, multiply by 17.1.

Knox NEJM 335 (8):569-576;1996

Screening for Active Disease

- In HIV TB high incidence countries, screening for active disease involves collection of sputa for cough any duration, fever, weight loss
  - Absence of sx have a negative predictive value of 90-97%; Positive predictive value is low
- In LIC, screening for TB disease is dictated by symptomatic women with a history of risk factors
  - No published data regarding efficacy of screening practices

Treatment of TB Disease in Pregnancy

- Treatment of TB Disease varies little with pregnancy
- PZA not approved in the US in pregnant women but used in the remainder of the world
- Canada suggests PZA use in severe cases
- Pyridoxine (B6) should be given although little data to support increased neuropathy in pregnancy

Breastfeeding

- Breastfeeding does not transmit TB
  - No documented cases of transmission from breast milk
- Formula fed infants remain at high risk of infection
- Anti-tuberculous drugs cross into breast milk in small amounts
  - Serum level no more than 20% of the therapeutic level for INH
    - Less than 11% for others
  - No toxic effects reported
  - No indication to advise mom to “pump and dump”

Snider D.E., and Powell K.E.: Should women taking antituberculosis drugs breast-feed? Arch. Intern. Med. 1984; 144: pp. 589-590

Breastfeeding

- The issue is not transmission of the organism through breast milk but rather the proximity of the mother to baby during feeding in the case of a mother who is infectious (smear positive)
- CDC = On first line ATT and no longer infectious
- WHO= smear negative

PROPHYLACTIC ISONIAZID

PROTECTION OF INFANTS IN A TUBERCULOSIS HOSPITAL

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MEDICAL OFFICER

KING GEORGE V HOSPITAL, DURBAN, SOUTH AFRICA

The Lancet. 1959

Some of our mothers with their babies.

Study Summary

- Treatment – 10/1955 to 1/1959
  - Child kept in crib next to mom's bedside
  - 30 bed open ward, all women with active pulmonary TB
  - Infants given INH twice daily
  - Breastfed
  - No special precautions taken to prevent infection
    - "mothers are allowed to fondle their children as much as they wish"
  - Infants PPDs monthly, CXRs twice monthly
- Outcomes
  - 101 pregnancies, 103 live births
  - 2 stillborn, 3 died within 3 weeks
  - 98 healthy
    - 4 became PPD positive (mom's not giving INH)

Separation

- “INH therapy for newborns has been so effective that separation of mother and infant is no longer considered mandatory”
- Separation should occur *only* if
  - the mother is ill enough to require hospitalization
  - if she has been or is expected to become nonadherent to her treatment
  - if she is thought to be infected with a drug-resistant strain of *M. tuberculosis*

Summary

- The true incidence of TB in women is unclear
  - Influenced by biology, access or other factors?
- Because TB is primarily a disease of young adults; thus, much of the information about TB and women focus on the intersection between pregnancy/PP and TB
- TB remains a leading cause of death in women of childbearing years