TB 2018

David V. Condoluci, DO.,M.A.C.O.I.

TB

- TB is history they say
- Less tomorrow than today
- From TB we have little to fear
- Money is tight, that is for sure
- And it still takes 6-9 months to cure

Dr. Jason Stout

Successful Challenges to TB Control

- Foreign Born
- Delays in Detection
- Deficiencies in protecting contacts
- Large reservoir of persons with LTB (10-15 million)
- Maintaining public health expertise with declining numbers

Factors Likely Contributing to Burden of TB in Minorities

- In foreign-born minorities, TB may result from infection in country of origin
- Some minority groups have unequal distribution of TB risk factors (e.g., HIV infection), contributing to increased exposure to TB or increased risk of developing disease once infected with *M. tuberculosis*
- Lower socioeconomic status and crowded housing are linked to increased TB risk
- HIV

Multidrug-Resistant (MDR) TB Remains a Serious Public Health Concern in the United States

- MDR TB has decreased in foreign born and U.S. born, but decline greater in U.S. born
- 1993–2011, proportion of primary MDR TB in foreign born increased from 25% to 83%

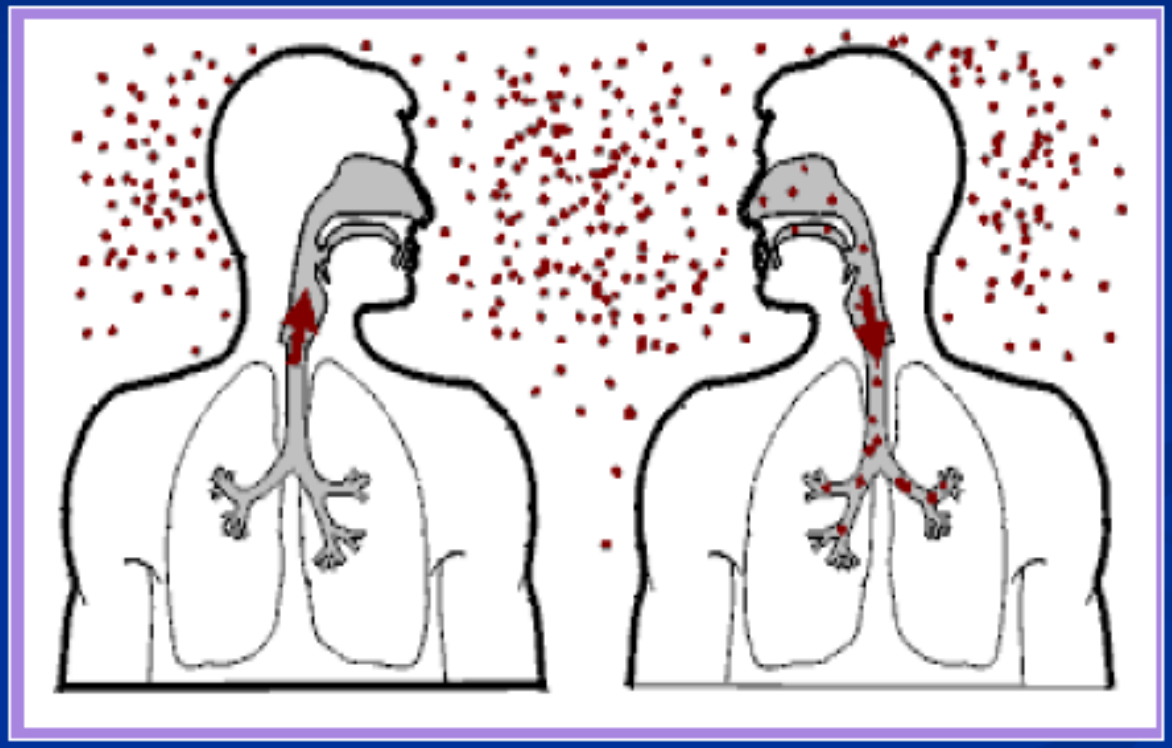
Extensively Drug-Resistant (XDR) TB in the United States

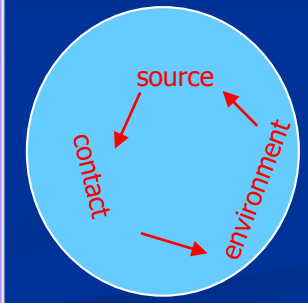
- **XDR TB is a rare type of MDR TB**
  - Resistant to INH, RIF, fluoroquinolones, and ≥1 of 3 injectable 2nd-line drugs
- **No apparent trend for XDR TB in the U.S.**

Transmission Factors

- Concentration of the organisms in spt
- Cavitary lesions
- Frequency and strength of cough
- Previous MTB infection
- Innate resistance
- Frequency and duration of exposure
- Dilution effect
- Ventilation
- UV light

Transmission and Pathogenesis





Triad of cavitary pulmonary disease + pos AFB smear + cough frequency are high risk factors. Indoor versus outdoor exposure

Latent TB Infection (LTBI)

- Granulomas may persist (LTBI), or may break down to produce TB disease
- 2 to 8 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA)
- The immune system is usually able to stop the multiplication of bacilli
- Persons with LTBI are not infectious and do not spread organisms to others

TB Infection	TB Disease
CXR: Normal	CXR: Abnormal
No Symptoms	Symptoms
Negative Sputum Culture	Positive Sputum Culture
Not a Case of TB	Case of TB
NOT INFECTIOUS	INFECTIOUS

Signs/Symptoms

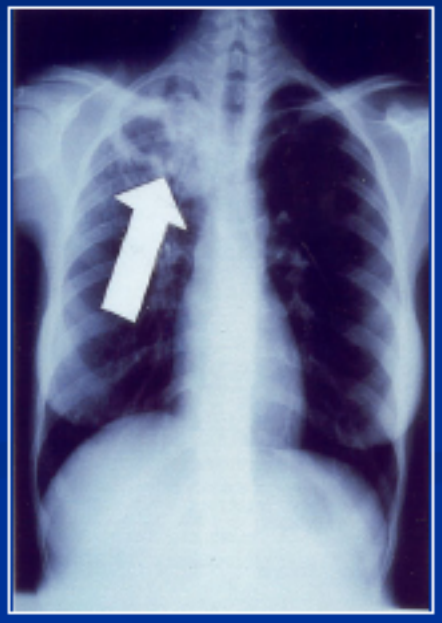
- Productive cough 3 weeks or longer
- Shortness of breath
- Chest pain
- Hemoptysis
- Night sweats/fever/chills
- Unexplained weight loss
- Fatigue

Suspect TB:

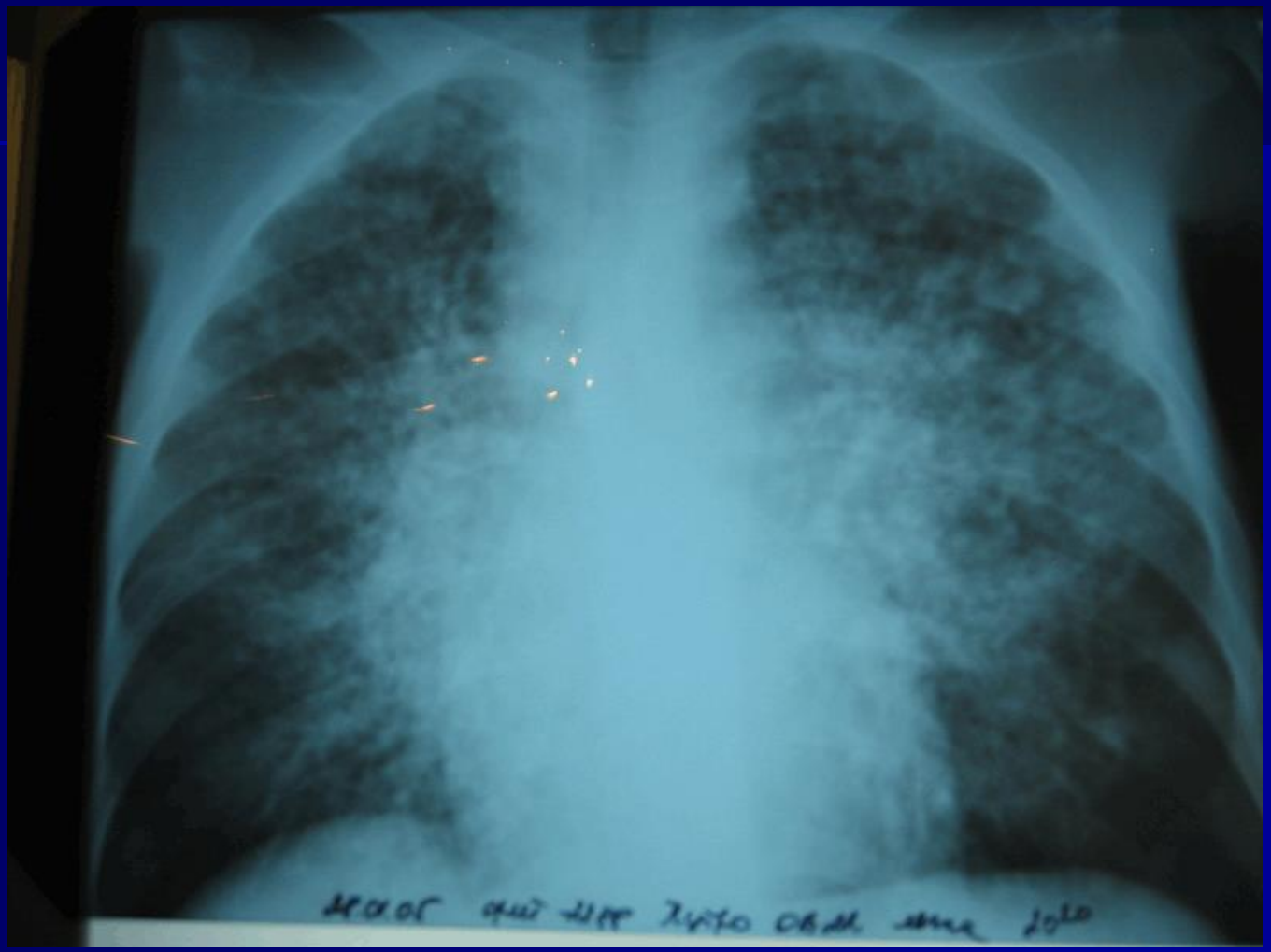
- Chest x-ray
  - Location of the infiltrate
  - Presence of a cavity
  - Hollow areas, dense areas, fluid on the lung or at margins
  - Normal x-ray = usually no infectious TB disease

Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB



Arrow points to cavity in patient's right upper lobe.



AFB Smear Results

- Positive
  - Need at least ***10,000*** bacilli per ml
  - Positive in about half those with TB disease
  - Signal a very infectious person
  - Other *mycobacteria* may make the smear a ***false positive***
- Negative
  - Too few bacilli to be seen directly under the microscope
  - Provides some reassurance that patient is less infectious to others

Cultures

- Use to confirm dx of TB
- Culture all specimens, even if smear –
- Result in 4-14 days when liquid medium systems used
- Susceptibility testing- *essential*

Rapid tests like PCR now standard

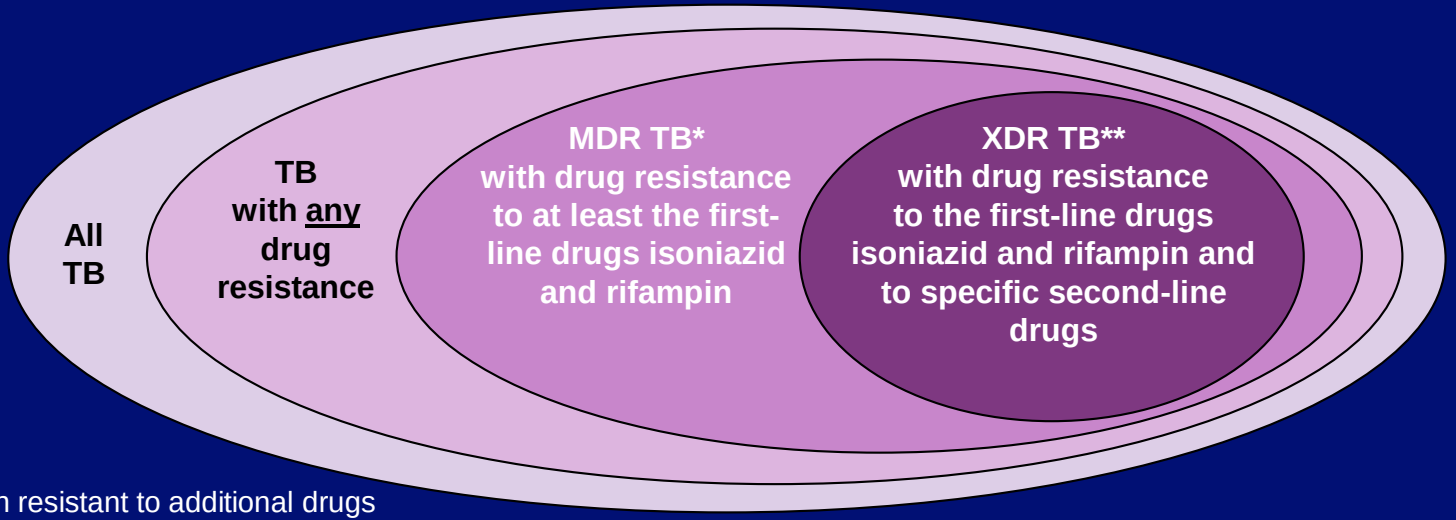
Colonies of *M. tuberculosis* growing on media

Drug-Resistant TB

- Caused by organisms resistant to one or more TB drugs
- Transmitted same way as drug-susceptible TB, and no more infectious
- Delay in detecting drug resistance may prolong period of infectiousness because of delay in starting correct treatment

Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB

- MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin
- XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs



*Often resistant to additional drugs

**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin

Interpreting the TST Reaction

≥5 mm induration is classified as positive in

- **HIV-infected persons**
- **Recent contacts of infectious TB**
- **Persons with fibrotic changes on chest radiograph consistent with prior TB**
- **Patients with organ transplants and other immunosuppressed patients**

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Mycobacteriology laboratory personnel
- Persons with conditions that increase risk for progressing to TB
- Children <4 years of age, or children and youth exposed to adults at high risk

Interpreting the TST Reaction (cont.)

≥15 mm is classified as positive in

- **Persons with no known risk factors for TB**

Targeted skin testing should only be conducted among high-risk groups

Factors that May Affect the Skin Test Reaction

Type of Reaction	Possible Cause
False-positive	• Nontuberculous mycobacteria • BCG vaccination • Problems with TST administration
False-negative	• Anergy • Viral, bacterial, fungal coinfection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid disease • Low protein states • Immunosuppressive drugs • Problems with TST administration

Special Considerations When Using TST

Boosting

- Some may have negative (waned) TST reaction when tested years after infection (e.g., older adults)
- Initial skin test may stimulate (boost) ability to react to PPD
- Subsequent positive boosted reaction may be misinterpreted as a new infection
- May still be considered for treatment if currently at high risk for TB disease

Special Considerations When Using TST (cont.)

Pregnant women

- **TST is safe and reliable for mother and fetus throughout pregnancy**
- **Give TST to pregnant women who have risk factors for infection or disease**

Treatment of Latent TB Infection (LTBI)

- Consists of 9 months of daily isoniazid (INH)
- Substantially reduces the infected person's risk of developing clinical TB
- Monitor patient at least monthly for symptoms of toxicity and adherence

Candidates for Treatment of LTBI

High-risk persons with positive IGRA test or TST reaction of ≥5 mm:

- **HIV-infected persons**
- **Recent contacts of persons with infectious TB**
- **Persons with fibrotic changes on chest radiograph consistent with prior TB**
- **Patients with organ transplants and other immunosuppressed patients**

Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm:

- **Recent arrivals (<5 yrs) from high-prevalence countries or regions (e.g., Asia, Africa, Eastern Europe, Latin America, and Russia)**
- **Injection drug users**
- **Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, hospitals, and long term care facilities)**
- **Mycobacteriology laboratory personnel**

Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm (cont.):

- **Persons with conditions that increase risk for TB:**
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure
  - Certain cancers (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung)
  - Gastrectomy or jejunoileal bypass
  - Weight loss of at least 10% below ideal body weight
  - Children <4 yrs of age; children/adolescents exposed to adults in high-risk categories

Candidates for Treatment of LTBI (cont.)

- **Low-risk persons with positive IGRA test or TST reaction of ≥15 mm:**
  - Persons with no known risk factors for TB generally should not be tested
- **Targeted testing programs should only be conducted among high-risk groups**
- **If low-risk persons are tested and have positive IGRA test or TST reaction ≥15 mm, evaluate for LTBI treatment**

Close Contacts with Negative IGRA or TST Result

- **Some contacts should be evaluated and treated for LTBI even with negative TB test results:**
  - Children under 4 yrs of age
  - Immunosuppressed persons
  - Others at high risk for progressing to disease once infected
- **Always rule out TB disease with chest radiograph and medical evaluation before treating for LTBI**
- **Give LTBI treatment (window prophylaxis) regardless of test result**
- **Retest 8–10 weeks after last exposure to allow for delayed immune response**

LTBI Treatment Regimens

Isoniazid (INH)

- **9-month daily regimen is preferred: 270 doses within 12 months**
  - Effective for HIV-infected as well as HIV-uninfected persons
  - Can be given twice weekly via DOT: 76 doses within 12 months
  - Children should always receive 9 months of therapy

LTBI Treatment Regimens

Isoniazid (INH) (cont.)

- 6-month regimen also generally acceptable: 180 doses within 9 months
- Can be given twice weekly via DOT: 52 doses within 9 months
- Not recommended for children, HIV infected, persons whose x-rays suggest previous TB

Rifampin (RIF)

- Alternative to INH is 4 months daily RIF:120 doses within 6 months
- Use of RIF contraindicated with some combinations of antiretroviral therapy
- In some instances where RIF cannot be used, rifabutin can be substituted

Recommendation Against the RIF/PZA Regimen

- **LTBI regimen of 2 months of RIF/PZA is no longer recommended owing to associated severe liver injury.**
- **PZA should *not* be offered to persons with LTBI, but should be included in multidrug regimens for treatment of TB as described in TB disease treatment section**

LTBI Treatment Regimens for Specific Situations

HIV-Infected Persons

- **Consult an expert in managing HIV and TB**
- **INH daily for 9-mo, rather than 6-mo, is optimal: 270 doses within 12 months**
- **RIF is generally contraindicated for persons taking protease inhibitors or delavirdine**
- **Rifabutin with dose adjustments can sometimes be substituted for RIF**

LTBI Treatment Regimens for Specific Situations (cont.)

Persons with Fibrotic Lesions Suggesting Previous TB

- **Should be treated for LTBI if they have**
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease
- **Treat only after active disease excluded with sputum testing**
- **Acceptable regimens include**
  - 9 months of INH
  - 4 months of RIF (with or without INH)
- **Persons with evidence of primary, healed TB not at increased risk for TB**

LTBI Treatment Regimens for Specific Situations (cont.)

Contacts of Persons with Multidrug-Resistant TB

- **Consider risk for progressing to MDR disease before recommending LTBI treatment**
- **When prescribing treatment for these contacts, consult an MDR TB expert**

LTBI Treatment Regimens for Specific Situations (cont.)

Pregnancy and Breast-Feeding

- 9 months of INH daily or twice weekly; give with vitamin B_6
- If cannot take INH, consult with TB expert
- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

Patient Monitoring

Before starting treatment for LTBI, clinicians should

- **Exclude possibility of disease (symptoms, chest radiograph)**
- **Determine if patient has history of treatment for LTBI or disease**
- **Determine contraindications to treatment**
- **Obtain information about current and previous drug therapy, including adverse reactions**
- **Recommend HIV testing, unless the patient declines (opt-out screening)**

Patient Monitoring (cont.)

- **Baseline laboratory testing not routinely indicated for all patients**
- **Baseline hepatic measurements are indicated for**
  - Patients with a liver disorder or liver disease
  - Patients with HIV infection
  - Pregnant women and those in immediate postpartum period
- **Patients with abnormal baseline tests should be monitored regularly**

Patient Monitoring (cont.)

At least monthly, evaluate for

- **Adherence to prescribed regimen**
- **Signs and symptoms of TB disease**
- **Signs and symptoms of adverse effects, especially hepatitis**
  - Jaundice, loss of appetite, fatigue, and/or muscle and joint aches

Treating TB Disease: General Principles

- Always treat with multiple drugs
- Never add a single drug to a failing regimen
- Treatment course depends on drugs selected. Usually 6 months, sometimes 9 months:
  - Four drugs for two months
    - INH-RIF-EMB-PZA
  - Two drugs for four or seven months
    - INH-RIF

How will we know if the treatment is effective?

- The symptoms improve
- Sputum smears become negative
- Sputum cultures change to negative, usually within 2 – 3 months
- The chest x-ray improves (important for kids)

Current Anti-TB Drugs

10 drugs FDA-approved for treatment of TB

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- Rifapentine (RPT)
- Streptomycin (SM)
- Cycloserine
- Capreomycin
- *ρ*-Aminosalicylic acid
- Ethionamide

Current Anti-TB Drugs (cont.)

- **Four first-line drugs considered standard treatment:**
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)

- **Rifabutin and rifapentine also considered first-line drugs in some circumstances**
- **Streptomycin (SM) formerly first-line drug, but now less useful owing to increased SM resistance**

TB Disease Treatment Regimens

- Four regimens recommended for treatment of drug-susceptible TB, with different options for number of doses and for length of continuation phase
- Initial phase: standard four drugs (INH, RIF, PZA, EMB) for 2 months (one excludes PZA)
- Continuation phase: additional 4 months; 7 months for some patients

TB Disease Treatment Regimens (cont.)

- **When to use 7-month continuation phase:**
  - Disease is cavitary and sputum culture is positive at end of initial phase;
  - Initial phase excluded PZA; or
  - Once-weekly INH and RPT used in continuation phase, and culture is positive at end of initial phase.

Regimen 1 for Treatment of Pulmonary, Drug-Susceptible TB 6-Month Standard Regimen for Most Patients

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks

4-month continuation phase options

1) INH, RIF daily (7 or 5 days/week) for 18 weeks

2) INH, RIF intermittently (2 days/week or 1 day/week for INH, rifapentine) for 18 weeks

Regimen 2 for Treatment of Pulmonary, Drug-Susceptible TB 6-Month Daily + Intermittent Dosing Options

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 2 weeks, *then* 2 days/week for 6 weeks

4-month continuation phase options

1) INH, RIF intermittently (2 days/week) for 18 weeks

2) INH, RPT intermittently (1 day/week) for 18 weeks

Treatment Completion

- Defined as ingesting prescribed number of doses within specified time
- Duration depends on drugs used, isolate's susceptibility, and patient's response to drugs
- Most patients can be treated with 6- or 9-mo therapy; 6 mo is used for most patients

Treatment Regimens for Specific Situations (cont.)

HIV-Infected Persons (cont.)

- If possible, use a rifamycin for the entire course of therapy, along with ARV therapy
- A major concern: RIF interacts with some PIs and NNRTIs
- Rifabutin has fewer drug interactions and may be used instead of RIF
- Drug dosages may need adjusting; consult expert

Conditions Requiring Additional Considerations (cont.)

Multidrug-resistant TB (MDR TB)

- Presents high risk for treatment failure, relapse, further acquired resistance, and/or death
- Clinicians unfamiliar with its treatment should seek expert consultation
- Always use DOT to ensure adherence

Definitions

MDR TB: TB isolate that is resistant to both isoniazid and rifampin

XDR TB: MDR + resistance to fluoroquinolone and 1 of the 3 injectable drugs (amikacin, kanamycin, capreomycin)

- **Primary drug resistance:**
  - Infected with TB which is already drug resistant
- **Secondary (acquired) drug resistance:**
  - Drug resistance develops during treatment

Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs

Pyrazinamide

Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin

Injectable agents

Amikacin
Capreomycin
Streptomycin
Kanamycin

Step 2

Add 2nd line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second line drugs

Cycloserine
Ethionamide
PAS

Step 3

If there are not 4-6 drugs available consider 3rd line in consult with MDRTB experts

Consider use of these

Third line drugs

Imipenem Linezolid Macrolides
Amoxicillin/Clavulanate

Principles for Managing MDR TB

American Thoracic Society, Centers for Disease Control & Prevention, & Infectious Diseases Society of America, 2003

- Patients should receive either hospital-based or domiciliary DOT
- A single drug should never be added to a failing regimen
- When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is *in vitro* susceptibility
- Sufficient numbers of oral drugs should be started at onset of therapy to make sure there is an adequate regimen once the injectable agent is discontinued
- Do not limit the regimen to 3 agents if other previously unused drugs that are likely to be active are available

Principles for Managing MDR TB

American Thoracic Society, Centers for Disease Control & Prevention, & Infectious Diseases Society of America, 2003

- Intermittent therapy should not be used in treating MDR TB
- The use of drugs to which there is demonstrated *in vitro* resistance is not encouraged because there is little or no efficacy of these drugs
- A good response does not justify continuation of an inadequate regimen
- Serum therapeutic drug level monitoring should generally be utilized, especially for the bactericidal drugs and those most toxic
- Consultation with an expert in the care of drug resistant tuberculosis should be sought

Infectiousness

Patients should be considered infectious if they

- Are coughing
- Are undergoing cough-inducing or aerosol-generating procedures, or
- Have sputum smears positive for acid-fast bacilli and they
- Are not receiving therapy
- Have just started therapy, or
- Have poor clinical response to therapy

Thank You

Lower Respiratory Infections

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CAP

- 5.6 Million cases per year
- Number one cause of infectious deaths in the us
- 10 billion in costs
- High mortality

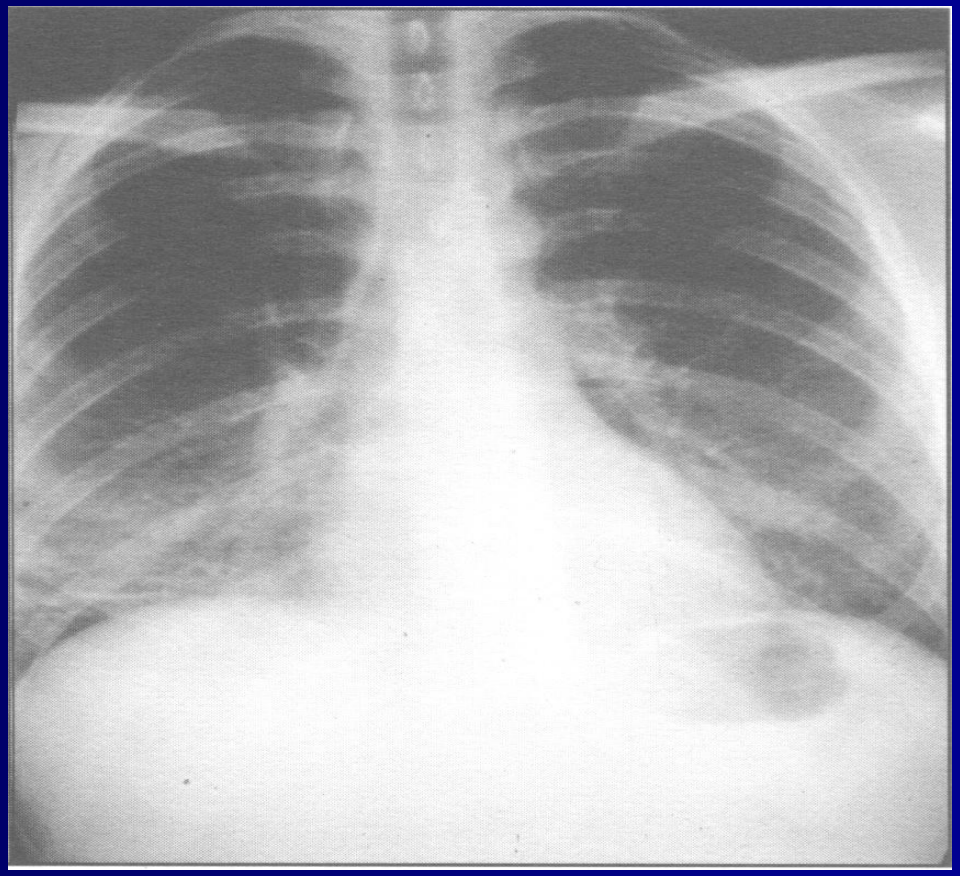
Emerging Pathogens

- Traditional organisms
- MRSA
- CRE
- ESBL
- Viruses such as metapneumo virus

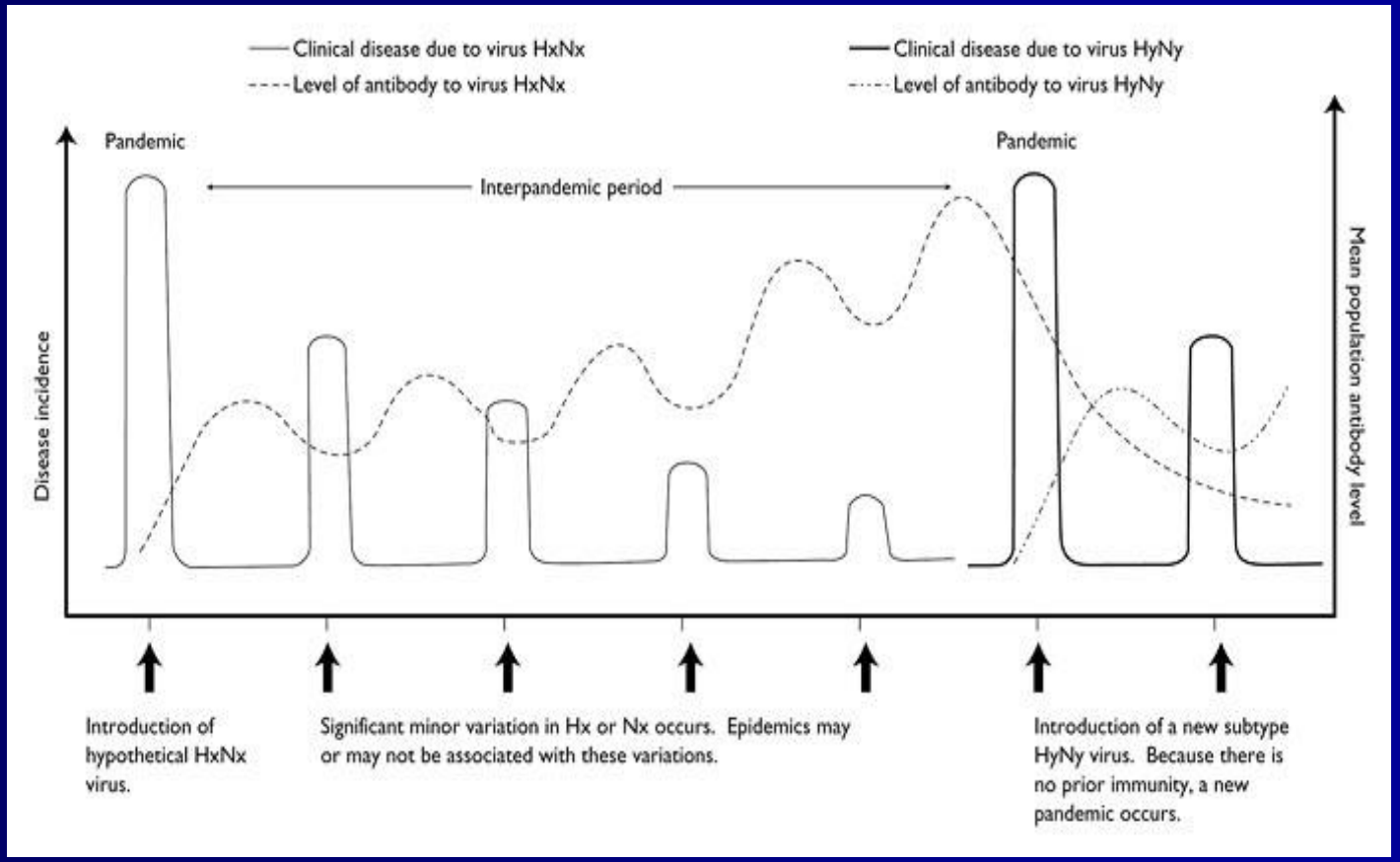
Factors Contributing To Antibiotic Resistance

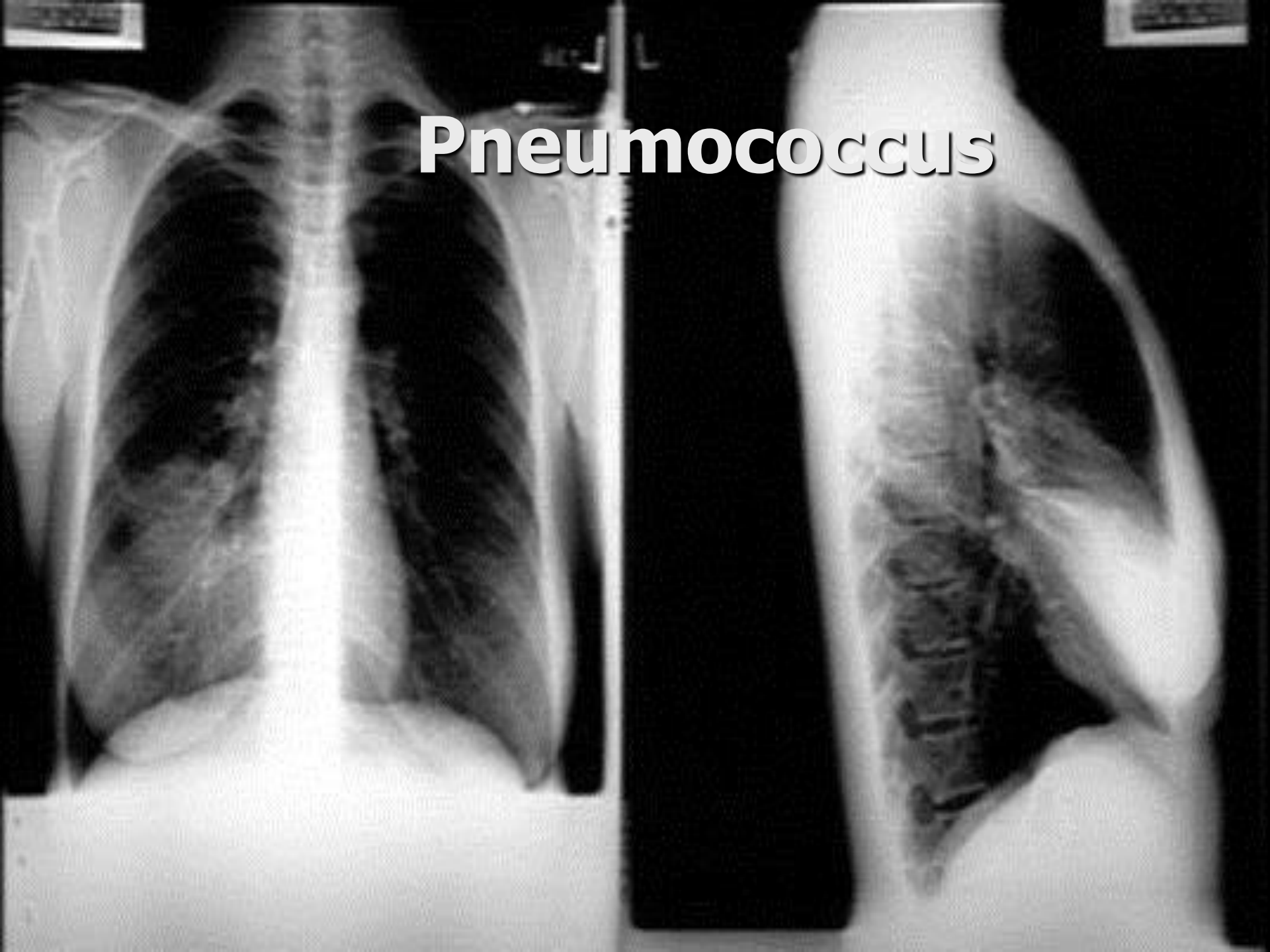
- Increased severity of illness
- Severely immunocompromised patients
- New devices and procedures
- Resistance in the community
- Ineffective infection control and compliance
- Inappropriate antibiotic usage
- Greater antibiotic usage

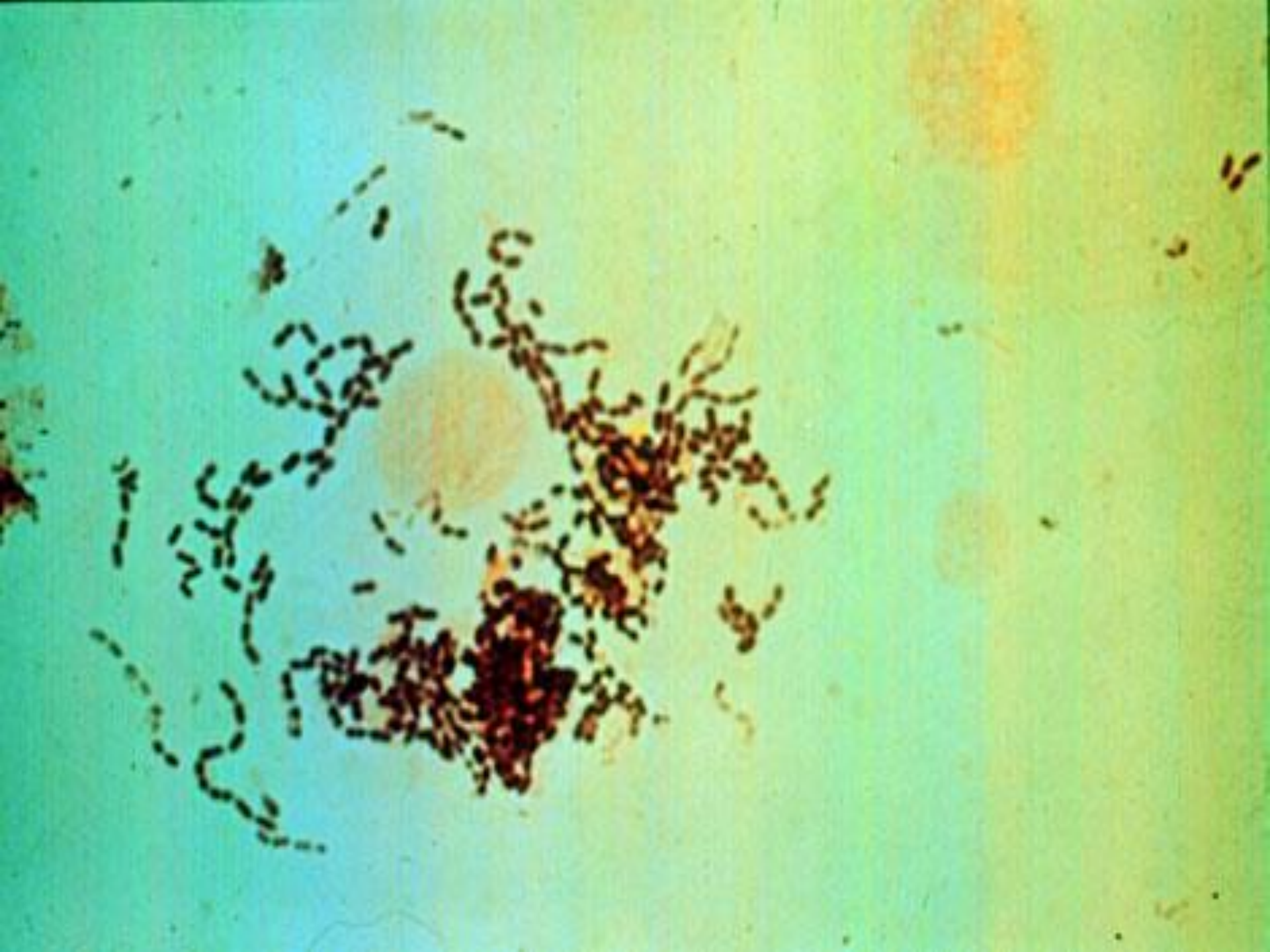
Influenza



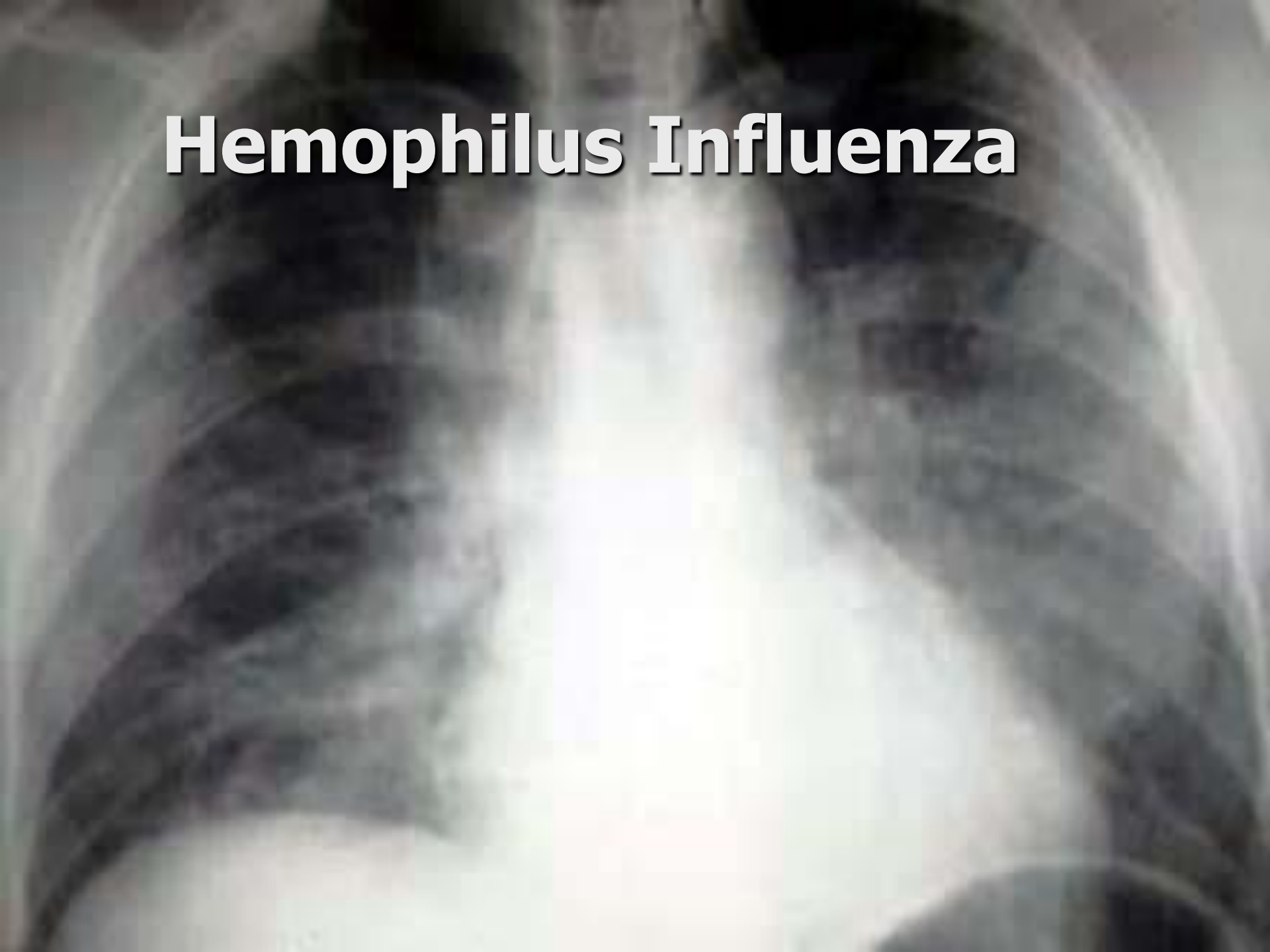
Influenza

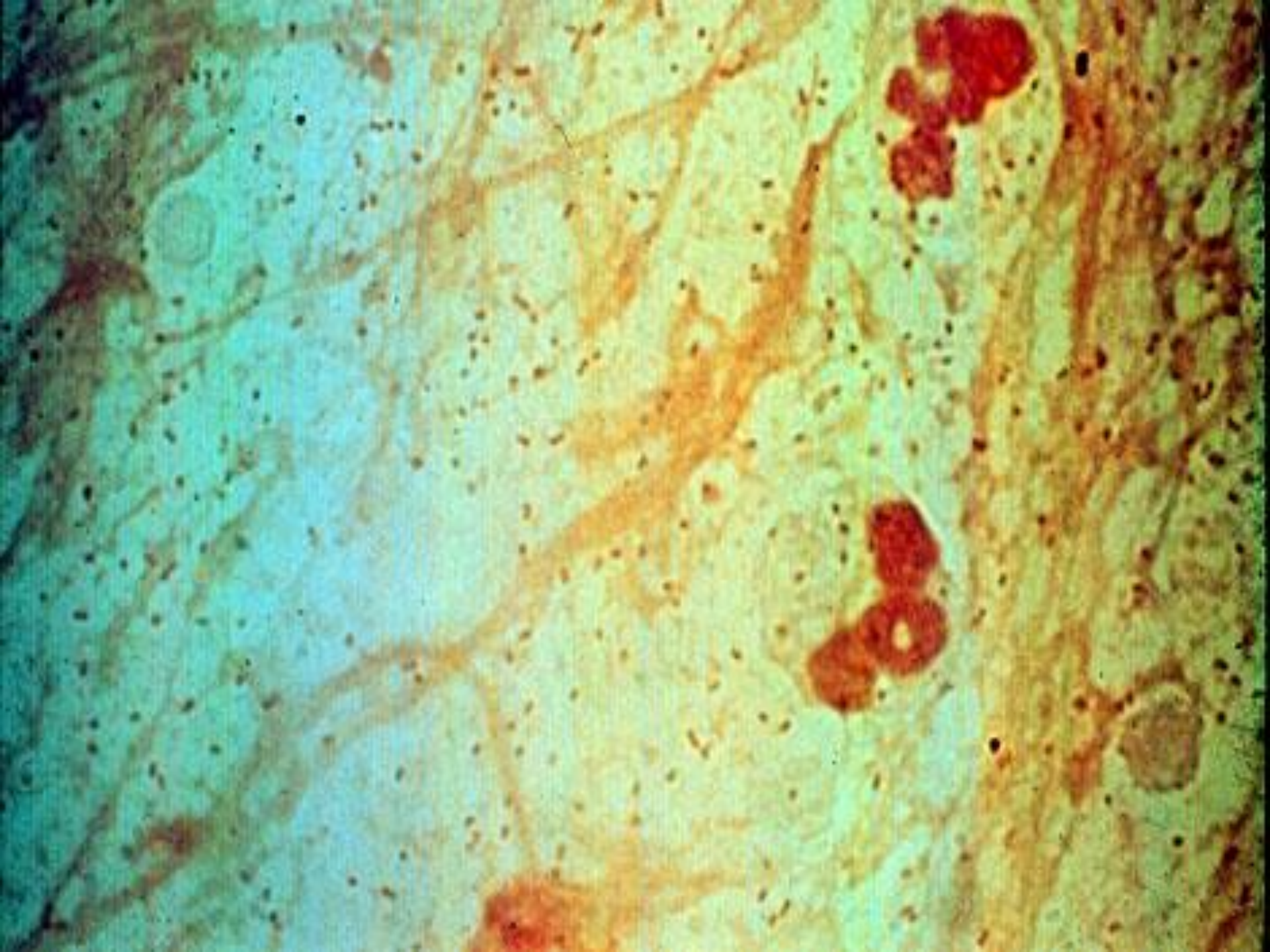

Clinical disease due to virus HxNx
Level of antibody to virus HxNx
Clinical disease due to virus HyNy
Level of antibody to virus HyNy
Pandemic
Interpandemic period
Pandemic
Disease incidence
Mean population antibody level
Introduction of hypothetical HxNx virus.
Significant minor variation in Hx or Nx occurs. Epidemics may or may not be associated with these variations.
Introduction of a new subtype HyNy virus. Because there is no prior immunity, a new pandemic occurs.

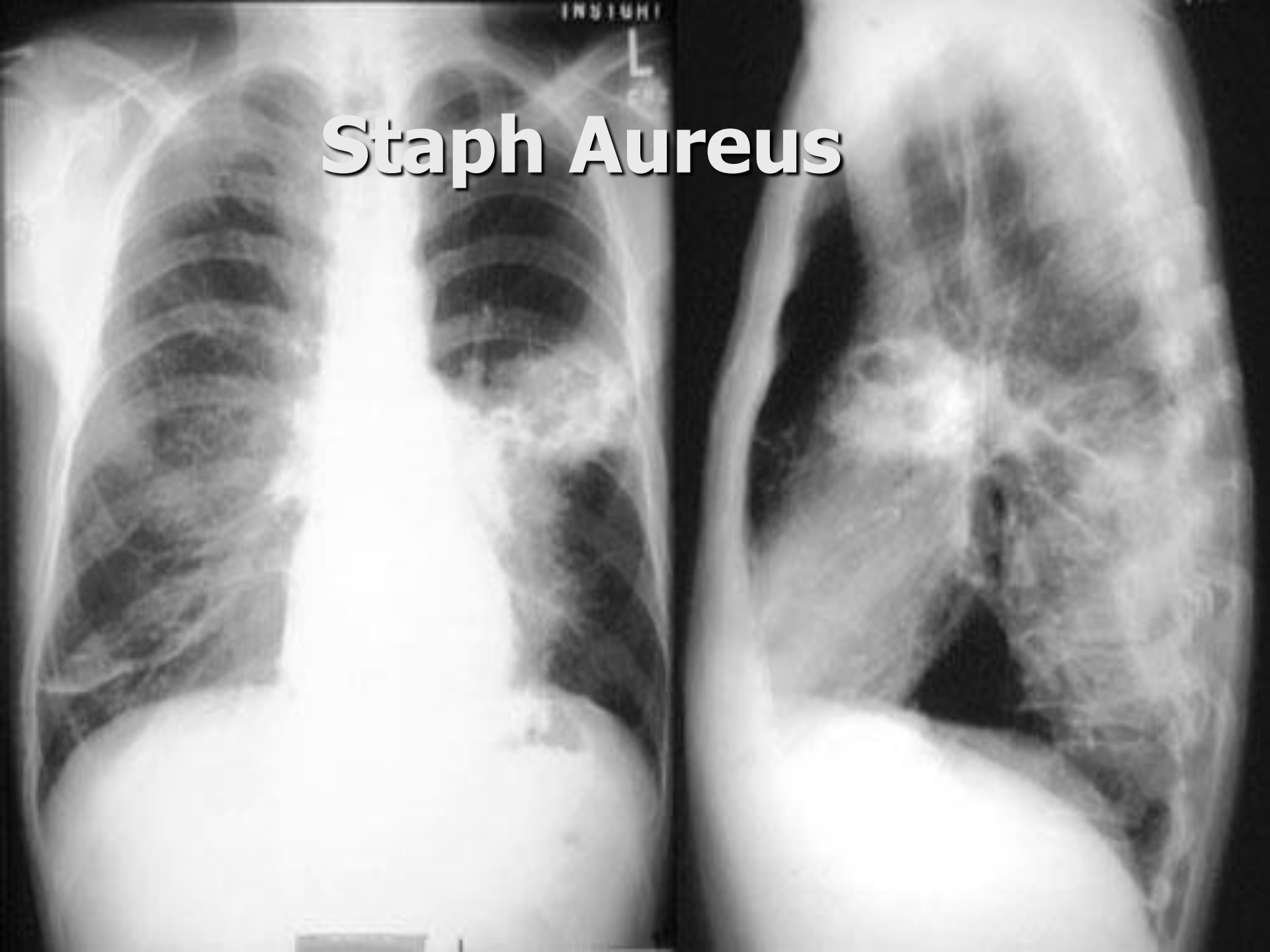

Pneumococcus

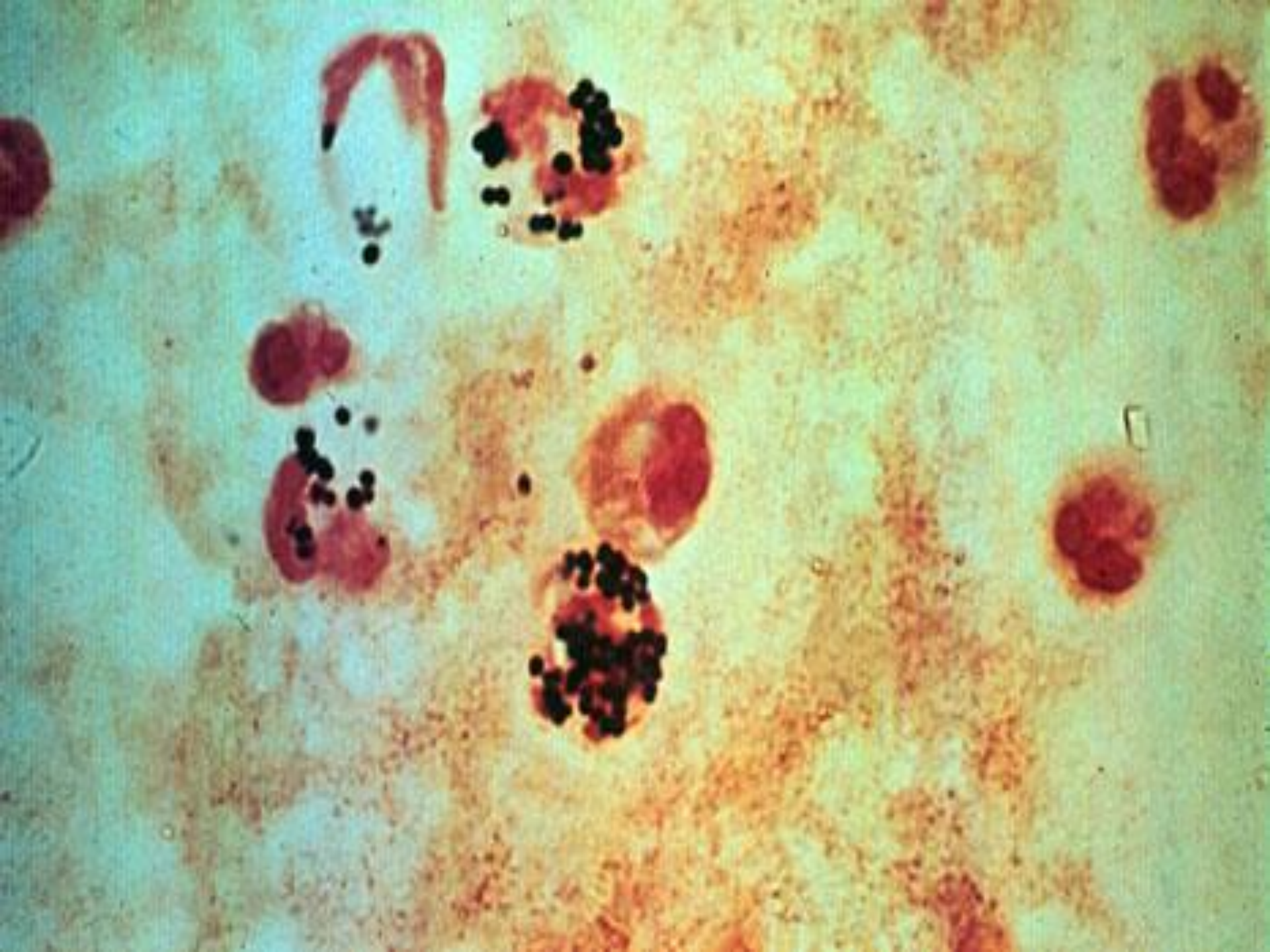


Hemophilus Influenza





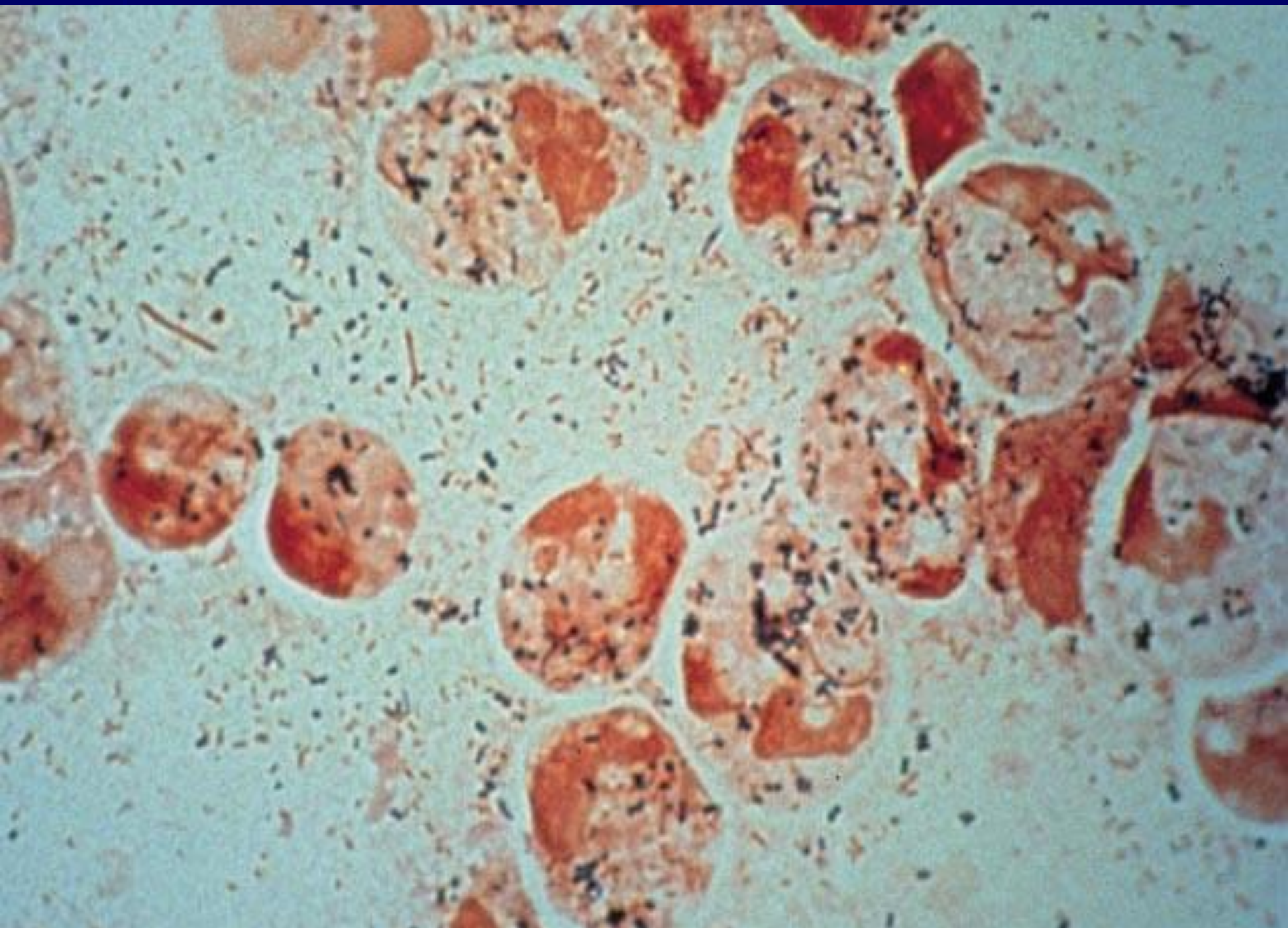

Staph Aureus

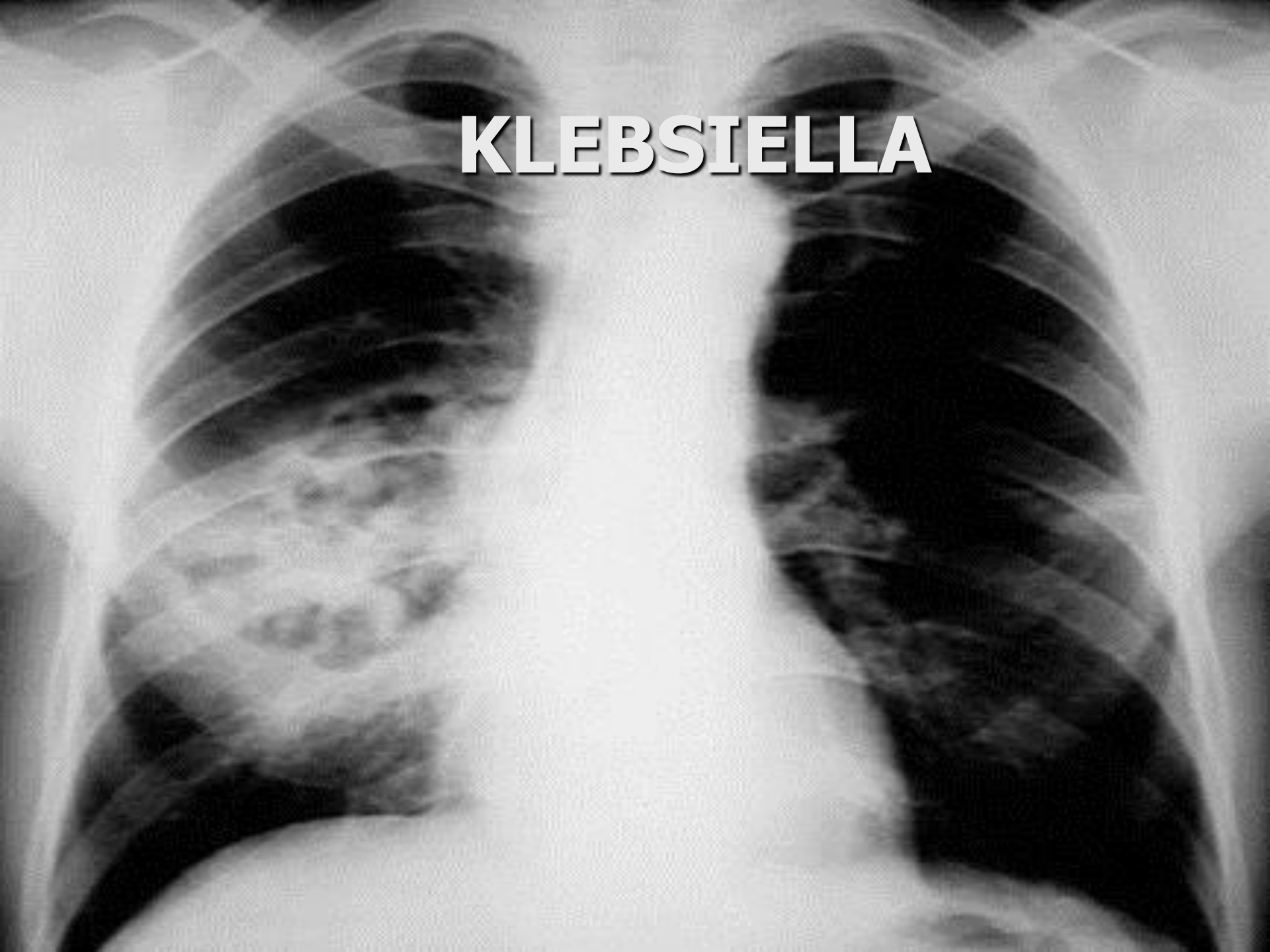


MRSA and VISA

- MRSA
- Detection requires vigilance in micro lab (MIC8)
- Long term/frequent vanco use
- Patient fails vanco
- Treatment

MIXED ANAEROBIC

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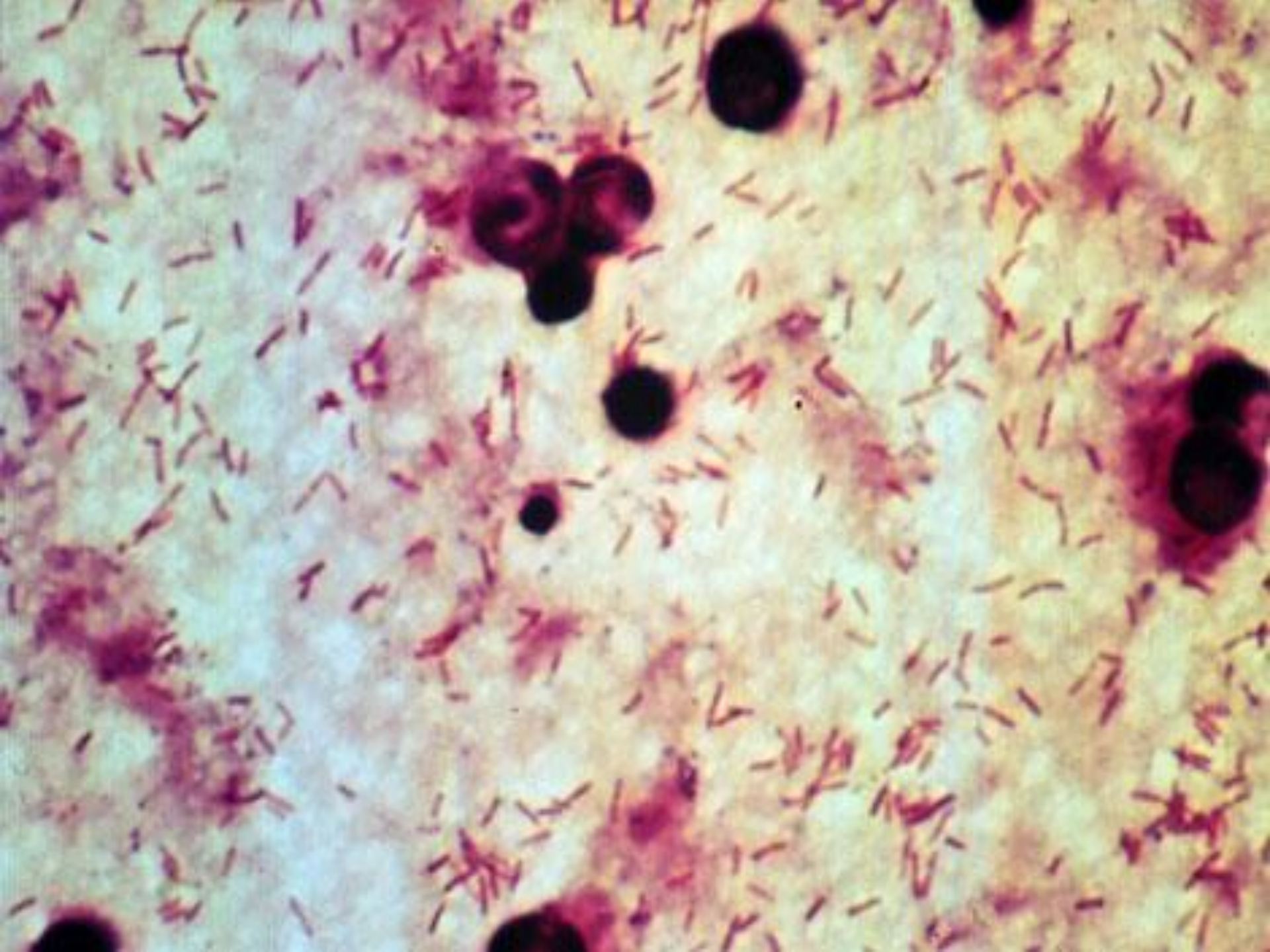
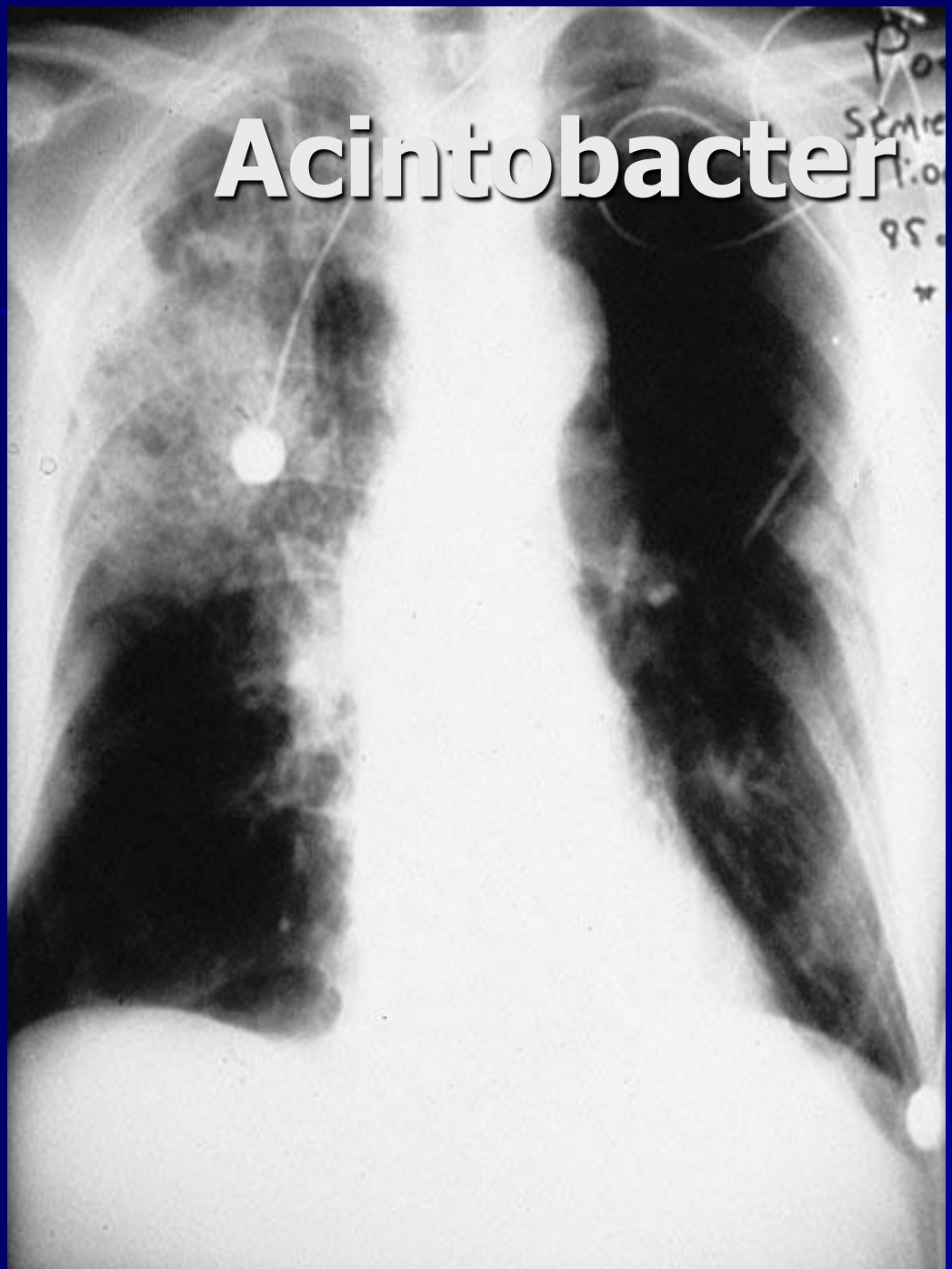
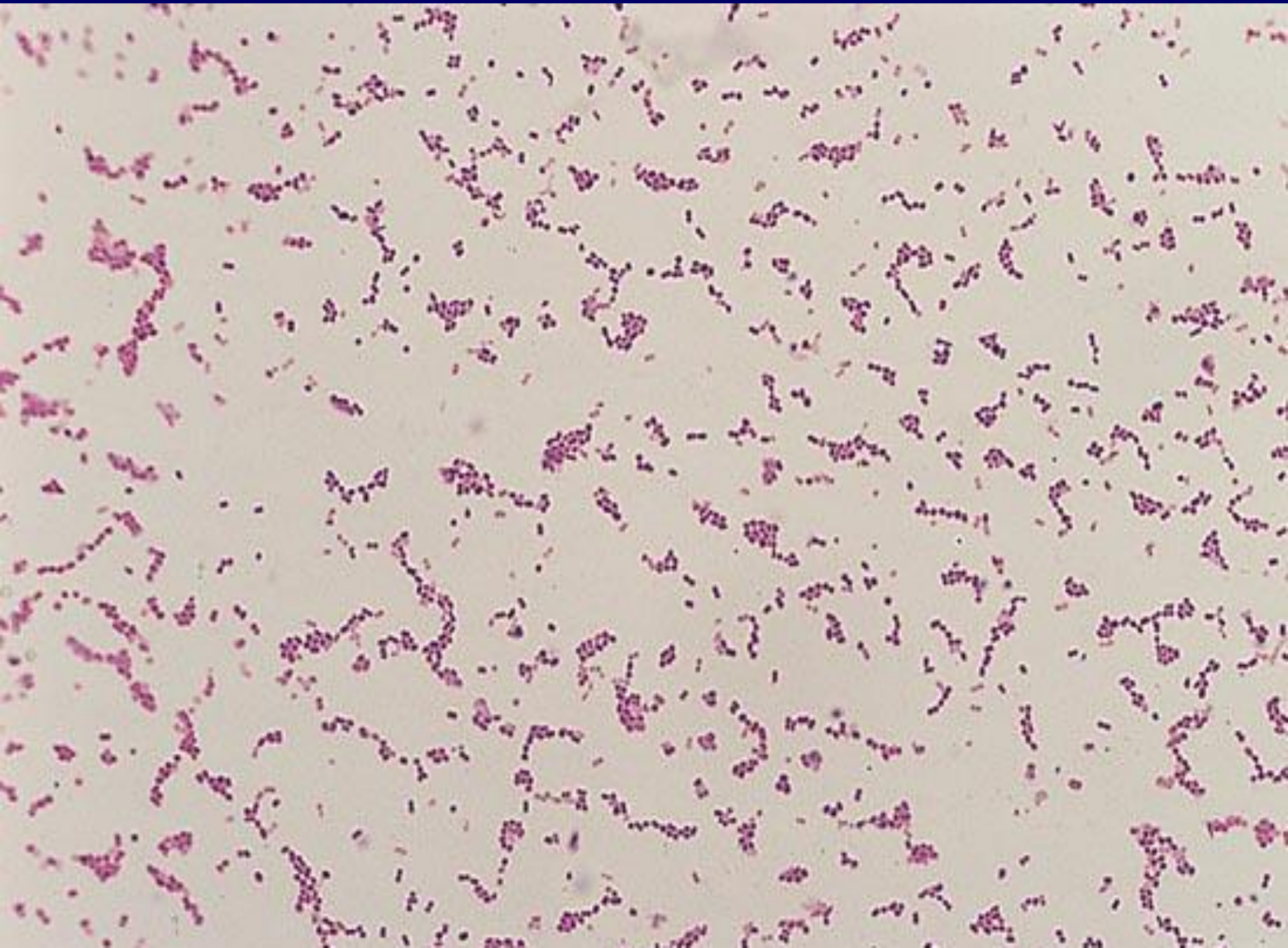


Acintobacter





Acinetobacter

- Frequent us of aminoglycosides, quinolones, ureidopenicillins and third generation cephalosporins
- Numerous outbreaks
- Higher mortality rates
- Endemic in some hospitals

Table 5. Clinical indications for more extensive diagnostic testing.

Indication	Blood culture	Sputum culture	*Legionella* UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X[a]
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X[b]
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X[c]
Positive *Legionella* UAT result		X[d]	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X[e]

NOTE. NA, not applicable; UAT, urinary antigen test.

[a] Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.

[b] Fungal and tuberculosis cultures.

[c] See table 8 for details.

[d] Special media for *Legionella*.

[e] Thoracentesis and pleural fluid cultures.

Empirical Treatment: IDSA/ATS Consensus Guidelines

Outpatient treatment

- Previously healthy, no antibiotics in 3 months
  - Macrolide (1st choice) or
  - Doxycycline
- Co-morbid conditions or antibiotics within 3 months (select a different class)
  - Respiratory fluoroquinolone: moxifloxacin, gemifloxacin, or levofloxacin (750 mg)
  - Beta-lactam (especially high dose amoxicillin) plus a macrolide (1st choice) or doxycycline

CAP Hospitalization

- CURB-65 (confusion, uremia, respiratory rate, low blood pressure, and age 65 or greater
- Objective criteria such as the home situation, ability to take medications, and outpatient support services
- ICU for septic shock and closer monitoring due to respiratory failure

Empirical Treatment: IDSA/ATS Consensus Guidelines

Inpatient treatment, non-ICU

- Respiratory fluoroquinolone or
- Beta-lactam (cefotaxime, ceftriaxone, ampicillin; consider ertapenem) plus a macrolide (1st choice) or doxycycline

Empirical Treatment: IDSA/ATS Consensus Guidelines

Inpatient treatment, ICU

- Beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus
- Azithromycin or a respiratory fluoroquinolone

➢For penicillin allergy: respiratory fluoroquinolone + aztreonam

Empirical Treatment: IDSA/ATS Consensus Guidelines

For suspected *Pseudomonas aeruginosa*:

- Antipneumococcal, antipseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg) Or
- The above beta-lactam plus an aminoglycoside and either azithromycin or a respiratory fluoroquinolone

➢For penicillin allergy: substitute aztreonam for the beta-lactam

Empirical Treatment: IDSA/ATS Consensus Guidelines

Inpatient therapy, concern for community methicillin-resistant *Staphylococcus aureus* (MRSA):

- Add vancomycin or linezolid to regimen you would select otherwise

LRI

- Still severe disease with morbidity and mortality
- Get a working diagnosis
- Obtain laboratory data and x-rays
- Start therapy
- Make sure clinical course fits
- Re-evaluate if patient is not improving

Thank You