

Tuberculosis

Pathogenesis • morphologic patterns • clinicopathologic diagnosis

Clinical pathology of *Mycobacterium tuberculosis*

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Learning objectives

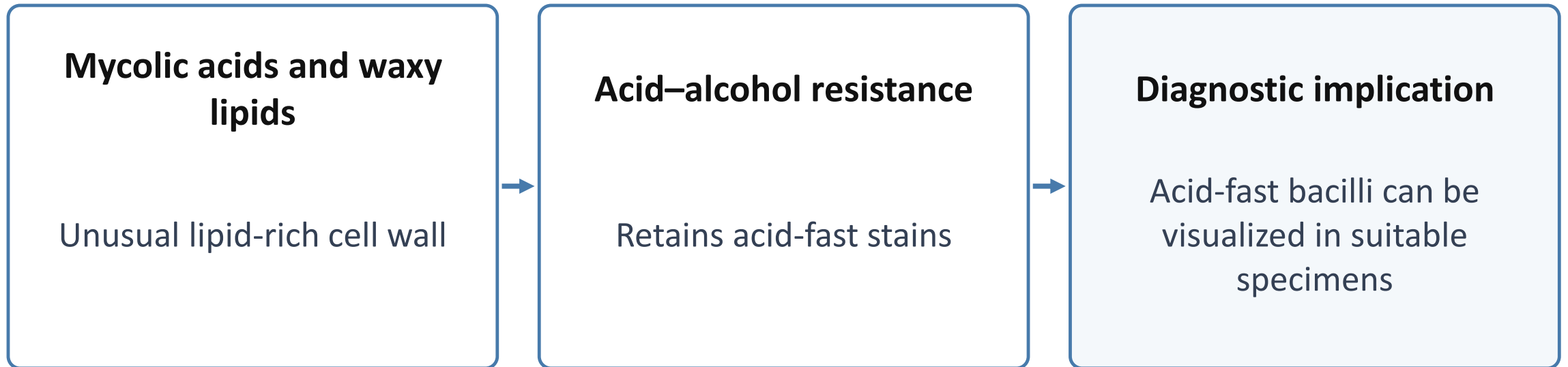
- Explain survival of M. Tuberculosis in macrophages and the development of Th1 immunity.
- Distinguish primary, postprimary, progressive, and disseminated tuberculosis.
- Interpret granulomatous morphology alongside microbiologic and immune-based tests.
- Recognize how impaired cellular immunity changes the clinical and tissue phenotype.

Tuberculosis is both pulmonary and systemic

M. Tuberculosis causes a chronic infection that can persist silently or produce destructive disease.

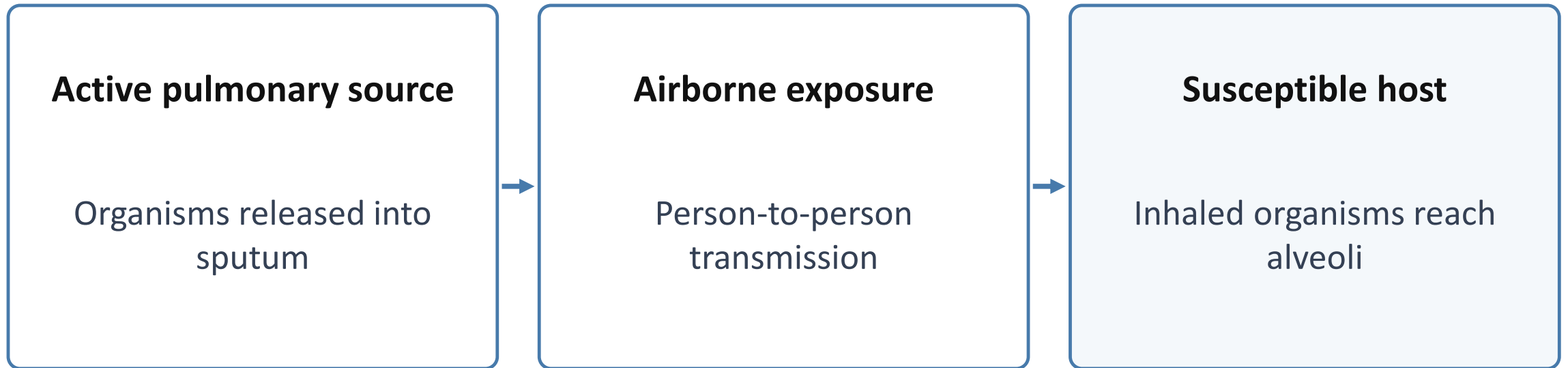
- The lung is the usual site of entry and a major site of clinical disease.
- Lymphatic and hematogenous spread can seed distant organs.
- The tissue response reflects the interaction between bacterial persistence and host immunity.

The mycobacterial cell wall explains acid-fastness



Acid-fastness is a property of the organism; It does not identify M. Tuberculosis by itself.

Transmission is predominantly airborne



Cavitary airway disease is particularly relevant to infectious sputum production.

Mycobacterium bovis is a distinct exposure route

- M. Bovis can produce oropharyngeal or intestinal tuberculosis after ingestion of contaminated milk.
- Routine pasteurization makes this route uncommon where pasteurized milk is standard.
- The exposure remains relevant where bovine tuberculosis and unpasteurized milk coexist.
- Most pulmonary tuberculosis instead follows airborne human-to-human spread.

The textbook burden figures refer to 2022

Approximately 10.6 million incident cases worldwide in 2022.

- The same source reports approximately 1.3 million TB deaths in that year.
- These are historical figures reproduced from the supplied 11th-edition text.
- They must not be presented as current 2026 surveillance estimates.

Exposure and progression have overlapping risk factors

Exposure-prone settings	Progression-prone conditions
Crowding and poverty	HIV infection or other immunosuppression
Prisons, shelters, long-term care	Diabetes and malnutrition
High-burden exposure environments	Silicosis, renal failure, Hodgkin lymphoma
Risk of inhaling infectious aerosols	Risk of failing to contain infection

Infection is not synonymous with active disease

Latent infection	Active tuberculosis
Organisms may persist for years	Bacteria are associated with symptomatic disease
No clinical disease at present	Pulmonary or extrapulmonary manifestations
Immune sensitization may be detectable	Direct microbiologic tests assess disease
Reactivation possible if defenses fall	Airway disease may be transmissible

Natural history depends on containment

Inhalation and primary infection

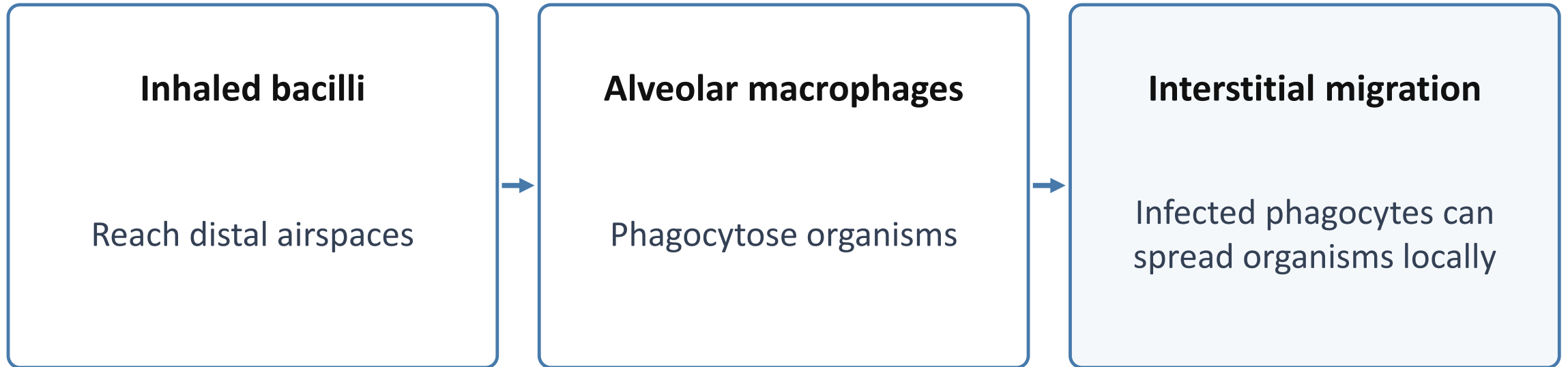
Effective Th1 containment

Granuloma → fibrosis ± calcification;
Organisms may remain latent

Inadequate containment

Progressive primary disease or later
reactivation → tissue destruction and
spread

Alveolar macrophages are the initial host cells

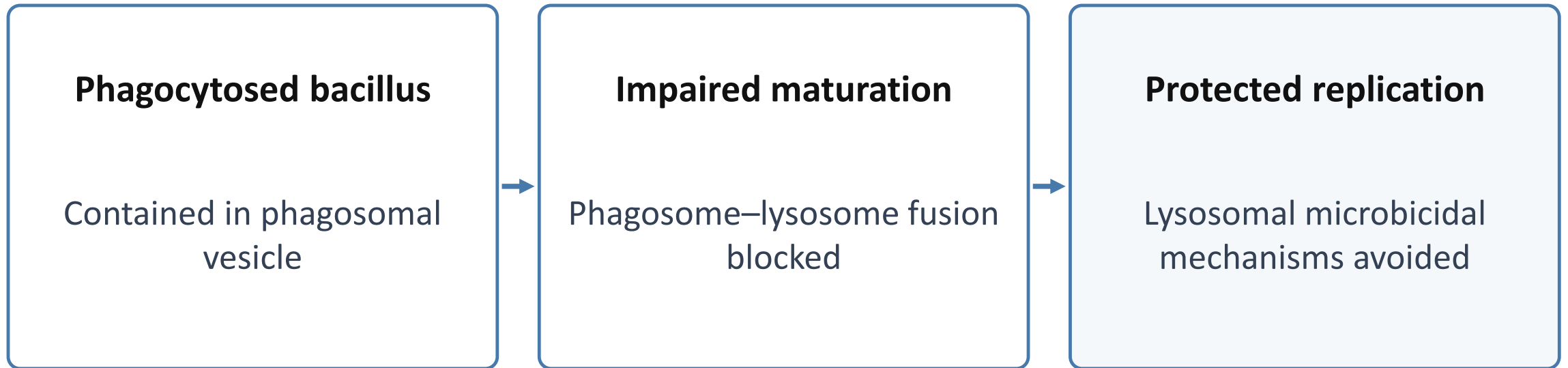


Macrophages and dendritic cells become participants in early infection.

Macrophage entry uses specific receptors

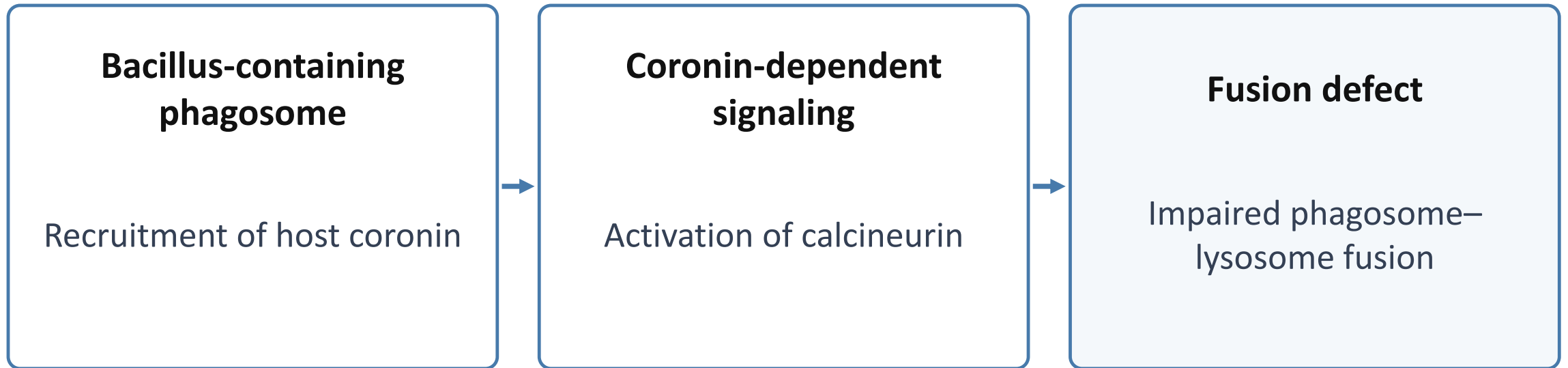
- Phagocytosis involves mannose-binding lectin and complement receptor 3 (CR3).
- Entry into macrophages does not ensure bacterial destruction.
- The ability to survive after uptake is central to early intracellular replication.
- Infected alveolar macrophages move into interstitial tissue.

Tubercle bacilli prevent phagolysosome maturation



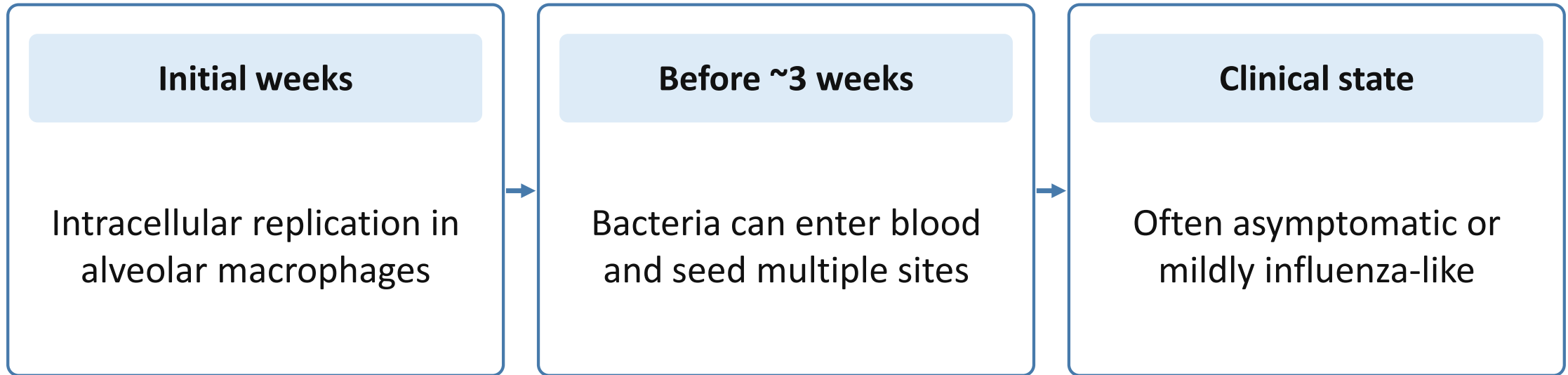
Native schematic of a source-described intracellular sequence—not an electron micrograph.

Coronin and calcineurin support intracellular survival



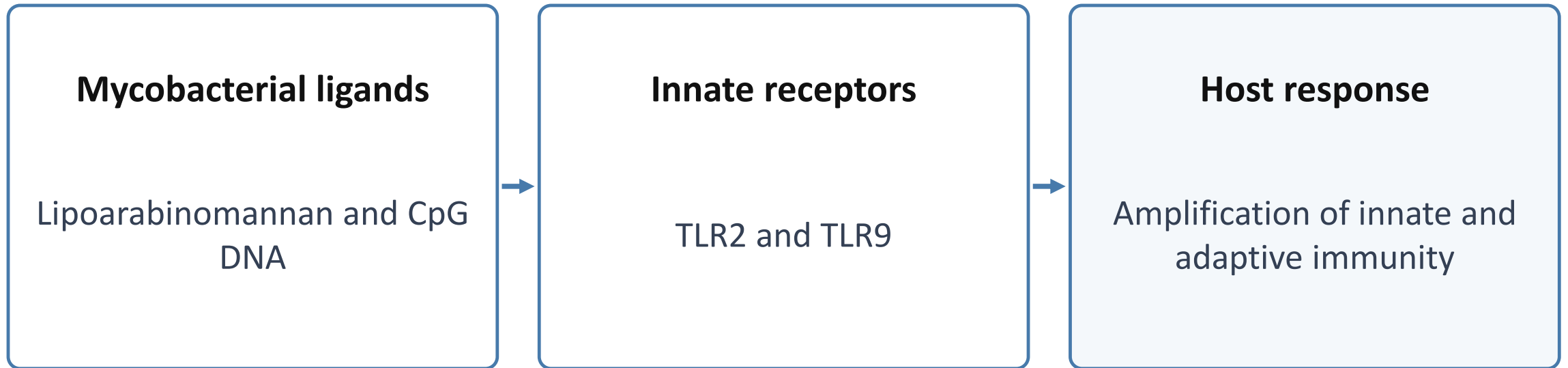
The source describes this mechanism as a contributor to phagolysosome blockade.

Early infection can disseminate before immunity matures



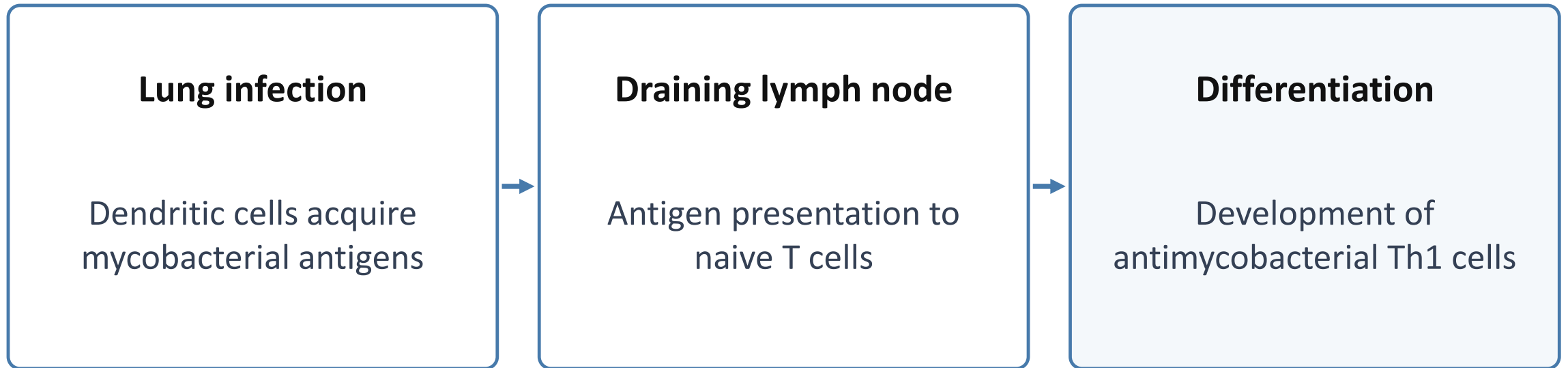
Early hematogenous seeding does not imply that clinically apparent lesions develop in every seeded site.

Innate recognition begins adaptive immune signaling



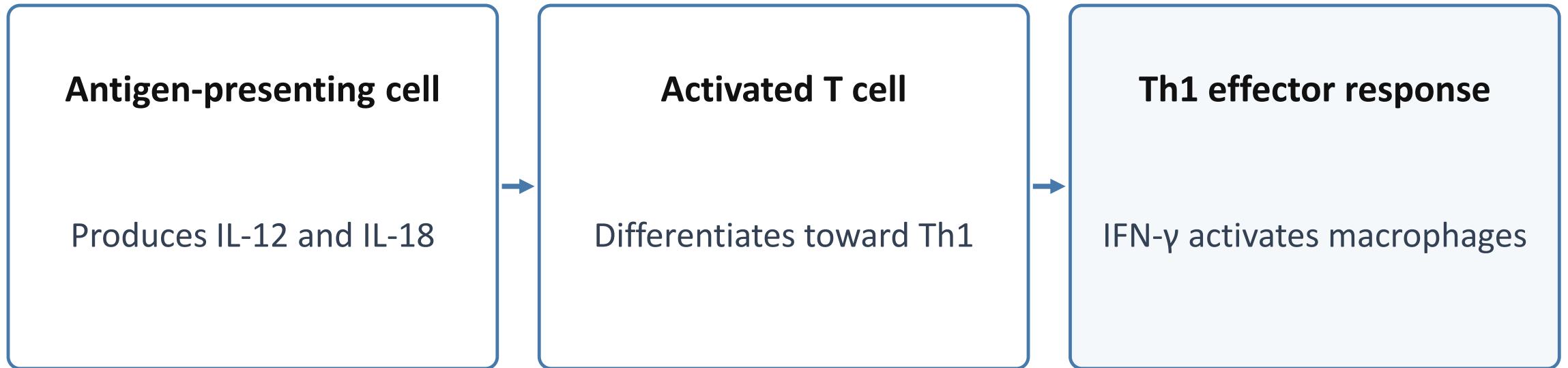
Neutrophils can also be infected; The organism resists their killing.

Dendritic cells connect the lung to draining nodes



A cellular immune response becomes evident after approximately three weeks.

IL-12 and IL-18 favor Th1 differentiation



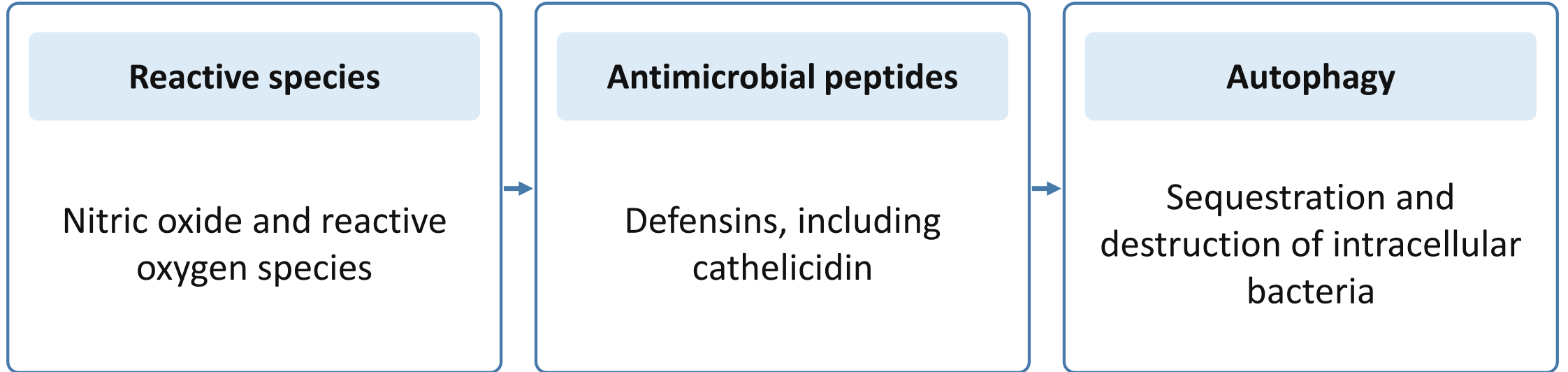
TLR2 stimulation contributes to dendritic-cell IL-12 production.

IFN- γ is central to macrophage activation

Th1-derived IFN- γ enables macrophages to contain intracellular M. Tuberculosis.

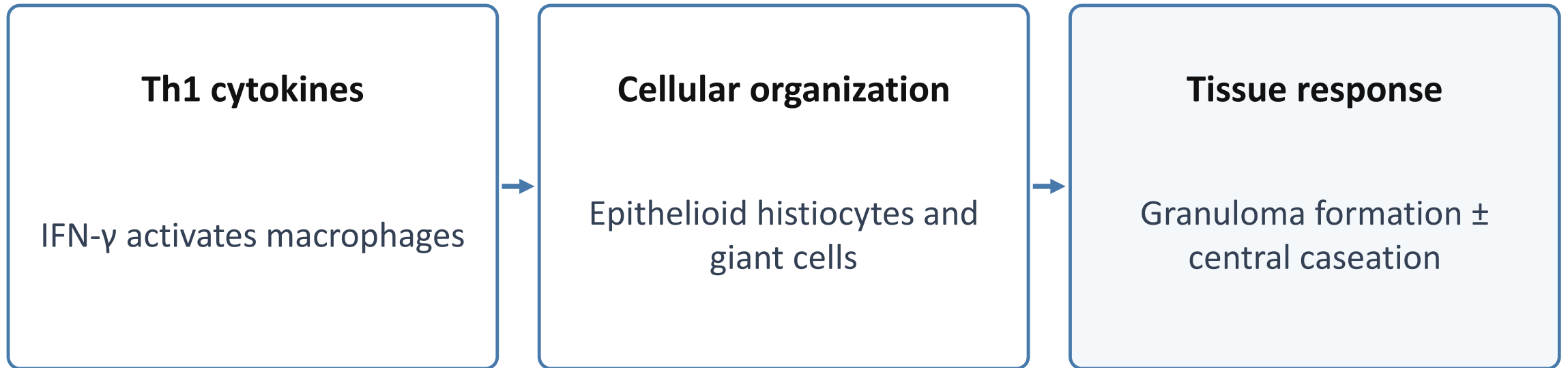
- It stimulates microbicidal machinery within activated phagocytes.
- It promotes antimicrobial peptide activity and autophagy.
- Insufficient Th1 function predisposes to dissemination and reactivation.

Activated macrophages use several effectors



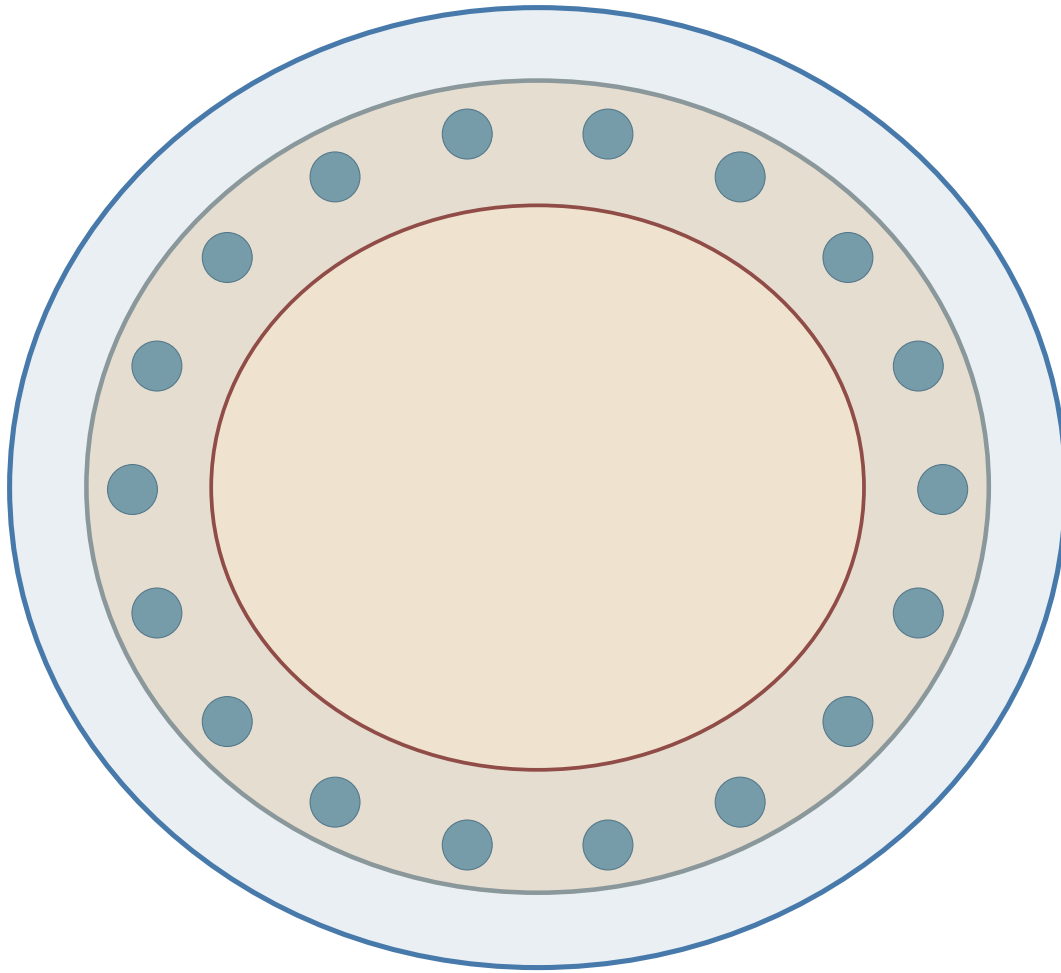
These effects are promoted by IFN- γ ; No single mechanism alone explains containment.

Granulomas are a product of cellular immunity



This response constrains infection but can also injure tissue.

A tubercle has a recognizable cellular architecture



Central caseation

Granular, acellular-appearing necrotic center

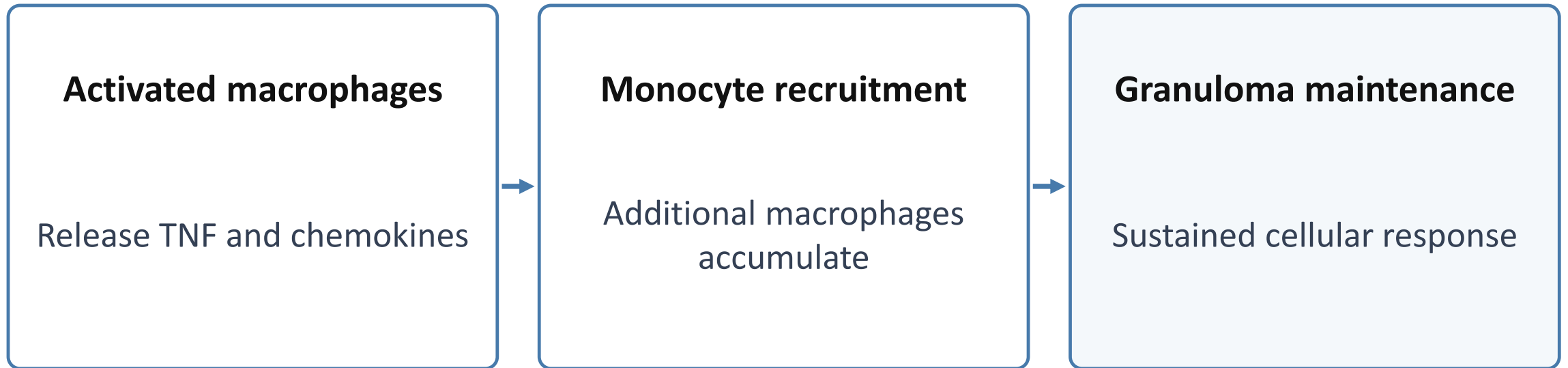
Epithelioid histiocytes $\pm$ giant cells

Activated macrophage aggregates

Peripheral lymphocytes / fibroblastic rim

Schematic—not a histologic specimen

TNF promotes granuloma-associated recruitment



TNF-antagonist therapy increases the risk of tuberculosis reactivation.

Protective immunity creates immunopathology

Containment benefit	Tissue injury cost
Macrophage activation inhibits replication	Th1-driven caseation
Granuloma restricts bacterial spread	Granuloma coalescence and necrosis
Fibrosis can stabilize the primary focus	Cavitation can destroy lung architecture
Latency may persist for decades	Reactivation with waning host defenses

Several host states weaken TB control

- HIV-associated CD4+ T-cell loss disrupts Th1-dependent resistance.
- Glucocorticoids, TNF antagonists, and transplant immunosuppression increase risk.
- Renal failure, malnutrition, and advanced age can compromise containment.
- Risk reflects both the host immune response and prior exposure.

IL-12-pathway defects can cause severe mycobacterial disease

Inherited impairment of the IL-12/Th1 axis illustrates the necessity of cellular immunity.

- The source identifies IL-12 receptor $\beta 1$ loss as one example.
- Such defects increase susceptibility to severe tuberculosis.
- They can also predispose to illness caused by ordinarily less virulent mycobacteria or BCG.

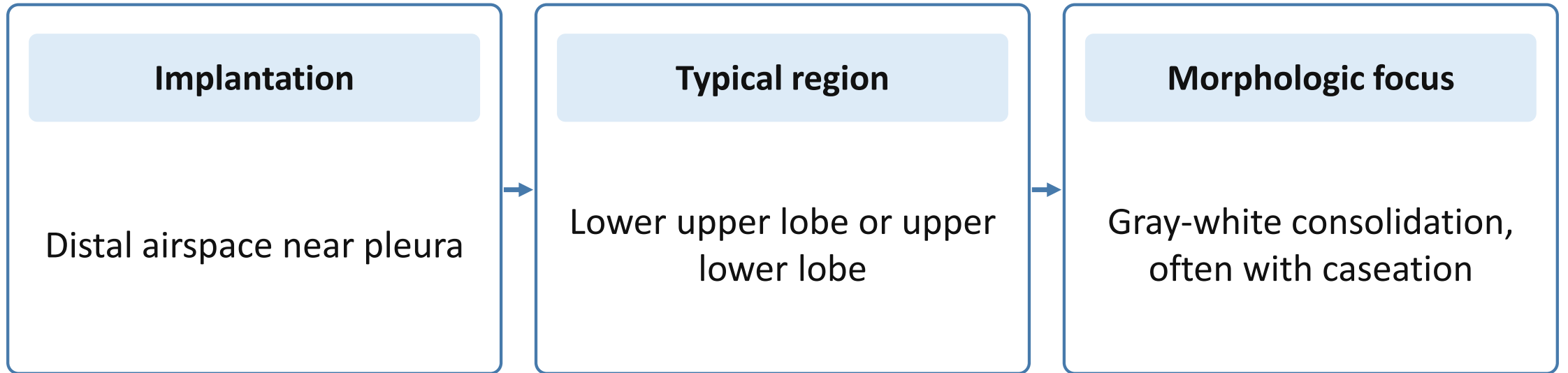
Primary and postprimary TB are pathophysiologically distinct

Primary tuberculosis	Secondary tuberculosis
First infection of an unsensitized host	Disease in a previously sensitized host
Exogenous acquisition	Reactivation or exogenous reinfection
Subpleural initial focus and hilar node reaction	Classically apical upper-lobe focus
Often contained; May progress	Rapid tissue response; Cavitation relatively common

Primary infection is often clinically inapparent

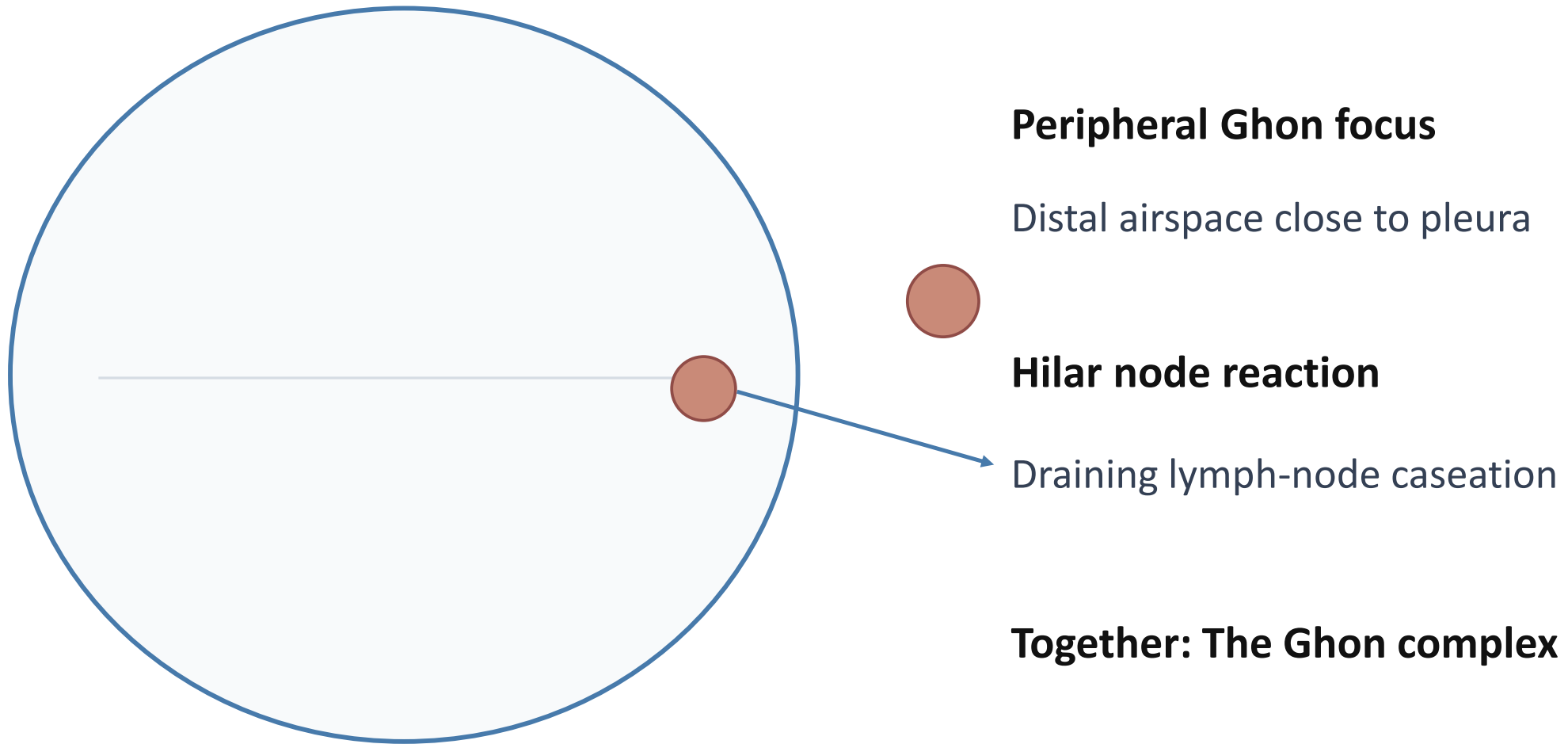
- In healthy hosts the first infection frequently causes no clinical symptoms.
- A transient fever or pleural effusion may occur.
- The source states that clinically significant primary disease develops in a minority of newly infected people.
- A small residual fibrocalcific Ghon focus may be the only evidence.

The primary pulmonary focus is usually subpleural



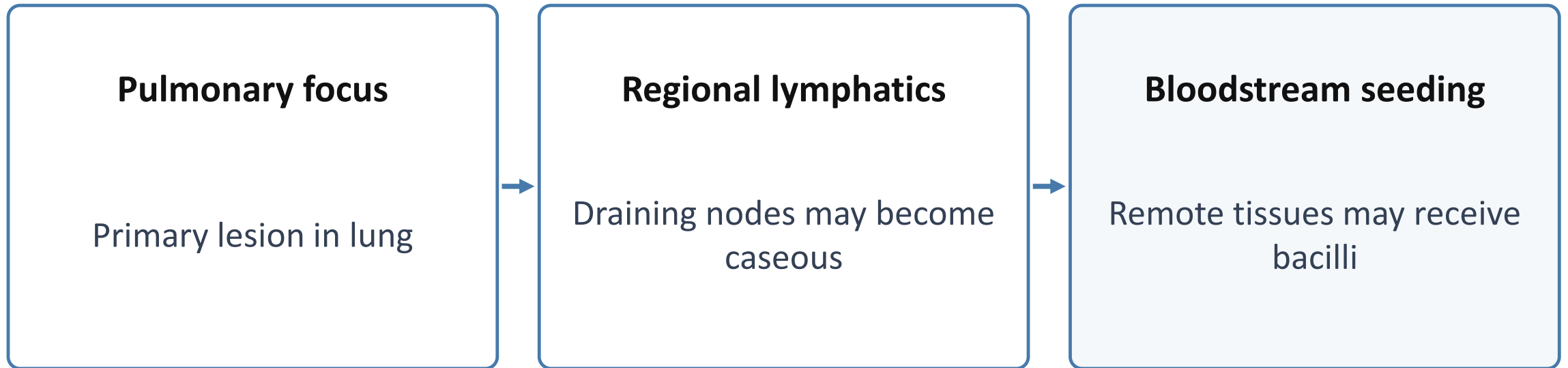
A typical Ghon focus measuring about 1–1.5 cm.

Ghon complex combines lung and nodal lesions



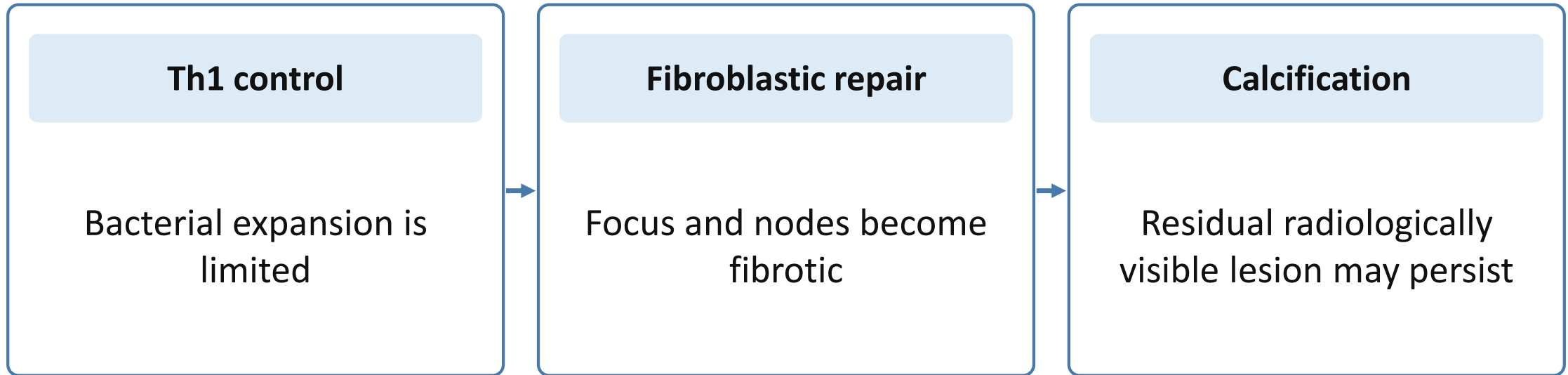
Lung: Schematic representation

Primary disease can spread via lymph and blood



Early dissemination may occur even when later cellular immunity prevents overt organ lesions.

Cell-mediated immunity usually heals the primary complex



The text notes that viable bacilli may remain dormant in some apparently healed foci.

Progressive primary TB can mimic bacterial pneumonia

Progressive primary TB	Typical postprimary pattern
Lobar consolidation	Apical upper-lobe involvement
Hilar lymphadenopathy	Lymph nodes less prominent early
Pleural effusion may occur	Cavitation develops relatively readily
Can disseminate to meninges or multiple organs	Can progress locally or disseminate

Primary dissemination explains early severe presentations

Uncontrolled primary pulmonary infection

```
graph TD; A[Uncontrolled primary pulmonary infection] --> B[Lymphohematogenous spread<br/>Meningeal involvement or systemic miliary disease]; A --> C[Pulmonary progression<br/>Consolidation, regional nodes, and pleural involvement];
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Lymphohematogenous spread

Meningeal involvement or systemic
miliary disease

Pulmonary progression

Consolidation, regional nodes, and
pleural involvement

Both caseating and noncaseating tubercles occur

Caseating granuloma	Noncaseating granuloma
Central granular necrotic material	No central caseous necrosis
Surrounding epithelioid histiocytes	Epithelioid histiocytes persist
Giant cells and lymphocytic rim may be seen	Giant cells and lymphocytes may be seen
Typical, but not universal, morphology	Does not exclude tuberculosis

Immunocompromise can abolish typical granulomas

Effective cellular immunity	Severe cellular immunodeficiency
Organized granulomas often present	Granulomas may be poorly formed or absent
Caseation may reflect tissue injury	Numerous organisms within macrophages
Bacillary load can be low in fibrotic lesions	Histology may be dominated by infected phagocytes

Postprimary TB reflects reactivation or reinfection

Previously sensitized individual

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graph TD; A[Previously sensitized individual] --> B[Endogenous reactivation]; A --> C[Exogenous reinfection]; B --> D[Dormant organisms resume growth as immune resistance declines]; C --> E[New inoculum triggers disease in a previously exposed host];
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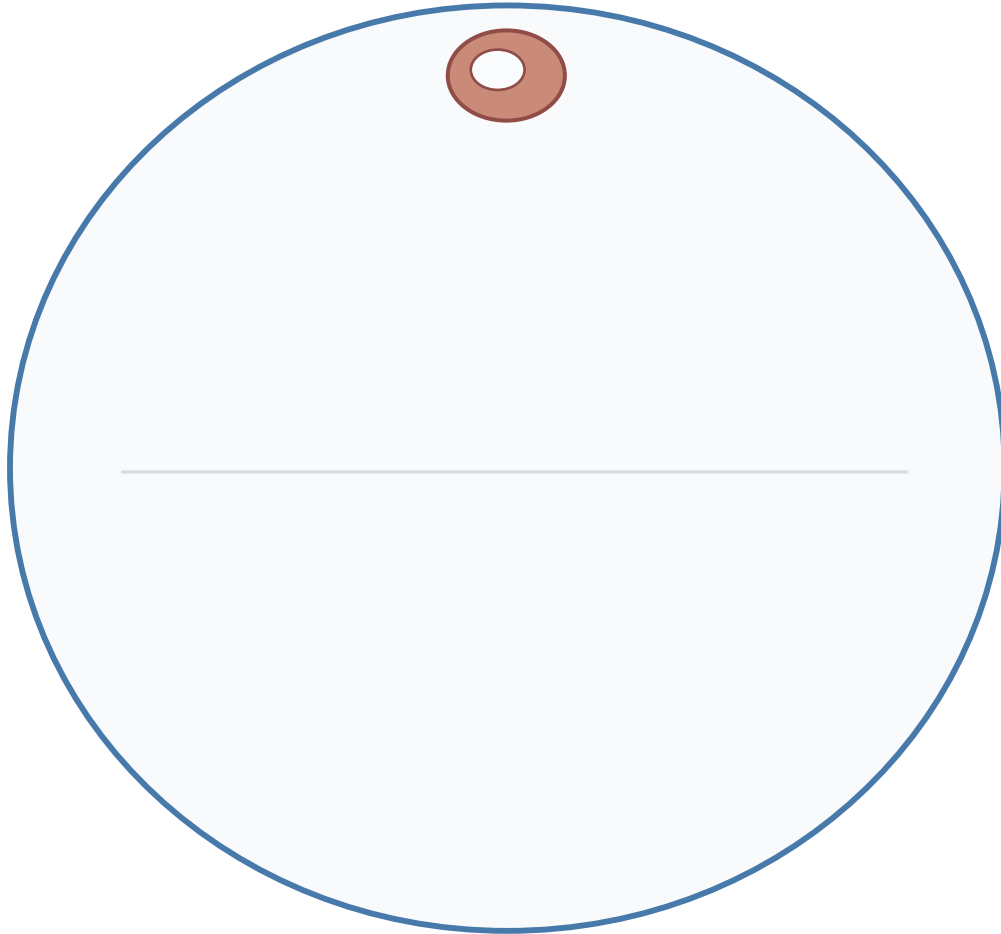
Endogenous reactivation

Dormant organisms resume growth as immune resistance declines

Exogenous reinfection

New inoculum triggers disease in a previously exposed host

Secondary TB classically begins near the apex



Postprimary apical focus

Small, sharply bounded focus close to apical pleura

Central caseation $\pm$ peripheral fibrosis

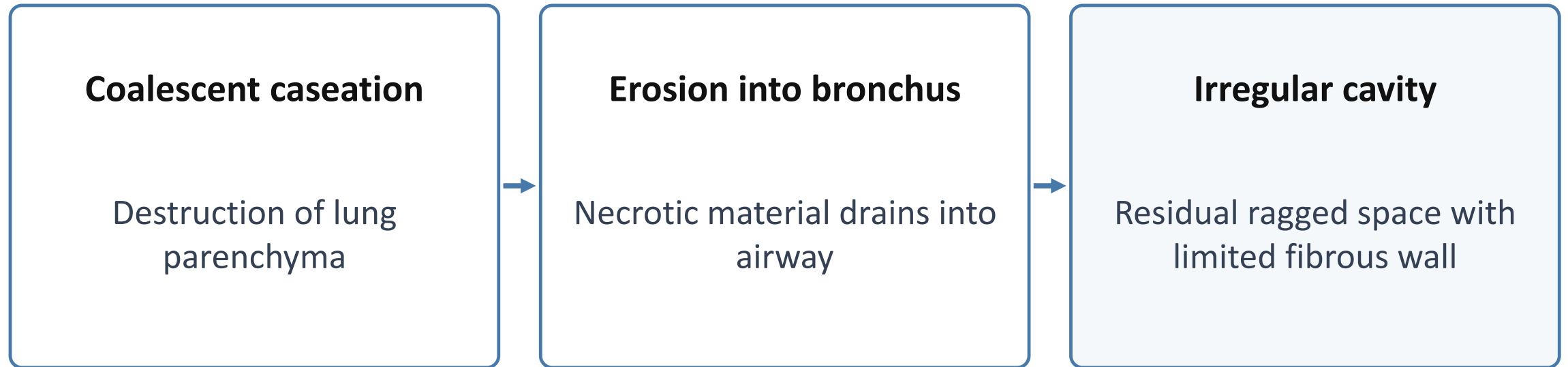
Cavitation may develop with disease progression

Lung: Schematic representation

A sensitized host mounts a brisk local reaction

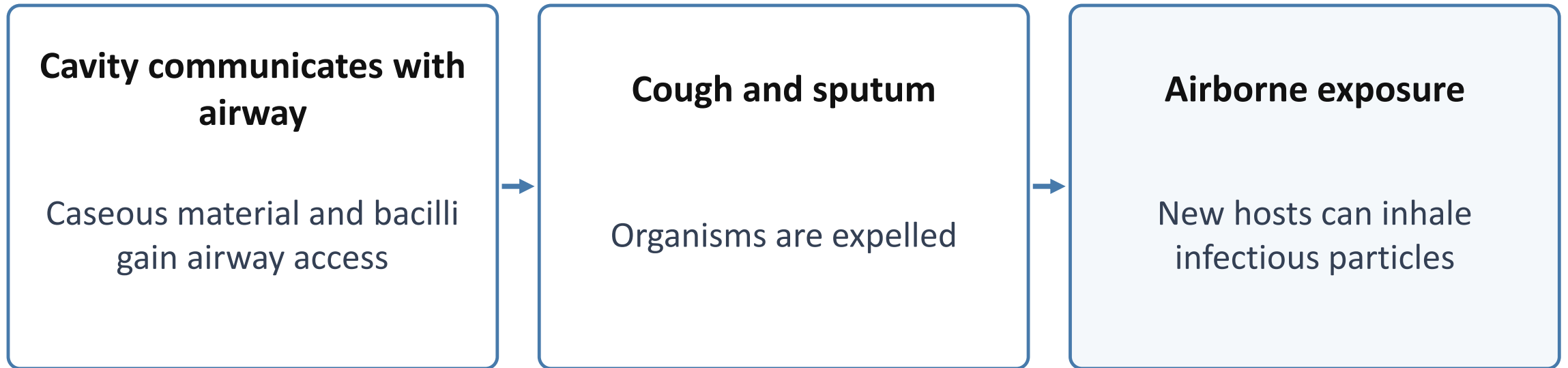
- Pre-existing delayed-type hypersensitivity promotes prompt tissue inflammation.
- The lesion initially tends to become locally walled off.
- Regional lymph nodes are less prominent early than in primary TB.
- Untreated lesions can progress to caseation and cavitation.

Cavitation follows evacuation of caseous tissue



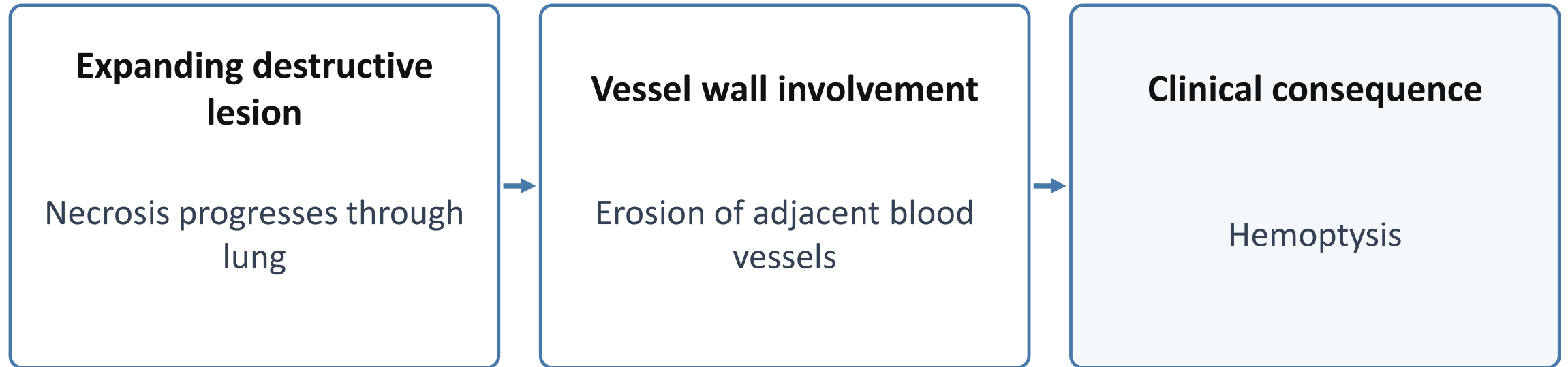
Schematic mechanism; Not a radiograph or gross specimen.

Cavitary disease can amplify transmission



Source-to-host spread is linked to the anatomy of the lesion.

Vascular erosion explains hemoptysis



Hemoptysis is a complication of destructive pulmonary lesions; Its absence does not exclude TB.

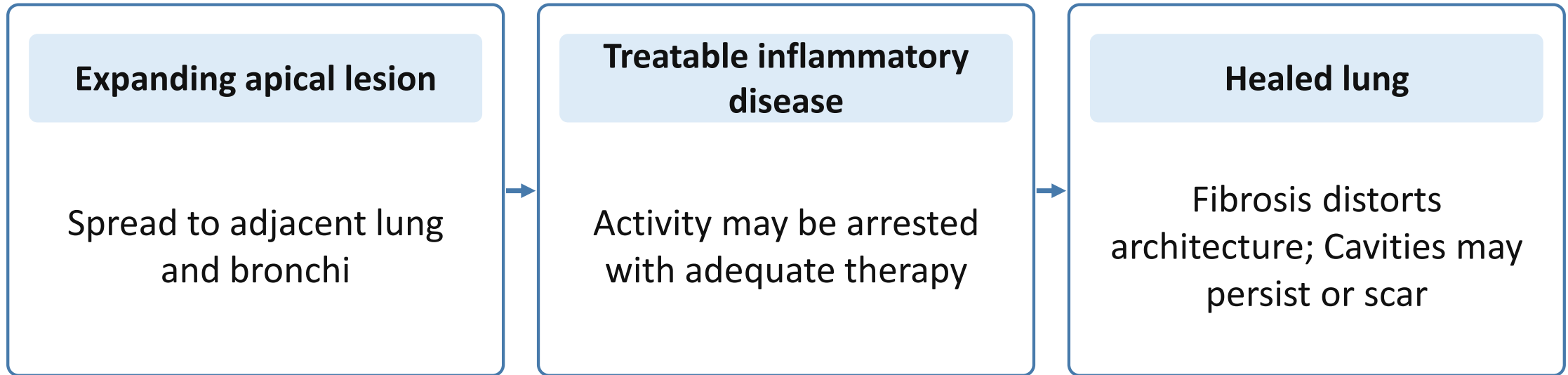
Systemic symptoms reflect inflammatory mediators

- Insidious malaise, anorexia, and weight loss may precede prominent pulmonary symptoms.
- Fever is often low grade and remittent, with night sweats.
- Activated macrophage cytokines, including TNF, contribute to systemic illness.
- Localized secondary disease can also be asymptomatic.

Progressive lung disease produces respiratory symptoms

- Sputum production may increase as pulmonary involvement progresses.
- Sputum can change from mucoid to purulent.
- Cavitation and tissue destruction are associated with bronchial involvement.
- Pleuritic pain can signal extension to pleural surfaces.

Progression can leave lasting architectural damage



The pathologic outcome depends on microbial control and host tissue repair.

Pleural extension has several morphologic outcomes

Pleural manifestation	Structural implication
Serous pleural effusion	Fluid accumulation in pleural space
Tuberculous empyema	Infected pleural collection
Obliterative fibrous pleuritis	Healing with substantial fibrosis

Anatomic pathways determine the pattern of spread

Progressive pulmonary focus

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graph TD; A[Progressive pulmonary focus] --> B[Airways and lymphatics]; A --> C[Vascular routes]; B --> D["Endobronchial, laryngeal, regional, or pulmonary extension"]; C --> E["Miliary pulmonary or systemic dissemination"];
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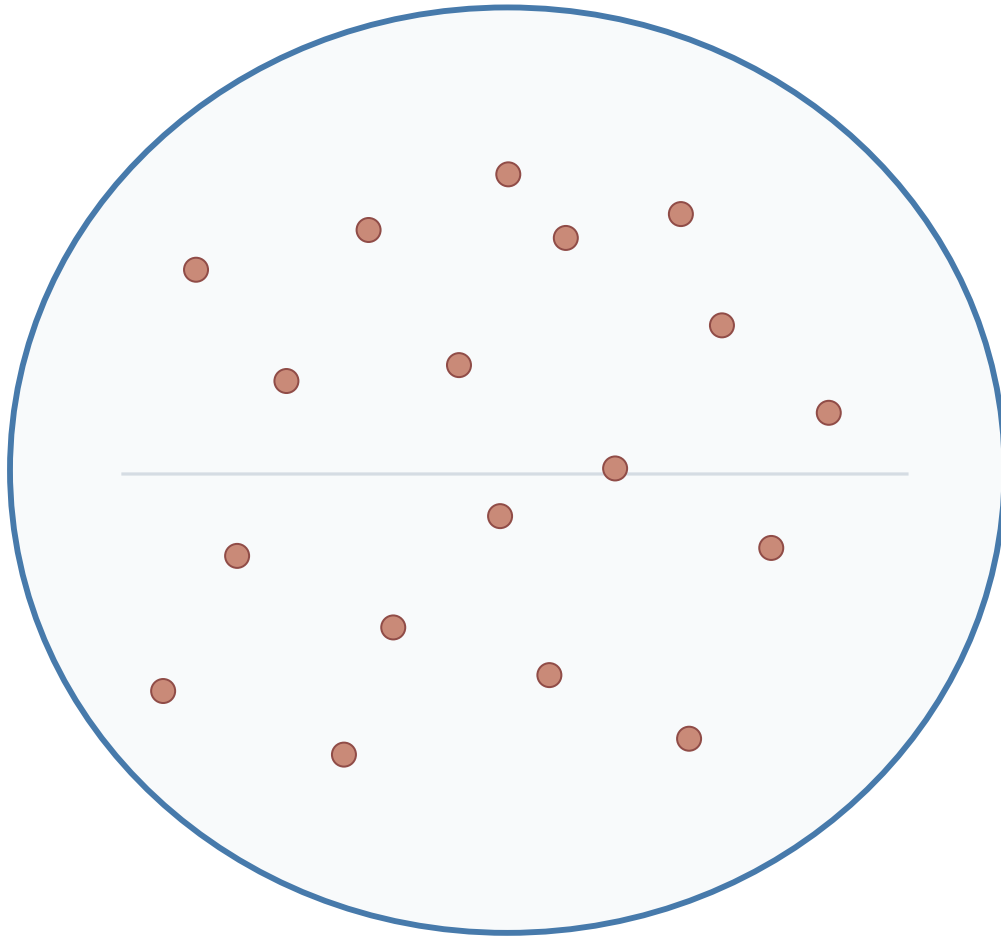
Airways and lymphatics

Endobronchial, laryngeal, regional, or
pulmonary extension

Vascular routes

Miliary pulmonary or systemic
dissemination

Miliary pulmonary TB reflects hematogenous reseeding



Lung: Schematic representation

Multiple tiny pulmonary foci

Hematogenous reseeding creates many distributed lesions

Individual foci may coalesce

Schematic distribution, not a gross specimen

Systemic miliary TB involves many organs

Dissemination mechanism	Frequent organ targets
Entry into systemic arterial blood	Liver and spleen
Widespread microvascular seeding	Bone marrow and adrenals
Formation of multiple small tubercles	Meninges and kidneys
Potential involvement of nearly any tissue	Fallopian tubes and epididymis

Tuberculosis may present outside the lungs

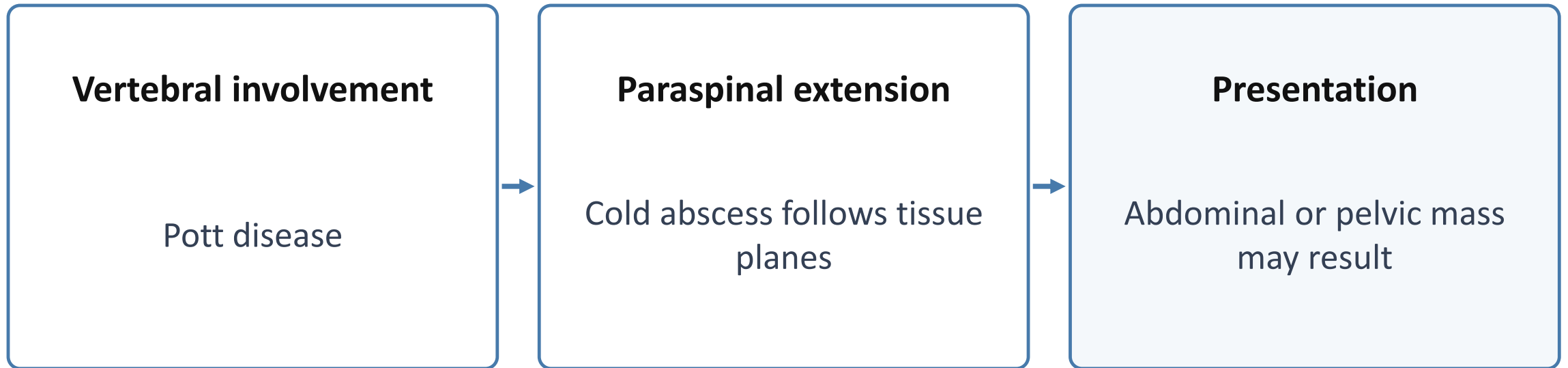
Hematogenous seeding may produce clinically dominant disease in a single distant organ.

- Meninges: Tuberculous meningitis.
- Kidneys and adrenals: Renal tuberculosis or adrenal destruction.
- Bone: Tuberculous osteomyelitis; Vertebral disease is Pott disease.
- Fallopian tubes: Tuberculous salpingitis.

Cervical lymphadenitis is a common extrapulmonary form

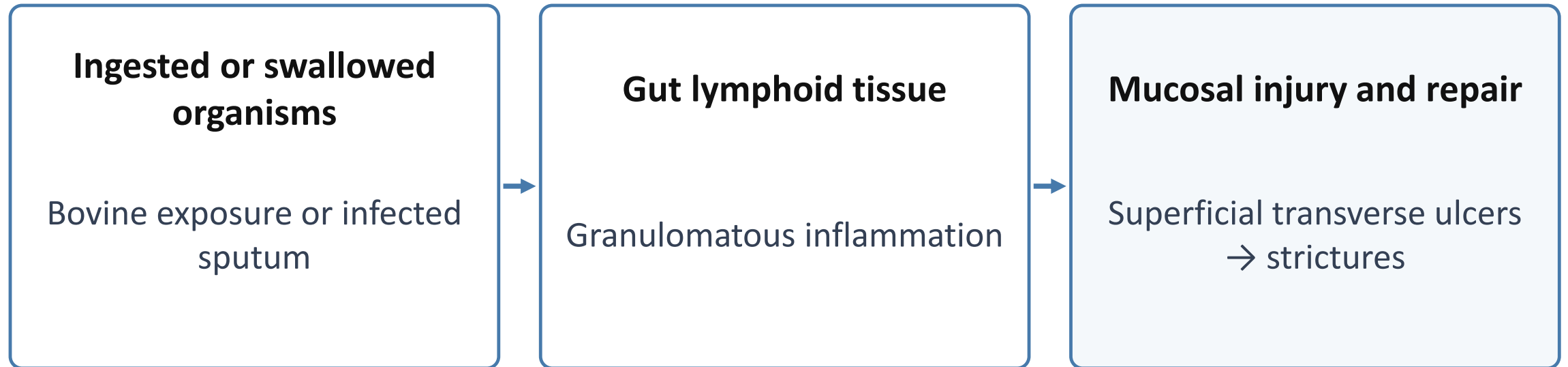
- Tuberculous lymphadenitis often affects cervical nodes (“scrofula”).
- It is the most frequent extrapulmonary presentation.
- HIV-negative patients more often have localized, unifocal nodal disease.
- HIV-positive patients often have multifocal disease and systemic involvement.

Vertebral TB may create cold paraspinal abscesses



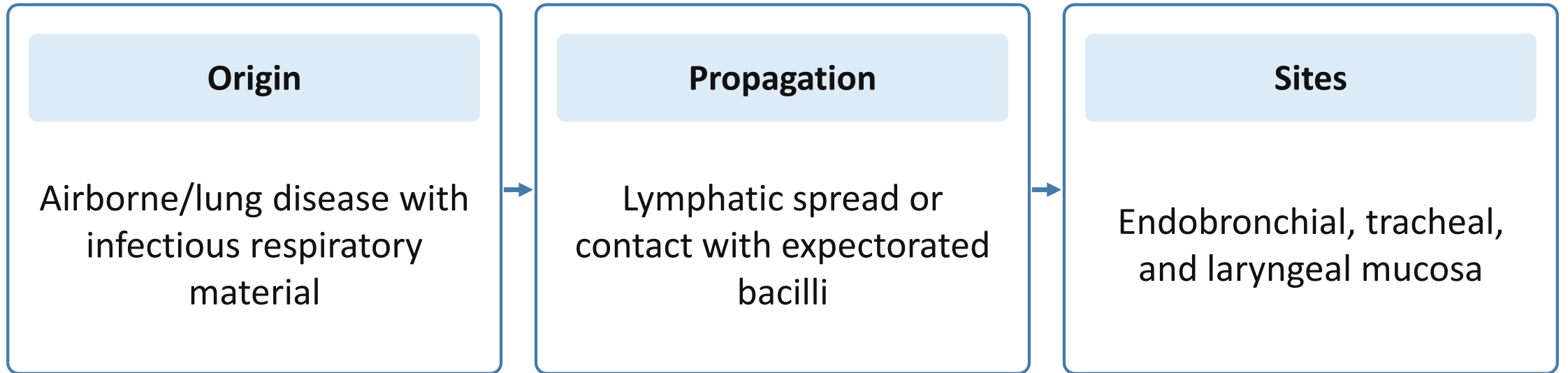
“Cold abscess” is a clinicopathologic term; This slide is a mechanism schematic.

Intestinal TB may ulcerate and stricture the ileum



The ileum is a characteristic site in the source description.

Upper airway TB follows local spread



Minute granulomatous lesions may only be evident microscopically.

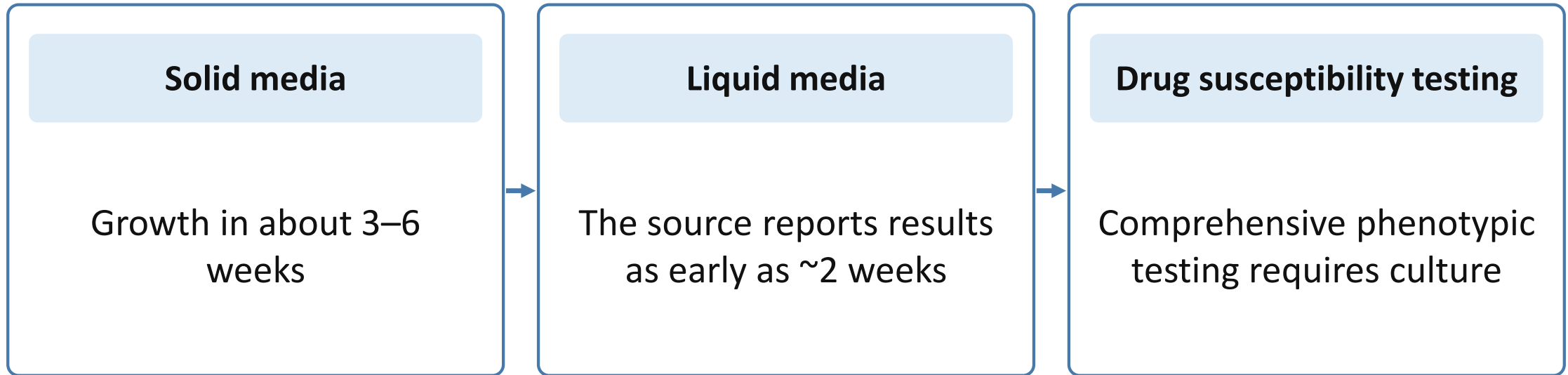
TB testing answers two different questions

Is active disease present?	Has an immune response occurred?
AFB smear or culture	Interferon- γ release assay (IGRA)
PCR for mycobacterial DNA	Tuberculin/PPD skin test
Direct organism detection; Susceptibility testing	Evidence of immunologic sensitization
Specimen-based clinical diagnosis	Cannot alone identify active disease

Sputum smears are rapid but not fully specific

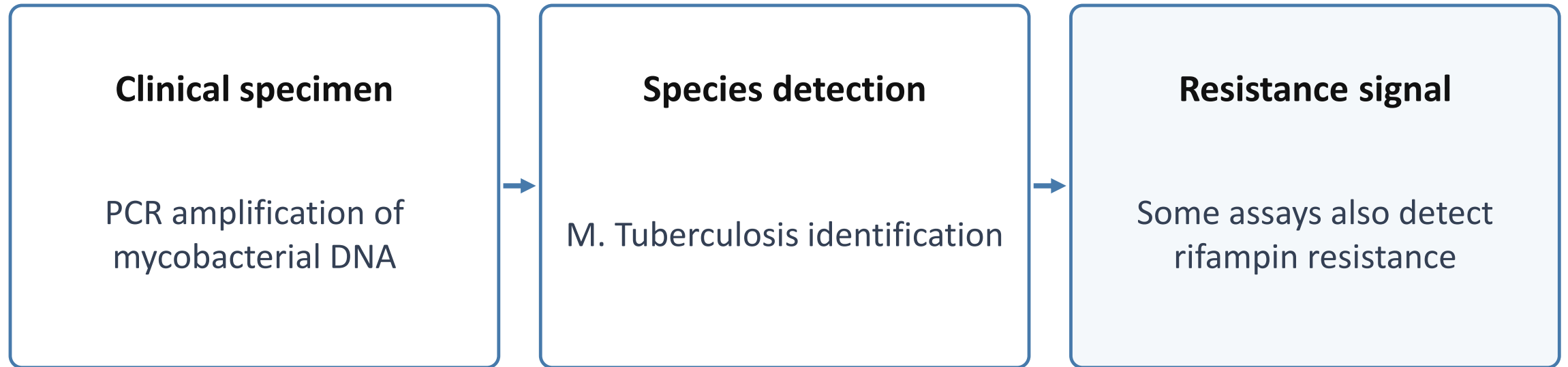
- An acid-fast smear looks for organisms that retain stain after acid–alcohol decolorization.
- A positive acid-fast smear does not by itself identify the mycobacterial species.
- Smear-negative disease can still be present, particularly in immunocompromised patients.
- Use organism-specific molecular testing and culture in suspected active tuberculosis.

Culture identifies viable organisms and enables DST



These time frames are textbook descriptions, not guarantees for individual specimens.

Molecular assays speed organism and resistance detection



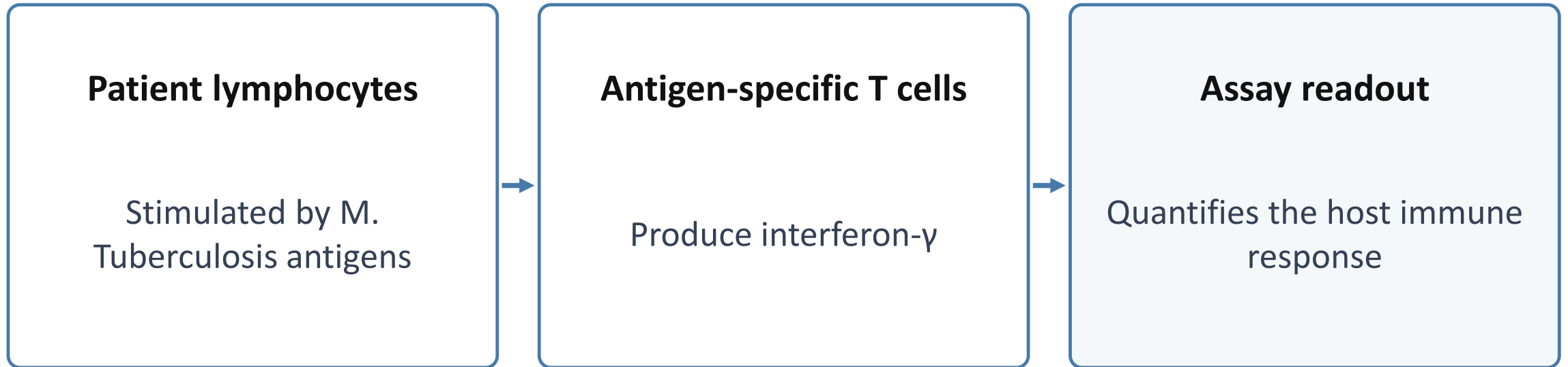
Molecular results complement, rather than universally replace, culture and susceptibility testing.

Latent TB tests measure T-cell memory

Neither IGRA nor tuberculin testing reliably distinguishes latent infection from active tuberculosis.

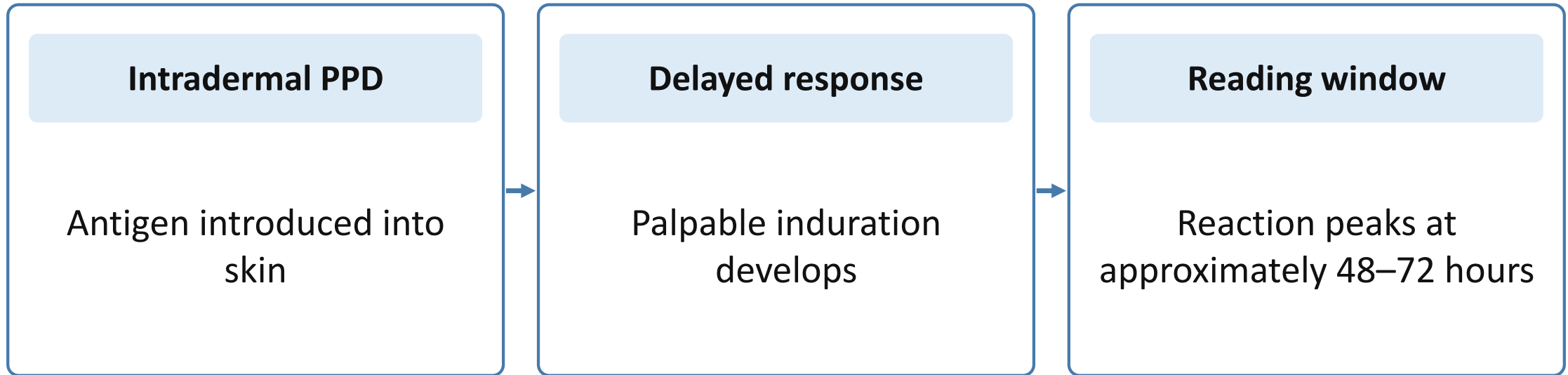
- Both reflect T-cell recognition of mycobacterial antigens.
- Results must be interpreted with exposure, symptoms, imaging, and microbiology.
- Immunosuppression may weaken test responses despite true infection.

IGRA measures IFN- γ release after antigen challenge



IGRA positivity is evidence of sensitization, not proof of active disease.

Tuberculin testing is a delayed immune response



Interpretation concerns measured induration and risk context; The source does not specify cutoffs here.

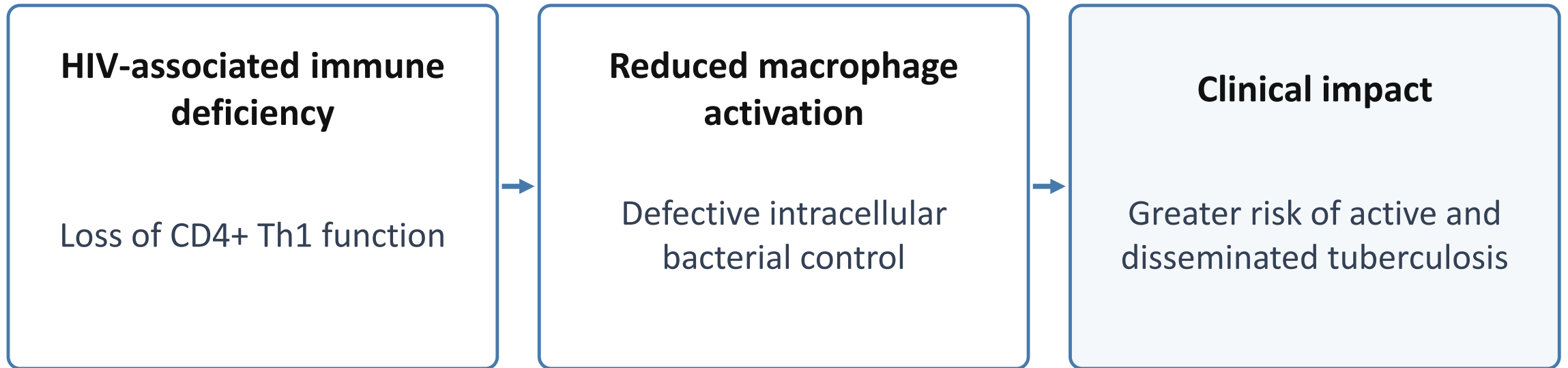
Negative immune-based tests cannot exclude TB

- False-negative immune tests occur with immunosuppression and malnutrition.
- Active tuberculosis itself may be associated with impaired test responses.
- Other cited settings include sarcoidosis, Hodgkin lymphoma, and certain viral infections.
- Investigate suspected active disease with appropriate direct tests despite negative screening assays.

BCG and atypical mycobacteria can affect TST

Tuberculin skin test	IGRA
May be positive after BCG vaccination	False-positive results from BCG are uncommon
May cross-react with atypical mycobacteria	More antigen-specific immunologic signal
Can be negative despite active TB	Can also be falsely negative with impaired T-cell immunity

HIV weakens the main defense against tuberculosis

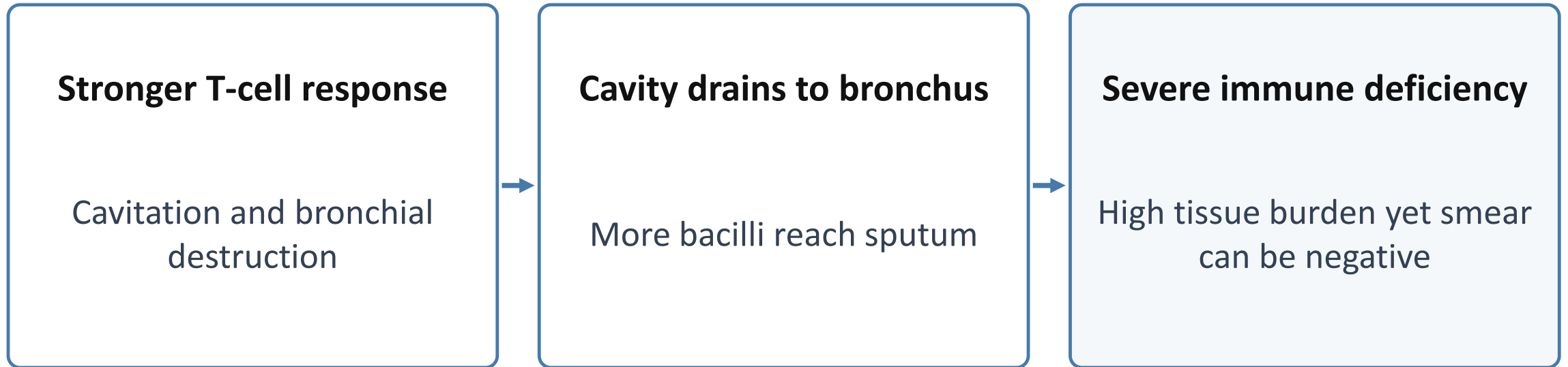


Antiretroviral treatment reduces, but does not eliminate, tuberculosis risk.

Advanced HIV alters pulmonary and tissue findings

Preserved cellular immunity	Marked CD4+ deficiency
Granulomas and cavitory destruction common	Characteristic granulomas may be absent
Cavitation can discharge bacilli into sputum	Less airway destruction may lower sputum bacilli
Apical disease can be prominent	Multifocal or atypical pulmonary patterns may occur
Disease may remain localized	Extrapulmonary involvement becomes more frequent

The sputum smear paradox is immunopathologic



The source offers this as the likely explanation; It is not a universal rule.

Diagnosis requires triangulation of evidence

Evidence domain	Interpretive limitation
Morphology: Granuloma $\pm$ necrosis	Not uniquely specific for M. Tuberculosis
Acid-fast stain	Shows bacilli, not species identity
PCR for M. Tuberculosis	Rapid direct detection; Specimen sensitivity varies
Culture and DST	Viable organism and phenotypic susceptibility
TST or IGRA	Sensitization; Does not classify active disease

Anatomic patterns link morphology to clinical behavior

Dominant pattern	Pathologic / clinical connection
Primary subpleural focus + hilar nodes	Ghon complex; Can heal by fibrosis and calcification
Apical caseating postprimary focus	Fibrosis or cavitation with infectious sputum
Miliary small nodules	Blood-borne dissemination to lung or many organs
Disorganized lesions in immune deficiency	Higher bacillary loads without classic granulomas

Clinical application: A healed primary complex

Clinical question

A previously asymptomatic individual has a small calcified pulmonary focus associated with calcified hilar lymph nodes. What process best explains this paired pattern?

Interpretation: A healed Ghon complex following primary infection.

Pathologic rationale

The subpleural parenchymal lesion and regional caseating nodes may undergo fibrosis and calcification when Th1 immunity controls the infection.

Clinical application: A destructive apical cavity

Clinical question

An adult develops night sweats and weight loss. Imaging shows an apical lesion communicating with a bronchus; Sputum may be infectious. What pathologic sequence produced the cavity?

Interpretation: Postprimary caseation with bronchial erosion and evacuation of necrotic material.

Pathologic rationale

The sensitized host mounts a tissue-damaging reaction; Drainage of necrotic material produces a cavitory space.

Clinical application: Extensive TB with few granulomas

Clinical question

A patient with advanced HIV has numerous acid-fast bacilli in tissue macrophages but little organized granulomatous inflammation. Does the absent classic granuloma exclude tuberculosis?

Interpretation: No. Defective T-cell immunity can prevent typical granuloma formation.

Pathologic rationale

In severely immunocompromised hosts, bacterial burden may be high despite minimal granulomatous architecture and a negative sputum smear.

Five pathologic principles to retain

- 1 Intracellular survival precedes the protective Th1 response.
- 2 IFN- γ -mediated macrophage activation controls bacilli but can generate caseous necrosis.
- 3 Primary Ghon complexes and apical postprimary lesions have distinct anatomic patterns.
- 4 Cavitation links parenchymal destruction with airway infectiousness.
- 5 Granulomas, acid-fast staining, molecular tests, culture, and immune tests answer different diagnostic questions.

Reference and figure conventions

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 8, “Infectious Diseases,” pp. 334–338.

This lecture follows the textbook’s pathogenesis, morphology, clinical presentation, and diagnostic framework.

All displayed pathology diagrams are original schematics; they are not histologic, radiologic, or gross clinical specimens.

Epidemiologic numbers shown refer explicitly to 2022; test descriptions reflect the textbook, not a current practice guideline.