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Review Article

Human Chlamydial Infections: From Intracellular Pathogenesis to Molecular Diagnosis, Therapeutic Challenges, and Emerging Perspectives

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Abstract

Human chlamydial infections remain a substantial microbiological and public-health challenge because members of the genus Chlamydia depend on intracellular growth, produce diverse clinical syndromes and frequently escape clinical recognition. *Chlamydia trachomatis* causes common sexually transmitted infections, trachoma and neonatal disease, whereas *C. pneumoniae and C. psittaci* are associated with respiratory and zoonotic disease. This structured narrative review synthesizes recent advances in taxonomic characterization, developmental biology, molecular host–pathogen interactions, immune-mediated stress responses, clinical diagnosis, treatment and genomic surveillance. Particular emphasis is placed on the biphasic elementary-body/reticulate-body cycle, the inclusion membrane and type III secretion effectors, and the role of interferon-gamma–associated nutrient restriction in experimentally observed persistence. Nucleic acid amplification tests provide the foundation of contemporary diagnosis, although assay accuracy varies by platform and specimen and nucleic acid detection does not establish bacterial viability. Current treatment recommendations prioritize doxycycline for uncomplicated *C. trachomatis* infection in nonpregnant adults, with specific exceptions for pregnancy and invasive or zoonotic syndromes. The literature supports a clear distinction between laboratory persistence, reinfection, residual post-treatment nucleic acid and genetically mediated resistance. We highlight the potential of validated point-of-care tests, direct-from-sample genomics and viability-oriented approaches, while identifying translational uncertainties and surveillance gaps. A structured search approach is documented without claiming systematic review methodology.

Keywords: *Chlamydia trachomatis; Chlamydia pneumoniae; Chlamydia psittaci*; type III secretion; intracellular persistence; NAAT; genomic surveillance; treatment.

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1. INTRODUCTION

Chlamydial infections occupy a distinctive position at the interface of clinical microbiology, molecular cell biology and public health. Members of the family Chlamydiaceae infect mucosal or other epithelial surfaces, yet their propagation is dependent on the intracellular environment. Consequently, routine bacteriological methods developed for extracellular organisms cannot be directly transferred to this group. The organisms also exhibit an unusual differentiation programme that changes bacterial architecture, metabolism and infectivity during the infection cycle. A microbiology-centred synthesis is therefore useful for connecting the laboratory phenotype with clinical manifestations and therapeutic decisions [1–4].

The principal human pathogen, *Chlamydia trachomatis*, produces sexually transmitted urogenital and anorectal infections, ocular trachoma, neonatal disease and lymphogranuloma venereum (LGV). The World Health Organization estimated 128.5 million incident sexually transmitted *C. trachomatis* infections in people aged 15–49 years in 2020. The combination of frequent asymptomatic infection, onward transmission, repeat exposure and reproductive complications accounts for much of its burden. Other species expand the clinical spectrum: C. pneumoniae is associated with respiratory disease, while *C. psittaci* causes zoonotic psittacosis after exposure to birds [5–8].

Recent research has reshaped the field in several areas. Type III secretion effectors and inclusion-membrane proteins are now recognized as major determinants of host manipulation; experiments have revealed a more nuanced relationship between nutrient acquisition, innate immunity and nonproductive

bacterial states; and diagnostic practice has shifted towards highly sensitive nucleic acid amplification tests (NAATs). Nevertheless, the terms persistence, chronic infection, reinfection and antimicrobial resistance are sometimes used interchangeably despite denoting different biological and clinical phenomena [2,3,9,10].

This narrative review integrates foundational discoveries with recent studies and guidance, placing particular emphasis on molecular pathogenesis, stress-induced persistence, species-specific diagnostic strategies and antimicrobial management. It also identifies limits of current evidence and priorities for resource-constrained clinical laboratories

2. Literature-search approach and narrative synthesis

This manuscript is a structured narrative review, not a systematic review or meta-analysis. Literature was identified through targeted searches of PubMed/MEDLINE and publicly accessible guidance from WHO, CDC and European professional groups, focusing on publications available up to 1 November 2026. Search concepts combined the terms *Chlamydia trachomatis, Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia abortus*, Chlamydiales, developmental cycle, elementary body, reticulate body, inclusion membrane, type III secretion, persistence, interferon gamma, tryptophan, diagnosis, nucleic acid amplification, molecular point-of-care, whole-genome sequencing, treatment, vaccine and antimicrobial resistance. Boolean operators and species-specific combinations were used to locate focused reviews, primary investigations and guidelines.

Priority was given to peer-reviewed articles published between January 2022 and November 2026, including molecular-mechanistic experiments, clinical diagnostic studies, comparative treatment trials, genomic work and major evidence-based recommendations. Earlier landmark studies were retained when required to explain foundational mechanisms or interpret treatment effectiveness. Citations were selected for relevance, methodological clarity and clinical applicability rather than according to a predetermined quality score. Special caution was applied when interpreting mechanistic claims derived exclusively from immortalized cell lines, animal models or experimental antibiotic exposure.

Titles, abstracts and accessible full texts were considered narratively; evidence was organized into microbiological themes rather than pooled quantitatively. No formal exhaustive record screening, duplicate independent selection, risk-of-bias assessment or quantitative meta-analysis was performed. Accordingly, no PRISMA flow diagram or claim of systematic coverage is presented. This section describes the review approach but is not equivalent to a reproducible systematic-review search log; for journal submission, authors should retain final database-specific query strings and exact execution dates.

3. Taxonomy, reservoirs and strain diversity

The order Chlamydiales comprises obligate intracellular microorganisms with substantial genomic and ecological diversity. Within the family Chlamydiaceae, current usage generally unites clinically relevant organisms in the genus Chlamydia, including former Chlamydophila species. Chlamydial taxonomy is important because host range, mode of transmission, tissue tropism and expected diagnostic specimen differ appreciably among species. Human-associated and animal-associated strains should not be interpreted as interchangeable entities [2,4].

C. trachomatis is predominantly a human pathogen. Classical serovars A, B, Ba and C are associated with trachoma; D–K are generally linked to non-LGV urogenital and extragenital infection; and invasive L1–L3 variants cause LGV. Serovar groupings remain epidemiologically informative, although genomic variation, recombination and clinical diversity are not fully represented by serotyping alone. Molecular tests that detect C. trachomatis at the species level ordinarily do not distinguish LGV from non-LGV strains unless additional discriminatory targets are included.

C. pneumoniae circulates principally between humans through the respiratory route. C. psittaci infects diverse avian hosts, with zoonotic transmission usually following inhalation of aerosolized contaminated material. Bird ownership, veterinary activities, poultry-related work and environmental exposure are therefore relevant clinical clues. *C. abortus* is associated particularly with reproductive disease in sheep and goats and may cause severe pregnancy-associated human infection. The One Health perspective is essential because laboratory surveillance confined to human clinical specimens will miss important reservoirs and exposure pathways [7,8].

Chlamydial genomes are relatively reduced, reflecting long-standing dependence on host resources. Comparative genomics has identified conserved developmental and secretion pathways together with variable regions influencing tissue adaptation, immune interactions and evolutionary lineage. New core-genome multilocus sequence typing approaches and improved direct-from-swab sequencing methods have strengthened the prospects for harmonized genomic surveillance [11,12].

Table 1: Principal chlamydial species of importance in human medicine

Species	Reservoir/transmission	Clinical associations
C. trachomatis	Human / sexual, ocular, perinatal	Genital and anorectal infection, LGV, trachoma, neonatal disease
C. pneumoniae	Human / respiratory	Upper and lower respiratory infection
C. psittaci	Birds / aerosolized excreta and secretions	Psittacosis and atypical pneumonia
C. abortus	Small ruminants / zoonotic exposure	Rare severe pregnancy-associated infection

4. Developmental biology and bacterial cell structure

The hallmark of chlamydial biology is an ordered developmental cycle that alternates between two major forms. The elementary body (EB) is small, compact and infectious, whereas the reticulate body (RB) is metabolically active and primarily replicative. Upon attachment to a permissive epithelial cell, the EB is internalized into a membrane-bound compartment and differentiates into an RB. Repeated rounds of division enlarge the inclusion, followed by secondary differentiation to EBs that can be released to infect neighboring cells. For many *C. trachomatis* systems, the developmental cycle is approximately 48–72 hours, but timing depends on the organism and experimental context [2,3].

The classic EB-RB distinction is a useful framework but does not imply that every organism changes synchronously or that intermediates are absent. Molecular studies increasingly support heterogeneous transition states, coordinated regulation of early, middle and late gene expression and distinct metabolic demands during differentiation. Cell-wall-associated structures are particularly intriguing. Despite unusual peptidoglycan architecture, chlamydiae generate a localized peptidoglycan ring linked to cell division. This helps resolve aspects of the historical 'chlamydial anomaly' in which sensitivity to cell-wall-active agents appeared inconsistent with earlier difficulty in detecting conventional peptidoglycan [2,3].

The inclusion is not a passive vacuole. It is progressively remodeled to obtain nutrients, avoid destructive trafficking and sustain intracellular replication. Membrane composition changes over time, and bacterial effector proteins help direct interactions with organelles and cytoskeletal components. The host cell is consequently both an essential supplier of metabolites and a source of hostile immune signals. Figure 1 summarizes the cycle as a schematic biological sequence rather than a quantitative kinetic model.

Exit from the infected cell may occur through lysis or extrusion, two processes with potentially different consequences for inflammation and dissemination. Whether the relative contribution of these routes varies consistently by clinical syndrome remains an active area of investigation. Importantly, nonproductive infections and stress-induced aberrant forms should not be confused with normal developmental intermediates.

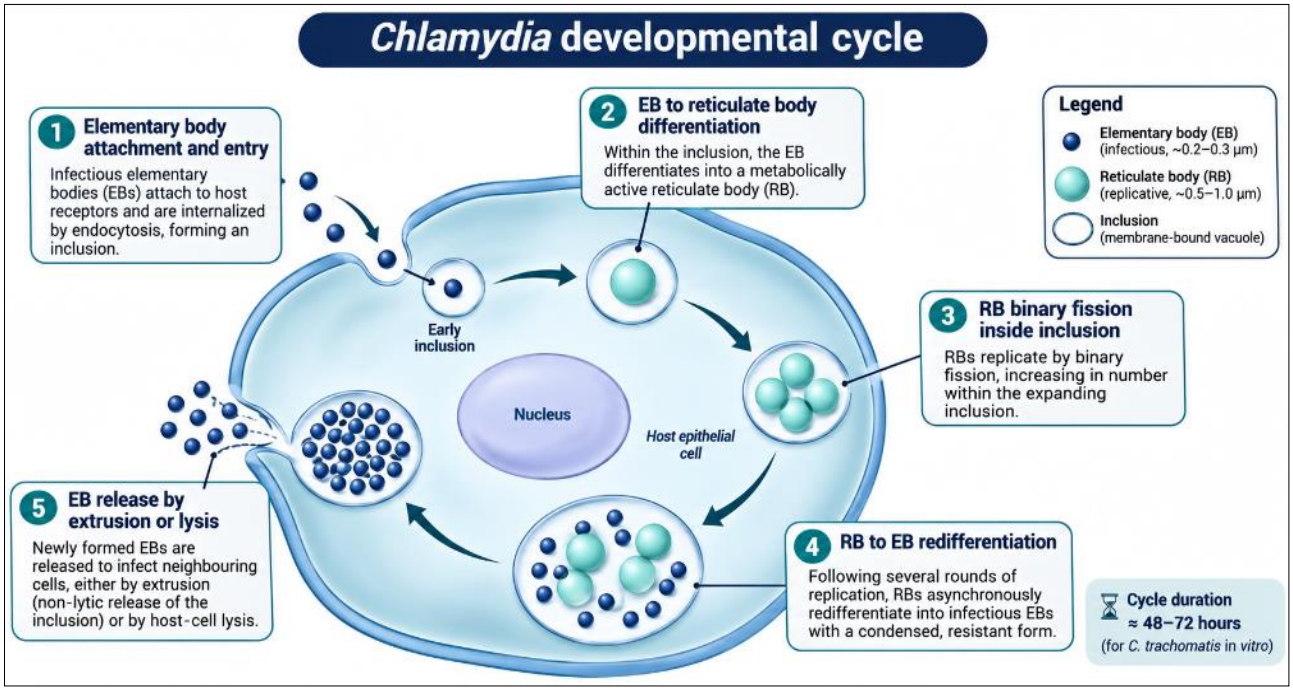


Figure 1: Original explanatory schematic of the developmental cycle

5. Molecular mechanisms of host-cell invasion and intracellular survival

C. trachomatis invasion requires coordinated interaction between bacterial surface proteins, host receptors and cytoskeletal remodeling. Upon contact, the type III secretion system (T3SS) delivers proteins into the host cytosol. The translocated actin-recruiting phosphoprotein TarP is among the best-characterized effectors and promotes events contributing to actin reorganization. These entry-associated responses create a localized environment that facilitates bacterial uptake rather than relying exclusively on ordinary host endocytosis [2,13].

Subsequently, inclusion membrane proteins (Incs) establish an interface through which the pathogen recruits, modifies or excludes host components. Inc proteins participate in interactions with vesicular transport systems, lipid metabolism and organelle positioning, yet individual members differ in timing, binding partners and functional redundancy. Recent reviews summarize the diversity of these interactions, while a 2026 mechanistic study of CT226 and the LRRFIP1-containing host complex illustrates that some effectors may regulate rather than simply maximize bacterial growth [14,15].

The inclusion membrane also influences innate immune recognition. Bacterial effectors can interact with host ubiquitination systems and inflammatory signaling pathways, including components of NF-kappaB and cGAS–STING networks. Specific claims require care: an interaction observed after ectopic expression does not necessarily establish its contribution during natural infection; genetic complementation and physiologically relevant models provide stronger evidence. The effects of a secreted protein may depend on the cell type, strain and infection phase [9,13].

Intracellular nutrient acquisition is equally central to survival. Chlamydiae depend on host-derived amino acids, nucleotides and lipids, and infection induces remodeling of host metabolic networks. Work using primary cervical epithelial cells has highlighted altered host metabolism, supporting the need to move beyond transformed laboratory lines. However, metabolic profiles in cultured cells are not direct proxies for nutrient availability in a human genital or respiratory mucosa [16].

Host cell death and inflammatory signaling must be balanced. Premature death of infected cells may interrupt pathogen development, while prolonged cell survival provides time for replication. Chlamydial proteins influence apoptotic and other stress pathways in ways that may differ across experimental systems. A unified mechanistic account should therefore integrate bacterial differentiation, inclusion organization, metabolic exchange and the inflammatory context rather than treating these as isolated virulence factors.

6. Host immunity, immunopathology and microbial persistence

Epithelial recognition of chlamydial infection initiates cytokine and chemokine responses that recruit innate immune cells and shape subsequent adaptive immunity. Pattern-recognition pathways, inflammatory mediators and cell-autonomous defense mechanisms all contribute, although their relative importance differs across tissues and species. Th1-type cellular responses and interferon-gamma (IFN-gamma) are particularly relevant to control of C. trachomatis, while dysregulated or repeated inflammatory responses may contribute to tissue damage [9,10].

In human epithelial cells, IFN-gamma induces indoleamine 2,3-dioxygenase 1 (IDO1), which degrades tryptophan and restricts its availability. Because *C. trachomatis* relies on external tryptophan, this depletion can impair growth. Many genital strains possess a partial trpAB operon that allows synthesis of tryptophan from environmental indole under suitable conditions, whereas ocular lineages differ in this capacity. The availability of indole within a polymicrobial mucosal niche may therefore modify responses to immune-induced starvation, although clinical consequences cannot be inferred from genomic capability alone [2,9,10].

IFN-gamma can alter additional host metabolic programmes, including STAT1-dependent regulation of c-Myc and downstream pathways supplying nucleotides and intermediary metabolites. The resulting changes may suppress efficient developmental progression even when tryptophan salvage occurs. Such findings demonstrate why 'persistence' should not be reduced to a single gene, cytokine or morphological trait. It represents a family of stress-associated states shaped by multiple bacterial and host variables.

In cell culture, nutrient restriction, iron limitation and some antibiotic exposures produce enlarged aberrant RBs, reduced cell division, altered transcription and a decline in infectious EB production. Genome replication and metabolic activity may continue in some models despite loss of ordinary cytokinesis. When the stressor is removed, certain infected cells resume productive development and release new EBs. This reversibility is experimentally persuasive but does not by itself demonstrate that clinically persistent symptoms reflect viable bacteria [2,9,10].

Distinguishing biological categories is essential. Recurrent infection denotes a new episode after prior infection and frequently follows re-exposure. Microbiological treatment failure implies inadequate eradication after a suitable regimen, but interpretation depends on treatment adherence, sampling interval and assay behavior. Clinical persistence refers to continuing symptoms or pathology, potentially due to postinfectious inflammation even after microbiological clearance. Laboratory persistence refers to an altered bacterial state

under defined conditions. Genetically stable antimicrobial resistance is a separate phenotype and has not become a widely established explanation for recurrent human C. trachomatis infection [17,18].

The biological model is summarized in Figure 2. Its major limitation is translational: most experiments use defined cell lines or organoids and specific stressors, whereas human tissues contain mixed microbial communities, varying immune states, hormonal influences and uneven drug penetration. Future work should combine longitudinal sampling, viability-oriented assays, host transcriptomics and strain genomics to test how often laboratory persistence maps onto clinically meaningful infection.

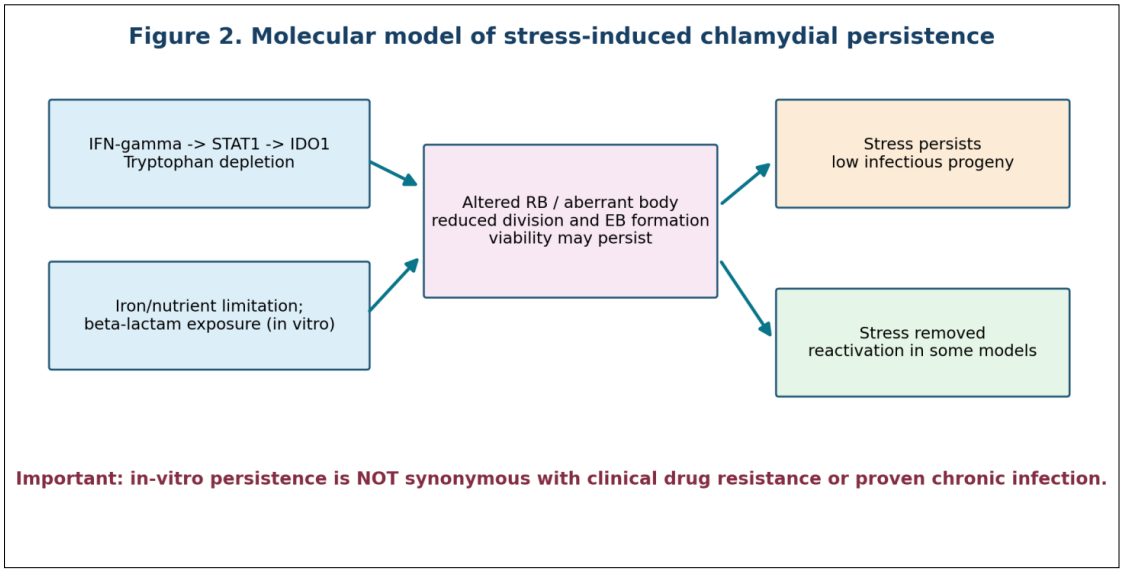


Figure 2: Original schematic of stress-induced persistence, emphasizing its predominantly experimental evidence base

7. Human disease spectrum and clinical consequences

Genital *C. trachomatis* infection is frequently asymptomatic and can remain unrecognized without screening. Women may present with cervicitis, abnormal discharge, dysuria or pelvic pain, while men may experience urethritis or epididymitis. Ascending infection may result in pelvic inflammatory disease, tubal injury, ectopic pregnancy and infertility. The risk and timing of individual complications vary and should not be treated as inevitable outcomes of every untreated infection [5,17].

Anorectal infection can be asymptomatic or associated with proctitis. LGV strains may invade lymphatic tissues and cause inguinal lymphadenopathy or severe anorectal symptoms. This distinction matters diagnostically because species-level NAAT positivity does not establish LGV. Testing policies should consider symptoms, anatomical exposure, epidemiological risk and laboratory capacity. Pharyngeal infection may also be detected, although its epidemiological significance is not identical to that of genital or rectal infection [6,17].

Perinatal exposure can produce neonatal conjunctivitis or pneumonia, with diagnostic and therapeutic approaches distinct from those used in adults. In ocular trachoma, repeated transmission in endemic communities drives chronic conjunctival inflammation and scarring. Prevention thus requires broader interventions than treatment of individual cases, including hygiene, environmental improvements and appropriately designed public health programmes [19].

C. pneumoniae causes upper and lower respiratory infection, including bronchitis and atypical pneumonia. Symptoms are nonspecific, so clinical presentation alone cannot reliably distinguish it from other respiratory pathogens. *C. psittaci* may produce fever, headache, myalgia and pneumonia, sometimes with systemic complications. A history of bird exposure can direct testing but does not prove disease; conversely, absence of a recognized exposure does not completely exclude infection [7,8,20].

C. abortus represents an important zoonotic concern, particularly in pregnant persons exposed to infected sheep or goats and materials from animal parturition. Because these events are uncommon and potentially severe, suspected cases require coordination between clinicians, reference microbiology laboratories, occupational health and veterinary services. Species identification is especially important when respiratory or zoonotic NAAT panels have incomplete chlamydial coverage.

8. Specimen selection and preanalytical quality

The highest-performing assay cannot compensate for sampling the wrong anatomical site. For

uncomplicated *C. trachomatis* infection, vaginal swabs are generally preferred specimens for women and first-catch urine is commonly recommended for men. Depending on exposure and symptoms, rectal or pharyngeal swabs should be collected using a validated assay and the appropriate transport system. Patient-collected samples may increase uptake of testing, but performance claims are platform- and specimen-specific [6,21].

First-catch urine is distinct from midstream urine used in routine bacteriological culture. Instructions must address collection volume, recent voiding when relevant, transport medium and storage. Molecular laboratories should monitor inhibition controls, transport failures, specimen identity, contamination risk and invalid results. Interpretation is particularly difficult when bacterial burden approaches the analytical detection limit; a negative result may require reconsideration when high clinical suspicion and preanalytical concerns coexist.

For *C. pneumoniae*, upper or lower respiratory samples are selected according to clinical presentation and available assay validation. For psittacosis, respiratory specimens may be preferred, but blood or other materials can have a role depending on the reference service. Early communication with the laboratory is important, particularly when unusual zoonotic infections are suspected or specialized species-specific PCR is needed [7,8].

Culture is not a routine option for standard laboratories and can entail substantial biosafety issues, especially for zoonotic species. Preanalytical protocols should therefore be standardized around molecular assays, with written criteria for referral, repeat testing and additional characterization.

9. Conventional and molecular laboratory methods

Cell culture historically provided a means to demonstrate viable chlamydial organisms but requires susceptible host cells, specialized expertise and time. Its principal roles today are research and select reference-laboratory activities rather than first-line testing of uncomplicated urogenital disease. Direct antigen detection methods have been used in certain settings, but their sensitivity generally falls short of well-validated molecular amplification tests. Serology may contribute to selected respiratory or zoonotic investigations but is weakened by delayed antibody responses, prior exposure, assay heterogeneity and cross-reactivity [21–23].

NAATs have become the preferred approach for genital *C. trachomatis* detection because of their high diagnostic accuracy and suitability for noninvasive samples. Contemporary platforms use different amplification chemistries and genetic targets; dual-target strategies can mitigate vulnerability to target variation. It is inappropriate to assign a single universal sensitivity or specificity across all assays, collection sites and populations. A 2026 review of laboratory NAATs emphasized that validated assays often achieve high sensitivity and specificity while identifying ongoing gaps in extragenital self-collection authorization and viability testing [21].

Multiplex syndromic platforms can detect *C. trachomatis* together with *N. gonorrhoeae* and other pathogens when warranted. Their advantages include specimen efficiency and reduced turnaround time; limitations include cost, incomplete target coverage and potential over-interpretation of multiple positive findings. Detection of microbial nucleic acid does not necessarily imply that a particular organism is the cause of all symptoms in a polymicrobial syndrome.

Rapid molecular point-of-care testing is attractive because actionable results may be delivered during the same visit. A prior systematic review reported substantially better sensitivity for molecular point-of-care methods than for antigen-based approaches, but performance varies among products. International field evaluations, including work undertaken in Morocco, underline the need for independent validation in the intended population, environment and anatomical specimen [24–26].

Whole-genome sequencing offers high-resolution discrimination for evolutionary analyses and surveillance. Direct sequencing from clinical swabs can avoid culture requirements but faces low pathogen DNA fraction, host DNA background and contamination problems. Newer enrichment methods and standardized core-genome schemes may make genomic data increasingly comparable between laboratories [11,12]. Metagenomic sequencing may help identify uncommon respiratory pathogens, particularly in severe cases when targeted testing is inconclusive, but high costs and uncertain clinical specificity currently limit indiscriminate use [27].

Post-treatment NAAT interpretation demands caution. Residual DNA or RNA may persist despite organism clearance. Thus, a positive result soon after therapy is not sufficient evidence of resistance. If test of cure is indicated, guideline-recommended intervals should be respected, and the test result interpreted with symptoms, prior treatment, partner exposure and sampling details. Table 2 compares major methods without assuming identical performance across platforms.

Table 2: Diagnostic methods: expected performance characteristics, benefits and limitations

Technique	Performance considerations	Advantages	Limitations / interpretation
Cell culture	Depends on viability, sampling and host-cell system	Recovery of viable organism in reference settings	Slow, technically demanding; biosafety constraints
Serology	Variable by assay, timing and species	Supplemental for selected respiratory/zoonotic cases	Cross-reactivity; previous exposure; not recommended for routine genital diagnosis
Antigen detection	Generally less sensitive than validated NAATs	Potential low-cost workflow	Misses low-load infection; performance highly product dependent
Laboratory NAAT / real-time PCR	Often high sensitivity and specificity when validated; no universal percentage	Preferred for C. trachomatis; scalable; multiplex options	Nucleic acids may persist after cure; specimen/site validation required
Molecular point of care	Can approach laboratory NAAT performance for well-validated products	Results at visit; fewer losses to follow-up	Cost, invalids, quality control; performance differs by platform
WGS / targeted sequencing	Depends on pathogen DNA fraction and read quality	Typing, genomic epidemiology, research	Costs, bioinformatics, host background; not routine first-line
Metagenomic sequencing	Broad detection; clinical performance context dependent	Unusual severe respiratory and zoonotic cases	Contamination, cost, uncertain causal attribution

10. Antimicrobial treatment: species- and syndrome-specific considerations

Current WHO recommendations and the 2025 European guideline favor doxycycline 100 mg orally twice daily for seven days in nonpregnant adolescents and adults with uncomplicated genital, anorectal or oropharyngeal C. trachomatis infection. Single-dose azithromycin is an alternative in selected situations where adherence to a multi-dose regimen is a serious concern or doxycycline is unavailable, but relative efficacy differs by site [6,17,28].

Randomized studies have been influential. In one trial among men with rectal chlamydia, microbiological cure at four weeks was higher after doxycycline than after azithromycin. The CHLAZIDOXY trial among women with concurrent vaginal and anorectal infection also favored doxycycline for anorectal cure. These data support the emphasis on anatomical site and reinforce that apparent post-treatment positivity should first prompt evaluation of regimen selection, adherence and reinfection rather than an assumption of acquired resistance [29–31].

Pregnancy requires a different regimen because tetracyclines are generally avoided. Azithromycin 1 g orally once is recommended for genital chlamydial infection during pregnancy under major guidance; follow-up NAAT at approximately four weeks is advised to confirm clearance. LGV generally requires doxycycline 100 mg twice daily for 21 days. Neonatal and complicated infections require syndrome-specific clinical assessment rather than simple extrapolation from adult uncomplicated infection [17,28].

C. pneumoniae respiratory infection may be treated with a macrolide or an appropriate alternative when antimicrobial therapy is clinically indicated, taking into account severity and patient factors. *C. psittaci* psittacosis is usually treated with doxycycline, with macrolides considered where tetracyclines are contraindicated, including selected children or pregnancy contexts. Treatment duration and route in severe psittacosis are individualized; consultation with infectious disease specialists may be needed. In suspected zoonotic pregnancy-associated illness, urgent specialist assessment is essential [7,8].

Partner notification and treatment are critical for control of genital infection, and retesting after treatment is intended to detect reinfection. Prevention strategies should also address counseling, access to testing and locally applicable partner-services policies. Table 3 summarizes representative regimens; it is a review-level comparison and not a substitute for individual clinical prescribing guidance.

Table 3: Representative antimicrobial regimens and key clinical considerations

Infection / situation	Recommended approach	Duration / follow-up	Clinical caveat
Uncomplicated genital/rectal/pharyngeal *C.trachomatis*, nonpregnant adult	Doxycycline 100 mg orally twice daily	7 days	Azithromycin 1 g once is an alternative in selected circumstances; rectal cure may be lower

Infection / situation	Recommended approach	Duration / follow-up	Clinical caveat
C.trachomatis in pregnancy	Azithromycin 1 g orally once	Single dose; NAAT test of cure ~4 weeks	Follow pregnancy-specific guidelines
LGV (C. trachomatis L1–L3)	Doxycycline 100 mg orally twice daily	21 days	Assess invasive disease and partner services
C. pneumoniae respiratory infection	Azithromycin or another appropriate macrolide; alternative doxycycline when suitable	Case-specific	Treat when clinically indicated; age and pregnancy matter
C. psittaci psittacosis	Doxycycline preferred	Individualized; often 10–14 days in practice	Severe illness needs expert review; macrolide if tetracycline contraindicated
Suspected *C. abortus* zoonosis	Urgent specialist-directed management	Individualized	High concern in pregnancy; notify reference and public-health services

11. Antimicrobial resistance, treatment failure and stewardship

The widespread antimicrobial-resistance crisis affects many bacterial pathogens, but claims about Chlamydia must be proportionate to the available evidence. Stable, widespread acquired resistance to first-line treatment has not been demonstrated as a major problem in human *C. trachomatis* infection. Laboratory susceptibility measurement is difficult because growth depends on viable host cells and because conventional broth microdilution standards used for extracellular organisms are not directly applicable [2,18].

When a repeat NAAT is positive, several alternative explanations deserve systematic consideration: a new sexual exposure, treatment nonadherence, an initially suboptimal regimen for a particular anatomical site, testing too soon after therapy, sampling variability and, less commonly, true persistent viable infection. These possibilities must be evaluated before labeling the episode a resistant infection. Clinical symptoms may also continue after clearance due to mucosal inflammation or another pathogen.

Beta-lactam exposure can drive aberrant morphology in some cell-culture models without proving that such treatment is clinically useful. Likewise, IFN-gamma-mediated metabolic restriction can reduce infectious progeny but does not establish susceptibility to particular antimicrobial classes. In vitro susceptibility observations can depend on cell line, bacterial developmental stage, timing of exposure and definition of the readout. Future microbiological research requires harmonized assay methodologies and carefully defined clinical endpoints.

Stewardship therefore involves using recommended regimens, avoiding treatment of unvalidated positive results outside the clinical context, preventing reinfection and limiting unnecessary broad-spectrum prescriptions. In respiratory disease, antimicrobial choice should be guided by illness severity and likely etiology; positive serology alone may not justify prolonged treatment.

12. Prevention, public health and One Health integration

The population-level impact of chlamydial infection is driven not only by organism characteristics but also by delayed diagnosis and barriers to care. Screening strategies, affordable molecular testing, timely therapy and partner services can reduce untreated infection reservoirs. Programmes should be adapted to local epidemiology and avoid assuming that incidence in high-income countries can be generalized to low-resource contexts [5,32].

Trachoma prevention requires coordinated elimination programmes involving treatment of active infection where indicated, surgery for trichiasis, facial hygiene and improved water and sanitation environments. These interventions address repeated community transmission and its inflammatory sequelae rather than only individual ocular infection [19].

For psittacosis, prevention includes appropriate bird husbandry, wet cleaning to reduce aerosolized dust, veterinary investigation of ill birds and occupational protection. In suspected *C. abortus* exposure, obstetric and veterinary public health coordination is particularly important. Cross-sector surveillance can identify animal sources and clarify clusters that might otherwise be classified as pneumonia of unknown cause [7,8].

Human vaccine development remains a major unmet need. Candidate antigens and immunization strategies aim to induce protective mucosal and cellular responses without exacerbating immunopathology. An effective vaccine will require rigorous evidence of safety, durable protective efficacy and activity across strain diversity. Vaccine research is promising, but no licensed human C. trachomatis vaccine is currently available.

13. Emerging research directions

The next phase of chlamydial research should bridge molecular mechanisms and clinical outcomes. Genetic perturbation of bacterial effectors, advanced organoid systems and single-cell technologies can

identify which pathways are essential in a physiological tissue context. However, phenotypes should be reproduced in independent strains and relevant models before being classified as robust therapeutic targets. Recent investigations of inclusion-associated effectors and host chromatin or metabolic changes point towards a highly integrated host–pathogen system [15,16,33].

Viability-aware diagnostics would address a central gap left by standard NAATs. RNA-based measurements, differential nucleic-acid approaches, culture-linked validation and longitudinal clearance studies may help determine whether pathogen detection reflects viable organisms. Any new marker should be prospectively validated against meaningful clinical outcomes rather than assuming that a molecular signal directly represents transmissibility or treatment failure [22].

Genomic surveillance could clarify strain diversity, transmission and outbreaks, especially if collection is linked to clinical and epidemiological metadata. Standardized genomic nomenclature, laboratory quality assurance and transparent analytic pipelines are prerequisites for comparability. For rare species, metagenomic investigations may improve recognition, but broad sequencing must be interpreted against environmental contamination, specimen quality and the background frequency of respiratory microorganisms.

Finally, equitable diagnostics deserve attention. Implementation studies should consider price, workflow, turnaround time, invalid-test frequency and access to appropriate treatment. Independent field studies are essential in settings such as North Africa, where rapid molecular platforms may substantially improve infection control only if affordable and supported by training and quality systems.

13.1 Laboratory implementation, quality assurance and reporting

Implementation begins with clearly defined clinical indications, a specimen-to-assay matrix, and verification of the molecular platform on the anatomical sites that will be accepted. The laboratory should establish whether a product is approved or locally validated for clinician-collected or self-collected vaginal, urine, rectal and pharyngeal specimens. Validity at one site cannot be assumed to imply validity at another. In particular, human nucleic acid and inhibitory substances differ by matrix, and collection devices may be incompatible with certain amplification chemistries. A local standard operating procedure should specify specimen identification, collection medium, transport limits, storage temperature, internal controls and rejection criteria.

Quality assurance is more than a positive and a negative control in every amplification run. It includes regular monitoring of invalid results, low-positive signals where available, lot-to-lot variation, environmental contamination and discrepancies between platform software and laboratory information systems. A dual-target assay can offer resilience against target variation, but only if both targets are understood and appropriately interpreted. Participation in external quality assessment schemes and periodic review of analytical performance are especially important where molecular testing has recently replaced antigen methods or where multiplex panels are used across several clinical units.

A structured report should identify the organism and specimen site, use unambiguous positive or negative language, and state relevant limitations such as incomplete species coverage. When a respiratory panel includes C. pneumoniae but not C. psittaci, a negative result must not be used to exclude psittacosis in a patient with compatible pneumonia and bird exposure. Similarly, a positive *C. trachomatis* NAAT does not necessarily determine whether an anorectal syndrome is caused by an LGV strain. Species-specific follow-up amplification or referral is appropriate when the result could materially change management.

Post-treatment reporting requires careful communication. Routine qualitative NAATs detect a molecular target and cannot establish whether an organism is culturable or transmissible. A repeat positive result obtained too early after treatment may prompt unnecessary antibiotics unless the laboratory and clinician consider residual nucleic acids. Where a test of cure is warranted, the clinical team should communicate the date of treatment completion, regimen, adherence concerns and possible re-exposure. Laboratories may include concise interpretive comments, but the language should avoid declaring resistant infection from a positive NAAT alone.

Finally, laboratories in resource-constrained settings should prioritize timely access to validated *C. trachomatis* testing, reliable referral pathways for uncommon chlamydiae, and quality indicators linked to patient outcomes. Useful indicators include specimen rejection frequency, invalid amplification rate, time from collection to verified result, clinical notification delay and proportion of eligible patients receiving appropriate follow-up. Economic evaluations should include repeat visits, potential prevention of sequelae and lost-to-follow-up risk rather than comparing instrument acquisition costs alone. Close collaboration between microbiology, sexually transmitted infection clinics, respiratory services and veterinary surveillance can convert laboratory data into actionable public-health information.

14. Critical appraisal and limitations of the evidence

Several evidence asymmetries shape this review. *C. trachomatis* has received far more detailed

mechanistic and clinical investigation than respiratory or zoonotic chlamydiae. Consequently, species differences are often obscured when findings from a single model are generalized to the genus. Even within C. trachomatis, laboratory strains and cervical cell lines may not capture variation in ocular, rectal and upper-genital-tract infections.

The interpretation of persistence is a particular limitation. Aberrant-body morphology, reduced infectious yield and retained nucleic acid are not equivalent endpoints. Published results frequently derive from short-term cell culture under severe experimental stress, whereas human infection develops in more heterogeneous environments. Claims linking persistence to infertility, repeated positive tests or antibiotic failure should therefore be framed as hypotheses requiring appropriately controlled clinical studies [9,10].

Diagnostic accuracy figures also require context. Sensitivity and specificity depend on assay design, organism burden, specimen type, comparator standard, population and operator performance. Comparisons across studies with different reference standards may be misleading. For these reasons, Table 2 emphasizes strengths, limitations and interpretation rather than pooled universal accuracy estimates.

As a narrative review, article selection was purposive and may miss eligible publications. No exhaustive protocol, independent screening or formal risk-of-bias scoring was undertaken, so the results should not be interpreted as a systematic evidence synthesis. Moreover, many novel candidate interventions remain preclinical, and their clinical effectiveness cannot yet be inferred.

15. CONCLUSIONS

Human chlamydial infections provide a paradigmatic example of how intracellular microbial biology shapes laboratory diagnosis, host injury and antimicrobial management. The biphasic developmental cycle, membrane-bound inclusion and dependence on host metabolism distinguish Chlamydia from typical bacterial pathogens. Advances in effector biology and stress responses have deepened mechanistic understanding, but translation of laboratory persistence to human disease remains incomplete.

Validated molecular amplification testing is now central to *C. trachomatis* diagnosis, while respiratory and zoonotic infections require targeted testing informed by clinical history, specimen quality and assay availability. Correct interpretation of post-treatment NAAT results is crucial because residual nucleic acids, reinfection and true microbiological failure are different scenarios. Contemporary treatment guidelines favor doxycycline for uncomplicated infection in nonpregnant adults, with species- and syndrome-specific alternatives.

Future priorities include clinically validated viability markers, integrated pathogen–host analyses, standardized genomic surveillance, access to point-of-care molecular diagnostics and effective vaccine strategies. Progress will depend on multidisciplinary collaboration among microbiologists, clinicians, epidemiologists and veterinary public health specialists.

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