Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/njm1kg13

EMERGING CHALLENGES IN TREATING SCRUB TYPHUS: THE ROLE OF ANTIBIOTIC RESISTANCE AND INNOVATIVE APPROACHES

J. Suriakumar[1], R. Akila[2], R. Gopinathan[1] and T. Murugalakshmi [3*]

[1]Department of Microbiology, Government Medical College, Dindigul, Tamil Nadu, India
[2]Département of Pathology, Thanjavur Medical College, Thanjavur, Tamil Nadu, India.
[3*]Department of Pharmacology, Government Medical College, Dindigul, Tamil Nadu, India

[*]**Corresponding author:** T. Murugalakshmi
*Department of Pharmacology, Government Medical College, Dindigul, Tamil Nadu, India

Abstract
Scrub typhus, caused by the intracellular bacterium *Orientia tsutsugamushi*, is a significant vector-borne disease transmitted by infected chiggers. It remains endemic in various regions, including parts of Asia and the Pacific Islands. While doxycycline and azithromycin are effective treatments, the emergence of antibiotic-resistant strains of *O. tsutsugamushi* presents a growing threat to treatment efficacy and patient outcomes. This review explores the mechanisms behind antibiotic resistance, the impact on treatment success, and the challenges faced in managing resistant strains. Furthermore, we discuss strategies such as surveillance and monitoring, the development of new antibiotics, alternative therapeutic approaches, and improved vector control measures to combat this public health threat. Addressing these challenges requires global cooperation, research, and enhanced healthcare systems to ensure effective treatment of scrub typhus in the face of evolving antibiotic resistance.

Keywords: Scrub typhus, Orientia tsutsugamushi, Antibiotic Resistance, Doxycycline, Vector Control

Introduction

Scrub typhus is an infectious disease transmitted by vectors and caused by the rickettsial bacteria *Orientia tsutsugamushi*. It is mostly spread to humans via the biting of infected chiggers, the larval stage of trombiculid mites [1]. These mites are widely found in Southeast Asia's rural and forested regions, the Pacific Islands, Northern Australia, and parts of the Indian subcontinent. The disease is endemic in many locations, especially in agricultural districts where people are more likely to be exposed due to regular interaction with mite-infested settings [2].

Scrub typhus often presents with fever, headache, myalgia, and malaise, followed by the formation of a distinctive eschar at the site of the chigger bite. The presence of an eschar, a necrotic ulcer, or scab is an important diagnostic characteristic of the condition. In addition to the eschar, a maculopapular rash may develop, and in severe cases, scrub typhus can result in multi-organ failure, acute respiratory distress syndrome, septic shock, and death. Scrub typhus can be fatal if not treated, with severe cases necessitating urgent care and extended hospitalization [3 & 4]. Early diagnosis and treatment are critical for avoiding complications and improving patient outcomes.

Doxycycline is recommended as the first-line treatment for scrub typhus due to its excellent efficacy in eliminating the pathogen and avoiding illness progression. Other antibiotics, such as azithromycin, chloramphenicol, and tetracycline [5], are also used in some circumstances, especially in people who are intolerant to doxycycline. These antibiotics function by blocking bacterial protein synthesis, focusing on the intracellular nature of *O. tsutsugamushi* and preventing its multiplication within host cells. Despite the drugs' established efficiency, the rise of antibiotic-resistant O. tsutsugamushi strains poses a substantial challenge to scrub typhus care [6].

Antibiotic resistance in *O. tsutsugamushi* has been a major concern in recent years, with certain strains demonstrating reduced sensitivity or total resistance to doxycycline and other routinely used antibiotics. This resistance complicates treatment while also increasing the likelihood of treatment failure, protracted sickness, and higher morbidity and mortality [7]. The processes behind antibiotic resistance in *O. tsutsugamushi* are still unknown due to the pathogen's complicated biology as an obligate intracellular bacterium, which makes it challenging to examine using normal laboratory procedures [8]. However, issues such as antibiotic abuse and misuse in both human and veterinary medicine, a lack of access to early and reliable diagnostic testing, and insufficient treatment regimens in resource-constrained settings all contribute to the development of resistance strains [9].

The widespread expansion of antibiotic-resistant *O. tsutsugamushi* strains jeopardizes efforts to manage and ultimately eradicate scrub typhus. As the availability of efficient treatment choices decreases, healthcare practitioners may struggle to manage severe cases of the disease, potentially leading to more widespread outbreaks and higher healthcare expenses [10 & 11]. This circumstance emphasizes the critical need for ongoing research into alternate therapeutic choices, improved diagnostic capabilities, and public health policies for combating antibiotic resistance.

In addition to the obstacles caused by resistance, additional factors such as inadequate healthcare infrastructure, delayed diagnosis, and a lack of knowledge compound the issue in endemic areas. The complexities of treating scrub typhus, especially in cases involving resistant strains, highlight the necessity for a multifaceted approach to combating the growing problem of antibiotic resistance [12 & 13]. To address this issue, coordinated efforts must be made in research, surveillance, public health initiatives, and the development of new diagnostic and treatment methods to prevent further complications in scrub typhus management.

1. The Antibiotic Resistance Challenge

Antibiotic resistance is a serious global health concern, and its impact on scrub typhus management is increasing. Scrub typhus, caused by *O. tsutsugamushi*, is usually treated with doxycycline, however the rise of resistant strains is threatening treatment efficacy. This resistance is caused by causes such as antibiotic overuse and misuse, especially in resource-constrained countries where diagnostic services are poor. Resistant strains complicate disease treatment, resulting in extended illness, higher expenditures, and increased death [14]. *O. tsutsugamushi* is an intracellular infection; hence the mechanisms behind resistance remain unknown. Treatment failures with doxycycline have been observed, and alternatives such as azithromycin and chloramphenicol are frequently ineffective. The rising resistance problem challenges efforts to control scrub typhus, particularly in developing nations with limited healthcare resources [15]. To combat antibiotic resistance, new drugs must be developed, diagnostic techniques improved, and responsible antibiotic usage promoted. Public health activities, improved diagnostic skills, and vector control methods are also critical for lowering the disease burden and preventing future resistance [16]. Addressing this issue is critical for providing efficient treatment and avoiding the spread of scrub typhus worldwide.

1.1 Mechanisms of resistance

Scrub typhus is caused by the intracellular bacterium *Orientia tsutsugamushi* (*O. tsutsugamushi*), which is fundamentally more difficult to treat than extracellular infections. Its intracellular lifestyle makes it difficult for many antibiotics, particularly those that are less lipophilic (such as beta-lactams), to penetrate and reach therapeutic levels inside host cells, where the bacteria live [6].

O. tsutsugamushi resistance to conventional antibiotics such as doxycycline and azithromycin is caused by a variety of mechanisms. Drug-target site alterations are a major factor to resistance. Mutations in these target areas diminish antibiotic efficacy by preventing them from binding and suppressing bacterial processes. Furthermore, bacteria may use efflux pumps—protein channels in the bacterial cell membrane—to actively remove antibiotics from the cell before they can exert their effects. Furthermore, changes in the bacterial cell wall or membrane might impede antibiotic penetration and drug accumulation within the cell, conferring resistance [17 & 18]. These mechanisms exacerbate the treatment of scrub typhus and underline the critical need for alternate therapeutic techniques.

1.2 Impact on Treatment

The rise of antibiotic resistance in *O. tsutsugamushi* has had a substantial influence on scrub typhus treatment and care, complicating patient outcomes and raising the risk of serious sequelae.

Doxycycline Resistance: For many years, doxycycline was the primary treatment for scrub typhus. However, doxycycline resistance has arisen in some locations, resulting in delayed therapeutic responses. This leads to longer infection durations since the pathogen is not efficiently removed by usual treatment. In these circumstances, patients may recover more slowly and are more likely to develop consequences such as organ failure, shock, and sepsis [19].

Azithromycin Resistance: Azithromycin, which is frequently used as an option for patients who are intolerant to doxycycline or in areas with limited availability to doxycycline, is also showing rising resistance. This is especially concerning for anyone with doxycycline contraindications, such as pregnant women or young children. Because of azithromycin's decreased efficacy, there are fewer alternatives for treating resistant scrub typhus cases, complicating management efforts, particularly in resource-limited settings [20 & 21].

Treatment Failures: Antibiotic-resistant O. tsutsugamushi strains have a high probability of treatment failure. When first-line antibiotics such as doxycycline and azithromycin are ineffective, the infection may worsen, leading to more serious outcomes such as multi-organ failure, sepsis, and death. The introduction of resistance strains adds to the load on healthcare systems and raises treatment costs, necessitating the use of alternative, sometimes less effective antibiotics and longer hospital stays [22 & 23].

Table 1 highlights the complex and multifactorial nature of resistance in *O. tsutsugamushi*, making treatment more challenging and underscoring the need for alternative therapeutic approaches.

Table: 1The key mechanisms of antibiotic resistance in *O. tsutsugamushi* and their implications for treatment

Mechanism of Resistance	**Explanation**	**Impact on Treatment**	**Ref**
Intracellular Lifestyle	*O. tsutsugamushi* is an obligate intracellular bacterium, residing inside host cells.	Limits the penetration of many antibiotics, especially those that are not lipophilic (e.g., beta-lactams).	[24]
Alteration in Drug-Target Sites	Mutations in the bacterial target sites reduce the binding affinity of antibiotics like doxycycline and azithromycin.	Reduces the effectiveness of commonly used antibiotics, leading to treatment failure.	[25]
Efflux Pumps	*O. tsutsugamushi* may utilize efflux pumps to actively expel antibiotics from the bacterial cell.	Reduces the intracellular concentration of antibiotics, preventing them from reaching effective levels.	[26]
Mutations in Cell Membrane	Changes in the bacterial cell membrane or wall can limit antibiotic entry into the cell.	Restricts the uptake of antibiotics, decreasing the drug's ability to exert its therapeutic effects.	[27]

1.3 Factors contributing to resistance:

Several linked factors influence the formation and dissemination of antibiotic resistance in *O. tsutsugamushi*, making resistant strains more likely to survive and multiply. These factors include both biological features of the pathogen and larger socio-environmental circumstances.

Overuse and Misuse of Antibiotics: Antibiotic overuse and misuse are major contributors to resistance in both human health and agriculture. Antibiotics are frequently misused in endemic areas, either by self-medication or the administration of wrong doses. This applies selective pressure to *O. tsutsugamushi*, promoting the survival of resistant strains [14].

Inadequate Treatment Regimens: In resource-limited situations, insufficient treatment regimens may result in incomplete or ineffective antibiotic courses. This enables bacteria to thrive and build resistance mechanisms. Furthermore, in certain situations, patients may discontinue medicines prematurely once they feel better, contributing to the survival of resistant germs [28].

Lack of Rapid Diagnostic Tools: Patients may receive unsuitable or inadequate treatment because to the lack of accurate, quick diagnostic tests for *O. tsutsugamushi* and its resistance profile. This delay in discovering resistant strains limits prompt adjustments to antibiotic therapy, allowing resistant infections to proliferate [29].

Limited Surveillance of Resistance: There is insufficient antibiotic resistance surveillance in many regions of the world, particularly in rural or remote locations where scrub typhus is common. Without adequate monitoring, the appearance and spread of resistant strains are difficult to detect early on, impeding efforts to deploy control measures and modify treatment procedures [30].

Cross-Resistance and Genetic Adaptation: *O. tsutsugamushi* has a high genetic variability, allowing the pathogen to adapt to environmental stressors such as antibiotic exposure via mutations and horizontal gene transfer. This enables germs to quickly acquire resistance genes and propagate them throughout populations, complicating treatment strategies [31].

Poor Vector Control and Environmental Factors: *O. tsutsugamushi*'s persistence and expansion are attributed to environmental factors such as poor vector management. Inadequate control of chiggers, the vectors responsible for transferring the germs, results in greater exposure rates, increasing the likelihood of antibiotic use and the development of resistance. Furthermore, environmental factors like as climate change may influence the spread of mites and illness, exacerbating the issue of resistance [32 & 33].

2. Poor Vector Control and Environmental Factors

Poor vector control and other environmental variables contribute significantly to the spread of *O. tsutsugamushi* and the development of antibiotic resistance. These factors not only influence scrub typhus transmission, but they also make it more difficult to control the disease and prevent resistant forms from emerging [34].

Inadequate Vector Control Measures: Chiggers, the larvae of trombiculid mites, are the major vectors that transmit *O. tsutsugamushi* to humans. In many endemic areas, vector management techniques such as insecticides, acaricides, and habitat alteration are inadequate or poorly administered. Inadequate chigger population control leads to increased human exposure to infected mites, which increases the incidence of scrub typhus and, as a result, the need of antibiotics. Antibiotics are widely abused in attempts to treat the condition, which raises selective pressure on O. tsutsugamushi and contributes to resistance development [13 & 35].

Environmental and Climatic Factors: Environmental factors such as humidity, temperature, and seasonal fluctuations all have an impact on chigger distribution and population dynamics. Warmer weather and higher rainfall promote mite multiplication, hence increasing their transmission potential. Chigger populations may increase or spread to new areas in places with volatile or unpredictable weather patterns as a result of climate change, increasing the risk of scrub typhus. This not only increases the number of instances, but it also feeds the loop of antibiotic usage by encouraging more patients to seek treatment, allowing resistant strains to develop [36].

Deforestation and Human Encroachment: Deforestation and human encroachment on rural and forested regions increase the risk of humans coming into touch with chiggers, which thrive in these

habitats. Human populations move into these places, increasing their risk of mite bites and contributing to the spread of *O. Tsutsugamushi* [37]. This increased human exposure to infected vectors raises the demand for antibiotic treatments, encouraging overuse and misuse of antibiotics in these areas, which contributes to the development of antibiotic resistance [38].

Poor Sanitation and Living Conditions: Inadequate housing and a lack of effective pest control in rural or impoverished areas create conditions in which humans and chiggers cohabit. This close contact increases the risk of mite bites and the requirement for antibiotic treatment. These unsanitary living circumstances, together with the inappropriate or partial use of antibiotics, create an excellent environment for the creation and spread of resistant *O. tsutsugamushi* strains [39].

Poor vector control and environmental conditions work together to exacerbate the spread of scrub typhus, resulting in a cycle of increased infection rates, higher antibiotic consumption, and more potential for resistance development. To address these difficulties, coordinated strategies that combine effective vector control, environmental management, and appropriate antibiotic use are critical for slowing disease spread and preventing resistance development.

2.1 Lack of Rapid Diagnostic Tools

One of the most significant issues in treating antibiotic resistance in scrub typhus is a lack of quick diagnostic techniques for detecting resistance patterns and identifying the most effective medications in real time. Traditional diagnostic approaches, such as culture-based techniques, are slow and may take several days to yield results. This delay can result in improper antibiotic therapy, allowing resistant strains of *O. tsutsugamushi* to persist and spread, complicating patient management [12 & 40]. Molecular approaches, which could discover resistance markers more quickly, are rarely available in endemic areas due to high prices, a lack of infrastructure, and technical expertise. While these approaches have the potential to deliver faster and more precise antibiotic resistance data, their restricted availability impedes effective and prompt treatment decisions [41]. The lack of rapid diagnostic platforms causes delays in the detection of resistant strains and the administration of suitable medicines, contributing to increased morbidity and mortality. To close this gap, there is an urgent need for the development and widespread adoption of low-cost, user-friendly diagnostic tools that can quickly identify both *O. tsutsugamushi* and its resistance profile, allowing healthcare providers to make more informed treatment decisions and reduce the risk of future resistance development.

2.2 Limited therapeutic options

The treatment of antibiotic-resistant scrub typhus is a developing concern due to the scarcity of effective therapeutic options. Because *O. tsutsugamushi* is an intracellular infection, the development of new medications that can successfully combat it is sluggish. This gives clinicians limited options for treating resistant infections, especially when first-line medicines like doxycycline or azithromycin fail [42]. In many circumstances, practitioners are obliged to use older antibiotic combinations that may be less effective or require longer treatment times. These antibiotics may also be associated with a higher risk of side effects, making them less appealing for patients. For example, chloramphenicol, an alternative to doxycycline, can have serious adverse effects, including bone marrow suppression, limiting its usage, particularly in susceptible groups like as children and pregnant women [43 & 44]. The lack of new, effective antibiotics for treating intracellular bacteria exacerbates the situation, as resistance patterns arise. Without newer therapeutic agents, dependence on existing medications may lead to increased treatment failures and difficulties in scrub typhus management, underscoring the critical need for research into new antibiotics and alternative treatment options.

2.3 Complications of Severe Cases

In extreme cases of scrub typhus, where patients develop multi-organ failure, septic shock, or encephalitis, antibiotic resistance to first-line treatments such as doxycycline and azithromycin greatly increases the chance of death. When *O. tsutsugamushi* strains develop resistance to these

first-line medicines, the infection becomes much more difficult to treat, and the risk of consequences increases [45].

Multi-organ failure and septic shock are life-threatening illnesses that necessitate prompt and aggressive interventions, such as intensive care unit support, organ-specific therapies, and, in many cases, the use of alternative antibiotics. However, in resource-constrained contexts where healthcare infrastructure may be inadequate, these therapies are not always available [46]. This complicates the care of severe scrub typhus cases and raises the risk of bad outcomes.

The difficulty is exacerbated by the scarcity of new antibiotics capable of properly treating resistant strains, requiring practitioners to rely on older, less effective medications. These problems underscore the need for increased healthcare access, more effective therapies, and better diagnostic skills, especially in areas where scrub typhus is most common [47]. Without addressing these gaps, the risk of mortality in severe instances will continue to climb, emphasizing the critical need for comprehensive methods to combat both the disease and antibiotic resistance.

3. Strategies for addressing antibiotic resistance in scrub typhus

Combating antibiotic resistance in scrub typhus necessitates a multifaceted approach that includes medical, environmental, and public health interventions. As resistance to frontline medicines such as doxycycline and azithromycin emerges, it is critical to deploy effective methods to slow the emergence of resistance, improve treatment results, and avoid further problems.

3.1. Surveillance and Monitoring

Improving antibiotic stewardship is crucial in the fight against antibiotic resistance, especially in the case of scrub typhus. Antibiotic stewardship entails encouraging the appropriate use of antibiotics, ensuring that they are only administered when absolutely necessary, and that they are used at the proper dosages and times. This technique helps to reduce antibiotic abuse and misuse, which both contribute to the development of resistance in *O. Tsutsugamushi* [48 & 49].

Antibiotic stewardship includes educating and training healthcare providers on how to use antibiotics appropriately. This includes advice on choosing the appropriate antibiotic, dose, and treatment length, as well as knowing when antibiotic therapy is unneeded. By increasing healthcare practitioners' understanding, they can make better decisions while treating scrub typhus, lowering the likelihood of improper antibiotic use and resistance [50 & 51].

Following evidence-based treatment guidelines for scrub typhus is also critical. These guidelines assist clinicians in prescribing antibiotics correctly and effectively, reducing the risk of over-prescription and resistance development. Furthermore, limiting self-medication is a vital part of stewardship.

3.2. Research and Development of New Antibiotics

The development of novel antibiotics that target *O. tsutsugamushi* is critical in addressing the rising problem of antibiotic resistance. As resistance to first-line medicines such as doxycycline and azithromycin grows, new antibiotics are urgently required to tackle resistant bacteria and improve patient outcomes. One intriguing path is the development of novel antibiotic classes, particularly those capable of disrupting bacterial cell wall formation or targeting *O. tsutsugamushi*'s specific intracellular processes. Given that *O. tsutsugamushi* is an intracellular bacteria, antibiotics that can enter host cells and target the pathogen within its cellular context are particularly important [11 & 42].

In addition to developing new antibiotics, research into complementary medicines should be prioritized. These could include immunotherapy or other medications that improve the efficacy of current antibiotics. For example, adjunct medicines that modify the immune response or impair bacterial defence mechanisms may improve the effectiveness of conventional antibiotics, particularly in cases where resistance has already evolved. Combining these adjunct medicines with regular antibiotic treatment may allow for lower antibiotic dosages, less side effects, and a slower development of resistance [52].

3.3 Alternative Treatment Regimens

Combination therapy, which involves employing two or more antibiotics to target separate elements of bacterial metabolism, appears to be a promising technique for overcoming scrub typhus resistance. Combining antibiotics with diverse modes of action reduces the risk that *O. tsutsugamushi* will acquire resistance to the treatment [53]. Investigating the synergistic effects of routinely used antibiotics, such as doxycycline or azithromycin, with newer medicines or older, repurposed medications may provide new therapy options. This method has the potential to improve the efficacy of existing medications while also opening up new treatment options for resistant infections [6].

In addition to combination therapy, non-antibiotic techniques may provide novel answers to resistant scrub typhus. Phage therapy is one such strategy, in which bacteriophages—viruses that selectively target and kill bacteria—are used as a therapeutic. Phage treatment has showed potential in treating antibiotic-resistant illnesses by providing a different way to target the bacteria. Similarly, antimicrobial peptides, which are naturally occurring proteins that can break bacterial cell membranes, could be an efficient way to attack *O. tsutsugamushi* without using standard antibiotics [54 & 55].

Combination therapies and non-antibiotic treatments such as phage therapy and antimicrobial peptides could be investigated to develop novel treatment regimens to meet the growing challenge of antibiotic resistance in scrub typhus. These alternate tactics provide hope for overcoming the limitations of conventional antibiotic therapies and developing more effective alternatives for controlling resistant illnesses.

3.4 Vector Control and Prevention

Effective vector management and prevention techniques are critical for controlling scrub typhus and minimizing the establishment of antibiotic-resistant variants. One of the key methods for controlling the disease is to use insecticides and personal protective measures to prevent mite bites. These precautions can include using insect repellent, wearing protective clothing, and limiting exposure to locations where mites are widespread. The frequency of scrub typhus can be reduced by limiting human contact with infected chiggers, which minimizes the possibility of *O. tsutsugamushi* becoming resistant to antibiotics [11 & 56].

In addition to vector control, community education is an important component of prevention. Raising public knowledge of the risks of scrub typhus and teaching them on correct prevention techniques, such as avoiding mite-infested regions and seeking early medical treatment, can help to drastically lower the disease burden. Educating communities in endemic areas about the necessity of following recommended antibiotic regimens and avoiding self-medication can also assist to reduce the spread of resistant strains [57 & 58].

Mass drug administration (MDA) in high-risk locations could also be a proactive technique for reducing the number of new infections and limiting the opportunity for resistance to develop. Antibiotics can be administered to entire communities, particularly in areas with high transmission rates, to reduce the spread of *O. tsutsugamushi* and prevent resistance from developing. MDA programs, when well planned and performed, can benefit the entire population by lowering infection rates and reducing the total need for individual antibiotic treatments [59].

These vector control techniques, preventive strategies, and community-based initiatives can all assist to reduce scrub typhus, slow the spread of antibiotic resistance, and enhance public health outcomes.

These table 2 strategies focus on improving diagnostics, awareness, global collaboration, and regulation, all of which are critical to addressing the growing issue of antibiotic resistance in scrub typhus. Let me know if you need any further adjustments or additional strategies!

Table: 2 Strategies for addressing antibiotic resistance in scrub typhus

Strategy	Key Points	Ref
Strengthening Diagnostic Capacity	- Invest in rapid and accurate diagnostic tests to identify resistant strains early. - Utilize molecular diagnostic methods for faster and more precise detection of *O. tsutsugamushi* resistance.	[60]
Public Health Awareness Campaigns	- Educate the public about the risks of antibiotic misuse and self-medication. - Raise awareness of the importance of completing prescribed antibiotic regimens.	[61]
Collaborative International Research	- Foster global collaborations to track antibiotic resistance trends and share data. - Support international initiatives for the development of novel therapies and vaccines.	[62]
Regulation and Control of Antibiotic Use	- Implement stricter regulations on the sale and distribution of antibiotics, particularly in endemic regions. - Monitor antibiotic prescriptions in healthcare settings to prevent overuse and misuse.	[63]

Conclusion

The rise of antibiotic resistance in Orientia tsutsugamushi, the cause of scrub typhus, poses a significant threat to worldwide public health. The increasing prevalence of resistance jeopardizes the efficacy of current therapy regimens and raises the risk of treatment failure, complications, and mortality. Addressing this issue requires a diverse approach, which includes improved surveillance, the development of new antibiotics, and novel treatment options. Furthermore, effective vector control and prevention strategies will be critical in lowering the scrub typhus burden and minimizing resistance dissemination. Only worldwide collaboration, research, and enhanced healthcare infrastructure can effectively address the rising tide of antibiotic resistance in scrub typhus.

Financial support and sponsorship

None

Conflicts of interest

There are no conflicts of interest.

References

1. PENG PY, CAI YP, XU L, ZHA YJ, YANG BS. The epidemiology of scrub typhus all over the world: A systematic literature review. Asian Journal of Advances in Research. 2021 Feb 11:96-109.
2. Chakraborty S, Sarma N. Scrub typhus: an emerging threat. Indian Journal of Dermatology. 2017 Sep 1;62(5):478-85.
3. Chang WH, Hung CH. Ocular inflammation in tsutsugamushi disease–a case report. European Journal of Ophthalmology. 2024 Jun 17:11206721241262840.
4. Kumar D, Jakhar SD. Emerging trends of scrub typhus disease in southern Rajasthan, India: A neglected public health problem. Journal of Vector Borne Diseases. 2022 Oct 1;59(4):303-11.
5. Paris DH, Day NP. SECTION VI Bacterial Infections. Manson's Tropical Infectious Diseases. 2023 Jul 14:326.
6. Srivastava P, Shukla A, Singh R, Kant R, Mishra N, Behera SP, Dwivedi GR, Yadav DK. Orientia tsutsugamushi: An Unusual Intracellular Bacteria—Adaptation Strategies, Available Antibiotics, and Alternatives for Treatment. Current Microbiology. 2024 Aug;81(8):236.
7. Roat G, Singh R, Kumar S, Tank L, Mosalpuri A, Dadhich A, Jain S. AN OBSERVATIONAL STUDY ON CLINICAL SPECTRUM, DIAGNOSIS, COMPLICATIONS AND THERAPEUTIC OUTCOME OF SCRUB TYPHUS: AN EMERGING RICKETTSIAL INFECTION. Int J Acad Med Pharm. 2023;5(3):1796-801.

8. Mehl J. The Role of Bacterial RNA as a Pathogen-Associated Molecular Pattern in Orientia tsutsugamushi Infection.
9. Ademulegun FG, Uyigue PO, Onemu SO, Ojo B, Oduwole OA. Emerging and Re-Emerging Bacterial Infections: An Overview. Sokoto Journal of Medical Laboratory Science. 2024;9(4):151-68.
10. Rao RS, Ghate SD, Shastry RP, Kurthkoti K, Suravajhala P, Patil P, Shetty P. Prevalence and heterogeneity of antibiotic resistance genes in Orientia tsutsugamushi and other rickettsial genomes. Microbial Pathogenesis. 2023 Jan 1;174:105953.
11. Rajaiah P. Scrub typhus, a mite-borne rickettsiosis: innovative approaches for intervention strategies. Discover Medicine. 2024 Sep 30;1(1):58.
12. Sivasubramanian BP, Abdul Khader AH, Ravikumar DB, Dominic Savio FV, Thirupathy U, Thiruvadi V, Prasad R, Thokala H, Qadeer H, Venkataperumal DP, Gupta A. Comprehensive review on cardiac manifestation of scrub typhus. Frontiers in Tropical Diseases. 2024 Sep 20;5:1375087.
13. Gitau MS, Asiago OH, Rogers OO, Reddy KS, PradeepKumar B, Sudheer A, Pasala PK, Swarna P. A Comprehensive Review on Scrub Typhus: Epidemiology, Transmission, Diagnosis and Management. UTTAR PRADESH JOURNAL OF ZOOLOGY. 2024 Apr 4;45(8):93-105.
14. Lu D, Wang T, Luo Z, Ye F, Qian J, Zhang J, Wang C. Evaluation of the therapeutic effect of antibiotics on scrub typhus: a systematic review and network meta-analysis. Frontiers in Public Health. 2022 Apr 27;10:883945.
15. van Schaik EJ, Fratzke AP, Gregory AE, Dumaine JE, Samuel JE. Vaccine development: obligate intracellular bacteria new tools, old pathogens: the current state of vaccines against obligate intracellular bacteria. Frontiers in Cellular and Infection Microbiology. 2024 Mar 19;14:1282183.
16. Kanan M, Ramadan M, Haif H, Abdullah B, Mubarak J, Ahmad W, Mari S, Hassan S, Eid R, Hasan M, Qahl M. RETRACTED: Empowering Low-and Middle-Income Countries to Combat AMR by Minimal Use of Antibiotics: A Way Forward. Antibiotics. 2023 Oct 2;12(10):1504.
17. Chunduru K, A. R M, Poornima S, Hande H M, Devaki R, Varghese GM, Saravu K. Clinical, laboratory profile and molecular characterization of Orientia tsutsugamushi among fatal scrub typhus patients from Karnataka, India. Infectious Diseases. 2024 Mar 3;56(3):220-9.
18. Gupta N, Boodman C, Jouego CG, Van Den Broucke S. Doxycycline vs azithromycin in patients with scrub typhus: a systematic review of literature and meta-analysis. BMC Infectious Diseases. 2023 Dec 18;23(1):884.
19. Mehta KK, Jayalal JA, Lele J, Joshi P, Rekha S, Vora A, John B. A Stepwise Guide for Differential Diagnosis and Management of Acute Fever in Primary Care: An Indian Perspective. Evaluation. 2022 Apr;120(4).
20. Sharma A, Mahajan V, Guglani V, Singla N, Saini SS. Open-labeled Randomized Controlled Trial on Efficacy of Azithromycin Versus Doxycycline in Pediatric Scrub Typhus. The Pediatric Infectious Disease Journal. 2023 Dec 1;42(12):1067-72.
21. Prieto Sánchez P. Does doxycycline post exposure prophylaxis prevent sexually transmitted Infections in women and achieve minimum Inhibitory concentrations in vaginal Mucosa?: a population-based prospective cohort.
22. Chavarría-Bencomo IV, Nevárez-Moorillón GV, Espino-Solís GP, Adame-Gallegos JR. Antibiotic resistance in tick-borne bacteria: a One Health approach perspective. Journal of Infection and Public Health. 2023 Dec 1;16:153-62.
23. Kumar K, Patnaik R, Kumari H, Sharma N. Acute Febrile Illness: A Systematic Review Of Infectious Aetiologies Among Patients. Journal of Pharmaceutical Negative Results. 2022 Dec 21:5079-93.
24. Chen Y, Jiang Y, Xue T, Cheng J. Strategies for the eradication of intracellular bacterial pathogens. Biomaterials Science. 2024.
25. Fisher DJ, Beare PA. Recent advances in genetic systems in obligate intracellular human-pathogenic bacteria. Frontiers in Cellular and Infection Microbiology. 2023 Jun 19;13:1202245.

26. Beaudoin C. Evolution of targets at the host-pathogen interface (Doctoral dissertation).
27. Atwal S, Wongsantichon J, Giengkam S, Saharat K, Pittayasathornthun YJ, Chuenklin S, Wang LC, Chung T, Huh H, Lee SH, Sobota RM. The obligate intracellular bacterium Orientia tsutsugamushi differentiates into a developmentally distinct extracellular state. Nature communications. 2022 Jun 23;13(1):3603.
28. Badro DA. Chronic Kidney Disease Management in Developing Countries. InHandbook of Medical and Health Sciences in Developing Countries: Education, Practice, and Research 2023 Apr 20 (pp. 1-146). Cham: Springer International Publishing.
29. Tjampakasari CR, Kiranasari A, Abas GM. Rickettsia as an agent of neglected Rickettsia infection. Journal of Clinical Microbiology and Infectious Diseases. 2024 Jun 19;4(1):6-10.
30. Wang Q, Ma T, Ding F, Lim A, Takaya S, Saraswati K, Sartorius B, Day NP, Maude RJ. Global and regional seroprevalence, incidence, mortality of, and risk factors for scrub typhus: A systematic review and meta-analysis. International Journal of Infectious Diseases. 2024 Sep 1;146:107151.
31. Khan MA, Amin A, Farid A, Ullah A, Waris A, Shinwari K, Hussain Y, Alsharif KF, Alzahrani KJ, Khan H. Recent advances in genomics-based approaches for the development of intracellular bacterial pathogen vaccines. Pharmaceutics. 2022 Dec 31;15(1):152.
32. Yanase T, Otsuka Y, Doi K, Tabaru Y, Arserim SK, Sasaki H, Özbel Y, Töz S, Ueda T, Tsuji N, Amoh Y. Other Medically Important Vectors. InMedical Entomology in Asia 2024 Aug 9 (pp. 149-230). Singapore: Springer Nature Singapore.
33. Mojahed N, Mohammadkhani MA, Mohamadkhani A. Climate crises and developing vector-borne diseases: a narrative review. Iranian journal of public health. 2022 Dec;51(12):2664.
34. Wang T, Meng F, Che T, Chen J, Zhang H, Ji Y, Fan Z, Zhao G, Zhang W, Jiang B, Xu Q. Mapping the distributions of blood-sucking mites and mite-borne agents in China: a modeling study. Infectious Diseases of Poverty. 2022 Apr 9;11(1):41.
35. Diaz JH. Mite-Human Interactions: Nuisances, Vectors, Parasites, Allergens, and Commensals. Elsevier; 2023 Dec 1.
36. Appugol KA, Mangang IB, Loganathan M. Rising Concerns in Entomophagy. AGRICULTURE & FOOD E-NEWSLETTER. 2022 Apr:10.
37. Blache N, Chalvet-Monfray K, Déprés C, Morand S. A scoping review of the impacts of forest dynamics on acari-borne diseases: beyond forest fragmentation.
38. Endale H, Mathewos M, Abdeta D. Potential causes of spread of antimicrobial resistance and preventive measures in one health perspective-a review. Infection and Drug Resistance. 2023 Dec 31:7515-45.
39. Narendar R, Krishnan J. Unraveling the Impact of Rickettsial Infections. Vector Borne Diseases: Current Trends and Public Health Perspectives. 2024:9.
40. Riffaud CM, Rucks EA, Ouellette SP. Persistence of obligate intracellular pathogens: alternative strategies to overcome host-specific stresses. Frontiers in Cellular and Infection Microbiology. 2023 May 22;13:1185571.
41. Vashisht V, Vashisht A, Mondal AK, Farmaha J, Alptekin A, Singh H, Ahluwalia P, Srinivas A, Kolhe R. Genomics for emerging pathogen identification and monitoring: Prospects and obstacles. BioMedInformatics. 2023 Dec 7;3(4):1145-77.
42. Sharma D, Sharma A, Singh B, Kumar S, Verma SK. Neglected scrub typhus: an updated review with a focus on omics technologies. Asian Pacific Journal of Tropical Medicine. 2022 Dec 1;15(12):531-41.
43. Janssen RM, Oerlemans AJ, Van Der Hoeven JG, Ten Oever J, Schouten JA, Hulscher ME. Why we prescribe antibiotics for too long in the hospital setting: a systematic scoping review. Journal of Antimicrobial Chemotherapy. 2022 Aug 1;77(8):2105-19.
44. Singhal M, Agrawal M, Bhavna K, Sethiya NK, Bhargava S, Gondkar KS, Joshi K, Rana VS, Sahoo J, Arora MK. Chloramphenicol and tetracycline (broad spectrum antibiotics). InAntibiotics-Therapeutic Spectrum and Limitations 2023 Jan 1 (pp. 155-165). Academic Press.

45. Dahiphle AV, Achliya A, Chhajed N, Rode V, Bhise K. Study of Clinical and Demographic Profile of Scrub Typhus Patients Admitted to a Tertiary Care Hospital in Central India. International Journal of Integrated Health Sciences. 2024 Mar 30;12(1):24-30.
46. Choudhuri AH, Das B, editors. Interpreting Laboratory Tests in Intensive Care. CRC Press; 2024 Dec 30.
47. Muteeb G, Rehman MT, Shahwan M, Aatif M. Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. Pharmaceuticals. 2023 Nov 15;16(11):1615.
48. Jain HK, Das A, Dixit S, Kaur H, Pati S, Ranjit M, Dutta A, Bal M. Development and implementation of a strategy for early diagnosis and management of scrub typhus: an emerging public health threat. Frontiers in Public Health. 2024 Apr 10;12:1347183.
49. Ahmed S. Agriculture and Zoonotic Diseases in Farmers in India. Int. J. Agric. Env. Sustain. 2024;6(1):1.
50. Varghese GM, Dayanand D, Gunasekaran K, Kundu D, Wyawahare M, Sharma N, Chaudhry D, Mahajan SK, Saravu K, Aruldhas BW, Mathew BS. Intravenous doxycycline, azithromycin, or both for severe scrub typhus. New England Journal of Medicine. 2023 Mar 2;388(9):792-803.
51. Vanramliana, Pautu L, Lalmalsawma P, Rosangkima G, Sarma DK, Chinzah H, Malvi Y, Kodali NK, Amarthaluri C, Balasubramani K, Balabaskaran Nina P. Epidemiology of scrub typhus and other rickettsial infections (2018–22) in the hyper-endemic setting of Mizoram, North-East India. PLoS Neglected Tropical Diseases. 2023 Nov 1;17(11):e0011688.
52. Londoño AF, Farner JM, Dillon M, Grab DJ, Kim Y, Scorpio DG, Dumler JS. Benidipine impairs innate immunity converting sublethal to lethal infections in a murine model of spotted fever rickettsiosis. PLOS Neglected Tropical Diseases. 2024 Feb 26;18(2):e0011993.
53. Sathya Jeevitha B, Krishnan J. Scrub typhus-An Integrated Omics Approach. Vector Borne Diseases: Current Trends and Public Health Perspectives. 2024 Dec 17:61.
54. Durr HA, Leipzig ND. Advancements in bacteriophage therapies and delivery for bacterial infection. Materials Advances. 2023;4(5):1249-57.
55. Zhou S, Liu Z, Song J, Chen Y. Disarm the bacteria: what temperate phages can do. Current Issues in Molecular Biology. 2023 Feb 1;45(2):1149-67.
56. Singh B, Kumar D, Kumar G, Saroha P, Vikram K, Gupta SK, Singh H. Insecticidal Paint: An Alternate Integrated Vector Management Strategy for Mosquito Control. Process Safety and Environmental Protection. 2024 Mar 30.
57. Pandey RP, Konyak MB, Soni M, Saikia S, Chang T, Gogoi I, Khongstid I, Sharma M. Scrub typhus: epidemiology, clinical presentations, and diagnostic approaches.
58. Khairkar M, Vagha S, Deotale V. Review on Scrub Typhus: An Important Etiology of Acute Undifferentiated Fever Illness. Cureus. 2023 Oct;15(10).
59. Shaw JA. Vector-Borne/Zoonotic Diseases. InHistorical Diseases from a Modern Perspective: The American Experience 2024 Jun 30 (pp. 65-100). Cham: Springer Nature Switzerland.
60. Sumit, Gupta S, Kaushal A. Advanced Diagnostic Techniques for Scrub Typhus: From Conventional Methods to Nanotechnology Solutions. ChemistrySelect. 2024 Sep 11;9(34):e202402240.
61. Sulis G, Sayood S, Gandra S. How can we tackle the overuse of antibiotics in low-and middle-income countries?. Expert Review of Anti-infective Therapy. 2023 Nov 2;21(11):1189-201.
62. Srivastav AK, Das P, Srivastava AK. Future Trends, Innovations, and Global Collaboration. InBiotech and IoT: An Introduction Using Cloud-Driven Labs 2024 Sep 25 (pp. 309-398). Berkeley, CA: Apress.
63. Kumar R. Epidemiological Challenges in India. InHandbook of Epidemiology 2024 Apr 5 (pp. 1-27). New York, NY: Springer New York.